SUPPLEMENTARY MATERIALS 3 – Evidence Report

2024 American College of Rheumatology (ACR) Guideline for the Screening, Treatment, and Management of Lupus Nephritis

Lupus Nephritis Guideline Evidence Summary

Evidence reports for each PICO question and for each comparison under the PICO questions. For comparative data (randomized clinical trials and nonrandomized studies of intervention), we assessed the certainty of the evidence using the GRADE approach and presented it in a summary of findings table (evidence profile) while for noncomparative data (single arm data) we presented the evidence in a table summarizing the outcomes without using the GRADE approach to assess the certainty of the evidence.

P1. In SLE patients with unexplained proteinuria, hematuria, or impaired kidney function, is knowing the kidney histology by biopsy associated with better outcomes than not knowing the kidney histology?

Population: Patients with SLE with otherwise unexplained

- Proteinuria alone
- Glomerular hematuria with or without proteinuria with normal kidney function
- Impaired kidney function

Intervention: Percutaneous kidney biopsy

Comparator: No percutaneous kidney biopsy

Outcomes:

- Additional or different diagnosis identified (e.g., thrombotic microangiopathy (TMA), acute tubular necrosis (ATN), diabetes mellitus (DM) or arteriosclerosis / arteriolosclerosis.) that impacts decision for and choice of therapy
- Reduction of proteinuria
- Preservation of kidney function
- ESKD (dialysis or transplant)
- Adverse effects of biopsy

Summary: The literature search identified 30 studies, all observational and the majority non-comparative (n=25), that addressed this PICO question. The observational and non-comparative nature of the data limits the strength and utility of the included evidence. Below the results are summarized according to outcome.

1. **Additional or different diagnosis identified that impacts decision for and choice of therapy:** Six studies directly or indirectly addressed this outcome. Studies identified additional pathologic diagnoses impacting therapy (TMA, arteriosclerosis, lupus podocytopathy, and vasculitis).
2. **Reduction of proteinuria:** There were four studies addressing this outcome, the majority of which had significant limitations. One study reported an unknown level of proteinuria in 1/3rd of subjects at follow-up (5/15). Another study only assessed proteinuria at the time of renal biopsy and noted that nephrotic range proteinuria was not present in any of the patients with class II or V LN but was present in 27% of those with class III or IV LN. A third study had a composite endpoint of modified primary efficacy renal response that only included patients achieving both proteinuria ≤0.7 g/day **and** estimated glomerular filtration rate ≥60 mL/min/1.73 m2 or ≤20% below the baseline value. The last study found that among 79 adult patients with membranous LN on renal biopsy, 34% had proteinuria >1 gram/24 hours.
3. **Preservation of kidney function:** 7 studies addressed this outcome. One study found that the risk of chronic renal insufficiency (serum Cr >5 mg/dl for at least 3 months) was lower in patients that received a renal biopsy within 2 years of LN symptom onset (8%(vs. >2 years after symptom onset (30%). Another study found that the risk of serum creatinine >110 micromol/liter was lower in patients that received a renal biopsy after 4 months (24%) vs. those that received a renal biopsy after 15 months (53%). In all studies, 6-54% of patients had abnormal renal function following renal biopsy.
4. **ESKD:** Thirteen studies addressed rates of ESKD in the population of interest. Rates of ESKD ranged from 0% to 40%. Renal biopsy within 4-6 months was associated with lower rates of ESKD (0-10%) vs. delayed renal biopsy (23-40%). In one study, patients with class IV LN comprised the majority that later developed ESKD (88%). In that study, one patient with class V LN developed ESKD but none of the patients with class I, II, III, or VI LN developed ESKD.

5. **Adverse effects of biopsy:** Two retrospective cohort studies addressed bleeding complications among adult SLE patients undergoing renal biopsy. These studies found a total bleeding rate of 16-20%, minor bleeding rate of 10-13% (hematoma or hematuria), and major bleeding rate of 7% (need for intervention or transfusion).

Non-Comparative Evidence Summary Table

Outcomes (Name + Summary)	Author, year, RefID	Study type	Duration of follow up	Population (number and description, age)	Intervention used in relevant population (Describe the intervention)	Results	Comments
ESKD	Faurschou 2006	Retrospective cohort study	Median (range): 6.1 (0.1–30.0 yrs)	91 SLE patients undergoing initial renal biopsy (within 6 months of symptom onset vs >6 months after symptom onset). Median age 30 (IQR 22-32)	Renal biopsy	Renal biopsy within 6 months of symptoms: 6/61 with ESKD Renal biopsy >6 months of symptoms: 7/30 with ESKD	In all cases, immunosuppressive treatment was initiated or intensified within one month following renal biopsy. No patient received intensive immunosuppressive treatment in the period between the onset of nephritis symptoms and renal biopsy.
	Fiehn 2003, 2840	Retrospective observational study	9-10 years	56 adult SLE patients aged 18-70 with >500 mg/day proteinuria. Compared renal biopsy before 1990 (mean time to biopsy was 15.4 months) vs renal biopsy after 1990 (mean time to biopsy was 3.9 months)	Renal biopsy	Renal biopsy after 15.4 months: 6/15 with ESKD Renal biopsy after 3.9 months: 0/41 with ESKD	comparing 2 eras with different time for renal biopsies
	Kim 2022, 4679	Retrospective cohort study	Median 33 months (IQR 22-49)	13 adult SLE patients who had a relapse of proteinuria after receiving corticosteroids alone for a median of 25 days Median age (IQR): 37 (27–51)	Renal biopsy	Before biopsy: 0/13 with ESKD After biopsy: 0/13 with ESKD	

	Stamenkovic 1986, 8568	Retrospective cohort study	Mean 8.2 years	Adult and pediatric patients with SLE Mean age 28.5 years (range 3-61)	Renal biopsy	ESKD: 3/57	
	Wang 2014, 9602	Retrospective cohort study	Median 42 months (range 1-360)	202 adult/pediatric patients with biopsy-proven LN Age Mean: 33.1, SD: 11.5, range: 14-90	Renal biopsy	ESKD: 0/202	
	McCurdy 1992, 5857	Retrospective cohort study	mean (range) 5.9 (1-14) years	90 Pediatric SLE patients w/ elevated Cr <12yr 58%; >=12 42%	Renal biopsy	ESKD: 16/90	
	Esdaile 1991, 2624	Retrospective cohort study	1 year	87 adult and pediatric patients with LN Mean age 27 (range 5-68)	Renal biopsy	ESKD: 1/87	
	Gan 2002, 3068	Retrospective cohort study	1-20 years (mean 4.5)	50 adult Singaporean patients with SLE Mean age 35.4 (range 18-79)	Renal biopsy	ESKD: 6/50	
	Grishman 1982, 3434	Retrospective cohort study	Mean 6.3 years (2-10)	Adult/pediatric patients with class III LN (mean age 28)	Renal biopsy	ESKD: 2/15	
	Schwartz 2008, 8079	Retrospective cohort study	113-126 months	Adult patients with LN class III or IV	Renal biopsy	ESKD: 22/83	ESKD= serum Cr>6 mg/dl or RRT
	Sloan 1996, 8437	Retrospective cohort study		Adult patients with membranous LN	Renal biopsy	ESKD: 19/79	

	Elmougy 2015, 2569	Retrospective cohort study	Mean 4.1 years (range 2 months-12 years)	Egyptian pediatric patients with LN	Renal biopsy	ESKD: 1/111	
	Derksen 1992, 2239	Retrospective cohort study	Median 53.5 months (range 2-192)	56 adults with biopsy-proven LN (median age 25)	Renal biopsy	Total ESKD: 8/56	Class 1 ESKD: 0/2 Class 2 ESKD: 0/10 Class 3 ESKD: 0/10 Class 4 ESKD: 7/28 Class 5 ESKD: 1/5 Class 6 ESKD: 0/1
Adverse effects of biopsy: bleeding	Kang 2023a, 4469	Retrospective cohort study	Not specified	277 adult patients with SLE undergoing renal biopsy (mean age 35)	Renal biopsy	Bleeding: 55/277 Major Bleeding: 19/277 Minor Bleeding: 36/277	Minor: hematoma or hematuria Major: need for transfusion or intervention
	Jordan 2014, 4337	Retrospective cohort study	Not specified	199 adult patients with SLE (mean age 35.18), 215 total renal biopsies	Renal biopsy	Bleeding: 32/199 Major Bleeding: 13/199 Minor Bleeding: 19/199	Minor: subcapsular hematoma, perinephric hematoma regardless of size, or hematuria requiring only close observation Major: need for transfusion, surgical revision of hematoma, embolization, sepsis, nephrectomy or death
Additional or different diagnosis identified	Tao 2008, 8898	Retrospective cohort study	Not specified	19 patients with LN complicated by malignant hypertension who underwent renal biopsy between Jan 2002 and Dec 2006 Median age (range): 24.4 (15-41)	Renal biopsy	Arteriosclerosis: 2/19 TMA 11/19	

	Hernandez-Molina 2015, 3753	Retrospective cohort study	Median follow-up 2.4 years	SLE with renal biopsy, ≥1 year of post-biopsy follow-up and at least two aCL (IgG-IgM), anti-β2GP-I (IgG-IgM) and/or lupus anticoagulant (LAC) determinations 12 weeks apart	Renal biopsy	Chronic TMA: 11/90 Acute TMA: 3/90	
	Shah 2018, 8182	Retrospective cohort study	Not specified	155 patients with SLE	Renal biopsy	Chronic TMA (zonal cortical scarring and tubular thyroidization): 29/155	
	Strufaldi 2021, 8665	Retrospective cohort study	Median 30.5 months in TMA group and 28 months in no TMA group	253 adult patients with LN	Renal biopsy	TMA: 43/253	
	Wang 2014, 9602	Retrospective cohort study	Median 42 months (range 1-360)	202 adult/pediatric patients with biopsy-proven LN Age Mean: 33.1, SD: 11.5, range: 14-90	Renal biopsy	Lupus podocytopathy: 13/202	Note that they found patients with more severe podocytopathy had better outcomes when treated with calcineurin inhibitors
	Mejia-Vilet 2017, 5931	Retrospective cohort study	N/A	Adult patients with biopsy-proven LN	Renal biopsy	TMA: 23/429 Arteriosclerosis: 189/429 Vasculitis: 11/429	Thrombotic microangiopathy (TMA) defined as "luminal narrowing of the vessel caused by eosinophilic and fucsinophilic deposits with staining for fibrin, associated with endothelial edema and luminal thrombi (acute) or mucoid edema of the intima and "onion skin" intimal fibrodysplasia (chronic)"

							Arteriosclerosis (AS) defined as "thickening of the medial layer of the interstitial arteries and/or arteriolar hyalinosis" True renal vasculitis (TRV) defined as "fibrinoid necrosis of the arterial wall associated with infiltration of the vessel wall by inflammatory cells"
Reduction of Proteinuria	Grishman 1982, 3434	Retrospective cohort study	Mean 6.3 years (2-10)	Adult/pediatric patients with class III LN (mean age 28)	Renal biopsy	4/15 no proteinuria 5/15 mild proteinuria 1/15 nephrotic range proteinuria 5/15 unknown proteinuria	
	Sloan 1996, 8437	Retrospective cohort study		Adult patients with membranous LN	Renal biopsy	Proteinuria >1 g/d: 27/79	
	Cooper Blenkinsopp 2022, 1894	Retrospective cohort study	2 years	Adult patients with class III, IV, V or mixed LN	Renal biopsy	modified primary efficacy renal response: 114/173	urine protein:creatinine ratio (≤0.7 g/day) and estimated glomerular filtration rate (≥60 mL/min/1.73 m2 or ≤20% below the baseline value)
	Das 2010, 2104	Prospective cohort study	At time of biopsy	30 adult SLE patients median age 25.1 years	Renal biopsy	Class III/IV nephrotic proteinuria: 6/22 Class III/IV non nephrotic proteinuria: 16/22 Class II/V nephrotic proteinuria: 0/5 Class II/V non nephrotic proteinuria: 4/5	nephrotic range (>3.5g/1.73m2 of body surface area/day)

Preservation of kidney function	Fiehn 2003, 2840	Retrospective observational study	9-10 years	56 adult SLE patients aged 18-70 with >500 mg/day proteinuria. Compared renal biopsy before 1990 (mean time to biopsy was 15.4 months) vs renal biopsy after 1990 (mean time to biopsy was 3.9 months)	Renal biopsy	Renal biopsy after 15.4 months: 8/15 with Cr >110 micmol/l Renal biopsy after 3.9 months: 10/41 with Cr >110 micmol/l	comparing 2 eras with different time for renal biopsies
	Esdaile 1994, 2626	Retrospective cohort study	Median follow-up 7.1 years	87 Adult/pediatric patients with LN	Renal biopsy	Short duration before biopsy (within 2 years of LN onset): 6/77 CRI Long duration before biopsy (≥2 years after LN onset): 3/10 CRI	Chronic renal insufficiency (CRI): serum Cr >5 mg/dl for at least 3 months
	Wang 2014, 9602	Retrospective cohort study	Median 42 months (range 1-360)	202 adult/pediatric patients with biopsy-proven LN Age Mean: 33.1, SD: 11.5, range: 14-90	Renal biopsy	Doubling of serum Cr: 13/202	
	Esdaile 1991, 2624	Retrospective cohort study	1 year	87 adult and pediatric patients with LN Mean age 27 (range 5-68)	Renal biopsy	Normal serum Cr: 75/87	
	Grishman 1982, 3434	Retrospective cohort study	Mean 6.3 years (2-10)	Adult/pediatric patients with class III LN (mean age 28)	Renal biopsy	Normal renal function: 9/15	
	Schwartz 1987, 8078	Retrospective cohort study	5 years	adult patients with SLE	Renal biopsy	Chronic renal failure (Cr >=4.0 mg/dl): 16/73	

	Elmougy 2015, 2569	Retrospective cohort study	Mean 4.1 years (range 2 months-12 years)	Egyptian pediatric patients with LN	Renal biopsy	Normal serum Cr: 62/136	

References:

- Randomized controlled trials:
  None

- Comparative observational studies: (indirect comparison)

Refid	Author	Year	Title
	Faurschou et al	2006	Prognostic Factors in Lupus Nephritis: Diagnostic and Therapeutic Delay Increases the Risk of Terminal Renal Failure
2840	Fiehn et al	2003	Improved clinical outcome of lupus nephritis during the past decade: importance of early diagnosis and treatment
4679	Kim et al	2022	Renal outcomes of transient proteinuria in patients with systemic lupus erythematosus treated with corticosteroid therapy alone
4337	Jordan et al	2014	Association of thrombotic microangiopathy and intimal hyperplasia with bleeding post-renal biopsy in antiphospholipid antibody-positive patients
2626	Esdaile et al	1994	The benefit of early treatment with immunosuppressive agents in lupus nephritis

- Single-arm studies:

Refid	Author	Year	Title
4469	Kang E et al	2023	Risk of bleeding-related complications after kidney biopsy in patients with systemic lupus erythematosus
8898	Tao et al	2008	Lupus nephritis complicated with malignant hypertension: from renal vascular pathology to clinical relevance
3753	Hernandez-Molina et al	2015	Thrombotic microangiopathy and poor renal outcome in lupus patients with or without antiphospholipid syndrome
8182	Shah et al	2018	Zonal cortical scarring and tubular thyroidization in kidney biopsies of patients with SLE—histologic indicator for antiphospholipid antibodies
8568	Stamenkovic et al	1986	Renal biopsy in SLE irrespective of clinical findings : long-term follow-up
8665	Strufaldi et al	2021	Renal thrombotic microangiopathy associated to worse renal prognosis in Lupus Nephritis
9602	Wang et al	2014	Podocyte involvement in lupus nephritis based on the 2003 ISN/RPS system: a large cohort study from a single centre
5857	McCurdy et al	1992	Lupus Nephritis: prognostic factors in children
2624	Esdaile et al	1991	Predictors of One Year Outcome in Lupus Nephritis: The improtance of Renal Biopsy

3434	Grishman et al	1982	Focal segmental lupus nephritis
5931	Mejia-Vilet et al	2017	Prognostic significance of renal vascular pathology in lupus nephritis
8078	Schwartz et al	1987	The prognosis of segmental glomerulonephritis in systemic lupus erythematosus
8079	Schwartz et al	2008	The prognosis and pathogenesis of severe lupus glomerulonephritis
8437	Sloan et al	1996	Long-term outcome in systemic lupus erythematosus membranous glomerulonephritis
1894	Cooper Blenkinsopp et al	2022	Renal response at 2 years post biopsy to predict long-term renal survival in lupus nephritis: a retrospective analysis of the Hopkins Lupus Cohort
2104	Das et al	2010	Clinicopathological profile of renal changes in systemic lupus erythematosus
2569	Elmougy et al	2015	Lupus Nephritis in Egyptian children: a 16 year experience
2239	Derksen et al	1992	The long-term clinical outcome of 56 patients with biopsy proven lupus nephritis followed at a single center

- Studies reviewed and excluded:

Refid	Author	Year	Title	Comments
7903	Salvatore et al	2012	Collapsing Glomerulopathy in 19 Patients with Systemic Lupus Erythematosus or Lupus-Like Disease	Excluded given irrelevant outcomes and lack of comparison group. All 19 patients in this study had collapsing glomerulopathy on biopsy.
7904	Sam et al	2013	Lupus-like membranous nephropathy: Is it lupus or not?	Excluded given irrelevant outcomes and lack of comparison group. All 36 patients had lupus membranous GN
9559	Wang et al	2008	Induction treatment of proliferative lupus nephritis with leflunomide combined with prednisone: a prospective multi-centre observational study	Irrelevant intervention (leflunomide)
8275	Shilov et al	1994	Prognostic factors in lupus nephritis treated with cyclophosphamide pulses	Irrelevant outcome: rate of renal deterioration (1/SCr0-1/SCr1)/T
1975	Cramer et al	2007	Clinical presentation and outcome in a cohort of paediatric patients with membranous lupus nephritis	Irrelevant outcome

P2. In SLE patients with LN who have achieved at least a partial renal response who develop recurrent /worsening proteinuria, hematuria, or impaired kidney function, is knowing the kidney histology by biopsy associated with better outcomes than not knowing the kidney histology?

Population: LN patients who flare after having achieved a complete or partial renal remission with

- Increased proteinuria alone
- Increased glomerular hematuria with or without proteinuria with stable kidney function
- Worsening kidney function

Intervention: Percutaneous kidney biopsy
Comparator: No percutaneous kidney biopsy
Outcomes:

- Additional or different diagnosis identified (e.g., TMA, ATN, class change, medication effect e.g., calcineurin inhibitor (CNI) nephrotoxicity, DM, or arteriosclerosis / arteriolosclerosis), that impacts decision for and choice of therapy
- Reduction of proteinuria
- Preservation of kidney function
- ESKD (dialysis or transplant)
- Adverse effects of biopsy

Summary: The literature search identified 12 studies, all observational and non-comparative, that addressed this PICO question. In many of these studies, the indication for repeat renal biopsy was not described in detail. Several studies included patients who underwent repeat renal biopsies for nephritis flare or progression of renal disease but also included patients who may have had per-protocol biopsies. The studies did not always differentiate the outcomes between these groups. This limitation, in addition to the observational and non-comparative nature of the data, diminish the strength and utility of the included evidence. Below the results are summarized according to outcome.

6. **Additional or different diagnosis identified (class change) that impacts decision for and choice of therapy:** Eleven studies directly or indirectly addressed this outcome. In seven of these studies, class change was identified in over 50% of patients, with improvement vs. worsening varying by study and indication for biopsy.
7. **Reduction of proteinuria:** One study addressed reduction in proteinuria in patients undergoing repeat renal biopsy. The study found that proteinuria was reduced on follow up in 65% (17/26) patients who had nephrotic range proteinuria at the time of their repeat renal biopsy.
8. **Preservation of kidney function:** Two studies addressed this outcome. One study found that in 25 patients who underwent repeat renal biopsy for nephritic flare, 16 (64%) had a GFR reduction of >30% at a median of 3 years of follow up. The other study, by the same authors 20 years earlier, found that 17/31 (55%) of patients who had a repeat renal biopsy for persistent disease activity or nephritis flare had doubling of their creatinine at a median follow up of 10.4 years.
9. **ESKD:** Five studies addressed rates of ESKD in the population of interest. However, only 3 of these studies specified rates of ESKD in those who had repeat biopsies (the remaining 2 described rates of ESKD in a larger lupus nephritis population in which a sub-group underwent repeat renal biopsies). In these 3 studies, rates of ESKD ranged from 8 to 26% depending on the indication for repeat renal biopsy (i.e. for flare & what type of flare, vs. per protocol).
10. **Adverse effects of biopsy:** One study addressed potential adverse effects associated with repeat renal biopsies, specifically bleeding complications. The study found a 28% bleeding rate in those who underwent repeat biopsy. The indication for repeat biopsy was not specified.

Non-Comparative Evidence Summary Table

Outcomes (Name + Summary)	Author, year, RefID	Study type	Duration of follow up	Population (number and description, age)	Intervention used in relevant population (Describe the intervention)	Results	Comments

Adverse effects of biopsy: Bleeding (major and minor)	Kang 2023, 4469	Retrospective observational study	2 days	25 patients with lupus nephritis who underwent repeat renal biopsy	Renal biopsy	7/25 patients with bleeding complications (2 major, 5 minor)	The population undergoing repeat biopsy is not specified (i.e. we do not know if the patients achieved at least partial remission nor do we know if they had recurrent proteinuria/hematuria or worsening kidney function)
Additional or different diagnosis identified: Class change	Lee 1984, 5053	Retrospective observational study	Range: 5-141 months (f/u varied by class)	50 patients with lupus nephritis who underwent repeat renal biopsy; Age: Mean ~23 years; Range (18-37)	Renal biopsy	28/50 patients had class change on repeat biopsy (8 became more severe class)	Indication for biopsy is not given (i.e. for cause vs. per protocol); biopsies improved from III/IV to II/V; among worsening 3 went from II to IV; 2 went from III to IV; 1 went from V to III and 2 went from V to IV
	Gan 2002, 3068	Retrospective observational study	Mean: 4.5 years, range 1-20 years	9 patients with lupus nephritis who underwent repeat renal biopsy from a larger cohort of 50 patients with lupus nephritis; Age: Mean 35.4 years; Range 18-79	Renal biopsy	5/9 patients had class change (3 became more severe class)	Indication for biopsy is not given (i.e. for cause vs. per protocol); 2 went from class IV to VI, 1 went from class V to IV
	Gao 2012, 3090	Retrospective observational study	Mean: 26.3 +/- 29.4 months after intial bx	47 patients with class IV lupus nephritis who underwent repeat renal biopsy because they did not achieve clinical remission after intial treatment; Age: Mean 29.3 years; Range 13 - 66	Renal biopsy	27/47 patients had class change (all became less severe)	Clinical remission defined as: 24 hour urine protein < 0.5 g/day; transformed from class IV to class II, III, or V
	Garin 1976, 3131	Retrospective observational study	Mean: 22 months; range 2 – 103 months	25 pediatric patients with lupus nephritis; Age: Median 12 years; Range 7-18	Renal biopsy	17/25 patients had class change (3 became more severe)	Indication for repeat biopsy unclear; 18 cases with class IV initially, 2 with class III, 5 with class V

	Grishman 1982, 3434	Case series	Minimum 2 years; average 6.3, range 2 to 20 years	15 patients with lupus nephritis class III, of which 5 underwent repeat renal biopsy; Age: mean 28, range 13 – 45 years	Renal biopsy	1/5 patients who underwent repeat renal biopsy had class change to more severe	Indication for repeat biopsy unclear; class change from III to IV in 1 patient
	Grishman 1982, 3435	Case series	Not stated	179 patients with lupus nephritis; 42 of whom had 2 or more biopsies or autopsy; Age not specified	Renal biopsy	13/42 patients showed class change (9 patient worsened class)	Age of population and indication for repeat biopsies was not specified; class change not specified
	Yang 1994, 9932	Retrospective cohort study	Mean: 59 months (Range 12 – 159 months)	167 children with lupus nephritis, of which 36 underwent repeat renal biopsy; Age: Mean 13.1, SD 2.3 years	Renal biopsy	7/36 patients showed class change (5 worsened, 2 improved)	Repeat biopsy done 6 months to 5 years after initial for therapeutic monitoring or progressive deterioration but indication not specified in each case; 2 cases went from III to IV; 3 cases went from class II to IV and, 2 cases went from class IV to II
	Moroni 1999, 6299	Retrsopective cohort study	Median 10.5 years (25, 75^{th} percentiles = 5.85 and 17.5 years)	31 patients with lupus nephritis who underwent repeat renal biopsy for persistent proteinuria or increasing creatinine; Age: Median 23, 25^{th} percentile = 18, 75^{th} percentile 31)	Renal biopsy	21/31 patients showed class change	In the 7 patients with non-nephrotic range proteinuria who had repeat bx, 6 improved classes (IV to II or III), 1 was unchanged. In the 12 patients with nephrotic range proteinuria who had repeat bx, 7 were unchanged (one changed from II to III, several from V to III). In the 19 patients with increased creatinine who had repeat bx, 9 worsened (III to IV) and 9 were unchanged.

	Moroni 2022, 6301	Retrospective cohort study	Median: 23 years (Range 17.5 – 32 years)	61 patients who underwent repeat renal biopsy for flare or per protocol from larger cohort of 203 patiens with lupus nephritis; Age: median 28, IQR 22 - 36	Renal biopsy	Class change in 29/61 patients (47%); worsened in 8 cases)	21 cases had bx for proteinuric flare; 25 cases had bx for nephritic flare, and 14 cases had per protocol bx; "class transformation occurred in 47% of patients, 71.5% of the patients in class V (3 patients switched to class III and two to class IV), 57% in class III (one patient changed to class II and three to class IV) and 34% in class IV"
	Wang 2008, 9559	Prospective cohort study	6 months	13 patients of a larger cohort of 70 patients treated with leflunomide for induction of proliferative lupus nephritis who underwent repeat renal bx; Age mean 31.3, SD 9.5 in larger cohort	Renal biopsy	Class change in 11/13 patients (all improved)	Indication for bx was not specified; class change from IV → III in 10, V/III → V in 1
	Stamenkovik 1986, 8568	Retrospective cohort study	Mean: 97.8 months (Range 24 – 180 months)	13 patients with lupus nephritis who underwent repeat renal biopsy from a larger cohort of 57 patients with lupus nephritis; Age: mean 28.5 years, Range 3 – 61 years	Renal biopsy	Class change in 8/13 patients (6 improved, 2 worsened)	Indication for renal biopsy not specified for each case; 2 improved from class IV to class II, 3 improved from class IV to class I; 1 improved from II to I; 1 went from I to IV, and 1 from II to III
ESKD	Yang 1994, 9932	Retrospective cohort study	Mean: 59 months (Range 12 – 159 months)	167 children with lupus nephritis, of which 36 underwent repeat renal biopsy; Age: Mean 13.1, SD 2.3 years	Renal biopsy	10/167 with ESKD	ESKD reported for whole cohort, rate not specified in those who had repeat bx; Repeat bx was done for progression or monitoring but outcomes not specified by group

	Gan 2002, 3068	Retrospective observational study	Mean: 4.5 years, range 1-20 years	9 patients with lupus nephritis who underwent repeat renal biopsy from a larger cohort of 50 patients with lupus nephritis; Age: Mean 35.4 years; Range 18-79	Renal biopsy	6/50 with ESKD	Number of those undergoing repeat bx with ESKD not reported
	Moroni 1999, 6299	Retrsopective cohort study	Median 10.5 years (25, 75th percentiles = 5.85 and 17.5 years)	31 patients with lupus nephritis who underwent repeat renal biopsy for persistent proteinuria or increasing creatinine; Age: Median 23, 25th percentile = 18, 75th percentile 31)	Renal biopsy	8/31 patients with ESKD	
	Moroni 2022, 6301	Retrospective cohort study	Median: 23 years (Range 17.5 – 32 years)	61 patients who underwent repeat renal biopsy for flare or per protocol from larger cohort of 203 patiens with lupus nephritis; Age: median 28, IQR 22 - 36	Renal biopsy	12/61 w/ ESKD (4/22 w/ bx for proteinuric flare, 7/25 w/ bx for nephritic flare, 1/14 w/ bx per protocol)	22 cases had bx for proteinuric flare; 25 cases had bx for nephritic flare, and 14 cases had per protocol bx
	Stamenkovik 1986, 8568	Retrospective cohort study	Mean: 97.8 months (Range 24 – 180 months)	13 patients with lupus nephritis who underwent repeat renal biopsy from a larger cohort of 57 patients with lupus nephritis; Age: mean 28.5 years, Range 3 – 61 years	Renal biopsy	1/13 with ESKD at time of study	Indication for renal biopsy not specified for each case
Reduction of Proteinuria	Moroni 1999, 6299	Retrsopective cohort study	Median 10.5 years (25, 75th percentiles = 5.85	31 patients with lupus nephritis who underwent repeat renal biopsy for persistent proteinuria or increasing creatinine; Age:	Renal biopsy	6/31 patients in remission with <0.2 g/day proteinuria; 8/31 with non-nephrotic proteinuria (median 1.8 g/d; 25th/75th and and 2 g/d)	17 patients had nephrotic syndrome at study admission, median proteinuria value for all 31 patients was 4.6 g/day (25th/75th percentile 1.75/6.65 g/day); at time

			and 17.5 years)	Median 23, 25th percentile = 18, 75th percentile 31)			of repeat bx, 26 patients with nephrotic syndrome and median proteinuria 5.0 g/day (25th/75th percentile 2.2/6.9 g/day)
Preservation of kidney function	Moroni 1999, 6299	Retrsopective cohort study	Median 10.5 years (25, 75th percentiles = 5.85 and 17.5 years)	31 patients with lupus nephritis who underwent repeat renal biopsy for persistent proteinuria, nephrotic flare, or increasing creatinine; Age: Median 23, 25th percentile = 18, 75th percentile 31)	Renal biopsy	14/31 patients with normal renal function (median Cr 0.85 mg/dL, 25th/75th percentile, 0.8/1), while 17/31 with doubling of plasma creatinine	
	Moroni 2022, 6301	Retrospective cohort study	Median: 3 years (Range 2 - 13.3 years)	61 patients who underwent repeat renal biopsy for flare or per protocol from larger cohort of 203 patiens with lupus nephritis; Age: median 28, IQR 22 - 36	Renal biopsy	25/61 w/ Kidney function impairment (KFI) (6/22 w/ bx for proteinuric flare, 16/25 w/ bx for nephritic flare, 3/14 w/ bx per protocol)	KFI = decrease in eGFR >30% confirmed by at least 3 determinations for at least 3 months; 22 cases had bx for proteinuric flare; 25 cases had bx for nephritic flare, and 14 cases had per protocol bx

Table 1.

Author, Year	Population	Intervention	Comparator	Outcomes
Kang 2023	Patients with lupus nephritis	Renal biopsy	None	Adverse effects of biopsy: Bleeding (major and minor)
Lee 1984	Patients with lupus nephritis	Renal biopsy	None	Additional or different diagnosis identified: Class change
Stamenkovic 1986	Patients with lupus nephritis	Renal biopsy	None	Additional or different diagnosis identified: Class change; ESKD
Wang 2008	Patients with lupus nephritis	Renal biopsy	None	Additional or different diagnosis identified: Class change
Yang 1994	Patients with lupus nephritis	Renal biopsy	None	Additional or different diagnosis identified: Class change; ESKD
Moroni 1999	Patients with lupus nephritis	Renal biopsy	None	Additional or different diagnosis identified: Class change; ESKD; Reduction of proteinuria; preservation of kidney function
Gan 2002	Patients with lupus nephritis	Renal biopsy	None	Additional or different diagnosis identified: Class change; ESKD
Gao 2012	Patients with lupus nephritis	Renal biopsy	None	Additional or different diagnosis identified: Class change
Garin 1976	Patients with lupus nephritis	Renal biopsy	None	Additional or different diagnosis identified: Class change
Grishman 1982	Patients with lupus nephritis	Renal biopsy	None	Additional or different diagnosis identified: Class change
Grishman 1982	Patients with lupus nephritis	Renal biopsy	None	Additional or different diagnosis identified: Class change
Moroni 2022	Patients with lupus nephritis	Renal biopsy	None	Additional or different diagnosis identified: Class change; ESKD; preservation of kidney function

References:

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single-arm studies:

Refid	Author	Year	Title
4469	Kang E et al	2023	Risk of bleeding-related complications after kidney biopsy in patients with systemic lupus erythematosus
5053	Lee H et al	1984	Course of renal pathology in patients with systemic lupus erythematosus
8568	Stamenkovic I et al	1986	Renal biopsy in SLE irrespective of clinical findings: long-term follow-up

9559	Wang H et al	2008	Induction treatment of proliferative lupus nephritis with leflunomide combined with prednisone: a prospective multi-centre observational study
9932	Yang L et al	1994	Lupus Nephritis in Children- A Review of 167 Patients
6299	Moroni G et al	1999	Clinical and Prognostic Value of Serial Renal Biopsies in Lupus Nephritis
3068	Gan H et al	2002	Clinical Outcomes of Patinets with Biopsy proven lupus Nephritis in NUH (National University Hospital)
3090	Gao J et al	2012	Characteristics and influence factors of pathologic transformation in the subclasses of class IV lupus nephritis
3131	Garin E et al	1976	Nephritis in SLE in children
3434	Grishman E et al	1982	Focal segmental lupus nephritis
3435	Grishman E et al	1982	Patterns of Renal Injury in SLE: Light and Immunofluorescence Microscoic Observation
6301	Moroni G et al	2022	Predictors of increase in chroncity index and of kidney function impairment at repeat biopsy in lupus nephritis

- Studies reviewed and excluded:

Refid	Author	Year	Title	Comments
8365	Singh A et al	2014	Protocol Renal Biopsy in Patients with Lupus Nephritis: A Single Center Experience	Excluded because population is not relevant to PICO question. Study describes repeat biopsies (per protocol) in patients treated for initial episode of lupus nephritis. Repeat bx are done within 6 months of initial biopsy and treatment. No follow up data after per protocol biopsy was collected.

P3. In SLE patients with fixed (persistent) unexplained proteinuria with or without glomerular hematuria or impaired kidney function, is performing a kidney biopsy based on the level of proteinuria associated with better outcomes than not basing biopsy on level of proteinuria?

Population: Patients with SLE who have **fixed or persistent proteinuria** with or without impaired kidney function and with or without glomerular hematuria.

- 200 – 500 mg/day proteinuria with or without impaired kidney function and with or without glomerular hematuria
- >500 mg/d proteinuria with or without impaired kidney function and with or without glomerular hematuria

Intervention: Percutaneous kidney biopsy

Comparator: No percutaneous kidney biopsy

Outcomes:

- Kidney diagnosis identified (e.g., LN vs TMA, ATN, CNI nephrotoxicity, DM, arteriosclerosis / arteriolosclerosis) that impacts decision for and choice of therapy
- Reduction of proteinuria
- Preservation of kidney function
- ESKD (dialysis or transplant)
- Adverse effects of biopsy

TABLE 1. included studies

Author, Year	Population (number and description, age)	Intervention	Outcomes	Notes

Carlucci 2022	275/317 SLE patients (ACR or SLICC criteria) with LN that had either 1st (n=113) or 2nd kidney Bx (n=162) for UPCR>0.5.	Renal Bx	Preservation of kidney function: CKD5; Doubling of SCr. Reduction of proteinuria. Kidney diagnosis: "actionable" Class of LN vs not.	UPCR was 0.5-1 in 54 cases (20%) and ≥1 in 221 (80%) cases. (42 cases were excluded because they did not have LN, had advanced sclerosing pathology or no UPCR data were available). (mutlicenter multi-race AMP study). Patients followed for 1 year. Different patients with 1st and 2nd Bx. (PICO1,3, 4)
Faurschou2006	91 SLE patients with LN on Renal bx.	Renal Bx	ESKD.	Median (IQR) level of proteinuria at time of Bx: 4.8 (1.7-12.5) g/day. (PICO 1,3)
Fiehn 2003	56 SLE patients with LN on Renal bx either in earlier or later decade.	Renal Bx	ESKD. Preservation of kidney function: Scr>1.24mg/dl.	Median proteinuria levels were 46 (24-212) vs 17 (2-90) g/L respectively for Bx in earlier or later decade. (PICO1,3)
Kang 2023	SLE patients that underwent 1st renal biospy (n=277) and 2nd renal Bx (n=25).	Renal Bx	AE: Bleeding minor and major.	No information on theshold level of proteinuria for Bx. Mean (SD) proteinuria 2.3 (1.8)g/d vs 3.1 (2.3)g/d for patients without vs with bleeding. (PICO1-5)
Jordan 2014	SLE patients (n=199) with 215 renal biopsies perfomed for Proteinuria≥500mg/dl, abnormal urin sediment, or elevated SCr, or those with high probability of TMA.	Renal Bx	AE: bleeding minor and major. Kidney diagnosis (TMA)	Three goups of patients: SLE=80; SLE/APS=48; SLE/aPL=87. (PICO1-4)
Wallace 1988	27 SLE (ACR criteria) patients with refractory LN-nephrotic syndrome (class III=5, IV=17, V=5), despite ≥ 3month initial induction therapeutic trial of steroids and immunosuppressives.	Renal Bx	ESKD. Prervation of kidney function: Good response (Normalization SCr and resolution of nephrotic proteinuria) or poor response	
Fava 2022	SLE patients (ACR or SLICC criteria) with at least 2 kidney biopsies. Biopsies were performed for proteinuria (UPCR>0.5) or unexplained worsening renal function. N=220 pts and N=542 biopsies	Renal Bx	ESKD.	
Stamenkovic 1986	57 Pediatric and adult SLE patients who underwent their 1st kidney biopsy systematically (whether there were clinical signs of renal involvement or not). Then 13 patients had a 2nd Bx and 4 had a 3rd biopsy for cause.	Renal Bx	ESKD. Preservation of kidney function: no worsening kidney disease. Kidney diagnosis: silent lupus nephritis.	
Yang 1994	167 pediatric SLE (ACR criteria) patients (<18 yo) who had a renal Bx within 1 year of disease onset. Biopsy triggers: Hematuria (>10 rbc/hpf); pyuria (>10 wbc/hpf); proteinuria (>100mg/dl or >1g/L); deteriorating kidney function. Class II=55; Class III=30; Class IV=69; Class V=13.	Renal Bx	ESKD. Preservation of kidney function: Improved kidney function; worse kidney function.	

	Repeat Biopsy in n=36 patients, 6 months-5 years later, for therapeutic monitoring or for progreasive renal deterioration			
Garin 1976	25 pediatric SLE patients (ACR criteria) with LN on kidney biopsy. N=19 patients also had a repeat biopsy. Renal disease suggested by one of the following; a.proteinuria> 200 mg/d. b.hematuria (>2rbc/hpf) c. eGFR< 80 ml/min/1.73m2. d.concentrating ability<800mOsm/Kg of water following 12 h fast	Renal Bx	ESKD	Class IV (DPGN): 18/25. Class III (FGN)=2/25. Class V (MGN): 5/25. No detailed data on proteinuria, EGFR (PICO 1,3,4)
Grishman and Churg 1982	15 pediatric and adult SLE patients had 19 renal biopsies and 1 autopsy demonstrating pure focal segmental LN. At baseline, only 2 patients had proteinuria in the nephrotic range. One patient had normal UA and the others had mild to moderate proteinuria (0.2g/d-3.1g/d).	Renal Bx	ESKD. Preservation of kidney function: SCr increase. Proteinuria decrease.	(PICO1,3,4)

Summary of the Evidence

12 single-arm studies were reviewed with regard to the PICO3 question. Four studies included pediatric patients: Garin 1976, Ghrishman and Curg 1982, Grishman 1982, Stamenkovich 1986, Yang 1994.

Two studies looked at renal biopsies performed for low threshold levels of proteinuria:

1-Carlucci 2022 studied 275/310 SLE patients (ACR or SLICC criteria) with LN that had either 1st (n=113) or 2nd kidney Bx (n=162) for UPCR>0.5 (for suspected de novo, ongoing activity, or new relapse). All patients were managed with SOC based on the clinical judgment of treating physicians. UPCR was 0.5-1 in 54 cases (20%) and ≥1 in 221 (80%) cases. The excluded 42 cases were excluded because they did not have LN (n=22; 7%), had advanced sclerosing pathology (n=13; 4%) or no UPCR data were available. Patients that had renal biopsy for spot UPCR 0.5-1 (UPCR<1) had Class I+II LN in 12/54 (22%) of cases compared to those with UPCR≥1: 11/221 (5%) of cases. The latter had higher rates of proliferative LN (PLN) or class V disease. Therefore, "actionable" LN classes were found in the majority of biopsies even in cases with UPCR<1 (78%). Furthermore, activity indices (AI) and chronicity indices (CI) were not different in the 2 groups, supporting kidney biopsies with UPCR 0.5-1. UPCR<1 patients developed a doubling of SCr at 0% rate in 12 months compared to 5% for those with UPCR≥1. These data were mostly driven by 2nd Bx: 7/134 (5%), rather than 1st Bx data: 1/70 (1.4%). In patients with UPCR<1 and LN Class III, IV, V, or Mixed (42/54), 39% of them had neither pyuria or hematuria, despite having a median AI 4.5 and CI 3. In patients with biopsies for UPCR 0.5-1 (UPCR<1) and "actionable" LN classes (III, IV, V, mixed), reduction of proteinuria to <0.5 in 12 months occurred in 23/29 of them (79%) and only 4/29 (14%) increased UPCR to >1. **All of the above** support the value of performing a biopsy for UPCR 0.5-1, even in those SLE patients without an active sediment.

2-Stamenkovic 1986 studied 57 **pediatric** and adult SLE patients who underwent their 1st kidney biopsy systematically (whether there were clinical signs of renal involvement or not). Then 13 patients had a 2nd Bx and 4 had a 3rd biopsy for cause. Of those, 29/57 (51%) had proteinuria>250 mg/L, 15/57 (26.3%) had active urinary sediment, and 23/57 (40.4%) had an SCr>90umol/L (1.02 mg/dl). Of 24/57 (42%) SLE patients with no clinical renal disease, 6/24 (25%) had silent LN on biopsy: 5 had class IV and 1 class V (despite no clinical renal disease). They were treated aggressively according to their histology and all did very well (High dose prednisone and AZA 2mg/kg). Class I/II patients were treated only with low-dose steroids for extrarenal manifestations. Three patients had class VI at their 1st Bx and progressed to ESKD rapidly after Bx. 51/54 remaining patients (94.4%) had no worsening of their kidney disease. One had ESKD after 28 months, one worse SCr (1.28mg/dl), and one with proteinuria at 3.2 g/d. There were 7/13 class conversions at the 2nd Bx, with most proliferative cases converting to class I/II LN 5/7 (71.4%). **In summary**, 25% of SLE patients without clinical signs of LN had silent "actionable" LN that was treated accordingly and successfully. Overall biopsy seemed beneficial in dictating treatment and prognosis.

There were 2 studies evaluating risk of ESKD based on timing of renal biopsy from onset of LN.
Faurschou 2006 compared LN patients with renal biopsy performed within 6 months of symptoms (early) versus after 6 months of symptoms (Late). Early biopsy patients developed ESKD less often (10%) than late biopsy patient (23%), most likely because they received treatment earlier (right after biopsy). **Fiehn 2003** compared LN patients with renal biopsy performed before 1990 (Earlier decade) versus after 1990 (Later decade). Later decade biopsy patients had their biopsy much earlier since the onset of proteinuria and had no ESKD compared to earlier decade patients (40% ESKD). Serum creatinine (SCr) at the end of followup was >1.24 mg/dl in less patients (24%) from the Later decade biopsy group compared to the Earlier decade biopsy group (53%). Levels of proteinuria (median (IQR)) wererelatively high in both studies: Faurschou: 4.8 (1.7-12.5) g/d and Fiehn 4.6 (2.4-21.2) and 1.7 (0.2-9) g/d for earlier and later decades. **Both of these studies** support a kidney biopsy as early as possible in order to treat based on histology characteristics as early as possible.

Yang 1994 studied 167 **pediatric** (<18 yo) SLE (ACR criteria) patients who had a renal Bx within 1 year of disease onset. Biopsy triggers included Hematuria (>10 rbc/hpf), pyuria (>10 wbc/hpf), proteinuria (>100mg/dl or >1g/L), and deteriorating kidney function. LN class breakdown: Class II=55; Class III=30; Class IV=69; Class V=13. Repeat Biopsy was performed in 36 patients, 6 months-5 years later, for therapeutic monitoring or for progressive renal deterioration. Class IV, V and (less so) class III patients were treated more aggressively than class II patients. Overall improved/controlled renal function was achieved in 118/167 (70.6%). This was less evident in Class IV patients: 38/69 (55%) and class V pts (62%), compared to classes III (86%) and II (84%). ESKD developed in 10/167 (6%) of patients after a mean follow up of 59 months. This was more evident in class IV LN, as 7/69 (10%) of such patients developed ESKD. Regarding repeat biopsies, **overall class conversion occurred in 7/36 (19.4**%). Conversion of class II to class IV occurred in 3/13 (23%) patients and class IV to class II in 2/14 (14%). **In summary,** kidney Bx helped predict poorer outcomes in those with class IV disease and better outcomes in those with class II, III, and V diseases.
Wallace 1988 studied 27 patients with refractory LN- nephrotic syndrome (class III=5, IV=17, V=5) despite a therapeutic trial of steroids and immunosuppressives (≥ 3 months). Four patients (15%) developed ESKD 2 years later. Only 7/27 (26%) patients were good responders (Normalization SCr and resolution of nephrotic proteinuria). Good responders were more likely to have received pulse steroids (p=0.069) and chronicity index <4 (p=0.048). **In summary chronicity** (CI<4) was useful in predicting better outcomes

Two studies assessed bleeding risk after kidney biopsies.
Kang 2023, retrospectively evaluated 277 patients with lupus nephritis who underwent kidney biopsy. Bleeding occurred in 55/277 (20%). Major bleeding occurred in 7% and minor bleeding in 13%.
Jordan 2014 compared biopsy outcomes in patients with SLE and evidence of kidney disease (with Proteinuria ≥500mg/dl, abnormal urine sediment, or elevated SCr, or in those with high probability of TMA) without (n=80) or with APS (n=48) or APL antibodies (LAC or anticardiolipin mod/high titers; n=87). Those with APS/APL had higher incidence of bleeding and major bleeding (19% and 9%) vs those with only SLE (7.5% and 1%). Independent predictors of bleeding included LAC+, age>40 and Scr>4.5 mg/dl. HTN was not a factor (BP was controlled before Bx). Major bleed patients had high prevalence of TMA (67%) and severe FIH (33%) in biopsies. Two of 13 major bleed cases had PLT<100,000/ul (but >50,000/ul). Bleeds occurred ≤3days after Bx procedure, but in 1 case after 14 days. Of note, those patients with APS/APL had higher incidence of TMA (25% and 23%) vs those with only SLE (7%). **C**onsidering both studies, post renal Bx bleeding occured in 7.5-20% of patients and major bleeding in 1-7% of patients. Risk factors included CKD, PLT<100,000/ul and perhaps aPL antibodies. APL in LN patients is associated with higher incidence of TMA on biopsy.

Table of outcomes

Outcomes (Name + Summary)	Author, year	Study design	Duration of follow up	Population (number and description, age)	Intervention	Results	Comments

ESKD	**Faurschou 2006**	Retrospective analysis of cohort data. Multicenter Danish study	Median (IQR)=6.1 (1.8-9.5) years (from 1st renal biopsy to ESRD or end of study period)	91 SLE patients (ACR criteria) with LN on Renal bx. Median (IQR) level of proteinuria at time of Bx: 4.8 (1.7-12.5) g/day Age: Median (IQR): 30 (22-42)	Renal Biopsy	ESKD: 13/91 (14%) ESRD rate: 21/1000 pt-yrs, or 17% in 10 years	Immunosuppressive treatment initiated/intensified within 1 month after 1st renal biopsy **Duration of LN prior to 1st biopsy**: median (IQR): 0.12 (0.02-0.86) years **Median (IQR) proteinuria at time of Bx**: 4.8 (1.7-12.5) g/day
				Subset of patients with renal biopsy within 6 month of symptoms **(early**). N=61	Renal Biopsy (early)	ESKD 6/61 (10%) ESRD rate: 13.8/1000 pt-yrs.	Class IV LN , Scr>140umol/l, and tubular atrophy were additional independent RF for ESRD
				Subset of patients with renal biopsy after 6 month of symptoms **(Late**). N=30	Renal Biopsy (late)	ESKD 7/30 (23%). ESRD rate: 47.1/1000 pt-yrs.	**Late vs Early Bx HR** (CI)=9.3 (1.8-47); p=0.006
	Fiehn 2003	Retrospective cohort. Single center German study.	1-225 months	56 SLE patients (ACR criteria) with LN on renal Bx. Ages: 18–70.	Renal Biopsy	ESKD 6/56 (11%)	Treatment was similar in both decades Lost to Fup 6/56
			Median (IQR)=95 (9-225) months	Subset of LN pts (n=15) seen between 1980-1989 (**Earlier decade**). Median proteinuria 4.6 (2.4-21.2) g/dl SCr>110 umol/L: N=6 (40%) Ages: median (range): 29 (19–67)	Renal Biopsy (late)	ESKD 6/15 (40%)	**Time from 1st detection of proteinuria until Kidney Bx (Mean(SD)range): 15.4 (15.6); range 5-60 months** Median SCr at Bx: 110 (50-430) umol/L Proteinuria>3g/d: n=9/15 (60%)
			Median (IQR)=24 (1-120) months	Subset of LN pts (n=41) seen between 1990-2000 (**Later decade**). Median proteinuria 1.7 (0.2-9) g/dl (p=0.008) SCr>110 umol/L: N=7 (17%). P=0.02	Renal Biopsy (early)	ESKD 0/41 (0%)	**Time from 1st detection of proteinuria until Kidney Bx (Mean(SD)range): 3.9 (4.7); range 1-24months** Median SCr at Bx: 70 (30-250) umol/L Proteinuria>3g/d: n=14/41 (34%)

				Ages: median (range): 35 (18–70)			
	Fava 2022	Retrospective cohort. Single center (Hopkins)	NA	220 LN patients with at least 2 kidney biopsies. N=542 biopsies Age: Median (range): 28 (9-60) at 1st biopsy 54% African Americans, 27% Caucasians	Renal Biopsy	ESKD 5/220 (2.3%)	Pure Class V LN at 2nd biopsy (after previous proliferative LN at 1st biopsy) predicts ESRD.
	Stamenkovic 1986	Retrospective cohort. Single center (Switzerland)	Mean folowup from 1st biopsy was 8.2 years	54 SLE patients with 1st Bx showing no evidence of class VI Pediatric and adult Ages: mean (range): 28.5 (3-61) years	Renal Biopsy	ESRD: 1/54	Treatment according to Class of LN.
	Wallace 1988	Retrospective cohort. Single center (Cedar Sinai)	2 years	27 SLE (ACR criteria) patients with refractory LN-nephrotic syndrome (class III, IV, V) despite ≥ 3month initial induction therapeutic trial of steroids and immunosuppressives. Mean (SD) age: 33.66 (16.14) years	Renal Biopsy	ESKD: 4/27 (15%)	Therapeutic trial: a. Prednisone 1mg/kg for >=3 months. B. AZA >=2mg/kgX 90d; c. CYC >=2mg/kg orallyX 90 days, or at least 3 IV CYC of at least 600 mg each. D. nitrogen mustard, and E. chlorambucil.
	Yang 1994	Retrospective cohort. Single center (Taiwan)	Mean (range): 59 (12-159) months.	167 **pediatric** SLE (ACR criteria) patients (<18 yo) who had a renal Bx within 1 year of disease onset. Ages mean (range); 13.1 (6-17) years.	Renal Biopsy	Overall: ESKD: 10/167 (6%) Class IV ESKD 7/69 (10%)	Biopsy triggers: Hematuria (>10 rbc/hpf); pyuria (>10 wbc/hpf); proteinuria (>100mg/dl); deteriorating kidney function. Class II=55; Class III=30; Class IV=69; Class V=13.
	Moroni 1999	Retrospective cohort. Two Italian centers	Median (IQR): 10.5 (IQR 5.85, 17.5) years after the initial renal biopsy	31 SLE (ACR) patients with bx-proven LN. Urine protein>1g/day (median (IQR) = 4.6 (1.75-6/6.5 g/d)), and/or elevated SCr level at presentation (n=15) After 1st (basal) Bx, all had a 2nd kidney Bx. N=7 had a 3rd Biopsy.	Renal Biopsy	ESKD: 8/31 (26%)	Repeat renal biopsies were performed for: A. persistent non-nephrotic proteinuria (n=7), B. persistent (n=6)/relapsing nephrotic proteinuria (n=6 for a total of 12), or C. worsening kidney function by either slow or fast increase in SCr of ≥50% than basal value (n=19).

				Median age 23 years (IQR 18,31)			
	Garin 1976	Retrospective cohort. (Single center;FL)	Median (range): 22 (2-103) months	25 **pediatric** SLE patients (ACR criteria) with LN on kidney biopsy. 19 also had a repeat biopsy. Class IV (DPGN): 18/25 Class III (FGN)=2/25 Class V (MGN): 5/25 Ages medium (Range) = 12 (7- 18) years	Renal Biopsy	ESKD: 3/25 (12%) ESKD in class IV: 3/18 (16.7%)	Renal disease suggested by one of the following; a.proteinuria> 200 mg/d. (Nephrotic syndrome with proteinuria >50 mg/kg/d and serum albumin< 3 g/dl) b.hematuria (>2rbc/hpf) c. eGFR< 80 ml/min/1.73m2 d.concentrating ability<800mOsm/Kg of water following 12 h fast
	Grishman and Churg 1982a	Retrospective cohort. (Single center;NY)	Fup: 6.3 (2-20) years	15 pediatric and adult SLE patients had 19 renal biopsies and 1 autopsy demonstrating **pure focal segmental LN** **Percentage of glomeruli involved** by segmental lesions: 29% (6%- 80%). Ages 28 (13-45)	Renal Bx	ESKD: 2/15	At baseline, 2 patients had nephrotic proteinuria;1 patient had none and the rest had mild to moderate proteinuria (0.2g/d-3.1g/d). Only one patient had elevated SCr of 2.4MG/DL.
	Carlucci 2022	Restrospective cohort Multicenter, multi-ethnic (AMP study)	12 months	275 SLE patients (ACR or SLICC criteria) with LN that had either 1st or 2nd kidney Bx for **UPCR>0.5.**	Renal Biopsy	ESRD=7/193 (4%)	Biopsy as "clinically indicated". UPCR spot (good correlation with 24h UPCR) in all patients Treatment similar in both groups (per treating physician)
Preservation of kidney function	**Fiehn 2003**	Retrospective cohort. Single center German study.	1-225 months	56 LN patients with complete clinical, laboratory and renal Bx data. Ages: 18–70.	Renal Biopsy	SCR>1.24 mg/dl: 18/56 (32%)	Treatment similar in both decades
			Median (IQR)=95 (9-225) months	LN pts seen between 1980-1989 (**Earlier decade**). N=15 Ages: median (range): 29 (19–67)	Renal Biopsy	SCr>1.24mg/dl: 8/15 (53%)	

			Median (IQR)=24 (1-120) months	LN pts seen between 1990-2000 (**Recent decade**). N=41 Ages: median (range): 35 (18–70)	Renal Biopsy	SCr>1.24 mg/dl: 10/41 (24%)	
	Carlucci 2022 Carlucci 2022	Restrospective cohort Multicenter, multi-ethnic (AMP study)	12 months	LN patients with either 1st or 2nd kidney Bx and **UPCR 0.5-1 (UPCR<1).** N=54 Ages (mean (SD): 38.5 (13.1)	Renal Biopsy	Doubling SCr=0/38.	
				LN patients with either 1st or 2nd kidney Bx and **UPCR≥1.** N=221 Ages (mean (SD): 34.6 (11.2)	Renal Biopsy	Doubling SCr =8/168(5%); p=NS	Mostly **driven by 2nd Bx data: 7/134** (5%), rather than 1st Bx data: 1/70 (1.4%). Implication for smoldering or relapsing LN
	Stamenkovic 1986	Retrospective cohort. Single center (Switzerland)	Mean folowup from 1st biopsy: 8.2 years	54 SLE patients with 1st Bx showing no evidence of class VI **Pediatric** and adult Ages: mean (range): 28.5 (3-61) years	1st Renal Biopsy	Preservation of Kidney Function 51/54 (94.4%)	1 pt with ESKD, 1 pt with Incr in SCr (113 umol/l), and 1 pt with signif proteinuria (3.2g/d)
				SLE patients (N=54) with 1st Bx showing no evidence of class VI. **Patients with PLN on 1st Bx=35 or progression to PLN on 2nd Bx=2**	1st Renal Biopsy	Preservation of Kidney Function 34/37(92%)	1 pt with ESKD, 1 pt with Incr in SCr (113 umol/l or 1.28mg/dl), and 1 pt with signif proteinuria (3.2g/d)
	Wallace 1988	Retrospective cohort. Single center (Cedar Sinai)	2 years	27 Patients with **refractory LN- nephrotic syndrome** (class III, IV, V) despite therapeutic trial of steroids and immunosuppressive (>= 3months) Class III= 5/27 (18.5%); Class IV=17/27 (63%); Class V=5/27 (18.5%) Mean (SD) age: 33.66 (16.14) years	Renal Biopsy	Good response: 7/27 (26%)	Good response: SCr normalized and no longer nephrotic syndrome (n=7). Good responders were more likely to have received pulse steroids (p=0.069) and chronicity index <4 (p=0.048)
	Grishman and Churg 1982a	Retrospective cohort.	Fup: 6.3 years (2-20 years)	15 pediatric and adult SLE patients had 19 renal biopsies and 1 autopsy demonstrating pure focal segmental LN.	Renal Bx	SCr increase: 6/15 (40%) ESKD 2/15 Scr (1.4-2.5mg/d): 4/15	Only one patient had elevated SCr: 2.4mg/dl at baseline

		(Single center;NY)		At baseline, only 2 patients had proteinuria in the nephrotic range. One patient had normal UA and the others had mild to moderate proteinuria (0.2g/d-3.1g/d). Age 28 (13-45)			
Kdney diagnosis identified	**Carlucci 2022**	Restrospective cohort Multicenter, multi-ethnic (AMP study)	NA	310 LN patients with either 1st or 2nd kidney Bx for UPCR>0.5.	Renal Biopsy	**Non Sclerosing LN** 275/310 (89%) Sclerosing LN 13/310 (4%) **Other** 22/310 (7%)	LN vs other kidney disease Non-sclerosisng vs sclerosing LN
				54 LN patients with either 1st or 2nd kidney Bx and **UPCR 0.5-1 (UPCR<1).** Ages (mean (SD): 38.5 (13.1)		PLN 31/54 (57.4%) Class V: 11/54 (20.4%) **Class I+II; 12/54 (22%)**	Proliferative LN (PLN) includes classes, III, IV and mixed. **Implication: 78% of pts with UPCR<1 had PLN or class V LN** requiring immunosuppression
				221 LN patients with either 1st or 2nd kidney Bx and **UPCR≥1.** Ages (mean (SD): 34.6 (11.2)		PLN 149/221 (67.4%) Class V: 61/221 (27.6%) **Class I+II; 11/221 (5%)**	**P=0.0001** for Class I/II in the 2 groups (UPCR<1 and ≥1) P=0.0496 and 0.0424 for class III and IV respectively P=NS for class V
Kdney diagnosis identified	**Jordan 2014**	Single tertiary center retrospective study from London, England	NA	215 biopsies in 199 SLE patients with Proteinuria≥500mg/dl, abnormal urin sediment, or elevated SCr, or in those with high probability of TMA. Age Mean (SD): 35.18 Race: 50% white; 28% African; 22% Asian	Renal Biopsy	TMA: 38/215 (18%)	Three goups: SLE=80; SLE/APS=48; SLE/aPL=87. (Biased towads more APS/APL patients)
				SLE=80;		TMA: 6/80 (7%)	SLE by ACR criteria.

				SLE/APS=48;		TMA: 12/48 (25%)	APS by Sapporo criteria.
				SLE/aPL=87		TMA: 20/87 (23%)	LAC by DRVVT. ACL (anticardiolipin) Moderate/high levels >20 u/ml (3SD above mean of normal range) No data for anti-b2GP1 antibodies
Silent LN	**Stamenkovic 1986**	Retrospective cohort. Single center (Switzerland)	Mean folowup from 1st biopsy was 8.2 years	57 **Pediatric** and adult SLE patients who underwent their 1st kidney biopsy systematically (whether there were clinical signs of renal involvement or not). Then 13 patients had a 2nd Bx and 4 had a 3rd biopsy for cause. Ages: mean (range): 28.5 (3-61) years	1st Renal Biopsy	Silent LN 6/57 (10.5%) Class IV: 5/57 (9%) Class V: 1/57 (1.8%)	Treatment according to Class of LN. Persistent low complement, proteinuria and active sediment were arguments for repeat biopsy **All 6 patients with silent LN did well**
				24 patients had no clinical signs of renal disease: 24/57 (42.1%)	1st Renal Biopsy	Silent LN 6/24 (25%) of those with no clinical signs of renal disease	(Patients with evidence of renal disease: Proteinuria>250 mg/L: 29/57 (51%) Active Urin sediment: 15/57 (26.3%) SCr>90umol/L (1.02 mg/dl): 23/57 (40.4%))
Reduction of proteinuria	**Carlucci 2022**	Restrospective cohort Multicenter, multi-ethnic (AMP study)	12 months	36 LN patients with either 1st or 2nd kidney Bx and UPCR 0.5-1 **(UPCR<1).** Ages (mean (SD): 38.5 (13.1)	Renal Biopsy	UPCR 1-2: 5/36 (14%) UPCR 0.5-1: 4/36 (11%) **UPCR<0.5: 27/36 (75%)**	
				8 LN patients with either 1st or 2nd kidney Bx and UPCR 0.5-1 **(UPCR<1). Class II** Ages (mean (SD): 38.5 (13.1)	Renal Biopsy	UPCR 1-2: 1/7 (14%) UPCR 0.5-1: 2/7 (29%) **UPCR<0.5: 4/7 (57%)**	

				29 LN patients with either 1st or 2nd kidney Bx and UPCR 0.5-1 **(UPCR<1). Class III, IV, V, Mixed** Ages (mean (SD): 38.5 (13.1)	Renal Biopsy	UPCR 1-2: 4/29 (14%) UPCR 0.5-1: 2/29 (7%) **UPCR<0.5=23/29 (79%)**	**In patients with UPCR<1 and LN Class III, IV, V, or Mixed: 39% of patients had neither pyuria or hematuria, despite havng a median AI 4.5 and CI 3.**
	Stamenkovic 1986	Retrospective cohort. Single center (Switzerland)	Mean folowup from 1st biopsy was 8.2 years	54 **Pediatric** and adult SLE patients with 1st Bx showing no evidence of class VI Ages: mean (range): 28.5 (3-61) years	1st Renal Biopsy	Proteinuria increase: 1/54 (1.9%)	Patient with Class IIb at 1st bx, class IIIb at 2nd Bx, and class IIIb at 3rd biopsy. Proteinuria 3.2g/24h. Time 84 months (from 1st Bx)
	Grishman and Churg 1982a	Retrospective cohort. (Single center;NY)	Fup: 6.3 years (2-20 years)	15 pediatric and adult SLE patients had 19 renal biopsies and 1 autopsy demonstrating pure focal segmental LN. Nephrotic syndrome 2/15 Mild-Mod proteinuria: 12/15 Normal 1/15 Age 28 (13-45)	Renal Bx	Change in proteinuria: Nephrotic syndrome 1/15 from 1/15 Mild-Mod proteinuria: 5/10 from 12/15 **Normal 4/10 (40%) from 1/15 (6.7%)**	Mild-Mod proteinuria: 0.2g/d-3.1g/d. Excluded from end of Fup 2 ESKD patiens and 3 patients without proteinuria data (10 instead of 15 patients total).
Bleeding	Kang, 2023	Single tertiary center retrospective study from Korea	NA	SLE patients that underwent 1st renal biospy (n=277) and 2nd renal Bx (n=25). Age Mean (SD): 35(14)	Renal Biopsy	Bleeding: 55/277 (19.9%) Minor bleeding: 36/277 (13%) Major bleeding: 19/277 (6.9%)	Kidney transplants excluded. US-guided Bx by nephrology or radiologists. ASA/Clopidogrel discontinued >7 days before biopsy. All hospitalized for ≥1 night (bed rest); sandbag over Bx site for>6 hours and BP measured every 1 hour.
	Jordan 2014	Single tertiary center retrospective study from London, England	NA	SLE patients (n=199) with 215 renal biopsies perfomed for Proteinuria≥500mg/dl, abnormal urin sediment, or elevated SCr, or those with high probability of TMA. Age Mean (SD): 35.18 Race: 50% white; 28% African; 22% Asian	Renal Biopsy	Bleeding: 32/215 (14.8%) Minor bleeding: 19/215 (8.8%) Major bleeding: 13/215 (6%)	**Most bleeds ≤3days from Bx date.** **(1 signif bleed 14 days after Bx date).** Multivariate predictors of bleed included: age>40, SCr>400 umol/L (4.5 mg/dl), lupus anticoagulant (LAC).

				SLE with APL/APS=135 biopsies	Renal Biopsy	Bleeding: 26/135 (19%) Major bleeding: 12/135 (9%)	**TMA and Severe Fibrous intimal hyperplasia (FIH**) were more frequent in patients with major bleed (67% and 33% respectively) compared to those with minor bleed (7% and 0%) and no bleed (27% and 2%)

- **References:**
  - Randomized controlled trials: None
  - Comparative observational studies: None
  - Single-arm studies:

Refid	Author	Year	Title	Comments
	Faurschou	2006	Prognostic Factors in Lupus Nephritis: Diagnostic and Therapeutic Delay Increases the Risk of Terminal Renal Failure	
	Fiehn	2003	Improved clinical outcome of lupus nephritis during the past decade: importance of early diagnosis and treatment	
	Kang	2023	Risk of bleeding-related complications after kidney biopsy in patients with systemic lupus erythematosus	
	Carlucci	2022	High incidence of proliferative and membranous nephritis in SLE patients with low proteinuria in the Accelerating Medicines Partnership	
	Fava	2022	History of proliferative glomerulonephritis predicts end stage kidney disease in pure membranous lupus nephritis	
	Jordan	2014	Association of thrombotic microangiopathy and intimal hyperplasia with bleeding post-renal biopsy in antiphospholipid antibody-positive patients	
	Stamenkovic	1986	Renal biopsy in SLE irrespective of clinical findings : long-term follow-up	
	Wallace	1988	Predictive Value of Clinical, Laboratory, Pathologic, and Treatment Variables in Steroid/Immunosuppressive Resistant Lupus Nephritis	
	Yang	1994	Lupus Nephritis in Children- A Review of 167 Patients	
	Moroni	1999	Clinical and Prognostic Value of Serial Renal Biopsies in Lupus Nephritis	

	Garin	1976	Nephritis in SLE in children	
	Grishman	1982	Focal segmental lupus nephritis	

- Studies reviewed and excluded:

None

P.4: In SLE patients with inadequate response to treatment at ≥ 6 months, is knowing the kidney histology from a repeat (for-cause) kidney biopsy associated with better outcomes than not knowing the kidney histology?

Population: Patients with LN on biopsy being treated with appropriate immunosuppression (including changing / more aggressive therapy) in whom proteinuria does not improve or worsens, and/or kidney function does not improve or worsens and/or glomerular hematuria does not improve or worsens.

Intervention: Percutaneous kidney biopsy

Comparator: No percutaneous kidney biopsy

Outcomes:

- Additional or different kidney diagnosis identified on histopathology (e.g., TMA, ATN, class change, medication effect e.g., CNI nephrotoxicity, DM or arteriosclerosis / arteriolosclerosis) results in a change in therapy
- Reduction of proteinuria
- Preservation of kidney function
- ESKD (dialysis or transplant)
- Adverse effects of biopsy

Table 1. Studies included

Author, year, RefID	Population (mean/median age in yrs)	Intervention	Comparison	Outcome	Reason for Repeat Biopsy
Kang 2023, 4469	Adults (mean age 35)	Repeat renal biopsy	N/A	Bleeding	Not reported
Tang 2009, 8880	Adults (mean age 27.9+/-10.7)	Repeat renal biopsy	N/A	Serum creatinine Urinary protein	Not reported
Fava 2022, 2750	Adults and children with at least 2 renal biopsies (median (range) age: 28 (9-60))	Repeat renal biopsy	N/A	ESRD LN class change	Abnormal proteinuria or unexplained decline of renal function

Lee 1984, 5053	Adults with at least 2 renal biopsies between 1962-1982 (mean age 23; range 18-37)	Repeat renal biopsy	N/A	LN class change	Clinical or laboratory evidence of change in renal status or as part of a prospective study of lupus nephropathy
Wang 2022, 9581	Adults with at least 2 renal biopsies (mean (SD) age: 30.1±11.3)	Repeat renal biopsy	N/A	LN histological class transformation	Hematuria or proteinuria
Yang 1994, 9932	Children with LN (mean age: 13.1, SD 2.3)	Repeat renal biopsy	N/A	ESKD Decline in eGFR LN histological class change that could impact therapy	Abnormal urinalysis including pyuria, hematuria, or proteinuria
Moroni 1999, 6299	Adults with biopsy-proven LN with persistent proteinuria or worsening kidney function (median age: 23 (25^{th} & 75^{th}% 18 & 31)	Repeat renal biopsy	N/A	Doubling of creatinine to >2 mg/dl, ESRD	A) Improvement of renal disease but persistence of nonnephrotic proteinuria (7 pts) B) Persistent (6 pts) or relapsing (6 pts) nephrotic syndrome C) Increase in plasma Cr level caused by either a slow or fast increase in plasma Cr level of at least 50% greater than the basal value (19 pts)
Gao 2012, 3090	Adults and children (mean age: 29.3, range 13-66)	Repeat renal biopsy	N/A	LN class transformation Proteinuria	Not reaching clinical remission after therapy (remission defined as 24-h urine protein <0.5 g/day)
Moroni 2022, 6301	Adults (median (IQR) age: 34 (28-45) years at time of second biopsy)	Repeat renal biopsy	N/A	LN class switch (identification of additional kidney diagnosis) Kidney function impairment (KFI) ESRD	Proteinuric flare, nephritic flare and protocol biopsy

- **Summary of Evidence:**

  The excluded references did not address this PICO questions because don't report on the role of repeat kidney biopsy in LN. Both studies used histological characteristics from a single biopsy as prognostic factors or predictive variables for outcomes in LN (there was not a second or repeat biopsy involved).

  The literature on the value of repeat kidney biopsies in LN is sparse and consists mostly of retrospective and prospective single-arm studies. Studies reported outcomes on repeat kidney biopsies in all patients in a LN cohort and did not specify that repeat biopsies were done only in those with inadequate response to therapy at >=6 months. Most studies addressed the value of repeat kidney biopsies in determining the likelihood of transformation from one LN class to another. Tang et al (2009) found that there was a tendency for chronicity index to increase and activity index to decrease from initial to repeat biopsy. Moroni et al (2022) also showed that at repeat biopsy, chronicity index increased in 44 (72%) and did not increase in 17 (28%). Nephritic syndrome and serum Cr >1.6 mg/dL at presentation correlated with chronicity index increase (p=0.031, 0.027). Fava et al (2022) showed that LN class switch may occur at any time, even after multiple biopsies with the same class; their study showed that LN class V transitioned to proliferative LN in 41% of 220 cases, whereas proliferative LN transitioned to pure LN class V in 18% and to class I or II in 8% of 220 cases. Gao et al (2012) showed that 27/47 (57%) patients transformed from LN class IV to another class, and in LN class IV, Class IV-S had higher rate of transformation to class II than class IV-G (57% vs. 27%). In each subclass, active lesion showed higher rate of transformation to class II than active/chronic lesion (IV-G:41.2% vs. 12.5%; IV-S: 71.4% vs. 42.8%). Immunosuppressive therapy, urine protein, and vascular lesions were independent risk factors for pathologic transformation. Patients who maintained in class IV had higher BP, obvious proteinuria, declined kidney function, and lower C3 level. In contrast, in children, a study by Yang et al (1994) suggested that LN class remained stable in the vast majority of cases of repeat renal biopsies (29 of 36 [80.6%]).

  Renal function (serum Cr or eGFR) was worse in LN class IV compared with other LN classes in children (Yang et al 1994). Tang et al (2009) showed that serum Cr tended to improve from first to repeat biopsy (355+/-237 to 236+/-205 umol/L). Repeat renal biopsies may also provide insight into risk for ESKD. Fava et al (2022) showed that 5/56 (9%) of patients with pure LN class V developed ESKD within 2 yrs, all preceded by proliferative LN in the first biopsy (log rank p=0.024). Yang et al (1994) showed that CKD and ESKD is more likely in patients with persistent HTN, anemia, increased serum Cr, and decreased CrCl at initial biopsy.

  Urine protein, like renal function, tended to improve from first to last renal biopsy: 3.77+/-1.78 to 1.29+/-1.53 g/day (Tang et al 2009). Furthermore, all patients showed improvement in proteinuria after reinforcement of therapy based on renal biopsy findings (Moroni et al 1999).

  Only one study looked at risk of bleed after a repeat renal biopsy (Kang et al 2023). This study found that any bleed occurred in 7/25 (28%), of which minor bleed occurred in 5 and major bleed occurred in 2. This suggests that bleeding risk is not significantly greater in repeat biopsy compared to initial biopsy.

- **Table 2. Outcomes**

Outcome	Author, year, RefID	Study Design	Follow up Duration	Population	Intervention	Result	Notes
Adverse events	Kang 2023, 4469	Retrospective cohort study	2002-2020	Adults (mean age 35)	2nd renal biopsy (25 of 277 total patients)	Any bleeding - 7/25 (28%) Minor bleeding – 5/25 (20%)* Major bleeding – 2/25 (8%)**	*Minor – perinephric hematoma **Major – requiring RBC transfusion, IR, or surgery and hemodynamic instability requiring inotropic support **N.B:** they report on the first events of the first biopsy and on the second biopsy. We only included the outcomes of the second biopsy.
Change in histology or LN class	Tang 2009, 8880	Retrospective cohort study	37.9+/-38.5 months	Adults (mean age 27.9+/-10.7)	Repeat renal biopsy	From first to last renal biopsy: **Active index:** 8.31+/- 3.11 to 6.31+/-3.22 **Chronic index:** 2.75+/-2.44 to 4.69+/-2.61	Comparing mean (SD) of the active and chronic index between the first biopsy and the second biopsy.
	Fava 2022, 2750	Prospective cohort study	1993-2019	Adults and children (median (range) age: 28 (9-60)) (n=220, 542 biopsies)	Repeat renal biopsy	**From Pure LN class V:** to proliferative LN: 17/41 to class VI: 1/41 to class I/II: 1/41 **From Proliferative LN:** to pure LN class V: 29/162 to VI: 3/162 to I/II: 13/162 **From class I/II:** To class V: 5/17 To proliferative: 8/17 To VI: 1/17	Class switch may occur at any time, even after multiple biopsies with the same class
	Lee 1984, 5053	Retrospective cohort study	29.8 to 60.3 months	Adults with at least 2 renal biopsies between 1962-1982 (mean age 23; range 18-37)	Repeat renal biopsy	**LN class IV to non-proliferative LN class**: 10/24 (41.7%) • To class V: 5 • To class II: 4 • To class I: 1 **LN class III to non-proliferative LN class:** 8/14 (57.1%) • To class V: 4 • To class II: 4	

						LN class III & IV to non-proliferative LN class: 18/38 (47.4%) • To class V: 9 • To class II: 8 • To class I: 1 **LN class II to another class**: 5/6 (83.3%) • To class I: 1 • To class IV: 3 • To class V: 1 **LN class V to another class:** 3/6 (50.0%) • To class III, IV: 3	
	Wang 2022, 9581	Retrospective cohort study	5 years	Adults with at least 2 renal biopsies (mean (SD) age: 30.1±11.3)	Repeat renal biopsy	**Transformation from class II:** 14/16 (87.5%) showed transformation from LN class II to LN class III (n=3), IV (n=3), V+III (n=3), V+IV (n=3), or V (n=2)	Histological transformation after 1st relapse: 13 Histological transformation after 2nd relapse: 1 14/16 patients with repeat renal biopsy were in proteinuria group (0.43-2.8 g/24h) -12/14 patients in proteinuria group had histological transformation 2/16 patients with repeat renal biopsy were in hematuria group -2/2 patients in hematuria group had histological transformation
	Yang 1994, 9932	Retrospective cohort study	1979-1991	Children with LN: Mean (SD) age: 13.1 (2.3)	Repeat renal biopsy	LN class stable: 29/36 (80.6%) LN class progressive: 5/36 (13.9%) LN class regressive: 2/36 (5.6%)	Progressive: -LN class II to IV (n=3) -LN class III to IV (n=2) Regressive: -LN class IV to II (n=2)

	Gao 2012, 3090	Retrospective cohort study	26.32+/-29.37 months	Adults and children **mean (range) age:** 29.3 (13-66)	Repeat renal biopsy	**Patients transformed from LN class IV:** 27/47 (57%) transformed: • To class II: 17 • To class III: 5 • To class V: 5	• Class IV-S had higher rate of transformation to class II than class IV-G (57% vs. 27%) • In each subclass, active lesion showed higher rate of transformation to class II than active/chronic lesion (IV-G:41.2% vs. 12.5%; IV-S: 71.4% vs. 42.8%)
	Moroni 2022, 6301	Retrospective cohort study	23 years	Adults **Median (IQR) age**: 34 (28-45) years	Repeat renal biopsy	At repeat biopsy, chronicity index increased in 44/61 (72%).	Events leading to second biopsy were: -Proteinuric flares in 21 (36%) cases -Nephritic flares in 25 (41%) -Protocol biopsy or clinical decisions in 14 (23%). Nephritic syndrome and serum Cr >1.6 mg/dL at presentation correlated with chronicity index increase (p=0.031, 0.027)
Proteinuria	Tang 2009, 8880	Retrospective cohort study	37.9+/-38.5 months	Adults mean (SD) age: 27.9+/-10.7	Repeat renal biopsy	From first to last renal biopsy: Urine protein (mean+/-SD, g/day): 3.77+/-1.78 to 1.29+/-1.53	
	Moroni 1999, 6299	Retrospective cohort study	10.5 years	Adults with biopsy-proven LN with persistent proteinuria or worsening kidney function Median (IQR) age: 23 (18-31)	Repeat renal biopsy	Improvemnet but persistent of non-nephrotic proteinuria: 7/31 Persistent or relapsing nephrotic syndrome: 11/31	
	Moroni 2022, 6301	Retrospective cohort study	23 yrs	Adults (median (IQR) age: 34 (28-45) years at time of second biopsy)	Repeat renal biopsy	Proteinuria, g/day: at first biopsy versus second biopsy: 3.3 (1.8-5.6) versus 2.4 (1-5)	.

Serum Cr or eGFR	Tang 2009, 8880	Retrospective cohort study	37.9+/-38.5 months	Adults (mean age 27.9+/-10.7)	Repeat renal biopsy	From first to last renal biopsy: Mean (SD) SCr (umol/L): 355+/-237 to 236+/-205	
	Moroni 1999, 6299	Retrospective cohort study	10.5 yrs	Adults with biopsy-proven LN with persistent proteinuria or worsening kidney function (median age: 23 (25^{th} & 75^{th}% 18 & 31)	Repeat renal biopsy	Doubling of Cr: 17/31 (53%)	
	Moroni 2022, 6301	Retrospective cohort study	23 yrs	Adults (median (IQR) age: 34 (28-45) years at time of second biopsy)	Repeat renal biopsy	eGFR: at first biopsy versus second biopsy: 66(44-99.5) versus 66.5 (42-87)	.
ESKD	Fava 2022, 2750	Prospective cohort study	1993-2019	Adults and children (median (range) age: 28 (9-60))	Repeat renal biopsy	5/56 (9%) of patients with pure LN class V developed ESKD within 2 yrs, all preceded by proliferative LN in first biopsy	
	Yang 1994, 9932	Retrospective cohort study	1979-1991	Children with LN (mean age: 13.1, SD 2.3)	Repeat renal biopsy	Renal survival at 5 outcomes: 135/145 (93.1%)	
	Moroni 2022, 6301	Retrospective cohort study	23 yrs	Adults (median (IQR) age: 34 (28-45) years at time of second biopsy)	Repeat renal biopsy	ESRD: 12/61 (20%)	.
	Moroni 1999, 6299	Retrospective cohort study	10.5 yrs	Adults with biopsy-proven LN with persistent proteinuria or worsening kidney function	Repeat renal biopsy	ESRD (dialysis): 8/31	

				(median age: 23 (25^{th} & 75^{th}% 18 & 31)			

References of the included studies:

Author	Year	RefID	Title
Kang	2023	4469	Risk of bleeding-related complications after kidney biopsy in patients with systemic lupus erythematosus
Tang	2009	8880	Clinical features and renal outcome in lupus patients with diffuse crescentic glomerulonephritis
Fava	2022	2750	History of proliferative glomerulonephritis predicts end stage kidney disease in pure membranous lupus nephritis
Lee	1984	5053	Course of renal pathology in patients with systemic lupus erythematosus
Wang	2022	9581	Long-term renal outcomes of mesangial proliferative lupus nephritis in Chinese patients
Yang	1994	9932	Lupus Nephritis in Children- A Review of 167 Patients
Moroni	1999	6299	Clinical and Prognostic Value of Serial Renal Biopsies in Lupus Nephritis
Gao	2012	3090	Characteristics and influence factors of pathologic transformation in the subclasses of class IV lupus nephritis
Moroni	2022	6301	Predictors of increase in chronicity index and of kidney function impairment at repeat biopsy in lupus nephritis

- Randomized controlled trials: None
- Comparative observational studies: None
- Single-arm studies: 9

- **Excluded References:**

Author	Year	RefID	Title	Reason for exclusion
Wallace	1998	9507	Predictive Value of Clinical, Laboratory, Pathologic, and Treatment Variables in Steroid/Immunosuppressive Resistant Lupus Nephritis	NOT a repeat renal biopsy study

Shilov	1994	8275	Prognostic factors in lupus nephritis treated with cyclophosphamide pulses	NOT a repeat renal biopsy study

P.5. In SLE patients with LN and complete or partial renal response of at least one year on subsequent (maintenance) therapy (immunosuppressive medication with or without corticosteroids), is knowing the renal histology on a repeat "protocol" biopsy associated with better outcomes than not knowing the renal histology?

Population: Patients with LN diagnosed by a kidney biopsy who have been treated with immunosuppression subsequent (maintenance) therapy, and achieved/ maintained a complete or partial renal response for at least a year

- Complete renal response for at least one year
- Partial renal response for at least one year

Intervention: Percutaneous kidney biopsy

Comparator: No percutaneous kidney biopsy

Outcomes:

- Histopathology results in change and/or continuation of therapy
- Histopathology results in withdrawal of therapy (ie no activity seen on biopsy)
- Risk of LN flare
- ESKD
- Adverse effects of biopsy

Table 1. All Included Studies for PICO 5				
Author, Year	**Population**	**Intervention**	**Comparator**	**Outcomes**
Kang 2023	Patients with SLE	Repeat Renal Biopsy	none	Bleeding
Zappitelli 2004	Patients with SLE, biopsy occurred before age 18	Repeat Renal Biopsy	none	Proteinuria, eGFR, serum Cr
Lee 1984	LN patients with at least 2 kidney biopsies	Repeat Renal Biopsy	none	class change
Stoenoiu 2012	LN patients undergoing per protocol repeat biopsies	Repeat Renal Biopsy	none	AE of biopsy
Wang 2022	LN; repeated renal biopsy after renal relapse	Repeat Renal Biopsy	none	histological transformation
Yang, 1994	All patients had renal biopsy for diagnosis of LN, and some had a repeat biopsy	Repeat Renal Biopsy	none	ESKD, declining in creatinine/eGFR, histopathology results in change in LN class that could impact therapy
Malvar-2020	Patients with proliferative LN had been on immunosuppression for at least 42 months, had responded, and had maintained their clinical response for at least 12 months before the repeat kidney biopsy	Repeat Renal Biopsy	none	LN flare after therapy tapered for NIH activity index = 0
Parodis 2020	Patients with incident biopsy-proven proliferative LN.	Repeat Renal Biopsy	none	Renal relapse, Renal function deterioration
Valeri 1994	Patients with LN	Repeat Renal Biopsy was performed in 15 patients	none	Histopathology results in change and/or continuation of therapy
Moroni 2022	Adult patients with biopsy-proven LN undergoing second renal biopsy either for flare or per protocol	Repeat Renal Biopsy	none	Identification of additional kidney diagnosis (class switch), kidney function impairment (KFI), ESRD
Singh 2014	Patients with LN undergoing biopsy at diagnosis and 6 months after	Repeat biopsy 6 mos. after diagnosis	none	Complete remission, partial remission, no response, change in activity index (AI) and chronicity index (CI) from baseline to 6 mos., change in variables at baseline to 6 mos.

Summary of evidence.

Eleven studies (1-11) met inclusion criteria and examined the impact of repeat kidney biopsy in patients with lupus nephritis. Two studies examined the rates of adverse events with a repeat kidney biopsy and noted that overall low rates (3-8%) of major adverse events, such as major bleeding or hematoma (1, 4). Next, three studies (2, 8, 10) examined the associations between LN flares and repeat biopsy. One study noted no correlation between clinical parameters and WHO LN class on repeat kidney biopsy time and no change in clinical parameters at the time of repeat biopsy compared to initial biopsy (2), while another study reported 55% of the patients undergoing

repeat biopsy had a significant deterioration in creatinine over time (10). Finally, one study noted higher NIH activity index scores in repeat biopsy were associated with higher risk of LN flares while higher NIH chronicity index in repeat biopsy was associated with worse kidney function over time (8).

Four studies reported LN class change on repeat kidney biopsy (3, 5, 6, 11). Two studies reported no difference in rates of class change on repeat biopsy (3, 6). Wang et al. noted significant correlation between clinical parameters and class change with 86% of patients with proteinuria and 100% of patients with hematuria had class change on repeat biopsies (5). Finally, Singh et al reported 25% class transformation on repeat biopsies after 6 mos. of therapy and greater chronicity scores on repeat biopsy compared to initial biopsy despite 6 mos. of LN therapy (11). However, no significant trend reported regarding class transformation (IV to other classes) on repeat biopsy (3,5,6,10).

Three studies examined change in therapy based on histologic findings on repeat kidney biopsy (7, 9, 10), mycophenolate was tapered in patients with NIH Activity Index of 0 on repeat kidney biopsy (7); while for patients with NIH activity score of 5 or greater additional induction therapy was given (9). Finally, Moroni et al. reported that repeat biopsy helped guide LN therapy change in ~50% of patients with rising creatinine.

Table 2. Results

Outcome	Author, year	Design	Follow up	Population	Intervention	Outcomes	Notes
Adverse effects of renal biopsy	Kang, 2023	Single center, retrospective	Not reported	Patients with SLE who underwent repeat renal biopsy (n=25)	Repeat renal biopsy	Minor Bleeding: 7/25; Major Bleeding: 2/25; All bleeding: 7/25	*Minor – perinephric hematoma **Major – requiring RBC transfusion, IR, or surgery and hemodynamic instability requiring inotropic support N.B: they report on the first events of the first biopsy and on the second biopsy. We only included the outcomes of the second biopsy.
	Stoenoiu 2012	Multicenter, Intervention-based (per protocol)	24 mos.	N=30, 97% female, 80% Caucasian, class III, IV, or V	Per protocol repeat biopsies after 2 years of treatment with AZA or MMF	2/60 biopsies complicated by pain and imaging-confirmed hematoma, both cases self-limited	
Risk of LN flare (change in GFR or UPC)	Zappitelli, 2004	Single center, retrospective	Not reported	Patients with LN	Repeat renal biopsy	Repeat biopsy versus initial biopsy: **-eGFR:** 111.6 ± 8.3 versus 118.4 ± 7.2 **-UPCr** 0.81 ± 0.5 versus 0.8 ± 0.3	
	Parodis, 2020	Multicenter LN database (Euro-lupus &	Per-protocol repeat biopsies were performe	Patients with LN	Repeat renal biopsy	**Renal Flare:** 9/22 flared with NIH Activity score of 2 or greater; 7/14 flared with Activity score of 3 or greater.	Higher Activity Index scores in biopsy associated with higher LN flares (1.2±0.95, p-value = 0.007); while higher chronicity index on repeat biopsy associated with higher

		MAINTAIN cohorts), Intervention-based (per protocol)	d after a median [interquartile range (IQR)] time of 24.3 (21.3–26.2) months. Patients were followed for a total median (IQR) time of 131.5 (73.8–178.2) months from baseline, and 107.7 (49.7–153.5) months from the repeat biopsy			**Increase in serum creatinine:** 5/13 patients had higher serum creatinine with NIH chronicity index of 3 or more on repeat biopsy (sustained increase of 120% of baseline levels)	worsening of creatinine (1.8±0.95; p-value 0.016)
	Moroni, 1999	Single center, retrospective	3.6 years	Patients with LN	Repeat biopsy	**Doubling of Serum creatinine:** 17/31 in who underwent repeat renal biopsy	
LN class change	Lee, 1984	Single center, retrospective	~12 weeks	Patients with LN	Repeat biopsy	**Class change:** 28/50	**Class II (5/6):** To class I: 1/6 To Class IV: 3/6 To Class V: 1/6 **Class III (10/14):** To class II: 4/14

							To class IV: 2/14 Class V: 4/14 **Class IV (10/24):** To class I: 1/24 To class II:4/24 To class V: 5/25 **Class V (3/6):** To Class III/IV: 3/6
	Wang, 2022	Single center, retrospective	16 mos.	Patients with LN	Repeat biopsy	**Change in class overall:** 14/16	Histological transformation to LN classes III, IV, V + III, V + IV (each with 3 patients) and LN class V (2 patients).
	Yang, 1994	Single center, retrospective	59 mos.	Patients with LN	Repeat biopsy	**Change in class:** 5/14	Change in class from IV to II: 2/14; Class change from II to IV: 3/13
	Singh, 2014	Single center, retrospective	6 mos.	Patients with LN (n=40)	Repeat biopsy at 6 mos.	**Class transformation:** 10/40 (25%) **Activity Index** reduced after 6 mos. 2.50 vs. 6.05. **Chronicity index** increased from 0.65 to 2.52.	8 class IV-A LN changed to class IV-C and two patients of class IV–A/C progressed to class IV-C. Regression of histological class was seen in one class IV LN changing to class II LN.
Therapy change per repeat biopsy findings	Malvar, 2020	Single center, retrospective	26 months	Patients with LN	Repeat biopsy	**Histologic activity:** 21/76 **No histologic activity and immunosuppression was stopped:** 55/76	6/55 patients flared after MMF was tapered.
	Valeri, 1994	Single center, prospective	5 years	Patients with LN	Repeat biopsy	3/13 had NIH Activity index >5 on repeat biopsy and received therapy change; 9 out of 13 had improvement in NIH activity scores after 12-15 mos. of therapy	
	Moroni, 1999	Single center,	3.6 years	Patients with LN	Repeat biopsy	All patients (n=7) with new/persistent proteinuria who	Repeat biopsy helped guide LN therapy change in ~50% of patients with rising creatinine

		retrospectiv e				underwent repeat biopsy had rx change; 11 out of 19 patients with rising creatinine who underwent repeat bx had therapy change	

Ref #	Author, Year	Title
1	Kang 2023	Risk of bleeding-related complications after kidney biopsy in patients with systemic lupus erythematosus
2	Zappitelli 2004	Clinicopathological study of the WHO classification in childhood lupus nephritis
3	Lee 1984	Course of renal pathology in patients with systemic lupus erythematosus
4	Stoenoiu 2012	"Repeat kidney biopsies fail to detect differences between azathioprine and mycophenolate mofetil maintenance therapy for lupus nephritis: data from the MAINTAIN Nephritis Trial"
5	Wang 2022	Long-term renal outcomes of mesangial proliferative lupus nephritis in Chinese patients
6	Yang, 1994	Lupus Nephritis in Children- A Review of 167 Patients
7	Malvar-2020	Kidney biopsy–based management of maintenance immunosuppression is safe and may ameliorate flare rate in lupus nephritis
8	Parodis 2020	Per-protocol repeat kidney biopsy portends relapse and long-term outcome in incident cases of proliferative lupus nephritis
9	Valeri 1994	Intravenous pulse cyclophosphamide treatment of severe lupus nephritis: a prospective five year study
10	Moroni 1999, 2022	Clinical and Prognostic Value of Serial Renal Biopsies in Lupus Nephritis; Predictors of increase in chronicity index and of kidney function impairment at repeat biopsy in lupus nephritis
11	Singh 2014	Protocol renal biopsy in patients with lupus nephritis: a single center experience

References:
RCT: None
Comparative: None
Non-comparative studies: 11 studies

P.6 In SLE patients with class II LN without lupus podocytopathy on biopsy and without presence of extrarenal SLE activity requiring therapy, does treatment with renin-angiotensin-aldosterone system inhibitors (RAAS-I) and steroid with or without additional immunosuppressive therapy - versus RAAS-I therapy alone - lead to improved outcomes?

Population:
- Active Class II LN without lupus podocytopathy

Intervention:
- No RAAS-I mentioned with CS and Immunosuppressant

Comparator:

- No RAAS-I mentioned with CS

Outcomes:

- LN Flares

Table 1: P.6: In SLE patients with class II LN without lupus podocytopathy on biopsy and without presence of extrarenal SLE activity requiring therapy, does treatment with renin-angiotensin-aldosterone system inhibitors (RAAS-I) and steroid with or without additional immunosuppressive therapy - versus RAAS-I therapy alone - lead to improved outcomes?							
Study name (year) country	**Study design**	**Population**	**Intervention details**	**Comparator details**	**Outcomes with available data**	**Outcomes measures**	**Outcome timepoint**
Wang 2022 China	Non-randomized observational study	Class II LN Adults Age: Mean (SD) 30.1 (11.3) Asians	Prednisone dosage of 20–30 mg/d for 4–8 weeks tapered to 10 mg/d for maintenance only and other immunosuppressive agents	Prednisone dosage of 20–30 mg/d for 4–8 weeks tapered to 10 mg/d for maintenance only	LN Flares	Risk ratio	36 months

Evidence summary: 1 non-randomized observational study addresses PICO 6 question. One outcome (LN flares) was evaluated at 12 months, 24 months, and 36 months. Concerning LN flares at 36 months, the absolute effect was 600 fewer per 1,000 (from 700 fewer to 480 fewer) favoring RAAS-I and CS and Immunosuppressant. Outcome was were very low certainty evidence due to risk of bias and imprecision and indirectness due to no mention of patients taking RAAS-I in both arms.

Question: RAAS + CS + IS compared to RAAS + CS for Class II LN

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**RAAS + CS + IS**	**RAAS + CS**	**Relative (95% CI)**	**Absolute (95% CI)**		
LN Flares												
1[1]	non-randomised studies	serious[a]	not serious	very serious[b]	serious[c]	none	34/89 (38.2%)	15/15 (100.0%)	**RR 0.40** (0.30 to 0.52)	**600 fewer per 1,000** (from 700 fewer to	⨁◯◯◯ Very low	CRITICAL

										480 fewer)		

CI: confidence interval; **RR:** risk ratio

Explanations

a. Risk of bias was assessed using Robins-I, high risk of bias was assessed due to confounding.

b. Prioritized PICO question assessed patients taking RAAS-I and CS and Immunosuppressants vs RAAS-I and CS. In the included study no mention of patients taking RAAS-I.

c. Small number of patients

References

Randomized clinical trials: none

Comparative nonrandomized studies: 1

1.Wang, Shaofan, Chen, Duqun, Zuo, Ke, Xu, Feng, Hu, Weixin. Long-term renal outcomes of mesangial proliferative lupus nephritis in Chinese patients. Clinical Rheumatology; 2022.

Non-comparative studies: none

P6. In SLE patients with class II LN without lupus podocytopathy on biopsy and without presence of extrarenal SLE activity requiring therapy, does treatment with renin-angiotensin-aldosterone system inhibitors (RAAS-I) and steroid with or without additional immunosuppressive therapy - versus RAAS-I therapy alone - lead to improved outcomes?

P6-a) In SLE patients with class II LN without lupus podocytopathy on renal biopsy, with proteinuria >0.5 gm/d, and without glomerular hematuria or decreased kidney function, does treatment with RAAS-I and steroid therapy - versus RAAS-I therapy alone - lead to improved outcomes in reduction in proteinuria, preservation of kidney function, LN flare risk, development of ESKD, treatment related adverse effects and cumulative steroid dose?

P6-d) In SLE patients with class II LN without lupus podocytopathy on renal biopsy, with proteinuria >0.5 gm/d and glomerular hematuria without decreased kidney function, does treatment with RAAS-I and steroid therapy - versus RAAS-I therapy alone - lead to improved outcomes in reduction in proteinuria, preservation of kidney function, LN flare risk, development of ESKD, treatment related adverse effects and cumulative steroid dose?

P6-g) In SLE patients with class II LN without lupus podocytopathy on renal biopsy, with proteinuria >0.5 gm/d and decreased kidney function, with or without glomerular hematuria, does treatment with RAAS-I and steroid therapy - versus RAAS-I therapy alone - lead to improved outcomes in reduction in proteinuria, preservation of kidney function, LN flare risk, development of ESKD, treatment related adverse effects and cumulative steroid dose?

Intervention:

- Corticosteroids

Outcomes:

- Remission

Outcomes (Name + Summary)	Author, year, RefID	Study type	Duration of follow up	Population (number and description, age)	Intervention used in relevant population (Describe the intervention)	Results	Comments
	Bakr,2004.(ID: 699)	Non-comparative	Mean 25.6 ± 22.4 months	8 Patients – Class II	6 Patients took oral steroids, 2 patients took Pulse MP	RR: 7/8 (87.5%)	Remission was defined as normal urine analysis, blood pressure, and serum creatinine

Renal response (RR)				Mean Age 11.9 ± 2.6 years			with no evidence of active extrarenal manifestations.

Evidence summary:
Bakr 2004 was conducted in patients with pediatric onset Class LN II. Renal Response (remission) was observed in 7/8 (87.5%) of patients. Remission was defined as normal urine analysis, blood pressure, and serum creatinine with no evidence of active extrarenal manifestations. No information about RAAS-I was available.
Bakr, A. Epidemiology treatment and outcome of childhood systemic lupus erythematosus in Egypt. Pediatr Nephrol 20, 1081–1086 (2005). https://doi.org/10.1007/s00467-005-1900-2

P6. In SLE patients with class II LN without lupus podocytopathy on biopsy and without presence of extrarenal SLE activity requiring therapy, does treatment with renin-angiotensin-aldosterone system inhibitors (RAAS-I) and steroid with or without additional immunosuppressive therapy - versus RAAS-I therapy alone - lead to improved outcomes?

P6-c) In SLE patients with class II LN without lupus podocytopathy on renal biopsy, with proteinuria >0.5 gm/d, and without glomerular hematuria or decreased kidney function, does treatment with RAAS-I and steroid therapy plus CNI versus RAAS-I therapy alone - lead to improved outcomes in reduction in proteinuria, preservation of kidney function, LN flare risk, development of ESKD, treatment related adverse effects and cumulative steroid dose?

P6-f) In SLE patients with class II LN without lupus podocytopathy on renal biopsy, with proteinuria >0.5 gm/d and glomerular hematuria without decreased kidney function, does treatment with RAAS-I and steroid therapy plus CNI versus RAAS-I therapy alone - lead to improved outcomes in reduction in proteinuria, preservation of kidney function, LN flare risk, development of ESKD, treatment related adverse effects and cumulative steroid dose?

P6-i) In SLE patients with class II LN without lupus podocytopathy on renal biopsy, with proteinuria >0.5 gm/d and decreased kidney function, with or without glomerular hematuria, does treatment with RAAS-I and steroid therapy plus CNI versus RAAS-I therapy alone - lead to improved outcomes in reduction in proteinuria, preservation of kidney function, LN flare risk, development of ESKD, treatment related adverse effects and cumulative steroid dose?

Intervention:
- Tacrolimus

Outcomes:
- Complete renal response
- Proteinuria
- Creatinine

Outcomes (Name + Summary)	Author, year, RefID	Study type	Duration of follow up	Population (number and description, age)	Intervention used in relevant population (Describe the intervention)	Results	Comments
	Tanaka,2009. (ID: 8846)	Non-comparative	Median of 18 months	5 Patients – Class II	**Tac** (3 mg/day, 0.04 - 0.075 mg/kg) without dose increases	CRR: 4/5 (80%)	Complete response" was defined as an improvement in the ECLAM index (a ~

Complete renal response (CRR)				Median Age 18 (9-25)	of concomitantly administered prednisolone		50% decrease compared with the baseline value) 1 patient did not achieve either complete or partial response
Difference in Protein/Creatinine Ratio	Tanaka,2009. (ID: 8846)	Non-comparative	Median of 18 months	5 Patients – Class II Median Age 18 (9-25)	**Tac** (3 mg/day, 0.04 - 0.075 mg/kg) without dose increases of concomitantly administered prednisolone	Median of -0.01 (Range: 0.02 – -0.14)	
Serum CR	Tanaka,2009. (ID: 8846)	Non-comparative	Median of 18 months	5 Patients – Class II Median Age 18 (9-25)	**Tac** (3 mg/day, 0.04 - 0.075 mg/kg) without dose increases of concomitantly administered prednisolone	Median of 0.085 (Range: 0 – 0.1)	

Evidence summary:
Tanaka 2009 was conducted in patients with pediatric onset LN, however the median age at time of evaluation was 18 (range: 9-25). Tanaka 2009 showed a decrease of 0.01 in Protein/Creatinine Ratio. While an increase of 0.085 was reported for Serum CR. Regarding complete response, 4/5 (80%) of patients achieved CR at 6 months.

References:
Tanaka H, Oki E, Tsuruga K, Yashiro T, Hanada I, Ito E. Management of young patients with lupus nephritis using tacrolimus administered as a single daily dose. Clin Nephrol. 2009 Dec;72(6):430-6. PMID: 19954719.

P.7a In SLE patients with active, newly diagnosed or flare of Class III/IV LN, is treatment with pulse intravenous glucocorticoids followed by moderate-high dose glucocorticoids compared to pulse intravenous glucocorticoids followed by low dose glucocorticoids associated with improved outcomes?

Population:
- Active Class III/IV LN

Intervention:
- Pulse intravenous glucocorticoids followed by moderate-high dose glucocorticoids

Comparator:
- Pulse intravenous glucocorticoids followed by low dose glucocorticoids

Outcomes:

- Reduction of proteinuria
- Preservation of kidney function
- Risk of LN flares
- ESKD (dialysis or transplant)
- Treatment related adverse effects including infection; also decrease >30% from baseline eGFR for CNI's, depression/suicide for belimumab

Table 1: P.7a pulse intravenous glucocorticoids followed by moderate-high dose glucocorticoids versus pulse intravenous glucocorticoids followed by low dose glucocorticoids

Study name (year) country	Study design	Population	Intervention details	Comparator details	Outcomes with available data	Outcome measures	Outcome time point
Bandhan 2022 Bangladesh	Randomized clinical trial	LN patients Class 3,4: proportions not reported. Age: Mean (SD) LD: 26.56 (6.41) HD: 30.25 (8.63) (Adults) Ethnicity not reported	pulse intravenous glucocorticoids followed by moderate-high dose glucocorticoids All the patients received CYC pulses monthly for 6 months (0.75-1 g/m2 ev) (NIH protocol)	pulse intravenous glucocorticoids followed by low dose glucocorticoids All the patients received CYC pulses monthly for 6 months (0.75-1 g/m2 ev) (NIH protocol)	Complete response Partial response Proteinuria	Risk ratio	24 weeks
Zeher 2011 Hungary	Randomized clinical trial	LN patients Class 3,4,5. proportions not reported. Age: Mean (SD) standard dose 32.2 (8.5), reduced dose 34.2 (10.7) (Adults) Multiple ethnicities.	Pulse intravenous glucocorticoids followed by moderate-high dose glucocorticoids All patients received EC-MPS (Enteric coated-mycophenolate sodium) at a dose of 2160 mg/day (MMF 3 equivalent)	Pulse intravenous glucocorticoids followed by low dose glucocorticoids All patients received EC-MPS (Enteric coated-mycophenolate sodium) at a dose of 2160 mg/day (MMF 3 equivalent)	Complete response Partial response Adverse events Serious adverse events	Risk ratio	not reported
Bharati 2019 India	Randomized clinical trial	LN patients All class 3,4 concomitant with 5. Age: Range from 12-70 years (Adults/pediatrics)	Pulse intravenous glucocorticoids followed by moderate-high dose glucocorticoids	Pulse intravenous glucocorticoids followed by low dose glucocorticoids All patients received MMF 2g/day	Complete or partial response Infections	Risk ratio	24 weeks

		Ethnicity not reported	All patients received MMF 2g/day				

Evidence summary: 3 randomized studies address PICO 7.a question.
Regarding efficacy, complete response was assessed by two studies showing a RR (CI) 0.84 (0.51 to 1.39) with similar results in both regimens at 24 weeks. The composite outcome "complete response + partial response" at 24 weeks was reported in 3 studies. **The RR (CI) is RR 1.11 (0.70 to 1.76)**, showing no difference between two regimens, with low certainty of evidence. In addition, the outcome "proteinuria <500 mg/day", was assessed by one study, displaying similar results between two glucocorticoids treatments, RR (CI) 1.00 (0.58 to 1.71).
In safety outcomes there is one study reporting serious adverse events with and RR 1.86 (0.61 to 5.68), showing an apparent increased risk in the intervention group (pulse + mod-high dose of GC). Regarding infections, just one study addressed this outcome with RR 7.00 (0.41 to 120.16). This result is imprecise because low number of events but does not rule out an apparent increased risk in the pulse + mod-high dose of GC, with a very low certainty of evidence.

Evidence summary from a Systematic review: These results are extracted from a newly published systematic review *(Figueroa-Parra et al)*, assessing complete response and serious infections in patients taking GC with and without GC pulse during initial therapy for LN across arms of published RCTs. Data is presented as rates % (95% confidence intervals).
For oral prednisone at 25 mg/day plus GC pulses, the predicted rates of CR, and serious infections were **25.0** (10.4–39.6%)**, and 3.5** (2.6–4.4), respectively.
Increasing the dose of prednisone to 60 mg/day plus GC pulses, leads to higher rates of CR and serious infections, **42.1** (22.9–61.2), and **13.1** (10.1–16.2), respectively.

Evidence profile

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	P7.a Pulse IV glucocorticoids followed by moderate-high dose glucocorticoids	pulse IV glucocorticoids followed by low dose glucocorticoids	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Complete response												
2[1,2]	randomised trials	serious[a]	not serious	not serious	serious[b]	none	16/58 (27.6%)	18/55 (32.7%)	**RR 0.84** (0.51 to 1.39)	**52 fewer per 1,000** (from 160 fewer to 128 more)	⊕⊕◯◯ Low	
Partial response												
2[1,2]	randomised trials	serious[a]	not serious	not serious	serious[b]	none	22/58 (37.9%)	17/55 (30.9%)	**RR 1.24** (0.75 to 2.05)	**74 more per 1,000** (from 77 fewer to	⊕⊕◯◯ Low	

										325 more)		
Complete or partial response												
3[1,2,3]	randomised trials	serious[c]	not serious	not serious	very serious[b]	none	45/68 (66.2%)	38/65 (58.5%)	**RR 1.11** (0.70 to 1.76)	**64 more per 1,000** (from 175 fewer to 444 more)	⊕◯◯◯ very Low	
Proteinuria <500 mg/day												
1[1]	randomised trials	serious[d]	not serious	not serious	serious[b]	none	8/12 (66.7%)	10/15 (66.7%)	**RR 1.00** (0.58 to 1.71)	**0 fewer per 1,000** (from 280 fewer to 473 more)	⊕⊕◯◯ Low	
Adverse events												
1[2]	randomised trials	not serious	not serious	not serious	serious[b]	none	35/42 (83.3%)	30/39 (76.9%)	**RR 1.08** (0.87 to 1.35)	**62 more per 1,000** (from 100 fewer to 269 more)	⊕⊕⊕◯ Moderate	
Serious adverse events												
1[2]	randomised trials	not serious	not serious	not serious	serious[b]	none	8/42 (19.0%)	4/39 (10.3%)	**RR 1.86** (0.61 to 5.68)	**88 more per 1,000** (from 40 fewer to 480 more)	⊕⊕⊕◯ Moderate	
Infections												
1[3]	randomised trials	serious[e]	not serious	not serious	very serious[b]	none	3/10 (30.0%)	0/10 (0.0%)	**RR 7.00** (0.41 to 120.16)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕◯◯◯ very Low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. The risk of bias of Zeher 2011 is low and weight 53% (contributes 50% to the outcome) and the ROB of Bandhan 2022 is high and also contributes 50% to the outcome. Bandhan has high ROB because of concerns in randomization.

b. Very low number of patients in each arm. Very wide absolute CI. Small sample size

c. Bandhan has high ROB because of randomization process and Bharati has high ROB because of deviations from interventions.

d. High ROB because concerns in randomization process

e. It is only one study. the overall safety ROB is high because mainly deviations from interventions and the measurement of infection outcome

References

1.I, Bandhan. Outcome of low-dose prednisolone use for the induction of remission in lupus nephritis patients. Int J Rheum Dis ; 2022.

2.M, Zeher. Efficacy and safety of enteric-coated mycophenolate sodium in combination with two glucocorticoid regimens for the treatment of active lupus nephritis. . Lupus; 2011.

3.J, Bharati. Comparison of Two Steroid Regimens in Induction Therapy of Proliferative Lupus Nephritis: A Randomized Controlled Trial. . Indian J Nephrol. 2019 Sep-Oct; 2019.

Randomized clinical trials:

3

Comparative nonrandomized studies

-

Non-comparative studies:

-

Systematic review:

Figueroa-Parra, Gabriel et al. "Impact of Glucocorticoid Dose on Complete Response, Serious Infections, and Mortality During the Initial Therapy of Lupus Nephritis: A Systematic Review and Meta-Analysis of the Control Arms of Randomized Controlled Trials." Arthritis & rheumatology (Hoboken, N.J.), 10.1002/art.42920. 20 May. 2024, doi:10.1002/art.42920

Studies read and excluded:

P7b In SLE patients with active, newly diagnosed or flare of Class III/IV LN, is treatment with "X" compared to treatment with "Y" for initial therapy (detailed in table) associated with improved outcomes in pediatrics

Population:

- Active LN

Intervention:

- Pulse dose steroid + moderate-high dose corticosteroid

Comparator:

- Moderate-high dose corticosteroid

Outcomes:

- LN Flare
- Preservation of kidney function

Table 1: In SLE patients with active, newly diagnosed or flare of Class III/IV LN, is treatment with • Pulse dose steroid + moderate-high dose corticosteroid compared to treatment with Moderate-high dose corticosteroid for initial therapy associated with improved outcomes?

Study name (year) country	Study design	Population	Intervention details	Comparator details	Outcomes with available data	Outcomes measures	Outcome timepoint
Barron 1982 USA	Non-Randomized Study	Class 3,4 LN Pediatrics 11.4 +/- 3.6; high dose group 11.9 +/- 2.9 Multiple Ethnicities	Six daily pulses of methylprednisolone (30 mg/kg/day, not to exceed I gm/day), followed by prednisone orally, initially 2'mg/kg/day.	Oral high-dose prednisone therapy, initially 2 mg/kg/day.	LN Flare Preservation of kidney function	Risk ratio	3-6 months

Evidence summary: One non-randomized observational study addressed 7b. The study reported on LN flares with an absolute effect of 30 fewer per 1,000 (from 336 fewer to 624 more). Regarding preservation of kidney function, which was assessed by change in gfr (ml/min/l.73 m), it favored pulse steroids as it led to a less reduction. The outcome was based on very low certainty evidence due to risk of bias and imprecision.

Evidence summary from a systematic review: These results are extracted from a newly published systematic review *(Figueroa-Parra et al)*, assessing complete response and serious infections in patients taking GC with and without GC pulse during initial therapy for LN across arms of published RCTs. Data is presented as rates % (95% confidence intervals).
For oral prednisone at 60 mg/day (without pulses), the predicted rates of CR and serious infections were **34.6** (16.9–52.3), and **12.1**(9.3–14.9), respectively. Adding GC pulses for oral prednisone at 60 mg/day leads to higher rates of CR with **42.1** (22.9–61.2). However, it doesn't lead to a significant difference in the rates of serious infections with **13.1**(10.1–16.2).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pulse	No Pulse	Relative (95% CI)	Absolute (95% CI)		
LN Flares												
1[1]	non-randomised studies	serious[a]	not serious	not serious	very serious[b]	none	4/7 (57.1%)	9/15 (60.0%)	**RR 0.95** (0.44 to 2.04)	**30 fewer per 1,000** (from 336 fewer to 624 more)	⨁◯◯◯ Very low	CRITICAL
Preservation of kidney function (continous)												
1[1]	non-randomised studies	serious[a]	not serious	not serious	very serious[b]	none	7	15	-	MD **3 lower ml/min/l.73 m** (25.39	⨁◯◯◯ Very low	CRITICAL

										lower to 19.39 higher)		

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Risk of Bias was assessed using ROBINS-I, was assessed to be high due to confounding.

b. Imprecision due to Wide CI

References

1.Barron, K S, Person, D A, Brewer, E J Jr, Beale, M G, Robson, A M. Pulse methylprednisolone therapy in diffuse proliferative lupus nephritis.. The Journal of pediatrics; 1982.

Randomized clinical trials: None

Comparative nonrandomized studies: 1

Non-comparative studies: None

Systematic review:

Figueroa-Parra, Gabriel et al. "Impact of Glucocorticoid Dose on Complete Response, Serious Infections, and Mortality During the Initial Therapy of Lupus Nephritis: A Systematic Review and Meta-Analysis of the Control Arms of Randomized Controlled Trials." Arthritis & rheumatology (Hoboken, N.J.), 10.1002/art.42920. 20 May. 2024, doi:10.1002/art.42920

Studies read and excluded: None

P.7c In SLE patients with active, newly diagnosed or flare of Class III/IV LN, is treatment with pulse intravenous glucocorticoids followed by low dose glucocorticoids compared to moderate-high dose oral glucocorticoids associated with improved outcomes?

Population:

- Active Class III/IV LN

Intervention:

- Pulse intravenous glucocorticoids followed by low dose glucocorticoids

Comparator:

- Moderate-high dose oral glucocorticoids

Outcomes:

- Reduction of proteinuria
- Preservation of kidney function
- Risk of LN flares
- ESKD (dialysis or transplant)
- Treatment related adverse effects including infection; also decrease >30% from baseline eGFR for CNI's, depression/suicide for belimumab

Table 1: P.7c: pulse intravenous glucocorticoids followed by low dose oral glucocorticoids versus moderate-high dose oral glucocorticoids

Study name (year) country	Study design	Population	Intervention details	Comparator details	Outcomes with available data	Outcomes measures	Outcome timepoint
Yee 2003 European multicentre	Randomized Clinical Trial	LN patients Class 3: 11/29 (38%) Class 4: 18/29 (62%) Adults Age: Mean (SD) 32.2 (11.7) in continuous, 42.4 (11.8) in pulse Multiple ethnicities	Pulse intravenous glucocorticoids followed by low dose oral glucocorticoids Pulse CYC therapy IV 10 mg/kg three weekly for four doses, then orally at the same dose split over two days at four weekly intervals for 9 months, and finally at six weekly intervals for 12 months.	Moderate-high dose oral glucocorticoids Daily oral CYC 2 mg/kg/ day for 3 months. After 3 months, the oral CYC was changed to daily oral azathioprine 1.5 mg/kg/day.	ESKD Adverse events Infections	Risk ratio	3.7 years

Evidence summary: 1 randomized study address PICO 7.b question. Regarding adverse events and infections, the RR (CI) between the two regimens of glucocorticoids is 1.03 (0.40 to 2.61) and 0.98 (0.33 to 2.94), respectively, showing no difference between these two regimens, although the result is very imprecise and with very low quality of evidence. Concerning ESKD there is 76% less risk of ESKD with GC pulse + low dose GC strategy, RR 0.24 (0.01 to 4.65), although again the result is imprecise and with very low quality of evidence.

Evidence summary from a systematic review: These results are extracted from a newly published systematic review *(Figueroa-Parra et al)*, assessing complete response and serious infections in patients taking GC with and without GC pulse during initial therapy for LN across arms of published RCTs. Data is presented as rates % (95% confidence intervals).
For oral prednisone at 25 mg/day plus GC pulses, the predicted rates of CR, and serious infections were **25.0** (10.4–39.6), and **3.5%** (2.6–4.4), respectively.
Starting on prednisone at 60 mg/day even without GC pulses leads to higher rates of CR and serious infections, 34.6 (16.9–52.3), and 12.1(9.3–14.9), respectively.

Evidence profile

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	P.7c pulse intravenous glucocorticoids	moderate-high dose oral glucocorticoids	Relative (95% CI)	Absolute (95% CI)		

							followed by low dose oral glucocorticoids					
Adverse events												
1[1]	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	5/13 (38.5%)	6/16 (37.5%)	**RR 1.03** (0.40 to 2.61)	**11 more per 1,000** (from 225 fewer to 604 more)	⊕◯◯◯ Very low	
ESKD												
1[1]	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	0/13 (0.0%)	2/16 (12.5%)	**RR 0.24** (0.01 to 4.65)	**95 fewer per 1,000** (from 124 fewer to 456 more)	⊕◯◯◯ Very low	
Infection												
1[1]	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	4/13 (30.8%)	5/16 (31.3%)	**RR 0.98** (0.33 to 2.94)	**6 fewer per 1,000** (from 209 fewer to 606 more)	⊕◯◯◯ Very low	

confidence interval; **RR:** risk ratio

Explanations

a. Just one study with some concerns in ROB.

b.There was small sample size, sample number of events, and CI was very wide)

References:

1.Yee C-S. EULAR randomized controlled trial of pulse cyclophosphamide and methylprednisolone versus continuous cyclophosphamide and prednisolone followed by azathioprine and prednisolone in lupus nephritis. Ann Rheum Dis 2003;63:525–529. doi: 10.1136/ard.2002.003574.

Randomized clinical trials:

1

Comparative nonrandomized studies

-

Non-comparative studies:

Systematic review:

Figueroa-Parra, Gabriel et al. "Impact of Glucocorticoid Dose on Complete Response, Serious Infections, and Mortality During the Initial Therapy of Lupus Nephritis: A Systematic Review and Meta-Analysis of the Control Arms of Randomized Controlled Trials." Arthritis & rheumatology (Hoboken, N.J.), 10.1002/art.42920. 20 May. 2024, doi:10.1002/art.42920

Studies read and excluded:

P.7d In SLE patients with active, newly diagnosed or flare of Class III/IV LN, is treatment with RAAS-I compared to non-RAAS-I associated with improved outcomes?

Population:

- Active Class III/IV LN.

Intervention:

- RAAS-I

Comparator:

- No RAAS-I

Outcomes:

- Reduction of proteinuria
- Preservation of kidney function
- Risk of LN flares
- ESKD (dialysis or transplant)
- Treatment related adverse effects including infection; also decrease >30% from baseline eGFR for CNI's, depression/suicide for belimumab

Table 1: P.7d: RAAS versus No RAAS

Study name (year) country	Study design	Population	Intervention details	Comparator details	Outcomes with available data	Outcomes measures	Outcome timepoint
Daza 2005 Mexico	Randomized Clinical Trial	LN patients with proteinuria >0.5 g/day Class LN: not reported Adults Age (years) Group 1: 26.6(±10.1) Group 2: 23.5(±7.8) Ethnicity: not reported	RAAS-I All patients had been, for at least the last 6 months, on a regular LN treatment, consisting in daily oral corticosteroids and monthly parental (IV) cyclophosphamide.	No RAAS-I All patients had been, for at least the last 6 months, on a regular LN treatment, consisting in daily oral corticosteroids and monthly parental (IV) cyclophosphamide.	Proteinuria: Change from baseline Glomerular filtration rate: Change from baseline	Mean difference	6 months
Lu 2008 China	Non-randomized comparative study	LN patients with proteinuria	RAASI plus MMF	No RAAS-I plus MMF	Response (complete plus partial response)	RR	6 months

		mean (SD): 4.70 ± 2.37. Class 3,4 Adults					
Chang 2022	Non-randomized comparative study	Pediatric patients with LN	RAAS-I	No RAAS-I	Steroids discontinuation		

Evidence summary: One randomized study addresses the PICO 7.d question. Only two efficacy outcomes (continuous proteinuria and continuous glomerular filtration rate) are addressed by this study. All patients received the same immunosuppressive SOC treatment, but one group received RAAS-I and another group did not receive RAAS-I. Regarding proteinuria outcome, the patients in the RAAS-I arm showed a significant decrease in proteinuria (2.75 g/day less) at 24 weeks compared to those patients not receiving RAAS-I. Concerning glomerular filtration rate, patients in the RAAS-I arm showed higher rates at 24 weeks (25.33 ml/min higher) compared to those not receiving RAAS-I.
Two nonrandomized studies compared also RAAS-I versus NO RAAS-I, reporting on the response (complete or partial) which was higher in the RAAS-I group, and rate of Steroid discontinuation which was higher in RAAS-I arm. The overall certainty for the RCT is low and for the non-randomized study was very low.

Note:
There is a subgroup in the lupus GL project plan in this comparison (RAAS-I vs no RAAS-I): the subgroup is patients with proteinuria <0.5 g/day. However, there is no RCT addressing this comparison in that population. All the patients in Daza 2005 study have proteinuria >0.5 g/day (it was an inclusion criterion for them). In Lu 2008, all patients baseline proteinuria was 4.7 (2.37).

Evidence profile

Certainty assessment							№ of patients		Effect			
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**P.7d RAAS**	**No RAAS**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**	**Importance**
Proteinuria (Continuous)												
1[1]	randomised trials	serious[a]	not serious	not serious	serious[b]	none	9	9	-	MD **2.75 lower** (3.81 lower to 1.69 lower)	⨁⨁◯◯ Low	
GFR (Continuous)												
1[1]	randomised trials	serious[a]	not serious	not serious	serious[b]	none	9	9	-	MD **25.33 higher** (2.26 higher to	⨁⨁◯◯ Low	

										48.41 higher)		
Response (complete or partial)												
1	non-randomised studies	Serious[c]	not serious	not serious	very serious[b]	none	77/92 (83.7%)	99/191 (51.8%)	**RR 1.61** (1.37 to 1.90)	**316 more per 1,000** (from 192 more to 466 more)	⨁◯◯◯ Very low	
Steroids discontinuation												
1	non-randomised studies	Serious[c]	not serious	not serious	very serious[b]	none	NA	NA	**HR: 1.5 (1.1 to 3)**	**NA**	⨁◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference

Explanations

a. high ROB: Although they are randomized, at baseline the populations were different.

b. very wide CI in the overall result, small sample size.

c.We used ROBINs I and we downgraded for risk of bias because of concerns about confounding.

References

1. Daza, . Captopril effect on prostaglandin E2, thromboxane B2 and proteinuria in lupus nephritis patients. Prostaglandins & other Lipid Mediators 78 (2005) 194–201.doi:10.1016/j.prostaglandins.2005.08.001.

2. F L, Y T, X P, et al. A prospective multicentre study of mycophenolate mofetil combined with prednisolone as induction therapy in 213 patients with active lupus nephritis. Lupus. 2008;17(7):622-629. doi:10.1177/0961203308089428

3. Chang, Joyce C et al. "Use of renin angiotensin aldosterone system inhibitors in children with lupus and time to glucocorticoid discontinuation." *Kidney international* vol. 102,2 (2022): 395-404. doi:10.1016/j.kint.2022.04.023

Randomized clinical trials: 1
Comparative nonrandomized studies: 2
Non-comparative studies:
Studies read and excluded:

P.7e In SLE patients with active, newly diagnosed or flare of Class III/IV LN, is treatment with IV Cyclophosphamide (NIH protocol) compared to IV Cyclophosphamide (Eurolupus protocol) associated with improved outcomes?

Population:

- Active Class III/IV LN

Intervention:

- IV Cyclophosphamide (NIH protocol)

Comparator:

- IV Cyclophosphamide (Eurolupus protocol)

Outcomes:

- Reduction of proteinuria
- Preservation of kidney function
- Risk of LN flares
- ESKD (dialysis or transplant)
- Treatment related adverse effects including infection; also decrease >30% from baseline eGFR for CNI's, depression/suicide for belimumab

Table 1: P.7e: CYC (NIH) versus CYC (Eurolupus)

Study name (year) country	Study design	Population	Intervention details	Comparator details	Outcomes with available data	Outcomes measures	Outcome timepoint
Houssiau 2002 European multicenter	Randomized Control Trial	LN patients Class 3: 21/90 (23%), Class 4: 62/90 (68%), Class 5: 7/90 (7.7%) Adults Age: mean (SD): 31(11) Multiple ethnicities	CYC (NIH)	CYC (Eurolupus)	Complete response + Partial response LN flares ESKD Serious adverse events Infections	Risk ratio	48 weeks
Mehra 2018 India	Randomized Control Trial	LN patients Class 3: 28/75 (37%) Class 4: 47/75 (63%) Adults: Mean (SD) age: low-dose CYC 30.71 (10.04), high-dose 27.24 (10.60) Ethnicity: Asians	CYC (NIH)	CYC (Eurolupus)	Complete response Complete + partial response Infections Leukopenia	Risk ratio	52 weeks
Sahay 2018 India	Randomized Control Trial	LN patients Class 3: 18/96 (18%) Class 4: 45/96 (47%)	CYC (NIH)	CYC (Eurolupus)	Complete response Partial response ESKD	Risk ratio	24 weeks

		Class 3+5 or 4+5: 33/96 (34%) Adults: Mean age (years) NIH CYC 28.21±9.33 Eurolupus CYC: 29.25±10.50 Ethnicity: Not reported			Serious adverse events Infections Leukopenia		

Evidence summary:

Three RCTs compare NIH CYC vs Eurolupus CYC for initial treatment of class III/IV LN with low or very low-quality evidence, because of concerns about **risk of bias** (randomization: differences in the baseline characteristics of the patients and loss to follow up leading to missing data) and **imprecision** (small sample size, leading to wide confidence intervals).

Both strategies show similar rates of complete and partial responses. However, 2 studies evaluate the composite outcome complete + partial response (as one outcome) in which, the CYC NIH is associated with higher rates (38% higher) than the CYC Eurolupus.
Both treatments show similar rates of LN flares and progression to ESKD.
Regarding adverse events, there are similar rates of serious adverse events, infections, and leukopenia between both treatments.

N.B:

- Sahay 2018 is a 3-arm RCT, comparing CYC (NIH) versus CYC (Eurolupus) versus MMF. For this PICO question, we extracted data comparing CYC (NIH) versus CYC (Eurolupus) only.
- A minimally important difference was assumed to be 5%. This will be determined by the core team and the panel.

Evidence profile: RCT data

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CYC (NIH)**	**CYC (Eurolupus)**	**Relative (95% CI)**	**Absolute (95% CI)**		
Complete response												
2[1,2]	randomised trials	serious[a]	not serious	not serious	serious[b]	none	54/93 (58.1%)	34/78 (43.6%)	**RR 1.35** (1.00 to 1.84)	**153 more per 1,000** (from 0 fewer to 366 more)	⨁⨁◯◯ Low	
Partial response												

1[2]	randomised trials	serious[c]	not serious	not serious	very serious[d]	none	10/56 (17.9%)	9/40 (22.5%)	**RR 0.79** (0.36 to 1.77)	**47 fewer per 1,000** (from 144 fewer to 173 more)	⊕⊕◯◯ Low	

Complete plus partial response

2[1,3]	randomised trials	not serious	not serious	not serious	serious[b]	none	57/83 (68.7%)	41/82 (50.0%)	**RR 1.38** (1.06 to 1.79)	**190 more per 1,000** (from 30 more to 395 more)	⊕⊕⊕◯ Moderate	

LN flares

1[3]	randomised trials	not serious	not serious	not serious	very serious[d]	none	13/46 (28.3%)	12/44 (27.3%)	**RR 1.04** (0.50 to 1.82)	**11 more per 1,000** (from 136 fewer to 224 more)	⊕⊕◯◯ Low	

ESKD

2[2,3]	randomised trials	serious[a]	not serious	not serious	serious[b]	none	3/102 (2.9%)	2/84 (2.4%)	**RR 1.26** (0.21 to 7.53)	**6 more per 1,000** (from 19 fewer to 155 more)	⊕⊕◯◯ Low	

Serious adverse events

2[2,3]	randomised trials	serious[a]	not serious	not serious	serious[b,d]	none	3/102 (2.9%)	4/84 (4.8%)	**RR 0.70** (0.15 to 3.14)	**14 fewer per 1,000** (from 40 fewer to 102 more)	⊕⊕◯◯ Low	

Infection

3[1,2,3]	randomised trials	serious[e]	not serious	not serious	very serious[d,]	none	24/139 (17.3%)	20/122 (16.4%)	**RR 1.05** (0.58 to 1.76)	**8 more per 1,000** (from 69 fewer to 125 more)	⨁◯◯◯ Very Low	

Leukopenia

2[1,2]	randomised trials	serious[e]	not serious	not serious	very serious[b]	none	7/93 (7.5%)	14/78 (17.9%)	**RR 0.72** (0.09 to 5.53)	**50 fewer per 1,000** (from 163 fewer to 813 more)	⨁◯◯◯ Very Low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Sahay 2018 has high ROB because of concerns about randomization and missing data. The study contributes to 50% of the overall result.
b. We downgraded for imprecision once or twice depending on whether the CI crosses one side of the MID or both sides of the MID
c. Sahay 2018 is the only study that has high ROB mainly from the randomization process and missing data.
d. Very wide overall result CI
e. Mehra and Sahay studies with high ROB

References

1.S, Mehra. Comparing the efficacy of low-dose vs high-dose cyclophosphamide regimen as induction therapy in the treatment of proliferative lupus nephritis: a single center study. Rheumatology International (2018) 38:557–568 doi.org/10.1007/s00296-018-3995-3.
2.M, Sahay. Mycophenolate versus Cyclophosphamide for Lupus Nephritis. Indian J Nephrol 2018 Jan-Feb;28(1):35-40. doi: 10.4103/ijn.IJN_2_16..
3.F, Houssiau. The Euro-Lupus Nephritis Trial, a Randomized Trial of Low-Dose Versus High-Dose Intravenous Cyclophosphamide. ARTHRITIS & RHEUMATISM Vol. 46, No. 8, August 2002, pp 2121–2131 DOI 10.1002/art.10461 .

Randomized clinical trials:

3

Comparative nonrandomized studies

-

Non-comparative studies:

-

Studies read and excluded:

P7e In SLE patients (peds) with active, newly diagnosed or flare of Class III/IV LN, is treatment with “X” compared to treatment with “Y” for initial therapy (detailed in table) associated with improved outcomes in pediatrics

Population:

- Active LN

Intervention:

- CYC (NIH)

Comparator:

- CYC (Eurolupus)

Outcomes:

- Complete response
- Partial response
- Complete plus partial response
- Preservation of kidney function
- Infection
- Cytopenia

Table 1: In SLE patients with active, newly diagnosed or flare of Class III/IV LN, is treatment with CYC (NIH) compared to treatment with CYC (Eurolupus) for initial therapy (detailed in table) associated with improved outcomes in pediatrics

Study name (year) country	Study design	Population	Intervention details	Comparator details	Outcomes with available data	Outcomes measures	Outcome timepoint
Wang 2024 USA	Non-Randomized Study	Class 3,4 concomitant class 5 Pediatrics Mean age: 14.7 SD (2) Multiple Ethnicities	CYC (NIH)	CYC (Eurolupus)	Complete response Partial response Complete plus partial response Preservation of kidney function Infection Cytopenia	Risk ratio	12 months

Evidence summary: One non-randomized observational study addressed 7e. The study reported on Complete response with an absolute effect of 177 more per 1,000 (from 9 more to 468 more) favoring NIH protocol partial response with an absolute effect 51 more per 1,000 (from 98 fewer to 261 more), and complete plus partial response with an absolute effect 228 more per 1,000 (from 76 more to 414 more). Regarding preservation of kidney function, measure by difference in creatinine from baseline, the MD was 1.4 lower (13.04 lower to 10.24 higher). For infection the absolute effect was 11 fewer per 1,000 (from 69 fewer to 148 more) while for cytopenia favored Eurolupus protocol with an absolute effect of 92 more per 1,000 (from 6 fewer to 515 more). The outcomes were based on very low certainty evidence due to risk of bias and imprecision.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NIH	Eurolupus	Relative (95% CI)	Absolute (95% CI)		

Complete Response

1[1]	non-randomised studies	serious[a]	not serious	not serious	serious[b]	none	35/87 (40.2%)	13/58 (22.4%)	**RR 1.79** (1.04 to 3.09)	**177 more per 1,000** (from 9 more to 468 more)	⊕⊕◯◯ Low	

Partial response

1[1]	non-randomised studies	serious[a]	not serious	not serious	serious[b]	none	45/87 (51.7%)	27/58 (46.6%)	**RR 1.11** (0.79 to 1.56)	**51 more per 1,000** (from 98 fewer to 261 more)	⊕⊕◯◯ Low	

Complete plus partial response

1[1]	non-randomised studies	serious[a]	not serious	not serious	serious[b]	none	80/87 (92.0%)	40/58 (69.0%)	**RR 1.33** (1.11 to 1.60)	**228 more per 1,000** (from 76 more to 414 more)	⊕⊕◯◯ Low	

Infection

1[1]	non-randomised studies	serious[a]	not serious	not serious	serious[b]	none	8/87 (9.2%)	6/58 (10.3%)	**RR 0.89** (0.33 to 2.43)	**11 fewer per 1,000** (from 69 fewer to 148 more)	⊕⊕◯◯ Low	

Cytopenia

1[1]	non-randomised studies	serious[a]	not serious	not serious	serious[b]	none	11/87 (12.6%)	2/58 (3.4%)	**RR 3.67** (0.84 to 15.94)	**92 more per 1,000** (from 6 fewer to 515 more)	⊕⊕◯◯ Low	

Preservation of kidney function (continuous)

1[1]	non-randomised studies	serious[a]	not serious	not serious	serious[b]	none	87	58	-	MD **1.4 lower** (13.04 lower to 10.24 higher)	⨁⨁◯◯ Low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Risk of bias was assessed using ROBINS-I, was found to be critical due to confounding and selection bias.

b. Imprecision due to small number of patients

References

1.Wang, Christine S, Sadun, Rebecca E, Zhou, Wenru, Miller, Kristen R, Pyle, Laura, Ardoin, Stacey P, Bacha, Christine, Hause, Emily, Hui-Yuen, Joyce, Ling, Nicole, Pereira, Maria, Riebschleger, Meredith, Rouster-Stevens, Kelly, Sarkissian, Aliese, Shalen, Julia, Soulsby, William, Twilt, Marinka, Wu, Eveline Y, Lewandowski, Laura B, Wenderfer, Scott E, Cooper, Jennifer C, Nephritis, Childhood,Arthritis,and,Rheumatology,Research,Alliance,(CARRA),Lupus. Renal Response Outcomes of the EuroLupus and National Institutes of Health . Arthritis & rheumatology (Hoboken, N.J.); 2024.

Randomized clinical trials: None
Comparative nonrandomized studies: 1
Non-comparative studies: None
Studies read and excluded: None

P.7f In SLE patients with active, newly diagnosed or flare of Class III/IV LN, is treatment with IV CYC compared to oral CYC associated with improved outcomes?

Population:
- Active Class III/IV LN

Intervention:
- IV Cyclophosphamide (IV CYC)

Comparator:
- Oral Cyclophosphamide (oral CYC)

Outcomes:
- Reduction of proteinuria
- Preservation of kidney function
- Risk of LN flares
- ESKD (dialysis or transplant)
- Treatment-related adverse effects including infection; also decrease >30% from baseline eGFR for CNI's, depression/suicide for belimumab

Table 1: P.7f: IV CYC versus oral CYC							
Study name (year) country	**Study design**	**Population**	**Intervention details**	**Comparator details**	**Outcomes with available data (synthesis method/metric)**	**Outcome measures**	**Outcome timepoint**

Yee 2003 European centers	RCT	LN patients Class 3: 11/29 (38%). Class 4: 18/29 (62%)	IV CYC	oral CYC	ESKD Adverse events Infections Cytopenias	Risk ratio	3.7 years
Koo 2016 Korea	Nonrandomized study	Adults. Mean (SD): 31.2 +/- 9.8 LN class 3,4 concomitant	IV CYC	oral CYC	Remission	Risk ratio	
Mok 2001 China	Nonrandomized study	Adults, Class 3,4	IV CYC	oral CYC	Response, proteinuria, GFR, LN flare up	Risk ratio	24 months
Mok 2004 China	Nonrandomized study	Adults, Class 3,4	IV CYC	oral CYC	Response, LN flare up	Risk ratio	6 months

Evidence summary

Only one RCT study addresses the comparison between IV CYC vs oral CYC in initial treatment in LN Class III and IV. This study shows a similar progression to ESKD between both treatments. The rates of adverse events, infections, and cytopenia are similar between both treatments.
3 NRS assessed the response rate, proteinuria, GFR, and LN flare-up. The overall certainty of the evidence was very low due to concerns about the risk of bias and imprecision.

Evidence profile

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IV CYC**	**oral CYC**	**Relative (95% CI)**	**Absolute (95% CI)**		
ESKD												
1[1]	randomised trials	serious[a]	not serious	serious[b]	very serious[c]	none	0/13 (0.0%)	2/16 (12.5%)	**RR 0.23** (0.01 to 3.29)	**96 fewer per 1,000** (from 124 fewer to 286 more)	⨁◯◯◯ Very low	
Adverse events												
1[1]	randomised trials	serious[a]	not serious	serious[b]	very serious[c]	none	5/13 (38.5%)	6/16 (37.5%)	**RR 1.03** (0.40 to 2.61)	**11 more per 1,000** (from 225 fewer to	⨁◯◯◯ Very low	

										604 more)		

Infections

1[1]	randomised trials	serious[a]	not serious	serious[b]	very serious[c]	none	4/13 (30.8%)	5/16 (31.3%)	**RR 0.98** (0.33 to 2.94)	**6 fewer per 1,000** (from 209 fewer to 606 more)	⊕◯◯◯ Very low	

Cytopenia

1[1]	randomised trials	serious[a]	not serious	serious[b]	very serious[c]	none	1/13 (7.7%)	3/16 (18.8%)	**RR 0.41** (0.05 to 3.49)	**111 fewer per 1,000** (from 178 fewer to 467 more)	⊕◯◯◯ Very low	

Complete response

3	non-randomised studies	Serious[f]	not serious	not serious	serious	none	109/252 (43.3%)	83/130 (63.8%)	**RR 0.71** (0.57 to 0.89)	**185 fewer per 1,000** (from 275 fewer to 70 fewer)	⊕⊕◯◯ Low	

Partial response

2	non-randomised studies	Serious[f]	not serious	not serious	serious	none	32/118 (27.1%)	30/114 (26.3%)	**RR 1.06** (0.69 to 1.64)	**16 more per 1,000** (from 82 fewer to 168 more)	⊕⊕◯◯ Low	

Complete or partial response

2	non-randomised studies	Serious[f]	not serious	not serious	serious	none	85/118 (72.0%)	105/114 (92.1%)	**RR 0.78** (0.69 to 0.89)	**203 fewer per 1,000** (from 286 fewer to 101 fewer)	⊕⊕◯◯ Low	

Proteinuria (change from baseline g/day)

1	non-randomised studies	Serious[f]	not serious	not serious	serious	none	22	21	-	MD **0** (0.46 lower to	⊕⊕◯◯ Low	

										0.46 higher)		

LN flare up

2	non-randomised studies	Serious[f]	not serious	not serious	serious	none	24/118 (20.3%)	39/114 (34.2%)	**RR 0.57** (0.37 to 0.89)	**147 fewer per 1,000** (from 216 fewer to 38 fewer)	⊕⊕◯◯ Low	

GFR (change from baseline)

1	non-randomised studies	Serious[f]	not serious	not serious	serious	none	22	21	-	MD **7.9 lower** (12.84 lower to 2.96 lower)	⊕⊕◯◯ Low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Concerns in the randomization process and 14% loss of follow-up

b. The IV CYC group is not entirely "IV". Just the 4 first doses are IV, after that the CYC is oral. This decreases directness.

c. Very low sample, low number of events, and very wide CI

d. We downgraded for ROB because no adjustment for confounding was done.

e. Wide CI.

f. We used ROBINs I for assessment, we downgraded for ROB because outcomes were not adjusted for confounding.

References

1.Yee. EULAR randomised controlled trial of pulse cyclophosphamide and methylprednisolone versus continuous cyclophosphamide and prednisolone followed by azathioprine and prednisolone in lupus nephritis. Ann Rheum Dis 2003;63:525–529. doi: 10.1136/ard.2002.003574

2. Koo, H S et al. “Remission of proteinuria indicates good prognosis in patients with diffuse proliferative lupus nephritis.” *Lupus* vol. 25,1 (2016): 3-11. doi:10.1177/0961203315595130

3. Mok, Chi Chiu et al. “Predictors and outcome of renal flares after successful cyclophosphamide treatment for diffuse proliferative lupus glomerulonephritis.” *Arthritis and rheumatism* vol. 50,8 (2004): 2559-68. doi:10.1002/art.20364

4. Mok, C C et al. “Treatment of diffuse proliferative lupus glomerulonephritis: a comparison of two cyclophosphamide-containing regimens.” *American journal of kidney diseases : the official journal of the National Kidney Foundation* vol. 38,2 (2001): 256-64. doi:10.1053/ajkd.2001.26084

Studies included:

Randomized clinical trials: 1

Non-randomized comparative studies: 3

Single arm studies: none

P7.g In SLE patients with active, newly diagnosed or flare of Class III/IV LN, is treatment with Cyclophosphamide-containing regimen compared to treatment with MMF/MPA for initial therapy associated with improved outcomes?

Population: Patients with LN

Intervention: IV Cyclophosphamide-containing regimen

Comparison: MMF/MPA

Outcomes:

- Reduction of proteinuria
- Preservation of kidney function
- Risk of LN flares
- Cumulative steroid dose
- Treatment-related adverse effects including infection
- ESKD (dialysis or transplant)

Table 1.

P7.g Any (IV) CYC versus MMF/MPA

Study name (year) country	Study design	Population	Intervention details	Comparator details	Outcomes with available data	Outcome measures	Outcome timepoint
Sahay 2018 India	RCT	LN patients Adults/Pediatrics **Mean±SD age:** NIH: 28.21±9.327; ELNT: 29.25±10.497; MMF:22.21±5.89; (6% of the population was under age of 15) Ethnicity: South Asian Class 3: 27/144 (18.75%); Class 4: 66/144 (45.8%); Class 3/4+5: 51/144 (35.4%)	IV CYC	MMF	Complete response, ESKD, Serious adverse events, Infections, Leukopenia	Risk ratio	24 weeks / 6 months
Sedhain 2018 Nepal	RCT	LN patients Adults Mean±SD age: 25.43±10.17 Ethnicity: Asians Class 3/3+5: CYC 23.8%, MMF 19%; Class 4/4+5: CYC 76.2%, MMF 62%; Class 5: CYC 0%, MMF 19%	IV CYC	MMF	Complete response, Infections	Risk ratio	24 weeks / 6 months

Mendonca 2017 India	RCT	LN patients Adults Mean (SD) age: MMF 26.0 (10.8), IV CYC 25.7 (10.3) Ethnicity: Asians Class 3: MMF 5.9%, IV CYC 4.3%; Class 4: MMF 70.6%, IV CYC 65.2%; Class 5: MMF 11.7%, IV CYC 13.1%; Class 3/4+5: MMF 17.6%, IV CYC 17.4%	IV CYC	MMF	Complete response, Infections, Proteinuria (Continuous)	Risk ratio Mean difference	24 weeks / 6 months
Anutrakulchai 2015 Multicenter Asia	RCT	LN patients Adults Mean (SD) age: CYC 30.2(7.0); EC-MPS 35.4(12.9) Ethnicity: Asians All were class 3,4. Class 4/59. Class 4: 55/59.	IV CYC	EC-MPS	Complete response, Serious adverse events, Infections	Risk ratio	52 weeks / 12 months
Rathi 2016 India	RCT	LN patients Adults Ethnicity: Asians Mean (SD) age 30.6 (9.5) years in CYC group; 28.3 (9.5) in MMF group Class 3, 3/5: 17/100; Class 4, 4/5: 57/100; Class 5: 26/100	IV CYC	MMF	Complete response, Partial response, Complete + partial response, Adverse events	Risk Ratio	24 weeks / 6 months
El-Shafey 2010 Egypt	RCT	LN patients Adults/pediatrics	IV CYC	MMF	Complete response, Partial response, Complete + partial response, Adverse events leading to withdrawal,	Risk ratio, Mean difference	24 weeks / 6 months

		Age: Mean (range): 27 (15-55) Ethnicity not reported Class 3: 32% Class 4: 68%			Serious adverse events, ESKD, Infections, Leukopenia, Proteinuria (continuos)		
Isenberg 2010a International	RCT	LN patients Adults/Pediatrics Age: Mean (SD) age: MMF 32.2(11), IV CYC 28.8(10.2) Class 3: 10% Class 4: 24% Class 3/5: 14% Class 4/5: 30% Class 5: 21% Ethnicity: African Americans	IV CYC	MMF	Proteinuria (continuous)	Mean difference	24 weeks / 6 months
Isenberg 2010b International	RCT	LN patients Adults/Pediatrics Mean (SD) age: MMF 28.8(8.53), IV CYC 27.3(9.44) Class 3: 4% Class 4: 39% Class 3/5: 7% Class 4/5: 42% Class 5: 7% Ethnicity: Asians	IV CYC	MMF	Proteinuria (continuous)	Mean difference	24 weeks / 6 months
Isenberg 2010c International	RCT	LN patients Adults/Pediatrics Mean (SD) age: MMF 27.2 (11.01), IV CYC 26.6 (10.58) Class 3: 13/147 8.8%	IV CYC	MMF	Proteinuria (continuous)	Mean difference	24 weeks / 6 months

		Class 4: 98/147 66.6% Class 3/5: 9/147 6.1% Class 4/5: 8/147 5.4% Class 5: 19/147 12.9% Ethnicity: White					
Isenberg 2010d International	RCT	LN patients Adults/Pediatrics Mean (SD) age: MMF 27.2 (9.58), IV CYC 25.8 (8.74) Class 3: 6/54 11.1% Class 4: 25/54 46.3% Class 3/5: 4/54 7.4% Class 4/5: 8/54 14.8% Class 5: 11/54 20.4% Ethnicity: Other	IV CYC	MMF	Proteinuria (continuous)	Mean difference	24 weeks / 6 months
Wang 2007 China	RCT	LN patients Adults Age: Mean (SD): MMF: 32.2 +/- 12.0; CYC: 30.8 +/- 12.7 Ethnicity: Asians All are class 4 or 4+5. Proportions not reported.	IV CYC	MMF	Complete response, Infections, Proteinuria (continuous), Leukopenia	Risk ratio Mean difference	24 weeks / 6 months
Ginzler 2005 United States	RCT	LN patients Adults Age: Mean (SD)32+-10 (MMF), 31+-9 (CYC) class 3: 15%, class 4: 54% , class 5: 19%, mixed 11% Multiple ethnicities	IV CYC	MMF	Complete response, Partial response, Complete + partial response, ESKD, LN relapse, Infections, Leukopenia, Proteinuria (continuous)	Risk ratio Mean difference	24 weeks / 6 months
Appel 2009a (Overall)	RCT	LN patients	IV CYC	MMF	Complete Response, Adverse events, Serious	Risk ratio	24 weeks / 6 months

International		Adults/Pediatrics Age Mean (SD) age: 31.9 (10.7) III/III+V: 58 (15,7%), IV/IV+V 252 (68.1%), V only 60(16.2%) Multiple ethnicities			adverse events, Infections		
Appel 2009b (For class 3+4 (b))	RCT	LN patients III/III V: 58 (15,7%), IV/IV V 252 (68.1%), V only 60(16.2%) Adults Mean (SD) age: 31.9 (10.7) Multiple ethnicities	IV CYC	MMF	Partial response Complete + partial response	Risk ratio	24 weeks / 6 months
Ong 2005 Malaysia	RCT	Active lupus nephritis Adults/Pediatrics CYC: Age, 30.5 (8.7) CYC LN classes (n= 25): III: 2 (8%);III+IV: 0 (0%); IV: 17 (68%); IV+V: 6 (24%) MMF: Age, 31.3 (9.9) MMF LN classes (n=19): III: 2 (8%);III+IV: 0 (0%); IV: 17 (68%); IV+V: 6 (24%) Asians	IV CYC Induction CYC 0.75-1 g/m2 BSA monthly	MMF Induction MMF 2 g/day	Complete response, Partial response, Complete plus partial response, Leukopenia	Risk ratio	24 weeks / 6 months
Li 2012 China	RCT	Active Lupus Nephritis Adults/Pediatrics TAC (n=20): Age, 29 (17-50) MMF (n=20): 26.5 (16-62) CYC (= 20): 33 (17-64) TAC: Class III/IV (65%); Class III/IV+V (25%); Class V (10%) MMF: Class III/IV (70%); Class III/IV+V (15%); Class V (15%)	IV CYC CYC (IV): 0.5-0.75g/m2 BSA monthly.	MMF 1.5g/d (<=55kg) or 2g/d (>55kg).	Complete response, Partial response, Complete + partial response, Infection, Leukopenia	Risk ratio	24 weeks / 6 months

		CYC: Class III/IV (65%); Class III/IV+V (20%); Class V (15%) Asians					

Evidence summary: There were 12 RCTs with data for comparing IV CYC versus MMF in patients with class III/IV LN. Eleven and 10 studies showed similar rates of complete or partial renal response at 6 months between CYC-containing regimens and MMF/MPA, with moderate-low certainty of the evidence, affected by risk of bias and imprecision. Adverse events (overall and serious) also were similar between CYC and MMF with low or very low certainty. Infections were pooled from 9 RCTs, demonstrating a higher rate in CYC regimens. ESKD was rare at 6 months and the analysis did not show differences between CYC and MMF/MPA, because of important imprecision due to the small number of events and patients pooled.

Evidence profile:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**(IV) CYC**	**MMF/MPA**	**Relative (95% CI)**	**Absolute (95% CI)**		
Complete response												
11	randomised trials	serious[a]	not serious	not serious	not serious	none	174/547 (31.8%)	162/486 (33.3%)	**RR 0.93** (0.78 to 1.11)	**23 fewer per 1,000** (from 73 fewer to 37 more)	⊕⊕⊕◯ Moderate	
Partial response												
10	randomised trials	serious[a]	not serious	not serious	serious[b]	none	91/332 (27.4%)	89/277 (32.1%)	**RR 0.89** (0.70 to 1.14)	**35 fewer per 1,000** (from 96 fewer to 45 more)	⊕⊕◯◯ Low	
Complete plus partial response												
7	randomised trials	serious[a]	not serious	not serious	serious	none	234/423 (55.3%)	228/378 (60.3%)	**RR 0.92** (0.82 to 1.03)	**48 fewer per 1,000** (from 109 fewer to 18 more)	⊕⊕◯◯ Low	
Adverse events												
2	randomised trials	serious[c]	not serious	not serious	not serious	none	268/308 (87.0%)	293/322 (91.0%)	**RR 0.98** (0.95 to 1.02)	**18 fewer per 1,000**	⊕⊕⊕◯ Moderate	

										(from 45 fewer to 18 more)		

Adverse events leading to withdrawal

2	randomised trials	serious[a]	serious[e]	not serious	very serious[b,d,f]	none	1/37 (2.7%)	3/34 (8.8%)	**RR 0.42** (0.06 to 3.10)	**51 fewer per 1,000** (from 83 fewer to 185 more)	⊕◯◯◯ Very low	

Serious adverse events

4	randomised trials	serious[c]	not serious	not serious	not serious	none	44/421 (10.5%)	50/391 (12.8%)	**RR 0.96** (0.67 to 1.36)	**5 fewer per 1,000** (from 42 fewer to 46 more)	⊕⊕⊕◯ Moderate	

ESKD

4	randomised trials	serious[a]	not serious	not serious	serious[b,d,f]	none	10/200 (5.0%)	7/163 (4.3%)	**RR 1.32** (0.50 to 3.47)	**14 more per 1,000** (from 21 fewer to 106 more)	⊕⊕◯◯ Low	

LN relapse

1	randomised trials	not serious	not serious	not serious	very serious[d,f]	none	8/69 (11.6%)	8/71 (11.3%)	**RR 1.03** (0.41 to 2.59)	**3 more per 1,000** (from 66 fewer to 179 more)	⊕⊕◯◯ Low	

Infections

9	randomised trials	serious[c]	not serious	not serious	not serious	none	149/481 (31.0%)	100/433 (23.1%)	**RR 1.55** (1.30 to 1.86)	**127 more per 1,000** (from 69 more to 199 more)	⊕⊕⊕◯ Moderate	

Leukopenia

6	randomised trials	serious[c]	not serious	not serious	serious[d,f]	none	48/249 (19.3%)	31/201 (15.4%)	**RR 1.47** (1.00 to 2.16)	**72 more per 1,000** (from 0 fewer to 179 more)	⊕⊕◯◯ Low	

Proteinuria (change from baseline)

5	Randomized trials	serious[c]	not serious	not serious	serious[b]	none	261	265	-	MD **0.05 higher** (0.51 lower to 0.59 higher)	⊕⊕◯◯ Low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Concerns on randomization and missing data.

b. Unable to discriminate clinically significant difference, 95% C.I. crosses 5% minimally important difference.

c. Concerns with randomization, missing data, and outcome ascertainment.

d. Small sample size.

e. One study address adult population and other pediatric population.

f. Small number of events.

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Included studies:
Randomized clinical trials: 12
Comparative non-randomized studies: none
Non-comparative studies (single arm): none
Studies read and exclude: none

P7g In SLE (peds) patients with active, newly diagnosed or flare of Class III/IV LN, is treatment with "X" compared to treatment with "Y" for initial therapy (detailed in table) associated with improved outcomes in pediatrics

Population:
- Active LN

Intervention:
- IV CYC

Comparator:
- MMF

Outcomes:
- Complete response
- Partial response
- Complete plus partial response
- Preservation of kidney function
- LN Flares

Table 1: In SLE patients with active, newly diagnosed or flare of Class III/IV LN, is treatment with IV CYC compared to treatment with MMF for initial therapy (detailed in table) associated with improved outcomes in pediatrics

Study name (year) country	Study design	Population	Intervention details	Comparator details	Outcomes with available data	Outcomes measures	Outcome timepoint
Basu 2016 India	Non-Randomized Study	Class 3,4,5 Pediatrics Range in age: 3.5-13.8 South Asia	CYC pulses 500mg/m2 once every forthnight	MMF 1200mg/m2 daily	•Complete response •Partial response •Complete plus partial response •Preservation of kidney function •LN Flares	Risk ratio	1 month

Demir 2022 Turkey	Non-Randomized Study	Class 3,4 concomitant class 5, 5 Pediatrics Mean age:13.3 (10.4–15.8)	500–1000 mg/m2/day (maximum 750 mg/dose) for three to six doses	Orally at a dose of 1200 mg/m2	Complete response •Partial response •Complete plus partial response LN Flares	Risk ratio	NA
Chen 2023 Taiwan	Non-Randomized Study	Class 3,4 concomitant class 5, 5 Pediatrics Mean age:13.9 (12.2-16.1)	500- 1000 mg/m2 monthly for 6 months	Twice a day at 300-600 mg/m2	•Complete response •Partial response •Complete plus partial response	Risk ratio	6 months

Evidence summary: Three non-randomized observational studies addressed 7g. The study reported on Complete response with an absolute effect of 55 more per 1,000 (from 120 fewer to 315 more), partial response with an absolute effect 75 fewer per 1,000 (from 205 fewer to 154 more), and complete plus partial response with an absolute effect 45 fewer per 1,000 (from 161 fewer to 98 more). Regarding preservation of kidney function, which was reported by Basu et al, which favored IV CYC with an absolute effect 53 more per 1,000 (from 218 fewer to 458 more), as well as LN flare with an absolute effect 50 more per 1,000 (from 106 fewer to 570 more). The outcomes were based on very low certainty evidence due to risk of bias and imprecision.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV CYC	MMF	Relative (95% CI)	Absolute (95% CI)		
Complete response												
3[1,2,3]	non-randomised studies	serious[a]	not serious	not serious	very serious[b]	none	30/53 (56.6%)	19/38 (50.0%)	**RR 1.11** (0.76 to 1.63)	**55 more per 1,000** (from 120 fewer to 315 more)	⨁◯◯◯ Very low	CRITICAL
Partial response												
3[1,2,3]	non-randomised studies	serious[a]	not serious	not serious	very serious[b]	none	15/53 (28.3%)	15/38 (39.5%)	**RR 0.81** (0.48 to 1.39)	**75 fewer per 1,000** (from 205 fewer to 154 more)	⨁◯◯◯ Very low	CRITICAL

Complete plus partial response

3[1,2,3]	non-randomised studies	serious[a]	not serious	not serious	very serious[b]	none	45/53 (84.9%)	34/38 (89.5%)	**RR 0.95** (0.82 to 1.11)	**45 fewer per 1,000** (from 161 fewer to 98 more)	⊕◯◯◯ Very low	CRITICAL

Preservation of kidney function

1[2]	non-randomised studies	serious[a]	not serious	not serious	very serious[b]	none	12/15 (80.0%)	9/12 (75.0%)	**RR 1.07** (0.71 to 1.61)	**53 more per 1,000** (from 218 fewer to 458 more)	⊕◯◯◯ Very low	CRITICAL

LN Flare

2[1,2]	non-randomised studies	serious[a]	not serious	not serious	very serious[b]	none	7/37 (18.9%)	4/23 (17.4%)	**RR 1.29** (0.39 to 4.28)	**50 more per 1,000** (from 106 fewer to 570 more)	⊕◯◯◯ Very low	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Risk of bias was assessed using ROBINS-I, was found to be critical due to confounding and selection bias.

b. Wide CI crossing both MID

References

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Randomized clinical trials:
Comparative nonrandomized studies
3
Non-comparative studies:
Studies read and excluded:

P.7h In SLE patients with active, newly diagnosed or flare of Class III/IV LN, is treatment with IV CYC compared to MMF + CNI associated with improved outcomes?

Population:
- Active Class III/IV LN

Intervention:
- IV Cyclophosphamide (IV CYC)

Comparator:
- MMF + Calcineurin inhibitors

Outcomes:
- Reduction of proteinuria
- Preservation of kidney function
- Risk of LN flares
- ESKD (dialysis or transplant)
- Treatment related adverse effects including infection; also decrease >30% from baseline eGFR for CNI's, depression/suicide for belimumab

Table 1. Included studies.

Study name (year) Country	Study design	Population	Intervention details	Comparator details	Outcomes with available data	Outcome measures	Outcome timepoint
Bao 2008 China	Randomized controlled trial	LN patients Adults Age: CYC: 30.6 ± 4.6; MMF: 27.2 ± 7.1 Class: All concomitant IV+V. Asians	IV CYC (NIH protocol)	MMF + CNI (tacrolimus) MMF 2 g/day Tacrolimus: (target blood levels within 5 to 7 ng/ml)	Complete response, Proteinuria, Infections	Risk Ratio Mean difference	6 months (Some patients at 9 months, but it doesn't say how many)
Liu 2015 China	Randomized controlled trial	LN patients Adults Age: 31.9 (24.1- 40.5) Class III 19/362 (5.2%); Class IV 150/362 (41.4%); Class V 69/362 (19.1); Class III+V 26/362 (7.2); Class IV+V 98/362 (27.1) Ethnicity: Asian	IV CYC (NIH protocol) IV CYC was initiated at a dose of 0.75 g/m^2 body surface area and then adjusted to a dose of 0.5 to 1.0 g/m^2 body surface area	MMF (0.5 g twice daily) + Tacrolimus (2 mg twice daily)	Complete response, Partial response, Complete + Partial response, Change in Proteinuria, Change in eGFR, Adverse events, Serious adverse events, Adverse events leading to withdrawal, Infection, Leukopenia, >30%	Risk ratio Mean difference	24 weeks / 6 months

			every 4 weeks for 6 doses.		reduction from baseline eGFR		
Ye 2022 China	Randomized controlled trial	LN patients Adults Age: CYC 30.6 ± 8.7; MMF 31.2±9.3. Class: CYC:3+5: 12, 4+5: 16 MMF+TAC:3+5: 13, 4+5: 15 Ethnicity: Asian	IV CYC (NIH protocol)	MMF + CNI (tacrolimus) MMF: 20-30 mg/kg day TAC: 0.06-0.08 mg/kg day	Complete response, Partial response, Proteinuria, Adverse events, Infections	Risk ratio Mean difference	72 weeks

Evidence summary: There were only three RCTs for the comparison of CYC-containing regimens versus MMF/MPA plus CNI. All the RCT arms of MMF/MPA + CNI used tacrolimus. Overall, the complete response was more likely in those patients receiving MMF+CNI than those on CYC arms. There were similar partial and complete plus partial responses. The change in proteinuria after treatment was greater for those patients on MMF+CNI. The risk of adverse events (overall and serious) was similar for both interventions. Infections were also similar between CYC-containing regimens and MMF+CNI. The overall certainty was judged as low to very low due to concerns about imprecision and the risk of bias (loss to follow-up).

Evidence profile

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IV CYC**	**MMF + CNI**	**Relative (95% CI)**	**Absolute (95% CI)**		
Complete response												
3	randomised trials	serious[d]	not serious[a]	not serious	serious	none	35/131 (26.7%)	62/131 (47.3%)	**RR 0.58** (0.42 to 0.80)	**199 fewer per 1,000** (from 275 fewer to 95 fewer)	⨁⨁◯◯ Low	
Partial response												
2	randomised trials	serious[d]	not serious	not serious	very serious[c]	none	41/111 (36.9%)	28/111 (25.2%)	**RR 1.85** (0.62 to 5.55)	**214 more per 1,000** (from 96 fewer to 1,000 more)	⨁◯◯◯ very Low	

Complete plus Partial Response

1	randomised trials	serious[d]	not serious	not serious	serious[c]	none	60/85 (70.6%)	68/84 (81.0%)	**RR 0.87** (0.73 to 1.04)	**105 fewer per 1,000** (from 219 fewer to 32 more)	⊕⊕◯◯ Low	

Proteinuria

3	randomised trials	not serious	not serious	not serious	serious	none	227	228	-	MD **0.95 higher** (0.41 higher to 1.49 higher)	⊕⊕⊕◯ Moderate	

Change in eGFR (continous)

1	randomised trials	not serious	not serious	not serious	very serious[b,c]	none	181	181	-	MD **3.96 higher** (3.35 lower to 11.27 higher)	⊕⊕◯◯ Low	

Adverse events

2	randomised trials	serious[d]	not serious	not serious	very serious[c]	none	110/209 (52.6%)	97/209 (46.4%)	**RR 1.48** (0.64 to 3.43)	**223 more per 1,000** (from 167 fewer to 1,000 more)	⊕◯◯◯ very Low	

Serious Adverse Events

1	randomised trials	serious[d]	not serious	not serious	very serious[c]	none	5/181 (2.8%)	13/181 (7.2%)	**RR 0.38** (0.14 to 1.06)	**45 fewer per 1,000** (from 62 fewer to 4 more)	⊕◯◯◯ very Low	

Adverse Events leading to Withdrawal

1	randomised trials	serious[d]	not serious	not serious	very serious[c]	none	3/181 (1.7%)	10/181 (5.5%)	**RR 0.30** (0.08 to 1.07)	**39 fewer per 1,000** (from 51 fewer to 4 more)	⊕◯◯◯ very Low	

Infections

3	randomised trials	serious[d]	not serious[a]	not serious	serious	none	53/229 (23.1%)	54/229 (23.6%)	**RR 1.01** (0.63 to 1.63)	**2 more per 1,000** (from 87 fewer to 149 more)	⊕⊕◯◯ Low	

Leukopenia

1	randomised trials	serious[d]	not serious	not serious	serious[c]	none	12/181 (6.6%)	1/181 (0.6%)	**RR 12.00** (1.58 to 91.33)	**61 more per 1,000** (from 3 more to 499 more)	⊕⊕◯◯ Low	

>30% reduction from baseline GFR

1	randomised trials	serious[d]	not serious	not serious	very serious[c]	none	0/181 (0.0%)	2/181 (1.1%)	**RR 0.20** (0.01 to 4.14)	**9 fewer per 1,000** (from 11 fewer to 35 more)	⊕◯◯◯ very Low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Difference in follow-up, one study report results at 72 weeks (Ye 2022) versus 24 weeks (Bao 2008 & Liu 2015)

b. Small sample size.

c. Unable to discriminate minimally important difference. A small number of events

d. Concerns on missing data and outcome ascertainment.

References:

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Randomized clinical trials: 3

Comparative nonrandomized studies: None

Non-comparative studies: None

Studies read and excluded:

P.7h.o,p.q.cc In SLE patients with active, newly diagnosed or flare of Class III/IV LN, is treatment with IV CYC compared to MMF + CNI associated with improved outcomes?

Intervention:
- CNI plus MMF

Outcomes:
- Reduction of proteinuria
- Preservation of kidney function
- Risk of LN flares
- ESKD (dialysis or transplant)
- Treatment related adverse effects including infection; also decrease >30% from baseline eGFR for CNI's, depression/suicide for belimumab.

Patient important outcomes (addressed in the study only):
- Complete renal response
- Partial renal response
- Proteinuria
- Creatinine / eGFR
- Relapse
- Adverse events

Table 1. Pico 7. CNI plus MMF in LN in pediatric population

Study name (year) country	Study design	Population	Intervention details	Comparator details	Outcomes with available data	Outcome measures	Outcome time point
Zheng, 2023 China	Single arm	LN patients 34/36 were biopsied III:3/34, IV:10/34, V:1/34, V+III:5/34, V+IV:15/34 Age: mean ± SD: 11 (8-12) Ethnicity: Asians	**MMF** was initiated at 10–15 mg/kg.d (maximum 1 g/d), twice daily (every 12 h). The dosage was titrated to maintain an area under the time concentration curve (AUC) from 0 to 12 h of MMF between 20 and 45 mg.h/L. **Tacrolimus** was initiated at 0.1 mg/kg.d (maximum 4 mg/d),	There is no comparator (single arm study)	Complete response Partial response Proteinuria Creatinine eGFR Flares Adverse events (decrease in eGFR and infections)	Proportions	CRR, PRR, proteinuria, creatinine, eGFR: 6 and 12 months eGFR: 24 months Flares, adverse events: Follo-up time: 37.5 months

			twice daily (every 12 h), maintaining a blood concentration between 5 and 7 ng/mL.				

Evidence summary:
This single-arm study evaluated multitarget therapy in 36 Chinese children with lupus nephritis as initial therapy with debut disease but also refractory to conventional therapy.
In terms of efficacy, there were 21% and 66.7% complete response rates at 6 and 12 months, respectively.
Proteinuria decreased by at least 2 grams in 24 hours (a significant decrease compared to baseline) at 6 and 12 months.
The glomerular filtration rate decreased at 6 months, but not significantly compared to baseline values. But at 12 and 24 months eGFR maintained stable values.
The follow-up period was 37.5 months (IQR 14.0-53.3), in which the LN relapse rate was 5/36 (13.8%).
The infection rate was 11.1% throughout the follow-up period.

Outcomes (Name + Summary)	Author, year, RefID	Study type	Duration of follow up	Population (number and description, age)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Complete renal response (CRR)	Zheng, 2023. (ID: 10270)	Non-comparative	6 months	- Patients with LN III, IV, III+V, IV+V.	**MMF** was initiated at 10–15 mg/kg.d (maximum 1 g/d), twice daily (every 12 h). The dosage was titrated to maintain an area under the time concentration curve (AUC) from 0 to 12 h of MMF between 20 and 45 mg.h/L. **Tacrolimus** was initiated at 0.1 mg/kg.d (maximum 4 mg/d), twice daily (every 12 h), maintaining a blood concentration between 5 and 7 ng/mL.	CRR: 22/36 (61%)	CRR was defined as the level of 24-h-UP less than 0.5 g, normal level of eGFR or no more than 10% above baseline values. There were 36 patients. 8 received multitarget therapy at the beginning because they had V component (III + V or IV + V). 28 received MMF or CYC at the beginning. They didn't achieve CRR at 6 months. After that they received multitarget therapy. **But the results are after receiving multitarget therapy. (index date: Beginning of multitarget therapy)**

Complete renal response (CRR)	Zheng, 2023. (ID: 10270)	Non-comparative	12 months	- Patients with LN III, IV, III+V, IV+V.	MMF + Tacrolimus at the same dose describe above.	CRR: 24/36 (66.7%)	CRR was defined as the level of 24-h-UP less than 0.5 g, normal level of eGFR or no more than 10% above baseline values.
Partial renal response (PRR)	Zheng, 2023. (ID: 10270)	Non-comparative	6 months	- Patients with LN III, IV, III+V, IV+V.	MMF + Tacrolimus at the same dose describe above.	PRR: 12/36 (33.3%)	Partial remission (PR) was defined as the level of 24-h-UP decreased by more than 50% and below the level of non-nephrotic range, with a stable or improved level of eGFR
Partial renal response (PRR)	Zheng, 2023. (ID: 10270)	Non-comparative	12 months	- Patients with LN III, IV, III+V, IV+V.	MMF + Tacrolimus at the same dose describe above.	PRR: 8/36 (22.2%)	Partial remission (PR) was defined as the level of 24-h-UP decreased by more than 50% and below the level of non-nephrotic range, with a stable or improved level of eGFR
Proteinuria	Zheng, 2023. (ID: 10270)	Non-comparative	6 months	- Patients with LN III, IV, III+V, IV+V.	MMF + Tacrolimus at the same dose describe above.	Proteinuria in gr as median (IQR) Baseline: 2.45 (1.76–5.76) 6 months*: 0.10 (0.10–0.30)	The proteinuria was 24h proteinuria.
Proteinuria	Zheng, 2023. (ID: 10270)	Non-comparative	12 months	- Patients with LN III, IV, III+V, IV+V.	MMF + Tacrolimus at the same dose describe above.	Proteinuria in gr median (IQR) Baseline: 2.45 (1.76–5.76) 12 months*: 0.10 (0.09–0.19)	The proteinuria was 24h proteinuria. The proteinuria was 24h proteinuria.
SCR (μmol/L)	Zheng, 2023. (ID: 10270)	Non-comparative	6 months	- Patients with LN III, IV, III+V, IV+V.	MMF + Tacrolimus at the same dose describe above.	Scr in umol/L median (IQR) Baseline: 50.0 (41.0–55.5) 6 months: 55.0 (40.8–64.3)	

SCR (μmol/L)	Zheng, 2023. (ID: 10270)	Non-comparative	12 months	- Patients with LN III, IV, III+V, IV+V.	MMF + Tacrolimus at the same dose describe above.	Scr in umol/L median (IQR) Baseline: 50.0 (41.0–55.5) 12 months: 46.5 (42.0–58.0)	
eGFR (ml/min/1.73 m2)	Zheng, 2023. (ID: 10270)	Non-comparative	6 months	- Patients with LN III, IV, III+V, IV+V.	MMF + Tacrolimus at the same dose describe above.	eGFR in ml/min median (IQR) Baseline: 104.7 (91.0–125.3) 6 months: 95.5 (86.3–115.7)	
eGFR (ml/min/1.73 m2)	Zheng, 2023. (ID: 10270)	Non-comparative	12 months	- Patients with LN III, IV, III+V, IV+V.	MMF + Tacrolimus at the same dose describe above.	eGFR in ml/min median (IQR) Baseline: 104.7 (91.0–125.3) 12 months: 107.8 (93.2–119.0)	
Flare or relapse	Zheng, 2023. (ID: 10270)	Non-comparative	37.5 months (IQR 14.0–53.3)	- Patients with LN III, IV, III+V, IV+V.	MMF + Tacrolimus at the same dose describe above.	5/36 (13.8%)	Proteinuric relapse was defined as the level of 24-h-UP increasing to more than 1 g after CR or more than 2 g after PR. Nephritic relapse was defined as the level of SCR increasing by more than 30% (or the level of eGFR decreasing by more than 10%), accompanied by the number of urinary red blood cells per high-power field of more than ten, which was glomerular hematuria after remission. The follow-up time of 36 children was 37.5 (IQR 14.0–53.3) months.

Adverse event (Decrease in eGFR)	Zheng, 2023. (ID: 10270)	Non-comparative	24 months	- Patients with LN III, IV, III+V, IV+V.	MMF + Tacrolimus at the same dose describe above.	eGFR (ml/min) median (IQR) baseline: 104.7 (91.0–125.3) 24 months: 112.2 (88.2–127.8)	This is the longest follow up that the eGFR is reported (24 months)
Adverse event (Infection)	Zheng, 2023. (ID: 10270)	Non-comparative	37.5 months (IQR 14.0–53.3)	- Patients with LN III, IV, III+V, IV+V.	MMF + Tacrolimus at the same dose describe above.	4/36 (11.1)	Infection including pneumonia, CMV infection, intestinal fungal infection, and paronychia was observed in one case each, all of them recovered after antibiotic treatments and discontinuation of multi-target therapy.

Reference: Zheng, X., Ouyang, X., Cheng, C. *et al.* Efficacy and safety of multi-target therapy in children with lupus nephritis. *Pediatr Res* **94**, 2040–2046 (2023). https://doi.org/10.1038/s41390-023-02747-3

P.7i In SLE patients with active, newly diagnosed or flare of Class III/IV LN, is treatment with IV CYC compared to CNI associated with improved outcomes?

Population:
- Active Class III/IV LN

Intervention:
- IV Cyclophosphamide (IV CYC)

Comparator:
- Calcineurin inhibitors

Outcomes:
- Reduction of proteinuria
- Preservation of kidney function
- Risk of LN flares
- ESKD (dialysis or transplant)
- Treatment-related adverse effects including infection; also decrease >30% from baseline eGFR for CNI's, depression/suicide for belimumab

Table 1

P7.i IV CYC versus CNI for initial treatment of SLE patients with Class III/IV							
Study name (year) Country	**Study design**	**Population**	**Intervention details**	**Comparator details**	**Outcomes with available data**	**Outcome measures**	**Outcome timepoint**
Chen 2011 China	RCT	Active Lupus Nephritis Adults Age(y): TAC 32.0 (10.8); IV CYC 31.9 (10.1) Class III TAC/IV CYC 2(4.8) /1(2.6) Class IV 29(69.0)/ 29(74.4) Class V 5(11.9)/ 4(10.3) Class V+IV or V+III 6(14.2)/ 5(12.8) Asians	IV CYC (NIH protocol) 750 mg/m2 of body surface area, then adjusted to 500-1,000 mg/m2 of body surface area every 4 weeks to maintain a nadir leukocyte count of 2.5-4.0 109/L for a total of 6 pulses	CNI (Tacrolimus) Tacrolimus 0.05 mg/kg/d divided into 2 daily doses at 12-hour intervals, and the dosage was titrated to achieve 12-hour trough blood concentrations of 5-10 ng/mL	Complete response, Partial response, Level of proteinuria (continuous), GFR, Serious adverse events, Infections, Leukopenia.	Risk ratio Mean difference	24 weeks / 6 months
Li 2012 China	RCT	Active Lupus Nephritis Adults/Pediatrics TAC (n=20): Age, 29 (17-50) MMF (n=20): 26.5 (16-62) CYC (= 20): 33 (17-64) TAC: Class III/IV (65%); Class III/IV+V (25%); Class V (10%) MMF: Class III/IV (70%); Class III/IV+V (15%); Class V (15%) CYC: Class III/IV (65%); Class III/IV+V (20%); Class V (15%) Asians	IV CYC (NIH protocol) CYC (IV): 0.5-0.75g/m^2 BSA monthly.	CNI (Tacrolimus) TAC: Initial dose of 0.08-0.1 mg/kg/d administered orally in two divided doses and was titrated to maintain 12-h trough levels at 6-8 ng/mL.	Complete response, Partial response, Complete + partial response, Infection, Leukopenia	Risk ratio	24 weeks / 6 months

Li 2022 China	RCT	Active Lupus Nephritis Adults/Pediatrics Mean (SD): CNI: 48.06±7.13, CYC:47.83±9.01 Classes not reported Asians	IV CYC (NIH protocol)	Calcineurin inhibitor (CNI) Tacrolimus	Complete response, Partial response, Complete + partial response, Leve lof proteinuria (continuous), Adverse events	Risk ratio Mean difference	52 weeks / 12 months
Zheng 2022	RCT	Active Lupus Nephritis Adults TAC (n= 158): Age, 34.3 (9.6) CYC (n= 156): Age, 34.1 (9.4) TAC: Class III (5%); Class IV (41%); Class III+V (11%); Class IV+V (29%); Class V (14%) CYC: Class III (5%); Class IV (37%); Class III+V (11%); Class IV+V (25%); Class V (13%) Asians	IV CYC (NIH Protocol) CYC (IV): 0.75 g/m2 BSA; thereafter, the target was 0.5 to 1.0 g/m2 BSA every 4 wks	Calcineurin Inhibitor (Tacrolimus) TAC: 4 mg/d. target trough level, 4-10 ng/mL	Complete response, Partial response, Complete + partial response, Level of proteinuria (continuous), Infection, Cytopenia, Leukopenia	Risk ratio Mean difference	24 weeks / 6 months

Evidence summary: There were only 4 RCTs to address this PICO. All used IV CYC and tacrolimus in Asian population.
The probability of achieving a complete response was lower in the patients who received IV CYC compared to those with CNI (Tacrolimus) alone. The partial and overall (complete + partial) response was similar for both interventions. The change in proteinuria and GFR was also higher for those patients in CNI arms. There seem to be no differences in serious adverse events, infections, and Cytopenias between CYC and CNI, but these analyses lacked precision due to the small number of events and there were also concerns in the ascertainment of the events (risk of bias). The overall certainty was judged as low to very low.

Evidence profile

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV CYC	CNI	Relative (95% CI)	Absolute (95% CI)	

Complete response

4	randomised trials	not serious	not serious	not serious	serious	none	82/218 (37.6%)	120/240 (50.0%)	**RR 0.76** (0.61 to 0.93)	**120 fewer per 1,000** (from 195 fewer to 35 fewer)	⊕⊕⊕◯ Moderate

Partial response

4	randomised trials	not serious	not serious	not serious	not serious	none	100/218 (45.9%)	109/240 (45.4%)	**RR 0.97** (0.89 to 1.07)	**14 fewer per 1,000** (from 50 fewer to 32 more)	⊕⊕⊕⊕ High

Complete plus partial response

4	randomised trials	not serious	not serious	not serious	serious	none	109/144 (75.7%)	132/161 (82.0%)	**RR 0.93** (0.83 to 1.05)	**57 fewer per 1,000** (from 139 fewer to 41 more)	⊕⊕⊕◯ Moderate

Proteinuria (Continuous)

2	randomised trials	not serious	not serious	not serious	serious	none	158	180	-	MD **0.06 higher** (0.22 lower to 0.33 higher)	⊕⊕⊕◯ Moderate

GFR (Continuous)

1	randomised trials	not serious	not serious	not serious	serious[a]	none	34	39	-	MD **0.06 higher** (1.36 lower to 1.48 higher)	⊕⊕⊕◯ Moderate

Serious adverse events

1	randomised trials	serious[b]	not serious	not serious	very serious[a,c]	none	1/34 (2.9%)	0/39 (0.0%)	**RR 3.43** (0.14 to 81.49)	NA	⊕◯◯◯ Very low

Infection

3	randomised trials	serious[b]	not serious	not serious	serious[a,c]	none	39/313 (12.5%)	31/333 (9.3%)	**RR 1.30** (0.65 to 2.62)	**28 more per 1,000** (from 33 fewer to 151 more)	⊕⊕◯◯ Low

Cytopenia

1	randomised trials	not serious	not serious	not serious	very serious[c]	none	9/142 (6.3%)	0/157 (0.0%)	**RR 20.99** (1.23 to 357.45)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕⊕◯◯ Low

Leukopenia

3	randomised trials	not serious	not serious	not serious	very serious[c]	none	18/196 (9.2%)	1/216 (0.5%)	**RR 6.76** (0.92 to 49.62)	**27 more per 1,000** (from 0 fewer to 225 more)	⊕⊕◯◯ Low

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. small sample size.

b. Concerns on missing data and outcome ascertainment.

c. small number of events.

References:

1. Chen W, Tang X, Liu Q, et al. Short-term Outcomes of Induction Therapy With Tacrolimus Versus Cyclophosphamide for Active Lupus Nephritis: A Multicenter Randomized Clinical Trial. Am J Kidney Dis. 2011;57(2):235-244. doi:10.1053/j.ajkd.2010.08.036

2. Li X, Ren H, Zhang Q, et al. Mycophenolate mofetil or tacrolimus compared with intravenous cyclophosphamide in the induction treatment for active lupus nephritis. Nephrol Dial Transpl. 2012;27(4):1467-1472. doi:10.1093/ndt/gfr484

3. Li L, Du Y, Ji J, Gao Y, Shi X qiang. Analysis of the safety and efficacy of tacrolimus combined with glucocorticoid in the treatment of lupus nephritis. Pak J Med Sci. 2022;38(5):1285-1291. doi:10.12669/pjms.38.5.5117

4. Zheng Z, Zhang H, Peng X, et al. Effect of Tacrolimus vs Intravenous Cyclophosphamide on Complete or Partial Response in Patients With Lupus Nephritis. Jama Netw Open. 2022;5(3):e224492. doi:10.1001/jamanetworkopen.2022.4492

Randomized clinical trials: 4

Comparative nonrandomized studies

- None

Non-comparative studies:

- None

Studies read and excluded:

Author	Title	Reason

Pal 2023	A Randomized Controlled Trial Comparing Remission Induction with Modified Multitarget Therapy with Intravenous Cyclophosphamide in Proliferative Lupus Nephritis	AZA was added to CNIs (not pure CNI)
Zhang 2020	Analysis of the Clinical Effects of the Combination of Mycophenolate Mofetil with Either Tacrolimus or Cyclophosphamide	CNI plus CYC but MMF was given in both arms

P7.j.n Belimumab plus standard of care versus standard of care
P8.f.k. Belimumab plus standard of care versus standard of care

Population: Patients with class III/IV LN
Intervention: Belimumab plus standard of care
Comparison: standard of care
Outcomes:

- Reduction of proteinuria
- Preservation of kidney function
- Risk of LN flares
- ESKD (dialysis or transplant)
- Treatment-related adverse effects including infection; also decrease >30% from baseline eGFR for CNI's, depression/suicide for belimumab
- Cumulative steroid dose

Table 1.

P8.k Initial IV CYC, then MMF/MPA plus belimumab versus MMF/MPA

Study name (year) country	Study design	Population	Intervention details	Comparator details	Outcomes with available data	Outcome measures	Outcome timepoint
Furie 2020 International	RCT	LN patients Adults, N=448 Mean (SD) age: BEL 33.7 (10.7), placebo 33.1 (10.6) Asian: 223/446 White: 148/446 Black: 61/446 American Indian or Alaska Native: 10/446 Class III or IV: 258 Class III and V or Class IV and V: 116 Class V: 72	Belimumab plus standard of care	Standard of care	Adverse events, adverse events leading to withdrawal, complete remission, partial remission, depression/suicide, ESKD, infection, partial remission, reduction of proteinuria, serious adverse events, serum Cr.	Risk ratio	104 weeks

Evidence summary: There was 1 RCT with data comparing belimumab + standard of care versus standard of care. Standard of care consists of either CYC for induction followed by AZA or MMF/MPA for induction and maintenance. Outcomes were assessed at 104 weeks (no outcomes were assessed at the end of induction therapy). This trial addresses both induction and maintenance together at the same time (that's why it addresses PICO 7 and 8). The overall certainty of the evidence was judged as moderate. There are concerns about imprecision only (small number of events or wide CI). Complete remission was higher in the Belimumab arm, 103 more per 1,000 (from 18 more to 221 more) while there were no clinically important differences for the partial remission. No ESRD events in the Belimumab arm versus one event in the Placebo arm. The rate of adverse events, Adverse events, Infection, leading to withdrawal was similar between both arms. Depression/Suicide rates were 22 fewer per 1,000 (from 48 fewer to 32 more).
Data about efficacy for CYC or MMF alone is presented below.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Belimumab plus standard of care	standard of care	Relative (95% CI)	Absolute (95% CI)		
Complete remission												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	67/223 (30.0%)	44/223 (19.7%)	**RR 1.52** (1.09 to 2.12)	**103 more per 1,000** (from 18 more to 221 more)	⨁⨁⨁◯ Moderate	
Partial remission												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	39/223 (17.5%)	38/223 (17.0%)	**RR 1.03** (0.68 to 1.54)	**5 more per 1,000** (from 55 fewer to 92 more)	⨁⨁⨁◯ Moderate	
ESRD												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	0/223 (0.0%)	1/223 (0.4%)	**RR 0.33** (0.01 to 8.14)	**3 fewer per 1,000** (from 4 fewer to 32 more)	⨁⨁⨁◯ Moderate	
Adverse events												
1	randomised trials	not serious	not serious	not serious	not serious	none	214/224 (95.5%)	211/224 (94.2%)	**RR 1.01** (0.97 to 1.06)	**9 more per 1,000**	⨁⨁⨁⨁ High	

										(from 28 fewer to 57 more)		
Adverse events leading to withdrawal												
1	randomised trials	not serious	not serious	not serious	serious	none	29/224 (12.9%)	29/224 (12.9%)	**RR 1.00** (0.62 to 1.62)	**0 fewer per 1,000** (from 49 fewer to 80 more)	⊕⊕⊕◯ Moderate	
Infection												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	15/224 (6.7%)	18/224 (8.0%)	**RR 0.83** (0.43 to 1.61)	**14 fewer per 1,000** (from 46 fewer to 49 more)	⊕⊕⊕◯ Moderate	
doubling of serum Cr												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	1/224 (0.4%)	1/224 (0.4%)	**RR 1.00** (0.06 to 15.89)	**0 fewer per 1,000** (from 4 fewer to 66 more)	⊕⊕⊕◯ Moderate	
Serious adverse events												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	58/224 (25.9%)	67/224 (29.9%)	**RR 0.87** (0.64 to 1.17)	**39 fewer per 1,000** (from 108 fewer to 51 more)	⊕⊕⊕◯ Moderate	
Depression/suicide												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	11/224 (4.9%)	16/224 (7.1%)	**RR 0.69** (0.33 to 1.45)	**22 fewer per 1,000** (from 48 fewer to 32 more)	⊕⊕⊕◯ Moderate	
Urinary protein to cr ratio (<0.5)												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	88/131 (67.2%)	70/124 (56.5%)	**RR 1.19** (0.98 to 1.45)	**107 more per 1,000**	⊕⊕⊕◯ Moderate	

										(from 11 fewer to 254 more)		

Belimumab plus CYC versus CYC:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Belimumab plus CYC	CYC alone	Relative (95% CI)	Absolute (95% CI)		
Complete response												
1	randomised trials	not serious	not serious	not serious	serious	none	11/59 (18.6%)	11/59 (18.6%)	**OR 1.07** (0.41 to 2.78)	**10 more per 1,000** (from 101 fewer to 203 more)	⊕⊕⊕◯ Moderate	
PERR												
1	randomised trials	not serious	not serious	not serious	serious	none	16/59 (27.1%)	20/59 (33.9%)	**OR 1.52** (0.66 to 3.49)	**99 more per 1,000** (from 86 fewer to 303 more)	⊕⊕⊕◯ Moderate	

Belimumab plus MMF versus MMF:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Belimumab plus MMF	MMF alone	Relative (95% CI)	Absolute (95% CI)		
Complete response												
1	randomised trials	not serious	not serious	not serious	serious	none	56/164 (34.1%)	33/164 (20.1%)	**OR 2.01** (1.19 to 3.38)	**135 more per 1,000** (from 29 more to 259 more)	⊕⊕⊕◯ Moderate	

PERR

1	randomised trials	not serious	not serious	not serious	serious	none	76/164 (46.3%)	56/164 (34.1%)	**OR 1.58** (1.00 to 2.51)	**109 more per 1,000** (from 0 fewer to 224 more)	⊕⊕⊕◯ Moderate	

CI: confidence interval; **RR:** risk ratio

Explanations

a. We downgraded for imprecision because of the wide CI

b. We downgrade for imprecision because of small number of events

References

Furie R, Rovin BH, Houssiau F, Malvar A, Teng YKO, Contreras G, Amoura Z, Yu X, Mok CC, Santiago MB, Saxena A, Green Y, Ji B, Kleoudis C, Burriss SW, Barnett C, Roth DA. Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis. N Engl J Med. 2020 Sep 17;383(12):1117-1128. doi: 10.1056/NEJMoa2001180. PMID: 32937045.

Included studies: 1

Randomized clinical trials: 1

Comparative non-randomized studies: None

Non-comparative studies (single arm): None

Studies read and exclude: None

P.7k In SLE patients with LN, does IV CYC plus anti-CD20 improve clinical outcomes compared IV CYC?

Population: SLE patients with LN

Intervention: IV CYC plus anti-CD20

Comparison: IV CYC

Outcomes:

- Reduction of proteinuria
- Preservation of kidney function
- Risk of LN flares
- ESKD (dialysis or transplant)
- Treatment related adverse effects including infection; also decrease >30% from baseline eGFR for CNI's, depression/suicide for belimumab

Table 1. Included studies

Study name (year)	Study design	Population	Intervention	Comparator	Outcomes with available data	Outcome measures	Outcome timepoint

Mysler 2013c International	Randomized controlled trial	Adults/peds (>16 years) Active LN Class III: 78/381, Class IV: 303/381, mixed class III/IV/V: 69/381 Multiple ethnic groups *These numbers include all the patients that entered the trial*	400 mg ocrelizumab + CYC	CYC alone	Complete response, Partial Response, Adverse events, Serious adverse events, Infections	RR	48 weeks
Mysler 2013d International	Randomized controlled trial	Adults/peds (>16 years) Active LN Class III: 78/381, Class IV: 303/381, mixed class III/IV/V: 69/381 Multiple ethnic groups *These numbers include all the patients*	1000 mg ocrelizumab + CYC	CYC alone	Complete response, Partial Response, Adverse events, Serious adverse events, Infections	RR	48 weeks

		that entered the trial					

Evidence summary: One randomized controlled trial (RCT) addresses this comparison. This RCT is double-armed, comparing antiCD20 plus standard therapy versus standard therapy (placebo). Standard therapy was CYC or MMF. There were also 2 different doses of ocrelizumab. So, **Mysler a, b** address AntiCD20 +MMF versus MMF, and **Mysler c,d** AntiCD20 +CYC versus CYC.
The outcomes were complete renal response (CRR), partial response (PR), adverse events, and infections. Two different treatment arms within this single RCT (c and d) were used for the estimations. Regarding CRR, the Risk Ratio (RR) and 95% confidence interval (95% CI) was 1.38 (0.67 to 2.86), with a low certainty evidence profile. For partial response, the RR was 1.75 (0.73 to 4.21) achieving a moderate evidence profile. Regarding safety outcomes, the risk for total adverse events in the IV CYC + anti-CD20 group compared to IV CYC alone showed an RR of 0.86 (0.70 to 1.05), while for serious adverse events the RR was 0.62 (0.29 to 1.32) with a low and very low certainty respectively. Finally, the estimated risk for infections was 1.13 (0.77 to 1.66) attaining a very low certainty profile. Despite all outcomes demonstrated a similar rate between treatment groups, safety outcomes had a lower certainty profile due to early termination and undetermined follow-up periods.

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**P.7k IV CYC plus anti-CD20**	**IV CYC**	**Relative (95% CI)**	**Absolute (95% CI)**	
Complete response (edited)											
1[1,a]	randomised trials	Very serious[b]	not serious	not serious	serious[c]	none	22/64 (34.4%)	7/28 (25.0%)	**RR 1.38** (0.67 to 2.86)	**95 more per 1,000** (from 82 fewer to 465 more)	⊕◯◯◯ Very low
Partial response (edited)											
1[1,a]	randomised trials	Very serious[b]	not serious	not serious	serious[c]	none	20/64 (31.3%)	5/28 (17.9%)	**RR 1.75** (0.73 to 4.21)	**134 more per 1,000** (from 48 fewer to 573 more)	⊕◯◯◯ Very low
Adverse events											
1[1,a]	randomised trials	Very serious[b]	not serious	not serious	serious[c]	none	65/95 (68.4%)	36/45 (80.0%)	**RR 0.86** (0.70 to 1.05)	**112 fewer per 1,000** (from 240 fewer to 40 more)	⊕◯◯◯ Very low

Serious adverse events

1[1,a]	randomised trials	Very serious[b]	not serious	not serious	serious[c]	none	26/95 (27.4%)	17/45 (37.8%)	**OR 0.62** (0.29 to 1.32)	**104 fewer per 1,000** (from 228 fewer to 67 more)	⊕◯◯◯ Very low

Infections

1[1,a]	randomised trials	Very serious[b]	not serious	not serious	serious[c]	none	48/95 (50.5%)	20/45 (44.4%)	**RR 1.13** (0.77 to 1.66)	**58 more per 1,000** (from 102 fewer to 293 more)	⊕◯◯◯ Very low

CI: confidence interval; **OR:** odds ratio; **RR:** risk ratio

Explanations

a. Two different arms from a single trial. Patients in c and d had different doses of anti-CD20 (ocrelizumab) and similar doses of CYC. The number of events was adjusted accordingly.

b. We used Rob 2 for risk of bias assessment and we downgraded twice because of large concerns about loss to follow-up and early termination of the trials. Around 60% of the patients in each arm were lost to follow-up.

c. We downgraded for imprecision because of a wide confidence interval.

References

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Included studies:

Randomized clinical trials:

- 1

Comparative non-randomized studies:

- None

Non-comparative studies (single arm):

- None

Studies read and exclude: None

P7.l In SLE patients with active, newly diagnosed or flare of Class III/IV LN, is treatment with MMF/MPA 3g compared to 2g for treatment with MMF/MPA for initial therapy associated with improved outcomes?

Population: Patients with LN

Intervention: MMF 2g/day

Comparison: MMF 3g/day

Outcomes:

- Reduction of proteinuria
- Preservation of kidney function
- Risk of LN flares
- Cumulative steroid dose
- Treatment-related adverse effects including infection

- ESKD (dialysis or transplant)

Table 1.

Study name (year) country	Study design	Population	Intervention	Outcomes with available data	Outcome measures	Outcome timepoint
Ginzler 2005 United States	RCT	LN patients Adults Age: Mean (SD)32+-10 (MMF), 31+-9 (CYC) class 3: 15%, class 4: 54% , class 5: 19%, mixed 11% Multiple ethnicities	MMF (3g/day)	Complete response, Partial response, Complete + partial response, ESKD, LN relapse, Infections, Leukopenia, Proteinuria (continuous)	Risk ratio, Mean difference	24 weeks / 6 months
Appel 2009a (Overall) International	RCT	LN patients Adults/Pediatrics Age Mean (SD) age: 31.9 (10.7) III/III+V: 58 (15,7%), IV/IV+V 252 (68.1%), V only 60(16.2%) Multiple ethnicities	MMF (3g/day)	Complete Response, Adverse events, Serious adverse events, Infections	Risk ratio	24 weeks / 6 months
Sedhain 2018 Nepal	RCT	LN patients Adults Mean±SD age: 25.43±10.17 Ethnicity: Asians Class 3/3+5: CYC 23.8%, MMF 19%;	MMF (3g/day) Patients in the MMF group were administered tablet mycophenolate mofetil at a starting dose of 750 mg twice daily if the weight was more than 50 kg. For those below 50 kg of body weight, the dose was started at	Complete response, Infections	Risk ratio	24 weeks /6 months

		Class 4/4+5: CYC 76.2%, MMF 62%; Class 5: CYC 0%, MMF 19%	500 mg twice daily and increased to 750 mg twice daily after 30 days.			
Mendonca 2017 India	RCT	LN patients Adults Mean (SD) age: MMF 26.0 (10.8), IV CYC 25.7 (10.3) Ethnicity: Asians Class 3: MMF 5.9%, IV CYC 4.3%; Class 4: MMF 70.6%, IV CYC 65.2%; Class 5: MMF 11.7%, IV CYC 13.1%; Class 3/4+5: MMF 17.6%, IV CYC 17.4%	MMF (3g/day) Oral MMF was given twice daily, titrated from 750 mg twice daily in the 1st week, and 1.0 g twice daily in the 2nd week, to a target dosage of 1.5 g twice daily	Complete response, Infections, Proteinuria (Continuous)	Risk ratio Mean difference	24 weeks / 6 months
Anutrakulchai 2015 Multicenter Asia	RCT	LN patients Adults Mean (SD) age: CYC 30.2(7.0); EC-MPS 35.4(12.9) Ethnicity: Asians All were class 3,4. Class 4/59. Class 4: 55/59.	EC-MPS (equivalent to 2 g/day)	Complete response, Serious adverse events, Infections	Risk ratio	52 weeks / 12 months
El-Shafey 2010 Egypt	RCT	LN patients Adults/pediatrics Age: Mean (range): 27 (15-55)	MMF (2g/day)	Complete response, Partial response, Complete + partial response, Adverse events leading to withdrawal, Serious adverse events, ESKD, Infections, Leukopenia, Proteinuria (continuos)	Risk ratio, Mean difference	24 weeks / 6 months

		Ethnicity not reported Class 3: 32% Class 4: 68%				
Ong 2005 Malaysia	RCT	Active lupus nephritis Adults/Pediatrics CYC: Age, 30.5 (8.7) CYC LN classes (n= 25): III: 2 (8%);III+IV: 0 (0%); IV: 17 (68%); IV+V: 6 (24%) MMF: Age, 31.3 (9.9) MMF LN classes (n=19): III: 2 (8%);III+IV: 0 (0%); IV: 17 (68%); IV+V: 6 (24%) Asians	MMF Induction MMF 2 g/day	Complete response, Partial response, Complete plus partial response, Leukopenia	Risk ratio	24 weeks / 6 months

Evidence summary: No studies directly compared 3g MMF versus 2g MMF. But out of 12 RCTs with data comparing IV CYC versus MMF in patients with class III/IV LN, 4 studies MMF was increased to reach 3g/day dose and in 3 studies it was increased to reach 2g/day dose. In the other trials, different doses or multiple doses were used. In this evidence report, we will use the single-arm data from the trials for each MMF dose to compare their outcomes. The outcomes for 3g MMF and 2g MMF are summarized below as ranges across studies.

Table of outcomes for studies using MMF with 3g/day and 2g/day:

Outcome	Study	MMF dose	Results	Comparison
Complete response	Ginzler 2005	MMF 3g/day	16/71(22.5%)	3g/day versus 2g/day, Range: 22-66% versus 25%-29%
	Appel 2009a		44/185 (23.7%)	
	Sedhain 2018		14/21 (66.66%)	
	Mendonca 2017		9/17 (52.94%)	
	Anutrakulchai 2015	MMF 2g/day	7/24 (29.16%)	
	El-Shafey 2010		6/24 (25%)	
	Ong 2005		5/17 (29.4%)	

Partial response	Ginzler 2005	MMF 3g/day	21/71(29.5%)	3g/day versus 2g/day, Range: 28-35% versus 33%-41%
	Sedhain 2018		6/21 (28.5%)	
	Mendonca 2017		6/17 (35.29%)	
	Anutrakulchai 2015	MMF 2g/day	10/24 (41.6%)	
	El-Shafey 2010		8/24 (33.33%)	
	Ong 2005		6/17 (35.29%)	
Proteinuria change from baseline	Ginzler 2005	MMF 3g/day	Mean difference (SD): -2.07 (0.31)	Higher change in proteinuria from baseline in 3g when compared 2g.
	Mendonca 2017		Mean difference (SD): -2.34 (2.9)	
	El-Shafey 2010	MMF 2g/day	Mean difference (SD):-1.3 (0.44)	
ESRD	Ginzler 2005	MMF 3g/day	4/71(5.6%)	
	El-Shafey 2010	MMF 2g/day	2/24 (8.3%)	
Adverse events	Appel 2009a	MMF 3g/day	177/184 (96.19%)	
Serious AE	Appel 2009a	MMF 3g/day	9/184 (4.89%)	3g/day versus 2g/day, Range: 5% versus 7-8%
	Anutrakulchai 2015	MMF 2g/day	2/27 (7.4%)	
	El-Shafey 2010		2/24 (8.3%)	
AE leading to withdrawal	El-Shafey 2010	MMF 2g/day	1/24 (4%)	
Renal flare ups	Ginzler 2005	MMF 3g/day	8/71 (11.26%)	
Infections	Appel 2009a	MMF 3g/day	19/184 (10.32%)	3g/day versus 2g/day, Range: 10-33% versus 4-50%
	Sedhain 2018		7/21 (33.33%)	
	Mendonca 2017		3/17 (17.64%)	
	Anutrakulchai 2015	MMF 2g/day	1/27 (3.7%)	
	El-Shafey 2010		12/24 (50%)	
Leukopenia	Ginzler 2005	MMF 3g/day	18/83(21.68%)	
	El-Shafey 2010	MMF 2g/day	4/24 (16.66%)	
Anemia	Ginzler 2005	MMF 3g/day	2/83 (2.4%)	3g/day versus 2g/day, Range: 2.4-12.5% versus 4.16%
	Appel 2009a		23/184 (12.5%)	
	El-Shafey 2010	MMF 2g/day	1/24 (4.16%)	

References

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3. Anutrakulchai S, Panaput T, Wongchinsri J, et al. A multicentre, randomised controlled study of enteric-coated mycophenolate sodium for the treatment of relapsed or resistant proliferative lupus nephritis: an Asian experience. Lupus Sci Medicine. 2016;3(1):e000120. doi:10.1136/lupus-2015-000120
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7. ONG LM, HOOI LS, LIM TO, et al. Randomized controlled trial of pulse intravenous cyclophosphamide versus mycophenolate mofetil in the induction therapy of proliferative lupus nephritis. Nephrology. 2005;10(5):504-510. doi:10.1111/j.1440-1797.2005.00444.x

Included studies:
Randomized clinical trials:
Comparative non-randomized studies:
Non-comparative studies (single arm):
7
Studies read and exclude:

PICO #7m: In SLE patients with active, newly diagnosed or flare of Class III/IV LN, is treatment MMF compared to CNI alone for initial therapy associated with improved outcomes?

Population: SLE patients with LN
Intervention: MMF
Comparison: CNI alone
Outcomes:

- Complete response
- Partial response
- LN flares
- Adverse events
- Infections
- Diabetes
- >30% reduction from baseline eGFR

Table 1.

Study name (year)	Study design	Population	Intervention details	Comparator details	Outcomes with available data	Outcome measures	Outcome timepoint
Mok 2016 China	RCT	Adults Active LN Asian ethnicity Age 35.5±12.8 years	Mycophenolate mofetil (MMF)/mycophenolic acid (MPA) at 2 grams daily MMF-equivalent	Calcineurin inhibitor (CNI)	Complete renal response Partial renal response LN flares Adverse events Infections	RR	6 months

		Class III/V: 54/150 Class IV/V: 68/150 Class V: 28/150			Diabetes >30% reduction from baseline eGFR		
Kamanamool 2018 Thailand	RCT	Adults Active LN Class III or IV: 57/83, Class V or class III/IV+V: 26/83	Mycophenolate mofetil (MMF)/mycophenolic acid (MPA) at 2 grams daily MMF-equivalent	Calcineurin inhibitor (CNI)	Complete renal response	RR	24 weeks
Li 2012 China	RCT	Adult patients with median age and range in groups treated with MMF: 26.5 (16–62); Tacrolimus 29 (17–50); and CYC 33 (17–64) with LN class III/IV: 40/60; III/IV+V: 12/60; V only: 8/60.	Mycophenolate mofetil (MMF)/mycophenolic acid (MPA) at 2 grams daily MMF-equivalent	Calcineurin inhibitor (CNI)	Complete renal response Partial response Infection.	RR	6 months

Evidence summary: Three randomized clinical trials addressed this PICO question. All were tacrolimus versus MMF All of them addressed Efficacy, while only two of them (Mok 2016 and Li 2012) had information to analyze safety outcomes. Regarding efficacy, MMF had a similar rate for Complete response in comparison to CNI alone with a Risk Ratio (RR) was 1.02 (0.83 to 1.26), and for partial response it showed RR of 0.83 (0.51 to 1.36). On the other hand, MMF was associated with a reduced risk for renal flares when compared to CNI alone with RR 0.68 (0.49 to 0.93) efficacy outcomes had a low degree of certainty for the evidence mainly due to risk of bias and imprecision. On the other hand, total adverse events were less frequent in MMF group in comparison to CNI alone with RR 0.83 (0.73 to 0.95), while similar rate in both treatment regimens was found for total adverse events RR 1.57 (0.95 to 2.59) and diabetes with RR 0.65 (0.11 to 3.77). And for >30% reduction from baseline eGFR, it had a lower rate in MMF compared to CNI alone with a RR of 0.05 (0.00 to 0.78), however safety outcomes were graded with low or very low certainty of the evidence, particularly for eGFR reduction, in which risk of bias arise from outcome reporting, randomization issues, and imprecision given by very small sample sizes and few events.

Evidence profile:

Certainty assessment	№ of patients	Effect	Certainty

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MMF	CNI	Relative (95% CI)	Absolute (95% CI)	
Complete response											
3[1,2,3]	randomised trials	serious[a]	not serious	not serious	serious[b]	none	78/138 (56.5%)	74/135 (54.8%)	**RR 1.02** (0.83 to 1.26)	**11 more per 1,000** (from 93 fewer to 143 more)	⊕⊕◯◯ Low
Partial response											
2[1,2]	randomised trials	serious[a]	not serious	not serious	serious[b]	none	22/96 (22.9%)	26/94 (27.7%)	**RR 0.83** (0.51 to 1.36)	**47 fewer per 1,000** (from 136 fewer to 100 more)	⊕⊕◯◯ Low
LN flares											
1[2]	randomised trials	serious[a]	not serious	not serious	serious[c]	none	32/76 (42.1%)	46/74 (62.2%)	**RR 0.68** (0.49 to 0.93)	**199 fewer per 1,000** (from 317 fewer to 44 fewer)	⊕⊕◯◯ Low
Adverse events											
1[2]	randomised trials	serious[b,d]	not serious	not serious	serious[c]	none	59/76 (77.6%)	69/74 (93.2%)	**RR 0.83** (0.73 to 0.95)	**159 fewer per 1,000** (from 252 fewer to 47 fewer)	⊕⊕◯◯ Low
Infections											
2[1,2]	randomised trials	serious[a,d]	not serious	not serious	serious[b]	none	31/96 (32.3%)	19/94 (20.2%)	**RR 1.57** (0.95 to 2.59)	**115 more per 1,000** (from 10 fewer to	⊕⊕◯◯ Low

										321 more)	

Diabetes

1[2]	randomised trials	serious[a]	not serious	not serious	very serious[b,c]	none	2/76 (2.6%)	3/74 (4.1%)	**RR 0.65** (0.11 to 3.77)	**14 fewer per 1,000** (from 36 fewer to 112 more)	⊕◯◯◯ Very low

>30% reduction from baseline eGFR

1[2]	randomised trials	serious[a,d]	not serious	not serious	very serious[b,c]	none	0/76 (0.0%)	10/74 (13.5%)	**RR 0.05** (0.00 to 0.78)	**128 fewer per 1,000** (from 30 fewer to --)	⊕◯◯◯ Very low

CI: confidence interval; **RR:** risk ratio

Explanations

a. Risk of bias due to issues with randomization and missing data.

b. Wide confidence interval and small sample size.

c. Small sample size

d. Risk of bias due to outcome reporting

References

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Included studies:

Randomized clinical trials:

- 3

Comparative non-randomized studies:

- None

Non-comparative studies (single arm):

- None

Studies read and exclude:

PICO# 7O: In SLE patients with active, newly diagnosed or flare of Class III/IV LN, is treatment with MMF/MPA plus CNI compared to treatment with MMF/MPA alone for initial therapy associated with improved outcomes?

Population: SLE patients with LN
Intervention: MMF/MPA plus CNI
Comparison: MMF/MPA alone
Outcomes:

- Complete response
- Partial response
- Infections
- Adverse events
- Serious adverse events
- Adverse events leading to withdrawal
- Level of proteinuria
- >30% reduction from baseline eGFR
- Diabetes mellitus
- Hypertension

Table 1.

Study name (year)	Study design	Population (sample size: intervention/control)	Intervention details	Comparator details	Outcomes with available data (synthesis method/metric)	Outcome measures	Outcome timepoint
Rovin 2019a	RCT	Adult patients with active LN. Class III or IV: 178/265; Class 5: 39/265; Mixed (III+V or IV+V): 48/265 and mean (SD) age of 31.7 (10.5) years and multiple ethnicities.	Mycophenolate mofetil (MMF)/mycophenolic acid (MPA) + Low dose voclosporin	Mycophenolate mofetil (MMF)/mycophenolic acid (MPA) at 2 grams daily MMF-equivalent	Complete response Infections Adverse events Serious adverse events	RR	48 weeks
Rovin 2019b	RCT	Adult patients with active LN. Class III or IV: 178/265; Class 5: 39/265; Mixed (III+V or IV+V): 48/265 and mean (SD) age of 31.7 (10.5) years and multiple ethnicities.	Mycophenolate mofetil (MMF)/mycophenolic acid (MPA) + High dose voclosporin	Mycophenolate mofetil (MMF)/mycophenolic acid (MPA) at 2 grams daily MMF-equivalent	Complete response Infections Adverse events Serious adverse events	RR	48 weeks
Rovin 2021	RCT	Active LN Pure class III: 49; Pure class IV: 168; Pure class V: 50; Class II + V: 1; Class III + V: 44; Class IV + V: 45.	Oral voclosporin (23·7 mg twice daily), on a background of mycophenolate mofetil (1 g twice daily) and rapidly tapered low-dose oral steroids	MMF (1g) + low dose oral steroids	Complete response Partial response Adverse events Serious adverse events Level of proteinuria >30% reduction from baseline eGFR	RR	52 weeks

		Median (range) age (Voclosporin) 31 (18-62) vs. (Placebo) 32 (18-72)					

Evidence summary: Two randomized clinical trials (RCTs) addressed this PICO question, one of which included a comparison between two different arms, according to the dose of Voclosporin in the treatment group: low dose (Rovin 2019a) and high dose (Rovin 2019b). Both trials addressed complete response, adverse events, serious adverse events, >30% reduction from baseline eGFR, and adverse events leading to withdrawal. Partial response, infection, level of proteinuria, diabetes, and hypertension were only analyzed with information from either one of the RCTs. Complete response, partial response showed a higher rate in the group of MMF + CNI versus MMF/MPA alone. Infections, adverse events, serious adverse events, >30% reduction from baseline eGFR, adverse events leading to withdrawal, diabetes, and hypertension showed similar rates between groups treated with MMF + CNI and MMF alone. Overall certainty is moderate to low due to concerns about imprecision.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**MMF/MPA plus CNI**	**MMF/MPA**	**Relative (95% CI)**	**Absolute (95% CI)**		
Complete response												
3[1,2]	randomised trials	not serious	not serious	not serious	serious[a]	none	152/356 (42.7%)	61/266 (22.9%)	**RR 1.83** (1.42 to 2.36)	**190 more per 1,000** (from 96 more to 312 more)	⨁⨁⨁◯ Moderate	
Partial response												
1[1]	randomised trials	not serious	not serious	not serious	serious[c]	none	125/179 (69.8%)	92/178 (51.7%)	**RR 1.35** (1.14 to 1.60)	**181 more per 1,000** (from 72 more to 310 more)	⨁⨁⨁◯ Moderate	
Infection												
2[2]	randomised trials	not serious	not serious	not serious	serious[c]	none	23/177 (13.0%)	7/88 (8.0%)	**RR 1.61** (0.72 to 3.62)	**49 more per 1,000** (from 22 fewer to 208 more)	⨁⨁⨁◯ Moderate	

Adverse events

3[1,2]	randomised trials	not serious	not serious	not serious	very serious[c]	none	262/355 (73.8%)	173/266 (65.0%)	**RR 2.13** (0.83 to 5.50)	**735 more per 1,000** (from 111 fewer to 1,000 more)	⊕⊕◯◯ low	

Serious adverse events

3[1,2]	randomised trials	not serious	not serious	not serious	serious[c]	none	48/355 (13.5%)	39/266 (14.7%)	**RR 1.20** (0.57 to 2.51)	**29 more per 1,000** (from 63 fewer to 221 more)	⊕⊕⊕◯ Moderate	

Level of proteinuria

1[1]	randomised trials	not serious	not serious	not serious	very serious[e]	none	81/179 (45.3%)	41/178 (23.0%)	**RR 1.96** (1.44 to 2.69)	**221 more per 1,000** (from 101 more to 389 more)	⊕⊕◯◯ low	

>30% reduction from baseline eGFR

3[1,2]	randomised trials	not serious	not serious	not serious	serious[c,]	none	23/356 (6.5%)	18/266 (6.8%)	**RR 1.08** (0.59 to 1.95)	**5 more per 1,000** (from 28 fewer to 64 more)	⊕⊕⊕◯ Moderate	

Adverse events leading to withdrawal

3[1,2]	randomised trials	not serious	not serious	not serious	serious[c]	none	50/356 (14.0%)	35/266 (13.2%)	**RR 1.02** (0.67 to 1.57)	**3 more per 1,000** (from 43 fewer to 75 more)	⊕⊕⊕◯ Moderate	

Diabetes

2[2]	randomised trials	not serious	not serious	not serious	very serious[c,g]	none	1/177 (0.6%)	1/88 (1.1%)	**RR 0.49** (0.03 to 7.72)	**6 fewer per 1,000** (from 11	⊕⊕◯◯ low	

										fewer to 76 more)		

Hypertension

2[2]	randomised trials	not serious	not serious	not serious	very serious[c,g]	none	4/177 (2.3%)	0/88 (0.0%)	**RR 2.51** (0.30 to 21.20)	**3 fewer per 1,000** (from 21 fewer to 0 fewer)	⊕⊕◯◯ low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Wide confidence intervals may affect decision-making.
b. Due to sample size and size effect increasing over time
c. Small sample size and wide confidence intervals
e. Low sample size
f. The confidence interval crosses 5% minimally important difference.
g. Few events

References

1.Rovin BH, Teng YKO,Ginzler EM,Arriens C,Caster DJ,Romero-Diaz J,Gibson K,Kaplan J,Lisk L,Navarra S,Parikh SV,Randhawa S,Solomons N,Huizinga RB. Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind,randomised,multicentre,placebo-controlled,phase 3 trial. Lancet. 2021 May 29,10.1016/S0140-6736(21)00578-X.,397(10289):2070-2080. .
2.Rovin BH, Solomons N,Pendergraft WF 3rd,Dooley MA,Tumlin J,Romero-Diaz J,Lysenko L,Navarra SV,Huizinga RB,AURA-LV Study Group. A randomized,controlled double-blind study comparing the efficacy and safety of dose-ranging voclosporin with placebo in achieving remission in patients with active lupus nephritis. Kidney Int. 2019 Jan,30420324.,95(1):219-231.,doi:,10.1016/j.kint.2018.08.025.,Epub,2018,Nov,9.. .

Randomized clinical trials: 2
Non-randomized comparative studies: none
Single arm studies: none

PICO# 7r: In SLE patients with active, newly diagnosed or flare of Class III/IV LN, is treatment with MMF/MPA plus anti CD-20 therapy compared to treatment with MMF/MPA alone for initial therapy associated with improved outcomes?

Population: SLE patients with LN
Intervention: MMF/MPA plus anti CD-20 therapy
Comparison: MMF/MPA alone
Outcomes:

- Complete response
- Partial response
- Complete plus partial response
- Level of proteinuria
- Adverse events
- Serious adverse events
- Infection
- GFR

Table 1.

Study name (year)	Study design	Population	Intervention details	Comparator details	Outcomes with available data	Outcome measures	Outcome timepoint
Furie 2022 Multicentric	RCT	Adults from Multiple ethnicities with active LN or active/chronic LN within 6 months of screening (concomitant class V was permitted). Total patients with Patients with kidney biopsy had Class IV lupus nephritis 75 (66%) and concomitant class V were 37 (33%) mean age (SD) in obinituzumab group was 33.1 (9.8) and in placebo group 31.9(10.1).	Obinutuzumab + MMF	MMF alone	Complete response, Complete plus partial response. Adverse events, Serious adverse events	RR	52 weeks
Mysler 2013a Multicentric	RCT	Adults with Active LN Class III: 78/381, class IV: 303/381, mixed class III/IV/V: 69/381	400 mg ocrelizumab + MMF	Mycophenolate mofetil (MMF)/mycophenolic acid (MPA) at 3 grams daily MMF-equivalent	Complete response, Partial Response, Complete plus partial response, Adverse events, Serious adverse events, Infections	RR	48 weeks
Mysler 2013b Multicentric	RCT	Adults with Active LN Class III: 78/381, class IV: 303/381, mixed class III/IV/V: 69/381	1000 mg ocrelizumab + MMF 3mg/day	Mycophenolate mofetil (MMF)/mycophenolic acid (MPA) at 3 grams daily MMF-equivalent	Complete response, Partial Response, Complete plus partial response, Adverse events, Serious adverse events, Infections	RR	48 weeks
Rovin 2012 Multicentric	RCT	Adults Multiple ethnicities with active LN Class III: 24/144; Class III/V: 25/144; Class IV: 71/144; Class IV/V: 24/144 Mean (SD) age 30.6 (9.5) years	RTX 1000 mg IV Day 1, 15, 168, 182, MMF 1.5-3 g/day until at least week 52	MMF 1.5-3 g/day until at least week 52	Complete response, Complete plus partial response, Level of proteinuria, Adverse events, Serious adverse events, Infection	RR	52 weeks
Rovin 2023 Multicentric	RCT	Adult patients with active LN with a Mean (SD) age 33.1 (9.8) years in Obinituzumab + MMF	Obinituzumab 1000 mg IV Day 1, and weeks 2, 24, and 26 + MMF	Mycophenolate mofetil (MMF)/mycophenolic acid (MPA) at	LN flare-up, GFR	RR	52 weeks

Posthoc analysis of the NOBILITY trial		group; and mean age of 31.9 (10.1) in MMF group. Class III or III/V: 31/125; Class IV or IV/V: 94/125.		2 grams daily MMF-equivalent			

Evidence summary:
Four randomized clinical trials (RCTs) compared the effects of MMF/MPA plus anti-CD-20 therapy versus MMF/MPA alone in patients with active class III or IV lupus nephritis, one of them included information from two arms at different doses of ocrelizumab as the anti-CD20 agent (Mysler 2013 a and b). In the NOBILITY trial, the follow-up time was 104 weeks, but we had primary outcomes at 54 weeks, we used follow-up at 54 weeks for this PICO question (initial therapy).
All trials reported complete response, while partial response or the composite of complete and partial response were obtained from two RCTs. Safety outcomes, such as adverse events, serious adverse events, and infections, were available from three trials. The efficacy outcomes of MMF/MPA plus anti CD-20 versus MMF/MPA alone showed similar rates of complete response, partial response, complete plus partial response, and proteinuria (dichotomous), with a very low to low certainty of evidence, mainly due to risk of bias from missing outcome data. For the GFR, the mean difference was lower in the MMF/MPA plus anti CD-20 group than in the MMF/MPA alone group, with a low certainty of evidence. The safety outcomes of MMF/MPA plus anti CD-20 versus MMF/MPA alone showed similar rates of adverse events, serious adverse events, and infections, with a low or very low certainty of evidence.

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MMF/MPA plus anti CD-20 therapy	MMF/MPA	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Complete response												
5[1,2,3,4]	randomised trials	serious[a]	not serious	not serious	serious	none	78/219 (35.6%)	74/228 (32.5%)	**RR 1.09 (0.79 to 1.51)**	29 more per 1,000 (from 68 fewer to 166 more)	⨁⨁◯◯ Low	CRITICAL
Partial response												
2[2]	randomised trials	serious[a]	not serious	not serious	serious[b]	none	24/84 (28.6%)	20/94 (21.3%)	**RR 1.35** (0.75 to 2.44)	**74 more per 1,000** (from 53 fewer to 306 more)	⨁⨁◯◯ Low	CRITICAL

Renal flare up

1[4]	randomised trials	serious[a]	not serious	not serious	serious	none	2/63 (3.1%)	11/62 (%)	**RR 0.18** (0.04 to 0.77)	145 fewer per 1,000 (from 170 fewer to 41 fewer)	⊕⊕◯◯ Low	CRITICAL
Complete plus partial response												
4[1,2,3]	randomised trials	serious[a]	not serious	not serious	serious[c]	none	132/220 (60%)	109/225 (48.4%)	**RR 1.22** (0.97 to 1.55)	107 more per 1,000 (from 15 fewer to 266 more)	⊕⊕◯◯ Low	CRITICAL
Adverse events												
4	randomised trials	very serious[a]	not serious	not serious	not serious	none	229/294 (77.9%)	226/292 (77.4%)	**RR 1.01** (0.95 to 1.07)	**8 more per 1,000** (from 39 fewer to 54 more)	⊕⊕◯◯ Low	CRITICAL
Serious adverse events												
4	randomised trials	serious[a]	serious[d]	not serious	serious[b]	none	81/294 (27.6%)	81/292 (27.7%)	**RR 0.95** (0.57 to 1.58)	**14 fewer per 1,000** (from 119 fewer to 161 more)	⊕◯◯◯ Very low	CRITICAL
Infections												
3	randomised trials	serious[a]	serious[d]	not serious	serious[c]	none	138/231 (59.7%)	164/231 (71.0%)	**RR 0.79** (0.52 to 1.20)	**149 fewer per 1,000** (from 341 fewer to 142 more)	⊕◯◯◯ Very low	CRITICAL
GFR (continuous)												
1	randomised trials	serious[a]	not serious	not serious	serious[c]	none	63	62	-	MD **4.09 higher** (0.2 higher to	⊕⊕◯◯ Low	CRITICAL

										7.98 higher)		

Level of proteinuria (UPC <1)

1	randomised trials	serious[a]	not serious	not serious	serious[c]	none	18/38 (47.4%)	22/41 (53.7%)	**RR 0.88** (0.57 to 1.37)	**64 fewer per 1,000** (from 231 fewer to 199 more)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Risk of bias coming from randomization, reporting, and missing outcome data.
b. Low sample size and wide confidence intervals
c. Low sample size
d. Confidence intervals do not overlap and studies showed marked heterogeneity.

References

1.Furie RA, Aroca G,Cascino MD,Garg JP,Rovin BH,Alvarez A,Fragoso-Loyo H,Zuta-Santillan E,Schindler T,Brunetta P,Looney CM,Hassan I,Malvar A. B-cell depletion with obinutuzumab for the treatment of proliferative lupus nephritis: a randomised,double-blind,placebo-controlled trial. Ann Rheum Dis. 2022 Jan, 34615636, 81(1):100-107.,doi:,10.1136/annrheumdis-2021-220920.,Epub,2021,Oct,6.,PMID:, PMC8762029., PMCID:. .
2.Mysler EF, Spindler AJ,Guzman R,Bijl M,Jayne D,Furie RA,Houssiau FA,Drappa J,Close D,Maciuca R,Rao K,Shahdad S,Brunetta P. Efficacy and safety of ocrelizumab in active proliferative lupus nephritis: results from a randomized,double-blind,phase III study. Arthritis Rheum. 2013 Sep, 23740801., 65(9):2368-79.,doi:,10.1002/art.38037.,PMID:. .
3.Rovin BH, Furie R,Latinis K,Looney RJ,Fervenza FC,Sanchez-Guerrero J,Maciuca R,Zhang D,Garg JP,Brunetta P,Appel G, Apr, LUNAR,Investigator,Group.,Efficacy,and,safety,of,rituximab,in,patients,with,active,proliferative,lupus,nephritis:,the,Lupus,Nephritis,Assessment,with,Rituximab,study., Arthritis,Rheum.,2012, 22231479., 64(4):1215-26.,doi:,10.1002/art.34359.,Epub,2012,Jan,9.,PMID:. .
4.Rovin BH, Furie RA,Ross Terres JA,Giang S,Schindler T,Turchetta A,Garg JP,Pendergraft WF 3rd,Malvar A. Kidney Outcomes and Preservation of Kidney Function With Obinutuzumab in Patients With Lupus Nephritis: A Post Hoc Analysis of the NOBILITY Trial. Arthritis Rheumatol. 2024 Feb, 37947366., 76(2):247-254.,doi:,10.1002/art.42734.,Epub,2023,Nov,10.,PMID:. .

Randomized clinical trials: 4
Nonrandomized comparative studies: none
Single arm studies: none
Read and excluded: none

P.7s In SLE patients with active, newly diagnosed or flare of Class III/IV LN, is treatment with AntiCD20 plus Belimumab compared to AntiCD20 alone associated with improved outcomes?

Population:

- Active Class III/IV LN

Intervention:

- AntiCD20 plus Belimumab

Comparator:

- AntiCD20 alone

Outcomes:

- Reduction of proteinuria
- Preservation of kidney function
- Risk of LN flares
- ESKD (dialysis or transplant)
- Treatment-related adverse effects including infection; also decrease >30% from baseline eGFR for CNI's, depression/suicide for belimumab
-

Table 1. Included studies.

Study name (year) Country	Study design	Population	Intervention details	Comparator details	Outcomes with available data	Outcome measures	Outcome timepoint
Atisha-Fregoso 2021 China	Randomized controlled trial	LN patients Adults: >18 years Mean age (SD): 34.5 (9.14) versus 32.3 (11.43) Class 3: 2/43 Class 4: 15/43 Class 3+5: 8/43 Class 4+5: 18/43	CYC plus CD-20 therapy plus belimumab	CYC plus anti-CD 20 therapy alone	Complete response, Partial response, complete plus partial response, Adverse events, Infection, ESRD	Risk Ratio	48 weeks

Evidence summary:

1 RCT addressed anti-CD20 plus Belimumab versus anti-CD20. Both arms were given CYC also. The population was recurrent or refractory that's why we downgraded for indirectness. For complete response, partial response, and response (complete plus partial) there were no clinically important differences between arms. The rate of ESRD was lower in the anti-CD20 plus Belimumab, and the infection rate was higher in the anti-CD20 arm. The overall certainty of the evidence was judged as very low because of concerns about the risk of bias, indirectness, and imprecision.

Evidence profile:

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	P.7s anti-CD-20 therapy plus belimumab	anti-CD 20 therapy alone	Relative (95% CI)	Absolute (95% CI)	
Complete plus partial response											
1	randomised trials	serious[a]	not serious	serious[b]	very serious[c]	none	10/21 (47.6%)	9/22 (40.9%)	**RR 1.16** (0.59 to 2.28)	**65 more per 1,000** (from 168 fewer to	⨁◯◯◯ Very low

										524 more)	
Complete response											
1	randomised trials	serious[a]	not serious	serious[b]	very serious[c]	none	5/21 (23.8%)	5/22 (22.7%)	**RR 1.05** (0.35 to 3.10)	**11 more per 1,000** (from 148 fewer to 477 more)	⨁◯◯◯ Very low
Partial response											
1	randomised trials	serious[a]	not serious	serious[b]	very serious[c]	none	5/21 (23.8%)	4/22 (18.2%)	**RR 1.31** (0.41 to 4.22)	**56 more per 1,000** (from 107 fewer to 585 more)	⨁◯◯◯ Very low
Adverse events											
1	randomised trials	serious[a]	not serious	serious[b]	very serious[c]	none	21/21 (100.0%)	22/22 (100.0%)	**RR 1.00** (0.92 to 1.09)	**0 fewer per 1,000** (from 80 fewer to 90 more)	⨁◯◯◯ Very low
Infection											
1	randomised trials	serious[a]	not serious	serious[b]	very serious[c]	none	2/21 (9.5%)	5/22 (22.7%)	**RR 0.42** (0.09 to 1.93)	**132 fewer per 1,000** (from 207 fewer to 211 more)	⨁◯◯◯ Very low
ESRD											
1	randomised trials	serious[a]	not serious	serious[b]	very serious[c]	none	1/21 (4.8%)	3/22 (13.6%)	**RR 0.35** (0.04 to 3.10)	**89 fewer per 1,000** (from 131 fewer to 286 more)	⨁◯◯◯ Very low

CI: confidence interval; **RR:** risk ratio

Explanations
a. We downgraded for risk of bias because of loss to follow-up.
b. We downgraded for indirectness for 2 reasons. First, patients were recurrent or refractory, but our question is in patients with active nephritis but not refractory. Second, the intervention arms were CYC plus antiCD20 plus belimumab versus CYC plus antiCD20, CYC was given in both arms.
c. We downgraded for imprecision because of the small sample size leading to wide CI
References:
Atisha-Fregoso, Yemil et al. "Phase II Randomized Trial of Rituximab Plus Cyclophosphamide Followed by Belimumab for the Treatment of Lupus Nephritis." *Arthritis & rheumatology (Hoboken, N.J.)* vol. 73,1 (2021): 121-131. doi:10.1002/art.41466

Randomized clinical trials: 1
Nonrandomized clinical trial: none
Single arm studies: none
Read and excluded: none

P7.v In SLE patients with active, newly diagnosed or flare of Class III/IV LN and decreased kidney function, is treatment with Cyclophosphamide-containing regimen compared to treatment with MMF/MPA for initial therapy associated with improved outcomes?

Population: Patients with LN and decreased kidney function
Intervention: Cyclophosphamide-containing regimen
Comparison: MMF/MPA
Outcomes:

- Reduction of proteinuria
- Preservation of kidney function
- Risk of LN flares
- Cumulative steroid dose
- Treatment-related adverse effects including infection
- ESKD (dialysis or transplant)

Table 1.
P. 7v Cyclophosphamide-containing regimen versus MMF/MPA in patients with decreased kidney function

Study Name (year) Country	Study design	Population	Intervention details	Comparator details	Outcomes with available data	Outcome measure	Outcome timepoint
Walsh 2013	Randomized Clinical Trial	Adults with eGFR <30 ml/min/1.73m^2 Age, median [IQR]: 40 [35-45] (CYC), 31 [25-42.5] Class 3: 3(CYC)/2(MMF), Class 4: 9(CYC)/18(MMF), Class 5: 2(CYC)/1(MMF)	IV Cyclophosphamide 0.5-1.0 g/m2 monthly	MMF (target, 3 g/d)	Complete response, Infection, Serious adverse events, ESKD	RR	6 months

Evidence summary: Only one study addressed this PICO question for patients with decreased kidney function. It is a post-hoc analysis of a multicenter RCT (Walsh 2013), reporting their outcomes at 6 months.
The meta-analysis for demonstrated with low certainty, no differences in complete response, serious adverse events, and infections between CYC-containing regimens and MMF/MPA. There were no events for the outcome of ESKD for either group. These results suffer from serious imprecision due to the small number of patients, events, and studies.

Evidence profile:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cyclophosphamide-containing regimen	MMF/MPA	Relative (95% CI)	Absolute (95% CI)		
Complete Response												
1	randomised trials[a]	serious	not serious	not serious	very serious[b]	none	2/12 (16.7%)	4/20 (20.0%)	**RR 0.83** (0.18 to 3.88)	**34 fewer per 1,000** (from 164 fewer to 576 more)	⨁◯◯◯ Very low	
Serious adverse events												
1	randomised trials[a]	serious	not serious	not serious	very serious[b]	none	7/12 (58.3%)	9/20 (45.0%)	**RR 1.30** (0.66 to 2.56)	**135 more per 1,000** (from 153 fewer to 702 more)	⨁◯◯◯ Very low	
Infections												
1	randomised trials[a]	serious	not serious	not serious	very serious[b]	none	7/11 (63.6%)	14/20 (70.0%)	**RR 0.91** (0.53 to 1.55)	**63 fewer per 1,000** (from 329 fewer to 385 more)	⨁◯◯◯ Very low	
ESKD												
1	randomised trials[a]	serious	not serious	not serious	extremely serious[c]	none	0/12 (0.0%)	0/20 (0.0%)	not pooled	see comment	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio
Explanations

a. This result corresponds to a subgroup analysis from an RCT, but not an exclusive trial for patients with decreased kidney function. This may impact randomization.
b. Very small number of events and patients per group.
c. No events during follow-up.

References

Walsh M, Solomons N, Lisk L, Jayne DRW. Mycophenolate Mofetil or Intravenous Cyclophosphamide for Lupus Nephritis With Poor Kidney Function: A Subgroup Analysis of the Aspreva Lupus Management Study. Am J Kidney Dis. 2013;61(5):710–5.

Included studies:

Randomized clinical trials: 1

Comparative non-randomized studies: None

Non-comparative studies (single arm): None

Studies read and exclude: None

P7.x In African American SLE patients with active, newly diagnosed or flare of Class III/IV LN, is treatment with Cyclophosphamide-containing regimen compared to treatment with MMF/MPA for initial therapy associated with improved outcomes?

Population: African American patients with LN

Intervention: Cyclophosphamide-containing regimen

Comparison: MMF/MPA

Outcomes:

- Reduction of proteinuria
- Preservation of kidney function
- Risk of LN flares
- Cumulative steroid dose
- Treatment-related adverse effects including infection
- ESKD (dialysis or transplant)
-

Table 1.

P7.x CYC-containing regimen versus MMF/MPA in African American population

Study Name (year) Country	Study design	Population	Intervention details	Comparator details	Outcomes with available data	Outcome measure	Outcome timepoint
Isenberg 2010a	Randomized Clinical Trial	African Americans with LN Mean (SD) age: MMF 32.2 (11); IV-CYC 28.8 (10.2)	IV Cyclophosphamide (NIH protocol)	Mycophenolate mofetil (MMF)/mycophenolic acid (MPA) at 3 grams daily MMF-equivalent	Renal response, Level of proteinuria (Change from baseline), Adverse events, Serious adverse events, Infection	MD, RR	6 months

		Class 3: MMF 5, IV-CYC 2 Class 4: MMF 10, IV-CYC 7 Class 3/5: MMF 6, IV-CYC 4 Class 4/5: MMF 12, IV-CYC 9 Class 5: MMF 8, IV-CYC 7					

Evidence summary: Only one study addressed this question for African American population. There was no difference in the renal response (defined as a decrease in urine protein/creatinine ratio (P/Cr), measured over 24 h, to <3 in patients with baseline nephrotic range P/Cr, or by 50% in patients with sub-nephrotic baseline P/Cr (<3)), the level of proteinuria (change from baseline), overall or serious adverse events, and infections after 6 months for the patients who received CYC-containing regimen versus MMF/MPA. The evidence has serious risk of bias and imprecision with a final low certainty of this result.

Evidence profile:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**P.7x Cyclophosphamide-containing regimen**	**MMF/MPA in African American population**	**Relative (95% CI)**	**Absolute (95% CI)**		
Renal Response												
1	randomised trials	serious[a]	not serious	not serious	Very serious	none	8/20 (40.0%)	14/26 (53.8%)	**RR 0.74** (0.39 to 1.41)	**140 fewer per 1,000** (from 328 fewer to 221 more)	⨁⨁◯◯ Low	
Level of Proteinuria (continuous)												
1	randomised trials	serious[a]	not serious	not serious	serious	none	20	26	-	MD **0.6 higher** (0.83 lower to 2.03 higher)	⨁⨁◯◯ Low	
Adverse Events												

1	randomised trials	serious[a]	not serious	not serious	serious	none	18/18 (100.0%)	25/26 (96.2%)	**RR 1.03** (0.92 to 1.16)	**29 more per 1,000** (from 77 fewer to 154 more)	⊕⊕◯◯ Low	

Serious adverse events

1	randomised trials	serious[a]	not serious	not serious	serious	none	3/18 (16.7%)	7/26 (26.9%)	**RR 0.62** (0.18 to 2.08)	**102 fewer per 1,000** (from 221 fewer to 291 more)	⊕⊕◯◯ Low	

Infections

1	randomised trials	serious[a]	not serious	not serious	serious	none	10/18 (55.6%)	21/26 (80.8%)	**RR 0.69** (0.44 to 1.08)	**250 fewer per 1,000** (from 452 fewer to 65 more)	⊕⊕◯◯ Low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Post-hoc analysis and randomization wasn't based on GFR which impacts randomization.

References

1.Isenberg D, Appel GB, Contreras G, Dooley MA, Ginzler EM, Jayne D, et al. Influence of race/ethnicity on response to lupus nephritis treatment: the ALMS study. Rheumatology Oxf Engl. 2010;49(1):128–40.

Included studies:
Randomized clinical trials: 1
Comparative non-randomized studies: None

Non-comparative studies (single arm): None

Studies read and exclude: None

P7.z In *Hispanic* SLE patients with active, newly diagnosed or flare of Class III/IV LN, is treatment with Cyclophosphamide-containing regimen compared to treatment with MMF/MPA for initial therapy associated with improved outcomes?

Population: Hispanic patients with LN
Intervention: Cyclophosphamide-containing regimen

Comparison: MMF/MPA
Outcomes:

- Reduction of proteinuria
- Preservation of kidney function
- Risk of LN flares
- Cumulative steroid dose
- Treatment-related adverse effects including infection
- ESKD (dialysis or transplant)

P7.z CYC-containing regimen versus MMF/MPA in Hispanic

Study Name (year) Country	Study design	Population	Intervention details	Comparator details	Outcomes with available data	Outcome measure	Outcome timepoint
Isenberg 2010d	Randomized Clinical Trial	Hispanic with LN. No data about the class or the age for this specific population.	IV Cyclophosphamide (NIH protocol)	Mycophenolate mofetil (MMF)/mycophenolic acid (MPA) at 3 grams daily MMF-equivalent	Complete or partial response, proteinuria	MD, OR	6 months
Mejia-Vilet 2015 Mexico	Non-randomized study	Hispanic with LN. Class 3,4,5, concomitant Age: adults, mean age for all the groups =30 years	IV CYC	MMF	Renal flare up	HR	36 months

Evidence summary: 1 RCT and 1 NRS addressed CYC versus MMF in Hispanics. Response (Complete or partial) was lower in the IV CYC arm (298 fewer per 1,000 (from 440 fewer to 98 fewer)) and the LN flare-up rate was higher in the IV CYC arm (259 more per 1,000 (from 35 more to 475 more). Change in proteinuria (UPCR) was higher in the MMF arm (mean difference of 0.9). The overall certainty of the evidence was low due to the small sample size. No studies compared adverse events in CYC versus MMF in Hispanic

Evidence profile:

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV CYC	MMF/MPA	Relative (95% CI)	Absolute (95% CI)	
Complete or partial response											
1	randomised trials	serious	not serious	not serious	serious	none	16/50 (32.0%)	34/56 (60.7%)	**OR 0.29** (0.13 to 0.67)	**298 fewer per 1,000** (from 440	⊕⊕◯◯ Low

										fewer to 98 fewer)	

Change in proteinuria (UPCR)

1	randomised trials	not serious	not serious	not serious	serious	none	49	53	-	MD **0.9 lower** (0.53 lower to 2.33 higher)	⊕⊕⊕◯ Moderate

LN flare up

1	non-randomised studies	serious	not serious	not serious	serious	none	42/66 (63.6%)	24/63 (38.1%)	**HR 2.13** (1.12 to 4.04)	**259 more per 1,000** (from 35 more to 475 more)	⊕⊕◯◯ Low

CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **OR:** odds ratio

References:

1-Isenberg, David et al. “Influence of race/ethnicity on response to lupus nephritis treatment: the ALMS study.” *Rheumatology (Oxford, England)* vol. 49,1 (2010): 128-40. doi:10.1093/rheumatology/kep346

2-Mejía-Vilet, Juan Manuel et al. “Comparison of Lupus Nephritis Induction Treatments in a Hispanic Population: A Single-center Cohort Analysis.” *The Journal of rheumatology* vol. 42,11 (2015): 2082-91. doi:10.3899/jrheum.150395

Randomized clinical trial: 1
Non-randomized study: 1
Single-arm studies: None
Read and exclude: None

P7.bb In Asian SLE patients with active, newly diagnosed or flare of Class III/IV LN, is treatment with Cyclophosphamide-containing regimen compared to treatment with MMF/MPA for initial therapy associated with improved outcomes?

Population: Asian patients with LN
Intervention: Cyclophosphamide-containing regimen
Comparison: MMF/MPA
Outcomes:

- Reduction of proteinuria
- Preservation of kidney function
- Risk of LN flares
- Cumulative steroid dose
- Treatment-related adverse effects including infection
- ESKD (dialysis or transplant)

Table 1.

P7.bb Cyclophosphamide-containing regimen versus MMF/MPA in Asian population							
Study Name (year) Country	**Study design**	**Population**	**Intervention details**	**Comparator details**	**Outcomes with available data**	**Outcome measure**	**Outcome timepoint**
Appel 2009d International	RCT	Adults/Pediatrics Asian patients with LN Mean (SD) age: 31.9 (10.7) III/III V: 58 (15,7%), IV/IV V 252 (68.1%), V only 60 (16.2%)	IV CYC (0.5 to 1.0 g/m^2 in monthly pulses) + prednisone of max start dose of 60mg/d.	MMF (target dosage 3 g/d) + prednisone of max start dose of 60mg/d.	Complete + partial response	Risk ratio	24 weeks / 6 months
Anutrakulchai 2015 Thailand	RCT	Adults Mean (SD) age: CYC 30.2(7.0); EC-MPS 35.4(12.9) Ethnicity: Asians All were class 3,4. Class 4/59. Class 4: 55/59.	IV CYC	EC-MPS	Complete response, Partial Response, Serious adverse events, Infections	Risk ratio	52 weeks / 12 months
Li 2012 China	RCT	Active Lupus Nephritis Adults/Pediatrics TAC (n=20): Age, 29 (17-50) MMF (n=20): 26.5 (16-62) CYC (= 20): 33 (17-64) TAC: Class III/IV (65%); Class III/IV+V (25%); Class V (10%) MMF: Class III/IV (70%); Class III/IV+V (15%); Class V (15%) CYC: Class III/IV (65%); Class III/IV+V (20%); Class V (15%) Asians	IV CYC CYC (IV): 0.5-0.75g/m2 BSA monthly.	MMF 1.5g/d (<=55kg) or 2g/d (>55kg).	Complete response, Partial response, Complete + partial response, Infection, Leukopenia	Risk ratio	24 weeks / 6 months

Isenberg 2010b International	RCT	Adults/Pediatrics Mean (SD) age: MMF 28.8(8.53), IV CYC 27.3(9.44) Class 3: 4% Class 4: 39% Class 3/5: 7% Class 4/5: 42% Class 5: 7% Ethnicity: Asians	IV CYC	MMF	Proteinuria (continuous)	Mean difference	24 weeks / 6 months
Mendonca 2017 India	RCT	Adults Mean (SD) age: MMF 26.0 (10.8), IV CYC 25.7 (10.3) Ethnicity: Asians Class 3: MMF 5.9%, IV CYC 4.3%; Class 4: MMF 70.6%, IV CYC 65.2%; Class 5: MMF 11.7%, IV CYC 13.1%; Class 3/4+5: MMF 17.6%, IV CYC 17.4%	IV CYC	MMF	Complete response, Partial Response, Infections, Proteinuria (Continuous)	Risk ratio Mean difference	24 weeks / 6 months
Rathi 2016 India	RCT	Adults Ethnicity: Asians Mean (SD) age 30.6 (9.5) years in CYC group; 28.3 (9.5) in MMF group Class 3, 3/5: 17/100; Class 4, 4/5: 57/100; Class 5: 26/100	IV CYC	MMF	Complete response, Complete + partial response, Adverse events	Risk Ratio	24 weeks / 6 months
Sedhain 2018 Nepal	RCT	Adults Mean±SD age: 25.43±10.17 Ethnicity: Asians Class 3/3+5: CYC 23.8%, MMF 19%; Class 4/4+5: CYC 76.2%, MMF 62%; Class 5: CYC 0%, MMF 19%	IV CYC	MMF	Complete response, Partial Response, Infections	Risk ratio	24 weeks / 6 months
Wang 2007 China	RCT	Adults	IV CYC	MMF	Complete response, Partial Response,	Risk ratio Mean difference	24 weeks / 6 months

		Age: Mean (SD): MMF: 32.2 +/- 12.0; CYC: 30.8 +/- 12.7 Ethnicity: Asians All are class 4 or 4+5. Proportions not reported.			Infections, Proteinuria (continuous), Leukopenia		
Ong 2005 Malaysia	RCT	Active lupus nephritis Adults/Pediatrics CYC: Age, 30.5 (8.7) CYC LN classes (n= 25): III: 2 (8%);III+IV: 0 (0%); IV: 17 (68%); IV+V: 6 (24%) MMF: Age, 31.3 (9.9) MMF LN classes (n=19): III: 2 (8%);III+IV: 0 (0%); IV: 17 (68%); IV+V: 6 (24%) Asians	IV CYC Induction CYC 0.75-1 g/m2 BSA monthly	MMF Induction MMF 2 g/day	Complete response, Partial response, Complete plus partial response, Leukopenia	Risk ratio	24 weeks / 6 months

Evidence summary: There were 9 RCTs in Asian population comparing IV CYC versus MMF/MPA in patients with class III/IV LN. RCTs addressing the outcomes of complete and partial responses showed similar rates for CYC and MMF/MPA. We have concerns about risk of bias and serious imprecision. The change in proteinuria and GFR was also similar with the same concerns for imprecision and risk of bias. Adverse events (overall and serious), leukopenia, and infections were similar for CYC-containing regimens and MMF/MPA. The evidence certainty for all the outcomes is low or very low.

Evidence profile:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**P.7bb Cyclophosphamide-containing regimen**	**MMF/MPA**	**Relative (95% CI)**	**Absolute (95% CI)**		
Complete Response												
7	randomised trials	serious[a]	not serious	not serious	serious[b]	none	68/174 (39.1%)	71/158 (44.9%)	**RR 0.92** (0.73 to 1.16)	**36 fewer per 1,000** (from 121	⨁⨁◯◯ Low	

										fewer to 72 more)		
Partial Response												
6	randomised trials	serious[a]	not serious	not serious	serious[b]	none	40/124 (32.3%)	36/108 (33.3%)	**RR 0.96** (0.66 to 1.39)	**13 fewer per 1,000** (from 113 fewer to 130 more)	⊕⊕◯◯ Low	
Complete plus Partial Response												
5	randomised trials	serious[a]	not serious	not serious	serious[b]	none	104/166 (62.7%)	98/158 (62.0%)	**RR 1.01** (0.86 to 1.18)	**6 more per 1,000** (from 87 fewer to 112 more)	⊕⊕◯◯ Low	
Level of Proteinuria (continuous)												
3	randomised trials	serious[a]	not serious	not serious	serious[b]	none	51	53	-	MD **0.8 higher** (0.28 lower to 1.89 higher)	⊕⊕◯◯ Low	
GFR change (continuous)												
1	randomised trials	serious[a]	not serious	not serious	extremely serious[b,c]	none	50	50	-	MD **2.5 lower** (17.21 lower to 12.21 higher)	⊕◯◯◯ Very low	
Adverse Events												
2	randomised trials	serious[d]	not serious	not serious	serious[b]	none	79/110 (71.8%)	91/112 (81.3%)	**RR 0.93** (0.82 to 1.04)	**57 fewer per 1,000** (from 146 fewer to 33 more)	⊕⊕◯◯ Low	
Leukopenia												

3	randomised trials	serious[d]	not serious	not serious	very serious[b,c]	none	15/55 (27.3%)	7/46 (15.2%)	**RR 1.47** (0.73 to 2.99)	**72 more per 1,000** (from 41 fewer to 303 more)	⊕◯◯◯ Very low	

Serious adverse events

2	randomised trials	serious[d]	not serious	not serious	very serious[b,c]	none	22/92 (23.9%)	23/89 (25.8%)	**RR 0.98** (0.49 to 1.95)	**5 fewer per 1,000** (from 132 fewer to 246 more)	⊕◯◯◯ Very low	

Infections

6	randomised trials	serious[d]	not serious	not serious	serious[b]	none	58/167 (34.7%)	59/156 (37.8%)	**RR 0.97** (0.69 to 1.35)	**11 fewer per 1,000** (from 117 fewer to 132 more)	⊕⊕◯◯ Low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Concerns on randomization and missing data.

b. Unable to discriminate clinically significant difference, 95% C.I. crosses 5% minimally important difference.

c. Small sample size

d. Concerns with randomization, missing data, and outcome ascertainment.

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Included studies:

Randomized clinical trials:

- 9

Comparative non-randomized studies: None

Non-comparative studies (single arm): None

Studies read and exclude: None

P8a and P8q. In SLE patients who have undergone initial therapy for active Class III/IV LN, is tapering steroids to less than 5 mg over less than 6 months versus more than 6 months associated with improved outcomes?

Populations:

- Class III/IV, III/IV plus V LN, with a complete or partial response after induction therapy.

Intervention:

- Oral steroids tapered to less than 5 mg over less than 6 months.

Populations:

- Oral steroids tapered to less than 5 mg over more than 6 months.

Outcomes:

- Reduction of proteinuria
- Preservation of kidney function
- Risk of LN flares
- ESKD (dialysis or transplant)
- Treatment-related adverse effects including infection; also decrease >30% from baseline eGFR for CNI's, depression/suicide for belimumab.
- Cumulative steroid dose

Table1. Included studies.

Study name (year) country	Study design	Population	Intervention	comparator	Tapering of steroids	Outcomes with available data	Outcome time point
Houssiau 2010 Belgium (27 European centers)	RCT	Age: >14 years, Adults/Pediatrics. class (III; IV, Vc; Vd)	Induction: CYC Maintenance: AZA	Induction: CYC Maintenance: MMF	Oral steroid was tapered to each a dose of <5 mg over more than 6 months.	ESRD, renal flare up, doubling of Cr, infection , leukopenia, Anemia,	3 years

Kaballo 2016 Sudan	RCT	>18 years. Adults African Class 3: 32/.81, Class 4: 34/81, Class 4/5: 15/81	Induction: CYC Maintenance: AZA	Induction: CYC Maintenance: MMF	Oral steroid was tapered to each a dose of 5 mg at 15 months	ESRD, Renal flare up, infection , Adverse events, complete remission, partial remission	3 years
Galbraith 2014 Canada	RCT	LN patients Adults, N=15 Mean (SD) age: 34.2 (11.2) Class III: 4 Class IV: 10 Class V: 8	LN with partial remission randomized to prednisone withdrawal. (tapered to 0 mg over a period of less than 6 months)	LN with partial remission randomized to prednisone continuation (tapered to 7.5 mg dose and then maintained (<10 mg))	This trial was only about tapering, data reported in the intervention and comparison. In the first arm if was tapered to a 0 mg in less than 6 months period	Adverse events; fracture; infection; risk of LN flares, T2DM	3 years

Evidence summary: There are no studies comparing tapering of steroids to less than 5 mg over less than or more than 6 months. We used single-arm data (both arms were included) about tapering from 3 RCTs addressing maintenance. Other RCTs about maintenance either don't report a specific tapering protocol or the protocol doesn't fit the PICO question. This data has many limitations as there are multiple other factors affecting the outcomes (maintenance therapy used, and population at baseline were both different within the study and between the studies)

Outcome	Study	Tapering	Outcome
Anemia	Houssiau 2010	Oral steroid was tapered to each a dose of <5 mg over more than 6 months.	2/105 (2%)
Doubling of Cr	Houssiau 2010	Oral steroid was tapered to each a dose of <5 mg over more than 6 months.	7/105 (7%)
ESRD	Houssiau 2010	Oral steroid was tapered to each a dose of <5 mg over more than 6 months.	2/105 (2%)
	Kaballo 2016	Oral steroid was tapered to each a dose of 5 mg at 15 months	5/81 (6%)
Renal flare ups	Houssiau 2010	Oral steroid was tapered to each a dose of <5 mg over more than 6 months.	23/105 (22%)
	Kaballo 2016	Oral steroid was tapered to each a dose of 5 mg at 15 months	8/81 (10%)
	Galbraith 2014	Oral steroid was tapered to 0 mg over a period of less than 6 months	1/7 (14%)
Infection	Houssiau 2010	Oral steroid was tapered to each a dose of <5 mg over more than 6 months.	57/105 (54%)
	Kaballo 2016	Oral steroid was tapered to each a dose of 5 mg at 15 months	21/81 (26%)
	Galbraith 2014	Oral steroid was tapered to 0 mg over a period of less than 6 months	2/7 (28%)

Leukopenia	Houssiau 2010	Oral steroid was tapered to each a dose of <5 mg over more than 6 months.	13/105 (12%)
Complete remission	Kaballo 2016	Oral steroid was tapered to each a dose of 5 mg at 15 months	44/81 (54%)
Partial remission	Kaballo 2016	Oral steroid was tapered to each a dose of 5 mg at 15 months	17/81 (21%)
AE	Kaballo 2016	Oral steroid was tapered to each a dose of 5 mg at 15 months	59/81 (73%)
	Galbraith 2014	Oral steroid was tapered to 0 mg over a period of less than 6 months	2/7 (73%)
Fracture	Galbraith 2014	Oral steroid was tapered to 0 mg over a period of less than 6 months	0/7
DM	Galbraith 2014	Oral steroid was tapered to 0 mg over a period of less than 6 months	0/7

References:

1. Houssiau, Frédéric A et al. "Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: results from the MAINTAIN Nephritis Trial." *Annals of the rheumatic diseases* vol. 69,12 (2010): 2083-9. doi:10.1136/ard.2010.131995
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3. Galbraith, Lauren et al. "The Steroids In the Maintenance of remission of Proliferative Lupus nephritis (SIMPL) pilot trial." Canadian journal of kidney health and disease vol. 1 30. 28 Nov. 2014, doi:10.1186/s40697-014-0030-9

Randomized clinical trial: none
Non-randomized study: none
Single arm study: 3

P8.b Steroid tapered to < 10 mg/d at < 6 mo vs Steroid tapered to < 10 mg/d at > 6 mo

Population: Patients with class III/IV LN
Intervention: Steroid regimen with other therapies: Steroid tapered to < 10 mg/d at < 6 months
Comparison: Steroid regimen with other therapies: Steroid tapered to < 10 mg/d at > 6 months
Outcomes:

- Reduction of proteinuria
- Preservation of kidney function
- Risk of LN flares
- ESKD (dialysis or transplant)
- Treatment related adverse effects including infection; also decrease >30% from baseline eGFR for CNI's, depression/suicide for belimumab
- Cumulative steroid dose

Table 1.

P8.b Steroid regimen with other therapies: Steroid tapered to < 10 mg/d at < 6 mo vs Steroid tapered to < 10 mg/d at > 6 mo

Study name	Study design	Population	Intervention details	Comparator details	Outcomes with available data	Outcome measures	Outcome timepoint

(year) country							
Galbraith 2014 Canada	RCT	LN patients Adults, N=15 Mean (SD) age: 34.2 (11.2) Class III: 4 Class IV: 10 Class V: 8	LN with partial remission randomized to prednisone withdrawal. (tapered to 0 mg over a period of less than 6 months)	LN with partial remission randomized to prednisone continuation (tapered to 7.5 mg dose and then maintained (<10 mg))	Adverse events; fracture; infection; risk of LN flares, T2DM	Risk ratio	3 years

Evidence summary:

There was 1 RCT with data comparing steroid tapered to 0 over < 6 months vs steroid tapered to < 10 mg/d at > 6 months (7.5 mg). This was a piloting trial. Adverse events and fractures were higher in the > 6 months group. The risk of LN flares was higher in the >6 months group. The overall certainty is very low certainty of the evidence due to the large concerns about imprecision (very small sample size and events) and risk of bias.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Steroid tapered to < 10 mg/d at < 6 mo	Steroid tapered to < 10 mg/d at > 6 mo	Relative (95% CI)	Absolute (95% CI)		
Adverse events												
1	randomised trials	serious	not serious	not serious	very serious[a]	none	2/7 (28.6%)	4/8 (50.0%)	**RR 0.57** (0.15 to 2.23)	**215 fewer per 1,000** (from 425 fewer to 615 more)	⨁◯◯◯ very low	
Fracture												
1	randomised trials	serious	not serious	not serious	very serious[a]	none	0/7 (0.0%)	1/8 (12.5%)	**RR 0.38** (0.02 to 7.96)	**78 fewer per 1,000** (from 123 fewer to 870 more)	⨁◯◯◯ very low	

Infection

1	randomised trials	serious	not serious	not serious	very serious[a]	none	2/7 (28.6%)	2/8 (25.0%)	**RR 1.14** (0.21 to 6.11)	**35 more per 1,000** (from 198 fewer to 1,000 more)	⊕◯◯◯ very low	

Risk of LN flares

1	randomised trials	serious	not serious	not serious	very serious[a]	none	1/7 (14.3%)	3/8 (37.5%)	**RR 0.38** (0.05 to 2.88)	**232 fewer per 1,000** (from 356 fewer to 705 more)	⊕◯◯◯ very low	

T2DM

1	randomised trials	serious	not serious	not serious	very serious[a]	none	0/7 (0.0%)	0/8 (0.0%)	not pooled	-	⊕◯◯◯ very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. very small sample size and event rate leading to wide CI

References

Galbraith L, Manns B, Hemmelgarn B, Walsh M. The Steroids In the Maintenance of remission of Proliferative Lupus nephritis (SIMPL) pilot trial. Can J Kidney Health Dis. 2014 Nov 28;1:30. doi: 10.1186/s40697-014-0030-9. PMID: 25780619; PMCID: PMC4349625.

Included studies: 1

Randomized clinical trials: 1
Comparative non-randomized studies: 0
Non-comparative studies (single arm): 0
Studies read and exclude: 0

P8.c After initial therapy CYC: cyclophosphamide quarterly for 2 years duration vs. MMF/MPA

Population: Patients with class III/IV LN
Intervention: Following initial therapy monthly IV CYC then Quarterly IV monthly CYC (NIH protocol) for two years
Comparison: Following initial therapy monthly IV CYC then MMF/MPA
Outcomes:

- Reduction of proteinuria
- Preservation of kidney function
- Risk of LN flares
- ESKD (dialysis or transplant)
- Treatment related adverse effects including infection; also decrease >30% from baseline eGFR for CNI's, depression/suicide for belimumab

- Cumulative steroid dose

Table 1.

P8.c Initial IV CYC, then Quarterly IV monthly CYC (NIH protocol) for two years vs MMF/MPA

Study name (year) country	Study design	Population	Intervention details	Comparator details	Outcomes with available data	Outcome measures	Outcome timepoint
Contreras 2004 USA	RCT	LN patients Adults, N=59 Mean (SD) age: AZA 33 (10), CYC 33 (12), MMF 32 (11) Ethnicity: Black/Hispanic Class III: 12 Class IV: 46 Class Vb: 1	IV CYC induction, then quarterly CYC maintenance	IV CYC induction, then MMF	Cumulative steroid dose, ESKD, infection, leukopenia, risk of LN flares	Risk ratio	1-3 years

Evidence summary:

There was 1 RCT with data comparing IV CYC maintenance vs MMF maintenance in patients with class III/IV after receiving monthly IV CYC induction therapy, with low certainty of the evidence (very low moderate certainty of evidence (concerns risk of bias (there are differences in the patient's baseline characteristics and about imprecision)). Progression to ESKD, infection, leukopenia, and risk of LN flares were higher in the CYC group maintenance group.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	cyclophosphamide quarterly for 2 years duration	MMF/MPA	Relative (95% CI)	Absolute (95% CI)		
Cumulative steroid dose (mg/kg/day)												
1	randomised trials	serious	not serious	not serious	serious[a]	none	20	20	-	MD **0.06 higher** (0.02 higher to 0.1 higher)	⨁⨁◯◯ Low	

ESKD

1	randomised trials	serious	not serious	not serious	serious[b]	none	3/20 (15.0%)	1/20 (5.0%)	**RR 3.00** (0.34 to 26.45)	**100 more per 1,000** (from 33 fewer to 1,000 more)	⊕⊕◯◯ Low	

Infection

1	randomised trials	serious	not serious	not serious	serious[b]	none	15/20 (75.0%)	6/20 (30.0%)	**RR 2.50** (1.22 to 5.11)	**450 more per 1,000** (from 66 more to 1,000 more)	⊕⊕◯◯ Low	

Leukopenia

1	randomised trials	serious	not serious	not serious	serious[b]	none	10/20 (50.0%)	2/20 (10.0%)	**RR 5.00** (1.25 to 19.99)	**400 more per 1,000** (from 25 more to 1,000 more)	⊕⊕◯◯ Low	

Risk of LN flares

1	randomised trials	serious	not serious	not serious	serious[b]	none	8/20 (40.0%)	3/20 (15.0%)	**RR 2.67** (0.82 to 8.62)	**251 more per 1,000** (from 27 fewer to 1,000 more)	⊕⊕◯◯ Low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. small sample size

b. small sample size leading to wide CI

References

Contreras G, Pardo V, Leclercq B, Lenz O, Tozman E, O'Nan P, Roth D. Sequential therapies for proliferative lupus nephritis. N Engl J Med. 2004 Mar 4;350(10):971-80. doi: 10.1056/NEJMoa031855. PMID: 14999109.

Included studies: 1

Randomized clinical trials: 1

Comparative non-randomized studies: 0

Non-comparative studies (single arm): 0

Studies read and exclude: 0

Lupus nephritis

PICO: 8 In SLE patients who have undergone initial therapy for active Class III/IV LN, is treatment with "X" compared to treatment with "Y" for subsequent therapy associated with improved outcomes?

P8.d After initial therapy CYC: cyclophosphamide quarterly for 2 years duration vs to AZA

Population: Patients with class III/IV LN
Intervention: Following initial therapy monthly IV CYC then Quarterly IV monthly CYC (NIH protocol) for two years
Comparison: Following initial therapy monthly IV CYC then AZA
Outcomes:

- Reduction of proteinuria
- Preservation of kidney function
- Risk of LN flares
- ESKD (dialysis or transplant)
- Treatment related adverse effects including infection; also decrease >30% from baseline eGFR for CNI's, depression/suicide for belimumab
- Cumulative steroid dose

Table 1.
P8.d Initial IV CYC, then Quarterly IV monthly CYC (NIH protocol) for two years vs AZA

Study name (year) country	Study design	Population	Intervention details	Comparator details	Outcomes with available data	Outcome measures	Outcome timepoint
Contreras 2004 USA	RCT	LN patients Adults, N=59 Mean (SD) age: AZA 33 (10), CYC 33 (12), MMF 32 (11) Ethnicity: Black/Hispanic Class III: 12 Class IV: 46 Class Vb: 1	IV CYC induction, then quarterly CYC maintenance	IV CYC induction, then AZA	Cumulative steroid dose, ESKD, infection, leukopenia, risk of LN flares	Risk ratio	1-3 years

Evidence summary:

There was 1 RCT with data comparing IV CYC maintenance vs AZA maintenance in patients with class III/IV after receiving monthly IV CYC induction therapy, with very low moderate certainty of evidence (concerns risk of bias (there are differences in the patient's baseline characteristics and about imprecision)). Progression to ESKD, infection, leukopenia, and risk of LN flares were higher in the CYC group.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	P.8d: After initial therapy CYC: cyclophosphamide quarterly for 2 years duration	to AZA	Relative (95% CI)	Absolute (95% CI)		
Cumulative steroid dose (mg/kg/day)												
1	randomised trials	serious	not serious	not serious	very serious[a]	none	20	19	-	MD **0.03 higher** (0.03 lower to 0.09 higher)	⨁⨁◯◯ very low	
ESKD												
1	randomised trials	serious	not serious	not serious	serious[b]	none	3/20 (15.0%)	1/19 (5.3%)	**RR 2.85** (0.32 to 25.07)	**97 more per 1,000** (from 36 fewer to 1,000 more)	⨁⨁◯◯ low	
Infection												
1	randomised trials	serious	not serious	not serious	serious[b]	none	15/20 (75.0%)	5/19 (26.3%)	**RR 2.85** (1.29 to 6.30)	**487 more per 1,000** (from 76 more to 1,000 more)	⨁⨁◯◯ low	
Leukopenia												
1	randomised trials	serious	not serious	not serious	serious[b]	none	10/20 (50.0%)	6/19 (31.6%)	**RR 1.58** (0.72 to 3.50)	**183 more per 1,000** (from 88 fewer to 789 more)	⨁⨁◯◯ low	
Risk of LN flares												

1	randomised trials	serious	not serious	not serious	Very serious[b]	none	8/20 (40.0%)	6/19 (31.6%)	**RR 1.27** (0.54 to 2.97)	**85 more per 1,000** (from 145 fewer to 622 more)	⨁◯◯◯ very low	

CI: confidence interval; MD: mean difference; RR: risk ratio

Explanations

a. low sample size

b. low sample size leading to wide CI

References

Contreras G, Pardo V, Leclercq B, Lenz O, Tozman E, O'Nan P, Roth D. Sequential therapies for proliferative lupus nephritis. N Engl J Med. 2004 Mar 4;350(10):971-80. doi: 10.1056/NEJMoa031855. PMID: 14999109.

Included studies: 1
Randomized clinical trials: 1
Comparative non-randomized studies: 0
Non-comparative studies (single arm): 0
Studies read and excluded:

-Grootscholten, C et al. "Azathioprine/methylprednisolone versus cyclophosphamide in proliferative lupus nephritis. A randomized controlled trial." Kidney international vol. 70,4 (2006): 732-42. doi:10.1038/sj.ki.5001630. **Reason:** AZA was part of the induction therapy

P8.e After initial therapy CYC: MMF vs AZA

Population: Patients with class III/IV LN
Intervention: Following initial therapy monthly IV CYC then MMF
Comparison: Following initial therapy monthly IV CYC then AZA
Outcomes:

- Reduction of proteinuria
- Preservation of kidney function
- Risk of LN flares
- ESKD (dialysis or transplant)
- Treatment related adverse effects including infection; also decrease >30% from baseline eGFR for CNI's, depression/suicide for belimumab
- Cumulative steroid dose

Table 1.

P8.e Initial IV CYC, then MMF vs AZA

Study name	Study design	Population	Intervention details	Comparator details	Outcomes with available data	Outcome measures	Outcome timepoint

(year) country							
Contreras 2004 USA	RCT	LN patients Adults, N=59 Mean (SD) age: AZA 33 (10), CYC 33 (12), MMF 32 (11) Ethnicity: Black/Hispanic Class III: 12 Class IV: 46 Class Vb: 1	IV CYC induction, then quarterly CYC maintenance	IV CYC induction, then MMF or AZA	Cumulative steroid dose, ESKD, infection, leukopenia, risk of LN flares	Risk ratio	1-3 years
Houssiau 2010 Belgium	RCT	LN patients Adults/Pediatrics, N=105 Mean (SD) age: AZA 33 (11), MMF 33 (10) Ethnicity (Caucasian/Asian/Black): AZA 41/4/7, MMF 42/5/6 Class III: 33 Class IV: 61 Class Vc: 3 Class Vd: 8	IV CYC induction, then MMF	IV CYC induction, then AZA	Anemia, ESKD, infection, leukopenia, preservation of kidney function, risk of LN flares	Risk ratio	48 months
Kaballo 2016 Sudan	RCT	LN patients Adults, N=81 Mean (SD) age: AZA 29.4 (11.6), MMF 27.1 (9.8) Ethnicity: African (Sudanese) Class III: 32 Class IV: 34 Class V + VI: 15	IV CYC induction, then MMF	IV CYC induction, then AZA	Adverse events, complete remission, ESKD, infection, partial remission, risk of LN flares	Risk ratio	36 months

Evidence summary:

There were 3 RCTs with data comparing maintenance with MMF vs AZA maintenance in patients with class III/IV after receiving monthly IV CYC induction therapy. For the adverse events, Anemia, and Leukopenia, Infection, rates were lower in MMF versus AZA. Patients on MMF had 45 fewer/1000 (CI: 210 fewer to 173 more), 31 fewer per 1,000 (from 38 fewer to 115 more), 182 fewer per 1,000 (from 220 fewer to 79 fewer), 76 more per 1,000 (from 40 fewer to 234 more), respectively. For complete, and partial remission, rates were higher in MMF compared to AZA with 37 more per 1,000 (from 147 fewer to 310 more) and 68 more per 1,000 (from 72 fewer to 402 more), respectively. ESRD was lower in MMF, 10 fewer per 1,000 (from 36 fewer to 82 more). Flare-up rates were lower in the MMF arm with 58 fewer per 1,000 (from 122 fewer to 56 more). The overall certainty of evidence is low due to concerns about the risk of bias (patients had differences in baseline characteristics and also lost to follow-up) and imprecision.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	P.8e: After initial therapy CYC: MMF	to AZA	Relative (95% CI)	Absolute (95% CI)		
Adverse events												
1	randomised trials	serious	not serious	not serious	serious[a]	none	29/41 (70.7%)	30/40 (75.0%)	**RR 0.94** (0.72 to 1.23)	**45 fewer per 1,000** (from 210 fewer to 173 more)	⨁⨁◯◯ Low	
Anemia												
1	randomised trials	serious	not serious	not serious	serious[b]	none	0/53 (0.0%)	2/52 (3.8%)	**RR 0.20** (0.01 to 3.99)	**31 fewer per 1,000** (from 38 fewer to 115 more)	⨁⨁◯◯ Low	
Complete remission												
1	randomised trials	serious	not serious	not serious	serious[a]	none	23/41 (56.1%)	21/40 (52.5%)	**RR 1.07** (0.72 to 1.59)	**37 more per 1,000** (from 147 fewer to 310 more)	⨁⨁◯◯ Low	
Cumulative steroid dose												

1	randomised trials	serious	not serious	not serious	serious[a]	none	20	19	-	MD **0.03 lower** (0.08 lower to 0.02 higher)	⊕⊕◯◯ Low	

ESKD

3	randomised trials	serious	not serious	not serious	serious[a]	none	4/114 (3.5%)	5/111 (4.5%)	**RR 0.78** (0.21 to 2.82)	**10 fewer per 1,000** (from 36 fewer to 82 more)	⊕⊕◯◯ Low	

Infection

3	randomised trials	serious	not serious	not serious	serious[a]	none	49/114 (43.0%)	40/111 (36.0%)	**RR 1.21** (0.89 to 1.65)	**76 more per 1,000** (from 40 fewer to 234 more)	⊕⊕◯◯ Low	

Leukopenia

2	randomised trials	serious	not serious	not serious	serious[a]	none	4/73 (5.5%)	17/71 (23.9%)	**RR 0.24** (0.08 to 0.67)	**182 fewer per 1,000** (from 220 fewer to 79 fewer)	⊕⊕◯◯ Low	

Partial remission

1	randomised trials	serious	not serious	not serious	serious[b]	none	10/41 (24.4%)	7/40 (17.5%)	**RR 1.39** (0.59 to 3.30)	**68 more per 1,000** (from 72 fewer to 402 more)	⊕⊕◯◯ Low	

Preservation of kidney function (doubling of cr)

1	randomised trials	serious	not serious	not serious	serious[b]	none	3/53 (5.7%)	4/52 (7.7%)	**RR 0.74** (0.17 to 3.13)	**20 fewer per 1,000** (from 64	⊕⊕◯◯ Low	

										fewer to 164 more)		

Risk of LN flares

3	randomised trials	serious	not serious	not serious	serious[a]	none	17/114 (14.9%)	23/111 (20.7%)	**RR 0.72** (0.41 to 1.27)	**58 fewer per 1,000** (from 122 fewer to 56 more)	⊕⊕◯◯ Low	

CI: confidence interval; MD: mean difference; RR: risk ratio

Explanations

a. low sample size

b. low sample size leading to wide CI

References

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2. Houssiau FA, D'Cruz D, Sangle S, Remy P, Vasconcelos C, Petrovic R, Fiehn C, de Ramon Garrido E, Gilboe IM, Tektonidou M, Blockmans D, Ravelingien I, le Guern V, Depresseux G, Guillevin L, Cervera R; MAINTAIN Nephritis Trial Group. Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: results from the MAINTAIN Nephritis Trial. Ann Rheum Dis. 2010 Dec;69(12):2083-9. doi: 10.1136/ard.2010.131995. Epub 2010 Sep 10. PMID: 20833738; PMCID: PMC3002764.

3. Kaballo BG, Ahmed AE, Nur MM, Khalid IO, Abu-Aisha H. Mycophenolate mofetil versus azathioprine for maintenance treatment of lupus nephritis. Saudi J Kidney Dis Transpl. 2016 Jul-Aug;27(4):717-25. doi: 10.4103/1319-2442.185233. PMID: 27424688.

Included studies: 3

Randomized clinical trials: 3

Comparative non-randomized studies: 0

Non-comparative studies (single arm): 0

Studies read and exclude: 0

P8.I.M In SLE (peds) patients who have undergone initial therapy for active Class III/IV LN, is treatment with “X” compared to treatment with “Y” for subsequent therapy associated with improved outcomes?

Intervention: CNI plus MMF

Outcomes:

- Reduction of proteinuria
- Preservation of kidney function
- Risk of LN flares
- ESKD (dialysis or transplant)
- Treatment related adverse effects including infection; also decrease >30% from baseline eGFR for CNI’s, depression/suicide for belimumab
- Cumulative steroid dose
-

Patient important outcomes (addressed in the study only):

- Proteinuria
- Preservation of kidney function: creatinine, eGFR.

- Flares
- Adverse events (Decrease in eGFR and infections)

Table 1. PICO 8. CNI plus MMF for subsequent therapy in LN in pediatric population							
Study name (year) country	**Study design**	**Population**	**Intervention details**	**Comparator details**	**Outcomes with available data**	**Outcome measures**	**Outcome time point**
Zheng, 2023 China	Single arm	LN patients 34/36 were biopsied III:3/34, IV:10/34, V:1/34, V+III:5/34, V+IV:15/34 Age: mean ± SD: 11 (8-12) Ethnicity: Asians	**MMF** was initiated at 10–15 mg/kg.d (maximum 1 g/d), twice daily (every 12 h). The dosage was titrated to maintain an area under the time concentration curve (AUC) from 0 to 12 h of MMF between 20 and 45 mg.h/L. **At the maintenance phase, the dosage of MMF was maintained between 0.25 and 0.5 g/d**. **Tacrolimus** was initiated at 0.1 mg/kg.d (maximum 4 mg/d), twice daily (every 12 h), maintaining a blood concentration between 5 and 7 ng/mL. **At the maintenance phase, blood concentration was maintained between 1 and 2 ng/mL.**	There is no comparator (single arm study)	Proteinuria Creatinine eGFR Flares Adverse events (decrease in eGFR and infections)	Proportions	Proteinuria, creatinine, eGFR: 12 and 24 months Flares, adverse events: Follow-up time: 37.5 months

Evidence summary:

This single-arm study evaluated multitargeted therapy in 36 Chinese children with lupus nephritis as initial and subsequent therapy with debutant disease but also refractory to conventional therapy.
In terms of efficacy, a decrease in proteinuria of more than 2 grams was observed at 12 and 24 months. eGFR maintained stable values at 12 and 24 months.
The follow-up period was 37.5 months (IQR 14.0-53.3). The LN recurrence rate was 5/36 (13.8%).
The infection rate was 11.1% during the entire follow-up period.

Outcomes (Name + Summary)	Author, year, RefID	Study type	Duration of follow up	Population (number and description, age)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Proteinuria	Zheng, 2023. (ID: 10270)	Non-comparative	12 months	- Patients with LN III, IV, III+V, IV+V.	**MMF** was initiated at 10–15 mg/kg.d (maximum 1 g/d), twice daily (every 12 h). The dosage was titrated to maintain an area under the time concentration curve (AUC) from 0 to 12 h of MMF between 20 and 45 mg.h/L. **At the maintenance phase, the dosage of MMF was maintained between 0.25 and 0.5 g/d**. **Tacrolimus** was initiated at 0.1 mg/kg.d (maximum 4 mg/d), twice daily (every 12 h), maintaining a blood concentration between 5 and 7 ng/mL. **At the maintenance phase, blood concentration was maintained between 1 and 2 ng/mL.**	Proteinuria in gr median (IQR) Baseline: 2.45 (1.76–5.76) 12 months*: 0.10 (0.09–0.19)	Proteinuria is 24h proteinuria
Proteinuria	Zheng, 2023. (ID: 10270)	Non-comparative	24 months	- Patients with LN III, IV, III+V, IV+V.	**MMF** was initiated at 10–15 mg/kg.d (maximum 1 g/d), twice daily (every 12 h). The dosage was titrated to maintain an area under the time concentration curve (AUC) from 0 to 12 h of MMF between 20 and 45 mg.h/L. **At the maintenance phase, the dosage of MMF was maintained between 0.25 and 0.5 g/d**. **Tacrolimus** was initiated at 0.1 mg/kg.d (maximum 4 mg/d), twice daily (every 12 h), maintaining a blood concentration between 5 and 7 ng/mL. **At the maintenance phase, blood concentration was maintained between 1 and 2 ng/mL.**	Proteinuria in gr median (IQR) Baseline: 2.45 (1.76–5.76) 24 months: 0.10 (0.10–0.24)	Proteinuria is 24h proteinuria
SCR (μmol/L)	Zheng, 2023. (ID: 10270)	Non-comparative	12 months	- Patients with LN III, IV, III+V, IV+V.	MMF + Tacrolimus at the same dose describe above.	Scr in umol/L median (IQR) Baseline: 50.0 (41.0–55.5) 12 months: 46.5 (42.0–58.0)	
SCR (μmol/L)	Zheng, 2023. (ID: 10270)	Non-comparative	24 months	- Patients with LN III, IV, III+V, IV+V.	MMF + Tacrolimus at the same dose describe above.	Scr in umol/L median (IQR) Baseline: 50.0 (41.0–55.5)	

						24 months: 45.5 (40.5–64.3)	
eGFR (ml/min/1.73 m2)	Zheng, 2023. (ID: 10270)	Non-comparative	12 months	- Patients with LN III, IV, III+V, IV+V.	MMF + Tacrolimus at the same dose describe above.	eGFR in ml/min median (IQR) Baseline: 104.7 (91.0–125.3) 12 months: 107.8 (93.2–119.0)	
eGFR (ml/min/1.73 m2)	Zheng, 2023. (ID: 10270)	Non-comparative	24 months	- Patients with LN III, IV, III+V, IV+V.	MMF + Tacrolimus at the same dose describe above.	eGFR in ml/min median (IQR) Baseline: 104.7 (91.0–125.3) 24 months: 112.2 (88.2–127.8)	
Flare or relapse	Zheng, 2023. (ID: 10270)	Non-comparative	37.5 months (IQR 14.0–53.3)	- Patients with LN III, IV, III+V, IV+V.	MMF + Tacrolimus at the same dose describe above.	5/36 (13.8%)	Proteinuric relapse was defined as the level of 24-h-UP increasing to more than 1 g after CR or more than 2 g after PR. Nephritic relapse was defined as the level of SCR increasing by more than 30% (or the level of eGFR decreasing by more than 10%), accompanied by the number of urinary red blood cells per high-power field of more than ten, which was glomerular hematuria after remission.

							The follow-up time of 36 children was 37.5 (IQR 14.0–53.3) months.
Adverse event (Decrease in eGFR)	Zheng, 2023. (ID: 10270)	Non-comparative	24 months	- Patients with LN III, IV, III+V, IV+V.	MMF + Tacrolimus at the same dose describe above.	eGFR (ml/min) median (IQR) baseline: 104.7 (91.0–125.3) 24 months: 112.2 (88.2–127.8)	This is the longest follow up that the eGFR is reported (24 months)
Adverse event (Infection)	Zheng, 2023. (ID: 10270)	Non-comparative	37.5 months (IQR 14.0–53.3)	- Patients with LN III, IV, III+V, IV+V.	MMF + Tacrolimus at the same dose describe above.	4/36 (11.1)	Infection including pneumonia, CMV infection, intestinal fungal infection, and paronychia was observed in one case each, all of them recovered after antibiotic treatments and discontinuation of multi-target therapy.

Reference: Zheng, X., Ouyang, X., Cheng, C. *et al.* Efficacy and safety of multi-target therapy in children with lupus nephritis. *Pediatr Res* **94**, 2040–2046 (2023). https://doi.org/10.1038/s41390-023-02747-3

P8j and P8e. In SLE patients who have undergone initial therapy for active Class III/IV LN, is treatment with AZA compared to treatment with MMF for subsequent therapy associated with improved outcomes?

Populations:
- Class III/IV, III/IV plus V LN, with a complete or partial response after induction therapy.

Intervention:
- AZA

Populations:
- MMF/MPA

Outcomes:
- Reduction of proteinuria

- Preservation of kidney function
- Risk of LN flares
- ESKD (dialysis or transplant)
- Treatment-related adverse effects including infection; also decrease >30% from baseline eGFR for CNI's, depression/suicide for belimumab.
- Cumulative steroid dose

Table1. Included studies.

Study name (year) country	Study design	Population	Intervention	comparator	Outcomes with available data	Outcome time point
Houssiau 2010 Belgium (27 European centers)	RCT	Age: >14 years, Adults/Pediatrics. class (III; IV, Vc; Vd)	Induction: CYC Maintenance: AZA	Induction: CYC Maintenance: MMF	ESRD, renal flare up, doubling of Cr, infection , leukopenia, Anemia,	3 years
Zhang 2022 China	RCT	18-65 years, Adults. Asian Classes III, IV, V, V + IlI or V + IV.	Induction: CYC Maintenance: AZA	Induction: MMF Maintenance: MMF	ESRD, Renal flare up, infection , cytopenia	60 months
Sundel 2012 Multinational	RCT	<18 years, Pediatrics: Subgroup analysis of pediatric data from **Dooley et al.**	Induction: CYC or MMF Maintenance: AZA	Induction: CYC or MMF Maintenance: MMF	ESRD, Renal flare up, doubling of Cr, Adverse events, , serious adverse events, adverse event leading to withdrawel, Infection,	3 years
Kaballo 2016 Sudan	RCT	>18 years. Adults African Class 3: 32/.81, Class 4: 34/81, Class 4/5: 15/81	Induction: CYC Maintenance: AZA	Induction: CYC Maintenance: MMF	ESRD, Renal flare up, infection , Adverse events, complete remission, partial remission	3 years
Dooley 2011 Multinational	RCT	Mean (SD) age: MMF 31.8±10.59, AZA 31.0±10.77. Adults/Pediatrics White: 48 (41.4%) vs 51 (45.9%) Black: 12 (10.3%) vs 11 (9.9%) Asian: 39 (33.6%) versus 37 (33.3) Class 3 or 3/5: MMF 17 (14.7%), AZA 12 (10.8%);	Induction: CYC or MMF Maintenance: AZA	Induction: CYC or MMF Maintenance: MMF	ESRD, Renal flare up, doubling of Cr, Adverse events, , serious adverse events, adverse event leading to withdrawel, Infection,	3 years

		Class 4 or 4/5: MMF 81 (69.8%), AZA 82 (73.9%), Class 5: MMF 18 (15.5%), AZA 17 (15.3%)				
Contreras 2004	RCT	Mean (SD) age: AZA 33 (10), CYC 33 (12), MMF 32 (11). Adults. Black: 27/59 Hispanic: 29/59 White: 3/59 All class 3, 4 (except one patient)	Induction: CYC Maintenance: AZA	Induction: CYC Maintenance: MMF	ESRD, Renal flare up, cumulative steroid dose, Leukopenia, Infection,	3 years

Evidence summary:
5 RCTs addressed the comparison of AZA versus MMF for maintenance therapy. Induction therapy was CYC or MMF in all the trials. Rates of ESRD, LN flare up, adverse events leading to withdrawal, serious adverse events, Anemia, doubling of Cr, and cytopenia were higher in the AZA maintenance arm when compared to the MMF maintenance arm while there was no important difference in the rates of Adverse events and infections between both arms. The overall certainty of the evidence was judged as low due to concerns about the risk of bias and imprecision (small number of events, wide CI).
The evidence for the pure pediatric population was derived from Sundel et al (a subgroup of Dooley et al). The evidence from pediatrics aligns with what was mentioned in the adult's section. The overall certainty was very low (concerns about risk of bias and imprecision).

Note: We compared AZA versus MMF for maintenance without considering the induction therapy used. For pure CYC as induction therapy, we have trials addressing it (we did a separate evidence report for it), but for MMF as induction therapy, we don't have any trial comparing maintenance therapy based on MMF induction in all patients.

Evidence profile (Adults or Mixed Adults/pediatrics):

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**AZA**	**MMF/MPA**	**Relative (95% CI)**	**Absolute (95% CI)**		
ESKD (dialysis or transplant)												
5	randomised trials	serious[a]	not serious	not serious	serious[b]	none	8/261 (3.1%)	5/277 (1.8%)	**RR 1.43** (0.47 to 4.31)	**8 more per 1,000** (from 10 fewer to 60 more)	⨁⨁◯◯ Low	

LN flare up

5	randomised trials	serious[a]	not serious	not serious	serious[c]	none	57/261 (21.8%)	42/277 (15.2%)	**RR 1.44** (1.00 to 2.07)	**67 more per 1,000** (from 0 fewer to 162 more)	⊕⊕◯◯ Low	

Adverse events leading to withdrawal

1	randomised trials	serious[a]	not serious	not serious	serious[c]	none	44/111 (39.6%)	29/115 (25.2%)	**RR 1.57** (1.06 to 2.32)	**144 more per 1,000** (from 15 more to 333 more)	⊕⊕◯◯ Low	

Adverse events

2	randomised trials	serious[a]	not serious	not serious	not serious	none	138/151 (91.4%)	142/156 (91.0%)	**RR 0.99** (0.95 to 1.03)	**9 fewer per 1,000** (from 46 fewer to 27 more)	⊕⊕⊕◯ Moderate	

Serious adverse events

1	randomised trials	serious[a]	not serious	not serious	serious[c]	none	37/111 (33.3%)	27/115 (23.5%)	**RR 1.42** (0.93 to 2.17)	**99 more per 1,000** (from 16 fewer to 275 more)	⊕⊕◯◯ Low	

Cumulative steroid dose (mg/kg/day)

1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	19	20	-	MD **0.03 higher** (0.02 lower to 0.08 higher)	⊕⊕◯◯ Low	

Anemia

1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	2/52 (3.8%)	0/53 (0.0%)	**RR 5.09** (0.25 to 103.62)	**0 fewer per 1,000**	⊕⊕◯◯ Low	

										(from 0 fewer to 0 fewer)		
Doubling of serum Cr												
2	randomised trials	serious[a]	not serious	not serious	serious[b]	none	9/163 (5.5%)	4/169 (2.4%)	**RR 2.08** (0.63 to 6.88)	**26 more per 1,000** (from 9 fewer to 139 more)	⊕⊕◯◯ Low	
Cytopenia												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	4/39 (10.3%)	2/47 (4.3%)	**RR 2.41** (0.47 to 12.47)	**60 more per 1,000** (from 23 fewer to 488 more)	⊕⊕◯◯ Low	
Infection												
6	randomised trials	serious[a]	not serious	not serious	not serious	none	143/269 (53.2%)	162/284 (57.0%)	**RR 0.95** (0.84 to 1.07)	**29 fewer per 1,000** (from 91 fewer to 40 more)	⊕⊕⊕◯ Moderate	
Leukopenia												
2	randomised trials	serious[a]	not serious	not serious	serious[b]	none	17/71 (23.9%)	4/73 (5.5%)	**RR 4.22** (1.50 to 11.89)	**176 more per 1,000** (from 27 more to 597 more)	⊕⊕◯◯ Low	
Complete remission												
1	randomised trials	serious[a]	not serious	not serious	serious[d]	none	21/40 (52.5%)	23/41 (56.1%)	**RR 0.94** (0.63 to 1.40)	**34 fewer per 1,000** (from 208 fewer to 224 more)	⊕⊕◯◯ Low	

Partial remission

1	randomised trials	serious[a]	not serious	not serious	serious[d]	none	7/40 (17.5%)	10/41 (24.4%)	**RR 0.72** (0.30 to 1.70)	**68 fewer per 1,000** (from 171 fewer to 171 more)	⊕⊕◯◯ Low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. We used ROB 2 for the assessment of the risk of bias. We downgraded because of concerns related to loss to follow and concerns that patients were different at baseline in some trials.

b. We downgraded for imprecision because of a small number of events.

c. We downgraded for imprecision because of wide CI.

d. We downgraded for imprecision because of the small sample size.

Evidence profile (Pediatrics):

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**AZA**	**MMF (peds)**	**Relative (95% CI)**	**Absolute (95% CI)**		
Adverse events												
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	8/8 (100.0%)	8/8 (100.0%)	**RR 1.00** (0.80 to 1.25)	**0 fewer per 1,000** (from 200 fewer to 250 more)	⊕◯◯◯ Very low	
Flare ups												
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	5/8 (62.5%)	1/8 (12.5%)	**RR 5.00** (0.74 to 33.78)	**500 more per 1,000** (from 33 fewer to 1,000 more)	⊕◯◯◯ Very low	
Adverse events leading to withdrawal												
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	5/8 (62.5%)	3/8 (37.5%)	**RR 1.67** (0.59 to 4.73)	**251 more per 1,000** (from 154	⊕◯◯◯ Very low	

										fewer to 1,000 more)		

Doubling of Cr

1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	1/8 (12.5%)	0/8 (0.0%)	**RR 3.00** (0.14 to 64.26)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕◯◯◯ Very low	

Serious adverse events

1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	3/8 (37.5%)	1/8 (12.5%)	**RR 3.00** (0.39 to 23.07)	**250 more per 1,000** (from 76 fewer to 1,000 more)	⊕◯◯◯ Very low	

Infection

1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	6/8 (75.0%)	7/8 (87.5%)	**RR 0.86** (0.53 to 1.38)	**123 fewer per 1,000** (from 411 fewer to 332 more)	⊕◯◯◯ Very low	

ESRD

1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	2/8 (25.0%)	0/8 (0.0%)	**RR 5.00** (0.28 to 90.18)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕◯◯◯ Very low	

Explanations

a. We downgraded for risk of bias due to concerns about the randomization process as these were subgroups from Dooley et al.

b. We downgraded twice for imprecision because of the small sample size and number of events.

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6. Contreras, Gabriel et al. “Sequential therapies for proliferative lupus nephritis.” *The New England journal of medicine* vol. 350,10 (2004): 971-80. doi:10.1056/NEJMoa031855

Randomized clinical trials: 6
Nonrandomized studies: none
Single-arm studies: none
Read and excluded: None

P8.f.k. Belimumab plus standard of care versus standard of care

Population: Patients with class III/IV LN
Intervention: Belimumab plus standard of care
Comparison: standard of care
Outcomes:

- Reduction of proteinuria
- Preservation of kidney function
- Risk of LN flares
- ESKD (dialysis or transplant)
- Treatment-related adverse effects including infection; also decrease >30% from baseline eGFR for CNI’s, depression/suicide for belimumab
- Cumulative steroid dose

Table 1.

P8.k Initial IV CYC, then MMF/MPA plus belimumab versus MMF/MPA

Study name (year) country	Study design	Population	Intervention details	Comparator details	Outcomes with available data	Outcome measures	Outcome timepoint
Furie 2020 International	RCT	LN patients Adults, N=448 Mean (SD) age: BEL 33.7 (10.7), placebo 33.1 (10.6) Asian: 223/446 White: 148/446 Black: 61/446	Belimumab plus standard of care	Standard of care	Adverse events, adverse events leading to withdrawal, complete remission, partial remission, depression/suicide, ESKD, infection, partial remission, reduction of proteinuria, serious adverse events, serum Cr.	Risk ratio	104 weeks

		American Indian or Alaska Native: 10/446 Class III or IV: 258 Class III and V or Class IV and V: 116 Class V: 72					

Evidence summary: There was 1 RCT with data comparing belimumab + standard of care versus standard of care. Standard of care consists of either CYC for induction followed by AZA or MMF/MPA for induction and maintenance. Outcomes were assessed at 104 weeks (no outcomes were assessed at the end of induction therapy). This trial addresses both induction and maintenance together. The overall certainty of the evidence was judged as moderate. There are concerns about imprecision only (small number of events or wide CI). Complete remission was higher in the Belimumab arm, **103 more per 1,000** (from 18 more to 221 more) while there were no clinically important differences for the partial remission. No ESRD events in the Belimumab arm versus one event in the Placebo arm. The rate of adverse events, Adverse events, Infection, leading to withdrawal was similar between both arms. Depression/Suicide rates were 22 fewer per 1,000 (from 48 fewer to 32 more).

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Belimumab plus standard of care	standard of care	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Complete remission												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	67/223 (30.0%)	44/223 (19.7%)	**RR 1.52** (1.09 to 2.12)	**103 more per 1,000** (from 18 more to 221 more)	⊕⊕⊕◯ Moderate	
Partial remission												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	39/223 (17.5%)	38/223 (17.0%)	**RR 1.03** (0.68 to 1.54)	**5 more per 1,000** (from 55 fewer to 92 more)	⊕⊕⊕◯ Moderate	
ESRD												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	0/223 (0.0%)	1/223 (0.4%)	**RR 0.33** (0.01 to 8.14)	**3 fewer per 1,000** (from 4	⊕⊕⊕◯ Moderate	

										fewer to 32 more)		
Adverse events												
1	randomised trials	not serious	not serious	not serious	not serious	none	214/224 (95.5%)	211/224 (94.2%)	**RR 1.01** (0.97 to 1.06)	**9 more per 1,000** (from 28 fewer to 57 more)	⊕⊕⊕⊕ High	
Adverse events leading to withdrawal												
1	randomised trials	not serious	not serious	not serious	serious	none	29/224 (12.9%)	29/224 (12.9%)	**RR 1.00** (0.62 to 1.62)	**0 fewer per 1,000** (from 49 fewer to 80 more)	⊕⊕⊕◯ Moderate	
Infection												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	15/224 (6.7%)	18/224 (8.0%)	**RR 0.83** (0.43 to 1.61)	**14 fewer per 1,000** (from 46 fewer to 49 more)	⊕⊕⊕◯ Moderate	
doubling of serum Cr												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	1/224 (0.4%)	1/224 (0.4%)	**RR 1.00** (0.06 to 15.89)	**0 fewer per 1,000** (from 4 fewer to 66 more)	⊕⊕⊕◯ Moderate	
Serious adverse events												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	58/224 (25.9%)	67/224 (29.9%)	**RR 0.87** (0.64 to 1.17)	**39 fewer per 1,000** (from 108 fewer to 51 more)	⊕⊕⊕◯ Moderate	
Depression/suicide												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	11/224 (4.9%)	16/224 (7.1%)	**RR 0.69** (0.33 to 1.45)	**22 fewer per 1,000** (from 48	⊕⊕⊕◯ Moderate	

										fewer to 32 more)		

Urinary protein to cr ratio (<0.5)

1	randomised trials	not serious	not serious	not serious	serious[a]	none	88/131 (67.2%)	70/124 (56.5%)	**RR 1.19** (0.98 to 1.45)	**107 more per 1,000** (from 11 fewer to 254 more)	⊕⊕⊕◯ Moderate	

CI: confidence interval; **RR:** risk ratio
Explanations
a. We downgraded for imprecision because of the wide CI
b. We downgrade for imprecision because of small number of events

References
Furie R, Rovin BH, Houssiau F, Malvar A, Teng YKO, Contreras G, Amoura Z, Yu X, Mok CC, Santiago MB, Saxena A, Green Y, Ji B, Kleoudis C, Burriss SW, Barnett C, Roth DA. Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis. N Engl J Med. 2020 Sep 17;383(12):1117-1128. doi: 10.1056/NEJMoa2001180. PMID: 32937045.
Included studies: 1
Randomized clinical trials: 1
Comparative non-randomized studies: None
Non-comparative studies (single arm): None
Studies read and exclude: None

P8. i,n: After initial therapy: MMF/MPA plus anti-CD-20 therapy vs. MMF/MPA alone.

Population: SLE patients with LN
Intervention: MMF/MPA plus anti-CD-20 therapy
Comparison: MMF/MPA alone
Outcomes:

- Complete response
- Complete plus partial response
- Level of proteinuria
- Adverse events
- Serious adverse events

Table 1. Included studies.

Study name (year)	Study design	Population	Intervention details	Comparator details	Outcomes with available data	Outcome measures	Outcome timepoint

Furie 2022 Multicentric	RCT	Adults from Multiple ethnicities with active LN or active/chronic LN within 6 months of screening (concomitant class V was permitted). Total patients with Patients with kidney biopsy had Class IV lupus nephritis 75 (66%) and concomitant class V were 37 (33%) mean age (SD) in obinituzumab group was 33.1 (9.8) and in placebo group 31.9(10.1).	Obinutuzumab + MMF	MMF alone	Complete response, Complete plus partial response. Adverse events, Serious adverse events	RR	104 weeks

Evidence summary:
One RCT addressed MMF/MPA plus anti-CD-20 therapy versus MMF/MPA alone. Outcomes were reported at 104 weeks. Induction and maintenance were MMF/MPA plus anti-CD-20 therapy versus MMF/MPA alone. Response (complete or complete plus partial) favored MMF/MPA plus anti-CD-20 therapy. Serious adverse events were **38 fewer per 1,000** (from 148 fewer to 160 more) in MMF/MPA plus anti-CD-20 therapy versus MMF/MPA alone. The overall certainty is low due to imprecision (small sample size)

Evidence profile:

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Anti-CD20 plus MMF/MPA**	**MMF/MPA**	**Relative (95% CI)**	**Absolute (95% CI)**	
Complete response											
1	randomised trials	not serious	not serious	not serious	serious[a]	none	26/63 (41.3%)	14/62 (22.6%)	**RR 1.83** (1.06 to 3.16)	**187 more per 1,000** (from 14 more to 488 more)	⨁⨁⨁◯ Moderate
Complete plus partial response											
1	randomised trials	not serious	not serious	not serious	serious[a]	none	34/63 (54.0%)	18/62 (29.0%)	**RR 1.86** (1.18 to 2.92)	**250 more per 1,000** (from 52 more to 557 more)	⨁⨁⨁◯ Moderate

UPCR <0.5

1	randomised trials	not serious	not serious	not serious	very serious[a]	none	23/63 (36.5%)	39/62 (62.9%)	**RR 0.58** (0.40 to 0.85)	**264 fewer per 1,000** (from 377 fewer to 94 fewer)	⊕⊕◯◯ Low

Adverse events

1	randomised trials	not serious	not serious	not serious	serious[a]	none	58/63 (92.1%)	54/62 (87.1%)	**RR 1.06** (0.94 to 1.19)	**52 more per 1,000** (from 52 fewer to 165 more)	⊕⊕⊕◯ Moderate

Serious adverse events

1	randomised trials	not serious	not serious	not serious	very serious[a]	none	16/63 (25.4%)	18/62 (29.0%)	**RR 0.87** (0.49 to 1.55)	**38 fewer per 1,000** (from 148 fewer to 160 more)	⊕⊕◯◯ Low

CI: confidence interval; **RR:** risk ratio

Explanations

a. We downgraded for imprecision, because of wide CI.

References

1.Furie RA, Aroca G,Cascino MD,Garg JP,Rovin BH,Alvarez A,Fragoso-Loyo H,Zuta-Santillan E,Schindler T,Brunetta P,Looney CM,Hassan I,Malvar A. B-cell depletion with obinutuzumab for the treatment of proliferative lupus nephritis: a randomised,double-blind,placebo-controlled trial. Ann Rheum Dis. 2022 Jan, 34615636, 81(1):100-107.,doi:,10.1136/annrheumdis-2021-220920.,Epub,2021,Oct,6.,PMID:, PMC8762029., PMCID:.

P8L. In SLE patients who have undergone initial therapy with MMF/MPA containing therapy for active Class III/IV LN, is treatment with CNI plus MMF/MPa compared to treatment with MMF/MPA for subsequent therapy associated with improved outcomes?

Populations:

- Class III/IV, III/IV plus V LN, with a complete or partial response after induction therapy.

Intervention:

- CNI plus MMF/MPA

Populations:

- MMF/MPA

Outcomes:

- Reduction of proteinuria
- Preservation of kidney function

- Risk of LN flares
- ESKD (dialysis or transplant)
- Treatment-related adverse effects including infection; also decrease >30% from baseline eGFR for CNI's, depression/suicide for belimumab.
- Cumulative steroid dose

Table 1. Included studies.

Study name (year) country	Study design	Population	Intervention	comparator	Outcomes with available data	Outcome time point
Saxena 2024 International	RCT	Adults: >18 years Mean age: 32.2 (10.3) versus 35.4 (11.6) White: 84/216 Asian: 60/216 Black: 25/216 Other: 47/216 Class 3: 35/216 Class 4: 101/216 Class 5: 31/216 Concomitant: 49/216	Induction: CNI plus MMF Maintenance: CNI plus MMF	Induction: MMF Maintenance: MMF	Renal flare up, GFR, Cr, Hypertension, Proteinuria, adverse events, infections, complete remission, partial remission	24 months (36 month with induction)

Evidence summary: 1 RCT is addressing the outcomes of CNI plus MMF versus MMF maintenance therapy following MMF-containing induction therapy. The overall certainty of evidence is moderate due to concerns about imprecision. There was no important difference for adverse events but Adverse events leading to withdrawal were fewer in CNI plus MMF (75 fewer per 1,000 (from 124 fewer to 22 more)). For complete remission and partial remission rates were higher in CNI plus MMF. For UPCR, there were 143 more per 1,000 (from 5 fewer to 331 more) in the CNI plus MMF arm. For GFR change from baseline, it favors CNI plus MMF (Mean difference MD 5.2 higher (1.07 higher to 9.33 higher)). Renal flare-ups were fewer per 1,000 (from 120 fewer to 141 more) in the CNI plus MMF.

Evidence profile:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CNI plus MMF/MPA	MMF/MPA	Relative (95% CI)	Absolute (95% CI)		
>30% reduction from baseline eGFR												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	14/116 (12.1%)	10/100 (10.0%)	**RR 1.21** (0.56 to 2.60)	**21 more per 1,000** (from 44 fewer to 160 more)	⨁⨁⨁◯ Moderate	
Adverse events												

1	randomised trials	not serious	not serious	not serious	serious[a]	none	100/116 (86.2%)	80/100 (80.0%)	**RR 1.08** (0.95 to 1.22)	**64 more per 1,000** (from 40 fewer to 176 more)	⊕⊕⊕◯ Moderate	

Adverse events leading to withdrawal

1	randomised trials	not serious	not serious	not serious	serious[a]	none	11/116 (9.5%)	17/100 (17.0%)	**RR 0.56** (0.27 to 1.13)	**75 fewer per 1,000** (from 124 fewer to 22 more)	⊕⊕⊕◯ Moderate	

Complete remission

1	randomised trials	not serious	not serious	not serious	serious[a]	none	59/116 (50.9%)	39/100 (39.0%)	**RR 1.30** (0.96 to 1.77)	**117 more per 1,000** (from 16 fewer to 300 more)	⊕⊕⊕◯ Moderate	

Partial remission

1	randomised trials	not serious	not serious	not serious	serious[a]	none	86/116 (74.1%)	69/100 (69.0%)	**RR 1.07** (0.91 to 1.27)	**48 more per 1,000** (from 62 fewer to 186 more)	⊕⊕⊕◯ Moderate	

GFR (change from baseline)

1	randomised trials	not serious	not serious	not serious	serious[a]	none	116	100	-	MD **5.2 higher** (1.07 higher to 9.33 higher)	⊕⊕⊕◯ Moderate	

Hypertension

1	randomised trials	not serious	not serious	not serious	serious[a]	none	10/116 (8.6%)	7/100 (7.0%)	**RR 1.23** (0.49 to 3.12)	**16 more per 1,000** (from 36	⊕⊕⊕◯ Moderate	

										fewer to 148 more)		
Infections												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	57/116 (49.1%)	43/100 (43.0%)	**RR 1.14** (0.85 to 1.53)	**60 more per 1,000** (from 65 fewer to 228 more)	⊕⊕⊕◯ Moderate	
Serious adverse events												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	21/116 (18.1%)	23/100 (23.0%)	**RR 0.79** (0.46 to 1.33)	**48 fewer per 1,000** (from 124 fewer to 76 more)	⊕⊕⊕◯ Moderate	
Renal flare ups												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	24/101 (23.8%)	19/73 (26.0%)	**RR 0.91** (0.54 to 1.54)	**23 fewer per 1,000** (from 120 fewer to 141 more)	⊕⊕⊕◯ Moderate	
≤0.5 mg/mg UPCR												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	63/99 (63.6%)	43/87 (49.4%)	**RR 1.29** (0.99 to 1.67)	**143 more per 1,000** (from 5 fewer to 331 more)	⊕⊕⊕◯ Moderate	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. We downgraded for imprecision because of the wide CI

References:

Saxena, Amit et al. “Safety and Efficacy of Long-Term Voclosporin Treatment for Lupus Nephritis in the Phase 3 AURORA 2 Clinical Trial.” Arthritis & rheumatology (Hoboken, N.J.) vol. 76,1 (2024): 59-67. doi:10.1002/art.42657

Randomized clinical trial: 1

Non-randomized study: none
Single arm study: None
Read and excluded: none

P8.o MMF/MPA or AZA or combination therapy: total duration of therapy of 3-5 years versus < 3 years

Population: Patients with class III/IV LN
Intervention: MMF/MPA or AZA or combination therapy total duration of therapy of 3-5 years
Comparison: MMF/MPA or AZA or combination therapy total duration of therapy <3 years
Outcomes:

- Reduction of proteinuria
- Preservation of kidney function
- Risk of LN flares
- ESKD (dialysis or transplant)
- Treatment related adverse effects including infection; also decrease >30% from baseline eGFR for CNI's, depression/suicide for belimumab
- Cumulative steroid dose

Table 1.

P8.o MMF/MPA or AZA or combination therapy: total duration of therapy of 3-5 years versus < 3 years

Study name (year) country	Study design	Population	Intervention details	Comparator details	Outcomes with available data	Outcome measures	Outcome timepoint
Jourde-Chiche 2022 France	RCT	LN patients Adults, N=96 Mean (SD) age: 3-5 years 37.5 (14); <3 years 36.7 (13.2) Ethnicity: Black/Hispanic Class III or IV, with or without class V	Maintenance with AZA or MMF for 3-5 years (continuation)	Maintenance with AZA or MMF for <3 years (discontinuation)	Anemia, infection, leukopenia, risk of LN flares	Risk ratio	2 years

Evidence summary:

There was 1 RCT with data comparing MMF/MPA or AZA or combination therapy: total duration of therapy of 3-5 years versus < 3 years, with moderate certainty of evidence, affected by imprecision. The risk of LN flare and doubling of Cr was higher in the <3 years duration group (**145 fewer per 1,000** (from 210 fewer to 23 more), **33 fewer per 1,000 (**from 41 fewer to 127 more), respectively. There were no events ESRD in both arms. Anemia and infection were higher in the 3-5 years duration group. The certainty of evidence was judged as **low** due to concerns related to the risk of bias (loss to follow-up) and imprecision (small sample size).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MMF/MPA or AZA or combination therapy: total duration of therapy of 3-5 years	MMF/MPA or AZA or combination therapy: total duration of therapy of < 3 years	Relative (95% CI)	Absolute (95% CI)		
ESRD												
1	randomised trials	serious	not serious	not serious	serious[a]	none	0/48	0/48	-	-	⨁⨁◯◯ low	
Doubling of serum Cr												
1	randomised trials	serious	not serious	not serious	serious[a]	none	0/48	2/48	**RR 0.20** (0.01 to 4.06)	**33 fewer per 1,000 (**from 41 fewer to 127 more)	⨁⨁◯◯ low	
Anemia												
1	randomised trials	serious	not serious	not serious	serious[a]	none	5/48 (10.4%)	2/48 (4.2%)	**RR 2.50** (0.51 to 12.26)	**63 more per 1,000** (from 20 fewer to 469 more)	⨁⨁◯◯ low	
Infection												
1	randomised trials	serious	not serious	not serious	serious[b]	none	19/48 (39.6%)	14/48 (29.2%)	**RR 1.36** (0.77 to 2.38)	**105 more per 1,000** (from 67 fewer to 402 more)	⨁⨁◯◯ low	
Leukopenia												

1	randomised trials	serious	not serious	not serious	very serious[b]	none	16/48 (33.3%)	17/48 (35.4%)	**RR 0.94** (0.54 to 1.64)	**21 fewer per 1,000** (from 163 fewer to 227 more)	⊕◯◯◯ very low	

Risk of LN flares

1	randomised trials	serious	not serious	not serious	serious[b]	none	5/48 (10.4%)	12/48 (25.0%)	**RR 0.42** (0.16 to 1.09)	**145 fewer per 1,000** (from 210 fewer to 23 more)	⊕⊕◯◯ low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. low sample size leading to wide CI.

b. low sample size

We downgraded for risk of bias because of concerns related to loss of follow-up (since the number of events is low, loss to follow-up is concerning)

References

Jourde-Chiche N, Costedoat-Chalumeau N, Baumstarck K, Loundou A, Bouillet L, Burtey S, Caudwell V, Chiche L, Couzi L, Daniel L, Deligny C, Dussol B, Faguer S, Gobert P, Gondran G, Huart A, Hummel A, Kalbacher E, Karras A, Lambert M, Le Guern V, Lebourg L, Loubière S, Maillard-Lefebvre H, Maurier F, Pha M, Queyrel V, Remy P, Sarrot-Reynauld F, Verhelst D, Hachulla E, Amoura Z, Daugas E; WIN-Lupus study group. Weaning of maintenance immunosuppressive therapy in lupus nephritis (WIN-Lupus): results of a multicentre randomised controlled trial. Ann Rheum Dis. 2022 Oct;81(10):1420-1427. doi: 10.1136/annrheumdis-2022-222435. Epub 2022 Jun 20. PMID: 35725295; PMCID: PMC9484365.

Included studies: 1

Randomized clinical trials: 1

Comparative non-randomized studies: None

Non-comparative studies (single arm): None

Studies read and exclude: None

P9-g) In patients with active, newly diagnosed or flare of Class V lupus nephritis, with proteinuria ≥ 1 gm and < 3.5 gm/day , what is the impact of **calcineurin inhibitors (CNI**) compared to not using CNI on reduction of proteinuria, prevention of renal flares, preservation of kidney function, cumulative glucocorticoid dose, damage, infections, and treatment-related adverse events?

P9-z) In patients with active, newly diagnosed or flare of Class V lupus nephritis, with proteinuria ≥ 3.5 gm/day, what is the impact of **calcineurin inhibitors (CNI**) compared to not using CNI on reduction of proteinuria, prevention of renal flares, preservation of kidney function, cumulative glucocorticoid dose, damage, infections, and treatment-related adverse events?

Population:

- Active Class V LN

Intervention:

- CNI

Comparator:

- IV CYC (No CNI)

Outcomes:

- Complete Response
- Type 2 Diabetes Mellitus
- Infection
- Leukopenia
- Hypertension
- Fracture

Table 1: P.9g and 9z In SLE patients with active, newly diagnosed or flare of Class V LN, is treatment with CNI compared to treatment with IV CYC for initial therapy associated with improved outcomes?

Study name (year) country	Study design	Population	Intervention details	Comparator details	Outcomes with available data	Outcomes measures	Outcome timepoint
Chen 2011 China	Randomized Clinical Trial	Class V LN Adults Age(y) TAC 32.0 (10.8)/ IVC 31.9 (10.1) Multiple Ethnicities Asian	Tacrolimus was started at a dosage of 0.05 mg/kg/d divided into 2 daily doses at 12-hour intervals, and the dosage was titrated to achieve 12-hour trough blood concentrations of 5-10 ng/mL	Pulse cyclophosphamide (750 mg/m2 of body surface area), which then was adjusted to 500-1,000 mg/m2 of body surface area every 4 weeks to maintain a nadir leukocyte count of 2.5-4.0 109/Lfor a total of 6 pulses	Complete Response Type 2 Diabetes Mellitus Infection Leukopenia Hypertension Fracture	Risk ratio	24 Months
Austin 2009 USA	Randomized Clinical Trial	Class V LN Adults Median age: 40 year (range 13 to 60 year) Multiple Ethnicities	Cyclosporine (initiated at 200 mg/m2 body surface area.)	IV CYC every other month (six doses, ranging from 0.5 to 1.0 g/m2 body surface area	Type 2 Diabetes Mellitus Infection Leukopenia Hypertension Fracture	Risk ratio	12 Months

Evidence summary: Two randomized study address PICO 9.g and 9z question. The study reported on Complete Resolution which favored CNI with an absolute effect of 316 more for CNI per 1,000 (from 360 fewer to 433 more). The outcome was based on very low certainty evidence due to risk of bias and imprecision. Regarding adverse events, Austin 2009 found that a reduced risk of infection (80 fewer per 1,000 (from 347 fewer to 393 more)), Leukopenia (100 fewer per 1,000 (from 132 fewer to 492 more)) in CNI versus CYC. While CNI lead to an increased risk for T2DM (Risk difference of 16.7%), and hypertension (Risk difference of 75.0%). No clinically significant difference was found in risk of fracture (34 fewer per 1,000 (from 168 fewer to 642 more)). All outcomes were very low certainty evidence due to risk of bias and imprecision. Both studies included a portion of patients with proteinuria > 1 and < 3.5 as well as patients with nephrotic range proteinuria, therefore evidence for PICO 9 g and 9 zz were combined.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CNI	CYC	Relative (95% CI)	Absolute (95% CI)		
Complete Response (follow-up: 6 months)												
1[1]	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	4/11 (36.4%)	0/9 (0.0%)	**RR 1.87** (0.01 to 2.19)	**316 fewer per 1,000** (from 360 fewer to 433 more)	⨁◯◯◯ Very low	CRITICAL
Type 2 Diabetes Mellitus (follow-up: 6 months)												
1[2]	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	2/12 (16.7%)	0/15 (0.0%)	**RR 6.15** (0.32 to 117.21)	**Risk difference of 16.7%**	⨁◯◯◯ Very low	CRITICAL
Infection (follow-up: 6 months)												
1[2]	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	7/12 (58.3%)	10/15 (66.7%)	**RR 0.88** (0.48 to 1.59)	**80 fewer per 1,000** (from 347 fewer to 393 more)	⨁◯◯◯ Very low	CRITICAL
Leukopenia (follow-up: 6 months)												
1[2]	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	0/12 (0.0%)	2/15 (13.3%)	**RR 0.25** (0.01 to 4.69)	**100 fewer per 1,000** (from 132 fewer to 492 more)	⨁◯◯◯ Very low	CRITICAL
Hypertension (follow-up: 6 months)												
1[2]	randomised trials	serious[a]	not serious	not serious	very serious[c]	none	9/12 (75.0%)	0/15 (0.0%)	**RR 23.38** (1.50 to 365.08)	**Risk difference of 75.0%**	⨁◯◯◯ Very low	CRITICAL
Fracture (follow-up: 6 months)												
1[2]	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	2/12 (16.7%)	3/15 (20.0%)	**RR 0.83** (0.16 to 4.21)	**34 fewer per 1,000** (from 168 fewer to 642 more)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Risk of bias was assessed by ROB2 to be high risk of bias due to randomization

b. Absolute CI crosses both MIDs

c. Small number of events and patients

References

1.Chen, Wei, Tang, Xueqing, Liu, Qinghua, Chen, Weiying, Fu, Ping, Liu, Fang, Liao, Yunhua, Yang, Zhenhua, Zhang, Jinli, Chen, Jian, Lou, Tanqi, Fu, Junzhou, Kong, Yaozhong, Liu, Zhengrong, Fan, An, Rao, Shaoqi, Li, Zhibin, Yu, Xueqing. Short-term outcomes of induction therapy with tacrolimus versus cyclophosphamide . American journal of kidney diseases : the official journal of the National Kidney ; 2011.

2ز Austin HA 3rd, Illei GG, Braun MJ, Balow JE. Randomized, controlled trial of prednisone, cyclophosphamide, and cyclosporine in lupus membranous nephropathy. J Am Soc Nephrol. 2009 Apr;20(4):901-11. doi: 10.1681/ASN.2008060665. Epub 2009 Mar 18. PMID: 19297556; PMCID: PMC2663831.

Randomized clinical trials: **1**

Comparative nonrandomized studies: None

Non-comparative studies: None

Studies read and excluded: None

P9-g) In patients with active, newly diagnosed or flare of Class V lupus nephritis, with proteinuria ≥ 1 gm and < 3.5 gm/day , what is the impact of **calcineurin inhibitors (CNI**) compared to not using CNI on reduction of proteinuria, prevention of renal flares, preservation of kidney function, cumulative glucocorticoid dose, damage, infections, and treatment-related adverse events?

P9-z) In patients with active, newly diagnosed or flare of Class V lupus nephritis, with proteinuria ≥ 3.5 gm/day, what is the impact of **calcineurin inhibitors (CNI**) compared to not using CNI on reduction of proteinuria, prevention of renal flares, preservation of kidney function, cumulative glucocorticoid dose, damage, infections, and treatment-related adverse events?

Population:

- Active Class V LN

Intervention:

- MMF

Comparator:

- Tacrolimus

Outcomes:

- Complete Response
- Partial Response
- Complete and Partial Response
- Level Proteinuria
- Creatinine

Table 1: P.9g and 9z In SLE patients with active, newly diagnosed or flare of Class V LN, is treatment with MMF compared to treatment with CNI for initial therapy associated with improved outcomes?

Study name (year) country	Study design	Population	Intervention details	Comparator details	Outcomes with available data	Outcomes measures	Outcome timepoint
Yap 2012 China	Randomized Clinical Trial	Class V LN Adults Mean (SD) age: MMF 36.01(15.7), TAC 40.01(12.5) Asian	MMF dose was 0.75–1 g b.i.d. for the first 6 months, then 0.75 g b.i.d. until the end of 12 months and 0.5 g b.i.d. during the second year.	Tac was commenced at 0.1–0.15 mg/kg per day in two divided doses, followed by titration to achieve the target 12 h trough blood level of 6–8 mg/L for the first 6 months, 5.0–5.9 mg/L for the subsequent 6 months and 3.0–4.9 mg/L during the second year.	Complete Response Partial Response Complete and Partial Response	Risk ratio	24 Months
Mok 2016 China	Randomized Clinical Trial	Class V LN Adults Age: MMF: 36.1+- 13.1, TAC: 36.2 +-14 Asians	MMF (2 g/day initially, augmented to up to 3 g/day if clinical response was suboptimal at month 3), in two divided doses for 6 months	TAC for 6 months (initial dosage 0.1 mg/kg/day in two divided doses, reduced to 0.06 mg/kg/day if clinical response was satisfactory at month	Complete Response Partial Response Complete and Partial Response Level Proteinuria Creatinine	Risk ratio, Mean Difference	6 Months

Evidence summary: 2 randomized study address PICO 9.g and 9z question. Both studies reported on complete and partial response with the absolute effect 42 fewer per 1,000 (from 279 fewer to 416 more), 215 more per 1,000 (from 51 fewer to 918 more) respectively. Both outcomes were very low certainty evidence due to risk of bias and imprecision. Mok 2016 reported on change in level of proteinuria and change in level of creatinine. MMF level to more reduction in proteinuria with a mean difference of 1.61 lower (3.01 lower to 0.21 lower) but less reduction in creatinine with a mean difference MD 2.3 higher (8.5 lower to 13.1 higher). Both outcomes were low certainty evidence due to risk of bias and imprecision. Both studies included a portion of patients with proteinuria ranging from > 1 and < 3.5 as well as nephrotic range proteinuria.

Certainty assessment	№ of patients	Effect	Certainty	Importance

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MMF	CNI	Relative (95% CI)	Absolute (95% CI)		
Complete Response												
2[1,2]	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	10/25 (40.0%)	10/19 (52.6%)	**RR 0.92** (0.47 to 1.79)	**42 fewer per 1,000** (from 279 fewer to 416 more)	⨁◯◯◯ Very low	CRITICAL
Partial Response												
2[1,2]	randomised trials	serious[a]	not serious	not serious	serious[c]	none	11/25 (44.0%)	4/19 (21.1%)	**RR 2.02** (0.76 to 5.36)	**215 more per 1,000** (from 51 fewer to 918 more)	⨁⨁◯◯ Low	CRITICAL
Complete and Partial Response												
2[1,2]	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	21/25 (84.0%)	14/19 (73.7%)	**RR 1.14** (0.83 to 1.57)	**103 more per 1,000** (from 125 fewer to 420 more)	⨁◯◯◯ Very low	CRITICAL
Change in level of proteinuria from baseline (follow-up: 6 months)												
1[2]	randomised trials	serious[a]	not serious	not serious	serious[d]	none	12	16	-	MD **1.61 lower** (3.01 lower to 0.21 lower)	⨁⨁◯◯ Low	CRITICAL
Change in creatinine from baseline (follow-up: 6 months)												
1[2]	randomised trials	serious[a]	not serious	not serious	serious[d]	none	12	16	-	MD **2.3 higher** (8.5 lower to 13.1 higher)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations
a. Risk of Bias was assessed using ROB 2, high risk of bias due to randomization
b. Absolute CI crosses MID on both sides
c. Absolute CI crosses MID on one side
d. Small number of included patients

References
1.Yap, Desmond Y H, Yu, Xueqing, Chen, Xiang-Mei, Lu, Fuming, Chen, Nan, Li, Xue-Wang, Tang, Colin So, Chan, Tak Mao. Pilot 24 month study to compare mycophenolate mofetil and tacrolimus in the . Nephrology (Carlton, Vic.); 2012.
2.Mok, Chi Chiu, Ying, King Yee, Yim, Cheuk Wan, Siu, Yui Pong, Tong, Ka Hang, To, Chi Hung, Ng, Woon Leung. Tacrolimus versus mycophenolate mofetil for induction therapy of lupus nephritis: . Annals of the rheumatic diseases; 2016.

Randomized clinical trials: 2
Comparative nonrandomized studies: None
Non-comparative studies: None
Studies read and excluded: None

P9-i) In patients with active, newly diagnosed or flare of Class V lupus nephritis, with proteinuria ≥ 1 gm and < 3.5 gm/day, what is the impact of an **intravenous cyclophosphamide regimen** versus **oral cyclophosphamide** regimen on reduction of proteinuria, prevention of renal flares, preservation of kidney function, cumulative glucocorticoid dose, treatment-related adverse events, and ESKD?

P9-bb) In patients with active, newly diagnosed or flare of Class V lupus nephritis, with proteinuria ≥ 3.5 gm/day, what is the impact of an **intravenous cyclophosphamide regimen** versus **oral cyclophosphamide** regimen on reduction of proteinuria, prevention of renal flares, preservation of kidney function, cumulative glucocorticoid dose, treatment-related adverse events, and ESKD?

Population:
- Active Class V LN

Intervention:
IV CYC

Comparator:
Oral CYC

Outcomes:
- Complete and Partial Response
- Serious Adverse Events
- ESKD

Table 1: P.9i and 9bb In SLE patients with active, newly diagnosed or flare of Class V LN, is treatment with IV CYC compared to treatment with Oral CYC for initial therapy associated with improved outcomes?

Study name (year) country	Study design	Population	Intervention details	Comparator details	Outcomes with available data	Outcomes measures	Outcome timepoint

Austin 1986 USA	Randomized Clinical Trial	Class V LN Adults Median age 27 Multiple Ethnicities	Intravenous cyclophosphamide (every three months, doses ranges from 0.5 to 1.0 per square meter of body surface) - both groups received low dose oral prednisone (dose up to 0.5 mg per kilogram per day)	Oral cyclophosphamide (up to 4 mg pr kilogram per day)	• Complete and Partial Response • Serious Adverse Events • ESKD	Risk ratio	4 years

Evidence summary: One randomized study address PICO 9.i and 9.bb question. The study reported on Complete and Partial response which favored IV CYC with an absolute effect of 79 more per 1,000 (from 166 fewer to 426 more). Regarding ESKD, 171 fewer per 1,000 (from 216 fewer to 184 more) developed ESKD in the IV CYC versus Oral CYC. As for serious adverse events, no clinical difference was found in terms of serious adverse events (39 more per 1,000) between IV CYC and Oral CYC. All outcomes were very low certainty evidence due to risk of bias and imprecision. Both studies included a portion of patients with proteinuria > 1 and < 3.5 as well as patients with nephrotic range proteinuria, therefore evidence for PICO 9 i and 9 bb were combined.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IV CYC**	**Oral CYC**	**Relative (95% CI)**	**Absolute (95% CI)**		
CR and PR												
1[1]	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	16/20 (80.0%)	13/18 (72.2%)	**RR 1.11** (0.77 to 1.59)	**79 more per 1,000** (from 166 fewer to 426 more)	⨁◯◯◯ Very low	CRITICAL
ESKD												
1[1]	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	1/20 (5.0%)	4/18 (22.2%)	**RR 0.23** (0.03 to 1.83)	**171 fewer per 1,000** (from 216 fewer to 184 more)	⨁◯◯◯ Very low	CRITICAL

Serious Adverse events

1[1]	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	3/20 (15.0%)	2/18 (11.1%)	**RR 1.35** (0.25 to 7.19)	**39 more per 1,000** (from 83 fewer to 688 more)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Risk of bias was assessed by ROB2 to be high risk of bias due to randomization

b. Imprecision due to Wide CI

References

1.Austin, H A 3rd, Klippel, J H, Balow, J E, le Riche, N G, Steinberg, A D, Plotz, P H, Decker, J L. Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs.. The New England journal of medicine; 1986.

Randomized clinical trials: 1

Comparative nonrandomized studies: None

Non-comparative studies: None

Studies read and excluded: None

P9-j) In patients with active, newly diagnosed or flare of Class V lupus nephritis, with proteinuria ≥ 1 gm and < 3.5 gm/day what is the impact of an **intravenous cyclophosphamide- containing regimen** compared to **MMF/MPA** on reduction of proteinuria, prevention of renal flares, preservation of kidney function, cumulative glucocorticoid dose, treatment-related adverse events, and ESKD?

P.9cc) In patients with active, newly diagnosed or flare of Class V lupus nephritis, with proteinuria ≥ 3.5 gm/day what is the impact of an **intravenous monthly cyclophosphamide regimen** compared to **MMF/MPA** on reduction of proteinuria, prevention of renal flares, preservation of kidney function, cumulative glucocorticoid dose, treatment-related adverse events, and ESKD?

Population:

- Active Class V LN

Intervention:

- IV Cyclophosphamide Monthly (NIH)

Comparator:

- 3 gm/d MMF equivalent

Outcomes:

- Complete Response
- Partial Response
- Infection
- Leukopenia

Table 1: P.9j and 9 cc: In SLE patients with active, newly diagnosed or flare of Class V LN, is treatment with IV CYC compared to treatment with MMF for initial therapy associated with improved outcomes?

Study name (year) country	Study design	Population	Intervention details	Comparator details	Outcomes with available data	Outcomes measures	Outcome timepoint
Radhakrishnan 2010 US multi-center	Randomized Clinical Trial	Class V LN 24 patients in the US study 60 patients in the ALMS study Adults Age: Mean (SD) 47 (12) Multiple ethnicities	IVC was given as monthly pulses according to the published National Institute of Health (NIH) protocol	MMF initiated at 500 mg twice daily, and advanced to a maximum of 3000 mg daily.	Complete Response Partial Response Infection Leukopenia	Risk ratio	24 weeks
Kapsia 2022 Greece	Non-randomized clinical trial	Membranous LN Caucasians	Cyclophosphamide (no further details)	Mycophenolic Acid (no further details)	LN Flare ESKD	Risk ratio	4 years

Evidence summary: 1 randomized study address PICO 9.j and 9 ccquestion. Concerning complete response, the absolute effect was 44 fewer patients out of 1000 favoring MMF, and for partial response it was 18 more per 1000 favoring CYC. Both outcomes were very low certainty evidence due to risk of bias and imprecision. Regarding infections and leukopenia, the RR (CI) between the two regimens CYC and MMF is 0.88 (1.27 to 1.14) and 21.0 (1.27 to 347.20), respectively, showing no difference between these two regimens in terms of infections but high risk of leukopenia in CYC. Both outcomes were very low certainty evidence due to risk of bias and imprecision. Both studies included a portion of patients with proteinuria > 1 and < 3.5 as well as patients with nephrotic range proteinuria, therefore evidence for PICO 9 j and 9 cc were combined.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV CYC Monthly	MMF	Relative (95% CI)	Absolute (95% CI)		
Complete Response												

1[1,a]	randomized trials	Serious [b]	not serious	not serious	very serious [c]	none	0/23 (0.0%)	1/17 (5.9%)	**RR 0.25** (0.01 to 5.79)	**44 fewer per 1,000** (from 58 fewer to 282 more)	⨁◯◯◯ Very low	CRITICAL

Partial Response

1[1,a]	randomized trials	Serious [b]	not serious	not serious	very serious [c]	none	14/23 (60.9%)	10/17 (58.8%)	**RR 1.03** (0.62 to 1.73)	**18 more per 1,000** (from 224 fewer to 429 more)	⨁◯◯◯ Very low	CRITICAL

Complete and Partial Response

1[1,a]	randomized trials	Serious [b]	not serious	not serious	very serious [c]	none	14/23 (60.9%)	11/17 (58.8%)	**RR 0.94** (0.53 to 1.52)	**18 more per 1,000** (from 224 fewer to 429 more)	⨁◯◯◯ Very low	CRITICAL

Leukopenia

1[1,a]	randomized trials	Serious [b]	not serious	not serious	very serious [c]	none	10/42 (23.8%)	0/42 (0.0%)	**RR 21.00** (1.27 to 347.20)	**Risk Reduction of 23.8%**	⨁◯◯◯ Very low	CRITICAL

ESKD

1[2]	non-randomised studies	serious[e]	not serious	not serious	very serious[d]	none	0/8 (0.0%)	0/13 (0.0%)	not pooled	see comment	⨁◯◯◯ Very low	CRITICAL

LN Flares

1[2]	non-randomised studies	serious[e]	not serious	not serious	very serious[c]	none	2/8 (25.0%)	2/13 (15.4%)	**RR 1.63** (0.28 to 9.36)	**97 more per 1,000** (from 111 fewer to 1,000 more)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Report includes Class V data from two studies (US and ALMS)

b. Risk of bias was assessed using ROB2, judged to be serious due to selection of the reported result and randomization.

c. Absolute CI crosses the MID (assumed to be 5%) on both sides

References

1.Radhakrishnan, Jai, Moutzouris, Dimitrios-Anestis, Ginzler, Ellen M., Solomons, Neil, Siempos, Ilias I., Appel, Gerald B.. Mycophenolate mofetil and intravenous cyclophosphamide are similar as induction therapy for class V lupus nephritis. Kidney International; 2010.

2. Kapsia E, Marinaki S, Michelakis I, Liapis G, Sfikakis PP, Tektonidou MG, Boletis J. New Insights Into an Overlooked Entity: Long-Term Outcomes of Membranous Lupus Nephritis From a Single Institution Inception Cohort. Front Med (Lausanne). 2022 Apr 14;9:809533. doi: 10.3389/fmed.2022.809533. PMID: 35492303; PMCID: PMC9047916.

Randomized clinical trials: 1
Comparative nonrandomized studies: None
Non-comparative studies: None
Studies read and excluded: None

P9-n) In patients with active, newly diagnosed or flare of Class V lupus nephritis, with proteinuria ≥ 1 gm and < 3.5 gm/day what is the impact of **MMF/MPA plus belimumab** compared to **MMF/MPA alone** on reduction of proteinuria, prevention of renal flares, preservation of kidney function, cumulative glucocorticoid dose, treatment-related adverse events, and ESKD?

P9-dd) In patients with active, newly diagnosed or flare of Class V lupus nephritis, with proteinuria ≥ 3.5 gm/day what is the impact of intravenous **cyclophosphamide plus belimumab compared to intravenous cyclophosphamide** on reduction of proteinuria, prevention of renal flares, preservation of kidney function, cumulative glucocorticoid dose, treatment-related adverse events, and ESKD?

P9-gg) In patients with active, newly diagnosed or flare of Class V lupus nephritis, with proteinuria ≥ 3.5 gm/day what is the impact of **MMF/MPA plus belimumab** compared to **MMF/MPA alone** on reduction of proteinuria, prevention of renal flares, preservation of kidney function, cumulative glucocorticoid dose, treatment-related adverse events, and ESKD?

P10-f) In patients with active Class V lupus nephritis who have undergone **initial therapy with a cyclophosphamide-containing regimen** and achieved a CR at 6-12 months, what is the impact of **MMF/MPA plus belimumab** compared to **MMF/MPA** on prevention of renal flares, preservation of kidney function, cumulative glucocorticoid dose, treatment-related adverse events, and ESKD

P10-j) In patients with active Class V lupus nephritis who have undergone **initial therapy with MMF/MPA-containing regimen** and achieved a CR at 6-12 months, what is the impact of **MMF/MPA plus belimumab** compared to **MMF/MPA** on prevention of renal flares, preservation of kidney function, cumulative glucocorticoid dose, treatment-related adverse events, and ESKD?

P10-s) In patients with active Class V lupus nephritis who have undergone **initial therapy with a cyclophosphamide-containing regimen** and achieved a PR at 6-12 months, what is the impact of **MMF/MPA plus belimumab** compared to **MMF/MPA** on prevention of renal flares, preservation of kidney function, cumulative glucocorticoid dose, treatment-related adverse events, and ESKD?

P10-w) In patients with active Class V lupus nephritis who have undergone **initial therapy with MMF/MPA-containing regimen** and achieved a PR at 6-12 months, what is the impact of **MMF/MPA plus belimumab** compared to **MMF/MPA** on prevention of renal flares, preservation of kidney function, cumulative glucocorticoid dose, treatment-related adverse events, and ESKD?

Population: Patients with class V LN

Intervention: Belimumab plus standard of care
Comparison: Standard of care
Outcomes:

- Complete Resolution
- Risk of LN flares

Table 1.

P9n and 9dd and 9gg and 10w and 10j and 10f and 10s Initial IV CYC, then MMF/MPA plus belimumab versus MMF/MPA

Study name (year) country	Study design	Population	Intervention details	Comparator details	Outcomes with available data	Outcome measures	Outcome timepoint
Furie 2020 Rovin 2022 International	RCT	LN patients Adults, N=448 Mean (SD) age: BEL 33.7 (10.7), placebo 33.1 (10.6) Asian: 223/446 White: 148/446 Black: 61/446 American Indian or Alaska Native: 10/446 Class III or IV: 258 Class III and V or Class IV and V: 116 **Class V: 72**	Belimumab plus standard of care	Standard of care	Adverse events, adverse events leading to withdrawal, complete remission, depression/suicide, infection, serious adverse events, risk of LN flare.	Risk ratio	104 weeks

Evidence summary: There was 1 RCT with data comparing belimumab + standard of care versus standard of care. Standard of care consists of either CYC for induction followed by AZA or MMF/MPA for induction and maintenance. Since standard of care encompassed multiple treatment options, this evidence report contains evidence to support 9n, 9dd, 9gg, 10f, 10j, 10s, 10w. Outcomes were assessed at 104 weeks (no outcomes were assessed at the end of induction therapy). This trial addresses both induction and maintenance together at the same time for **Class V** (that is why it addresses PICO 9 and 10). The overall certainty of the evidence was judged as moderate. There are concerns about risk of bias imprecision due to the population was a subgroup of the original RCT and therefore ROB was determined to be high due to selection and randomization as no stratification occurred for the different classes and imprecision due to small number of patients or small number of events or wide CI.

Complete remission was higher in the Belimumab arm, 28 more per 1,000 (from 134 fewer to 348 more) while the risk of LN flare was 223 fewer per 1,000 (from 344 fewer to 45 more). The rate of adverse events, Adverse events, Infection, leading to withdrawal was similar between both arms. Depression/Suicide rates were 22 fewer per 1,000 (from 48 fewer to 32 more).

Certainty assessment	№ of patients	Effect	Certainty	Importance

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Belimumab plus standard of care	standard of care	Relative (95% CI)	Absolute (95% CI)		
Complete remission												
1[1]	randomised trials	very serious[a]	not serious	not serious	Very serious[b]	none	12/36 (33.3%)	11/36 (30.6%)	**RR 1.09** (0.56 to 2.14)	**28 more per 1,000** (from 134 fewer to 348 more)	⨁◯◯◯ Very low	CRITICAL
Risk of LN Flare												
1[1]	randomised trials	very serious[a]	not serious	not serious	serious[b]	none	9/36 (25.0%)	15/36 (41.7%)	**HR 0.40** (0.14 to 1.15)	**223 fewer per 1,000** (from 344 fewer to 45 more)	⨁◯◯◯ Very low	CRITICAL
Adverse events												
1[1]	randomised trials	not serious	not serious	not serious	not serious	none	214/224 (95.5%)	211/224 (94.2%)	**RR 1.01** (0.97 to 1.06)	**9 more per 1,000** (from 28 fewer to 57 more)	⨁⨁⨁⨁ High	CRITICAL
Adverse events leading to withdrawal												
1[1]	randomised trials	not serious	not serious	not serious	serious[c]	none	29/224 (12.9%)	29/224 (12.9%)	**RR 1.00** (0.62 to 1.62)	**0 fewer per 1,000** (from 49 fewer to 80 more)	⨁⨁⨁◯ Moderate	CRITICAL
Infection												
1[1]	randomised trials	not serious	not serious	not serious	serious[d]	none	15/224 (6.7%)	18/224 (8.0%)	**RR 0.83** (0.43 to 1.61)	**14 fewer per 1,000** (from 46 fewer to 49 more)	⨁⨁⨁◯ Moderate	CRITICAL
Serious adverse events												

1	randomised trials	not serious	not serious	not serious	serious[c]	none	58/224 (25.9%)	67/224 (29.9%)	**RR 0.87** (0.64 to 1.17)	**39 fewer per 1,000** (from 108 fewer to 51 more)	⊕⊕⊕◯ Moderate	CRITICAL

Depression/suicide

1	randomised trials	not serious	not serious	not serious	serious[d]	none	11/224 (4.9%)	16/224 (7.1%)	**RR 0.69** (0.33 to 1.45)	**22 fewer per 1,000** (from 48 fewer to 32 more)	⊕⊕⊕◯ Moderate	CRITICAL

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. Risk of Bias was assessed using ROB2, population was a subgroup of the original RCT and therefore ROB was determined to be high due to selection and randomization as no stratification occured for the different classes.

b. Imprecision due to small number of patients

c. Imprecision due to wide CI

d. Small number of events

References

1.Rovin, Brad H., Furie, Richard, Teng, Y.K. Onno, Contreras, Gabriel, Malvar, Ana, Yu, Xueqing, Ji, Beulah, Green, Yulia, Gonzalez-Rivera, Tania, Bass, Damon, Gilbride, Jennifer, Tang, Chun-Hang, Roth, David A.. A secondary analysis of the Belimumab International Study in Lupus Nephritis trial examined effects of belimumab on kidney outcomes and preservation of kidney function in patients with lupus nephritis. Kidney International; 2022.

Furie R, Rovin BH, Houssiau F, Malvar A, Teng YKO, Contreras G, Amoura Z, Yu X, Mok CC, Santiago MB, Saxena A, Green Y, Ji B, Kleoudis C, Burriss SW, Barnett C, Roth DA. Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis. N Engl J Med. 2020 Sep 17;383(12):1117-1128. doi: 10.1056/NEJMoa2001180. PMID: 32937045.

Included studies: 1

Randomized clinical trials: 1

Comparative non-randomized studies: 0

Non-comparative studies (single arm): 0

Studies read and exclude: 0

P9-o) In patients with active, newly diagnosed or flare of Class V lupus nephritis, with proteinuria ≥ 1 gm and < 3.5 gm/day what is the impact of **MMF/MPA plus CNI** compared to **MMF/MPA alone** on reduction of proteinuria, prevention of renal flares, preservation of kidney function, cumulative glucocorticoid dose, treatment-related adverse events, and ESKD.

P9-hh) In patients with active, newly diagnosed or flare of Class V lupus nephritis, with proteinuria ≥ 1 gm and < 3.5 gm/day what is the impact of **MMF/MPA plus CNI** compared to **MMF/MPA alone** on reduction of proteinuria, prevention of renal flares, preservation of kidney function, cumulative glucocorticoid dose, treatment-related adverse events, and ESKD.

P10-g) In patients with active Class V lupus nephritis who have undergone initial therapy with a **cyclophosphamide-containing regimen** and achieved a CR at 6-12 months, what is the impact of **MMF/MPA plus a CNI** compared to **MMF/MPA** on prevention of renal flares, preservation of kidney function, cumulative glucocorticoid dose, treatment-related adverse events, and ESKD?

P10-k) In patients with active Class V lupus nephritis who have undergone **initial therapy with MMF/MPA** and achieved a CR at 6-12 months, what is the impact of **MMF/MPA plus a CNI** compared to **MMF/MPA** on prevention of renal flares, preservation of kidney function, cumulative glucocorticoid dose, treatment-related adverse events, and ESKD?

P10-t) In patients with active Class V lupus nephritis who have undergone initial therapy with a **cyclophosphamide-containing regimen** and achieved a PR at 6-12 months, what is the impact of **MMF/MPA plus a CNI** compared to **MMF/MPA** on prevention of renal flares, preservation of kidney function, cumulative glucocorticoid dose, treatment-related adverse events, and ESKD?

P10-x) In patients with active Class V lupus nephritis who have undergone **initial therapy with MMF/MPA -containing regimen** and achieved a PR at 6-12 months, what is the impact of **MMF/MPA plus a CNI** compared to **MMF/MPA** on prevention of renal flares, preservation of kidney function, cumulative glucocorticoid dose, treatment-related adverse events, and ESKD?

Population: Patients with class V LN
Intervention: MMF/MPA plus CNI
Comparison: MMF/MPA alone
Outcomes:

- Complete response
- Adverse events
- Serious adverse events

Table 1.

P9o, 9hh, P10g, 10k, 10t, and 10x plus CNI versus MMF/MPA

Study name (year) country	Study design	Population	Intervention details	Comparator details	Outcomes with available data	Outcome measures	Outcome timepoint
Rovin 2021	RCT	Active LN Pure class III: 49; Pure class IV: 168; Pure class V: 50; Class II + V: 1; Class III + V: 44; Class IV + V: 45. Median (range) age	Oral voclosporin (23·7 mg twice daily), on a background of mycophenolate mofetil (1 g twice daily) and rapidly tapered low-dose oral steroids	MMF (1g) + low dose oral steroids	Complete response Adverse events Serious adverse events	RR	52 weeks

		(Voclosporin) 31 (18-62) vs. (Placebo) 32 (18-72)					

Evidence summary: There was 1 RCT with data comparing MMF/MPA plus CNI versus MMF/MPA alone. Outcomes were assessed at 52 weeks (no outcomes were assessed at the end of induction therapy). This trial addresses both induction and maintenance together at the same time for **Class V** (that is why it addresses PICO 9 and 10). Also addressed different proteinuria levels for PICO 9 as the population included patients greater than and less than 3.5 gm.day. Addressed multiple comparisons for PICO 10 as the induction (initial therapy) included both MMF and CYC as well as included patients achieving PR and CR. The overall certainty of the evidence was judged as very low. There are concerns about risk of bias imprecision due to the population was a subgroup of the original RCT and therefore ROB was determined to be high due to selection and randomization as no stratification occurred for the different classes and imprecision due to small number of patients or small number of events or wide CI.

Complete remission was higher in the MMF/MPA plus CNI arm, **OR 2.70 (0.78 to 9.40)**. The adverse events were 22 more per 1,000 (from 53 fewer to 65 more) was similar between both arms. Serious adverse events were 5 fewer per 1,000 (from 77 fewer to 91 more).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CNI	Placebo	Relative (95% CI)	Absolute (95% CI)		
Complete Response (follow-up: 52 weeks)												
1[1]	randomised trials	very serious[a]	not serious	not serious	serious[b]	none	0/0	0/0	**OR 2.70** (0.78 to 9.40)	**3 fewer per 1,000** (from 9 fewer to 1 fewer)	⨁◯◯◯ Very low	CRITICAL
Adverse Events												
1[1]	randomised trials	not serious	not serious	not serious	serious[b]	none	162/178 (91.0%)	158/178 (88.8%)	**OR 1.28** (0.64 to 2.56)	**22 more per 1,000** (from 53 fewer to 65 more)	⨁⨁⨁◯ Moderate	CRITICAL
Serious Adverse Events												
1[1]	randomised trials	not serious	not serious	not serious	very serious[b]	none	37/178 (20.8%)	38/178 (21.3%)	**OR 0.97** (0.58 to 1.61)	**5 fewer per 1,000** (from 77 fewer to 91 more)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **OR:** odds ratio

Explanations

a. Risk of Bias was assessed using ROB2, population was a subgroup of the original RCT and therefore ROB was determined to be high due to selection and randomization as no stratification occurred for the different classes.

b. Imprecision due to Wide CI

References

1.Rovin, Brad H, Teng, Y K Onno, Ginzler, Ellen M, Arriens, Cristina, Caster, Dawn J, Romero-Diaz, Juanita, Gibson, Keisha, Kaplan, Joshua, Lisk, Laura, Navarra, Sandra, Parikh, Samir V, Randhawa, Simrat, Solomons, Neil, Huizinga, Robert B. Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): . Lancet (London, England); 2021.

Included studies: 1

Randomized clinical trials: 1

Comparative non-randomized studies: 0

Non-comparative studies (single arm): 0

Studies read and exclude: 0

P9. In SLE patients with active, newly diagnosed or flare of Class V LN, is treatment with" X" compared to treatment with "Y" for initial therapy (detailed in table) associated with improved outcomes?

P9-t) In patients with active, newly diagnosed or flare of Class V lupus nephritis, with proteinuria > 1 gm and < 3.5 gm/day what is the impact of Anti-CD20 therapy plus belimumab compared to anti-CD 20 therapy alone on reduction of proteinuria, prevention of renal flares, preservation of kidney function, cumulative glucocorticoid dose, treatment-related adverse events, and ESKD?

P9-mm) In patients with active, newly diagnosed or flare of Class V lupus nephritis, with proteinuria > 3.5 gm/day what is the impact of Anti-CD20 therapy plus belimumab compared to anti-CD 20 therapy alone on reduction of proteinuria, prevention of renal flares, preservation of kidney function, cumulative glucocorticoid dose, treatment-related adverse events, and ESKD?

Intervention:

- Rituximab

Outcomes:

- Renal response
- Relapse
- Proteinuria
- Creatinine
- Adverse events

Outcomes (Name + Summary)	Author, year, RefID	Study type	Duration of follow up	Population (number and description, age)	Intervention used in relevant population (Describe the intervention)	Results	Comments
	Chavarot,2017. (ID: 1609)	Non-comparative	6 months	15 Patients – Class V	**Rituximab** was administered as 2 infusions of 1g at day 0 and day 14 in 9 patients (60%) and 375mg/m2 once	At 6 months: CRR: 4/15 (27%) PRR: 8/15 (53%)	Complete renal remission (CR) was defined as a urine protein to creatinine ratio (UPCR) <0.5g/g and normal or near-normal (within

Renal response (CRR)				Median Age 37 years	per week for 4 weeks in 6 patients (40%).		10% of normal GFR if previously abnormal) GFR. Partial renal response (PR) was defined as a ≥50% reduction in proteinuria to subnephrotic levels and normal or near-normal GFR.
Relapse	Chavarot,2017. (ID: 1609)	Non-comparative	6, 12, 24 months	15 Patients – Class V Median Age 37 years	**Rituximab** was administered as 2 infusions of 1g at day 0 and day 14 in 9 patients (60%) and 375mg/m2 once per week for 4 weeks in 6 patients (40%).	At 6 months: 0/15 (0%) At 12 months: 1/15 (8%) At 24 months: 0/15 (0%)	
Difference in creatinine (mg/dl)	Chavarot,2017. (ID: 1609)	Non-comparative	6, 12, 24 months	15 Patients – Class V Median Age 37 years	**Rituximab** was administered as 2 infusions of 1g at day 0 and day 14 in 9 patients (60%) and 375mg/m2 once per week for 4 weeks in 6 patients (40%).	At 6 months: 0 mg/dL At 12 months: 0 mg/dL At 24 months: 0 mg/dL	
Difference in proteinuria (mg/dl)	Chavarot,2017. (ID: 1609)	Non-comparative	6, 12, 24 months	15 Patients – Class V Median Age 37 years	**Rituximab** was administered as 2 infusions of 1g at day 0 and day 14 in 9 patients (60%) and 375mg/m2 once per week for 4 weeks in 6 patients (40%).	At 6 months: - 3.7 g/g At 12 months: - 4.88 g/g At 24 months: - 4.89 g/g	
Adverse events	Chavarot,2017. (ID: 1609)	Non-comparative	6, 12, 24 months	15 Patients – Class V Median Age 37 years	**Rituximab** was administered as 2 infusions of 1g at day 0 and day 14 in 9 patients (60%) and 375mg/m2 once per week for 4 weeks in 6 patients (40%).	2/15	1 patient had nonsevere rhino-bronchitis 6 months after rituximab 1 patient cutaneous herpes zoster virus infection 26 months after rituximab

Evidence summary:

Chavarot 2017 was conducted in 15 patients' membranous LN that took Rituximab alone for induction therapy. At 6 months CRR was 4/15 (27%) while PRR was 8/15 (53%). For relapse, none of the patients had a relapse at 6 month follow-up, while 1 (8%) patient had an event at 12 months. No difference was observed in creatinine level from baseline. For proteinuria at 6 months there was a reduction of 3.7 g/g occurred while a reduction of 4.89 occurred at 24 months. 2 patients had adverse events; nonsevere rhino- bronchitis and cutaneous herpes zoster virus.

Reference:

Chavarot N, Verhelst D, Pardon A, Caudwell V, Mercadal L, Sacchi A, Leonardi C, Le Guern V, Karras A, Daugas E; Groupe Coopératif sur le Lupus Rénal. Rituximab alone as induction therapy for membranous lupus nephritis: A multicenter retrospective study. Medicine (Baltimore). 2017 Jul;96(27):e7429. doi: 10.1097/MD.0000000000007429. PMID: 28682905; PMCID: PMC5502178.

P11. If a LN patient has received adequate/appropriate standard treatment for active LN of any class and has not achieved at least a partial renal response (PRR) to that treatment by 6 months, is treatment with "X" compared to treatment with "Y" (detailed in table) associated with improved outcomes?

Population: LN patients being treated for active LN of any class who have been treated with adequate and appropriate standard therapy and who have been adherent to that therapy but have failed to achieve at least a partial renal response after 6 months of treatment.
Intervention: Rituximab versus MMF versus CNI versus CYC versus Leflunomide versus Belimumab
Outcomes:

- Reduction of proteinuria
- CRR
- PRR
- Preservation of kidney function
- LN Flare rate
- Cumulative steroid dose
- Treatment-related adverse effects including infection; also decrease >30% from baseline eGFR for CNI's, depression/suicide for belimumab
- ESKD (dialysis or transplant)

Summary of findings per outcome and per intervention:
Proteinuria:

- One single-arm study with tacrolimus (Tanaka 2007) showed a decrease of UPCr mean value from 1.22 at baseline to 0.78 at 1 month, 0.86 at 3 months, and 0.79 at 6 months, but the confidence intervals demonstrate that the results are very imprecise. Another study (Uchino 2017) showed that proteinuria decreased from 2.52 (2.89) to 2.11 (3.01), and for class IV decreased from 2.25 (1.81) to 0.43 (0.33) at the 6th month. Although there was also improvement in the UPCr ratio for the 4 patients in WHO class III and the 7 patients in WHO class V, the changes after tacrolimus treatment were not significant until the 6th month.
- In treatment with rituximab (Contis 2016) proteinuria dropped from 2.35 g/24 h at baseline to 0.28 g/24 h [0–0.5] at 1 year after rituximab treatment, and with IV rituximab 24-hour urinary albumin excretion decreased from mean (SD) 3.3 (3.1) grams to 0.4 (0.6) grams after 6 months (Garcia-Carrasco 2010).
- In treatment with leflunomide, urine protein dropped at baseline from mean (SD) 4.8 (2.7) g/24 hrs to 1.8 (1.2) g/24 hrs at 12 months (Zhang 2011).
- In treatment with CsA, at dose 2.5 mg/kg/ day a decrease of urinary protein concentration was observed as early as 2 weeks after CsA commencement from 167.4 +/- 42.5 to 105.2 +/- 13.6 mg/dl (Ogawa 2010), and at dose 3 mg/Kg/day from 1±1.8 g/d to 0.5±0.1 mg/day (Sheikholeslami 2018).
- MMF at a maximum mean dose of 1.39 ± 0.4 g (range 0.5–2.5 g) treatment resulted in reductions in protein excretion in 24 hours from 3.01 ± 2.5 g to 1.85 ± 3.6 g (Pisoni 2004) and at a median dose 1 g/day (range 250 mg-2 g/day) from 2.8 g/24hr at baseline to 0.5 g/24 hour at month 60.

Complete response:

- The rate of complete renal response ranged from as low as 19% in treatment with MMF at dose 2-3mg/d (Cortés-Hernández 2010) up to 75% in treatment with rituximab at dose 2×750 mg/m2 (max. 1 g) (Srsen 2020) but only in 4 patients, and 67% in 27 patients treated with CsA (Sheikholeslami 2018).

Partial response:

- The rate of partial remission rate ranged from 22% in treatment with CsA (Petri 2003) up to 61% in treatment with MMF (Rivera 2014).

ESRD:

- The rate of ESRD was 6% in treatment with MMF (Rivera 2014) and 11% in treatment with CsA (Petri 2003).

Adverse events:

- Total adverse events ranged between 33% to 42%, the infection rate was 24% (Rivera 2014) in treatment with MMF, and 40% (Malaviya, 1992) in treatment with IV CYC, and the rate of serious infections was 6% (Contis 2016) in treatment with rituximab and 12% (Shipa 2021) in treatment with belimumab.
- Mental health outcomes were reported in one study (Shipa 2021) in patients treated with belimumab and rate of suicidal ideation 8% and depression 15%.

Renal flare-ups:

- Renal flares reported in one study in patients treated with CsA and HCQ (400mg/d) with prednisone had a rate of 19% (Sheikholeslami 2018).

Outcomes (Name + Summary)	Author, year, RefID	Study type	Duration of follow up	Population (number and description, age)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Change in UPCr	Tanaka, 2007, 8844	Non-comparative study	6 months	6 patients with sle flare on cytotoxic therapy and steroids Age: median 20 (14-25 yrs)	Tacrolimus	UPCr baseline 1.22±1.94 (0.03–4.70) UPCr 1 mo: 0.78±1.51 (0.02–3.84) UPCr 3 mos: 0.86±1.85 (0.02–4.64) UPCr 6 mos: 0.79±1.73 (0.04–4.32)	Change in UPCr 6 mos after starting tacrolimus
Proteinuria	Uchino, 2017, 9223	Non-comparative study	6 mos.	LN patients with persistent proteinuria despite steroids and immunosuppression – treated with 2-3g tac for 6 mos. 23 patients; *Age : median 34.5 (17-61)*	Tacrolimus	the UPCR ratio at baseline was 2.52±2.89 and it decreased significantly to 2.11±3.01 by 2 months after the start of the study . This significant	LN patients with persistent proteinuria despite steroids and immunosuppression – treated with 2-3g tac for 6 mos.

						decrease of UPCR continued until 6 months (1.43±2.43).	
Proteinuria	Contis, 2016, 1885	Retrospective single arm observational study	12 months	17 patients who had failed induction with cyclophosphamide; age: median 36 years (30–44)	Rituximab 375mg/m2 weekly x 4 or 1 g at 0 and 14 days	For patients with CRR and PRR, proteinuria tapered from 2.35 g/24 h at baseline to 0.28 g/24 h [0–0.5] at 1 year after rituximab treatment ($p<0.0039$) and from 4 g/24 h to 1.32 g/24 h (0.76–5) ($p < 0.0067$) in NRR patients	
Proteinuria	Dooley, 1999, 2382	Retrospective single arm observational study	Mean 13.2 months (range, 3 to 24)	12 patients with relapsing or resistant lupus nephritis (class IV); age mean 34.8 (range, 16 to 48 years)	MMF and prednisone	mean UPC at entry of 5.45 :±: 3.37 to 2.92 :±: 2.52 at f/u; the mean change in UPC ratios was -2.53 :±: 3.76; P = 0.039	
Proteinuria decrease	Sheikholeslami 2018, 8242	Non-comparative study	40.7 months (±24.9)	Patients with class III LN (n=8), and class IV LN (n=19). Age 29.6 years (16-48 years)	Cyclosporine 3 mg/Kg/day preprendial. Previous immunosuppressants were discontinued but Prednisone and HCQ (400mg/d) were continued.	Urine protein from 3.1±1.8 g/d at BL, decreased to 0.5±0.1 mg/day (p=0.001)	
Reduction in proteinuria	Garcia-Carrasco 2010, 3111	Retrospective cohort study	6 months	13 SLE patients with clinically active LN despite at least one immunosuppressive agent (CYC = 4; MMF = 6; AZA = 3). Biopsy in 6/13 (III: 2/6; IV: 4/6).	IV rituximab 1 gram (with 500 mg IV MP) on Day 1 and Day 15 was added to current immunosuppressive regimen.	24-hour urinary albumin excretion decreased from mean (SD) 3.3 (3.1) grams to 0.4 (0.6) grams after 6 months	

				Median age 36 years (range 19-63).			
Urine protein change from baseline to 12 months	Zhang, 2011, 10165	Unclear if retrospective or prospective but single center observational study	12 months	N=31 patients, mean age 31 years (SD 12 years); LN class: class 2 -1, class 3- 11, class 4- 10, class 5- 9	Leflunomide- loading dose 0.8–1.2 mg/kg per day for 3–7 days, followed by 0.4–0.8 mg/kg maintenance	Mean (SD) urine protein at baseline- 4.8 (2.7) g/24 hrs and at 12 months- 1.8 (1.2) g/24 hrs	
Proteinuria reduction	Ogawa, 2010, 6683	Single-arm study	Mean follow-up 21.5 +/- 15.7 months	59 Japanese patients with active LN (51 refractory to steroids +/- other immunosuppressants, 8 with class IV disease or renal vasculitis). The mean age was 36.7 14.4 (SD) years (range 16–73 years)	Cyclosporine A at initial dosage of 100–150 mg/day according to individual body weight (approximately 2.5 mg/kg/ day) in divided doses. CsA dosage was adjusted, aiming for a trough plasma level of 80–150 ng/ml, and reduced by 25 mg/day when serum creatinine level or systolic blood pressure was elevated by 30% or more from the baseline value	Notably, a significant reduction (37%) of urinary protein concentration was observed as early as 2 weeks after CsA commencement (167.4 +/- 42.5 to 105.2 +/- 13.6 mg/dl, $p< 0.05$)	
Proteinuria	Petri, 2003, 7086	Single-arm study	10-47 months	9 patients with LN refractory to steroids and at least one immunosuppressant (mean +/- SD age was 35 +/- 10 years).5 with class IV LN and 4 with class V LN. 2 males and 7 females.	50 mg/kg of cyclophosphamide for 4 consecutive days followed by 5 g/kg granulocyte colony-stimulating factor until the neutrophil count was 1 109 /liter for 2 consecutive days	Decreased urine protein 24-hour excretion (mean difference 3.3 gm/day; $P = 0.01$)	

Proteinuria	Pisoni, 2004, 7178	Single-arm study	Minimum 3 months	59 patients with LN (1 class I, 11 class III, 12 class IV, 9 class V), treated with at least one other immunosuppressant in the past, Mean age 36.83 ± 8.8	MMF: maximum dose was 1.39 ± 0.4 g (range 0.5–2.5 g)	Significant reductions in protein excretion in 24 hours (initial 3.01 ± 2.5 g, follow-up 1.85 ± 3.6 g, p =0.001) and steroid doses (initial 17.71 ± 10.57 mg/day, follow-up 9.38 ± 6.37 mg/day, p < 0.0001).	Prior immunosuppressants included CYC, AZA and MTX
Proteinuria	Rivera, 2014, 7605	Single-arm study	Median follow-up 30 months (range 3-102)	85 White Spanish patients with LN (35 refractory and 50 relapsing). Most were aged 15–65 years (94.1%); those aged less than 15 years accounted for 2.4% and those aged more than 65 years accounted for 3.5%. Class II=1; class III=29; class IV=47; class V=8	Median MMF dose 1 g/day (range 250 mg-2 g/day)	Proteinuria: 2.8 g/24hr at baseline to 0.5 g/24 hour at month 60 (p<0.05)	
Proteinuria reduction	Jo´nsdo´ttir, 2010, 4324	Single-arm study	6 months	28 with proliferate and 15 with membranous LN	RTX 375 mg/m2 body surface area given weekly, 4 times or i.v. RTX 100 mg twice given 2 weeks apart, with standard pre-medication; i.v. CYC 500–1000 mg given twice (3 weeks apart); i.v. MP 250 mg given twice (3 weeks apart); and a taper of oral glucocorticoids.	Reduction of proteinuria from 4.6 (3.25; 6) down to 2.5 (0.8; 4) in membranous LN patients, and from 3.5 (2.7; 4.3) down to 1.7 (0.7; 1.9) in proliferative LN patients	

Complete renal response (CRR)	Cortés-Hernández 2010, (ID:1923)	Non-comparative	24 months	Patient with non-responding proliferative LN Age:32+-12	MMF 2 gr/day + tacrolimus 0.075 mg/kg/day	CRR: 6/17 (35%)	Patient with non-responding proliferative LN: Not achieving at least partial renal response to MMF 2-3 g CR was defined as urinary protein excretion <0.3g/24h, normal urinary sediment and stable renal function.
Complete renal response (CRR)	Cortés-Hernández 2010, (ID:1923)	Non-comparative	6 months	Patient with proliferative LN Age:32+-12	MMF 2-3 gr day	CRR: 13/70 (19%)	CR was defined as urinary protein excretion <0.3g/24h, normal urinary sediment and stable renal function.
Complete renal response (CRR)	Cortés-Hernández 2010, (ID:1923)	Non-comparative	12 months	Patient with proliferative LN Age:32+-12	MMF 2-3 gr day	CRR: 24/70 (34%)	CR was defined as urinary protein excretion <0.3g/24h, normal urinary sediment and stable renal function.
Complete renal response (CRR)	Cortés-Hernández 2010, (ID:1923)	Non-comparative	24 months	Patient with non-responding proliferative LN Age:32+-12	MMF 2 gr/day + tacrolimus 0.075 mg/kg/day	CRR: 6/17 (35%)	Patient with non-responding proliferative LN: Not achieving at least partial renal response to MMF 2-3 g CR was defined as urinary protein excretion <0.3g/24h, normal urinary sediment and stable renal function.

Complete renal remission	Contis, 2016, 1885	Retrospective single arm observational study	12 months	17 patients who had failed induction with cyclophosphamide; age: median 36 years (30–44)	Rituximab 375mg/m2 weekly x 4 or 1 g at 0 and 14 days	4/17 (24%) patients	CRR was defined as proteinuria under 0.2 g/ 24 h, a glomerular filtration rate stable or up to 90 ml/min, and inactive urinary sediment
Complete renal remission (CRR)	Sheikholeslami 2018, 8242	Non-comparative study	40.7 months (±24.9)	Patients with class III LN (n=8), and class IV LN (n=19). Age 29.6 years (16-48 years)	Cyclosporine (CsA) 3mg/Kg/day preprendial. Previous immunosuppressants were discontinued but Prednisone and HCQ (400mg/d) were continued.	Complete renal remission 18/27 (67%)	All pts failed previous treatment with prednisolone and adequate dose of either MMF or CYC for at least 3 months. A. CRR: Proteinuria<300 mg/d+Normal urin sediment+SCr and CrCl <=15% BL value+Normal serum albumon (3.5-5.5g/dl)
Complete renal response	Garcia-Carrasco 2010, 3111	Retrospective cohort study	6 months	13 SLE patients with clinically active LN despite at least one immunosuppressive agent (CYC = 4; MMF = 6; AZA = 3). Biopsy in 6/13 (III: 2/6; IV: 4/6). Median age 36 years (range 19-63).	IV rituximab 1 gram (with 500 mg IV MP) on Day 1 and Day 15 was added to current immunosuppressive regimen.	5/13 (38.4%) achieved a complete renal response at 6 months.	Complete renal remission defined as normal Cr and albumin levels, inactive urinary sediment, and 24-hr urinary albumin excretion < 0.5 g.

Complete response	Petri, 2003, 7086	Single-arm study	10-47 months	9 patients with LN refractory to steroids and at least one immunosuppressant (mean +/- SD age was 35 +/- 10 years).5 with class IV LN and 4 with class V LN. 2 males and 7 females.	50 mg/kg of cyclophosphamide for 4 consecutive days followed by 5 g/kg granulocyte colony-stimulating factor until the neutrophil count was 1 109 /liter for 2 consecutive days	CP 4/9 (44%)	For renal lupus, a partial response required a reduction of at least 50% in the 24-hour total protein excretion A complete responder was defined as having no disease activity and receiving physiologic or lower doses of prednisone and no other immunosuppressive drugs
Complete remission	Pinto, 2011, 7158	Single-arm study	Minimum 3 months	32 Colombian patients with LN refractory to steroids and at least 1 immunosuppressant (1 class II, 4 class III, 20 class IV, 7 class V). Mean age 29.7 +/- 8.9	All patients were treated with 1 g of RTX and 200 mg of intravenous methylprednisolone every two weeks for two doses, followed by prednisolone (PDN) 1 mg/kg per day, in addition to the immunosuppressive regimen they had been receiving	28% complete remission according to proteinuria, and 12.5% according to creatinine clearance. At 6 months in 65% (n = 20) of the patients. 12 months after RTX therapy, 61.53% of patients achieved complete or partial remission through proteinuria criteria, and 33% of them through creatinine clearance criteria	Complete remission was defined as proteinuria below 500 mg/24 h and creatinine clearance above 80 ml/min. Partial remission was defined as improvement of more than 50% in abnormal parameters at baseline evaluation, without any of them deteriorating, meaning a deteriorating 25% decrease in creatinine clearance, reaching dialysis or a 50% increase in proteinuria

Complete response	Rivera, 2014, 7605	Single-arm study	Median follow-up 30 months (range 3-102)	85 White Spanish patients with LN (35 refractory and 50 relapsing). Most were aged 15–65 years (94.1%); those aged less than 15 years accounted for 2.4% and those aged more than 65 years accounted for 3.5%. Class II=1; class III=29; class IV=47; class V=8	Median MMF dose 1 g/day (range 250 mg-2 g/day)	CR: 23/85 (27%)	Complete response was defined as a return to normal or previous eGFR and proteinuria ≤ 0.5 g/24 h.
Complete remission	Srsen 2020, 8562	Single-arm study	24-84 months	4 patients with pediatric SLE and LN (3 males and 1 female; 3 Croatians and 1 Albanian; 2 class IV and 2 class V). Age at diagnosis ranged from 8-15 years	In 3 patients, rituximab was administered in a dose 2×750 mg/m2 , (max. 1 g), that was combined with cyclophosphamide “mini pulses” (350 mg/m2) in 2 patients, and in 1 patient RTX was administered in 4 doses of 375 mg/m2	Complete Remission: 3/4 (75%)	response was defined as remission if the SLEDAI score after 6 months was 2 or less, and as partial improvement if SLEDAI score was 3 or higher after 6 months but at least 50% lower than before treatment with RTX
Partial renal remission	Contis, 2016, 1885	Retrospective single arm observational study	12 months	17 patients who had failed induction with cyclophosphamide; age: median 36 years (30–44)	Rituximab 375mg/m2 weekly x 4 or 1 g at 0 and 14 days	5/17 (29%)	PRR was defined as proteinuria between 0.2 g/24 h and 0.5 g/24 h, a glomerular filtration rate stable or up to 90 ml/min, and inactive urinary sedimen
Partial renal remission (CRR)	Sheikholeslami 2018, 8242	Non-comparative study	40.7 months (±24.9)	Patients with class III LN (n=8), and class IV LN (n=19). Age 29.6 years (16-48 years)	Cyclosporine 3mg/Kg/day preprendial. Previous immunosuppressants were discontinued	Partial renal remission 7/27 (26%)	CRR and PRR occurred 25.1±12.8 weeks after treatment with CsA. Proteinuria decrease to 300-2900mg/d

					but Prednisone and HCQ (400mg/d) were continued.		and at least 50% reduction in dl was >3g/d+Stabilization of renal function (change in SCr <20% BL vakue and/or improvement in renal function (reduction in SCr>20% BL value)+ urinary RBC<10 /hpf+Serum albumin >=3g/dl
Partial renal response	Garcia-Carrasco 2010, 3111	Retrospective cohort study	6 months	13 SLE patients with clinically active LN despite at least one immunosuppressive agent (CYC = 4; MMF = 6; AZA = 3). Biopsy in 6/13 (III: 2/6; IV: 4/6). Median age 36 years (range 19-63).	IV rituximab 1 gram (with 500 mg IV MP) on Day 1 and Day 15 was added to current immunosuppressive regimen.	5/13 (38.4%) achieved a partial response at 6 months. 10/13 (77%) achieved a complete or partial response.	Partial renal remission was defined as a >50% improvement in all renal parameters that were abnormal at baseline, with no deterioration in any parameter.
Partial renal response	Petri, 2003, 7086	Single-arm study	10-47 months	9 patients with LN refractory to steroids and at least one immunosuppressant (mean +/- SD age was 35 +/- 10 years).5 with class IV LN and 4 with class V LN. 2 males and 7 females.	50 mg/kg of cyclophosphamide for 4 consecutive days followed by 5 g/kg granulocyte colony-stimulating factor until the neutrophil count was 1 109 /liter for 2 consecutive days	PR 2/9 (22%)	
Partial remission	Pinto, 2011, 7158	Single-arm study	Minimum 3 months	32 Colombian patients with LN refractory to steroids and at least 1 immunosuppressant (1 class II, 4 class III, 20 class IV, 7 class V). Mean age 29.7 +/- 8.9	All patients were treated with 1 g of RTX and 200 mg of intravenous methylprednisolone every two weeks for two doses, followed by prednisolone (PDN) 1 mg/kg per day, in addition to	At 3 months 36% partial remission according to proteinuria, and 33% according to creatinine clearance. PR at 6 months in 65% (n = 20). In 12 months 61.53% of	Partial remission was defined as improvement of more than 50% in abnormal parameters at baseline evaluation, without any of them deteriorating, meaning a

					the immunosuppressive regimen they had been receiving	patients achieved complete or partial remission through proteinuria criteria, and 33% of them through creatinine clearance criteria	deteriorating 25% decrease in creatinine clearance, reaching dialysis or a 50% increase in proteinuria
Partial response	Rivera, 2014, 7605	Single-arm study	Median follow-up 30 months (range 3-102)	85 White Spanish patients with LN (35 refractory and 50 relapsing). Most were aged 15–65 years (94.1%); those aged less than 15 years accounted for 2.4% and those aged more than 65 years accounted for 3.5%. Class II=1; class III=29; class IV=47; class V=8	Median MMF dose 1 g/day (range 250 mg-2 g/day)	PR: 51/85 (61%)	Partial response was defined as a decrease in proteinuria to <3.5 g/24 h and a ≥ 50% decrease in proteinuria in patients with baseline proteinuria ≥ 3.5 g/24 h, or as a 50% decrease in proteinuria in patients with baseline proteinuria <3.5 g/24 h.
ESRD	Rivera, 2014, 7605	Single-arm study	Median follow-up 30 months (range 3-102)	85 White Spanish patients with LN (35 refractory and 50 relapsing). Most were aged 15–65 years (94.1%); those aged less than 15 years accounted for 2.4% and those aged more than 65 years accounted for 3.5%. Class II=1; class III=29; class IV=47; class V=8	Median MMF dose 1 g/day (range 250 mg-2 g/day)	ESRD: 5/85 (6%) Infections: 20/85	
ESRD	Petri, 2003, 7086	Single-arm study	10-47 months	9 patients with LN refractory to steroids and at least one immunosuppressant (mean +/- SD age was 35 +/- 10 years).5 with	50 mg/kg of cyclophosphamide for 4 consecutive days followed by 5 g/kg granulocyte colony-stimulating	1/9 (11%) ESRD leading to transplant	

				class IV LN and 4 with class V LN. 2 males and 7 females.	factor until the neutrophil count was 1 109 /liter for 2 consecutive days		
Adverse events	Zhang, 2011, 10165	Unclear if retrospective or prospective but single center observational study	12 months	N=31 patients, mean age 31 years (SD 12 years); LN class: class 2 -1, class 3- 11, class 4- 10, class 5- 9	Leflunomide- loading dose 0.8–1.2 mg/kg per day for 3–7 days, followed by 0.4–0.8 mg/kg maintenance	10/31 (33%) total adverse events; 0 infections	
Adverse effects	Dooley, 1999, 2382	Retrospective single arm observational study	Mean 13.2 months (range, 3 to 24)	12 patients with relapsing or resistant lupus nephritis (class IV); age mean 34.8 (range, 16 to 48 years)	MMF and prednisone	5/12 (42%) patients with adverse events (8 adverse events total including leukopenia, GI sxs, infection, pancreatitis hair thinning)	
Adverse Events	Sheikholeslami 2018, 8242	Non-comparative study	40.7 months (±24.9)	Patients with class III LN (n=8), and class IV LN (n=19). Age 29.6 years (16-48 years)	Cyclosporine 3mg/Kg/day preprendial. Previous immunosuppressants were discontinued but Prednisone and HCQ (400mg/d) were continued.	10/27 (37%) (HTN=2; GI=2; Gum hypertrophy 1; Hirsitism 2; Infection=2; tremor=1)	No death, severe infections
Treatment-related adverse events	Garcia-Carrasco 2010, 3111	Retrospective cohort study	6 months	52 SLE patients with clinically active SLE despite at least one standard immune-suppressive agent. 13/52 had active LN. Median age 36 (range 19-72) years.		2/52 developed serum sickness after first infusion. 1/52 discontinued due to pulmonary infection after first infusion. 2/52 had late-onset neutropenia without infection.	

						No other serious adverse events.	
Adverse event (leucopenia)	Cortés-Hernández 2010, (ID:1923)	Non-comparative	65 months	Patient with proliferative LN Age:32+-12	MMF 2-3 gr day	2/70 (3%)	Leucopenia
Adverse events	Uchino, 2017, 9223	Non-comparative study	6 mos.	LN patients with persistent proteinuria despite steroids and immunosuppression – treated with 2-3g tac for 6 mos. 23 patients; *Age : median 34.5 (17-61)*	Tacrolimus	Infections: 3/23 Creatinine increased 4/23 HTN: 1/23	
Adverse events	Ogawa, 2010, 6683	Single-arm study	Mean follow-up 21.5 +/- 15.7 months	59 Japanese patients with active LN (51 refractory to steroids +/- other immunosuppressants, 8 with class IV disease or renal vasculitis). The mean age was 36.7 14.4 (SD) years (range 16–73 years)	Cyclosporine A at initial dosage of 100–150 mg/day according to individual body weight (approximately 2.5 mg/kg/ day) in divided doses. CsA dosage was adjusted, aiming for a trough plasma level of 80–150 ng/ml, and reduced by 25 mg/day when serum creatinine level or systolic blood pressure was elevated by 30% or more from the baseline value	Renal dysfunction: 7/57, CsA was discontinued in four of them, while this was ameliorated by the reduction of the CsA dosage in the other three patients	

Infections	Malaviya, 1992, 5612	Single-arm study	Median 28 months (range 6-65 months)	48 patients with LN (43 biopsy-proven; 26 class IV, 2 class III, 10 class II, 1 minimal change, 4 membranoproliferative). Median age of disease onset 22 years (range 4-37)	0.5-0.75 g/m2 IV CYC for 3 weekly doses x 6 cycles. Also prednisolone 0.5-1 mg/kg x 4 weeks then tapered as per clinical course. HCQ 400 mg daily or chloroquine 250 mg daily for 6 months, then decreased to QOD dosing	19/48 (40%) infections	
Infections	Rivera, 2014, 7605	Single-arm study	Median follow-up 30 months (range 3-102)	85 White Spanish patients with LN (35 refractory and 50 relapsing). Most were aged 15–65 years (94.1%); those aged less than 15 years accounted for 2.4% and those aged more than 65 years accounted for 3.5%. Class II=1; class III=29; class IV=47; class V=8	Median MMF dose 1 g/day (range 250 mg-2 g/day)	Infections: 20/85 (24%)	
Serious infection	Contis, 2016, 1885	Retrospective single arm observational study	12 months	17 patients who had failed induction with cyclophosphamide; age: median 36 years (30–44)	Rituximab 375mg/m2 weekly x 4 or 1 g at 0 and 14 days	1/17 (6%)	Serious infection
Serious infections	Shipa, 2021, 8287	Phase 2, randomized, double-blind placebo-controlled, parallel-group, superiority trial	52 weeks	20 Adults w/ refractory LN (10 in belimumab group and 10 in placebo group)	Participants were treated with rituximab and 4 to 8 weeks later were randomly assigned (1:1) to receive intravenous belimumab or placebo for 52 weeks	Serious infections: 3/26 (12%) in belimumab and 4/26 (15%) in placebo	

Mental health outcomes	Shipa, 2021, 8287	Phase 2, randomized, double-blind placebo-controlled, parallel-group, superiority trial	52 weeks	20 Adults w/ refractory LN (10 in belimumab group and 10 in placebo group)	Participants were treated with rituximab and 4 to 8 weeks later were randomly assigned (1:1) to receive intravenous belimumab or placebo for 52 weeks	Suicidal ideation: 2/26 (8%) in belimumab, 0/26 in placebo Depression: 4/26 (15%) in belimumab, 5/26 in placebo	
Renal flare	Sheikholeslami 2018, 8242	Non-comparative study	40.7 months (±24.9)	Patients with class III LN (n=8), and class IV LN (n=19). Age 29.6 years (16-48 years)	Cyclosporine 3mg/Kg/day preprendial. Previous immunosuppressants were discontinued but Prednisone and HCQ (400mg/d) were continued.	Renal flare 5/27 (19%)	
Flare rate	Ogawa, 2010, 6683	Single-arm study	Mean follow-up 21.5 +/- 15.7 months	59 Japanese patients with active LN (51 refractory to steroids +/- other immunosuppressants, 8 with class IV disease or renal vasculitis). The mean age was 36.7 14.4 (SD) years (range 16–73 years)	Cyclosporine A at initial dosage of 100–150 mg/day according to individual body weight (approximately 2.5 mg/kg/ day) in divided doses. CsA dosage was adjusted, aiming for a trough plasma level of 80–150 ng/ml, and reduced by 25 mg/day when serum creatinine level or systolic blood pressure was elevated by 30% or more from the baseline value	During CsA therapy, the mean flare rate decreased by approximately 60% from 0.26 to 0.10 times/ patient-year	

Prednisone dose decrease	Sheikholeslami 2018, 8242	Non-comparative study	40.7 months (±24.9)	Patients with class III LN (n=8), and class IV LN (n=19). Age 29.6 years (16-48 years)	Cyclojujsporine 3mg/Kg/day preprendial. Previous immunosuppressants were discontinued but Prednisone and HCQ (400mg/d) were continued.	Pred dose from 25.1±18.1 mg/day, decreased to 4.7±3.2 mg/day (p=0.02)	
SCr stabilization	Sheikholeslami 2018, 8242	Non-comparative study	40.7 months (±24.9)	Patients with class III LN (n=8), and class IV LN (n=19). Age 29.6 years (16-48 years)	Cyclosporine 3mg/Kg/day preprendial. Previous immunosuppressants were discontinued but Prednisone and HCQ (400mg/d) were continued.	SCr from 0.94±0.3 mg/dl mg/day at BL, changed to 0.93±0.4 mg/day (p=NS)	No ESRD
CsA discontinuation	Sheikholeslami 2018, 8242	Non-comparative study	40.7 months (±24.9)	Patients with class III LN (n=8), and class IV LN (n=19). Age 29.6 years (16-48 years)	Cyclosporine 3mg/Kg/day preprendial. Previous immunosuppressants were discontinued but Prednisone and HCQ (400mg/d) were continued.	2/27 (7%); 3/27 (11%.) (AE: HTN, tremor, nausea 1 each)	
Creatinine	Dooley, 1999, 2382	Retrospective single arm observational study	Mean 13.2 months (range, 3 to 24)	12 patients with relapsing or resistant lupus nephritis (class IV); age mean 34.8 (range, 16 to 48 years)	MMF and prednisone	Mean serum creatinine significantly declined from 149.0 :±: 88.5 at entry to 123.2 :±: 62.4 μM/L at last follow-up; mean change in serum creatinine was -0.26±: 0.46; P =0.039	Creatinine

Creatinine clearance	Zhang, 2011, 10165	Unclear if retrospective or prospective but single center observational study	12 months	N=31 patients, mean age 31 years (SD 12 years); LN class: class 2 -1, class 3- 11, class 4- 10, class 5- 9	Leflunomide- loading dose 0.8–1.2 mg/kg per day for 3–7 days, followed by 0.4–0.8 mg/kg maintenance	Mean (SD) creatinine clearance at baseline- 76.8 (26.2) ml/min and at 12 months- 122.1 (24.2) ml/min	
Cumulative steroid dose	Contis, 2016, 1885	Retrospective single arm observational study	12 months	17 patients who had failed induction with cyclophosphamide; age: median 36 years (30–44)	Rituximab 375mg/m2 weekly x 4 or 1 g at 0 and 14 days	Median dose of prednisone dropped from 20mg a day(0–40) to 5 mg a day (0–20) ($p<0.002$).	
Serum protein/cretininine excretion	Pisoni, 2004, 7178	Single-arm study	Minimum 3 months	59 patients with LN (1 class I, 11 class III, 12 class IV, 9 class V), treated with at least one other immunosuppressant in the past, Mean age 36.83 ± 8.8	MMF: maximum dose was 1.39 ± 0.4 g (range 0.5–2.5 g)	Significant reductions in protein excretion in 24 hours (initial 3.01 ± 2.5 g, follow-up 1.85 ± 3.6 g, $p = 0.001$) and steroid doses (initial 17.71 ± 10.57 mg/day, follow-up 9.38 ± 6.37 mg/day, $p < 0.0001$). Serum creatinine levels, creatinine clearance, and EDTA-GFR values showed no significant change during treatment	Prior immunosuppressants included CYC, AZA and MTX
Mental health outcomes	Shipa, 2021, 8287	Phase 2, randomized, double-blind placebo-controlled, parallel-group, superiority trial	52 weeks	20 Adults w/ refractory LN (10 in belimumab group and 10 in placebo group)	Participants were treated with rituximab and 4 to 8 weeks later were randomly assigned (1:1) to receive intravenous belimumab or	Suicidal ideation: 2/26 (8%) in belimumab, 0/26 in placebo Depression: 4/26 (15%) in belimumab, 5/26 in placebo	

					placebo for 52 weeks		
Herpes zoster	Srsen 2020, 8562	Single-arm study	24-84 months	4 patients with pediatric SLE and LN (3 males and 1 female; 3 Croatians and 1 Albanian; 2 class IV and 2 class V). Age at diagnosis ranged from 8-15 years	In 3 patients, rituximab was administered in a dose 2×750 mg/m2 , (max. 1 g), that was combined with cyclophosphamide “mini pulses” (350 mg/m2) in 2 patients, and in 1 patient RTX was administered in 4 doses of 375 mg/m2	Herpes zoster: 2/4	response was defined as remission if the SLEDAI score after 6 months was 2 or less, and as partial improvement if SLEDAI score was 3 or higher after 6 months but at least 50% lower than before treatment with RTX

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P12. If a LN patient has received adequate/appropriate initial treatment for active LN of any class and did not achieve at least a partial renal response to that treatment after 6 months*, and then received an alternative standard treatment regimen and did not achieve at least a partial renal response after 6 months* (so now considered to have refractory LN), is treatment with “X” compared to treatment with “Y” (detailed in table) associated with improved outcomes?

Interventions*:*
-Anti CD20 therapy
-Belimumab
-CNI
-CYC
-Leflunomide
-MMF
-MMF+CNI
-Rituximab
Comparators:
-No pulse glucocorticoids given
-MMF/MPA alone
-CYC alone
-MMF/MPA/CYC alone
-MMF/MPA/CYC alone
-MMF/MPA/CYC alone
-MMF/MPA/CYC alone

-MMF/MPA/CYC alone
-MMF/MPA/CYC alone

Outcomes:

- Reduction of proteinuria
- CRR
- PRR
- Preservation of kidney function
- LN Flare rate
- ESKD (dialysis or transplant)
- Treatment related adverse effects including infection; also decrease >30% from baseline eGFR for CNI's, depression/suicide for belimumab
- Cumulative steroid dose

Anti-CD20 Therapy

Table 1. Studies included.

Author, year, RefID	Population	Intervention	Outcome
Davies 2013[1], 2123	18 patients with refractory lupus nephritis (having failed a median of 5 immunosuppressive agents); age: mean 29 years (range 21–45)	Rituximab + CYC	-Complete renal remission -Partial renal remission -ESRD -Creatinine -Proteinuria -Adverse events -LN Flare rate
Lateef 2010[2], 5002	7 adult patients (4 class IV LN, 1 class IV/V LN, 2 class V LN). Median age 28 (range 18-66). 5 Chinese, 1 Malay, 1 Indian. 6 female, 1 male	Rituximab+ CYC	-Complete Renal Response -Partial Renal Response -Infection
Srsen 2020[3], 8562	4 patients with pediatric SLE and LN (3 males and 1 female; 3 Croatians and 1 Albanian; 2 class IV and 2 class V). Age at diagnosis ranged from 8-15 years	Rituximab+ CYC	-Adverse Events -Infection

Pinto 2011[4], 7158	32 Colombian patients with LN refractory to steroids and at least 1 immunosuppressant (1 class II, 4 class III, 20 class IV, 7 class V). Mean age 29.7 +/- 8.9	Rituximab	-Complete Remission -Partial Remission -Infection
Catapano 2021[5], 1469	31 patients with relapsing or refractory SLE: 11 with renal involvement (biopsy proven/class not specified, n=9) Mean age 40.2 +/-12.8 years	Rituximab	-Complete and partial response -Proteinuria -Adverse events
Choi 2022[6], 1734	22 adult patients with refractory LN Median age=31 (Normal GFR) 43(decreased GFR) classes: III-IV	Rituximab	-Complete/partial renal remission
Jonsdottir 2024[7], 4324	Twenty-eight patients with proliferative LN and 15 with membranous LN after having failed common immunosuppressive therapy, including CYC in most patients. Age: Median 32	Rituximab	-Proteinuria -Creatinine
Atisha 2021[8], 596	22 patients Age: 32.3 ± 11.43 mixed ethnicity Class III,IV,III with V,IV with V	Rituximab	-ESRD -Infection -Complete/partial response
Kotagiri 2016[9]	14 patients (11 females, 3 males) were included in the study. Median age at study entry was 33 years (IQR: 24–39). The median chronic kidney disease stage on study entry was 2 (IQR: 1–3).	Rituximab	-Complete Response -Partial Response

Evidence summary:
9 studies were included, in which Rituximab was used in patients with SLE and LN. The outcomes reported complete/partial renal remission, ESRD, creatinine, proteinuria, and adverse events.

Table 2. Outcomes

Outcome	Author, year, RefID	Study Design	Follow up Duration	Population	Intervention	Result	
Complete renal remission	Pinto 2011[4], 7158	Single-arm study	3 months	32 Colombian patients with LN refractory to steroids and at least 1 immunosuppressant. (1 class II, 4 class III, 20 class IV, 7 class V). Mean age 29.7 +/- 8.9	All patients were treated with RTX and intravenous methylprednisolone, followed by prednisolone 1 mg/kg per day, in addition to the immunosuppressive regimen they had been receiving.	CRR: At 3 months: 9/32 (28%)	
	Atisha 2021[8] 596	Randomized Controlled trial	96 weeks	22 patients Age: 32.3 ± 11.43 Mixed ethnicity Class III,IV,IIIwith V,IV with V	all participants received methylprednisolone at a dose of 100 mg, Rituximab, and CYC (750 mg intravenously (IV) at weeks 0 and 2) Prednisone at a dosage of 40 mg/day was initiated, and then tapered.	CRR: 24 weeks: 5/22 48 weeks: 7/22 96 weeks: 4/22	
	Choi 2022[6] 1734	Single Arm	12 months	22 adult patients with refractory LN Median age=31 (Inormal GFR) 43(decreased GFR) classes: III-IV	Rituximab	CRR: 6 months: 8/22 12 months: 12/22	

	Davies, 2013[1], 2123	Retrospective single arm observational study	6 months	18 patients with refractory lupus nephritis (having failed a median of 5 immunosuppressive agents); age: mean 29 years (range 21–45)	Rituximab 1 g at 0 and 14 days with cyclophosphamide 500 mg IV and methylprednisolone 500 mg IV	CRR: 11/18	
	Lateef, 2010[2], 5002	Single-arm study	Median 18 months (range 12-36 months)	7 adult patients (4 class IV LN, 1 class IV/V LN, 2 class V LN). Median age 28 (range 18-66). 5 Chinese, 1 Malay, 1 Indian. 6 female, 1 male	two infusions of **RTX** (375 mg/m2), accompanied by intravenous CYC 500 mg two weeks apart.	CRR: 3/7	
	Srsen 2020[3], 8562	Single-arm study	24-84 months	4 patients with pediatric SLE and LN (3 males and 1 female; 3 Croatians and 1 Albanian; 2 class IV and 2 class V). Age at diagnosis ranged from 8-15 years	In 3 patients, rituximab was administered in a dose 2×750 mg/m2 , (max. 1 g), that was combined with cyclophosphamide “mini pulses” (350 mg/m2) in 2 patients, and in 1 patient RTX was administered in 4 doses of 375 mg/m2	CRR: 3/4	
	Catapano[5], 1469	Prospective study	Median FU 30 months	31 patients with relapsing or refractory SLE: 11 with renal involvement (biopsy proven/class not specified, n=9); 1 had minimal change diseae, 1 w clinial LN, 3 with ESRD (one transplanted 4.5 yrs prior to RTX, two on maintenance dialysis) Mean age 40.2 +/-12.8 years	15 patients received 4 RTX infusions at a dose of 375 mg/m2/week 16 received two infusions at a dose of 1000mg with a 2 week interval.	CRR: 3/6 with proliferative LN	

Partial renal remission	Kotagiri 2016[9]	RCT	18 months (IQR: 9–24)	14 patients (11 females, 3 males) were included in the study. Median age at study entry was 33 years (IQR: 24–39). The median chronic kidney disease stage on study entry was 2 (IQR: 1–3)	The median dose of rituximab used was 600 mg (IQR: 600–650).	At 5 months: 2/14	
	Pinto 2011[4], 7158	Single-arm study	Minimum 3 months	32 Colombian patients with LN refractory to steroids and at least 1 immunosuppressant (1 class II, 4 class III, 20 class IV, 7 class V). Mean age 29.7 +/- 8.9	All patients were treated with 1 g of RTX and 200 mg of intravenous methylprednisolone every two weeks for two doses, followed by prednisolone (PDN) 1 mg/kg per day, in addition to the immunosuppressive regimen they had been receiving	PRR: at 3 month 12/32 (36%)	
	Atisha 2021[8] 596	Randomized Controlled trial	24weeks,48 weeks, 96 weeks	22 patients Age: 32.3 ± 11.43 mixed ethnicity Class III,IV,IIIwith V,IV with V	all participants received methylprednisolone at a dose of 100 mg, rituximab at a dose of 1,000 mg, and CYC at a dose of 750 mg intravenously (IV) at weeks 0 and 2, based on the regimen described by Ng and colleagues (10). Prednisone at a dosage of 40 mg/day was initiated, with a prescribed taper to 10 mg/day by week 12, followed by ≤10 mg/day through week 96.	PRR: 24 weeks: 5/22 48 weeks: 2/22 96 weeks: 2/22	

	Davies[1], 2013, 2123	Retrospective single arm observational study	6 months	18 patients with refractory lupus nephritis (having failed a median of 5 immunosuppressive agents); age: mean 29 years (range 21–45)	Rituximab 1 g at 0 and 14 days with cyclophosphamide 500 mg IV and methylprednisolone 500 mg IV	PRR: 2/18	
	Lateef 2010[2], 5002	Single-arm study	Median 18 months (range 12-36 months)	7 adult patients (4 class IV LN, 1 class IV/V LN, 2 class V LN). Median age 28 (range 18-66). 5 Chinese, 1 Malay, 1 Indian. 6 female, 1 male	two infusions of RTX (375 mg/m2), accompanied by intravenous CYC 500 mg two weeks apart.	PRR: 4/7	
	Srsen 2020[3], 8562	Single-arm study	24-84 months	4 patients with pediatric SLE and LN (3 males and 1 female; 3 Croatians and 1 Albanian; 2 class IV and 2 class V). Age at diagnosis ranged from 8-15 years	In 3 patients, rituximab was administered in a dose 2×750 mg/m2, (max. 1 g), that was combined with cyclophosphamide "mini pulses" (350 mg/m2) in 2 patients, and in 1 patient RTX was administered in 4 doses of 375 mg/m2	PRR: 1/4	
	Catapano[5], 1469	Prospective study	Median FU 30 months	31 patients with relapsing or refractory SLE: 11 with renal involvement (biopsy proven/class not specified, n=9) Mean age 40.2 +/-12.8 years	15 patients received 4 RTX infusions at a dose of 375 mg/m2/week 16 received two infusions at a dose of 1000mg with a 2 week interveal.	PRR: 5/11	
	Choi 2022[6] 1734	Single Arm	6 and 12 months	22 adult patients with refractory LN Median age=31 (Inormal GFR) 43(decreased GFR) classes: III-IV	RTX: 1000mgx2 infusions, 500 mgx4 infusions, 500mg x3 infusions	PRR: At 6 months 2/22	

	Kotagiri 2016[9]	RCT	18 months (IQR: 9–24)	14 patients (11 females, 3 males) were included in the study. Median age at study entry was 33 years (IQR: 24–39). The median chronic kidney disease stage on study entry was 2 (IQR: 1–3)	The median dose of rituximab used was 600 mg (IQR: 600–650).	9/14	
ESRD	Davies 2013[1], 2123	Retrospective single arm observational study	6 months	18 patients with refractory lupus nephritis (having failed a median of 5 immunosuppressive agents); age: mean 29 years (range 21–45)	Rituximab 1 g at 0 and 14 days with cyclophosphamide 500 mg IV and methylprednisolone 500 mg IV	ESRD: 5/18	
	Jonsdottir 2024[7] 4324	Single Arm	3,6 and 12 months	Twenty-eight patients with proliferative LN and 15 with membranous LN after having failed common immunosuppressive therapy, including CYC in most patients. Age: Median 32	i.v. RTX 375 mg/m2 body surface area given weekly, four times or i.v. RTX 100 mg twice given 2 weeks apart, with standard pre-medication; i.v. CYC 500–1000 mg given twice (3 weeks apart); i.v. methylprednisolone 250 mg given twice (3 weeks apart); and a taper of oral glucocorticoids	ESRD: 2/28	
	Atisha 2021[8] 596	Randomized Controlled trial	2 years	22 patients Age: 32.3 ± 11.43 mixed ethnicity Class III,IV,III with V,IV with V	all participants received methylprednisolone at a dose of 100 mg, rituximab at a dose of 1,000 mg, and CYC at a dose of 750 mg intravenously (IV) at weeks 0 and 2, based on the regimen described by Ng and colleagues (10). Prednisone at a dosage of 40 mg/day was initiated, with a prescribed taper to 10 mg/day by week 12, followed by ≤10 mg/day through week 96.	ESRD: 3/22 (14%)	

Creatinine	Davies 2013[1], 2123	Retrospective single arm observational study	12 months	18 patients with refractory lupus nephritis (having failed a median of 5 immunosuppressive agents); Mean (range) Age: 29(21–45)	Rituximab 1 g at 0 and 14 days with cyclophosphamide 500 mg IV and methylprednisolone 500 mg IV	Mean (SD) Cr (umol/l): Baseline versus 1 year 124 (101) versus 169 (177)	
Proteinuria	Davies 2013[1], 2123	Retrospective single arm observational study	6 months & 12 months	18 patients with refractory lupus nephritis (having failed a median of 5 immunosuppressive agents); age: mean 29 years (range 21–45)	Rituximab 1 g at 0 and 14 days with cyclophosphamide 500 mg IV and methylprednisolone 500 mg IV	Mean (SD) PCR (mg/mmol): Baseline versus 1 year 419 (302) versus 162 (144)	
	Catapano[5], 1469	Prospective study	Median FU 30 months	31 patients with relapsing or refractory SLE: 11 with renal involvement (biopsy proven/class not specified, n=9); 1 had minimal change diseae, 1 w clinial LN, 3 with ESRD (one transplanted 4.5 yrs prior to RTX, two on maintenance dialysis) Mean age 40.2 +/-12.8 years	15 patients received 4 RTX infusions at a dose of 375 mg/m2/week 16 received two infusions at a dose of 1000mg with a 2 week interveal.	In 9 patients, proteinuria fell from median of 2.2 g/day at entry: -to **1.5** at 12 months -to 0.94 at 18 months -to 0.5 at 24 months	
Adverse events	Davies, 2013[1], 2123	Retrospective single arm observational study	12 months	18 patients with refractory lupus nephritis (having failed a median of 5 immunosuppressive agents); age: mean 29 years (range 21–45)	Rituximab 1 g at 0 and 14 days with cyclophosphamide 500 mg IV and methylprednisolone 500 mg IV	AE: 2/18	1 hypersensitivity reaction. 1 serious infection
	Catapano[5], 1469	Prospective study	Median FU 30 months	31 patients with relapsing or refractory SLE: 11 with renal involvement (biopsy proven/class not specified, n=9); 1 had minimal change diseae, 1 w clinial LN, 3 with ESRD (one transplanted 4.5 yrs prior to RTX, two on maintenance dialysis)	15 patients received 4 RTX infusions at a dose of 375 mg/m2/week 16 received two infusions at a dose of 1000mg with a 2 week interveal.	AE: 14/31 (45%)	

				Mean age 40.2 +/-12.8 years			
LN flare-up rate	Davies 2013[1], 2123	Retrospective single arm observational study	6 months to 6 years	18 patients with refractory lupus nephritis (having failed a median of 5 immunosuppressive agents); age: mean 29 years (range 21–45)	Rituximab 1 g at 0 and 14 days with cyclophosphamide 500 mg IV and methylprednisolone 500 mg IV	Flare up rate: 5/18	
Infection	Lateef 2010[2], 5002	Single-arm study	Median 18 months (range 12-36 months)	7 adult patients (4 class IV LN, 1 class IV/V LN, 2 class V LN). Median age 28 (range 18-66). 5 Chinese, 1 Malay, 1 Indian. 6 female, 1 male	two infusions of RTX (375 mg/m2), accompanied by intravenous CYC 500 mg two weeks apart. This was accompanied by high-dose	Infection: 0/7	
	Kotagiri 2016[9]	RCT	18 months (IQR: 9–24)	14 patients (11 females, 3 males) were included in the study. Median age at study entry was 33 years (IQR: 24–39). The median chronic kidney disease stage on study entry was 2 (IQR: 1–3)	The median dose of rituximab used was 600 mg (IQR: 600–650).	3/14	Herpes Zoster, cellulitis and Escherichia coli sepsis.
	Srsen 2020[3], 8562	Single-arm study	24-84 months	4 patients with pediatric SLE and LN (3 males and 1 female; 3 Croatians and 1 Albanian; 2 class IV and 2 class V). Age at diagnosis ranged from 8-15 years	In 3 patients, rituximab was administered in a dose 2×750 mg/m2 , (max. 1 g), that was combined with cyclophosphamide “mini pulses” (350 mg/m2) in 2 patients, and in 1 patient RTX was administered in 4 doses of 375 mg/m2	Herpes Zoster: 2/4	

	Atisha 2021[8] 596	Randomized Controlled trial	24weeks,48 weeks, 96 weeks	22 patients Age: 32.3 ± 11.43 mixed ethnicity Class III,IV,IIIwith V,IV with V	all participants received methylprednisolone at a dose of 100 mg, rituximab at a dose of 1,000 mg, and CYC at a dose of 750 mg intravenously (IV) at weeks 0 and 2, based on the regimen described by Ng and colleagues (10). Prednisone at a dosage of 40 mg/day was initiated, with a prescribed taper to 10 mg/day by week 12, followed by ≤10 mg/day through week 96.	Infections: 3/22	
Cumulative Steroid	Catapano[5], 1469	Prospective study	Median FU 30 months	31 patients with relapsing or refractory SLE: 11 with renal involvement (biopsy proven/class not specified, n=9); 1 had minimal change diseae, 1 w clinial LN, 3 with ESRD (one transplanted 4.5 yrs prior to RTX, two on maintenance dialysis) Mean age 40.2 +/-12.8 years	15 patients received 4 RTX infusions at a dose of 375 mg/m2/week 16 received two infusions at a dose of 1000mg with a 2 week interveal.	In 25 patients with 1 year FU, Prednisolone dose: Baseline: 10mg/d At 6 months: 8.3 mg/d At 12 months: 7.5mg/d At 24 months: 5.5mg/d	

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Belimumab Therapy:

Table 1. Studies included.

Author, year, RefID	Population (age,ethnicity,refractoryLN)	Intervention	Outcome
Atisha 2021[1] 596	21 patients Age: 32.3 ± 11.43 mixed ethnicity Class III,IV,IIIwith V,IV with V	Rituximab+ Blimumab	-ESRD -Infection -Complete/partial response
Kraaij 2020[3] 4831	15 patients had refractory disease, of which 12 (80%) had active LN at baseline Median age : 31 years (range 19–51	Rituximab+Belimumab	-Infection
Chen 2023[4], 674	25 patients with refractory lupus nephritis were included, with a median disease duration of 2 (0.75,7.5) years Age: 30.24+/- 10.56	18 in belimumab group (Rituximab + Belimumab)	-CRR -PRR

Evidence summary:
3 studies were included, all were RCTs in which patients were given anti-CD20 and Belimumab. The studies were RCTs but did not address comparisons of interest. The outcomes reported on were adverse events, ESRD, Infection, and complete/partial response

Table 2. Outcomes

Outcome	Author, year, RefID	Study Design	Follow up Duration	Population	Intervention	Result	

Complete renal remission	Atisha 2021[1] 596	RCT	24weeks,48 weeks, 96 weeks	21 patients Age: 32.3 ± 11.43 mixed ethnicity Class III,IV,IIIwith V,IV with V	Patients in the RCB group received belimumab IV at a dose of 10 mg/ kg at weeks 4, 6, and 8 and every 4 weeks thereafter through week 48	24 weeks: 5 48 weeks: 8 96 weeks: 5	
	Chen 2023[4], 674	RCT	19 (13, 29) months	25 patients (18 patients took belimumab) with refractory lupus nephritis were included, with a median disease duration of 2 (0.75,7.5) years Age: 30.24+/- 10.56	The dosing regimen for belimumab is 10 mg/kg, administered every 2 weeks for the first three doses, followed by once every 4 weeks	12/18 patients	(CRR) is defined as UPCR <0.5 g/g, absence of active urinary sediment, serum albumin 35 g/l, and normal serum creatinine (Scr) level.
Partial renal remission	Atisha 2021[1] 596	RCT	24weeks,48 weeks, 96 weeks	21 patients Age: 32.3 ± 11.43 mixed ethnicity Class III,IV,IIIwith V,IV with V	Patients in the RCB group received belimumab IV at a dose of 10 mg/ kg at weeks 4, 6, and 8 and every 4 weeks thereafter through week 48	24 weeks: 5 48 weeks: 3 96 weeks: 1	
	Chen 2023[4], 674	RCT	19 (13, 29) months	25 patients (18 patients took belimumab) with refractory lupus nephritis were included, with a median disease duration of 2 (0.75,7.5) years Age: 30.24+/- 10.56	The dosing regimen for belimumab is 10 mg/kg, administered every 2 weeks for the first three doses, followed by once every 4 weeks	1/18	Partial renal remission (PRR) is defined as a decrease in urinary protein of >50% from baseline, with UPCR <3.0 g/g, serum albumin >30 g/l, and normal or not >15% above baseline Scr level
ESRD	Atisha 2021[1] 596	RCT	24weeks,48 weeks, 96 weeks	21 patients Age: 32.3 ± 11.43 mixed ethnicity Class III,IV,IIIwith V,IV with V	Patients in the RCB group received belimumab IV at a dose of 10 mg/ kg at weeks 4, 6, and 8 and every 4 weeks thereafter through week 48	1 (5%) in the RCB group	This single participant in the RCB group who progressed to ESRD had a rapidly deteriorating condition at study entry, and was withdrawn at week 8 due to rising serum creatinine levels and proteinuria

Infection	Atisha 2021[1] 596	RCT	24weeks,48 weeks, 96 weeks	21 patients Age: 32.3 ± 11.43 mixed ethnicity Class III,IV,IIIwith V,IV with V	Patients in the RCB group received belimumab IV at a dose of 10 mg/ kg at weeks 4, 6, and 8 and every 4 weeks thereafter through week 48	soft tissue abscess (n = 1), cellulitis (n = 1), and urinary tract infection (n = 1).	The soft tissue abscess and cellulitis occurred in the same participant
	Kraaij 2020[3] 4831	RCT	104 weeks	15 patients had refractory disease, of which 12 (80%) had active LN at baseline Median age : 31 years (range 19–51)	RTX at Weeks 0 þ 2 and with intravenous 10 mg/kg BLM at Weeks 4 þ 6 þ 8 and then every 4 weeks until 104 weeks.	Infection requiring hospitalization : 3/15 Less serious infections: 9/15	Minor infection 8 (53.3) Upper respiratory tract 9 (60.0) Lower respiratory tract 3 (20.0) Urinary tract 4 (26.7) Urogenital infection 2 (13.3) Sinusitis 1 (6.7) Influenza 1 (6.7) Herpes simplex1 (6.7)t

References:

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CNI Therapy

Table 1. Studies included.

Study	Population	Intervention	Outcome
Edavalath 2022[1]	12 refractory LN patients Age: > 18 years Class III/IV LN	Refractory/relapsing LN patients were treated with CS+TAC (2–3 mg/day) for 6 months	Complete renal response Partial renal response Adverse effects Creatinine

Evidence summary:

1 study assessing tacrolimus in patients with refractory LN with the outcomes reported being complete/partial renal response, adverse effects, and adverse effects.

Table 2. Outcomes

Outcome	Author, year, RefID	Study Design	Follow up Duration	Population	Intervention	Result
Complete renal remission	Edavalath 2022	Single Arm	6 months	12 refractory LN patients Age: > 18 years Class III/IV LN	Refractory/relapsing LN patients were treated with CS+TAC (2–3 mg/day) for 6 months	4/12
Partial renal remission	Edavalath 2022	Single Arm	6 months	12 refractory LN patients Age: > 18 years Class III/IV LN	Refractory/relapsing LN patients were treated with CS+TAC (2–3 mg/day) for 6 months	7/12
Creatinine	Edavalath 2022	Single Arm	6 months	12 refractory LN patients Age: > 18 years Class III/IV LN	Refractory/relapsing LN patients were treated with CS+TAC (2–3 mg/day) for 6 months	1/12 had raised serum creatinine after 4 months
Adverse events	Edavalath 2022	Single Arm	6 months	12 refractory LN patients Age: > 18 years Class III/IV LN	Refractory/relapsing LN patients were treated with CS+TAC (2–3 mg/day) for 6 months	0/12

Reference:

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CYC Therapy

Table 1. Studies included.

Study	Population	Intervention	Outcome
Petri, 2003[1], 7086	9 patients with LN refractory to steroids and at least one immunosuppressant (mean +/- SD age was 35 +/- 10 years).5 with class IV LN and 4 with class V LN. 2 males and 7 females.	CYC	-Complete/Partial Renal Response -Proteinuria -ESRD

Table 2.

Outcome	Author, year, RefID	Study Design	Follow up Duration	Population	Intervention	Result	
Complete renal remission	Petri, 2003[1], 7086	Single-arm study	10-47 months	9 patients with LN refractory to steroids and at least one immunosuppressant (mean +/- SD age was 35 +/- 10 years).5 with class IV LN and 4 with class V LN. 2 males and 7 females.	50 mg/kg of cyclophosphamide for 4 consecutive days followed by 5 g/kg granulocyte colony-stimulating factor until the neutrophil count was 1 109 /liter for 2 consecutive days	4/9 CR	A complete responder was defined as having no disease activity and receiving physiologic or lower doses of prednisone and no other immunosuppressive drugs
Partial renal remission	Petri, 2003[1], 7086	Single-arm study	10-47 months	9 patients with LN refractory to steroids and at least one immunosuppressant (mean +/- SD age was 35 +/- 10 years).5 with class IV LN and 4 with class V LN. 2 males and 7 females.	50 mg/kg of cyclophosphamide for 4 consecutive days followed by 5 g/kg granulocyte colony-stimulating factor until the neutrophil count was 1 109 /liter for 2 consecutive days	2/9 PR	For renal lupus, a partial response required a reduction of at least 50% in the 24-hour total protein excretion
ESRD	Petri, 2003[1], 7086	Single-arm study	10-47 months	9 patients with LN refractory to steroids and at least one immunosuppressant (mean +/- SD age was	50 mg/kg of cyclophosphamide for 4 consecutive days followed by 5 g/kg granulocyte colony-	1/9 ESRD	

				35 +/- 10 years).5 with class IV LN and 4 with class V LN. 2 males and 7 females.	stimulating factor until the neutrophil count was 1 109 /liter for 2 consecutive days		
Proteinuria	Petri, 2003[1], 7086	Single-arm study	10-47 months	9 patients with LN refractory to steroids and at least one immunosup pressant (mean +/- SD age was 35 +/- 10 years).5 with class IV LN and 4 with class V LN. 2 males and 7 females.	50 mg/kg of cyclophosph amide for 4 consecutive days followed by 5 g/kg granulocyte colony-stimulating factor until the neutrophil count was 1 109 /liter for 2 consecutive days	Decreased urine protein 24-hour excretion Mean difference 3.3 gm/day	

Evidence summary:
One study addressed CYC alone in refractory LN, reporting on response, proteinuria, and ESRD.

References:

1. Petri M, Jones RJ, Brodsky RA. High-dose cyclophosphamide without stem cell transplantation in systemic lupus erythematosus. Arthritis Rheum. 2003 Jan;48(1):166-73. doi: 10.1002/art.10752. PMID: 12528116.

Leflunomide Therapy

Table 1: P11a and P12a							
Study name (year) country	**Study design**	**Population**	**Intervention details**	**Comparator details**	**Outcomes with available data**	**Outcomes measures**	**Outcome timepoint**
Zhang 2019 China	Randomized Clinical Trial	Class III,IV,V LN Adults LEF: 37.8±10.2, CTX:39.6±10.1 Asians	Oral Leflunomide loading dose 40 mg/day for 3 days followed by 20 mg/day + Prednisone.	Intravenous cyclophosphamide monthly at a dosage of 0.8–1.0 g + prednisone.	•Complete Response •Partial Response •Level of proteinuria •Preservation of kidney function •Serious adverse events •Infection •Leukopenia	Risk ratio	24 weeks

Evidence summary:

One randomized study address PICO 11a 12a question. The study reported on Complete Resolution not favoring either Leflunomide or No Leflunomide with absolute effect of 40 fewer per 1,000 (from 153 fewer to 186 more) while partial response favored Leflunomide with absolute effect 140 more per 1,000 (from 47 fewer to 419 more) and CR and PR favored Leflunomide with absolute effect 97 more per 1,000 (from 62 fewer to 305 more). Level of proteinuria was similar between both arms with a mean difference 0.1 higher (2.14 lower to 2.34 higher), while preservation of kidney function (measured by GFR) favored Leflunomide as the change from baseline was lower in the Leflunomide arm MD 6.6 lower (24.82 lower to 11.62 higher). No clinically significant difference was found in infection (14 fewer per 1,000 (from 152 fewer to 228 more)) and Leukopenia 2 more per 1,000 (from 18 fewer to 305 more).

Certainty assessment							**№ of patients**		**Effect**		**Certainty**	**Importance**
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Leflunomide**	**No Leflunomide**	**Relative (95% CI)**	**Absolute (95% CI)**		
Complete response												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Leflunomide	No Leflunomide	Relative (95% CI)	Absolute (95% CI)		
1[1]	randomised trials	serious[a]	not serious	seriousf	very serious[b]	none	11/48 (22.9%)	14/52 (26.9%)	**RR 0.85** (0.43 to 1.69)	**40 fewer per 1,000** (from 153 fewer to 186 more)	⊕◯◯◯ Very low	CRITICAL
Partial response												
1[1]	randomised trials	serious[a]	not serious	seriousf	serious[c]	none	27/48 (56.3%)	22/52 (42.3%)	**RR 1.33** (0.89 to 1.99)	**140 more per 1,000** (from 47 fewer to 419 more)	⊕⊕◯◯ Low	CRITICAL
Complete and Partial response												
1[1]	randomised trials	serious[a]	not serious	seriousf	serious[c]	none	38/48 (79.2%)	36/52 (69.2%)	**RR 1.14** (0.91 to 1.44)	**97 more per 1,000** (from 62 fewer to 305 more)	⊕⊕◯◯ Low	CRITICAL
Level of proteinuria												
1[1]	randomised trials	not serious	not serious	seriousf	serious[d]	none	48	52	-	MD **0.1 higher** (2.14 lower to 2.34 higher)	⊕⊕⊕◯ Moderate	CRITICAL
Preservation of kidney												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Leflunomide	No Leflunomide	Relative (95% CI)	Absolute (95% CI)		
1[1]	randomised trials	not serious	not serious	seriousf	serious[d]	none	48	52	-	MD **6.6 lower** (24.82 lower to 11.62 higher)	⊕⊕⊕◯ Moderate	CRITICAL
Infection												
1[1]	randomised trials	serious [a]	not serious	seriousf	very serious[b]	none	16/48 (33.3%)	18/52 (34.6%)	**RR 0.96** (0.56 to 1.66)	**14 fewer per 1,000** (from 152 fewer to 228 more)	⊕◯◯◯ Very low	CRITICAL
Leukopenia												
1[1]	randomised trials	serious [a]	not serious	seriousf	serious[e]	none	1/48 (2.1%)	1/52 (1.9%)	**RR 1.08** (0.07 to 16.84)	**2 more per 1,000** (from 18 fewer to 305 more)	⊕⊕◯◯ Low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Risk of bias was assessed using ROB2, was found to be high due to missing outcome data.
b. Wide CI crossing both MIDs (assumed to be 5%)
c. Wide CI crossing one MID (assumed to be 10%)
d. Small number of patients
e. Wide CU crossing one MID (assumed to be 5%)
F Patients were not refractory LN

References

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Randomized clinical trials:1

Comparative nonrandomized studies-

MMF/MPA

Table 1. Studies included.

Study	Population	Intervention	Outcome
Cortés-Hernández 2010[1], (ID:1923)	Patient with non- responding proliferative LN Age:32+-12	MMF	Renal Response
Rivera, 2014[2], 7605	patients with LN (35 refractory and 50 relapsing). Most were aged 15–65 years (94.1%);	MMF	Complete Renal Remission, partial renal remission,ESRD, Cr, proteinuria, infection
Buratti 2001[3] 1286	11 children included 9 females and 2 males with an average age at disease onset of 12.3 years (range 9 to 15.3). There were 4 Hispanic, 4 AfroAmerican, and 3 Caucasian patients. The mean disease duration was 2.9 years (range 0.8 to 7.8).	MMF	Renal Response, Steroid Discontinuation, proteinuria, infection, adverse events

Evidence summary:

3 studies addressing MMF use in patients with LN. The outcomes reported were complete renal remission, partial renal remission, ESRD, Cr, proteinuria, infection and adverse events.

Table 2. Outcomes

Outcome	Author, year, RefID	Study Design	Follow up Duration	Population	Intervention	Result	

Complete renal remission	Cortés-Hernández 2010[1], (ID:1923)	Non-comparative	6,12 months and 65 months	Patient with non-responding proliferative LN Age:32+-12	MMF 2 gr/day	at 6 months: 13/70 At 12 months: 24/70 At 65 months 2/70	CR was defined as urinary protein excretion <0.3g/24h, normal urinary sediment and stable renal function.
	Rivera, 2014[2], 7605	Single-arm study	Median follow-up 30 months (range 3-102)	85 White Spanish patients with LN (35 refractory and 50 relapsing). Most were aged 15–65 years (94.1%); those aged less than 15 years accounted for 2.4% and those aged more than 65 years accounted for 3.5%. Class II=1; class III=29; class IV=47; class V=8	Median MMF dose 1 g/day (range 250 mg-2 g/day)	CR: 23/85	Complete response was defined as a return to normal or previous eGFR and proteinuria ≤ 0.5 g/24 h. Partial response was defined as a decrease in proteinuria to <3.5 g/24 h and a ≥ 50% decrease in proteinuria in patients with baseline proteinuria ≥ 3.5 g/24 h, or as a 50% decrease in proteinuria in patients with baseline proteinuria <3.5 g/24 h. In both situations, eGFR had to have stabilized (±25%) or improved

Partial renal remission	Rivera, 2014[2], 7605	Single-arm study	Median follow-up 30 months (range 3-102)	85 White Spanish patients with LN (35 refractory and 50 relapsing). Most were aged 15–65 years (94.1%); those aged less than 15 years accounted for 2.4% and those aged more than 65 years accounted for 3.5%. Class II=1; class III=29; class IV=47; class V=8	Median MMF dose 1 g/day (range 250 mg-2 g/day)	PR: 51/85	
ESRD	Rivera, 2014[2], 7605	Single-arm study	Median follow-up 30 months (range 3-102)	85 White Spanish patients with LN (35 refractory and 50 relapsing). Most were aged 15–65 years (94.1%); those aged less than 15	Median MMF dose 1 g/day (range 250 mg-2 g/day)	ESRD: 5/85	

				years accounted for 2.4% and those aged more than 65 years accounted for 3.5%. Class II=1; class III=29; class IV=47; class V=8			
Creatinine	Rivera, 2014[2], 7605	Single-arm study	Median follow-up 30 months (range 3-102)	85 White Spanish patients with LN (35 refractory and 50 relapsing). Most were aged 15–65 years (94.1%); those aged less than 15 years accounted for 2.4% and those aged more than 65 years accounted for 3.5%. Class II=1; class III=29; class IV=47; class V=8	Median MMF dose 1 g/day (range 250 mg-2 g/day)	No significant difference in serum Cr or GFR	

	Buratti[3] 1286	Single Arm	9.8 months mean	11 children included 9 females and 2 males with an average age at disease onset of 12.3 years (range 9 to 15.3). There were 4 Hispanic, 4 AfroAmeric an, and 3 Caucasian patients. The mean disease duration was 2.9 years (range 0.8 to 7.8).	MMF (CellCept®, Roche Laboratorie s, Nutley, NJ, USA) was administere d twice daily at a dose range from 17 to 42 mg/kg/day (median 22) or 1.25 to 2.25 g qd (median 1g bid) total dose.	Creatinine clearance increased in 6/11 children. decreased in 2/11 remained stable in 3/11 Among the 6 children with a serum creatinine ≥ 1.2 mg/dl at baseline, levels increased in 3/6 remained stable in 1/6 and decreased in 2/6	
Proteinuria	Rivera, 2014[2], 7605	Single-arm study	Median follow-up 30 months (range 3-102)	85 White Spanish patients with LN (35 refractory and 50 relapsing). Most were aged 15–65 years (94.1%); those aged less than 15 years accounted for 2.4% and those aged more than 65	Median MMF dose 1 g/day (range 250 mg-2 g/day)	Proteinuria: 2.8 g/24hr at baseline to 0.5 g/24 hour at month 60	

				years accounted for 3.5%. Class II=1; class III=29; class IV=47; class V=8			
	Buratti 2001[3] 1286	Single Arm	9.8 months mean	11 children included 9 females and 2 males with an average age at disease onset of 12.3 years (range 9 to 15.3). There were 4 Hispanic, 4 AfroAmerican, and 3 Caucasian patients. The mean disease duration was 2.9 years (range 0.8 to 7.8).	MMF (CellCept®, Roche Laboratories, Nutley, NJ, USA) was administered twice daily at a dose range from 17 to 42 mg/kg/day (median 22) or 1.25 to 2.25 g qd (median 1g bid) total dose.	Out of 8 children with baseline proteinuria ≥ 0.5 g/24 h, decreased proteinuria in 5/8 children , unchanged values in 1/8 and increased proteinuria in 2/8 children	During the study all children received concomitant prednisone in various doses and 7/11 were on concomitant hydroxychloroquine
Adverse events	Buratti 2001[3] 1286	Single Arm	9.8 months mean	11 children included 9 females and 2 males with an average age at disease onset of 12.3 years (range 9 to 15.3). There were 4	MMF (CellCept®, Roche Laboratories, Nutley, NJ, USA) was administered twice daily at a dose range from 17 to	4/11 nausea, 1/11 itching/fatigue, 1/11 headaches, 1/11 transient generalized bodyaches	

				Hispanic, 4 AfroAmeric an, and 3 Caucasian patients. The mean disease duration was 2.9 years (range 0.8 to 7.8).	42 mg/kg/day (median 22) or 1.25 to 2.25 g qd (median 1g bid) total dose.		
Infection	Rivera, 2014[2], 7605	Single-arm study	Median follow-up 30 months (range 3-102)	85 White Spanish patients with LN (35 refractory and 50 relapsing). Most were aged 15–65 years (94.1%); those aged less than 15 years accounted for 2.4% and those aged more than 65 years accounted for 3.5%. Class II=1; class III=29; class IV=47; class V=8	Median MMF dose 1 g/day (range 250 mg-2 g/day)	Infections: 20/85	

	Buratti 2001[3] 1286	Single Arm	9.8 months mean	11 children included 9 females and 2 males with an average age at disease onset of 12.3 years (range 9 to 15.3). There were 4 Hispanic, 4 AfroAmerican, and 3 Caucasian patients. The mean disease duration was 2.9 years (range 0.8 to 7.8).	MMF (CellCept®, Roche Laboratories, Nutley, NJ, USA) was administered twice daily at a dose range from 17 to 42 mg/kg/day (median 22) or 1.25 to 2.25 g qd (median 1g bid) total dose.	1/11 herpes zoster virus infection with cerebritis 1/11 oral thrush	Infections possibly related to MMF were reported in 2 other children. One had necrotizing lymphadenitis and another a re-infection of a jaw cyst.
Steroid Discontinuation	Buratti 2001[3] 1286	Single Arm	9.8 months mean	11 children included 9 females and 2 males with an average age at disease onset of 12.3 years (range 9 to 15.3). There were 4 Hispanic, 4 AfroAmerican, and 3 Caucasian patients. The mean disease duration was 2.9	MMF (CellCept®, Roche Laboratories, Nutley, NJ, USA) was administered twice daily at a dose range from 17 to 42 mg/kg/day (median 22) or 1.25 to 2.25 g qd (median 1g bid) total dose.	discontinued in 1/11 children, tapered in 9/11 (mean drop 0.5 mg/kg/day, range 0.2 to 1) remained unchanged in1/11	

				years (range 0.8 to 7.8).			

References:

1. Cortés-Hernández J, Torres-Salido MT, Medrano AS, Tarrés MV, Ordi-Ros J. Long-term outcomes--mycophenolate mofetil treatment for lupus nephritis with addition of tacrolimus for resistant cases. Nephrol Dial Transplant. 2010 Dec;25(12):3939-48. doi: 10.1093/ndt/gfq322. Epub 2010 Jun 10. PMID: 20538787.
2. Rivera F, Mérida E, Illescas ML, López-Rubio E, Frutos MA, García-Frías P, Ramos C, Sierra M, Baltar J, Lucas J, Oliet A, Vigil A, Fernández-Juárez G, Segarra A, Praga M; Glomerular Spanish Glomerular Study Group (GLOSEN). Mycophenolate in refractory and relapsing lupus nephritis. Am J Nephrol. 2014;40(2):105-12. doi: 10.1159/000365256. Epub 2014 Jul 30. PMID: 25096639.
3. Buratti S, Szer IS, Spencer CH, Bartosh S, Reiff A. Mycophenolate mofetil treatment of severe renal disease in pediatric onset systemic lupus erythematosus. J Rheumatol. 2001 Sep;28(9):2103-8. PMID: 11550982.

MMF+CNI Therapy

Table 1. Studies included.

Study	Population	Intervention	Outcome
Mok 2013[1] 6185	21 patients ethnic chinese : class IV/III (33%), V þ III/IV (33%) and pure V (33%) 35.8 9.2 years	MMF+Tacrolimus	-Complete/Partial Renal Remission -Creatinine -Proteinuria -Adverse Events -Infections
Yap 2022[2] 9962	22 patients with LN (16 class III/IV V, 6 class V) Age: 43.9 +11.7	MMF+Tacrolimus	-Complete/Partial Renal Remission -ESRD -Adverse Events -Infections
Cortés-Hernández 2010[3], (ID:1923)	Patient with non-responding proliferative LN Age:32+-12	MMF+Tacrolimus	-Complete/Partial Renal Remission

Evidence summary:

3 studies in which patients with refractory LN were given MMF and Tacrolimus were included. The outcomes reported were complete/partial remission, creatinine, proteinuria, adverse events, and infections.

Table 2. Outcomes

Outcome	Author, year, RefID	Study Design	Follow up Duration	Population	Intervention	Result	
Complete renal remission	Mok 2013[1] 6185	Single arm study	12 months	21 patients ethnic chinese : class IV/III (33%), V þ III/IV (33%) and pure V (33%) 35.8 9.2 years	Twenty patients received the protocol-based 1 g/day of MMF (no change in dose throughout), with only one patient finally receiving 500 mg/day of MMF because of diarrhea. The mean daily dose of TAC received by the patients was 3.1 0.8 mg	9/21	
	Yap 2022[2] 9962	Single arm study	6, 12, 24, 36, 48, and 60 months	22 patients with LN (16 class III/IV V, 6 class V) Age: 43.9 +11.7	TAC was started at 0.07 mg/kg/d (Prograf with twice daily dosing), with TDM to aim for a 12-hour trough plasma TAC level of 4 to 6 mg/l. In patients with MMF total daily dose $1.5 g, the dose would be reduced by 500 mg when TAC was added, to aim for lower readings in the target range of MPA blood level	12 months: 8/22(36.4%) 24 months: 10/22(45.5%) 36 months: 10/22(45.5%)	
	Cortés-Hernández 2010[3], (ID:1923)	Non-comparative	24 months	Patient with non-responding proliferative LN Age:32+-12	MMF 2 gr/day + tacrolimus 0.075 mg/kg/day	CRR: 6/17	Patient with non-responding proliferative LN: Not achieving at least partial renal response to MMF 2-3 g CR was defined as urinary protein excretion <0.3g/24h, normal urinary sediment and stable renal function.

Partial renal remission	Mok 2013[1] 6185	Single arm study	12 months	21 patients ethnic chinese : class IV/III (33%), V þ III/IV (33%) and pure V (33%) 35.8 9.2 years	Twenty patients received the protocol-based 1 g/day of MMF (no change in dose throughout), with only one patient finally receiving 500 mg/day of MMF because of diarrhea. The mean daily dose of TAC received by the patients was 3.1 0.8 mg	5/21	
	Yap 2022[2] 9962	Single arm study	6, 12, 24, 36, 48, and 60 months	22 patients with LN (16 class III/IV V, 6 class V) Age: 43.9 +11.7	TAC was started at 0.07 mg/kg/d (Prograf with twice daily dosing), with TDM to aim for a 12-hour trough plasma TAC level of 4 to 6 mg/l. In patients with MMF total daily dose $1.5 g, the dose would be reduced by 500 mg when TAC was added, to aim for lower readings in the target range of MPA blood level	12 months: 5/22 24 months: 6/22 36 months: 7/22	
ESRD	Yap 2022[2] 9962	Single arm study	6, 12, 24, 36, 48, and 60 months	22 patients with LN (16 class III/IV V, 6 class V) Age: 43.9 +11.7	TAC was started at 0.07 mg/kg/d (Prograf with twice daily dosing), with TDM to aim for a 12-hour trough plasma TAC level of 4 to 6 mg/l. In patients with MMF total daily dose $1.5 g, the dose would be reduced by 500 mg when TAC was added, to aim for lower readings in the target range of MPA blood level	25.5 months:2 /22(9.1%) 5/22 (22.7%) had new onset CKD stage 3 or above	The 2 patients who progressed to end-stage kidney disease had prior CKD stage 3b and stage 4, respectively, with significantly lower eGFR at baseline (25.5 5.0 ml/min per 1.73 m2 , P < 0.001 compared with other patients).
Creatinine	Mok 2013[1] 6185	Single arm study	12 months	21 patients ethnic chinese : class IV/III (33%), V þ III/IV (33%) and pure V (33%) 35.8 9.2 years	Twenty patients received the protocol-based 1 g/day of MMF (no change in dose throughout), with only one patient finally receiving 500 mg/day of MMF because of diarrhea. The mean daily dose of TAC received by the patients was 3.1 0.8 mg	At baseline : Mean CrCl 81.2 to 77 at 12 months	No SD provided

Proteinuria	Mok 2013[1] 6185	Single arm study	12 months	21 patients ethnic chinese : class IV/III (33%), V þ III/IV (33%) and pure V (33%) 35.8 9.2 years	Twenty patients received the protocol-based 1 g/day of MMF (no change in dose throughout), with only one patient finally receiving 500 mg/day of MMF because of diarrhea. The mean daily dose of TAC received by the patients was 3.1 0.8 mg	Mean urine P/Cr: 3.2 (baseline) to 0.6 at 12 months	No SD provided
	Yap 2022[2] 9962	Single arm study	60 months	22 patients with LN (16 class III/IV V, 6 class V) Age: 43.9 +11.7	TAC was started at 0.07 mg/kg/d (Prograf with twice daily dosing), with TDM to aim for a 12-hour trough plasma TAC level of 4 to 6 mg/l. In patients with MMF total daily dose $1.5 g, the dose would be reduced by 500 mg when TAC was added, to aim for lower readings in the target range of MPA blood level	Mean (SD) 24- hour urine protein excretion g/d was 5.4 (4.1)and it decreased to 1.2 (1.7)	
Adverse events	Mok 2013[1] 6185	Single arm study	12 months	21 patients ethnic chinese : class IV/III (33%), V þ III/IV (33%) and pure V (33%) 35.8 9.2 years	Twenty patients received the protocol-based 1 g/day of MMF (no change in dose throughout), with only one patient finally receiving 500 mg/day of MMF because of diarrhea. The mean daily dose of TAC received by the patients was 3.1 0.8 mg	33 adverse events were reported in 18/21 patients (86%)	diarrhea (12%), cramps (9%), dyspepsia (6%), transient increase in serum Cr (6%), alopecia (4%), facial twitching (3%), tremor (3%) and diabetes mellitus (3%).
	Yap 2022[2] 9962	Single arm study	6, 12, 24, 36, 48, and 60 months	22 patients with LN (16 class III/IV V, 6 class V) Age: 43.9 +11.7	TAC was started at 0.07 mg/kg/d (Prograf with twice daily dosing), with TDM to aim for a 12-hour trough plasma TAC level of 4 to 6 mg/l. In patients with MMF total daily dose $1.5 g, the dose would be reduced by 500 mg when TAC was added, to aim for lower readings in the target range of MPA blood level	6 episodes of gastrointestinal symptoms occurred: 4 resolved after reduction of MMF dose 2 patients (9.1%) had diabetes mellitus before the addition of TAC 14 patients (63.6%) were on lipid-lowering therapy before addition of TAC	There was no acute kidney injury due to CNI nephrotoxicity

						3 patients (13.6%) showed worsening of hyperlipidemia, which responded to an increase in the dose of statin.	
Infection	Mok 2013[1] 6185	Single arm study	12 months	21 patients ethnic chinese : class IV/III (33%), V þ III/IV (33%) and pure V (33%) 35.8 9.2 years	Twenty patients received the protocol-based 1 g/day of MMF (no change in dose throughout), with only one patient finally receiving 500 mg/day of MMF because of diarrhea. The mean daily dose of TAC received by the patients was 3.1 0.8 mg	major infection requiring hospitalization (6%),infection not requiring hospitalization (excluding herpes) (27%), herpes infection (9%),	
	Yap 2022[2] 9962	Single arm study	6, 12, 24, 36, 48, and 60 months	22 patients with LN (16 class III/IV V, 6 class V) Age: 43.9 +11.7	TAC was started at 0.07 mg/kg/d (Prograf with twice daily dosing), with TDM to aim for a 12-hour trough plasma TAC level of 4 to 6 mg/l. In patients with MMF total daily dose $1.5 g, the dose would be reduced by 500 mg when TAC was added, to aim for lower readings in the target range of MPA blood level	16 episodes of infections occurred (occurrence rate of 1 in 7 patient-years) 10 of these infective episodes required hospitalization (4 gastroenteritis, 4 pneumonia, 1 acute pancreatitis, 1 urinary tract infection; hospitalization rate of 1 in 11 patient-years).	

References:

1. Mok CC, To CH, Yu KL, Ho LY. Combined low-dose mycophenolate mofetil and tacrolimus for lupus nephritis with suboptimal response to standard therapy: a 12-month prospective study. Lupus. 2013 Oct;22(11):1135-41. doi: 10.1177/0961203313502864. Epub 2013 Aug 30. PMID: 23995863.
2. Yap DYH, Li PH, Tang C, So BYF, Kwan LPY, Chan GCW, Lau CS, Chan TM. Long-Term Results of Triple Immunosuppression With Tacrolimus Added to Mycophenolate and Corticosteroids in the Treatment of Lupus Nephritis. Kidney Int Rep. 2021 Dec 14;7(3):516-525. doi: 10.1016/j.ekir.2021.12.005. PMID: 35257064; PMCID: PMC8897290.
3. Cortés-Hernández J, Torres-Salido MT, Medrano AS, Tarrés MV, Ordi-Ros J. Long-term outcomes--mycophenolate mofetil treatment for lupus nephritis with addition of tacrolimus for resistant cases. Nephrol Dial Transplant. 2010 Dec;25(12):3939-48. doi: 10.1093/ndt/gfq322. Epub 2010 Jun 10. PMID: 20538787

Rituximab Therapy:

Table 1: P11a and P12a						
Study name (year) country	**Study design**	**Population**	**Intervention details**	**Comparator details**	**Outcomes with available data**	**Outcomes measures**	**Outcome timepoint**
Zhang 2015 China	Randomized Clinical Trial	Refractory Severe LN Adults RTX: 38.7 ± 6.2, CTX: 39.1 ± 7.0 Asians	Intravenous pulse dose of 375 mg/m2 of RTX	Intravenous pulse delivery of 800 mg of CYC once every month.	•Complete Response •Partial Response •Complete and Partial Response •Level of proteinuria •Preservation of kidney function	Risk ratio	NA

Evidence summary:

One randomized study address PICO 12b question. The study reported on Complete Resolution favoring RTX with absolute effect of 429 more per 1,000 (from 131 more to 981 more) while partial response favored CYC with absolute effect 168 fewer per 1,000 (from 268 fewer to 43 more) and CR and PR favored RTX with absolute effect 263 more per 1,000 (from 51 more to 549 more). Change in creatinine favored RTX as it lead to a larger reduction of creatinine with a mean difference of 0.62 ranging from (14.3 lower to 15.54 higher) while change in proteinuria also favored RTX as it lead to a larger reduction (MD of 1.05) ranging from (0.18 higher to 1.92 higher).

Certainty assessment							**№ of patients**		**Effect**		**Certainty**	**Importance**
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**RTX**	**CYC**	**Relative (95% CI)**	**Absolute (95% CI)**		
Complete Resolution												
1[1]	randomised trials	serious[a]	not serious	not serious	serious[b]	none	27/42 (64.3%)	9/42 (21.4%)	**RR 3.00** (1.61 to 5.58)	**429 more per 1,000** (from 131 more to 981 more)	⊕⊕◯◯ Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RTX	CYC	Relative (95% CI)	Absolute (95% CI)		
Partial Response												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	8/42 (19.0%)	15/42 (35.7%)	**RR 0.53** (0.25 to 1.12)	**168 fewer per 1,000** (from 268 fewer to 43 more)	⨁⨁◯◯ Low	CRITICAL
Complete and Partial Response												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	35/42 (83.3%)	24/42 (57.1%)	**RR 1.46** (1.09 to 1.96)	**263 more per 1,000** (from 51 more to 549 more)	⨁⨁◯◯ Low	CRITICAL
Change in Creatinine (Preservation of Kidney Function)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	42	42	-	MD **0.62 higher** (14.3 lower to 15.54 higher)	⨁⨁◯◯ Low	CRITICAL
Change in Proteinuria												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	42	42	-	MD **1.05 higher** (0.18 higher to 1.92 higher)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations
a. Risk of bias was assessed using ROB2, was found to be high due to randomization (randomization method and baseline characteristics were not reported)
b. Small number of patients
References
1.Zhang, Jin, Zhao, Zhanzheng, Hu, Xiaozhou. Effect of Rituximab on Serum Levels of Anti-C1q and Antineutrophil Cytoplasmic . Cell biochemistry and biophysics; 2015.

Randomized clinical trials:1
Comparative nonrandomized studies-
Non-comparative studies:
Studies read and excluded:

P13. In SLE patients with (+)aPL / APS and thrombotic microangiopathy on kidney biopsy, does anticoagulation or immunosuppressive therapies compared to no additional medication improve clinical outcomes?
Population: SLE patients with LN and TMA
Intervention: Plasmapheresis +Anticoagulation
Comparison: No plasmapheresis
Outcomes:

- Reduction of proteinuria
- CRR
- PRR
- Preservation of kidney function
- LN Flare rate
- ESKD (dialysis or transplant)
- Treatment related adverse effects including infection
- Cumulative steroid dose

Table 1.

Study name (year)	Study design	Population	Intervention details	Comparator details	Outcomes with available data	Outcome measures	Outcome timepoint
Li 2016	Non-randomized study	70 patients (61 non-plasmapheresis , 9 plasmapheresis) Age :29.71 +10.23 Class II, III,IV,, III+IV, and V	Plasmapheresis	No Plasmapheresis	-CRR/PRR -ESRD -thromboembolism relapse rate	RR, MD	35.5 (8.5–71.2) median(range)

Evidence summary:
One NRS study compared the effect of plasmapheresis to no plasmapheresis in SLE patients with LN +TMA. The follow-up time was 35.5 months, and the outcomes of interest were CRR/PRR, adverse events, and ESRD. Response was higher in the plasmapheresis arm and ESRD was lower in the plasmapheresis arm. We downgraded for indirectness because they do not report whether anticoagulation was given or not in both arms, so just comparing plasmapheresis versus no plasmapheresis. The overall certainty is very low due to concerns about the risk of bias, indirectness, and imprecision.

Evidence profile:

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Plasmapheresis	No Plasmapheresis	Relative (95% CI)	Absolute (95% CI)	
ESRD											
1[1]	non-randomised studies	serious[a]	not serious	serious[b]	very serious[c]	none	2/9 (22.2%)	32/61 (52.5%)	**RR 0.42** (0.12 to 1.47)	**304 fewer per 1,000** (from 462 fewer to 247 more)	⨁◯◯◯ Very low
Complete/Partial Response											
1[1]	non-randomised studies	serious[a]	not serious	serious[b]	serious[c]	none	7/9 (77.8%)	13/61 (21.3%)	**RR 3.65** (2.01 to 6.62)	**565 more per 1,000** (from 215 more to 1,000 more)	⨁◯◯◯ Very low
Thrombolism relapse rate											
1[1]	non-randomised studies	serious[a]	not serious	serious[b]	serious[c]	none	6/9 (66.66%)	31/61 (50.81%)	**RR 1.31** (0.78 to 2.21)	**158 more per 1000** (from 112 fewer to 615 more)	⨁◯◯◯ Very low

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio
Explanations
a. Risk of bias was assessed using ROBINS-I and was found to be critical due to confounding and selection bias.
b. It is not stated that control patients took anticoagulants.
c. Wide confidence interval.

References
1.Li, Qiu-Yu, Yu, Feng, Zhou, Fu-De, Zhao, Ming-Hui. Plasmapheresis Is Associated With Better Renal Outcomes in Lupus Nephritis . Medicine; 2016

P13. In SLE patients with (+)aPL / APS and thrombotic microangiopathy on kidney biopsy, does anticoagulation or immunosuppressive therapies compared to no additional medication improve clinical outcomes?

Population: SLE patients with LN and TMA
Intervention: Eculizumab
Outcomes:

- Reduction of proteinuria
- CRR
- PRR
- Preservation of kidney function
- LN Flare rate
- ESKD (dialysis or transplant)
- Treatment related adverse effects including infection
- Cumulative steroid dose

Eculizumab

Table 1. Studies included.

Study	Population	Intervention	Outcome
Park, 2018[1], 6888	11 patients with LN and TMA 22-59 years of age Renal bx obtained in 8 out of 10 living patients and 1 autopsy pathology. LN and TMA seen in 7 out of 8 patients.	Eculizumab	Adverse Events ESRD

Evidence Summary:
1 non-comparative study included 11 patients with LN and TMA. The outcomes assessed were ESRD and adverse events.

Outcome	Author, year, RefID	Study Design	Follow up Duration	Population	Intervention	Result	
ESRD	Park, 20181, 6888	Retrospective review	median=63.5 weeks	11 patients with LN and TMA 22-59 years of age Renal bx obtained in 8 out of 10 living patients and 1 autopsy pathology. LN and TMA seen in 7 out of 8 patients.	All patients were treated with eculizumab- approved aHUS dosing schedule; 4 weekly doses of 900mg followed by 1200mg on week 5, repeated every 2 weeks.	ESRD: 3/10	7/10 living patients (70%) were on dialysis; 4 able to discontinue and 3 were ESRD

Infection	Park, 20181, 6888	Retrospective review		11 patients with LN and TMA 22-59 years of age Renal bx obtained in 8 out of 10 living patients and 1 autopsy pathology. LN and TMA seen in 7 out of 8 patients.	All patients were treated with eculizumab- approved aHUS dosing schedule; 4 weekly doses of 900mg followed by 1200mg on week 5, repeated every 2 weeks.	Infection: 1/11	This patient died of disseminated fungal infection No other infectious complications related to eculizumab tx.

Reference:

1. Park MH, Caselman N, Ulmer S, Weitz IC. Complement-mediated thrombotic microangiopathy associated with lupus nephritis. Blood Adv. 2018 Aug 28;2(16):2090-2094. doi: 10.1182/bloodadvances.2018019596. PMID: 30131343; PMCID: PMC6113612.

P14. In SLE patients with changes of lupus podocytopathy (diffuse epithelial cell foot process -podocyte- effacement) on kidney biopsy who are on RAAS-I therapy, does steroid with or without immunosuppressive therapy versus RAAS-I alone improve clinical outcomes?

Population: SLE patients with proteinuria > 0.5 gm with or without decreased kidney function, and changes of lupus podocytopathy (diffuse epithelial cell foot process -podocyte- effacement) on kidney biopsy

- Proteinuria > 0.5 gm
- Decreased kidney function with proteinuria > 0.5 gm

Interventions:

- RAAS-I with:
  - Steroid therapy (any dose)
  - Steroid therapy plus any immunosuppressive therapy (including MMF, AZA, CYC, CNI)

Comparator: RAAS-I alone

Outcomes:

- Reduction of proteinuria
- Preservation of kidney function
- Risk of LN flares
- ESKD (dialysis or transplant)
- Treatment-related adverse effects including infection; also decrease >30% baseline eGFR for CNI's, depression/suicide for belimumab

Summary of findings: Two studies had outcomes for this PICO question. One study (wang et al) included 202 patients with podocyte fusion but only 13 met the histological criteria for lupus podocytopathy and 128 had severe podocyte fusion. Patients with lupus podocytopathy were treated with steroids plus immunosuppressants. Complete response, partial response, and treatment failure rates were as follows: 3/13, 8/13, and 2/13, respectively. Another study had mixed treatments of steroids with MMF and CsA measured outcomes such as time of complete remission and 24 h urinary proteins with the mean (SD) value 3.40 (1.95) for the time of complete remission and 3.41 (0.30) g for 24 h urinary proteins (Abdelnabi, 2021).

Outcomes (Name + Summary)	Author, year, RefID	Study type	Duration of follow up	Population (number and description, age)	Intervention used in relevant population (Describe the intervention)	Results	Comments

Response to treatment	Wang, 2014, 9602	Retrospective	Median 42 months (range 1-360)	202 patients with renal biopsy-proven LN, age 33.1 years (S.D. 11.5, range 14-90). **Only 13/202 patients met the definition of lupus podocytopathy**.	Steroids plus CYC in 10 patients, Steroids plus AZA in 1, Steroids plus CNI in 1 Steroids plus lef in 1	**Complete remission:** 3/13 **Partial remission:** 8/13 **Treatment failure:** 2/13	Most patients in the two groups used ACE or ARBs.
Response to treatment	Wang, 2014, 9602	Retrospective	Median 42 months (range 1-360)	202 patients with renal biopsy-proven LN, age 33.1 years (S.D. 11.5, range 14-90). Only 13/202 patients met the definition of lupus podocytopathy. 128/202 had severe podocyte fusion	Evaluated 128 patients with severe podocyte fusion. All completed induction treatment with oral prednisone (0.8-1mg/kg/day or equivalents for 4-6 weeks and tapered gradually to a maintenance dose of 5-10mg/day). 89 received monthly IV CYC (600-800mg/month) for at least 6 consecutive months. 8 patients received MMF, 5 patients received LEF and 25 patients received ciclosporin A, 1 patient received tacrolimus	Divided into two: group 1 was 102 patients with CYC, MMF or LEF and group 2 was 26 patients with calcineurin inhibitors ciclosporin A or tacrolimus. Proportion of complete remission was higher in group 2 than in group 1 (65.4% vs 38.2%); proportions of partial remission(group 1 42.2%, group 2 23.1%, and treatment failure (group 1 19.6%, group 2 11.5%,)	Most patients in the two groups used ACE or ARBs.
Time of complete remission (weeks)	Abdelnabi, 2021, 19	Single-arm	18 months	7 patients with podocytopathy	Steroids +MMF + CsA. Rituximab is was used in resistant cases.	Mean (SD): 3.40 (1.95)	
24 h urinary proteins in g	Abdelnabi, 2021, 19	Single-arm	18 months	7 patients with podocytopathy	Steroids +MMF + CsA. Rituximab is was used in resistant cases.	Mean (SD): 3.41 (0.30)	

References:

1-Yan Wang, Feng Yu, Di Song, Su-Xia Wang, Ming-Hui Zhao, Podocyte involvement in lupus nephritis based on the 2003 ISN/RPS system: a large cohort study from a single centre, *Rheumatology*, Volume 53, Issue 7, July 2014, Pages 1235–1244, https://doi.org/10.1093/rheumatology/ket491

2-Abdelnabi, H.H. Is podocytopathy another image of renal affection in p-SLE?. *Pediatr Rheumatol* **19**, 57 (2021). https://doi.org/10.1186/s12969-021-00547-9

PICO#15. In SLE patients with presumed or biopsy-confirmed LN, does initiating HCQ (if not already taking and no contraindications) improve clinical outcomes compared to not taking HCQ?

Population: SLE patients with presumed or biopsy-proven LN who are not on HCQ (and have no contraindication to taking)
Intervention: HCQ
Comparator: No HCQ
Outcomes:

- Reduction of proteinuria
- Preservation of kidney function
- Risk of LN flare
- ESKD (dialysis or transplant)
- Treatment-related adverse effects (retinal and cardiac toxicity)
- Cumulative steroid dose

Table 1:

Author year	Study design	Population	Intervention	Comparator	Outcome	Measure
Gheet 2023 Egypt	Randomized clinical trial	Children with proliferative lupus nephritis (LN). **Pediatrics:** age between 9-18 years	HCQ	NO HCQ	Response, Risk of LN flare, adverse events, proteinuria, creatinine	RR, MD
Pena-Vizcarra 2023 Mexico	Non-randomized comparative study	Patients with Lupus nephritis **Adults**: 29 years (IQR 23-37) Hispanic	HCQ	NO HCQ	Risk of LN flare, ESKD	aHR
Xiong 2019 USA	Non-randomized comparative study	SLE patients with LN. **Adults,** Mean (SD) age: 39 ±14 versus 50 ±17. Caucasian: 68% African American: 27% Hispanic: 3% Asian: 2%	HCQ	NO HCQ	Dialysis, transplant, proteinuria, creatinine	RR, MD
Kasitanon 2006 USA	Non-randomized comparative study	Patients with membranous lupus nephritis. **Adults:** Mean age (SD): 29.9 (11.9) African American (55.2%)	HCQ	NO HCQ	Remission (complete, partial). proteinuria	RR, MD

Pediatrics:

Evidence summary: 1 RCT compared the outcomes of HCQ versus no HCQ in children with lupus nephritis. There is higher rates of complete, complete or partial response in patients taking HCQ, RR (CI): 1.5 (0.89-2.54), RR (CI): 1.16 (0.98-1.38) and lower rates of partial response in patients taking HCQ (RR (CI): 0.85 (0.45 to1.58)). Flare up rate was lower in patients taking HCQ, RR: 0.25 CI (0.03-2.11). 2/30 patients on HCQ had retinal toxicity, versus 0 in no HCQ arm. There was no clinically significant different in proteinuria and Cr after follow up between both arms. There were concerns about risk of bias in this study. Although randomized but there were differences between patients at baseline, and the number lost to follow up was also concerning. In addition to ROB, the sample size was sample (30 patients in each arm) leading to imprecision. All these factors lead to very low-low certainty in the evidence.

Evidence profile (pediatrics)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HCQ	no HCQ (Peds)	Relative (95% CI)	Absolute (95% CI)		
Complete response												
1[1]	randomised trials	serious[a]	not serious	not serious	serious[b,c]	none	18/30 (60.0%)	12/30 (40.0%)	**RR 1.50** (0.89 to 2.54)	**200 more per 1,000** (from 44 fewer to 616 more)	⨁⨁◯◯ Low	
Partial response												
1[1]	randomised trials	serious[a]	not serious	not serious	very serious[c]	none	11/30 (36.7%)	13/30 (43.3%)	**RR 0.85** (0.45 to 1.58)	**65 fewer per 1,000** (from 238 fewer to 251 more)	⨁◯◯◯ Very low	
Partial or complete response												
1[1]	randomised trials	serious[a]	not serious	not serious	serious[b]	none	29/30 (96.7%)	25/30 (83.3%)	**RR 1.16** (0.98 to 1.38)	**133 more per 1,000** (from 17 fewer to 317 more)	⨁⨁◯◯ Low	
LN flare up												
1[1]	randomised trials	serious[a]	not serious	not serious	very serious[c]	none	1/30 (3.3%)	4/30 (13.3%)	**RR 0.25** (0.03 to 2.11)	**100 fewer per 1,000** (from 129 fewer to	⨁◯◯◯ Very low	

										148 more)		
Retinal toxicity												
1[1]	randomised trials	serious[a]	not serious	not serious	very serious[c]	none	2/30 (6.7%)	0/30 (0.0%)	**RR 5.00** (0.25 to 99.95)		⨁◯◯◯ Very low	
Proteinuria (g/24 hours), change from baseline												
11	**randomised trials**	**seriousa**	**not serious**	**not serious**	**seriousb**	**none**	**30**	**30**	**-**	**MD** 0.07 higher **(1.2 lower to 1.34 higher)**	⨁⨁◯◯ **Low**	
Creatinine												
11	**randomised trials**	**seriousa**	**not serious**	**not serious**	**seriousb**	**none**	**30**	**30**	**-**	**MD** 0.07 higher **(0.03 lower to 0.17 higher)**	⨁⨁◯◯ **Low**	

CI: confidence interval; MD: mean difference; RR: risk ratio

Explanations

a. We assessed risk of bias using ROB 2. We have concerns about randomization process, as there were differences between the 2 groups at baseline, in addition to concerns about lost to follow up.

b. We downgraded for imprecision because of small sample size and wide confidence interval.

c. We downgraded twice for imprecision, because the CI is very wide and would cross both sides of the MID.

References

1.Gheet, F.S.,Dawoud,H.ES.,El-Shahaby,W.A. et al. Hydroxychloroquine in children with proliferative lupus nephritis: a randomized clinical trial. Eur J Pediatr 182,1685–1695 (2023). https://doi.org/10.1007/s00431-023-04837-0.

Randomized clinical trials: 1.

Studies read and excluded: None.

Adults:

Evidence summary: 3 comparative nonrandomized studies addressed the use of the HCQ in adults in LN. While 2 studies addressed complete response and partial response, only one study reported the data as aHR, with aHR (CI): 1.66 (1.13-2.43), 1.47 (1.07-2.01), respectively, and favoring HCQ. For ESRD, one study reported on aHR (0.29), and another one reported on the rate of dialysis and transplantation rates separately. For renal flare-up, aHR was 0.59 (0.40-0.88). HCQ was associated with lower rates of ESRD but there was imprecision explained by the wide confidence intervals. HCQ was associated with lower proteinuria and better kidney function (creatinine). 46/349 of patients on HCQ (minority were on chloroquine) had retinal toxicity. We have concerns about imprecision (wide CI) and for risk of bias (even though they adjusted for confounders we have other concerns about deviation from the intended treatment in the study and concerns about confounding and selection bias in other studies. All these factors lead to low/ very low certainty in the evidence.

Evidence profile (adults)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HCQ	No HCQ	Relative (95% CI)	Absolute (95% CI)		
Complete response (aHR)												
1	non-randomised studies	serious[a]	not serious	not serious	serious[b]	none	265 participants	33 participants	**HR 1.66** (1.13 to 2.43) [Complete response (aHR)]	**178 more per 1,000** (from 41 more to 316 more)	⨁◯◯◯ Very low	
							-	44.0%				
Partial response (aHR) (assessed with: No information about number of patients and baseline risk)												
1	non-randomised studies	serious[a]	not serious	not serious	serious[b]	none			**HR 1.47** (1.07 to 2.01) [Partial response (aHR)]	**-- per 1,000** (from -- to --)	⨁◯◯◯ Very low	
							-	0.0%				
ESRD (aHR)												
1	non-randomised studies	serious[a]	not serious	not serious	very serious[b]	none	265 participants	75 participants	**HR 0.29** (0.18 to 0.47) [ESRD (aHR)]	**292 fewer per 1,000** (from 350 fewer to 206 fewer)	⨁◯◯◯ Very low	
							-	45.3%				
Renal flare up (aHR)												
1	non-randomised studies	serious[a]	not serious	not serious	serious[b]	none	226 participants	49 participants	**HR 0.59** (0.40 to 0.88) [Renal flare up (aHR)]	**191 fewer per 1,000** (from 318 fewer to 47 fewer)	⨁◯◯◯ Very low	
							-	70.0%				

Transplantation (unadjusted)

1	non-randomised studies	not serious	not serious	not serious	very serious[d]	none	13/153 (8.5%)	37/88 (42.0%)	**RR 0.20** (0.11 to 0.36)	**336 fewer per 1,000** (from 374 fewer to 269 fewer)	⊕⊕◯◯ Low	

Dialysis (unadjusted)

1	non-randomised studies	serious[c]	not serious	not serious	very serious[d]	none	35/153 (22.9%)	56/88 (63.6%)	**RR 0.36** (0.26 to 0.50)	**407 fewer per 1,000** (from 471 fewer to 318 fewer)	⊕◯◯◯ Very low	

Retinal toxicity

1	non-randomised studies	serious[c]	not serious	not serious	not serious	none	46/349 (13.2%)	0/75 (0.0%)	**RR 20.19** (1.26 to 324.09)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕⊕⊕◯ Moderate	

Proteinuria (g/24 hours)

2	non-randomised studies	serious[c]	not serious	not serious	serious[b]	none	164	106	-	MD **1.41 lower** (2.17 lower to 0.66 lower)	⊕⊕◯◯ Low	

Kidney function (Serum creatinine)

1	non-randomised studies	serious[c]	not serious	not serious	serious[b]	none	153	88	-	MD **1.2 lower** (1.99 lower to 0.41 lower)	⊕⊕◯◯ Low	

CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

a. We used ROBINsI for assessment of ROB. Although the HR was adjusted there were concerns about deviation from the intended treatment. This was a database, and we are not sure when the patients were taking HCQ and for how long and some were registered as HCQ and chloroquine.

b. We downgraded for imprecision because of small sample size in the No HCQ arm and because of the wide CI.

c. We used ROBINsI for assessment of ROB. There are concerns about selection bias and confounding.

d. We downgraded for imprecision because of the wide confidence interval that would cross both sides of the MID

References Included:

1. Peña-Vizcarra ÓR, Zavala-Miranda MF, Juárez-Cuevas B, Márquez-Macedo SE, Hernández-Andrade A, Nordmann-Gomes A, Pérez-Arias AA, Morales-Buenrostro LE, Mejía-Vilet JM. Effect of antimalarials on clinical outcomes in lupus nephritis. Rheumatology (Oxford). 2023 Nov 1:kead576. doi: 10.1093/rheumatology/kead576. Epub ahead of print. PMID: 37930870.
2. Xiong WW, Boone JB, Wheless L, Chung CP, Crofford LJ, Barnado A. Real-world electronic health record identifies antimalarial underprescribing in patients with lupus nephritis. Lupus. 2019 Jul;28(8):977-985. doi: 10.1177/0961203319856088. Epub 2019 Jun 12. PMID: 31189414; PMCID: PMC6609095.
3. Kasitanon N, Fine DM, Haas M, Magder LS, Petri M. Hydroxychloroquine use predicts complete renal remission within 12 months among patients treated with mycophenolate mofetil therapy for membranous lupus nephritis. Lupus. 2006;15(6):366-370. doi:10.1191/0961203306lu2313oa

Randomized clinical trials: None.
Comparative- nonrandomized studies: 3
Studies read and excluded:

P16.P.17

Diagnostic test accuracy for anti-ds DNA:

Study	Test	c/o	Outcome	Sensitivity	Specificity	Notes
Mororni 2008	Anti-ds DNA	NA	LN flare up	**0.7**	**0.67**	
De Rosa 2018	Anti-ds DNA	NA	LN flare up	**0.54**	**NA**	Includes only 11 patients. 6/11
Mejia-Vilet 2021	Anti-ds DNA	NA	Active LN	**0.76**	**0.3**[#]	[#]Active LN versus inactive LN (including active SLE and inactive SLE)
Mejia-Vilet 2021	Anti-ds DNA	NA	LN flare up	**0.81**	**NA**	

Diagnostic test accuracy for C3 for renal flare up:

Study	Test	c/o	Outcome	Sensitivity	Specificity	Notes
Mororni 2008	C3	NA	LN flare up	**0.79**	**0.51**	
Birmingham 2010	C3	80 mg/dl	LN flare up	**0.7**	**0.73**	

Diagnostic test accuracy for C3 for renal response:

Study	Test	c/o	Outcome	Sensitivity	Specificity	Notes

Gomez Mendez_2019	C3	normalized >90 mg/dL	Renal response	**0.64**	**0.26**	

Diagnostic test accuracy for C4:

Study	Test	c/o	Outcome	Sensitivity	Specificity	Notes
Morormi 2008	C4	NA	LN flare up	**0.74**	**0.64**	
Birmingham 2010	C4	12 mg/dl	LN flare up	**0.49**	**0.74**	

Predictors of different renal outcomes

Anti-ds DNA predicting different renal outcomes:

Study	Test	Population	Outcome	Outcome (measure)	Outcome (result)
Kwon 2020	Anti-ds-DNA (higher level)	Patients with SLE followed up for LN	Lupus nephritis	HR (CI), multivariate analysis	1.066 (1.012-1.124)
Barnado 2019	Anti-ds-DNA (positive at 2 occasions versus normal)	Patients with SLE	Renal disease including nephritis[#]	aOR (CI)	4.60 (2.97 -7.14)
Sjöwall 2018	Anti-ds-DNA	Patients with SLE	Lupus nephritis versus no renal involvement	OR (CI)	2.9 (1.7-5.2)
Sjöwall 2018	Anti-ds-DNA	Patients with SLE	Active lupus nephritis versus inactive lupus nephritis	OR (CI)	4.8 (1.5-15.6)
Fasano 2020	Anti-ds-DNA	Patients with SLE followed up for LN	LN flare-ups	HR (CI)	21.67 (2.66, 176.52)
Ruchakorn 2019	Anti-ds-DNA (> 100.0 U/ml)	Patients with SLE followed for renal flare ups	Renal flare-ups	OR (CI), bivariate analysis	1.53 (0.99-2.35)
Fatemi 2016	Anti-dsDNA	Patients with SLE	LN flare up	HR (CI), univariate analysis	0.89 (0.28-2.82)
Wang 2022	A-dsDNA positive	Patients with class II LN	LN flare up	OR (CI), univariate analysis	0.885 (0.394-1.986)
Izmirly 2024	A-dsDNA positive	Patients with LN	Response (complete and partial) at 52 weeks	aOR (CI)	2.61 (0.93–7.33)
Tselios 2024	Anti-dsDNA + low C3/C4	Patients with LN	Progression of CKD (to more severe stage)	HR (CI)	2.72 (1.41 5.24)

Barnado 2019	Anti-ds-DNA (positive at 2 occasions versus normal)	Patients with SLE	Renal failure	aOR (CI)	2.30 (1.68 - 3.15)
Barnado 2019	Anti-ds-DNA (positive at 2 occasions versus normal)	Patients with SLE	ESRD	aOR (CI)	2.63 (1.51 -4.58)
Kwon 2020	Anti dsDNA	Patients with LN	Aggravation of tubulointerstitial damage at the second renal biopsy	OR (CI), univariate analysis	1.026 (0.988-1.065)

Complement predicting different renal outcomes:

Study	Test	Population	Outcome (predictor)	Outcome (measure)	Outcome (result)
Kwon 2020	C3	Patients with SLE followed up for LN	Lupus nephritis	HR (CI), multivariate analysis	0.979 (0.953-1.006)
Kwon 2020	C4	Patients with SLE followed up for LN	Lupus nephritis	HR (CI), multivariate analysis	0.931 (0.834-1.039)
Martin 2020	Low C3	Patients with SLE	Lupus nephritis	OR (p value)	5.03 (0.002)
Martin 2020	Low C4	Patients with SLE	Lupus nephritis	OR (p value)	5.1 (0.002)
Ishizaki 2015	C3	Patients with SLE	Lupus nephritis	OR (CI)	38.5 (4.3, 344.9)
Fasano 2020	Low C3	Patients with SLE followed up for LN	LN flare-ups	HR (CI)	5.95 (1.20, 29.54)
Fasano 2020	Low C4	Patients with SLE followed up for LN	LN flare-ups	HR (CI)	5.51(1.11, 27.33)
Ruchakorn 2019	C3 (<0.9 g/1):	Patients with SLE followed for renal flare ups	Renal flare-ups	OR (CI), multivariate analysis	3.27 (1.69-6.32)
Ruchakorn 2019	C4(<0.2 g/I):	Patients with SLE followed for renal flare ups	Renal flare-ups	OR (CI), multivariate analysis	1.08 (0.57-2.07)
Wang 2022	Low serum C3 (C3 <0.8 g/L)	Patients with class II LN	LN flare up	OR (CI), univariate analysis	1.457 (0.542-3.921)
Wang 2022	Low serum C4 (C4<0.1 g/L)	Patients with class II LN	LN flare up	OR (CI), univariate analysis	0.987 (0.441-2.209)
Zhang 2017	Low C3 at baseline	Patients with LN (peds)	LN flare up	OR (p value)	0.397 (0.473)
Fatemi 2016	C3 at first visit (Low)	Patients with SLE	LN flare up	HR (CI), univariate analysis	0.35 (0.11-1.17)
Fatemi 2016	C4 at first visit (Low)	Patients with SLE	LN flare up	HR (CI), univariate analysis	1.40 (0.44-4.40)
Sakamoto 2023	Low complement during the course	childhood-onset SLE	CKD	HR (CI), multivariate analysis	1.88 (0.81-4.35)
Petri 2020	Low C3	Patients with SLE	ESRD within 20 years	aRR (CI)	2.0 (1.32-3.03)

Wang 2022	Low C3 and/or C4	Patients with LN	Progression from low-grade proteinuria to UPCR >0.5 g/g,	aHR (CI)	2.6 (1.4 to 4.8)
Kwon 2020	C3	Patients with LN	Aggravation of tubulointerstitial damage at the second renal biopsy	OR (CI), univariate analysis	0.996 (0.972-1.019)
Kwon 2020	C4	Patients with LN	Aggravation of tubulointerstitial damage at the second renal biopsy	OR (CI), univariate analysis	1.016 (0.949-1.088)

Proteinuria predicting different renal outcomes:

Study	Test	Population	Outcome (predictor)	Outcome (measure)	Outcome (result)
Wang 2022	Proteinuria > 0.4 g/24 h	Patients with class II LN	LN flare up	OR (CI), univariate analysis	2.716 (0.555-13.297)
Zhang 2017	Proteinuria at baseline	Patients with LN (peds)	LN flare up	OR (p value)	1 (0.823)
Fatemi 2016	Urine protein (g/day)	Patients with SLE	LN flare up	HR (CI), Multivariate analysis	1.004 (1.002-1.006)
Won 2019	Proteinuria at baseline	Patients with LN	Renal flare-ups	HR(CI), Univariate analysis	1.061 (0.970-1.160)
Koo 2016	Increase in UPCR of 1g/g	Patients with proteinuria remission	Proteinuria Recurrence	RR (CI)	1.122 (1.025-1.228)
Kiyokawa 2020	UPCR (g/gCr)	Patients with LN and induction therapy	Complete response at 12 weeks	OR (CI) multivariate analysis	0.63 (0.05-1.08)
Sakamoto 2023	Proteinuria during the course	childhood-onset SLE	CKD	HR (CI) multivariate analysis	2.82 (0.77-10.35)
Won 2019	Proteinuria at baseline	Patients with LN	CKD	HR(CI), Univariate analysis	1.033 (0.862-1.237)
Petri 2020	History of Proteinuria (>500 mg/24 h)	Patients with SLE	ESRD within 20 years	aRR (CI)	2.75 (1.94 -3.89)
Izmirly 2024	UPCR > 25% decrease from baseline to week 12	Patients with LN	Response (complete and partial) at 52 weeks	aOR (CI)	2.61 (1.07–6.41)
Izmirly 2024	UPCR > 3 at baseline	Patients with LN	Response (complete and partial) at 52 weeks	aOR (CI)	3.71 (1.34–10.24)

Prognostic test accuracy for proteinuria and biomarkers

Prognostic test accuracy anti-ds DNA:

Study	Test	Cut-off	Population	Outcome	Sensitivity	Specificity	Notes
Kwon 2020	Anti-ds-DNA (higher level)	9.95 IU/ml	Patients with SLE followed up for LN	Lupus nephritis	1.00 (0.60-1.00)	0.71 (0.53-0.85)	
Mok 2016	Anti-ds-DNA	NA	Patients with SLE	Active renal disease	0.94	0.4	Comparator arms includes active non-renal, or non-active (explains the very low specificity)
Sjöwall 2018	Anti-ds-DNA	NA	Patients with SLE	Lupus nephritis versus no renal involvement	0.638	0.625	It is more specific for LN versus no renal involvement when compared to active versus inactive lupus nephritis
Sjöwall 2018	Anti-ds-DNA	NA	Patients with SLE	Active lupus nephritis versus inactive lupus nephritis	0.84	0.477	
Ishizaki 2015	Anti-ds-DNA	NA	Patients with SLE	Lupus nephritis	0.89	0.42	Silent lupus nephritis (biopsy proven LN)
Fasano 2020	Anti-ds-DNA	10 UI/ml	Patients with SLE	Renal flare-ups	0.87	0.83	
Meyer 2009	Anti-ds-DNA	NA	Patients with SLE	Lupus nephritis	0.933	0.42	
Fatemi 2016	Anti-dsDNA	Positive	Patients with SLE	Renal flare ups	NA	NA	NPV: 0.87 (0.73-0.96), PPV: 0.25 (0.11-0.45)
ESDAILE 1996	Anti-dsDNA	NA	Patients with SLE	Renal flare ups	0.53 (0.31 to 0.74)	0.69 (0.59 to 0.77)	
Tselios 2024	Anti-dsDNA	Positive	Patients with LN	Progression of CKD (to more severe stage)	0.667	0.479	
Wang 2022	Anti-dsDNA	Positive	Patients with LN	Progression from low-grade proteinuria to UPCR >0.5 g/g,	0.61	0.49	
Mejia-Vilet 2021	Anti-dsDNA	<57 UI/mL	Patients with LN	Complete response at 12 months	0.62	0.48	Measured at 6 months

Prognostic test accuracy C3:

Study	Test	Cut-off	Population	Outcome	Sensitivity	Specificity	Notes
Mok 2016	C3	low	Patients with SLE	Active renal disease	0.97	0.32	Comparator arms includes active non-renal, or non-active (explains the very low specificity
Martin 2020	C3	low	Patients with SLE	Lupus nephritis	0.74 (0.62- 0.85)	0.64 (0.41-0.83)	
Ishizaki 2015	C3	<65 mg/dl	Patients with SLE	Lupus nephritis	0.78	0.92	Silent lupus nephritis (biopsy proven LN)
Fasano 2020	C3	NA	Patients with SLE	Renal flare-ups	1	0.5	

Ruchakorn 2019	C3	<0.9 g/1	Patients with SLE followed for renal flare ups	Renal flare-ups	0.6957	0.5852	12 weeks follow up
Fatemi 2016	C3	low	Patients with SLE	Renal flare-ups	NA	NA	NPV: 0.9 (0.75-0.97), PPV: 0.28 (0.13-0.47)
ESDAILE 1996	C3	NA	Patients with SLE	Renal flare-ups	0.56 (0.34 to 0.75)	0.74 (0.65 to 0.81)	
Mejia-Vilet 2021	C3	>77 mg/dL	Patients with LN	Complete response at 12 months	0.86	0.45	Measured at 6 months

Prognostic test accuracy C4:

Study	Test	Cut-off	Population	Outcome	Sensitivity	Specificity	Notes
Martin 2020	C4	low	Patients with SLE	Lupus nephritis	0.70 (0.58-0.81)	0.68 (0.45-0.86)	
Fasano 2020	C4	NA	Patients with SLE	Renal flare-ups	1	0.62	
Fatemi 2016	C4	low	Patients with SLE	Renal flare ups	NA	NA	NPV: 0.88 (0.74-0.96), PPV: 0.28 (0.12-0.49)
ESDAILE 1996	C4	NA	Patients with SLE	Renal flare ups	0.53 (0.31 to 0.74)	0.65 (0.55 to 0.74)	
Mejia-Vilet 2021	C4	>22 mg/dL	Patients with LN	Complete response at 12 months	0.21	0.68	Measured at 6 months

Prognostic test accuracy C3/C4:

Study	Test	Cut-off	Population	Outcome	Sensitivity	Specificity
Tselios 2024	C3/C4	low	Patients with LN	Progression of CKD (to more severe stage)	0.556	0.548
Wang 2022	C3 and/or C4	Low serum C3< 80 mg/dl, C4 < 20 mg/dl.	Patients with LN	Progression from low-grade proteinuria to UPCR >0.5 g/g,	0.82	0.49

Prognostic test accuracy of proteinuria:

Study	Test	Cut-off	Population	Outcome	Sensitivity	Specificity	Notes
Liu 2019	UPCR (change from baseline at 3 months)	Change of 59%	Patients with LN	Remission at 6 months	0.74	0.72	
Fatemi 2016	Urine protein (g/day)	>500 mg/day	Patients with SLE	Renal flare ups	NA	NA	NPV: 0.85 (0.73-0.93), PPV: 0.43(0.1-0.81)

Mejia-Vilet 2021	Proteinuria	<1.50 g/g	Patients with LN	Complete response at 12 months	0.86	0.81	Measured at 6 months

Follow-up duration in patients with proteinuria remission:

In Koo 2016, they found that if a patient had proteinuria remission for 36.5 months with any recurrence, the cutoff of remission for 36.5 months has 70% sensitivity and 80% specificity that the patient will not have any renal flare-up in the future.

In the same study, they assessed the outcomes for having proteinuria recurrence versus not having a recurrence and they found that mortality is 1/59 (1.7%) versus 0/23 and ESRD is 1/59 (1.7%) versus 0/23 in patients with proteinuria versus patients without proteinuria respectively.

Monitoring intervals

Trial	Induction/maintenance?	24 hours urine	Intervals	UPCR	Intervals	Anti-Ds DNA, c3, c4	Intervals
BLISS-LN	Initial and subsequent therapy.	Yes	-At baseline. -Monthly (for the first year) -Every 6 months (for the second year)	UPCR	-At baseline -Monthly (for 2 years)	Yes	-At baseline -Monthly (for 2 years)
LUNAR	On Initial therapy	NA		UPCR	-At baseline -Monthly (for 1 year)	Yes	-At baseline -Monthly (for 1 year)
ALMS (Induction)	On Initial therapy	Yes	-At baseline, -At 2 weeks, and then monthly (6 months)	NA	NA	Yes	-At baseline, -At 2 weeks, and then monthly (6 months)
ALMS (maintenance)	On Subsequent therapy	Yes	-At baseline -Every 3 months (for 36 months)	NA	NA	Yes	-At baseline -Every 3 months (for 36 months)
AURORA 1	On Initial therapy	Yes	-At baseline -At 6 moths -At 12 months	UPCR	At weeks 1, 2, 4, 8, 12, 16, 20, 24, 30, 36, 42, 48, and 52	yes	-At baseline -At 6 moths -At 12 months
AURORA 2	On Subsequent therapy	NA		UPCR	-At Baseline -At weeks: 2,4,8, 16 weeks -Every 3 months (for 3 years)	yes	-At baseline, -At 12, 24, 30, 36 months

References of included studies for Monitoring:

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P 16.17. In SLE patients with presumed or biopsy proven LN does regularly monitoring proteinuria, anti-dsDNA antibody and C3,C4 at certain intervals lead to better outcomes than not checking these regularly?

Population: SLE patients

- On initial LN therapy
- On subsequent LN therapy
- Who have completed and stopped LN therapy

Intervention: Anti-ds DNA antibody and complement C3 and C4

- Every 1 month
- Every 2 months
- Every 3 months
- Every 6 months
- Yearly

Comparator: No regular schedule for testing

Outcomes:

- Reduction of proteinuria (if applicable)
- Preservation of kidney function
- LN flare

Table 1.

Study	Design	Population	Intervention	comparator	Outcome	Notes
Yap 2019	Non-randomized studies	Patients with biopsy proven LN and asymptomatic serological reactivation[#].	Preemptive therapy	No Preemptive therapy	Renal flare ups, eGFR, infections	[#]an increase of anti-dsDNA antibody titer from negative (<40IU/ mL) to >100IU/mL or (ii) when baseline anti-dsDNA level

						was40IU/mL, a 2-fold increase in anti-dsDNA antibody titer to>100IU/mL, with or without subnormal serum complement level.
Tseng 2006	Randomized clinical trial	Patients with SLE, clinically stable but with serological flare[$].	Moderate dose corticosteroids	Placebo	Severe SLE flare ups (including renal), mild/moderate SLE flare ups (including renal), adverse events, DM, HTN	[$]concomitant elevation of anti-dsDNA antibody levels by 25% (to the abnormal range) and an elevation of C3a levels by 50% (reaching an absolute level of =500 ng/ml) as compared with the previous 1-2 monthly visits.
Bootsma 1995	Randomized clinical trial	Patients with SLE, clinically stable but with a rise in the anti dsDNA level[!].	Early therapy	Conventional therapy[*]	Minor SLE flare ups, Major SLE flare ups, DM, HTN	[*]Conventional therapy means no treatment for serological flare ps. [!]A plasma sample was taken to be positive for anti-dsDNA when the value exceeded 10 IU/mL (3 SD above the mean for 50 healthy subjects). A rise in anti-dsDNA was defined as an increase of 25% of the level in a previous sample of at least 15 IU/mL.

Evidence summary: 3 studies compared the outcomes of early or preemptive therapy to no preemptive therapy based on elevation of anti-dsDNA or/and complement levels (serological flare but clinically stable). 1 was a non-randomized study in patients with biopsy-proven LN, while 2 randomized clinical trials assessed the outcomes in patients with SLE (we downgraded for indirectness because patients were with SLE and not purely with patients LN). The definition of serological flare varied across the studies. The overall certainty of the evidence was judged as very low because of risk of bias (patients were different at baseline with no adjustment for confounders, and because of the concerning loss to follow-up in Bootsma), imprecision (small sample size and a number of events), and indirectness. Based on a very low certainty evidence (patients who received preemptive therapy had lower rates of flare-ups (Renal, major SLE, minor SLE) and higher change in eGFR from baseline. The rate of adverse events and infections was slightly higher in the group who received preemptive therapy.

Evidence profile:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Preemptive therapy**	**no Preemptive therapy**	**Relative (95% CI)**	**Absolute (95% CI)**		
Renal flare ups												
1	non-randomised studies	serious	not serious	not serious	serious	none	5/53 (9.4%)	27/85 (31.8%)	**RR 0.30** (0.12 to 0.72)	**222 fewer per 1,000**	⨁⨁◯◯ Low	

										(from 280 fewer to 89 fewer)		
eGFR (change from baseline)												
1	non-randomised studies	serious	not serious	not serious	serious	none	53	85	-	MD **10.6 higher** (2.36 higher to 18.84 higher)	⊕⊕◯◯ Low	
Severe or major SLE flare ups												
2	randomised studies	serious	not serious	serious	serious	none	2/42 (4.8%)	14/45 (31.1%)	**RR 0.23** (0.06 to 0.83)	**240 fewer per 1,000** (from 292 fewer to 53 fewer)	⊕◯◯◯ Very low	
Mild/Moderate or minor SLE flare up (including renal flare ups)												
2	randomised studies	serious	not serious	serious	serious	none	4/42 (9.52%)	15/45 (33.33%)	**RR 0.79** (0.2 to 3.13)	**70 fewer per 1,000** (from 267 fewer to 710 more)	⊕◯◯◯ Very low	
Adverse events												
2	randomised trials	serious	not serious	serious	serious	none	30/42 (71.4%)	28/45 (62.2%)	**RR 1.15** (0.87 to 1.52)	**93 more per 1,000** (from 81 fewer to 324 more)	⊕◯◯◯ Very low	
Diabetes mellitus												
2	randomised trials	serious	not serious	serious	serious	none	0/42 (0.0%)	1/45 (2.2%)	**RR 0.36** (0.02 to 8.46)	**14 fewer per 1,000** (from 22 fewer to 166 more)	⊕◯◯◯ Very low	

HTN

2	randomised trials	serious	not serious	serious	serious	none	4/42 (9.5%)	1/45 (2.2%)	**RR 4.36** (0.53 to 36.12)	**75 more per 1,000** (from 10 fewer to 780 more)	⨁◯◯◯ Very low	

Infections

1	randomised trials	serious	not serious	serious	serious	none	12/53 (22.6%)	13/85 (15.3%)	**RR 1.48** (0.73 to 3.00)	**73 more per 1,000** (from 41 fewer to 306 more)	⨁◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

References:

Randomized clinical trials:

1-Tseng, Chung-E et al. “The effect of moderate-dose corticosteroids in preventing severe flares in patients with serologically active, but clinically stable, systemic lupus erythematosus: findings of a prospective, randomized, double-blind, placebo-controlled trial.” *Arthritis and rheumatism* vol. 54,11 (2006): 3623-32. doi:10.1002/art.22198

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Non-randomized studies:

3- Desmond Y H Yap, Lorraine P Y Kwan, Maggie K M Ma, Maggie M Y Mok, Gary C W Chan, Tak Mao Chan, Preemptive immunosuppressive treatment for asymptomatic serological reactivation may reduce renal flares in patients with lupus nephritis: a cohort study, *Nephrology Dialysis Transplantation*, Volume 34, Issue 3, March 2019, Pages 467–473, https://doi.org/10.1093/ndt/gfy024

P.18 In SLE patients with LN with ESKD, does kidney transplantation improve clinical outcomes compared to dialysis?

Population: Patients with LN and ESKD

Intervention: Kidney transplantation

Comparison: Hemodialysis or peritoneal dialysis

Outcomes:

- Quality of life
- Risk of SLE flare
- Disease damage
- Mortality
- Incidence of infection
- Incidence of CVD

Table 1.

Study name (year)	Study design	Population	Intervention details	Comparator details	Outcomes with available data	Outcome measures	Notes
Jorge 2022a USA	Comparative non-randomized study	-Adults. ESRD due to Lupus nephritis -Multiple ethnicities (47% African American, 41% white, 7% Asian, 8% other)	Kidney Transplantation	Patients on a waitlist (hemodialysis or peritoneal dialysis)	Cardiovascular disease (non-fatal)	RR, aHR	Mean age is not reported but 30% were younger than 30 years
Jorge 2019b USA	Comparative non-randomized study	-Adults mean age: 38 years -ESRD due to Lupus nephritis -Multiple ethnicities (African American: 45% versus 54%, White: 44% versus 35%, Asian: 6% versus 5%)	Kidney Transplantation	Patients on a waitlist (hemodialysis or peritoneal dialysis)	Cardiovascular disease (fatal), Mortality, Infections (fatal)	RR, aHR	
Kang 2011 Korea	Comparative non-randomized study	-Adults: Mean age (SD): (KT: 27 (8), HD: 30 (13), PD: 33(11)) -ESRD due to Lupus nephritis -Asian	Kidney Transplantation	Hemodialysis or Peritoneal dialysis	Cardiovascular disease, Mortality, Infections, SLE flare up	RR	
Wu 2014 Taiwan	Comparative non-randomized study	-Adults mean age (SD): 38.3 (16) -ESRD due to Lupus nephritis -Asian	Kidney Transplantation	Hemodialysis or Peritoneal dialysis	Mortality	RR	
Moon 2013 Korea	Comparative non-randomized study	-Adults Mean age (SD): 28 (7.3) -ESRD due to Lupus nephritis	Kidney Transplantation	Hemodialysis or Peritoneal dialysis	Mortality, SLE flare up	RR	Age at onset of LN

		-Asian					
Tsai 2019 Taiwan	Comparative non-randomized study	Adults Mean age (SD): (KT: 28.6 (9.7), HD: 36.4 (14.1), PD: 33.2 (11.5) -ESRD due to Lupus nephritis -Asian	Kidney Transplantation	Hemodialysis or Peritoneal dialysis	Cardiovascular disease, Mortality, Infections, SLE flare up	aHR, RR	Age at ESRD
Ntatsaki 2018 UK	Comparative non-randomized study	Adults, age >18 years, mean (SD): 31 (9) -ESRD due to Lupus nephritis	Kidney Transplantation	Hemodialysis or Peritoneal dialysis	Mortality	RR	Age at ESRD

Evidence summary: 7 comparative non-randomized studies addressing the PICO question. Mortality was reported in 6 studies. In Jorge et al, they reported on Hazard Ratio (HR) and did a full adjustment to confounders, and the results showed 70% reduction in all-cause mortality in the transplantation arm aHR (CI): 0.30(0.27 to 0.33). In all 6 studies (1,2,3,4,5,6), mortality was reported as unadjusted RR (number of events). Only 2 studies took into account the follow-up duration and adjusted for confounders (1,2). Since aHR is less biased than RR, then we will use aHR when available.
Cardiovascular events were examined in four studies. Transplantation was associated with a reduction in fatal cardiovascular events, non-fatal cardiovascular events, and unspecified cardiovascular events, with adjusted hazard ratios (aHR) of 0.26 (95% CI, 0.23 to 0.30) and 0.31 (95% CI, 0.18 to 0.53), and a relative risk (RR) of 0.32 (95% CI, 0.21 to 0.5), respectively. Infection was addressed by 3 studies. One study showed that transplantation was associated with 59% reduction in the fatal infection aHR (CI): 0.41 (0.32 to 0.52). The other 2 studies showed that RR (CI):1.03 (0.73 to 1.46). It is important to highlight that in the last 2 studies, the sample size was small and there was no adjustment for the confounders. SLE flare-ups were addressed by 3 studies, showing 71% reduction in SLE flare-ups in the transplantation population. In the three studies, there was no adjustment for confounders and the sample size was small.
N.B: We assumed that the minimal important difference (MID) for the outcomes is 5%, but this will be determined by the core team and the panel

Evidence profile:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Transplant**	**Dialysis (hemodialysis or peritoneal dialysis)**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality (HR)												
2[1,2]	non-randomised studies	not serious	not serious	not serious	not serious	none	5738 participants	3921 participants	**HR 0.30** (0.27 to 0.33) [Mortality (HR)]	**277 fewer per 1,000** (from 291 fewer to 263 fewer)	⊕⊕⊕⊕ High	

							-	43.4%				

Cardiovascular disease (Fatal events)

1[1]	non-randomised studies	not serious	not serious	not serious	not serious	none	5738 participants	3921 participants	**HR 0.26** (0.23 to 0.30) [Cardiovascular disease (Fatal events)]	**124 fewer per 1,000** (from 130 fewer to 117 fewer)	⊕⊕⊕⊕ High	
							-	17.2%				

Cardiovascular disease (Non-fatal events)

1[7]	non-randomised studies	not serious	not serious	not serious	not serious	none	3209 participants	5963 participants	**HR 0.31** (0.18 to 0.53) [Cardiovascular disease (Non-fatal events)]	**12 fewer per 1,000** (from 14 fewer to 8 fewer)	⊕⊕⊕⊕ High	
							-	1.7%				

Cardiovascular disease

3[2,4,7]	non-randomised studies	serious[a]	not serious	not serious	not serious	none	23/3266 (0.7%)	131/6059 (2.2%)	**RR 0.32** (0.21 to 0.50)	**15 fewer per 1,000** (from 17 fewer to 11 fewer)	⊕⊕⊕◯ Moderate	

Fatal Infections (HR)

1[1]	non-randomised studies	not serious	not serious	not serious	not serious	none	5738 participants	3921 participants	**HR 0.41** (0.32 to 0.52) [Fatal Infections (HR)]	**41 fewer per 1,000** (from 47 fewer to 33 fewer)	⊕⊕⊕⊕ High	
							-	7.0%				

Infection

2[2,4]	non-randomised studies	serious[a]	not serious	not serious	serious[b]	none	26/57 (45.6%)	45/96 (46.9%)	**RR 1.03** (0.73 to 1.46)	**14 more per 1,000** (from 127 fewer to	⊕⊕◯◯ Low	

										216 more)		

SLE flare up

3[2,4,5]	non-randomised studies	serious[a]	not serious	not serious	serious[b]	none	4/68 (5.9%)	32/114 (28.1%)	**RR 0.29** (0.11 to 0.77)	**199 fewer per 1,000** (from 250 fewer to 65 fewer)	⨁⨁◯◯ Low	

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. We use ROBINsI for assessing the Risk of bias (ROB). No adjustments for confounding were done for this outcome, that's why we downgraded for ROB.
b. We downgrade for imprecision because of the small sample size and small number of events

References

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2.2009, Tsai. Long-term outcomes in lupus patients receiving different renal replacement therapy.
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5.Moon, Su-Jin et al. “Predictors of end-stage renal disease and recurrence of lupus activity after initiation of dialysis in patients with lupus nephritis.” Clinical and experimental rheumatology vol. 31,1 (2013): 31-9.. .
6.Ntatsaki, Eleana et al. “Impact of pre-transplant time on dialysis on survival in patients with lupus nephritis.” Clinical rheumatology vol. 37,9 (2018): 2399-2404. doi:10.1007/s10067-018-4115-1. .
7.Jorge, April et al. “Kidney Transplantation and Cardiovascular Events Among Patients With End-Stage Renal Disease Due to Lupus Nephritis: A Nationwide Cohort Study.” Arthritis care & research vol. 74,11 (2022): 1829-1834. doi:10.1002/acr.24725. .

Included studies:

Randomized clinical trials:

- None

Comparative non-randomized studies:

- 7 studies (reference above)

Non-comparative studies (single arm):

Studies read and exclude:

P.19 In SLE patients with LN and ESKD, does use of hemodialysis impact clinical outcomes compared to peritoneal dialysis?

Population: Patients with LN and ESKD
Intervention: Hemodialysis
Comparator: Peritoneal dialysis
Outcomes:

- Quality of life
- Risk of SLE flare
- Disease damage
- Mortality
- Incidence of infection
- Incidence of CVD

Table 1. Included studies

Study name (year)	Study design	Populations	Intervention details	Comparator details	Outcomes with available data (synthesis method/metric)	Outcome measures
Kang 2011 Korea	comparative non-randomized study	-Adults: Mean age (SD): (HD: 30 (13), PD: 33(11)) -ESRD due to Lupus nephritis -Asian	Hemodialysis	Peritoneal dialysis	Mortality, CVD, CVD (fatal), Infections, Infections (fatal), SLE flare-up	RR
Wu 2014 Taiwan	comparative non-randomized study	-ESRD due to LN. -Adults mean age (SD): 38.3 (16) -Asian	Hemodialysis	Peritoneal dialysis	Mortality	RR
Kim 2022 Korea	comparative non-randomized study	-ESRD due to LN. -Adults mean age (SD): 38.3 (16)	Hemodialysis	Peritoneal dialysis	SLE flare-up, Infection	RR, aHR
Nossent 1990 Netherlands	comparative non-randomized study	-ESRD due to LN. -Adults Mean (SD): 28 (11.8)	Hemodialysis	Peritoneal dialysis	Mortality, CVD (fatal), Infection (fatal)	RR
Stock 1993 USA	comparative non-randomized study	-ESRD due to LN. -Adults Mean age: 26.2	Hemodialysis	Peritoneal dialysis	SLE flare-up	RR

Levy 2015 France	comparative non-randomized study	-ESRD due to LN. -Adults Mean (SD) age: 43.4 (16)	Hemodialysis	Peritoneal dialysis	Mortality, CVD (fatal), Infection (fatal)	RR
Tsai 2019 Taiwan	comparative non-randomized study	-ESRD due to LN. -Adults Mean age (SD): (HD: 36.4 (14.1), PD: 33.2 (11.5)	Hemodialysis	Peritoneal dialysis	Mortality, CVD, Infection, SLE flare-up	RR, aHR
Chang 2013 Taiwan	comparative non-randomized study	-ESRD due to LN. -Adults Mean (SD) age: 40.6 (15.8)	Hemodialysis	Peritoneal dialysis	Mortality, CVD (fatal), Infection (fatal)	RR
Weng 2009 Taiwan	comparative non-randomized study	-ESRD due to LN. -Adults	Hemodialysis	Peritoneal dialysis	Mortality	RR
Contreras 2014a USA	comparative non-randomized study	-ESRD due to LN. -Adults/Peds. Age >13 -Matched populations (propensity matching) Median age IQR: HD: 39 (29-48) versus PD 39 (29-48) -Majority are white and African American	Hemodialysis	Peritoneal dialysis	Mortality	RR, aHR
Contreras 2014b USA	comparative non-randomized study	-ESRD due to LN. -Adults, Age >13 Median age IQR: HD: 39 (29-48) versus PD 38 (28-50) -Majority are white and African American	Hemodialysis	Peritoneal dialysis	Mortality, CVD (fatal), Infection (fatal)	RR, aHR

Evidence summary:

A total of 10 comparative non-randomized studies are addressing Hemodialysis versus Peritoneal dialysis.

8 studies addressed mortality. 2 studies reported adjusted hazard ratios, aHR (CI): HR 0.92 (0.81 to 1.04), it showed an 8% reduction in Mortality in the hemodialysis arm. 8 studies (1,2,3,4,5,6,7,8) addressed Mortality using RR without adjustment for confounders or taking into account the time of follow-up. Since aHR is less biased measure than RR a and provides better evidence, we will use the aHR data when available.

5 studies reported on the RR for cardiovascular and infectious fatal events where RR (CI) was RR 1.07 (0.93 to 1.23), RR 1.05 (0.58 to 1.92), respectively. For cardiovascular disease, 2 studies report on it. It was higher in the hemodialysis arm with RR (CI): 2.36 (0.90 to 6.15). No adjustment for confounders was made and the small size and number of patients were small. SLE flare-up was addressed by 4 studies, only one study reported HR (CI): 0.77 (0.26 to 2.26), although it takes into account the time factor but here it was not adjusted for potential confounders. The 4 studies reported RR (CI) 1.13 (0.69 to 1.84). RR doesn't address the time factor, no adjustment for confounders was done, and the size of the peritoneal arm was small. All the factors mentioned (adjustment for confounding, time factor, small size and number of events) affect our certainty in the evidence.

N.B:

- Contreras 2014a and Contreras 2014b, but in a they did a propensity matching score in b they made adjustments based on the same co-variates.
- We assumed that the minimal important difference (MID) for the outcomes is 5%, but this will be determined by the core team and the panel

Evidence profile:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Hemodialysis**	**Peritoneal dialysis**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality (assessed with: adjusted HR)												
2[1,2]	non-randomised studies	not serious	not serious	not serious	not serious	none	9710 participants	1367 participants	**HR 0.92** (0.81 to 1.04) [Mortality]	**15 fewer per 1,000** (from 37 fewer to 8 more)	⊕⊕⊕⊕ High	
							-	21.4%				
Cardiovascular disease												
2[2,8]	non-randomised studies	serious[b]	not serious	not serious	serious[c]	none	27/70 (38.6%)	4/26 (15.4%)	**RR 2.36** (0.90 to 6.15)	**209 more per 1,000** (from 15 fewer to 792 more)	⊕⊕◯◯ Low	
Infection												
3[2,7,9]	non-randomised studies	serious[b]	not serious	not serious	serious[c]	none	33/166 (19.9%)	27/51 (52.9%)	**RR 0.40** (0.14 to 1.17)	**318 fewer per 1,000** (from 455 fewer to 90 more)	⊕⊕◯◯ Low	
SLE flare (including LN flare)												
4[2,7,8,10]	non-randomised studies	serious[b]	not serious	not serious	serious[c]	none	47/172 (27.3%)	14/57 (24.6%)	**RR 1.13** (0.69 to 1.84)	**32 more per 1,000** (from 76	⊕⊕◯◯ Low	

										fewer to 206 more)		
Cardiovascular disease (fatal)												
5[1,4,5,6,8]	non-randomised studies	serious[b]	not serious	not serious	not serious	none	357/2514 (14.2%)	298/1694 (17.6%)	**RR 1.07** (0.93 to 1.23)	**12 more per 1,000** (from 12 fewer to 40 more)	⊕⊕⊕◯ Moderate	
Infection (fatal)												
5[1,4,5,6,8]	non-randomised studies	serious[b]	not serious	not serious	not serious	none	131/2514 (5.2%)	79/1694 (4.7%)	**RR 1.05** (0.58 to 1.92)	**2 more per 1,000** (from 20 fewer to 43 more)	⊕⊕⊕◯ Moderate	
SLE flare up (HR)												
1[7]	non-randomised studies	serious[d]	not serious	not serious	serious[c]	none	96 participants	25 participants	**HR 0.77** (0.26 to 2.26) [SLE flare up (HR)]	**57 fewer per 1,000** (from 198 fewer to 244 more)	⊕⊕◯◯ Low	
							-	28.0%				

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. We downgraded for imprecision because the absolute CI is wide, ranging from 12 more to 166 more crossing minimal important difference (MID)
b. We used ROBINsI for assessment of ROB. We downgraded for risk of bias because of concerns related to confounders (no adjustment was made).
c. We downgraded for imprecision because of the small sample size and number of events.
d. We used ROBINsI for assessment of ROB. although they used HR to report the outcome, it wasn't adjusted for confounders.

References of included studies

1.Contreras, Gabriel et al. “Comparison of mortality of ESRD patients with lupus by initial dialysis modality.” Clinical journal of the American Society of Nephrology : CJASN vol. 9,11 (2014): 1949-56. doi:10.2215/CJN.02500314. .
2.2009, Tsai. Long-term outcomes in lupus patients receiving different renal replacement therapy.
3.Kang, Seok-Hui et al.. “Comparison of clinical outcomes by different renal replacement therapy in patients with end-stage renal disease secondary to lupus nephritis.” . The Korean journal of internal medicine vol. 26,1 (2011): 60-7. doi:10.3904/kjim.2011.26.1.60;

4.Kim, Young-Eun et al. “Disease Flare of Systemic Lupus Erythematosus in Patients With Endstage Renal Disease on Dialysis.” The Journal of rheumatology vol. 49,10 (2022): 1131-1137. doi:10.3899/jrheum.220101. .
5.Kang, Seok-Hui et al. “Comparison of clinical outcomes by different renal replacement therapy in patients with end-stage renal disease secondary to lupus nephritis.” The Korean journal of internal medicine vol. 26,1 (2011): 60-7. doi:10.3904/kjim.2011.26.1.60. .
6.Weng, Cheng-Hao et al. “Peritoneal dialysis and hemodialysis in systemic lupus erythematosus patients: comparison of clinical outcomes.” Kidney & blood pressure research vol. 32,6 (2009): 451-6. doi:10.1159/000266480. .
7.Nossent, H C et al. “Contribution of renal biopsy data in predicting outcome in lupus nephritis. Analysis of 116 patients.” Arthritis and rheumatism vol. 33,7 (1990): 970-7. doi:10.1002/art.1780330708. .
8.Chang, Yu-Sheng et al. “Survival analysis in systemic lupus erythematosus patients on maintenance dialysis: a nationwide population-based study in Taiwan.” Rheumatology (Oxford,England) vol. 52,1 (2013): 166-72. doi:10.1093/rheumatology/kes325. .
9.Levy, B et al. “Outcome of patients with systemic lupus erythematosus on chronic dialysis: an observational study of incident patients of the French National Registry 2002-2012.” Lupus vol. 24,10 (2015): 1111-21. doi:10.1177/0961203315578763. .
10.Stock, G G Jr,and N K Krane. “Treatment of end-stage renal disease due to lupus nephritis: comparison of six patients treated with both peritoneal and hemodialysis.” Advances in peritoneal dialysis. Conference on Peritoneal Dialysis vol. 9 (1993): 147-51.. .

Randomized clinical trials:
-None
Comparative non-randomized studies:
-10 Studies (references above)
Non-comparative studies:

Studies read and excluded:

Are outcomes improved for SLE patients on renal replacement therapy if they follow regularly with rheumatology in addition to nephrology?

P20. In SLE patients with LN who require renal replacement therapy (RRT), does regular follow up with rheumatology (in addition to nephrology) impact clinical outcomes compared to not following regularly with rheumatology?

Population: Patients with LN on RRT

- On dialysis
- S/p renal transplantation

Intervention: Regular rheumatology follow up
Comparator: No regular rheumatology follow up
Outcomes:

- SLE flare
- Hospitalization due to SLE
- Mortality
- Quality of life
- Disease damage

Evidence summary: One study compared the outcome of frequent (two or more times per year) versus infrequent (less than twice a year) rheumatology follow up in patients with ESRD and LN. Mortality might be lower in patients having frequent follow up with 134 fewer death per 1000 (180 fewer to 214 more) based on low certainty evidence because of risk of bias and imprecision.

Evidence profile:

Certainty assessment							№ of patients		Effect		Certainty	
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Frequent rheumatology follow up	Infrequent rheumatology follow up	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1	non-randomised studies	Serious[a]	not serious	not serious	serious	none	1/21 (4.8%)	9/48 (18.8%)	**RR 0.2879** (0.0387 to 2.1412)	**134 fewer per 1,000** (from 180 fewer to 214 more)	⨁⨁◯◯ Low	

CI: confidence interval; **RR:** risk ratio

[a:] We downgraded for risk of bias as it is non randomized without adjustment for potential confounders.

References:

1 non randomized study: Broder A, Khattri S, Patel R, Putterman C. Undertreatment of disease activity in systemic lupus erythematosus patients with endstage renal failure is associated with increased all-cause mortality. J Rheumatol. 2011 Nov;38(11):2382-9. doi: 10.3899/jrheum.110571. Epub 2011 Sep 1. PMID: 21885495; PMCID: PMC3774792.

P.21 In SLE patients with history of LN who are status post kidney transplantation, does taking HCQ post-transplant improve clinical outcomes compared to not taking it?

Population: SLE patients with LN s/p renal transplantation
Intervention: HCQ
Comparator: No HCQ
Outcomes:

- SLE flare (including LN flare)
- Hospitalization due to SLE
- Mortality
- Quality of life
- Disease damage

Table 1.								
Study name	**Study design**	**Population**	**Intervention details**	**Comparator arm**	**Outcomes with available data**	**Outcome measures**	**Outcome time point**	**Notes**

(year) country					(synthesis method/metric)			
Lentine 2020 USA	comparative nonrandomized study	-Patients who had renal transplantation due to lupus nephritis. -Adults, age >18* -Majority are African American: (804/1716) followed by White: (421/ 1716), Hispanic (351/1716), Other (140/1716)	HCQ	No HCQ	Mortality, Graft survival, Qt prolongation, Cardiomyopathy, Arrythmia, Retinal toxicity, Cytopenia	aHR	12-36 months	Patients were SLE (97.6%) or scleroderma (2.4%). *They don't report mean age.
Martinez-Lopez 2022 Spain	non-comparative study	-Patients post kidney transplantation due to LN. -Adults Mean age (SD): 39.8 (11.3)	HCQ	NA	SLE flare up.	ratio	Mean (SD): 15.0 (9.84) years	The main aim of the study was to compare patients with LN and PKD

Evidence summary:

2 studies addressed the use of HCQ post-transplantation in patients with ESRD due to LN. Each outcome was addressed by one study, all were comparative data except the SLE flare-up was non-comparative data. For mortality, the adjusted HR(CI) was 0.92 (0.49 to 1.72). Regarding cardiac toxicity (prolonged Qtc), cardiac toxicity (Ventricular arrhythmia), and cardiac toxicity (myopathy), the adjusted HR(CI) was 1.5 (0.96 to 2.35), aHR 1.50 (1.00 to 2.26), aHR 0.80 (0.09 to 7.48), respectively. For retinal toxicity, the adjusted HR(CI): 1.89 (0.15 to 24.40). Graft failure (all-cause) was only addressed by one study, with an adjusted HR(CI) is 0.87 (0.59 to 1.29). The adjusted HR for cytopenia was HR 1.31 (1.03 to 1.67). SLE flare-ups was addressed by one non-comparative study, where out of 21 patients on HCQ, 3 had SLE flare-ups (2/3 extrarenal flares, 1/3 renal).

N.B:

- Minimal important difference was assumed as 5%, this will be determined later on with the core team and the panel.
- In Lentine 2020, there were 3 arms. The first arm was on (tacrolimus, MMF, prednisone, and HCQ). The second arm was on (tacrolimus, MMF, prednisone, No HCQ). The third arm was on (other immunosuppressants and HCQ). For this PICO question, we compared the first and second arms where HCQ is the only different intervention.

Certainty assessment	№ of patients	Effect	Certainty	Importance

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adjusted HCQ	No HCQ	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1	non-randomised studies	not serious	not serious	not serious	serious[a]	none	301 participants	1415 participants	**HR 0.92** (0.49 to 1.72) [Mortality]	**4 fewer per 1,000** (from 25 fewer to 34 more)	⊕⊕⊕◯ Moderate	
							-	5.0%				
Cardiac Toxicity (Prolonged QTc)												
1	non-randomised studies	not serious	not serious	not serious	serious[b]	none	301 participants	1415 participants	**HR 1.50** (0.96 to 2.35) [Cardiac Toxicity (Prolonged QTc)]	**50 more per 1,000** (from 4 fewer to 130 more)	⊕⊕⊕◯ Moderate	
							-	11.0%				
Cardiac Toxicity (Ventricular arrhythmias)												
1	non-randomised studies	not serious	not serious	not serious	not serious	none	301 participants	1415 participants	**HR 1.50** (1.00 to 2.26) [Cardiac Toxicity (Ventricular arrhythmias)]	**15 more per 1,000** (from 0 fewer to 37 more)	⊕⊕⊕⊕ High	
							-	3.0%				
Cytopenia												
1	non-randomised studies	not serious	not serious	not serious	serious[a]	none	301 participants	1415 participants	**HR 1.31** (1.03 to 1.67) [Cytopenia]	**75 more per 1,000** (from 8 more to 152 more)	⊕⊕⊕◯ Moderate	
							-	31.0%				
Retinal Toxicity												
1	non-randomised studies	not serious	not serious	not serious	serious[b]	none	301 participants	1415 participants	**HR 1.89** (0.15 to 24.40)	**42 more per 1,000**	⊕⊕⊕◯ Moderate	

									[Retinal Toxicity]	(from 42 fewer to 664 more)		
							-	5.0%				

Cardiac Toxicity (Myopathy)

1	non-randomised studies	not serious	not serious	not serious	serious[c]	none	301 participants	1415 participants	**HR 0.80** (0.09 to 7.48) [Cardiac Toxicity (Myopathy)]	**1 fewer per 1,000** (from 5 fewer to 32 more)	⊕⊕⊕◯ Moderate	
							-	0.5%				

Graft Failure

1	non-randomised studies	not serious	not serious	not serious	not serious	none	301 participants	1415 participants	**HR 0.87** (0.59 to 1.29) [Graft Failure]	**15 fewer per 1,000** (from 47 fewer to 32 more)	⊕⊕⊕⊕ High	
							-	12.0%				

CI: confidence interval; HR: hazard ratio

Explanations

a. We downgraded for imprecision because the absolute values cross one of the MID (minimal important difference), assuming that the MID for mortality is 5%.

b. We downgraded for imprecision because the absolute values cross one of the MID (minimal important difference), assuming that the MID is 5%.

c. We downgraded for imprecision because of the small number of events.

Summary of evidence (non-comparative studies):

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description, age)	Intervention used in relevant population (Describe the intervention)	Results	Comments
SLE flares	Martinez-Lopez, 2022	Non-comparative study	Mean (SD) 15.0 (9.84) years	Patients post kidney transplantation due to LN. Mean (SD) age 39.8 (11.3) years at transplant	HCQ (all patients)	SLE flares: 3/21	Flares: 2/3 extrarenal flares, 1/3 renal. The main aim of the study was to compare patients with LN and PKD.

References:

Randomized clinical trials:

-None

Comparative nonrandomized studies:

-1 study: Lentine, Krista L et al. “Hydroxychloroquine and maintenance immunosuppression use in kidney transplant recipients: Analysis of linked US registry and claims data.” Clinical transplantation vol. 34,12 (2020): e14118. doi:10.1111/ctr.14118

Non-comparative studies:

-1 study: Martínez-López, David et al. “Long-term survival of renal transplantation in patients with lupus nephritis: experience from a single university centre.” Clinical and experimental rheumatology vol. 40,3 (2022): 581-588. doi:10.55563/clinexprheumatol/ri873i

Read and excluded:

P22. In SLE patients with LN at risk of developing ESKD, does preemptive kidney transplant improve clinical outcomes compared to initiating dialysis and no preemptive transplant?

Population: SLE patients with lupus nephritis (LN) at risk of developing ESKD
Intervention: Preemptive kidney transplant
Comparator: No preemptive transplant and dialysis
Outcomes:

- SLE flare
- Hospitalization due to SLE
- Graft survival
- Mortality
- Graft survival
- Quality of life
- Disease damage
- CVD
- Infections

Evidence summary: 1 study compared the outcomes of preemptive renal transplantation versus no preemptive renal transplantation in patients with SLE. This study showed that adjusted rates of graft failure and mortality in patients with preemptive renal transplantation are lower than in patients without preemptive renal transplantation. The overall certainty of evidence is very low due to ROB, and imprecision.

Evidence Evidence:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preemptive transplantation	No preemptive	Relative (95% CI)	Absolute (95% CI)		
Graft failure												
1	non-randomised studies	serious[a]	not serious	not serious	serious	none	NA	NA	**HR 0.69** (0.55 to 0.86)	**-- per 1,000** (from -- to --)	⨁⨁◯◯ Low	
Mortality												

1	non-randomised studies	serious[a]	not serious	not serious	serious	none	NA	NA	**HR 0.55** (0.36 to 0.84)	**-- per 1,000** (from -- to --)	⊕⊕◯◯ Low	

CI: confidence interval; **HR:** hazard ratio

Explanations

a. Although the HR was adjusted, they don't report for which factors they adjusted the analysis.

Reference:

1-Naveed, A et al. "Preemptive kidney transplantation in systemic lupus erythematosus." Transplantation proceedings vol. 43,10 (2011): 3713-4. doi:10.1016/j.transproceed.2011.08.092

P23. In SLE patients with LN and ESKD, does delaying transplant until clinical or serologic remission, compared to not delaying transplant, impact outcomes?

Population: SLE patients with lupus nephritis (LN) and ESKD
Intervention:
- Transplant with clinical disease activity
- Transplant with serologic activity only

Comparator:
- Transplant with SLE in clinical and serologic remission

Outcomes:
- Recurrent LN in graft
- SLE flare
- Hospitalization due to SLE
- Graft survival
- Mortality
- Quality of life
    - Disease damage

Evidence summary: One study compared the outcomes of transplantation between patients with SLEDAI >0 to SLEDAI=0 and the results showed no significant difference in the outcomes. It is worth mentioning that the HR is not adjusted for confounding and there are large concerns about imprecision because of the small sample size (30 patients) leading to very low certainty in the evidence.

Evidence report:

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLEDAI >0	SLEDAI =0	Relative (95% CI)	Absolute (95% CI)	
Chronic allograft dysfunction											
1	non-randomised studies	serious	not serious	not serious	very serious	none		6 participants	**HR 0.94** (0.25 to 3.57) [Chronic allograft dysfunction]	**21 fewer per 1,000** (from 341 fewer to 416 more)	⨁◯◯◯ Very low
							-	50.0%		**21 fewer per 1,000** (from 341 fewer to 416 more)	
Graft failure											
1	non-randomised studies	serious	not serious	not serious	very serious	none		7 participants	**HR 0.76** (0.12 to 4.75) [Graft failure]	**60 fewer per 1,000** (from 246 fewer to 512 more)	⨁◯◯◯ Very low
							-	28.5%		**60 fewer per 1,000** (from 246 fewer to 512 more)	

Table of outcomes

Outcome	Study	Population	Intervention	Comparison	Outcomes	Notes
Acute rejection	Chung 2014	Patients with ESRD due to LN	Non-renal SLE-DAI (each score increase)	NA	HR (CI): 1 (0.64-1.57)	**Mean follow-up time:** 8.18 years **Total number of patients in the study is:** 31

Recurrence of LN	Chung 2014	Patients with ESRD due to LN	Non-renal SLE-DAI (each score increase)	NA	HR (CI): 2.89 (0.88-9.47)	

Reference:

RCT: None
Non-randomized studies:
1-Chung, M-C et al. "Influence of pretransplantation dialysis time and lupus activity on outcome of kidney transplantation in systemic lupus erythematosus." *Transplantation proceedings* vol. 46,2 (2014): 336-8. doi:10.1016/j.transproceed.2013.11.085
Systematic review: Yap KS, Urowitz MB, Mahood Q, Medina-Rosas J, Sabapathy A, Lawson D, Su J, Gladman DD, Touma Z. The utility of lupus serology in predicting outcomes of renal transplantation in lupus patients: Systematic literature review and analysis of the Toronto lupus cohort. Semin Arthritis Rheum. 2017 Jun;46(6):791-797. doi: 10.1016/j.semarthrit.2016.09.008. Epub 2016 Sep 21. PMID: 27769590.

P24. In SLE patients s/p kidney transplant due to LN and who have +aPL or APS, does anticoagulation with warfarin, compared to no anticoagulation, result in improved outcomes?

Population: Patients who had a kidney transplant due to LN with aPL or APS and are not already on warfarin
Intervention: anticoagulation with warfarin
Comparator: no anticoagulation
Outcomes:

- Graft survival
- Mortality
- Vascular (thromboembolic) events
- Bleeding

Evidence summary: In patients with APS or +apL post kidney transplant, the rates of graft loss due to thrombosis were higher in the No AC arm when compared to patients on AC. This evidence is not derived from patients with LN (indirect evidence).
Table of outcomes.

Outcome	Population	Intervention: AC	Comparator: No AC	
Graft loss due to thrombosis	Patients with APS and post kidney transplantation	1/4	7/7	
Graft loss due to thrombosis	Patients with APS and post kidney transplantation	0/7	1/1	
Graft loss due to thrombosis	Patients with +apl and post kidney transplantation	0/10	2/45	

References:

1-Vaidya, Smita[1 2]; Sellers, Rachel[1]; Kimball, Pamela[3]; Shanahan, Thomas[4]; Gitomer, Jermy[5]; Gugliuzza, Kristine[1]; Fish, Jay C.[1]. FREQUENCY, POTENTIAL RISK AND THERAPEUTIC INTERVENTION IN END-STAGE RENAL DISEASE PATIENTS WITH ANTIPHOSPHOLIPID ANTIBODY SYNDROME: A Multicenter Study. Transplantation 69(7):p 1348-1352, April 15, 2000

2-Rubenwolf, P et al. “Antiphospholipidantikörpersyndrom: a priori eine Kontraindikation zur Nierentransplantation?” [Antiphospholipid antibody syndrome: a priori a contraindication to kidney transplantation?]. *Aktuelle Urologie* vol. 38,2 (2007): 132-6. doi:10.1055/s-2006-944306

Randomized clinical trials: None

Non randomized studies: 2

P25. In patients who had a kidney transplant due to LN and who have +aPL or APS, does aPL-directed immunosuppression result in improved outcomes compared to standard of care?

Population: Patients who had a kidney transplant due to LN with +aPL or APS

Intervention: Sirolimus

Comparison: No Sirolimus

Outcomes:

- Graft survival
- Mortality
- Vascular (thromboembolic) events
- Adverse effects of treatment (bleeding or infection)

Evidence summary: No studies addressing Sirolimus in patients with LN and +apl or APS. The following study addresses Sirolimus in patients with +APS without or with SLE (20/37(54%)), that’s why we downgraded for indirectness. In addition, patients were receiving Anticoagulation (not specified) in both arms. Rates of graft survival are higher in patients taking Sirolimus. No events of thrombosis occurred in each arm. The overall certainty of evidence was judged as very low due to risk of bias, imprecision, and indirectness.

Evidence profile:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sirolimus**	**No Sirolimus**	**Relative (95% CI)**	**Absolute (95% CI)**		
Graft survival												
1	non-randomised studies	serious	not serious	serious	very serious	none	7/10 (70.0%)	3/27 (11.1%)	**RR 6.30** (2.01 to 19.73)	**589 more per 1,000** (from 112 more to 1,000 more)	⨁◯◯◯ Very low	
Thrombosis												
1	non-randomised studies	serious	not serious	serious	very serious	none	0/10 (0.0%)	0/27 (0.0%)	not pooled	see comment	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Reference:

Canaud, Guillaume et al. “Inhibition of the mTORC pathway in the antiphospholipid syndrome.” *The New England journal of medicine* vol. 371,4 (2014): 303-12. doi:10.1056/NEJMoa1312890

RCT: none

Non randomized studies: 1