SUPPLEMENTARY MATERIALS 3 – Evidence Report

2025 American College of Rheumatology (ACR) Guideline for the Treatment of Systemic Lupus Erythematosus

SLE Guidelines Evidence Summary

We drafted an evidence report for each PICO question and comparison (where evidence was available). For PICOs that were informed by comparative data (evidence from randomized controlled trials or nonrandomized studies of interventions), we assessed the certainty of the evidence using the GRADE approach and presented the findings using GRADE evidence profiles. For PICOs that were informed by noncomparative data (e.g., single-arm studies or case series), we summarized the evidence in a table without conducting a formal certainty assessment using the GRADE approach as this evidence will be of very low certainty.

Does regular use of activity and damage measures improve clinical outcomes for patients with SLE?

P26. In patients with SLE, does use of regular assessment instruments versus not using these instruments impact clinical outcomes?

Population: Patients with SLE

Intervention:

- Disease activity measure at each visit
- Disease damage measure yearly

Comparator: No measures at visits

Outcomes:

- SLE Flare rate
- Disease damage
- Mortality
- Comorbidities
- Quality of life

Evidence summary:

Six studies assessed the long-term outcome and prognosis of disease remission and low disease activity. Studies showed that disease activity predicts lower rates of mortality and organ damage but doesn't correlate with better quality of life.

(1) A longer duration in remission predicts lower rates of accrue damage and mortality. (2) Patients who spend more time in LLDAS (>50% of their time) predict lower SDI and lower flares (regardless of severity). (3) Patients in LLDAS or patients in DORIS had lower rates of flares on follow-up. (4) Higher SLEDAI predicts higher mortality rates and organ damage. (5) SDI damage (SDI>0) and PGA at baseline were independently predictive of damage accrual. (6) SLEDAI and SLICC were not correlated with quality-of-life measures, SF-12 (PCS MCS). (7) A longer duration in disease remission state or LLDAS was associated with lower rates of organ damage.

Table of studies:

Author	Design	Population	Outcomes
Alarco'n 2019	Retrospective Cohort	Patients in remission (SLAM score =0 and prednisone 5 mg/day and no immunosuppressants) or Low disease activity (LDAS) ((not in remission), SLAM score 3, prednisone 7.5 mg/day, no immunosuppressants), or neither: active.	The longer the patients were in remission/LDAS, the less likely they were to have: 1-Accrue damage, RR (95% CI): **0.1773(0.1216 to 0.2584)** 2-Mortality, OR (95% CI): **0.303 (0.063 to 1.456)**
Franklyn 2015	Retrospective Cohort	Achievement of LLDAS was determined in 191 patients followed for a mean of 3.9 years. **Definition of LLDAS:** (1) SLE Disease Activity Index (SLEDAI)-2K ≤4, with no activity in major organ systems (renal, central nervous system (CNS), cardiopulmonary, vasculitis, fever) and no haemolytic anaemia or gastrointestinal activity; (2) no new lupus disease activity compared with the previous assessment; (3) a Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA)-SLEDAI physician global assessment (scale 0– 3) ≤1; (4) a current prednisolone (or equivalent) dose ≤7.5 mg daily; and (5) well tolerated standard maintenance doses of immunosuppressive drugs and approved biological agents.	Patients who spent greater than 50% of their observed time in LLDAS were less likely to have: An increase in SDI of ≥1, RR (95% CI): **(0.47, 0.28 to 0.79).** Flares (regardless of severity), HR (95% CI): **0.63 (0.52 to 0.77)**
Gerosa 2022	Retrospective	Long-term data were available for 221 patients with a mean follow-up of 28.5 ± 6.6 years from diagnosis. At the end of the observation (28.5 ± 6.6 years from diagnosis), 129 patients were both in LLDAS and DORIS remission and 41 patients were neither in LLDAS or DORIS remission. Remission was classified according to attainment of lupus low- disease-activity state (LLDAS) criteria or the Definitions Of Remission In SLE (DORIS) parameters.	-Patients in LLDAS at the 20-year timepoint had nearly half the risk of a flare within the following ten years compared to patients who were not in LLDAS, **HR (95% CI): 0.487, (0.305 to 0.778)** -Similar results were observed considering the attainment of DORIS remission at 20 years of disease, **HR (95% CI): 0.611 (0.338 to 0.963)**
Hill 2021	Retrospective cohort	1168 patients with ≥24 months of follow-up from the Hopkins Lupus Cohort were included. Disease activity in a 12-month observation period was calculated using adjusted mean Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) version of the SLE Disease Activity Index (SLEDAI) During follow-up (median 7 years)	In adjusted models, an increased SELENA-SLEDAI score increased the risk of: -Death (**HR=1.22, 95% CI 1.13 to 1.32**) -Renal damage (**HR=1.24, 95% CI 1.08 to 1.42**) -Cardiovascular damage (**HR=1.17, 95% CI 1.07 to 1.29**).

			Without prior damage, an increased adjusted mean SELENA-SLEDAI score increased the risk of overall damage accrual (**HR=1.09, 95% CI 1.04 to 1.15**).
Apostolpoulos 2020	Prospective cohort	A SLEDAI-2K score of 0 was taken to indicate the absence of clinical and serological disease activity; a subset of patients without disease activity during the study were defined by a time-adjusted mean SLEDAI-2K (AMS) score of 0.	In the model including AMS score, baseline SDI damage (SDI >0) was independently associated with damage accrual**, HR (95% CI): 1.32 (1.01–1.73).** In the other model, time-adjusted mean PGA score was independently associated with damage accrual, **HR (95% CI): 1.05 (1.02–1.08).**
Jolly 2004	Retrospective cohort	Patients with SLE	Correlation coefficients between disease activity and quality of life. -SLICC and PCS (-0.27) -SLEDAI and PCS (-0.29) -SLICC and MCS (-0.02) -SLEDAI and MCS (-0.15)
Petri 2018	Retrospective cohort	1,356 SLE patients in the Hopkins Lupus Cohort, followed up quarterly, with 77,105 person-months observed from 1987 to 2016	<u>Duration in clinical remission on treatment:</u> -<25% in clinical remission was associated with a relatively low rate of damage compared to never achieving that condition, RR (95% CI): 0.54(0.44-0.67). **RR decreases as the month in clinical remission increases.** <u>Duration in LLDAS:</u> Those patients who experienced LLDAS at least 50% of the time had relatively low rates of damage: RR, (95%CI) 0.63 (0.48-0.84) **RR decreases as the month in LLDAS increases.**

References:

1. Alarcón GS, Ugarte-Gil MF, Pons-Estel G, Vilá LM, Reveille JD, McGwin G Jr. Remission and low disease activity state (LDAS) are protective of intermediate and long-term outcomes in SLE patients. Results from

LUMINA (LXXVIII), a multiethnic, multicenter US cohort. *Lupus*. 2019;28(3):423-426. doi:10.1177/0961203319826693
2. Franklyn K, Lau CS, Navarra SV, et al. Definition and initial validation of a Lupus Low Disease Activity State (LLDAS). *Ann Rheum Dis*. 2016;75(9):1615-1621. doi:10.1136/annrheumdis-2015-207726
3. Gerosa, Maria et al. "Long-Term Clinical Outcome in Systemic Lupus Erythematosus Patients Followed for More Than 20 Years: The Milan Systemic Lupus Erythematosus Consortium (SMiLE) Cohort." *Journal of clinical medicine* vol. 11,13 3587. 22 Jun. 2022, doi:10.3390/jcm11133587
4. Hill DD, Eudy AM, Egger PJ, Fu Q, Petri MA. Impact of systemic lupus erythematosus disease activity, hydroxychloroquine and NSAID on the risk of subsequent organ system damage and death: analysis in a single US medical centre. *Lupus Sci Med*. 2021;8(1):e000446. doi:10.1136/lupus-2020-000446
5. Factors associated with damage accrual in patients with systemic lupus erythematosus with no clinical or serological disease activity: a multicentre cohort study Apostolopoulos, Diane et al.The Lancet Rheumatology, Volume 2, Issue 1, e24 - e30
6. Jolly M, Utset TO. Can disease specific measures for systemic lupus erythematosus predict patients health related quality of life?. *Lupus*. 2004;13(12):924-926. doi:10.1191/0961203304lu2034oa
7. Petri M, Magder LS. Comparison of Remission and Lupus Low Disease Activity State in Damage Prevention in a United States Systemic Lupus Erythematosus Cohort. Arthritis Rheumatol. 2018;70(11):1790-1795. doi:10.1002/art.40571

Treatment of SLE

P28a. In patients with stable SLE, what is the impact of lowering prednisone to 2.5, 5 or 7.5 mg daily on clinical outcomes and adverse effects compared to maintaining prednisone 10 mg daily?

Population: Stable SLE
Intervention: Prednisone 2.5 mg/day
Comparison: Prednisone 10 mg/day
Outcomes:

- Type 2 Diabetes mellitus

Table 1.

P28. 2.5 mg/day vs 10 mg/day

Study name (year) country	Study design	Population	Intervention details	Comparator details	Outcomes with available data	Outcome measures	Outcome timepoint
Chen 2015 Taiwan	NRSI	Patients with SLE (not all patients had stable disease)	Patients receiving prednisone <7.5 mg daily	Patients receiving prednisone >10 mg daily	Type 2 Diabetes mellitus	RR	-

Evidence summary:
One non-randomized studies of intervention informed the comparison of prednisone 2.5 mg/day vs 10 mg per day. All outcomes had low certainty of evidence due to risk of bias and indirectness as not all patients had stable disease. This evidence is based on studies where patients received

different dosages of prednisone and not the direct impact of lowering the dosage. The evidence showed that lower prednisone dose 2.5 mg/day, lead to less T2DM absolute effect 8 fewer per 1,000 (from 23 fewer to 16 more).

Evidence profile:

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	2.5 mg/day	10 mg/day	Relative (95% CI)	Absolute (95% CI)	
T2DM											
1[1]	non-randomised studies	serious[a]	not serious	serious[b,c]	not serious	none	19/509 (3.7%)	77/1698 (4.5%)	RR 0.82 (0.50 to 1.35)	8 fewer per 1,000 (from 23 fewer to 16 more)	⨁⨁◯◯ Low[a,b,c]

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

Explanations

a. Risk of bias assessed using ROBINs-I, found high due to confounding.
b. Indirectness due to not all patients having stable SLE
c. Indirectness as different steroid preparations were used.

References

1. Chen YM, Lin CH, Lan TH, et al. Hydroxychloroquine reduces risk of incident diabetes mellitus in lupus patients in a dose-dependent manner: a population-based cohort study. *Rheumatology (Oxford)*. 2015;54(7):1244-1249. doi:10.1093/rheumatology/keu451

Included studies:

Randomized clinical trials:

Comparative non-randomized studies:

1 Study

Non-comparative studies (single arm): none

Studies read and exclude: none

P28b. In patients with stable SLE, what is the impact of lowering prednisone to 2.5, 5 or 7.5 mg daily on clinical outcomes and adverse effects compared to maintaining prednisone 10 mg daily?
Population: Stable SLE

Intervention: Prednisone 5 mg/day
Comparison: Prednisone 10 mg/day
Outcomes:

- Type 2 Diabetes mellitus

Table 1.

Study name (year) country	Study design	Population	Intervention details	Comparator details	Outcomes with available data	Outcome measures	Outcome timepoint
Chen 2015 Taiwan	NRSI	Patients with SLE (not all patients had stable disease)	Patients receiving prednisone <7.5 mg daily	Patients receiving prednisone >10 mg daily	Type 2 Diabetes mellitus	RR	-

Evidence summary:

One non-randomized studies of intervention informed the comparison of prednisone 2.5 mg/day vs 10 mg per day. All outcomes had low certainty of evidence due to risk of bias and indirectness as not all patients had stable disease. This evidence is based on studies where patients received different dosages of prednisone and not the direct impact of lowering the dosage. The evidence showed that lower prednisone dose 2.5 mg/day, lead to less T2DM absolute effect25 fewer per 1,000(from 30 fewer to 17 fewer).

Evidence profile:

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	5 mg/day	10 mg/day	Relative (95% CI)	Absolute (95% CI)	
T2DM											
1[1]	non-randomised studies	serious[a]	not serious	serious[b,c]	not serious	none	75/3670 (2.0%)	77/1698 (4.5%)	RR 0.45 (0.33 to 0.62)	25 fewer per 1,000 (from 30 fewer to 17 fewer)	⨁⨁◯◯ Low[a,b,c]

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

Explanations

a. Risk of bias assessed using ROBINs-I, found high due to confounding.
b. Indirectness due to not all patients having stable SLE
c. Indirectness as different steroid preparations were used.

References

Chen YM, Lin CH, Lan TH, et al. Hydroxychloroquine reduces risk of incident diabetes mellitus in lupus patients in a dose-dependent manner: a population-based cohort study. *Rheumatology (Oxford)*. 2015;54(7):1244-1249. doi:10.1093/rheumatology/keu451

Included studies:

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

P28c. In patients with stable SLE, what is the impact of lowering prednisone to 2.5, 5 or 7.5 mg daily on clinical outcomes and adverse effects compared to maintaining prednisone 10 mg daily?
Population: Stable SLE
Intervention: Prednisone 7.5 mg/day
Comparison: Prednisone 10 mg/day
Outcomes:

- SLEDAI
- Organ Damage
- Cataracts
- Fractures
- Infections
- Type 2 Diabetes mellitus

Table 1.
P28. 7.5 mg/day vs 10 mg/day

Study name (year) country	Study design	Population	Intervention details	Comparator details	Outcomes with available data	Outcome measures	Outcome timepoint
Sawah 2015 USA	NRSI	Patients with SLE (not all patients had stable disease)	Patients receiving prednisone <7.5 mg daily	Patients receiving prednisone >7.5 mg daily	Organ Damage Cataracts Fractures	Adjusted HR	6.2 years
Assunção 2022	NRSI	Patients with SLE	Patients receiving	Patients receiving	SLEDAI	Adjusted HR	120 months

Portugal		(not all patients had stable disease)	prednisone <7.5 mg daily	prednisone >7.5 mg daily			
Yang 2018 Taiwan	NRSI	Patients with SLE (not all patients had stable disease)	Patients receiving steroid (unspecified if prednisone) <7.5 mg daily	Patients receiving steroid (unspecified if prednisone) 7.5 – 15 mg/daily mg daily	Infections	HR	1 Year
Chen 2015 Taiwan	NRSI	Patients with SLE (not all patients had stable disease)	Patients receiving prednisone <7.5 mg daily	Patients receiving prednisone >10 mg daily	Type 2 Diabetes mellitus	RR	-

Evidence summary:

Four non-randomized studies of intervention informed the comparison of prednisone 10 mg/day vs 7.5 mg per day. All outcomes had low certainty of evidence due to risk of bias and indirectness as not all patients had stable disease. This evidence is based on studies where patients received different dosages of prednisone and not the direct impact of lowering the dosage. The evidence showed that higher prednisone dose 10mg/day, lead to more GC-related organ damage, infections, fractures, T2DM and cataracts with trivial to no effect on change is SLEDAI from baseline (HR 1.04 (1.03 to 1.06)).

Evidence profile:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	10 mg/day	7.5 mg/day	Relative (95% CI)	Absolute (95% CI)		
Organ Damage												
1[1]	non-randomised studies	serious[a]	not serious	serious[b]	not serious	none	884	1315	**HR 1.74** (1.50 to 2.02)		⨁⨁◯◯ Low[a,b]	CRITICAL
Fractures												
1[1]	non-randomised studies	serious[a]	not serious	serious[b]	not serious	none	884	1315	**HR 2.16** (1.55 to 3.01)		⨁⨁◯◯ Low[a,b]	CRITICAL
Cataracts												
1[1]	non-randomised studies	serious[a]	not serious	serious[b]	not serious	none	884	1315	**HR 2.41** (1.78 to 3.27)		⨁⨁◯◯ Low[a,b]	CRITICAL

Infections

1[2]	non-randomised studies	serious[a]	not serious	serious[b]	not serious	none	396	338	**HR 1.40** (0.78 to 2.51)		⨁⨁◯◯ Low[a,b]	CRITICAL

SLEDAI

1[3]	non-randomised studies	serious[a]	not serious	serious[b]	not serious	none	160	70	**HR 1.04** (1.03 to 1.06)		- ⨁⨁◯◯ Low[a,b]	CRITICAL

T2DM

1[4]	non-randomised studies	serious[a]	not serious	serious[b,c]	not serious	none	77/1698 (4.5%)	50/2751 (1.8%)	**RR 2.50** (1.76 to 3.54)	**27 more per 1,000** (from 14 more to 46 more)	⨁⨁◯◯ Low[a,b,c]	CRITICAL

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

Explanations

a. Risk of bias assessed using ROBINs-I, found high due to confounding.
b. Indirectness due to not all patients having stable SLE
c. Indirectness as different steroid preparations were used.

References:

- Al Sawah S, Zhang X, Zhu B, et al. Effect of corticosteroid use by dose on the risk of developing organ damage over time in systemic lupus erythematosus-the Hopkins Lupus Cohort. *Lupus Sci Med*. 2015;2(1):e000066. Published 2015 Mar 11. doi:10.1136/lupus-2014-000066
- Yang SC, Lai YY, Huang MC, Tsai CS, Wang JL. Corticosteroid dose and the risk of opportunistic infection in a national systemic lupus erythematosus cohort. *Lupus*. 2018;27(11):1819-1827. doi:10.1177/0961203318792352
- Assunção H, Rodrigues M, Prata AR, Luís M, da Silva JAP, Inês L. Predictors of hospitalization in patients with systemic lupus erythematosus: a 10-year cohort study. *Clin Rheumatol*. 2022;41(10):2977-2986. doi:10.1007/s10067-022-06251-7
- Chen YM, Lin CH, Lan TH, et al. Hydroxychloroquine reduces risk of incident diabetes mellitus in lupus patients in a dose-dependent manner: a population-based cohort study. *Rheumatology (Oxford)*. 2015;54(7):1244-1249. doi:10.1093/rheumatology/keu451

Included studies:

Randomized clinical trials:

Comparative non-randomized studies:

4 Studies

Non-comparative studies (single arm):

Studies read and exclude: none

P29. In patients with organ- threatening SLE, what is the impact of pulse methylprednisolone (250-1000 mg) followed by prednisone taper compared to prednisone taper only on clinical outcomes and adverse medication effects?

Population: Patients with organ threatening SLE flare
Intervention: Pulse therapy (250-1000 mg IV for 1-3 days) followed by prednisone taper
Comparator: Oral prednisone taper only
Outcomes:

- SLE disease activity
- SLE Flare
- Hypertension
- Fractures
- Infections
- T2DM
- Cataracts
- SDI (disease damage)
- Osteoporosis
- Quality of Life

Evidence summary: A study with 233 patients with different SLEDIA groups found that Pulse methylprednisolone had an OR (95% CI) of 2.5 (1.04-6.23) of prolonged remission of SLE (over at least five visits). It is worth noting that only a minority of the total population had organ-threatening lupus, and the authors did not report it as a subgroup. They do report on the association between MP and average prednisone doses in patients with severe activity (SLEDAI>12, most of them had lupus nephritis) and found that the regression coefficient (95%CI) is –11.23 (-21.2 to –1.18%). (1)

Evidence summary from a systematic review:
These results are extracted from a 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 lupus nephritis 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, while for the same dose of oral GC and without GC pulse, the predicted rates of CR, and serious infections were **19.5%** (7.3-31.5)and **3.2%** (2.4-4.0) respectively. The same applies to other doses of oral GC with or without pulse GC.

When comparing pulse GC versus no pulse steroids the rates of complete response were higher in the pulse GC group, while for serious adverse events, the rates were comparable between both arms. (see table below).

N.B: This evidence was derived from lupus nephritis and was presented for the previous guidelines as there was no evidence available for other organs.

References:

1-Ruiz-Irastorza G, Paredes-Ruiz D, Herrero-Galvan M, Moreno-Torres V, Hernandez-Negrin H, Ruiz-Arruza I, Leonard C, Richez C, Lazaro E. Methylprednisolone Pulses and Prolonged Remission in Systemic Lupus Erythematosus: A Propensity Score Analysis of the Longitudinal Lupus-Cruces-Bordeaux Inception Cohort. Arthritis Care Res (Hoboken). 2024 Aug;76(8):1132-1138. doi: 10.1002/acr.25334. Epub 2024 May 2. PMID: 38529678.

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

Supplementary Table 4. Meta-regression predicted rates

Meta-regression predicted rates of complete response, serious infections, and death at six months according to glucocorticoid starting dose (mg/day) and use or not of glucocorticoid pulses.

	Complete Response, % (95% CI)		Serious Infections, % (95% CI)		Death, % (95% CI)	
Dose, mg/day	Non-GC Pulses	GC Pulses	Non-GC Pulses	GC Pulses	Non-GC Pulses	GC Pulses
20	17.8 (6.5–29.2)	22.9 (9.2–36.7)	2.6 (2.0, 3.3)	2.9 (2.2, 3.6)	0.1 (0.0–0.3)	0.2 (0.0–0.4)
25	19.5 (7.3–31.5)	25.0 (10.4–39.6)	3.2 (2.4–4.0)	3.5 (2.6–4.4)	0.2 (0.0–0.4)	0.3 (0.0–0.6)
30	21.3 (8.3–34.4)	27.1 (11.7–42.5)	3.9 (3.0–4.9)	4.3 (3.2–5.3)	0.3 (0.0–0.6)	0.4 (0.0–0.8)
35	23.3 (9.4–37.2)	29.4 (13.2–45.6)	4.7 (3.5–6.0)	5.2 (3.9–6.5)	0.4 (0.0–0.8)	0.6 (0.0–1.2)
40	25.3 (10.6–40.0)	31.7 (14.8–48.7)	5.7 (4.3–7.1)	6.3 (4.7–7.8)	0.6 (0.0–1.2)	0.9 (0.0–1.8)
45	27.5 (11.9–43.0)	34.2 (16.6–51.8)	6.9 (5.2–8.6)	7.6 (5.8–9.4)	0.9 (0.0–1.7)	1.3 (0.0–2.6)
50	29.8 (13.4–46.1)	36.7 (18.5–55.0)	8.4 (6.4–10.4)	9.2 (7.0–11.3)	1.3 (0.0–2.5)	1.9 (0.0–3.8)
55	32.1 (15.1–49.2)	39.4 (20.6–58.1)	10.1 (7.7–12.4)	11.0 (8.4–13.6)	1.8 (0.0–3.6)	2.8 (0.1–5.6)
60	34.6 (16.9–52.3)	42.1 (22.9–61.2)	12.1 (9.3–14.9)	13.1 (10.1–16.2)	2.7 (0.0–5.3)	4.0 (0.1–7.9)

GC: glucocorticoids; CI: confidence interval.

P30a. In patients with active SLE (newly diagnosed or flare) on treatment with HCQ and prednisone > 20 mg daily for > 4 weeks, does initiating immunosuppressive therapy (conventional and/or biologic) result in better clinical outcomes and fewer adverse medication effects compared to continuing on HCQ and prednisone alone at 6-12 months?

P31a. In patients with SLE treated with HCQ and persistent (> six months) use of prednisone >7.5 mg daily, does initiation of immunosuppressive therapy with a steroid taper result in better clinical outcomes and fewer adverse medication effects compared to continuing with HCQ and daily prednisone?

Population: Active SLE

Intervention: Initiating immunosuppressive therapy
Comparison: Not Initiating immunosuppressive therapy
Outcomes:

- SLEDAI
- SLAM
- SF-36
- Adverse Events
- Organ Damage
- Fractures
- Infections

Table 1.

P30/31. IS vs No IS

Study name (year) country	Study design	Population	Intervention details	Comparator details	Outcomes with available data	Outcome measures	Outcome timepoint
Fortin 2008 Canada	RCT	Patients with at least moderately active SLE 40.2 (34 – 48.2)	Patients receiving Immunosuppressant (MTX)	Placebo	SLEDAI SLAM SF-36 Adverse Events	Mean Difference RR	1 Year
You 2024 China	RCT	Patients with active SLE	oral prednisone (0.5 mg/kg/d) and hydroxychloroquine sulfate (5 mg/kg/d) and MMF (500 mg twice daily) (MMF group) for 96 weeks	oral prednisone (0.5 mg/kg/d) and hydroxychloroquine sulfate (5 mg/kg/d)	SLE Flares LLDAS Organ Damage Adverse Events	RR	2 Years
Sawah 2015 USA	NRSI	Patients with SLE Mean of 32.9	Patients receiving Immunosuppressant Duration of prednisone was unspecified	Patients not receiving Immunosuppressant	Organ Damage Fractures	HR	6.2 years
Hidekawa 2023 (3772)	NRSI	Patients with SLE	Patients receiving Immunosuppressant	Patients not receiving	Infections	OR	1-5 years

Italy		Median of 45 (35–57)		Immunosuppressant			
MERAYO-CHALICO 2013 (5975) Mexico	NRSI	Patients with SLE Mean of 33.85	Patients receiving Immunosuppressant	Patients not receiving Immunosuppressant	Infections	OR	Mean of 6.2 years

Evidence summary:

PICO 30 and 31 were informed by 2 RCT and 3 NRSI. No distinction could be made in relation to the original GC dosages, therefore the evidence informs both PICO questions. In Fortin 2008 (RCT), Initiation of immunosuppressive therapy lead to greater reduction in GC dose, SlEDAI, SLAM, as well as quality of life. Immunosuppressive therapy also lead to reduction in SLE flare and organ damage and greater achievement of LLDAS. However, more adverse events (unspecified) occurred the initiation of immunosuppressive therapy group. All outcomes had very low certainty evidence due to risk of bias, imprecision and indirectness due to not all patients taking prednisone and HCQ. For the 3 NRSI, Initiation of immunosuppressive therapy lead to more infections, and more organ damage, with little to no effect on fractures. All outcomes had very low certainty evidence due to risk of bias, imprecision and indirectness due to not all patients taking prednisone and HCQ.

Evidence profile:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Initiation of immunosuppressive therapy	Continuing HCQ and prednisone	Relative (95% CI)	Absolute (95% CI)		
Change in GC dose from baseline												
1[1]	randomised studies	Serious [a]	not serious	Serious c	Serious [d]	none	41	45		MD **22.3 lower** (36.2 lower to 5.4 lower)	⊕◯◯◯ Very Low[a,b,c]	CRITICAL
Change in SLEDAI from baseline												
1[1]	randomised studies	Serious [a]	not serious	Serious[c]	Serious [d]	none	41	45		MD **0.86 lower** (1.71 lower to 0.02 lower)	⊕◯◯◯ Very Low[a,b,c]	CRITICAL
Change in SLAM from baseline												
1[1]	randomised studies	Serious [a]	not serious	Serious[c]	Serious [d]	none	41	45		MD **1.04 lower** (2.56 lower to	⊕◯◯◯ Very Low[a,b,c]	CRITICAL

										0.52 more)		
Change in SF-36 from baseline												
1[1]	randomised studies	Serious [a]	not serious	Serious[c]	Serious [d]	none	41	45		MD **1.77 lower** (0.31 lower to 3.85 more)	⊕◯◯◯ Very Low[a,b,c]	CRITICAL
Adverse Events												
2[1,5]	randomised studies	Serious [a]	not serious	Serious[c]	Serious [d]	none	68/106 (64.1%)	61/110 (55.5%)	**RR 1.7** (0.91 to 3.19)	**388 more per 1,000** (from 50 fewer to 1,000 more) 235 more)	⊕◯◯◯ Very Low[a,b,c]	CRITICAL
SLE Flare												
1[5]	randomised studies	Serious [a]	not serious	not serious	Serious [d]	none	28/65 (43.1%)	41/65 (63.1%)	**RR 0.44** (0.22 to 0.90)	**353 fewer per 1,000** (from 492 fewer to 63 fewer))	⊕⊕◯◯ Low[a,d]	CRITICAL
LLDAS												
1[5]	randomised studies	Serious [a]	not serious	not serious	Serious [d]	none	27/65 (41.5%)	23/65 (35.4%)	**RR 1.30** (0.64 to 2.63)	**106 more per 1,000** (from 127 fewer to 577 more)	⊕⊕◯◯ Low[a,d]	CRITICAL
Organ Damage												
1[5]	randomised studies	Serious [a]	not serious	not serious	Serious [d]	none	2/65 (3.1%)	5/65 (7.7%)	**RR 0.38** (0.07 to 2.04)	**48 fewer per 1,000** (from 72 fewer to 80 more)	⊕⊕◯◯ Low[a,d]	CRITICAL
Organ Damage												
1[2]	non-randomised studies	Serious[b]	not serious	Serious[c]	Serious [d]	none	417	1782	**HR 1.225** (1.046 to 1.434)		⊕◯◯◯ Very Low[b,c,d]	CRITICAL
Fractures												
1[2]	non-randomised studies	serious[b]	not serious	Serious[c]	not serious	none	417	1782	**HR 0.992** (0.975 to 1.01)		⊕⊕◯◯ Low[b,c]	CRITICAL
Infections												
2[3,4]	non-randomised studies	serious[b]	not serious	Serious[c]	Serious e	none	416	676	**OR 1.61** (1.09 to 2.37)		⊕⊕◯◯ Low[b,c]	CRITICAL

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

Explanations

a. Risk of bias assessed using ROBINs-I, found high due missing outcomes

b. Risk of bias assessed using ROBINs-I, found high due to confounding.
c. Indirectness due to not all patients taking prednisone and HCQ
d. Small number of patients
e. Wide CI crossing MID

References

1. Fortin PR, Abrahamowicz M, Ferland D, et al. Steroid-sparing effects of methotrexate in systemic lupus erythematosus: a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum*. 2008;59(12):1796-1804. doi:10.1002/art.24068
2. Al Sawah S, Zhang X, Zhu B, et al. Effect of corticosteroid use by dose on the risk of developing organ damage over time in systemic lupus erythematosus-the Hopkins Lupus Cohort. *Lupus Sci Med*. 2015;2(1):e000066. Published 2015 Mar 11. doi:10.1136/lupus-2014-000066
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5. You Y, Zhou Z, Wang F, et al. Mycophenolate Mofetil and New-Onset Systemic Lupus Erythematosus: A Randomized Clinical Trial. *JAMA Netw Open*. 2024;7(9):e2432131. Published 2024 Sep 3. doi:10.1001/jamanetworkopen.2024.32131

Included studies:

Randomized clinical trials:

2 RCT

Comparative non-randomized studies:

3 Studies

Non-comparative studies (single arm):

Studies read and exclude:

PICO# 32: In SLE patients in remission on HCQ and prednisone 5 mg daily, does tapering off prednisone result in better clinical outcomes and fewer adverse medication effects?

Population: SLE patients in remission on HCQ and prednisone 5 mg daily.

Intervention: Taper off prednisone.
Comparison: Continuing prednisone.
Outcomes:

- SLE flare
- SLE disease activity
- Adrenal insufficiency.
- Hypertension
- Fractures
- Infections
- T2DM
- Cataracts
- SDI (disease damage)
- Osteoporosis
- Quality of life

Table 1.

P32. Taper off prednisone vs continuing prednisone in patients with SLE in remission on HCQ and prednisone 5 mg/day							
Study Name (year) **Country**	**Study design**	**Population**	**Intervention details**	**Comparator details**	**Outcomes with available data**	**Outcome measure**	**Outcome timepoint**
Mathian A, 2020 France	RCT	18 years or older, with a diagnosis of SLE according to the revised ACR classification criteria; a clinically quiescent SLE for at least 1 year defined as: (1) SELENA-SLEDAI score ≤4, (2) D or E British Isles Lupus Assessment Group (BILAG) 2004 scores in all organ systems except for the haematological system, for which a C score due to leucopenia, lymphopenia or isolated positive	Taper off prednisone (Completely withdrawn prednisone on day 0)	Continuing prednisone 5 mg/day	- SLE flare (measured by SFI, BILAG index) - SDI (Damage): Defined as how many patients have an increase in SDI at week 52. - Adrenal insufficiency - Infections - Fractures	Risk ratio SLE flare: Risk ratio and hazard ratio	52 weeks

		Coombs' test was tolerated and (3) Physician's Global Assessment=0 and a treatment regimen including prednisone 5 mg/day. Prednisone, antimalarials and/or immunosuppressive therapy had to be stable for at least one consecutive year before inclusion. Age: Taper off group, mean±SD 44±1.6. Continuing group, mean±SD 41±1.7.			- Cataracts		

Evidence summary: There was 1 RCT in Caucasian population comparing taper off prednisone versus continuing prednisone in patients with SLE in remission on HCQ and prednisone 5 mg/day. This RCT has 124 patients, with 52 weeks of follow-up and address 6 outcomes, as follows: SLE flare, SDI, adrenal insufficiency, cataracts, infections, fractures and cataracts. The proportion of patients experiencing a flare was higher in the taper off group as compared with the continuing group (RR 4.12 (1.47 to 11.53) measured by both SFI and BILAG indexes). The HR of experience a SLE flare with the taper off strategy is 5 (2.04 to 12.25). The increase in SDI scale (damage) at 52 weeks was similar in the two treatment groups with 95% CI of RR crossing the one. Also, the adverse events (adrenal insufficiency, infections, fractures and cataracts) were similar in the two strategy treatments.
The evidence certainty for all the outcomes is low.

Evidence profile
Question: Taper off compared to Continuing Prednisone for SLE in remission
Bibliography: Mathian A, et al. Ann Rheum Dis 2020;79:339–346

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Taper off	Continuing Prednisone	Relative (95% CI)	Absolute (95% CI)	

SLE flare according to SFI

1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	17/63 (27.0%)	4/61 (6.6%)	**RR 4.12** (1.47 to 11.53)	**205 more per 1,000** (from 31 more to 690 more)	⊕⊕◯◯ Low[a,b]
SLE flare according to BILAG index											
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	17/63 (27.0%)	4/61 (6.6%)	**RR 4.12** (1.47 to 11.53)	**205 more per 1,000** (from 31 more to 690 more)	⊕⊕◯◯ Low[a,b]
SLE flare HR											
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	0/0	0/0	**HR 5.00** (2.04 to 12.25)	**5 fewer per 1,000** (from 12 fewer to 2 fewer)	⊕⊕◯◯ Low[a,b]
SDI											
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	3/63 (4.8%)	0/61 (0.0%)	**RR 6.78** (0.36 to 128.60)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕⊕◯◯ Low[a,b]
Adrenal Insufficiency											
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	1/63 (1.6%)	0/61 (0.0%)	**RR 2.91** (0.12 to 69.99)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕⊕◯◯ Low[a,b]
Infections											
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	1/63 (1.6%)	2/61 (3.3%)	**RR 0.48** (0.05 to 5.20)	**17 fewer per 1,000** (from 31 fewer to 138 more)	⊕⊕◯◯ Low[a,b]
Cataracts											
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	1/63 (1.6%)	0/61 (0.0%)	**RR 2.91** (0.12 to 69.99)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕⊕◯◯ Low[a,b]
Fractures											
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	2/63 (3.2%)	0/61 (0.0%)	**RR 4.84** (0.24 to 98.88)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕⊕◯◯ Low[a,b]

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

Explanations

a. Concerns with randomization, missing data, and outcome ascertainment.
b. Wide interval confidence in the overall result.

References

1.Mathian A, et al. Ann Rheum Dis 2020, 79:339–346. Withdrawal of low-dose prednisone in SLE patients with a clinically quiescent disease for more than 1 year: a randomised clinical trial.

Included studies:

Randomized clinical trials: 1
Comparative non-randomized studies: none
Non-comparative studies (single arm): none

Studies read and exclude: none

PICO 33: Does HCQ dose of > 5 mg/kg result in better clinical outcomes and control of flares in patients with SLE compared to a dose of <=5 mg/kg?

Population: Patients with SLE taking HCQ
Intervention: HCQ dose of >5 mg/kg day
Comparison: HCQ <or= 5 mg/kg day
Outcomes:

- SLE disease activity
- SLE flare
- SDI (disease damage)
- Retinal toxicity
- Cardiac toxicity
- Mortality

Table 1.

P33. HCQ dose of > 5 mg/kg day vs HCQ <or = 5 mg/Kg day in patients with SLE taking HCQ							
Study Name (year) Country	**Study design**	**Population**	**Intervention details**	**Comparator details**	**Outcomes with available data**	**Outcome measure**	**Outcome timepoint**
Costedoat-Chalumeau, N, 2013 France	RCT	Adults with a diagnosis of SLE according to the ACR classification criteria 12; have received HCQ treatment for at least 6 months; have not had their HCQ dose modified for 2 months; have a stable daily dose of HCQ (200 or 400 mg every day); have stable SLE with steroid dose no higher than 0.5 mg/kg/day of prednisone equivalent and not increased	HCQ > 5 mg/kg Groups by serum concentration, not weight-based dose. (This group HCQ ≥1000 ng/ml)	HCQ <= 5mg/kg Groups by serum concentration, not weight-based dose. (This group HCQ 100-750 ng/ml)	- SLE flare: SELENA-SLEDAI flare composite score, between randomization and month 7. Briefly, this score includes three elements: the SELENA-SLEDAI score; an assessment of new or worsening disease activity, medication	Risk ratio SLE flare: Risk ratio and odds ratio	7 months

		during the preceding 3 weeks; have had no modification of an immunosuppressant during the previous 2 months and have a SELENA-SLEDAI) ≤ 12 Age: mean±SD, 40±11			changes and hospitalizations not captured with the use of the SLEDAI; and the score on the physician's global-assessment visual analogue scale.		
Wakiya 2020	NRSI	Adults with a diagnosis of SLE according to the ACR classification Mean age: > 5 mg/kg: 40.3±12.4 < 5 mg/kg 46.1±9.3	HCQ > 5 mg/kg	HCQ <= 5mg/kg	SLEDAI, CLASI	MD	6 months
Jimenez 2023 USA	NRSI	Patients with adult-onset and childhood-onset SLE who met the ACR criteria tha were non smokers 30.6 (interquartile range [IQR] 22.3–41.6)	HCQ > 5 mg/kg	HCQ <= 5mg/kg	Arrythmias	Adjusted HR	7.9 years
Almeida-Brasil 2022 Multinational	NRSI	Newly Diagnosed Adults with a diagnosis of SLE according to the ACR classification	HCQ > 5 mg/kg	HCQ <= 5mg/kg	Retinal Toxicity	HR	1.2 years

		Mean age: 34.7					

Evidence summary: There was 1 RCT in Caucasian population comparing HCQ <5 mg/kg versus HCQ>=5 mg/kg in SLE patients taking HCQ. This RCT has 176 patients, with 7 months of follow-up and address just 1 outcome: SLE flare. The study shows there is no difference in SLE flares between the two strategies of treatments with a RR 1.10 (0.67 to 1.82). Three NRSI informed the this PICO question. In Wakiya et al, a higher dose (>5 mg/kg) lead to a greater change in SlEDAI and CLASI from baseline. In Jimenez, the hazard ratio for retinal toxicity was HR 0.45 (0.17–1.18). In Almeida-Brasil, the hazard ratio for retinal toxicity was 2.35 (0.69 to 8.04). The evidence certainty for these outcomes was low, and was very low for retinal toxicity.

Evidence profile

Question: HCQ dose >5 mg/kg compared to HCQ dose <=5 mg/Kg for SLE patients taking HCQ

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HCQ dose >5 mg/kg	HCQ dose <=5 mg/Kg	Relative (95% CI)	Absolute (95% CI)		
SLE flare												
1[1]	randomised trials	not serious	not serious	not serious	Very serious[a]	none	24/87 (27.6%)	21/84 (25.0%)	**RR 1.10** (0.67 to 1.82)	**25 more per 1,000** (from 82 fewer to 205 more)	⊕⊕◯◯ Low[a]	
SLE flare												
1[1]	randomised trials	not serious	not serious	not serious	Very serious[a]	none	87	84	**OR 0.26** (0.08 to 0.86)		⊕⊕◯◯ Low[a]	
Change of SLE disease activity (SLEDAI)												
1[2]	Non-randomised studies	Serious[b]	not serious	not serious	Serious[a]	none	46	15	**MD 1.20** (-0.43 – 2.83)		⊕⊕◯◯ Low[a]	
Change of SLE disease activity (CLASI)												
1[2]	Non-randomised studies	Serious[b]	not serious	not serious	Serious[a]	none	46	15	**MD 0.6** (-1.15 – 2.35)		⊕⊕◯◯ Low[a]	
Arrythmias												
1[3]	Non-randomised studies	Serious[b]	not serious	not serious	Serious[a]	none	159	135	**HR** 0.45 (0.17– 1.18)		⊕⊕◯◯ Low[a,b]	
Retinal Toxicity												
1[4]	Non-randomised studies	Serious[b]	not serious	not serious	Very serious[a]	none	821	603	**HR 2.35** (0.69 to 8.04)		⊕◯◯◯ Very Low[a,b]	

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

Explanations

a. Wide confidence interval.
b. Risk of bias was assessed using ROBINS-I, was found to be high due to no adjustment for confounding

References

1.Costedoat-Chalumeau N, et al. Ann Rheum Dis 2013, 72:1786–1792.Hydroxychloroquine in systemic lupus erythematosus: results of a French multicentre controlled trial (PLUS Study)
2. Wakiya R, Kameda T, Nakashima S, Shimada H, Fahmy Mansour MM, Kato M, Miyagi T, Kadowaki N, Dobashi H. Efficacy and Safety of Hydroxychloroquine Therapy for Systemic Lupus Erythematosus Patients Depend on Administration Dose. Intern Med. 2020 Sep 1;59(17):2105-2112. doi: 10.2169/internalmedicine.4317-19. Epub 2020 Jun 9. PMID: 32522920; PMCID: PMC7516317.
3. Jimenez AL, Valle A, Mustehsan MH, Wang S, Law J, Guerrero MS, Mowrey WB, Horton DB, Briceno D, Broder A. Association of Hydroxychloroquine Dose With Adverse Cardiac Events in Patients With Systemic Lupus Erythematosus. Arthritis Care Res (Hoboken). 2023 Aug;75(8):1673-1680. doi: 10.1002/acr.25052. Epub 2023 Feb 3. PMID: 36331104; PMCID: PMC10156898.
4. Almeida-Brasil CC, Hanly JG, Urowitz M, Clarke AE, Ruiz-Irastorza G, Gordon C, Ramsey-Goldman R, Petri MA, Ginzler EM, Wallace DJ, Bae SC, Romero-Diaz J, Dooley MA, Peschken C, Isenberg D, Rahman A, Manzi S, Jacobsen S, Lim SS, van Vollenhoven R, Nived O, Jönsen A, Kamen DL, Aranow C, Sánchez-Guerrero J, Gladman DD, Fortin PR, Alarcon GS, Merrill JT, Kalunian K, Ramos-Casals M, Steinsson K, Zoma A, Askanase AD, Khamashta M, Bruce IN, Inanc M, Lukusa L, Bernatsky S. Retinal toxicity in a multinational inception cohort of patients with systemic lupus on hydroxychloroquine. Lupus Sci Med. 2022 Nov;9(1):e000789. doi: 10.1136/lupus-2022-000789. PMID: 36396267; PMCID: PMC9677013.

Included studies:

Randomized clinical trials:

1

Comparative non-randomized studies:

3

Non-comparative studies (single arm):

Studies read and exclude:

PICO 34 In patients with SLE on HCQ, does measuring HCQ blood levels lead to improved clinical outcomes or fewer adverse medication effects than no measuring levels?

Population: Patients with SLE taking HCQ
Intervention: Checking HCQ (whole blood/serum) levels
Comparison: Not checking levels
Outcomes:

- Adherence to medication
- SLE disease activity
- SLE flare
- Retinal toxicity
- Cardiac toxicity
- Thrombosis

Table 1.

P34. Checking HCQ levels vs not checking levels in patients with SLE taking HCQ							
Study Name (year) **Country**	**Study design**	**Population**	**Intervention details**	**Comparator details**	**Outcomes with available data**	**Outcome measure**	**Outcome timepoint**
Costedoat-Chalumeau, N, 2013 France	RCT	Adults with a diagnosis of SLE according to the ACR classification criteria 12; have received HCQ treatment for at least 6 months; have not had their	**Checking HCQ levels** (This group has baseline HCQ 100-750 ng/ml, but they	**Not checking HCQ levels** (This group has baseline HCQ 100-750 ng/ml,	- SLE flare: SELENA-SLEDAI flare composite score, between randomization and month 7.	Risk ratio Odds ratio	7 months

		HCQ dose modified for 2 months; have a stable daily dose of HCQ (200 or 400 mg every day); have stable SLE with steroid dose no higher than 0.5 mg/kg/day of prednisone equivalent and not increased during the preceding 3 weeks; have had no modification of an immunosuppressant during the previous 2 months and have a SELENA-SLEDAI) ≤ 12 Age: mean±SD, 40±11	change the dose of HCQ to reach levels >=1000 ng/ml. Then, they introduce a change after they know the levels)	but they do not change the dose of HCQ throughout the follow up)	Briefly, this score includes three elements: the SELENA-SLEDAI score; an assessment of new or worsening disease activity, medication changes and hospitalizations not captured with the use of the SLEDAI; and the score on the physician's global-assessment visual analogue scale.		

Evidence summary: There was 1 RCT in Caucasian population comparing checking whole blood HCQ levels versus not checking HCQ levels in SLE patients taking HCQ. The specifically strategy used in this study is in a group of 176 patients with whole blood HCQ levels between 100-750 ng/ml, they divided patients in 2 groups: one group (not checking HCQ levels) they do not change the dose of HCQ the patient is already taken and the second group (checking HCQ levels) they change the doses to reach levels >1000 ng/ml.
This RCT has 7 months of follow-up and address just 1 outcome: SLE flare. The study shows there is no difference in SLE flares between the two strategies of treatments with a RR 1.10 (0.67 to 1.82).
In a multivariate analysis, they divided patients between >=1000 ng/ml and <1000 ng/ml (post randomization values). And low values (<1000 ng/ml) was associated with SLE flares throughout the entire follow-up, OR=3.82 (95% CI1.16 to 12.58); p=0.027).
The evidence certainty for this outcome is very low.

Evidence profile

Question: Checking HCQ blood levels compared to not checking HCQ blood levels in SLE patients taking HCQ

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Checking HCQ blood levels	not checking HCQ blood levels	Relative (95% CI)	Absolute (95% CI)	
SLE flare											
1	randomised trials	not serious	not serious	very serious[a]	serious[b]	none	24/87 (27.6%)	21/84 (25.0%)	**RR 1.10** (0.67 to 1.82)	**25 more per 1,000** (from 82 fewer to 205 more)	⨁◯◯◯ Very low[a,b]
SLE flare (Adjusted)											
1	randomised trials	not serious	not serious	very serious[a]	serious[b]	none	39	57	**OR 3.82** (1.16 to 12.58)	**4 fewer per 1,000** (from 13 fewer to 1 fewer)	⨁◯◯◯ Very low[a,b]

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

Explanations

a. In the group "not checking levels", they know the HCQ blood levels, but they do not change the dose of HCQ throughout the follow up. In fact, all this group have HCQ whole blood baseline values between 100-750 ng/ml. In the group "checking levels", the know the HCQ blood levels (all the group have levels between 100-750 ng/ml) and they intended to reach levels >=1000 ng/ml, increasing the dosing of HCQ in this group of patients.
b. One RCT, with very wide CI.

References

1.Costedoat-Chalumeau N, et al. Ann Rheum Dis 2013, 72:1786–1792.Hydroxychloroquine in systemic lupus erythematosus: results of a French multicenter controlled trial (PLUS Study)

Included studies:

Randomized clinical trials:

- 1

Comparative non-randomized studies:

Non-comparative studies (single arm):

Studies read and exclude:

PICO 35a In patients with SLE, does routine treatment with HCQ (regardless of other therapies), improve clinical outcomes compared to not treating with HCQ

Population: Patients with SLE
Intervention: Treating with HCQ (unless a contraindication)
Comparison: Not treating with HCQ
Outcomes:

- Flare risk
- Damage accrual
- Mortality
- Corticosteroid related adverse effects (osteoporosis, infection, diabetes)
- Retinal toxicity
- Cardiac toxicity (Prolonged QTc and/or myopathy)
- Thrombosis
- Quality of life

Table 1.

P35a. HCQ versus No HCQ

Study name (year) country	Study design	Population	Intervention details	Comparator details	Outcomes with available data	Outcome measures	Outcome timepoint
Bykerk 1991 (Canadian Hydroxychloroquine Study) Canada	RCT	SLE patients with stable disease for at least 3 months. Adults HCQ 45±13.9, placebo 44±15.7 years	Continue HCQ	Withdraw HCQ (and continue placebo)	Flare risk	Risk ratio	24 weeks / 6 months
Kraak 1965 Netherlands	RCT	Patients with discoid lupus Adults Age unknown	HCQ	Placebo	Complete response (cutaneous or articular), Adverse events, Retinal toxicity	Risk ratio	12 months
Williams 1994 USA	RCT	SLE patients Adults Average age: HCQ 41 years Placebo 43 years	HCQ	Placebo	SLE disease activity (Joint pain, PGA, PJC, SJC), Complete response (cutaneous or articular),	Risk ratio Standardized Mean difference	42 months

					Complete and partial response, Adverse events		
Yokogawa 2016 Japan	RCT	Active CLE (including SLE) patients Adults HCQ mean age 43.1 SD 12.8; placebo 41.6 SD 12.7	HCQ	Placebo	Complete and partial response, SLE disease activity (CLASI, Joint pain, PGA), Quality of life Adverse events, Serious adverse events, Infections	Risk ratio, Standardized Mean difference, Mean difference	16 weeks
Grimaldi 2024	NRSI	SLE patients Adults No HCQ: 60.08(15.45), HCQ:55.48(11.21)	HCQ	No HCQ	Thrombotic Events	Adjusted OR	12 months
Hoque 2023	NRSI	SLE patients Adults	HCQ	No HCQ	Arrythmias	OR	8 years
Sakai 2020	NRSI	SLE patients Adults	HCQ	No HCQ	Infections	HR	8 months

Evidence summary: There were 4 RCTs with data for addressing the use of HCQ versus no HCQ in patients with SLE. One small RCT demonstrated that the use of HCQ reduced the risk of SLE flares at 24 weeks (RR 0.5, 95% CI 0.28-0.89) with low certainty due to imprecision. The use of HCQ also demonstrated higher rates of complete response (or complete remission) for cutaneous or articular domains in data derived from two RCTs (RR 2.86, 95% CI 1.47-5.56) with low certainty. SLE disease activity was not different between patients receiving or not receiving HCQ, but the data was scarce and came mostly from two small RCTs focused on articular and cutaneous manifestations, these trials were also inconsistent by assessing the outcomes at 16 weeks and 48 weeks (see below). Only one RCTs reported the quality of life outcome and it was improved among patients receiving HCQ against not receiving it but imprecise (MD -3.1, 95% CI -9.74 to 3.54).

There was no difference between HCQ and No HCQ groups in adverse events, retinal toxicity (short term, 16 weeks), or serious adverse events. Based on evidence from NRSI, arrythmias were similar between HCQ use and no use, as well as infections, while HCQ lead to lower risk of CV events (MI, Stroke,PE, VTE) (aOR(0.63 (0.51-0.78) Other comparative studies that looked at the adverse events of multiple rheumatological diseases however were not included as we utilized the best available evidence.

Evidence profile:

Certainty assessment							№ of patients		Effect		Certainty	
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HCQ	No HCQ	Relative (95% CI)	Absolute (95% CI)		
Flare risk												
1[1]	randomised trials	serious[b]	not serious	not serious	very serious[a]	none	9/25 (36.0%)	16/22 (72.7%)	**RR 0.50** (0.28 to 0.89)	**364 fewer per 1,000** (from 524 fewer to 80 fewer)	⨁◯◯◯ Very Low[a,b]	
SLE disease activity (joint pain)												
2[3,4]	randomised trials	serious[b]	serious[c]	not serious	serious[a]	none	68	29	-	SMD **0.13 higher** (0.33 lower to 0.58 higher)	⨁◯◯◯ Very low[a,b,c]	
SLE disease activity (PGA)												
2[3,4]	randomised trials	serious[b]	not serious	not serious	serious[a]	none	103	43	-	MD **0.24 higher** (0.17 lower to 0.66 higher)	⨁⨁◯◯ Low[a,b]	
SLE disease activity (CLASI)												
1[4]	randomised trials	not serious	not serious	not serious	very serious[a]	none	77	26	-	MD **1.4 lower** (3.73 lower to 0.93 higher)	⨁⨁◯◯ Low[a]	
SLE disease activity (PJC)												
1[3]	randomised trials	serious[b]	not serious	not serious	very serious[a]	none	26	17	-	MD **4.6 lower** (10.7 lower to 1.5 higher)	⨁◯◯◯ Very low[a,b]	
SLE disease activity (SJC)												
1[3]	randomised trials	serious[b]	not serious	not serious	very serious[a]	none	26	17	-	MD **1.7 higher** (1.63 lower to 5.03 higher)	⨁◯◯◯ Very low[a,b]	
Complete response (cutaneous or articular)												
2[2,3]	randomised trials	serious[b]	not serious	not serious	very serious[a]	none	16/60 (26.7%)	7/56 (12.5%)	**Risk Difference: 0.20 [0.10 , 0.30]**	-	⨁◯◯◯ Very low[a,b]	
Complete and partial response												
2[3,4]	randomised trials	not serious	not serious	not serious	serious[a]	none	53/78 (67.9%)	28/41 (68.3%)	**RR 1.13** (0.91 to 1.41)	**89 more per 1,000** (from 61 fewer to 280 more)	⨁⨁⨁◯ Moderate[a]	
Quality of life												
1[4]	randomised trials	not serious	not serious	not serious	very serious[a]	none	77	26	-	MD **3.1 lower** (9.74 lower to 3.54 higher)	⨁⨁◯◯ Low[a]	
Retinal toxicity												
1[2]	randomised trials	serious[b]	not serious	not serious	very serious[a]	none	1/20 (5.0%)	0/25 (0.0%)	**RR 3.71** (0.16 to 86.55)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low[a,b]	
Adverse events												
3[2,3,4]	randomised trials	serious[b]	not serious	not serious	serious[a]	none	72/137 (52.6%)	26/82 (31.7%)	**RR 1.13** (0.88 to 1.46)	**41 more per 1,000** (from 38 fewer to 146 more)	⨁⨁◯◯ Low[a,b]	
Serious adverse events												
1[4]	randomised trials	not serious	not serious	not serious	very serious[a]	none	1/77 (1.3%)	1/26 (3.8%)	**RR 0.34** (0.02 to 5.21)	**25 fewer per 1,000** (from 38 fewer to 162 more)	⨁⨁◯◯ Low[a]	

Infection

1[5]	Non-randomised studies	serious[d]	not serious	not serious	serious[c]	none	1095	1095	**HR 0.87** (0.57 to 1.31)	-	⨁⨁◯◯ Low[d,e]	

Arrythmias

1[6]	Non-randomised studies	Very serious[d]	not serious	not serious	not serious	none	11518	11518	**OR 0.96** (0.9 to 1.03)	-	⨁⨁◯◯ Low[d]	

Thrombotic Events (CV Events: MI,Stroke,PE,VTE)

1[7]	Non-randomised studies	Very serious[d]	not serious	not serious	not serious	none	10,141	7,647	**aOR 0.63** (0.57 to 0.70)	**25 fewer per 1,000** (from 38 fewer to 162 more)	⨁⨁◯◯ Low[a]	

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

Explanations

a. Very small number of patients.
b. Concerns regarding randomization process and outcome measurement.
c. Differences in timepoints of evaluation (16 weeks vs. 48 weeks).
d. Concerns regarding selection bias
e. wide confidence interval

References

1. Canadian Hydroxychloroquine Study Group. A Randomized Study of the Effect of Withdrawing Hydroxychloroquine Sulfate in Systemic Lupus Erythematosus. N Engl J Med. 1991;324(3):150–4.
2. Kraak JH, Ketel WG van, Prakken JR, Zwet WR van. The Value of Hydroxychloroquine (Plaquenil) for the Treatment of Chronic Discoid Lupus Erythematosus; a Double Blind Trial. Dermatology. 1965;130(5):293–305.
3. Williams HJ, Egger MJ, Singer JZ, Willkens RF, Kalunian KC, Clegg DO, et al. Comparison of hydroxychloroquine and placebo in the treatment of the arthropathy of mild systemic lupus erythematosus. J Rheumatol. 1994;21(8):1457–62.
4. Yokogawa N, Eto H, Tanikawa A, Ikeda T, Yamamoto K, Takahashi T, et al. Effects of Hydroxychloroquine in Patients With Cutaneous Lupus Erythematosus: A Multicenter, Double-Blind, Randomized, Parallel-Group Trial. Arthritis Rheumatol. 2017;69(4):791–9.
5. Sakai 2020
6. Hoque 2023
7. Grimaldi 2024

Included studies:

Randomized clinical trials:

- 4

Comparative non-randomized studies:
3
Non-comparative studies (single arm): none

Studies read and exclude: none

PICO 36: In patients with SLE who have achieved remission, does discontinuation of therapy at a particular time point affect clinical outcomes when compared to continuing therapy?

Population:

- Patients with SLE who have achieved remission
- Patient with SLE who have achieved low disease activity

Intervention:

- Discontinuation of immunosuppressive therapy
- Discontinuation of HCQ

Comparison: Not discontinuing therapy
Outcomes:

- Flare risk
- Damage accrual
- Mortality
- Corticosteroid related adverse effects of osteoporosis and diabetes
- Immunosuppressive therapy related adverse effects of infection and cytopenias for immunosuppressive therapy
- HCQ related adverse effects of retinal toxicity and cardiac toxicity (prolonged QTc and myopathy) for HCQ therapy
- Quality of life

Table 1.
P35. Discontinuation versus No discontinuation therapy

Study name (year) country	Study design	Population	Intervention details	Comparator details	Outcomes with available data	Outcome measures	Outcome timepoint
Bykerk 1991 (Canadian Hydroxychloroquine Study) Canada	RCT	SLE patients with stable disease for at least 3 months. Adults HCQ 45±13.9, placebo 44±15.7 years	Withdraw HCQ (and continue placebo)	Continue HCQ	Flare risk	Risk ratio	24 weeks / 6 months
Meinao 1996 Brazil	RCT	SLE patients Adults Age 33 and 31 years	Placebo	Chloroquine diphosphate	Flare risk	Risk ratio	12 months

Zen 2019 Italy	NRSI	SLE patients taking IS Adults 45 (13) years	Discontinuing IS at >1 year	Discontinuing IS at >2 year Discontinuing IS at >3 year	SLE Flare	OR	Up to 4 years
Chakravarty 2024 USA	RCT	SLE patients taking MMF a clinical SLEDAI score of less than 4 Adults (42 (SD 12·7)	Discontinuing MMF after at least 2 years	Maintenance MMF	SLE Flare Adverse events Infections	Risk Ratio	1 year

Evidence summary: There were two RCTs with data for addressing the discontinuation versus continuing HCQ in patients with SLE and one RCT for IS. The outcome of interest assessed by these two RCTs was the risk of flares, while for the RCT comparing MMF discontinuation vs Maintenance the outcomes were flares, adverse events and infections. The discontinuation of antimalarials (Hydroxychloroquine or Chloroquine) gives a higher risk of SLE flares (RR 2.33, 95% CI 1.37-3.95) with low certainty due to concerns in risk of bias and imprecision. For the one RCT on MMF, discontinuing MMF may lead to higher risk of flares (RR 1.87 (0.67 to 5.20). There may be no to little difference in the adverse events between discontinuation and maintenance (1.02 (0.89 to 1.16), however may have higher risk of infection (RR 1.39 (0.97 to 1.99)). Data odds of flare after discontinuing IS for one year was 0.31 (0.115 – 0.859), 2 years 0.19 (0.068 – 0.569), 3 years 0.14 (0.039 – 0.534)

Evidence profile:

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	discontinuation of therapy	continuing therapy	Relative (95% CI)	Absolute (95% CI)	
SLE flare (HCQ)											
2[1,2]	randomised trials	serious[a]	not serious	not serious	Very Serious[b]	none	26/34 (76.5%)	11/36 (30.6%)	**RR 2.33** (1.37 to 3.95)	**406 more per 1,000** (from 113 more to 901 more)	⊕◯◯◯ Very Low[a,b]
SLE flare (IS)											
1[3]	randomised trials	serious[a]	not serious	not serious	Serious[b]	none	9/50 (18%)	5/52 (9.6%)	**RR 1.87** (0.67 to 5.20)	84 more per 1,000 (from 32	⊕⊕◯◯ Low[a,b]

										fewer to 404 more)	

Adverse Events (IS)

1[3]	randomised trials	serious[a]	not serious	not serious	Serious[b]	none	45/50 (90%)	46/52 (88%)	**RR 1.02** (0.89 to 1.16)	**18 more per 1,000** (from 97 fewer to 142 more)	⊕⊕◯◯ Low[a,b]

Infections (IS)

1[3]	randomised trials	serious[a]	not serious	not serious	Serious[b]	none	32/50 (64%)	24/52 (46%)	**RR 1.39** (0.97 to 1.99)	**180 more per 1,000** (from 14 fewer to 457 more) 3 more to 901 more)	⊕⊕◯◯ Low[a,b]

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

Explanations

a. Concerns regarding randomization
b. Small number of patients.

References

1. Canadian Hydroxychloroquine Study Group. A Randomized Study of the Effect of Withdrawing Hydroxychloroquine Sulfate in Systemic Lupus Erythematosus. N Engl J Med. 1991;324(3):150–4.

2. Meinão I, Sato E, Andrade L, Ferraz M, Atra E. Controlled trial with chloroquine diphosphate in systemic lupus erythematosus. Lupus. 1996;5(3):237–41.

3. Chakravarty EF, Utset T, Kamen DL, Contreras G, McCune WJ, Aranow C, Kalunian K, Massarotti E, Clowse MEB, Rovin BH, Lim SS, Majithia V, Dall'Era M, Looney RJ, Erkan D, Saxena A, Olsen NJ, Ko K, Guthridge JM, Goldmuntz E, Springer J, D'Aveta C, Keyes-Elstein L, Barry B, Pinckney A, McNamara J, James JA. Mycophenolate mofetil withdrawal in patients with systemic lupus erythematosus: a multicentre, open-label, randomised controlled trial. Lancet Rheumatol. 2024 Mar;6(3):e168-e177. doi: 10.1016/S2665-9913(23)00320-X. Epub 2024 Jan 29. PMID: 38301682; PMCID: PMC10922882.

Intervention	Number of Patients	SLE Flare (OR (95% CI))
Discontinuing IS at >1 year	105	0.31 (0.115 – 0.859)
Discontinuing IS at >2 year	105	0.19 (0.068 – 0.569)
Discontinuing IS at >3 year	105	0.14 (0.039 – 0.534)

Included studies:

Randomized clinical trials:
- 2

Comparative non-randomized studies:
- **1**

Non-comparative studies (single arm):

Studies read and exclude:

Leukopenia

P37. In SLE patients with leukopenia, does adding, changing, or discontinuing immunosuppressive therapy improve clinical outcomes?

Population: SLE patients (may be on HCQ)
- Leukopenia not on immunosuppressive medication.
- Leukopenia on immunosuppressive medication (AZA, MMF/MPA, MTX or biologic therapy)

Intervention:
1. For non-immunosuppressed patients: addition of
   - Azathioprine
   - MMF/MPA
   - Glucocorticoid
2. For patients on immunosuppressants:
   - Stopping or lowering immunosuppressive therapy

Comparator:
- No treatment (or HCQ alone) (for patients not on immunosuppressive medications)
- Continuing therapy at same dose (for patients on immunosuppressive medications)

Outcomes:
1. WBC count (increase, decrease or no change)
2. Infection
3. Mortality
4. Disease flare
5. Disease damage

Summary of Evidence:

A limited evidence for this PICO question from four studies [(1), (2), (3), (4)] suggests that in patients with SLE and leukopenia who were treated with rituximab a leukocyte count increased from the mean 2.4 (0.5) up to 4.6 (0.7) [(2)], in patients treated with MMF leukopenia was decreased from 77% down to 62% [(3)], and that in SLE patients with refractory leukopenia a response rate to treatment with belimumab was 50% at 3 months and 65% at 6 months [(1)]. One study had patients with neutropenia treated with prednisone and immunosuppresives with infection rate of 75.7% [(1)].

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 rate	Fanouriakis, 2018, 2703	Single-arm	6 months	12 SLE patients with leukopenia refractory to at least one conventional immunosuppressant	Belimumab in combination with at least one disease modifying agent, HCQ (≥80%), followed by AZA and MTX	6/12 (50%) at 3 months 8/12 (65%) at 6 months	
Leukocyte count	Garcia-Carrasco, 2010, 3111	Single-arm	6 months	3 patients with leukocytopenia	Rituximab 1g plus 500 mg of IV MP on days 1 and 15	mean leukocyte counts increased from 2.4 (0.5) x 10^9/l to 4.6 (0.7) 10^9/l at 6 months	
Leukopenia	Tselios, 2016, 9155	Single-arm	12 months	13 patients with leukopenia and thrombocytopenia	MMF mean dose was 1350 ± 712.5 mg/day at baseline, 1512.5 ± 725 mg/day at 6 months, and 1662.5 ± 800 mg/day at 12 months	10/13 (77%) at 6 months, 8/13 (62%) at 12 months	
Infection	Martinez-Banos, 2006, 5724	Single-arm study	Not specified	33 cases of neutropenia (neutrophil count < 1000/ll) in patients with SLE	Prednisolone and mixed immunosuppresive drugs	25/33 (75.7%)	

References:

1. Fanouriakis A, Adamichou C, Koutsoviti S, Panopoulos S, Staveri C, Klagou A, et al. Low disease activity-irrespective of serologic status at baseline-associated with reduction of corticosteroid dose and number of flares in patients with systemic lupus erythematosus treated with belimumab: A real-life observational study. Seminars in arthritis and rheumatism. 2018;48(3):467-74.

2. Garcia-Carrasco M, Mendoza-Pinto C, Sandoval-Cruz M, Soto-Vega E, Beltran-Castillo A, Jimenez-Hernandez M, et al. Anti-CD20 therapy in patients with refractory systemic lupus erythematosus: a longitudinal analysis of 52 Hispanic patients. Lupus. 2010;19(2):213-9.
3. Tselios K, Gladman DD, Su J, Urowitz MB. Mycophenolate Mofetil in Nonrenal Manifestations of Systemic Lupus Erythematosus: An Observational Cohort Study. The Journal of rheumatology. 2016;43(3):552-8.
4. Martínez-Baños D, Crispín JC, Lazo-Langner A, Sánchez-Guerrero J. Moderate and severe neutropenia in patients with systemic lupus erythematosus. Rheumatology (Oxford, England). 2006;45(8):994-8.

Thrombocytopenia

P38. In SLE patients with thrombocytopenia that is chronic and asymptomatic, does addition of immunosuppressive medication impact clinical outcomes compared to not adding medication?

Population: SLE patients with thrombocytopenia (on HCQ or no therapy) that is chronic and asymptomatic:

- >50,000
- 10,000-50,000
- <10,000

Intervention:

- Glucocorticoid therapy
- Immunosuppressive therapy
- Biologic therapy

Comparator:

- No therapy or HCQ alone

Outcomes:

- Life-threatening bleed
- Mortality
- Treatment related adverse effects (infection)
- Disease flare
- Disease damage

P39. In SLE patients with acute and progressive thrombocytopenia on HCQ or no therapy, does addition of immunosuppressive therapy (or thrombopoietin agonists, or surgery) to glucocorticoid therapy lead to improved clinical outcomes compared to glucocorticoid therapy alone?

Populations: SLE patients with thrombocytopenia (on HCQ or no therapy), that is acute, progressive and symptomatic:

- >50,000
- 10,000 – 50,000
- <10,000

Intervention:

- Glucocorticoid therapy (high dose) plus
  - Immunosuppressive therapy
    - AZA
    - MMF/MPA
    - Cyclosporine
  - Anti-CD20 therapy
  - Splenectomy
  - IVIG
  - Eltrombopag

Comparator:

- Glucocorticoid therapy

Outcomes:

- Life-threatening bleed
- Mortality
- Treatment related adverse effects (infection)
- Disease flare
- Disease damage

Patient important outcomes (addressed in the study only):

Summary of Evidence: 3 comparative studies
-1 study (Arnal 2001, 523) included pediatric patients.
-1 comparative studies (Sun 2020, 8713) assessed P38 alone.
-2 comparative (Li 2023, 5197; Arnal 2001, 523), 5 single arm (Jung 2016, 4379; Hakim 1998, 3549; Zhou 2013, 10284; Levy 1999, 5167; Tselios 2016, 9155) assessed P38/P39. *In these studies, it wasn't specified whether it is acute or chronic thrombocytopenia.*
-1 non comparative (but comparing different IS) and addressing PICO 39 (patients with severe ITP, less than 30,000) was included.

N.B: Zhang 2018 and Ziakas 2005 are comparative but they pooled all immunosuppressive therapies together, that's why we didn't include in the evidence profiles but we kept their data in the tables below because of the scarcity of evidence.

P38. Comparative data (1 study only)

Evidence summary:

Sun 2020 (8713): 43 with SLE-ITP <50K. Retrospective cohort of 83 adults with CTD-ITP (43 SLE (2012 SLICC); 24 UCTD; 16 pSS) with refractory ITP that compared rituximab (32/43=74%) vs CsA (11/43=26%) among those with SLE-ITP and assessed responsiveness, mortality, bleed, infection. Greater response was seen among those taking rituximab (Response – complete+partial 32/53=60%; complete only 30/53=57%; partial only 13/53=25%) than CsA (Response – complete+partial 11/30=37%; complete only 12/30=40%; partial only 4/30=13%). Mortality was greater in CSA than rituximab (2/3=67% vs 1/3=33%), though infections were more common in rituximab than CSA (13/20=65% vs 7/20=35%). Life-threatening bleeds were present in both treatments (1/2=50% in each). Overall, infections and life-threatening bleeds among individuals taking rituximab for refractory ITP were common; however, there was a greater overall response (complete and partial) in that treatment cohort.
The overall certainty of very low due to risk of bias, indirectness (not all are SLE), imprecision.

Evidence profile:

Certainty assessment							№ of patients		Effect		Certainty	
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GC plus Rituximab	GC plus Cyclosporin	Relative (95% CI)	Absolute (95% CI)		
Response (complete plus partial)												
1[1]	non-randomised studies	serious[a]	not serious	serious[b]	very serious[c]	none	32/53 (60.4%)	11/30 (36.7%)	**RR 1.65** (0.98 to 2.77)	**238 more per 1,000** (from 7 fewer to 649 more)	⊕◯◯◯ Very low	
Mortality												
1[1]	non-randomised studies	serious[a]	not serious	serious[b]	very serious[c]	none	1/3 (33.3%)	2/3 (66.7%)	**RR 0.50** (0.08 to 2.99)	**333 fewer per 1,000** (from 613 fewer to 1,000 more)	⊕◯◯◯ Very low	
Life threatening bleed												

1[1]	non-randomised studies	serious[a]	not serious	serious[b]	very serious[c]	none	1/2 (50.0%)	1/2 (50.0%)	**RR 1.00** (0.14 to 7.10)	**0 fewer per 1,000** (from 430 fewer to 1,000 more)	⊕◯◯◯ Very low	

Infections

1[1]	non-randomised studies	serious[a]	not serious	serious[b]	very serious[c]	none	13/20 (65.0%)	7/20 (35.0%)	**RR 1.86** (0.94 to 3.66)	**301 more per 1,000** (from 21 fewer to 931 more)	⊕◯◯◯ Very low	

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

Explanations

a. We downgraded for risk of bias because of selection bias and confounding (no adjustment)
b. Not all patients were patients with SLE, some were with SS and other autoimmune diseases
c. We downgraded for imprecision, because of the very small sample size and number of events leading to a wide confidence interval

References:

1-Sun F, Chen J, Wu W, et al. Rituximab or cyclosporin in refractory immune thrombocytopenia secondary to connective tissue diseases: a real-world observational retrospective study. *Clin Rheumatol*. 2020;39(10):3099-3104. doi:10.1007/s10067-020-05152-x

P38.P.39 Comparative data (2 studies)

Evidence summary: 2 nonrandomized comparative studies, compared the outcomes for glucocorticoids alone versus other immunosuppressive therapies (AZA, cyclosporin) or IVIG or splenectomy. For Arnall 2001, they assessed response (partial or complete) on long-term or sustained response and all patients had thrombocytopenia of less than 50k. For li 2023 they don't mention whether this is a transient or sustained response thrombocytopenia of less than 30,000. The certainty of evidence is very low because of the critical risk of bias and very serious imprecision.
The response rate was higher in patients undergoing splenectomy with RR CI of 2.78 (1.47 to 5.26). For the other comparisons, the confidence intervals were very wide and the sample size very small which made it very difficult to conclude.

N.B: *These studies don't report whether thrombocytopenia is acute or chronic and asymptomatic*

Data for each study:

- Li 2023 (5197): 65 with SLE-ITP ≤30K. Retrospective cohort of 65 adults with SLE (2012 SLICC). LN, NPSLE, myocarditis, lupus pneumonitis, myositis, and severe vasculitis were excluded. Initial response to induction was higher in GC alone (10/13=77%) than GC+IVIG (23/34=68%); however, disease flares were more common in those who had received GC alone (3/13=23%) vs GC+IVIG (11/34=32%). Maintenance consisted of 4 groups – GC alone, GC+HCQ, GC+HCQ+ISA, GC+ISA (ISA: 1+ of AZA, MMF, CsA/tacrolimus, CTX, or RTX). Complete response alone was achieved from greatest to least frequency with GC+HCQ+ISA (20/27=74%); GC+HCQ (22/30=73%); GC alone (2/3=67%); GC+ISA (3/5=60), while complete+partial response was seen with greatest to least frequency among GC+HCQ+ISA (21/27=78%); GC +ISA (3/5=60%); GC+HCQ (22/30=73%); GC alone (0/3=0). Flares were most common in those with GC alone (3/3=100%), followed by GC+ISA (2/5=40%); GC+HCQ (8/30=27%); least common in GC+HCQ+ISA (6/27=22%). In summary, individuals exposed to IVIG at induction were less likely to have disease exacerbations at follow up. Individuals who were treated with combination GC+HCQ+ISA or GC+HCQ tended to have better response and fewer exacerbations of ITP than those with GC+ISA or GC+HCQ.

- Arnal 2001 (523): 44 with SLE-ITP <50K. Retrospective cohort of 59 adults/pediatric with definite (44/59) or incomplete (15/59) SLE (1982 ACR) associated with ITP. Diagnosis of TTP was

excluded. At long term follow up, response (complete+partial) varied among treatments from most to least: No therapy or HCQ alone (7/11=64%); GC+splenectomy (11/18=61%); GC alone (11/50=22%), IS alone (2/14=14%); GC+IVIG (0/31=0). Flares among splenectomized patients were (7/18=39%) similar to non-splenectomized (11/41=27%) p=0.4. NB: Many of the incomplete SLE had APLa+/VDRL+ so unlikely that they should be included as SLE.

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Evidence profile:

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Glucocorticoid therapy (high dose) plus other treatment	Glucocorticoid therapy alone	Relative (95% CI)	Absolute (95% CI)	
Response (complete plus partial): GC versus GC plus AZA											
1[1]	non-randomised studies	serious[a]	not serious	not serious	very serious[b]	none	0/3 (0.0%)	11/50 (22.0%)	**RR 0.55** (0.04 to 7.79)	**99 fewer per 1,000** (from 211 fewer to 1,000 more)	⨁◯◯◯ Very low
Response (complete plus partial): GC versus GC plus Cyclosporin											
1[1]	non-randomised studies	serious[a]	not serious	not serious	very serious[b]	none	0/4 (0.0%)	11/50 (22.0%)	**RR 0.44** (0.03 to 6.46)	**123 fewer per 1,000** (from 213 fewer to 1,000 more)	⨁◯◯◯ Very low
Response (complete plus partial): GC versus GC plus splenectomy											
1[1]	non-randomised studies	serious[a]	not serious	not serious	very serious[b]	none	11/18 (61.1%)	11/50 (22.0%)	**RR 2.78 (1.47 to 5.26)**	**392 more per 1,000 (from 103 more to 937 more)**	⨁◯◯◯ Very low
Response (complete plus partial): GC versus GC plus IVIG											
2[1,2]	non-randomised studies	serious[a]	not serious	not serious	very serious[b]	none	23/65 (35.4%)	21/63 (33.3%)	**RR 0.84** (0.58 to 1.22)	**53 fewer per 1,000** (from 140 fewer to 73 more)	⨁◯◯◯ Very low

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

Explanations

a. We downgraded for risk of bias because of selection bias and confounding (no adjustment)
b. We downgraded for imprecision, because of the very small sample size and number of events leading to a wide confidence interval

References:

1- Arnal C, Piette JC, Léone J, et al. Treatment of severe immune thrombocytopenia associated with systemic lupus erythematosus: 59 cases. *J Rheumatol*. 2002;29(1):75-83.

2-Li HJ, Zheng YQ, Chen L, Lin SP, Zheng XX. Risk factors of significant relapse and appropriate maintenance therapy strategy in SLE-associated immune thrombocytopenia. *Ther Adv Chronic Dis*. 2023;14:20406223231160688. Published 2023 Mar 21. doi:10.1177/20406223231160688

Comparing different immunosuppressive therapies:

Cimé-Aké et al 2024.

All patients received MTP, DXM, or PDN after having severe thrombocytopenia (<30, 000) and then followed by immunosuppressive therapy (induction therapy) with either AZA, MMF, CYC, RTX. The outcomes are below:

For remission:

- glucocorticoids plus AZA: 17/19 (90%)
- glucocorticoids plus MMF: 10/12 (82%)
- glucocorticoids plus CYC: 4/9 (43%)
- glucocorticoids plus RTX: 7/7 (100%)

Durable response:

- glucocorticoids plus AZA: 17/19 (90%)
- glucocorticoids plus MMF: 10/12 (82%)
- glucocorticoids plus CYC: 6/9 (67%)
- glucocorticoids plus RTX: 7/7 (100%)

Initial response:

- glucocorticoids plus AZA: 19/19 (100%)
- glucocorticoids plus MMF: 12/12 (100%)
- glucocorticoids plus CYC: 7/9 (78%)
- glucocorticoids plus RTX: 7/7 (100%)

Comparative but pooling all immunosuppressive therapy (2 studies):

4. Zhang 2018 (10208): 53 with SLE-ITP <20K. Retrospective cohort of mixed group of 131 hospitalized adults with CTD-ITP (70 pSS; 53 SLE (1982, 1986 ACR); 8 CTD) with ITP treated with GC+IVIG vs ISA (immunosuppressive agents). Of just over half (28/53=53%) who achieved response (complete+partial), there was greater response among those who received GC+IVIG (18/53=34%) than IS alone (10/53=19%). There were 6 deaths in the SLE cohort (6/53=11%); 4 (4/53=7%) from ITP-associated bleed (3 alveolar hemorrhage, 1 GIB). NB: it was not possible to discern the ISA (GC, IVIG, RTX, stem cell, CNI (CsA/Tac), CYC, vincristine, LEF, MMF, tripterygium glycosides) that patients with SLE received base on the study information.

5. Ziakas 2005 (10305): 50 with SLE-ITP <100K. Retrospective cohort of 50 adults with SLE (1982 ACR). Treatment with low dose IS: low dose glucocorticoid with/without DMARD (AZA or Methotrexate) vs high dose IS: high dose glucocorticoid (with/without CYC), to assess probability of relapse-free interval. There was no difference between low dose or high dose IS relapse free intervals (p=0.61).

Outcomes (Name + Summary)	Author, year, RefID	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Response	Zhang 2018 10208	Retrospective cohort single center (China)	3-56m	131 CTD-ITP PSS 70 (44.4, 15.4); SLE 53 (36.7, 14.1); other CTD 8 (46.0, 16.1)	GC+IVIG versus IS alone	18/53 versus 10/53	P39 Plt <20K on admission no response (NR) was defined as platelet count < 30 × 109/L or having an increase of less than 2-fold, partial remission (PR) was platelet count between 30 × 109/L and

				Age For SLE: (36.7, 14.1)			100 × 109/L with at least a doubling of the baseline value and complete remission (CR) was defined by achievement of platelet count ≥ 100 × 109/L ISAs immunosuppressive agents, GCS glucocorticoids, IVIG intravenous immunoglobulin, RTX rituximab, MSC mesenchymal stem cell, CNIs calcineurin inhibitors, including cyclosporine and tacrolimus, CYC cyclophosphamide, VCR vincristine, LEF leflunomide, MMF mycophenolate mofetil, TG tripterygium glycosides. *Comparison not of interest, but added data due to scarcity of evidence*
Disease flare	Ziakas 2005 10305	Retrospective Cohort Single center (Greece)	Up to 30 years	50 with SLE-ITP Age 27.4 (13.3)	Low dose IS (with or without DMARD) versus High dose IS (with or without CYC)	5/26 versus 17/22	P38 Plt <100K *Comparison not of interest, but added data due to scarcity of evidence*

Three single-arm studies assessed response to splenectomy for severe thrombocytopenia (Plt ≤20K or ≤50K):

1. Hakim 1998 (3549): 13 with SLE-ITP <50K. Retrospective cohort of 200 adults with SLE (1982 ACR criteria) 33 with plt <100K; 12 with plt <50K; TTP excluded. At follow up (9 years with range 5-14 years), 9/12 with severe thrombocytopenia (plt <50k x2 occasions, corticosteroid dose mean 42mg range 25-80mg presplenectomy) underwent splenectomy with complete response (plt >150K for >6 months) in 6/9 (66.7%) cases and partial response (plt 50-100k) in 2/9 (22.2%), with relapse in 2/9 (22.2%). No splenectomized patients experienced surgical complications. Seven of 9 (78%) required immunosuppression after splenectomy to sustain response. In some people with SLE-associated ITP with plt <50k, splenectomy is safe and may be associated with durable response that often includes longstanding immunosuppression.

2. Jung 2016 (4379): 230 with ITP <100K. Retrospective cohort of 230 adults with SLE (1982 ACR criteria). 3/47 with plt <20k were splenectomized, of whom 2/3 achieved complete response (>100,000/mm3 in 2 consecutive tests after treatment) and 1/3 was a nonresponder at 65.8±48.2 months

of follow up. In people with SLE-associated ITP with plt ≤20k, splenectomy is safe and may be associated with durable plt response.

3. Zhou 2013 (10284): 20 with ITP <100K. Retrospetive cohort of 20 adults with SLE (undefined criteria) and ITP underwent either open (11) or laparoscopic splenectomy (9). At 3 months, 20/20 (100%) achieved CR; at 6m CR was 15/20 (75%); PR was 3/20 (15%); NR 2/20 (10%). At median 42m (5-114m) follow up, CR was 12/20 (60%); PR 5/20 (25%); NR 3/20 (15%). Of these, 3/20 (15%) experienced early relapse. Over time (>3 year follow up) splenectomy is safe may be associated with durable response 17/20 (85%), although some may lose response from complete to partial 2/20 (10%) or to non response 1/20 (5%).

NB: It is difficult to isolate P38 from P39; studies often described absolute platelet counts as cutoffs for splenectomy. In some cases, splenectomy was performed for acute needs, in others in the same study, for chronic thrombocytopenia (Hakim 1998). Most studies noted splenectomy was not a first line therapy but done after recalcitrant ITP requiring ongoing immunosuppression (corticosteroids and/or immunosuppression). In some cases, IVIG was employed prior to splenectomy.

Three single-arm studies described response after immunosuppression, IVIG, and/or HCQ

1. Jung 2016 (4379): 230 with ITP <100K. A retrospective cohort of 230 adults with SLE-ITP (1982 ACR). 126 (54.8%) plt 50-100K, 57 (24.8%) plt 20-50K, and 47 (20.4%) plt <20K. Complete response (>100K in 2 consecutive tests after treatment) was achieved among those who had the following exposure to immunosuppression (not exclusive) – GC (179/207=86%); HCQ (157/177=89%); AZA (14/19=74%); Tacrolimus (7/7=100%); CYC (40/45=89%); IVIG (35/43=81%); Rituximab (1/2= 50%). Overall, SLE-ITP responds to immunosuppression, IVIG, HCQ, though there is a graded response associated with the degree of ITP.

2. Levy 1999 (5167): 3 with ITP <10K. Retrospective cohort of 20 adults with SLE (1982 ACR) who received IVIG 2g/kg (1-8 doses), of whom 3 had thrombocytopenia and received 1 dose of IVIG. 2/3=67% derived benefit (plt before to after IVIG: 10K to 250K; 4K to 140K), 1/3=33% had no response (no data). Of the 2 individuals who derived benefit, one was on no background immunosuppression, one on 5mg prednisone. The non-responder was on prednisone 60mg and CYC 1g. There is no definition of benefit/partial response. In some patients with thrombocytopenia, IVIG may be of benefit.

3. Tselios 2016 (9155): 3 with ITP <90K. A retrospective cohort of 177 adults with SLE (1997 ACR), 3 of whom had ITP and data and were treated with MMF. Cumulative baseline, 6 mo, 12 mo data were 49,667 ± 37,005/µl; 297,000 ± 316,564/µl; 88,000 ± 41,940/µl, respectively suggesting despite improvement at 6 months, some ongoing ITP at 12 month follow up.

References:

- Randomized controlled trials: None
- ***Nonrandomized comparative studies***: 4 studies
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- ***Single arm data:***

o Pamuk, Omer Nuri. "Thrombocytopenia in Patients with Systemic Lupus Erythematosus." European journal of rheumatology vol. 10,4 (2023): 159-162. doi:10.5152/eurjrheum.2023.23069

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- Single arm studies:

Outcomes (Name + Summary)	Author, year, RefID	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Mortality	Jung 2016 4379	Retrospective cohort single center (S. Korea)	65.8±48.2 months	230 adults w SLE, 126 (54.8%) plt 50-100K 57 (24.8%) plt 20-50K, and 47 (20.4%) plt <20K Mean age 41.8±15.3 years	Splenectomy, Immunosuppression	13/230 (6%) Deaths 7 infection 2 hemorrhage 2 renal failure/pulm edema 2 malignancy (ovarian, rectal)	P38/P39 Plt <100K Mortality in patients with complete remission (1.5%) was significantly lower than in those without complete remission (29.4%, P < 0.001)
Mortality	Hakim 1998 3549	Retrospective cohort single center (UK)	9 years (range 5-14)	200 adults with SLE 33 plt <100K 13 plt <50K	9/12 Splenectomy for severe cases	1/12 (12%) Death 1 (2m post-splenectomy, cholangiocarcinoma); 0/12 Death from thrombocytopenia or splenectomy complication	P38/P39 Plt <50K
Mortality	Zhou 10284 2013	Retrospective Single center	5-114m	20 ITP/SLE <100k (Open 11; 35.5±11.9; Laparoscopic 9; 33.3±9.9)	20/20 Splenectomy	0/20 Deaths	P38/P39 Plt <100K

		(China)					
Response	Hakim 1998 3549	Retrospective Single center (UK)	9 years (5-14y)	200 adults with SLE 33 plt <100K 13 plt <50K	9/13 Splenectomy for severe cases	6/9 (66.7%) CR 2/9 (22.2%) PR	P38/P39 Plt <50K CR (>150K >6m) PR (50-150K)
Response	Jung 2016 4379	Retrospective Single center (S. Korea)	65.8±48.2 months	230 adults with SLE 126 (55%) plt 50-100K 57 (25%) plt 20-50K 47 (20%) plt <20K Mean age 41.8±15.3 years	3/47 Splenectomy	2/3 (66.7%) CR 1/3 (33.3%) NR	P38/P39 Plt <100K CR (>100K x2 consecutive tests after treatment)
Response	Zhou 2013 10284	Retrospective Single center (China)	5-114m	20 ITP/SLE <100k (Open 11; 35.5±11.9; Laparoscopic 9; 33.3±9.9)	20/20 Splenectomy 11 Open 9 Lap	3m: CR 20/20 6m: CR 15/20; PR 3/20, NR 2/20 Long term: CR 12/20; PR 5/20; NR 3/20 Early Relapse: 3/20	P38/P39 Plt <100K (1) medically refractory, defined as an inability to maintain platelet count ≥50×109 /L for 12 weeks on medical therapy, including at least one bolus treatment with 500–1,000 mg methylprednisolone and 20 g/day intravenous immunoglobulin (IVIG) for 3 days; (2) medically dependent, defined as an inability to be weaned from medications without a decline in platelet count to pretreatment levels; or (3) medically intolerant, defined as cessation of medical

							treatments due to severe side effects.
Response	Levy 1999 5167	Retrospective cohort single center (Israel)	NA	20 adults with SLE 3 with ITP (4K, 10K, unknown)	IVIG 2g/kg (1-8 doses)	13/20 (65%) Benefit 4/20 (20%) Partial or temporary response 3/20 (15%) No benefit	P38/P39 Plt <10K NB no definition of plt benefit, response, no benefit
Response:Platelets (mean +/- SD)	Tselios 2016 9155	Retrospective Single center (Canada)	6-12m	177 Adults SLE Mean age 38.6 ± 11.7 yrs 3 ITP	IS – MMF	-0m 49,667 ± 37,005/µl -6m 297,000 ± 316,564/µl -12m 88,000 ± 41,940/µl	P38/39 Plt <90K Averages only for 3 with SLE-ITP
Response	Jung 2016 4379	Retrospective Single center (S. Korea)	65.8±48.2 months	230 adults with SLE 126 (55%) plt 50-100K 57 (25%) plt 20-50K 47 (20%) plt <20K Mean age 41.8±15.3 years	Severe (47/230) IS (danazol, azathioprine, cyc, IVIG, rituximab)	ITP CR Mild CR (116/126) Mod CR (49/57) Severe CR (31/47) GC CR (179/207); NR (28/207) HCQ CR (157/177); NR (27/177) Danazol CR (4/8); NR (4/8) AZA CR (14/19); NR (5/19) Tac CR (7/7); NR (0/7) CYC CR (40/45); NR (5/45) IVIG (CR 35/43); NR (8/43) Rituximab CR (1/2); NR (1/2) Relapse Mild (1.61±1.63) Mod (1.8±1.58, P < 0.001) Severe R (3.23±3.14)	P38/P39 Plt <100K CR >100,000/mm3 in 2 consecutive tests after treatment

- Studies reviewed and excluded:

Refid	Author	Year	Title	Comments
152	Acka	2021	Hematological involvement in pediatric systemic lupus erythematosus:	No specific data about thrombocytopenia; treatment group mixed cytopenias, fraction of whom

			A multi-center study	are thrombocytopenic, fraction of whom are other cytopenias
547	Artim	2019	The Effect of Mycophenolate Mofetil on Non-Renal Manifestations in Systemic Lupus Erythematosus: Results from Korean Lupus Network Registry	Treatment groups provided but no outcomes comparing rx or no rx; only outcomes comparing thrombocytopenia and no thrombocytopenia
624	Avina	2003	Long-term effectiveness of danazol corticosteroids and cytotoxic drugs in the treatment of hematologic manifestations of systemic lupus erythematosus	Cases of thrombocytopenia and hemolytic anemia mixed
820	Barron	2017	Splenectomy in systemic lupus erythematosus and autoimmune hematologic disease: a comparative analysis	For autoimmune thrombocytopenia <50K cannot distinguish among SLE, SLE/APS, APS only causes.
3347	Gonzalez	2016	Features associated with hematologic abnormalities and their impact in patients with systemic lupus erythematosus: Data from a multiethnic Latin American cohort	No specific data about thrombocytopenia
4386	Jung	2019	The Effect of Mycophenolate Mofetil on Non-Renal Manifestations in Systemic Lupus Erythematosus: Results from Korean Lupus Network Registry	No specific data about thrombocytopenia
5988	Merrill	2011	Assessment of flares in lupus patients enrolled in a phase II/III study of rituximab (EXPLORER)	No specific data about thrombocytopenia, only BILAG delta
5995	Merrill	2010	Efficacy and Safety of Rituximab in Moderately-to-Severely Active Systemic Lupus Erythematosus: The Randomized, Double-Blind, Phase II/III Systemic Lupus Erythematosus Evaluation of Rituximab Trial	No specific data about thrombocytopenia, only BILAG delta
8270	Shi	2023	Tacrolimus shows adequate efcacy in patients with antiphospholipid antibodies associated thrombocytopenia: a retrospective cohort study	APL-associated thrombocytopenia, though 17 with SLE (criteria not listed and they say they excluded for SLE-associated thrombocytopenia but unclear how they could know its APL vs SLE associated thrombocytopenia)

8292	Shobha	2023	Severe thrombocytopenia is associated with high mortality in systemic lupus erythematosus—analysis from Indian SLE Inception cohort for Research (INSPIRE)	No rx comparisons or unique outcomes
8649	Stratta	1992	Intravenous Cyclophosphamide Pulse Therapy in the Treatment of Systemic Lupus Erythematosus	No specific data about thrombocytopenia
8890	Tani	2018	Tacrolimus in non-Asian patients with SLE: a real-life experience from three European centres	No patients with thrombocytopenia
9324	Van Vollenhoven	2018	Efficacy and safety of ustekinumab, an IL-12 and IL-23 inhibitor, in patients with active systemic lupus erythematosus: results of a multicentre, double-blind, phase 2, randomised, controlled study	No specific data about thrombocytopenia
9550	Wang	2019	Protective effects of antimalarials in Chinese patients with systemic lupus erythematosus	No specific data about thrombocytopenia
9636	Watson	2015	The indications, efficacy and adverse events of rituximab in a large cohort of patients with juvenile-onset SLE	No specific data about thrombocytopenia

Hemolytic Anemia

P40. In SLE patients with autoimmune hemolytic anemia on HCQ or no therapy, does the addition of immunosuppressive therapy or surgery to glucocorticoid therapy improve clinical outcomes compared to glucocorticoid therapy alone?

Populations: SLE patients with autoimmune hemolytic anemia on HCQ or no therapy

Intervention:

1. Glucocorticoid therapy (high dose) plus
    1. Immunosuppressive therapy
        1. AZA
        2. MMF/MPA
        3. Cyclosporine
    2. Anti-CD 20 therapy
    3. Splenectomy
2. IVIG

Comparator: Glucocorticoid therapy alone

Outcomes:

1. SLE flare
2. Mortality
3. Disease damage

4. Treatment related adverse effects (infection); Decrease >30% from baseline eGFR for CNI (cyclosporine)

Summary of Evidence:

The evidence from single-arm studies for this PICO question was found in 11 studies (1-11). In one study patients taking the oral prednisone or high-dose methylprednisolone or Prednisone + azathioprine had the similar rates of complete (69% for OP and MP and 60% for OP+AZA respectivelly) and partial response (31%, 23% and 20%) (1). In other studies [(2), (7), (8)], patients taking Rtituximab for AIHA treatment had a complete response rate ranging from 69% (13 patients (8)) to 100% (4 patients only (2)), partial response ranging from 12.5% to 25%, and sustained response at 62% for two years. Mortality rate with RTX was 25% in a study (4) with only 4 patients and 8% in a study with 13 patients (8). IVIG had overall response to treatment of 69% (3) and mortality rate of 0% (4 patients only in a study) (5). In treatment with Pulse IV CYC (1 g/month) for 4 consecutive months PR was achieved at 82%, while prednisone less than or equal to 10 mg/day after follow up for 6 months after stoppage of IV CYC achieved PR at 47% and CR at 53% (9).

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 response	Gomard-Mennesson, 2006, 3316	Case-series	180 months	13 women with severe isolated autoimmune hemolytic anaemia (AHA)	Oral prednisone (mean dose of 1 mg/kg bw) as the first-line treatment	CR 9/13 (69%)	
Partial response	Gomard-Mennesson, 2006, 3316	Case-series	180 months	13 women with severe isolated autoimmune hemolytic anaemia (AHA)	Oral prednisone (mean dose of 1 mg/kg bw) as the first-line treatment	PR 4/13 (31%)	
Complete response	Gomard-Mennesson, 2006, 3316	Case-series	180 months	13 women with severe isolated autoimmune hemolytic anaemia (AHA)	High dose methylprednisolone (HDMP) defined as a dose >1.5 mg/kg/day at a mean dose of 5.4 (4.9) mg/kg bw/day (range 1.5–15)	CR 9/13 (69%)	
Partial response	Gomard-Mennesson, 2006, 3316	Case-series	180 months	13 women with severe isolated autoimmune hemolytic anaemia (AHA)	High dose methylprednisolone (HDMP) defined as a dose >1.5 mg/kg/day at a mean dose of 5.4 (4.9) mg/kg bw/day (range 1.5–15)	PR 3/13 (23%)	
Complete response	Gomard-Mennesson, 2006, 3316	Case-series	180 months	5 women with severe isolated autoimmune hemolytic anaemia (AHA)	Prednisone + azathioprine treatment	CR 3/5 (60%)	
Partial response	Gomard-Mennesson, 2006, 3316	Case-series	180 months	13 women with severe isolated autoimmune hemolytic anaemia (AHA)	Prednisone + azathioprine treatment	PR 1/5 (20%)]	

Complete response	Kumar, 2023, 4877	Case-series	100 weeks	4 pediatric SLE patients with with autoimmune hemolytic anemia	RTX 375 mg/m2 weekly for 4 doses (6 children) or 500 mg/m2 every 2 weeks for 2 doses (3 children).	4/4 (100%)	
Respone to treatment	Levy, 1999, 5167	Case-series	NA	5 SLE patients with autoimmune hemolytic anemia	IVIG 2 g/ kg body weight	3/5 (60%)	
Mortality	Lindholm, 2008, 5320	Case-series	52 months	4 patients with refractory autoimmune hemolytic anemia	RTX	1/4 (25%)	
Mortality	Nieto-Aristizabal, 2019, 6559	Case-series	NA	4 patients with hemolytic anemia	IVIG 2 g/kg for 5 days	0/4 (0%)	
Time to CR	Olfat, 2015, 6711	Case-series	12 months	8 patients with autoimmune hemolytic anemia	RTX 375 mg/m2 weekly for four doses or 500 mg/m2 every 2 weeks for two doses	median (IQR) of 85 (57–146) days to CR	
Response to treatment	Roumier, 2014, 7725	Case-series	15 months	53 AIHA patients	Prednison as first-line treatment at an initial dose of 1–2 mg/kg per day	Initial response rate in 46/53 cases (87%), half of the patients achieving CR and 38% PR, 7 patients (13%) were considered nonresponders	
Response to treatment	Roumier, 2014, 7725	Case-series	15 months	25 AIHA patients	RTX 4 weekly infusions at 375 mg/m2 or a fixed dose of 1,000 mg 2 weeks apart	Initial overall response (partial or complete) was achieved in 20 patients (80%), folllowed by relapse in 10 (50% of initial responders) after a mean of 14 (8) months.	
Complete response	Serris, 2017, 8167	Case-series	Median (range) 26.4 months (14.3-71.2)	16 patients with AIHA	RTX fixed dose of 1000 mg 2 weeks apart or 375 mg/ m2 weekly x 4	CR in 12/16 (75%, 95% CI: 47.6–92.7)	
Partial response	Serris, 2017, 8167	Case-series	Median (range) 26.4 months (14.3-71.2)	16 patients with AIHA	RTX fixed dose of 1000 mg 2 weeks apart or 375 mg/ m2 weekly x 4	PR in 2/16 (12.5%, 95% CI: 1.6–81.3), respectively	
Sustained response for 2 years	Serris, 2017, 8167	Case-series	Median (range) 26.4 months (14.3-71.2)	16 patients with AIHA	RTX fixed dose of 1000 mg 2 weeks apart or 375 mg/ m2 weekly x 4	10/16 (62.5%)	

Response to treatment	Terrier, 2010, 8971	Case-series	10 months	13 patients with AIHA	RTX 1 gm x 2 infusions or 375 mg/m2 x 4 infusions	Complete response 9 (69%) Partial response 2 (16%) No response 2 (15%)	
Mortality	Terrier, 2010, 8971	Case-series	10 months	13 patients with AIHA	RTX 1 gm x 2 infusions or 375 mg/m2 x 4 infusions	1/13 (8%)	
PR and NR	Thabet, 2014, 8987	Case-series	10 months	17 AIHA patients	Pulse IV CYC (1 g/ month) for 4 consecutive months	82 %, 14 patients achieved PR while the remaining 17 %, 3 patients showed NR	
CR and PR	Thabet, 2014, 8987	Case-series	10 months	17 AIHA patients	Less than or equal to 10 mg/day prednisone after follow up for 6 months after stoppage of IV CYC	47 %, 8 patients showed CR, while 53 %, 9 patients showed PR	
Improvement of clinical symptoms and laboratory indicators	Wang, 2023, 9568	Case-series	12 months	25 patients with hemolitic anemia	Belimumab ((10 mg/kg on weeks 0, 2, 4, and then every 4 weeks) + standard of care	From 25 down to 5 (2.6%) at 3 motnths, to 4 (2.3%) at 6 months, and 0% at 12 months	

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Neuropsychiatric

P41. In patients with active, newly diagnosed or flare of lupus myelitis*, what is the impact of the listed medical therapies on clinical outcomes compared to standard therapy of pulse steroid with or without CYC?

P42. In patients with active, newly diagnosed or flare of optic neuritis secondary to SLE (not NMO)*, does the addition of immunosuppressive therapy to glucocorticoid lead to improved clinical outcomes compared to glucocorticoid with or without CYC?

P43. In patients with active, newly diagnosed or flare of lupus seizure in the absence of stroke or other focal lesion, does glucocorticoid therapy with or without immunosuppressive or antithrombotic therapy improve clinical outcomes compared to anti-seizure therapy alone?

P44. In patients with acute confusional state secondary to active SLE, does glucocorticoid with additional (listed) therapies improve clinical outcomes compared to glucocorticoid with or without CYC?

P45. In patients with active, newly diagnosed or flare of lupus psychosis in the absence of stroke, does glucocorticoid with or without additional (listed) therapies improve clinical outcomes compared to antipsychotic therapy alone?

P46. In patients with active, newly diagnosed or flare of mononeuritis multiplex secondary to active SLE, does glucocorticoid with additional (listed) therapies improve clinical outcomes compared to glucocorticoid with or without CYC?

P47. In patients with small-fiber neuropathy secondary to active SLE, does addition of glucocorticoid or immunosuppressive therapy to symptomatic (non-immunosuppressive nerve-directed) therapy improve clinical outcomes compared to symptomatic therapy only?

P48. In patients with cognitive dysfunction or decline secondary to active SLE in the absence of stroke, does addition of glucocorticoid or immunosuppressive therapy to cognitive rehabilitation therapy improve clinical outcomes compared to cognitive rehabilitation therapy only?

P49. In SLE patients with ischemic stroke in the absence of aPL who have received acute stroke-directed therapy and/or procedure-based intervention, does addition of glucocorticoid, immunosuppressive therapy, or anticoagulation to antiplatelet therapy improve clinical outcomes compared to antiplatelet therapy only?

Population: SLE patients with different neurological manifestations
Interventions:

- **Belimumab**

Comparators:

- **Standard of care**

Outcomes:

- Neurologic damage
- Disease activity
- SLE flares
- SDI (disease damage)
- Mortality
- Quality of life
- Treatment-related adverse events of infection and cytopenias
- Functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)
- Cumulative glucocorticoid dose

Table 1.

Study	Design	Population	Intervention	Comparator	Outcomes	Notes
Manzi 2012	Post hoc analysis for BLISS 52 and BLISS 72	Patients with active SLE (only CNS or neurological)	Belimumab 10 mg	Standard of care (immunosuppressive therapy, or/and steroids, or/and HCQ)	BILAG improvement (Neurological) and SLEDIA improvement (CNS)	

Evidence summary: 1 posthoc analysis of the BLISS 52 and BLISS 72 trials compared Belimumab to standard of care in patients with neurological or CNS involvement. They don't specify the neurological presentations in the studies, but they report that they excluded patients with severe neurological involvement. For BILAG neurological improvement, it was 408 fewer per 1,000 (from 667 fewer to 250 more) in the Belimumab arm. For SLEDIA (CNS) improvement, it was 541 more per 1,000 (from 4 more to 1,000 more) in patients taking Belimumab. The overall certainty of evidence is very low due to concerns about risk of bias (posthoc analysis which will affect randomization) and imprecision (very small sample size and number of events leading to wide CI).

The trial excluded patients with severe neurological manifestations, and the core team think that our PICOs are addressing patients with severe neurological manifestations, so this evidence doesn't answer our questions.

Evidence report:

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

BILAG (neurological) improvement

1	randomised trials	serious	not serious	serious	very serious	none	3/7 (42.9%)	5/6 (83.3%)	**RR 0.51** (0.20 to 1.30)	**408 fewer per 1,000** (from 667 fewer to 250 more)	⊕◯◯◯ Very low	

SLEDIA (CNS) improvement

1	randomised trials	serious	not serious	serious	serious	none	12/19 (63.2%)	1/11 (9.1%)	**RR 6.95** (1.04 to 46.45)	**541 more per 1,000** (from 4 more to 1,000 more)	⊕⊕◯◯ Low	

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

References: 1 posthoc analysis of 2 RCTs (BLISS 52 and 72)

Manzi S, Sánchez-Guerrero J, Merrill JT, et al. Effects of belimumab, a B lymphocyte stimulator-specific inhibitor, on disease activity across multiple organ domains in patients with systemic lupus erythematosus: combined results from two phase III trials. *Ann Rheum Dis*. 2012;71(11):1833-1838. doi:10.1136/annrheumdis-2011-200831

P41. In patients with active, newly diagnosed or flare of lupus myelitis*, what is the impact of the listed medical therapies on clinical outcomes compared to standard therapy of pulse steroid with or without CYC?

P42. In patients with active, newly diagnosed or flare of optic neuritis secondary to SLE (not NMO)*, does the addition of immunosuppressive therapy to glucocorticoid lead to improved clinical outcomes compared to glucocorticoid with or without CYC?

P43. In patients with active, newly diagnosed or flare of lupus seizure in the absence of stroke or other focal lesion, does glucocorticoid therapy with or without immunosuppressive or antithrombotic therapy improve clinical outcomes compared to anti-seizure therapy alone?

P44. In patients with acute confusional state secondary to active SLE, does glucocorticoid with additional (listed) therapies improve clinical outcomes compared to glucocorticoid with or without CYC?

P45. In patients with active, newly diagnosed or flare of lupus psychosis in the absence of stroke, does glucocorticoid with or without additional (listed) therapies improve clinical outcomes compared to antipsychotic therapy alone?

P46. In patients with active, newly diagnosed or flare of mononeuritis multiplex secondary to active SLE, does glucocorticoid with additional (listed) therapies improve clinical outcomes compared to glucocorticoid with or without CYC?

P47. In patients with small-fiber neuropathy secondary to active SLE, does addition of glucocorticoid or immunosuppressive therapy to symptomatic (non-immunosuppressive nerve-directed) therapy improve clinical outcomes compared to symptomatic therapy only?

P48. In patients with cognitive dysfunction or decline secondary to active SLE in the absence of stroke, does addition of glucocorticoid or immunosuppressive therapy to cognitive rehabilitation therapy improve clinical outcomes compared to cognitive rehabilitation therapy only?

P49. In SLE patients with ischemic stroke in the absence of aPL who have received acute stroke-directed therapy and/or procedure-based intervention, does addition of glucocorticoid, immunosuppressive therapy, or anticoagulation to antiplatelet therapy improve clinical outcomes compared to antiplatelet therapy only?

Population: SLE patients with different neurological manifestations

Interventions:

- **Glucocorticoids plus CYC**

Comparators:

- **Glucocorticoids**

Outcomes:

- Neurologic damage
- Disease activity
- SLE flares
- SDI (disease damage)
- Mortality
- Quality of life
- Treatment-related adverse events of infection and cytopenias
- Functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)
- Cumulative glucocorticoid dose

Table 1.

Study	Design	Population	Intervention	Comparator	Outcomes
Barile-Fabris 2005	RCT	Patients with SLE and severe neurological manifestation, such as seizures, optic neuritis, peripheral or cranial neuropathy, coma, brainstem disease, or transverse myelitis.	Pulse IV glucocorticoid followed by high dose glucocorticoid plus CYC+ PLEX (plasma)	Pulse IV glucocorticoid followed by high dose glucocorticoid	Favorable response, relapse
Stojanovich 2003	RCT	SLE patients with only primary neuropsychiatric manifestations (NP-SLE). Different neurological manifestations	Glucocorticoids plus CYC	Glucocorticoids	Neurological damage

Evidence summary: 2 RCTs addressed CYC in patients with multiple neurological presentations.

-1 RCT compared Glucocorticoids plus CYC versus Glucocorticoids in patients with neuropsychiatric lupus (multiple presentations). For response, it was 404 more per 1,000 (from 59 more to 1,000 more) in the CYC arm, and for relapse, it was 407 fewer per 1,000 (from 548 fewer to 180 fewer) in CYC arm. This is based on very low certainty of evidence due to risk of bias imprecision (very low certainty evidence)
-1 RCT compared Pulse GC + oral CG + CYC versus Pulse GC + oral CG in patients with neuropsychiatric lupus (multiple presentations). For response, 485 more per 1,000 (from 60 more to 1,000 more)in the CYC arm. This is based on very low certainty of evidence due to risk of bias imprecision (very low certainty evidence)

Evidence profile, Glucocorticoids plus CYC versus Glucocorticoids:

Certainty assessment							№ of patients		Effect		Certainty	
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Glucocorticoids plus CYC	Glucocorticoids alone	Relative (95% CI)	Absolute (95% CI)		
Response												
1	randomised trials	serious	not serious	not serious	serious	none	23/37 (62.2%)	5/23 (21.7%)	**RR 2.86** (1.27 to 6.46)	**404 more per 1,000** (from 59 more to 1,000 more)	⨁⨁◯◯ Low	
Relapse												
1	randomised trials	serious	not serious	not serious	very serious	none	14/37 (37.8%)	18/23 (78.3%)	**RR 0.48** (0.30 to 0.77)	**407 fewer per 1,000** (from 548 fewer to 180 fewer)	⨁◯◯◯ Very low	

Population: SLE patients with different neurological manifestations

Interventions:

- **Pulse GC + oral CG + CYC**

Comparators:

- **Pulse GC + oral CG**

Outcomes:

- Neurologic damage
- Disease activity
- SLE flares
- SDI (disease damage)
- Mortality
- Quality of life
- Treatment-related adverse events of infection and cytopenias
- Functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)
- Cumulative glucocorticoid dose

Evidence profile, Pulse GC + oral CG + CYC versus Pulse GC + oral CG:

Certainty assessment	№ of patients	Effect	Certainty	Importance

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pulse IV glucocorticoid followed by high dose glucocorticoid with or without IV CYC	[placebo]	Relative (95% CI)	Absolute (95% CI)		
Response												
1	randomised trials	serious	not serious	not serious	very serious	none	18/19 (94.7%)	6/13 (46.2%)	**RR 2.05** (1.13 to 3.73)	**485 more per 1,000** (from 60 more to 1,000 more)	⨁◯◯◯ Very low	

CI: confidence interval; RR: risk ratio

References:

Randomized clinical trials: 2

- Barile-Fabris, L et al. "Controlled clinical trial of IV cyclophosphamide versus IV methylprednisolone in severe neurological manifestations in systemic lupus erythematosus." *Annals of the rheumatic diseases* vol. 64,4 (2005): 620-5. doi:10.1136/ard.2004.025528
- Stojanovich L, Stojanovich R, Kostich V, Dzjolich E. Neuropsychiatric lupus favourable response to low dose i.v. cyclophosphamide and prednisolone (pilot study). *Lupus*. 2003;12(1):3-7. doi:10.1191/0961203303lu251oa

P41.1 In patients with active, newly diagnosed or flare of lupus myelitis*, what is the impact of the listed medical therapies on clinical outcomes compared to standard therapy of pulse steroid with or without CYC?

*Text to include rational for using this term - we are treating inflammatory (and not purely ischemic) lesions.

Population: SLE patients with active, newly diagnosed or flare of lupus myelitis

Interventions:

- Pulse IV glucocorticoid followed by high dose glucocorticoid and IV CYC.

Comparators:

- Pulse IV glucocorticoid followed by high dose glucocorticoid.

Outcomes:

- Neurologic damage
- Disease activity
- SLE flares
- SDI (disease damage)
- Mortality
- Quality of life
- Treatment-related adverse events of infection and cytopenias
- Functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)

- Cumulative glucocorticoid dose

Table 1.

Study	Design	Population	Intervention	Comparator	Outcomes	Notes
Anh 2019	NRSI	Patients with transverse myelitis	Pulse IV glucocorticoid followed by high dose glucocorticoid plus CYC	Pulse IV glucocorticoid followed by high dose glucocorticoid	Favorable response, relapse	
Kovacs 2000	NRSI	Patients with transverse myelitis	Pulse IV glucocorticoid followed by high dose glucocorticoid plus CYC	Pulse IV glucocorticoid followed by high dose glucocorticoid	Neurological damage	

Evidence summary: 2 nonrandomized studies of intervention, comparing Pulse IV glucocorticoid followed by high dose glucocorticoid with/without CYC. For Favorable response it is comparable in both arms. For neurological damage, it was 200 more per 1,000 (from 236 fewer to 1,000 more) in the CYC arm. For Relapse, it was 165 fewer per 1,000 (from 415 fewer to 835 more) in the CYC arm. The number of patients included is very small and the studies are not randomized and the estimates are not adjusted, leading to very low certainty in the evidence.

Evidence profile :

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pulse IV glucocorticoid followed by high dose glucocorticoid plus CYC	Pulse IV glucocorticoid followed by high dose glucocorticoid	Relative (95% CI)	Absolute (95% CI)	
Favorable response											
1	non-randomised studies	serious	not serious	not serious	very serious	none	5/6 (83.3%)	5/6 (83.3%)	**RR 1.00** (0.60 to 1.66)	**0 fewer per 1,000** (from 333 fewer to 550 more)	⨁◯◯◯ Very low
Neurological damage											
1	non-randomised studies	serious	not serious	not serious	very serious	none	3/5 (60.0%)	2/5 (40.0%)	**RR 1.50** (0.41 to 5.45)	**200 more per 1,000** (from 236 fewer to 1,000 more)	⨁◯◯◯ Very low
Relapse											
1	non-randomised studies	serious	not serious	not serious	very serious	none	2/6 (33.3%)	3/6 (50.0%)	**RR 0.67** (0.17 to 2.67)	**165 fewer per 1,000** (from 415 fewer to 835 more)	⨁◯◯◯ Very low

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

Reference:

RCTs: None

Non-randomized comparative studies: 2 studies.

- Kovacs B, Lafferty TL, Brent LH, DeHoratius RJ. Transverse myelopathy in systemic lupus erythematosus: an analysis of 14 cases and review of the literature. *Ann Rheum Dis*. 2000;59(2):120-124. doi:10.1136/ard.59.2.120
- Ahn SM, Hong S, Lim DH, et al. Clinical features and prognoses of acute transverse myelitis in patients with systemic lupus erythematosus. *Korean J Intern Med*. 2019;34(2):442-451. doi:10.3904/kjim.2016.383

P41.2 In patients with active, newly diagnosed or flare of lupus myelitis*, what is the impact of the listed medical therapies on clinical outcomes compared to standard therapy of pulse steroid with or without CYC?

*Text to include rational for using this term - we are treating inflammatory (and not purely ischemic) lesions.

Population: SLE patients with active, newly diagnosed or flare of lupus myelitis
Interventions:

- Pulse IV glucocorticoid followed by high dose glucocorticoid and IV CYC +PLEX (plasma).

Comparators:

- Pulse IV glucocorticoid followed by high dose glucocorticoid.

Outcomes:

- Neurologic damage
- Disease activity
- SLE flares
- SDI (disease damage)
- Mortality
- Quality of life
- Treatment-related adverse events of infection and cytopenias
- Functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)
- Cumulative glucocorticoid dose

Table 1.

Study	Design	Population	Intervention	Comparator	Outcomes	Notes
Anh 2019	NRSI	Patients with transverse myelitis	Pulse IV glucocorticoid followed by high dose glucocorticoid plus CYC+ PLEX (plasma)	Pulse IV glucocorticoid followed by high dose glucocorticoid	Favorable response, relapse	
Kovacs 2000	NRSI	Patients with	Pulse IV glucocorticoid	Pulse IV glucocorticoid	Neurological damage	

		transverse myelitis	followed by high dose glucocorticoid plus CYC+ PLEX (plasma)	followed by high dose glucocorticoid		

Evidence summary:

2 nonrandomized studies of intervention, comparing Pulse IV glucocorticoid followed by high dose glucocorticoid with CYC +PLEX versus Pulse IV glucocorticoid followed by high dose glucocorticoid. For Favorable response it was 50 more per 1,000 (from 367 fewer to 842 more) in the PLEX arm. For neurological damage, it was 464 more per 1,000 (from 80 fewer to 1,000 more)) in the PLEX arm. For Relapse, it was 335 fewer per 1,000 (from 490 fewer to 1,000 more)in the PLEX arm. The number of patients included is very small and the studies are not randomized and the estimates are not adjusted, leading to very low certainty in the evidence.

Evidence profile :

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations exchange)	Pulse IV glucocorticoid followed by high dose glucocorticoid and CYC + PLEX (plasma)	Pulse IV glucocorticoid followed by high dose glucocorticoid	Relative (95% CI)	Absolute (95% CI)		
Favorable response												
1	non-randomised studies	serious	not serious	not serious	very serious	none	2/2 (100.0%)	5/6 (83.3%)	**RR 1.06** (0.56 to 2.01)	**50 more per 1,000** (from 367 fewer to 842 more)	⨁◯◯◯ Very low	
Neurological damage												
1	non-randomised studies	serious	not serious	not serious	very serious	none	4/4 (100.0%)	2/5 (40.0%)	**RR 2.16** (0.80 to 5.82)	**464 more per 1,000** (from 80 fewer to 1,000 more)	⨁◯◯◯ Very low	
Relapse												
1	non-randomised studies	serious	not serious	not serious	very serious	none	0/2 (0.0%)	3/6 (50.0%)	**RR 0.33** (0.02 to 4.65)	**335 fewer per 1,000** (from 490 fewer to 1,000 more)	⨁◯◯◯ Very low	

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

Reference:

RCTs: None

Non-randomized comparative studies: 2 studies.

- Kovacs B, Lafferty TL, Brent LH, DeHoratius RJ. Transverse myelopathy in systemic lupus erythematosus: an analysis of 14 cases and review of the literature. *Ann Rheum Dis*. 2000;59(2):120-124. doi:10.1136/ard.59.2.120
- Ahn SM, Hong S, Lim DH, et al. Clinical features and prognoses of acute transverse myelitis in patients with systemic lupus erythematosus. *Korean J Intern Med*. 2019;34(2):442-451. doi:10.3904/kjim.2016.383

P42. In patients with active, newly diagnosed or flare of optic neuritis secondary to SLE (not NMO)*, does the addition of immunosuppressive therapy to glucocorticoid lead to improved clinical outcomes compared to glucocorticoid with or without CYC?

Outcomes (please list the outcomes as reported in the project plan):

- Optic nerve damage
- Vision
- Disease activity
- Disease flares
- SDI (disease damage)
- Mortality
- Quality of life
- Treatment-related adverse events of infection and cytopenias
- Cumulative glucocorticoid dose

Patient important outcomes (addressed in the study only):

Evidence Summary:

One single-arm study addressed this PICO question (1). The vision was improved in 80% of patients.

Outcomes (Name + Summary)	Author, year, RefID	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Vision	Galindo-Rodriguez, 1999, 3060	Case series	6 months	10 patients with optic neuritis, mean age 35.1 years, sex not specified	Corticosteroids and IV cyclophosphamide pulses	8/10 (80%) had improved visual acuity	
Treatment-related adverse events-infection	Galindo-Rodriguez, 1999, 3060	Case series	6 months	10 patients with optic neuritis, mean age 35.1 years, sex not specified	Corticosteroids and IV cyclophosphamide pulses	16 had infections-seems this refers to "eyes" and not people	

References:

Randomized controlled trials:
-None

Comparative observational studies:
-None

Single arm studies: 1
-

Studies reviewed and excluded: none

References:
1. Galindo-Rodríguez G, Aviña-Zubieta JA, Pizarro S, Díaz de León V, Saucedo N, Fuentes M, et al. Cyclophosphamide pulse therapy in optic neuritis due to systemic lupus erythematosus: an open trial. The American journal of medicine. 1999;106(1):65-9.

P43. In patients with active, newly diagnosed or flare of lupus seizure in the absence of stroke or other focal lesion, does glucocorticoid therapy with or without immunosuppressive or antithrombotic therapy improve clinical outcomes compared to anti-seizure therapy alone?

Population: SLE patients with active, newly diagnosed or flare of lupus seizure in the absence of stroke or other focal lesion.

Outcomes (please list the outcomes as reported in the project plan):

- Seizure activity
- Neurologic damage
- SDI (disease damage)
- Mortality
- Quality of life
- Treatment-related adverse events of infection and cytopenias
- Functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)
- Cumulative glucocorticoid dose

Patient important outcomes (addressed in the study only):
Complete response defined as "Resolution of encephalopathy (acute confusional state)" or resolution of mononeuritis multiplex with "normal neurologic exam."

Evidence Summary:
Three single-arm studies addressed this PICO question, one with different doses of prednisone (1), one with azathioprine (2), and one with IV cyclophosphamide monthly pulses (3). In a study with prednisone, 83% of patients had neurologic disease improvement, and 17% of patients relapsed (1). In a study with azathioprine, patients had a mortality rate of 28% and hospitalization for SLE exacerbation rate of 24% (2). In a study with IV cyclophosphamide monthly pulses, the mortality rate was 8% and the infection rate was 11% (3).

Outcomes (Name + Summary)	Author, year, RefID	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Neurologic disease activity improvement vs relapse	Gibson, 1976, 3216	Observational cohort study	Variable/not defined	12 with seizures ("convulsions") out of 41 with neurologic lupus. Overall group is 95% female, 67% black, mean age 27 years	Prednisone- three groups of >100 mg, 30-100 mg or <30 mg per day	10/12 (83%) improved, 2/12 (17%) relapsed	4 patients with relapsed used prednisone dose <30 mg/day

Mortality	Ginzler, 1975, 3239	Combination of randomized patients and observational cohort study	Variable-total 101 patient years	54 patients with CNS +/- renal lupus	Azathioprine 2.5 mg/kg/day	15/54 (28%)	Combines patients with seizures or acute confusional state
Disease activity-hospitalization for SLE exacerbation	Ginzler, 1975, 3239	Combination of randomized patients and observational cohort study	Variable-total 101 patient years	54 patients with CNS +/- renal lupus	Azathioprine 2.5 mg/kg/day	13/54 (24%)	Combines patients with seizures or acute confusional state
Mortality	Gonzalez, 2005, 3330	Observational cohort study	Median 5 years (range 3 months to 15 years)	8 children with CNS lupus- 5 with seizures and 3 with psychosis	IV cyclophosphamide monthly pulses	3 (8%) deaths out of 38 children who received IV CYC	Population for outcomes included those with CNS lupus and other severe lupus manifestations
Adverse events-Infections	Gonzalez, 2005, 3330	Observational cohort study	Median 5 years (range 3 months to 15 years)	8 children with CNS lupus- 5 with seizures and 3 with psychosis out of 38 total with severe SLE who were studied together	IV cyclophosphamide monthly pulses	4 (11%) infections out of 38 children who received IV CYC	Population for outcomes included those with CNS lupus and other severe lupus manifestations

References:

Randomized controlled trials:

-None

Comparative observational studies:

-None

Single arm studies: 3

Studies reviewed and excluded: None

References:

1. Gibson T, Myers AR. Nervous system involvement in systemic lupus erythematosus. Annals of the rheumatic diseases. 1975;35(5):398-406.
2. Ginzler E, Sharon E, Diamond H, Kaplan D. Long-term maintenance therapy with azathioprine in systemic lupus erythematosus. Arthritis and rheumatism. 1975;18(1):27-34.
3. González B, Hernández P, Olguín H, Miranda M, Lira L, Toso M, et al. Changes in the survival of patients with systemic lupus erythematosus in childhood: 30 years experience in Chile. Lupus. 2005;14(11):918-23.

P44. In patients with acute confusional state secondary to active SLE, does glucocorticoid with additional (listed) therapies improve clinical outcomes compared to glucocorticoid with or without CYC?

*Note of clarification: per the 1999 ACR nomenclature and case definitions for neuropsychiatric lupus, "acute confusional state" is equivalent to "delirium." Neurologists often use the term "encephalopathy" to describe the same clinical state. No treatment option of anti-thrombotics in acute confusional state because the mechanism of acute confessional state is inflammatory and the issue of anti-thrombotics is usually not relevant. These questions pertain to acute confusional state in the absence of stroke**.**

Outcomes (please list the outcomes as reported in the project plan):

- Resolution of acute confusional state
- Neurologic damage
- Disease activity
- SDI (disease damage)
- Mortality
- Quality of life
- Treatment-related adverse events (infection, cytopenias)
- Functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)
- Cumulative glucocorticoid dose

Patient important outcomes (addressed in the study only):

- Complete response defined as "Resolution of encephalopathy (acute confusional state)."

Evidence summary:

Six single-arm studies addressed this PICO question (1-6). Resolution of neurologic lupus was 71% in patients on IV CYC (6), and improvement in psychiatric lupus was 92% in patients on high-dose glucocorticoids (1). Patients taking MMF and glucocorticoids had 88% of resolution of NPSLE (4). Resolution of acute confusional state was 64% in patients who had IV methylprednisolone pulse, then high dose oral prednisone and IV cyclophosphamide pulse every 2 weeks (5). Mortality ranged from 28% in patient on AZA (3), up to 40% in patients on a combination of IV MP, oral GC and IV CYC (5). The hospitalization for SLE exacerbation rate was 24% in patients on AZA (3).

Outcomes (Name + Summary)	Author, year, RefID	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Resolution of neurologic lupus (including acute confusional state and mononeuritis multiplex)	Petri, 2010, 7076	Randomized clinical trial, but only one arm is relevant to PICO	36 months	7 with neurologic lupus- combination of acute confusional state and mononeuritis multiplex. Does not give n with acute confusional state specifically, characteristics missing for NPSLE subgroup	IV Cyclophosphamide (monthly x 6 induction then every 3 months maintenance)	5/7 (71%) patients had complete response	Does not specify how many patients had mononeuritis multiplex vs acute confusional state for the sample size or the number who responded.
Mortality	Ginzler, 1975, 3239	Combination of randomized	Variable-total 101	54 patients with CNS +/- renal lupus, no	Azathioprine 2.5 mg/kg/day	15/54 (28%)	Combines patients with seizures or

		patients and observational cohort study	patient years	demographics provided			acute confusional state
Disease activity-hospitalization for SLE exacerbation	Ginzler, 1975, 3239	Combination of randomized patients and observational cohort study	Variable-total 101 patient years	54 patients with CNS +/- renal lupus, no demographics provided	Azathioprine 2.5 mg/kg/day	13/54 (24%)	Combines patients with seizures or acute confusional state
Improvement in psychiatric lupus	Abel, 1980, 29	Observational cohort study	Not reported	18 total patients with episodes of "psychiatric lupus" including organic brain syndrome, psychosis, psychoneurosis, or suicide attempt, and 12 were treated with prednisone	High dose glucocorticoids	11/12 (92%)	Mean dose prednisone as 46.6 mg/day
Resolution of acute confusional \\state	Baca, 1999, 656	Observational case series	Not reported	3 pediatric lupus patients with organic brain syndrome, all female, ages 12, 13, and 14 years	IV methylprednisolone and IV cyclophosphamide monthly x 3 months then every 2-3 months	3/3 (100%)	
Resolution of NPSLE	Gupta, 2017, 3495	Observational cohort study	Not reported	88 patients with NPSLE are analyzed together, including 11 with acute confusional state, overall 95% female, mean age 25.5 yrs	Mycophenolate and glucocorticoids	74/88 (84%) have complete response, 7/88 (8%) have partial response	All NPSLE analyzed together
Death	Li, 1992, 5217	Observational cohort study	Variable	28 patients with "mental disturbances of SLE", mean age 27.7, 5 males and 23 females; of those, 25 received the intervention	IV methylprednisolone pulse, then high dose oral prednisone and IV cyclophosphamide pulse every 2 weeks	10 deaths out of 25 (40%) patients who received the intervention	"mental disturbances of SLE" defined as organic brain syndrome, thought disturbances, emotional changes, behavior changes, or speech changes
Resolution of acute	Li, 1992, 5217	Observational cohort study	Variable	28 patients with "mental disturbances of	IV methylprednisolone pulse, then high dose	18 (64%) patients had improvement	"mental disturbances of SLE"

confusional state				SLE", mean age 27.7, 5 males and 23 females; of those, 25 received the intervention	oral prednisone and IV cyclophosphamide pulse every 2 weeks	or resolution of symptoms out of 25 patients who received the intervention	defined as organic brain syndrome, thought disturbances, emotional changes, behavior changes, or speech changes

References:

Randomized controlled trials:
-None
Comparative observational studies:
-None
Single arm studies: 6
Studies reviewed and excluded: None

1. Abel T, Gladman DD, Urowitz MB. Neuropsychiatric lupus. The Journal of rheumatology. 1980;7(3):325-33.
2. Baca V, Lavalle C, García R, Catalán T, Sauceda JM, Sánchez G, et al. Favorable response to intravenous methylprednisolone and cyclophosphamide in children with severe neuropsychiatric lupus. The Journal of rheumatology. 1999;26(2):432-9.
3. Ginzler E, Sharon E, Diamond H, Kaplan D. Long-term maintenance therapy with azathioprine in systemic lupus erythematosus. Arthritis and rheumatism. 1975;18(1):27-34.
4. Gupta N, Ganpati A, Mandal S, Mathew J, Goel R, Mathew AJ, et al. Mycophenolate mofetil and deflazacort combination in neuropsychiatric lupus: a decade of experience from a tertiary care teaching hospital in southern India. Clinical rheumatology. 2017;36(10):2273-9.
5. Li S, Wang J. The diagnosis and steroid "pulse" therapy of systemic lupus erythematosus associated with mental disturbances in the general hospital. Chinese medical sciences journal = Chung-kuo i hsueh k'o hsueh tsa chih. 1992;7(4):235-8.
6. Petri M, Brodsky RA, Jones RJ, Gladstone D, Fillius M, Magder LS. High-dose cyclophosphamide versus monthly intravenous cyclophosphamide for systemic lupus erythematosus: a prospective randomized trial. Arthritis and rheumatism. 2010;62(5):1487-93.

P45. In patients with active, newly diagnosed or flare of lupus psychosis in the absence of stroke, does glucocorticoid with or without additional (listed) therapies improve clinical outcomes compared to antipsychotic therapy alone?

Population: SLE patients with active, newly diagnosed or flare of lupus psychosis
Interventions: Antipsychotic therapy and addition of:

- Glucocorticoid therapy alone
- Glucocorticoids plus:
  - IV CYC
  - MMF/MPA
  - AZA
  - Anti-CD20 therapy
  - Anifrolumab
  - Belimumab
  - IVIG

Comparators: Antipsychotic therapy alone

Outcomes:

- Resolution of psychosis
- Prevention of recurrent psychosis
- Neurologic damage
- SDI (disease damage)
- Mortality
- Quality of life
- Treatment-related adverse events of infection and cytopenias
- Functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)
- Cumulative glucocorticoid dose

Patient important outcomes (addressed in the study only):

- Resolution of neurologic disease activity
- Outcome of neurologic disease activity- relapsed or improved
- Mortality
- Adverse events- infections
- Resolution of psychosis

Evidence Summary:

There are seven single-arm studies that addressed this PICO question (1-7). In studies with patients on IV CYC treatment a complete neurologic recovery was from 67% to 75% (3), and resolution of psychosis was 73% (4), infections rate was 11% (6), and mortality rate was 8% (6). In studies with patients on prednisone treatment the improvement rate was 68% and relapse rate was 36% (5), the improvement of psychiatric lupus was 92% (1), and resolution of psychosis was 100% (2). In a study with only two patients on IVIG, both had a resolution of pscychosis (7).

Outcomes (Name + Summary)	Author, year, RefID	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Combined result-Response-complete neurologic recovery, partial recovery with neurologic damage	Boumpas, 1991, 1136	Observational case series	Range 20-140 months	9 total, including 8 females, mean age 29 years	IV cyclophosphamide 0.75 g/m2 BSA monthly infusions x 2-6 doses.	6/9 (67%) had complete neurologic recovery, 3 (33%) had partial neurologic recovery	Combination of transverse myelitis, cerebritis, seizures, and psychosis
Neurologic recovery	Boumpas, 1991, 1136	Observational case series	Range 32-140 months	4 with psychosis, one of them also with cerebritis/seizures	IV cyclophosphamide 0.75 g/m2 BSA monthly infusions x 2-6 doses.	3/4 (75%) had complete neurologic recovery,1 (25%) had partial neurologic recovery	

Neurologic disease activity improvement vs relapse	Gibson, 1976, 3216	Observational cohort study	Variable/not defined	19 with psychosis, demographics not provided	Prednisone- three groups of >100 mg, 30-100 mg or <30 mg per day	13/19 (68%) improved, 6/19 (36%) relapsed	4 patients with relapse used prednisone dose <30 mg/day
Mortality	Gonzalez, 2005, 3330	Observational cohort study	Median 5 years (range 3 months to 15 years)	8 children with CNS lupus- 5 with seizures and 3 with psychosis	IV cyclophosphamide monthly pulses	3 (8%) deaths out of 38 children who received IV CYC	Population for outcomes included those with CNS lupus and other severe lupus manifestations
Adverse events- Infections	Gonzalez, 2005, 3330	Observational cohort study	Median 5 years (range 3 months to 15 years)	8 children with CNS lupus- 5 with seizures and 3 with psychosis out of 38 total with severe SLE who were studied together	IV cyclophosphamide monthly pulses	4 (11%) infections out of 38 children who received IV CYC	Population for outcomes included those with CNS lupus and other severe lupus manifestations
Resolution of psychosis	Levy, 1999, 5167	Observational cohort study	18 years in one patient, unknown in other	2 patients with lupus psychosis, both female, one age 44 and one age 28	IVIG- 2g/kg monthly dosing	2 (100%) had response/resolution of psychosis	
Improvement in psychiatric lupus	Abel, 1980, 29	Observational cohort study	Not reported	18 total patients with episodes of "psychiatric lupus" including organic brain syndrome, psychosis, psychoneurosis, or suicide attempt, and 12 were treated with prednisone	High dose glucocorticoids	11/12 (92%)	Mean dose prednisone as 46.6 mg/day
Resolution of psychosis	Appenzeller, 2008, 471	Observational cohort study	Mean 6. 2 years (SD 2.3), range 2.3–10.2 years	19 patients with acute psychosis at lupus disease onset, 17 were female, mean age 25.6 (SD 5.6)	Glucocorticoids 0.5-1.0 mg/kg/day + anti-psychotics	19/19 (100%)	All had resolution of acute psychosis
Prevention of recurrent psychosis	Appenzeller, 2008, 471	Observational cohort study	Mean 6. 2 years (SD 2.3), range 2.3–10.2 years	19 patients with acute psychosis at lupus disease onset, 17 were female, mean	Glucocorticoids 0.5-1.0 mg/kg/day + anti-psychotics	11/19 (58%)	The other 8 patients had recurrent psychosis

				age 25.6 (SD 5.6)			
Resolution of psychosis	Fanouriakis, 2016, 2715	Observational cohort study	Mean 50 months, IQR 70 months	11 patients with psychosis out of 46 with NPSLE, overall NPSLE had mean age 45 years (range 14–68 years) and 87% female	IV cyclophosphamide pulses	8 (73%) cases had complete resolution, 2 (18%) had partial resolution, 1 (9%) refractory to treatment	

References:

Randomized controlled trials:
-None

Comparative observational studies:
-None

Single arm studies: 7 studies
-
Studies reviewed and excluded: None

References:

1. Abel T, Gladman DD, Urowitz MB. Neuropsychiatric lupus. The Journal of rheumatology. 1980;7(3):325-33.
2. Appenzeller S, Cendes F, Costallat LT. Acute psychosis in systemic lupus erythematosus. Rheumatology international. 2008;28(3):237-43.
3. Boumpas DT, Yamada H, Patronas NJ, Scott D, Klippel JH, Balow JE. Pulse cyclophosphamide for severe neuropsychiatric lupus. The Quarterly journal of medicine. 1991;81(296):975-84.
4. Fanouriakis A, Adamichou C, Koutsoviti S, Panopoulos S, Staveri C, Klagou A, et al. Low disease activity-irrespective of serologic status at baseline-associated with reduction of corticosteroid dose and number of flares in patients with systemic lupus erythematosus treated with belimumab: A real-life observational study. Seminars in arthritis and rheumatism. 2018;48(3):467-74.
5. Gibson T, Myers AR. Nervous system involvement in systemic lupus erythematosus. Annals of the rheumatic diseases. 1975;35(5):398-406.
6. González B, Hernández P, Olguín H, Miranda M, Lira L, Toso M, et al. Changes in the survival of patients with systemic lupus erythematosus in childhood: 30 years experience in Chile. Lupus. 2005;14(11):918-23.
7. Levy Y, Sherer Y, Ahmed A, Langevitz P, George J, Fabbrizzi F, et al. A study of 20 SLE patients with intravenous immunoglobulin--clinical and serologic response. Lupus. 1999;8(9):705-12.

P46. In patients with active, newly diagnosed or flare of mononeuritis multiplex secondary to active SLE, does glucocorticoid with additional (listed) therapies improve clinical outcomes compared to glucocorticoid with or without CYC?

Outcomes (please list the outcomes as reported in the project plan):

- Resolution of mononeuritis multiplex

- Prevention of recurrent mononeuritis multiplex
- Neurologic damage
- SDI (disease damage)
- Mortality
- Quality of life

Patient important outcomes (addressed in the study only):
Complete response defined as "resolution of mononeuritis multiplex with normal neurologic exam."
Evidence Summary:
One single-arm study addressed this PICO question (1). Among 7 patients with neurologic lupus-combination of acute confusional state and mononeuritis multiplex treated with IV Cyclophosphamide, 5 patients had complete response.

Outcomes (Name + Summary)	Author, year, RefID	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Resolution of neurologic lupus (including acute confusional state and mononeuritis multiplex)	Petri, 2010, 7076	Randomized clinical trial, but only one arm is relevant to PICO	36 months	7 with neurologic lupus-combination of acute confusional state and mononeuritis multiplex. Does not give number with mononeuritis multiplex specificallys	IV Cyclophosphamide (monthly x 6 induction then every 3 months maintenance)	5 patients had complete response	Does not specify how many patients had mononeuritis multiplex vs acute confusional state for the sample size or the number who responded.

References:

Randomized controlled trials:
-None

Comparative observational studies:
-None

Single arm studies: 1
-

Studies reviewed and excluded: None

References:

1. Petri M, Brodsky RA, Jones RJ, Gladstone D, Fillius M, Magder LS. High-dose cyclophosphamide versus monthly intravenous cyclophosphamide for systemic lupus erythematosus: a prospective randomized trial. Arthritis and rheumatism. 2010;62(5):1487-93.

P48. In patients with cognitive dysfunction or decline secondary to active SLE in the absence of stroke, does addition of glucocorticoid or immunosuppressive therapy to cognitive rehabilitation therapy improve clinical outcomes compared to cognitive rehabilitation therapy only?

Outcomes (please list the outcomes as reported in the project plan):

- Further decline in cognitive ability
- Neurologic damage
- SDI (disease damage)
- Mortality
- Quality of life
- Treatment-related adverse events of infection and cytopenias
- Functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)
- Cumulative glucocorticoid dose

Patient important outcomes (addressed in the study only):

Evidence Summary:
There was one single-arm study that addressed this PICO question (1). Among 88 patients with NPSLE, 84% had a complete response, and 8% had a partial response.

Outcomes (Name + Summary)	Author, year, RefID	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Resolution of NPSLE activity	Gupta, 2017, 3495	Observational cohort study		88 patients with NPSLE are analyzed together, including 37 with seizure	Mycophenolate and glucocorticoids	74/88 (84%) have complete response, 7/88 (8%) have partial response	All NPSLE analyzed together

References:

Randomized controlled trials:
-None

Comparative observational studies:
-None

Single arm studies: 1
-
Studies reviewed and excluded: None
References:

1. Gupta N, Ganpati A, Mandal S, Mathew J, Goel R, Mathew AJ, et al. Mycophenolate mofetil and deflazacort combination in neuropsychiatric lupus: a decade of experience from a tertiary care teaching hospital in southern India. Clinical rheumatology. 2017;36(10):2273-9.

Mucocutaneous

Evidence Reports Informing Multiple PICOs

Comparative:
Belimumab vs SOC:

P50.4.f. Among SLE patients with active acute cutaneous lupus despite treatment with topical steroid and HCQ, does additional therapy, compared to no additional therapy, improve clinical outcomes?

P51.7.i. Among SLE patients with active SCLE or DLE on HCQ and topical steroid therapy, does the addition of listed therapies, compared to no additional therapy, improve clinical outcomes?
P53.5.m. In SLE patients with chilblains, does addition of the listed medical treatments compared to symptomatic measures (with or without topical therapies) lead to improved clinical outcomes?
P54.5.p. In SLE patients with cutaneous vasculitis, what is the impact of listed medical treatments compared to topical steroids alone or other standard therapy on clinical outcomes?
Population: SLE patients with mucocutaneous
Interventions: Belimumab

Comparator: Standard of Care
Outcomes:
BILAG improvement
SLEDAI improvement

Table 1.

Study	Design	Population	Intervention	Comparator	Outcomes
Manzi 2012[1]	Post hoc analysis for BLISS 52 and BLISS 72	Patients with active SLE	Belimumab 10 mg	Standard of care (immunosuppressive therapy, or/and steroids, or/and HCQ)	BILAG improvement and SLEDAI improvement
Zhang 2018[2]	RCT	Patients with active SLE (Asians)	Belimumab 10 mg	Standard of care (immunosuppressive therapy, or/and steroids, or/and HCQ)	BILAG improvement

Brunner 2020[3]	RCT	Pediatric patients with SLE	Belimumab 10 mg/kg	Standard of care	BILAG improvement

Evidence summary: Improvement of SLEDAI-2K (mucocutaneous) were higher in belimumab arm compared to standard of care, with an absolute effect (CI) of 99 more per 1,000(from 31 more to 175 more). This is based on very low certainty of evidence because of risk of bias (post hoc analysis without randomization) and imprecision (wide CI in absolute effect and small sample size). Whereas the BILAG score showed an absolute effect of 89 more per 1,000 (from 12 more to 179 more) in the study with post hoc analysis, and an effect of 133 more per 1,000(from 9 more to 293 more) in the RCT. These results are based on low certainty of evidence due to risk of bias (in the post hoc analysis without randomization) and imprecision in the RCT (wide CI in absolute effect).

A systematic review[4] was found having multiple articles assessing Belimumab in mucocutaneous SLE, however, most of the studies did not have results in the primary manuscript or supplementary material specific to mucocutaneous SLE, or included non-comparative data. Therefore, the only study included was Brunner 2020 which mentions pediatric population with SLE taking Belimumab. The absolute effect

Safety profile: For adverse events, serious adverse events, infections, adverse events leading to discontinuation, were comparable between both arms (CI between the borders of minimally importance difference) with moderate-high certainty of the evidence.

Evidence profile:

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Belimumab**	**Standard of care**	**Relative (95% CI)**	**Absolute (95% CI)**	
BILAG-Post hoc											
1[1]	randomised trials	serious[a]	not serious	not serious	serious[b]	none	150/315 (47.6%)	136/350 (38.9%)	**RR 1.23** (1.03 to 1.46)	**89 more per 1,000** (from 12 more to 179 more)	⊕⊕◯◯ Low[a,b]
BILAG-RCT											
1[2]	randomised trials	not serious	not serious	not serious	serious[b]	none	130/225 (57.8%)	47/106 (44.3%)	**RR 1.30** (1.02 to 1.66)	**133 more per 1,000** (from 9 more to	⊕⊕⊕◯ Moderate[b]

										293 more)		

SELENA-SLEDAI 2K Improvement-General Mucocutaneous

1[1]	randomised trials	serious[a]	not serious	not serious	serious[b]	none	249/454 (54.8%)	211/469 (45.0%)	**RR 1.22** (1.07 to 1.39)	**99 more per 1,000** (from 31 more to 175 more)	⊕⊕◯◯ Low[a,b]	

Adverse events

5	randomised trials	not serious	not serious	not serious	not serious	none	1597/1920 (83.2%)	1074/1242 (86.5%)	**RR 0.99** (0.96 to 1.02)	**9 fewer per 1,000** (from 35 fewer to 17 more)	⊕⊕⊕⊕ High	

Adverse events leading to discontinuation (Dichotomous)

5	randomised trials	not serious	not serious	not serious	not serious	none	129/1754 (7.4%)	101/1242 (8.1%)	**RR 0.90** (0.70 to 1.16)	**8 fewer per 1,000** (from 24 fewer to 13 more)	⊕⊕⊕⊕ High	

Serious adverse events

5	randomised trials	not serious	not serious	not serious	not serious	none	256/1920 (13.3%)	208/1242 (16.7%)	**RR 0.83** (0.70 to 0.98)	**28 fewer per 1,000** (from 50 fewer to 3 fewer)	⊕⊕⊕⊕ High	

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

Explanations

a. Non-randomized study (Post hoc analysis)
b. Wide CI in absolute effect

Certainty assessment							№ of patients		Effect		Certainty	
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Belimumab	Standard of care	Relative (95% CI)	Absolute (95% CI)		

BILAG-Peds

1	randomised trials	not serious	not serious	not serious	very serious[a,b]	none	22/43 (51.2%)	13/27 (48.1%)	**RR 1.06** (0.65 to 1.73)	**29 more per 1,000** (from 169 fewer to 351 more)	⊕⊕◯◯ Low[a,b]	

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

Explanations

a. Small sample size and number of events

b. Wide absolute CI

References: Randomized clinical trials (2 RCTs, and 1 post hoc analysis)

1. Manzi S, Sánchez-Guerrero J, Merrill JT, et al. Effects of belimumab, a B lymphocyte stimulator-specific inhibitor, on disease activity across multiple organ domains in patients with systemic lupus erythematosus: combined results from two phase III trials. *Ann Rheum Dis*. 2012;71(11):1833-1838. doi:10.1136/annrheumdis-2011-200831
2. Zhang, Fengchun et al. “A pivotal phase III, randomised, placebo-controlled study of belimumab in patients with systemic lupus erythematosus located in China, Japan and South Korea.” *Annals of the rheumatic diseases* vol. 77,3 (2018): 355-363. doi:10.1136/annrheumdis-2017-211631
3. Brunner HI, Abud-Mendoza C, Viola DO, Calvo Penades I, Levy D, Anton J, Calderon JE, Chasnyk VG, Ferrandiz MA, Keltsev V, Paz Gastanaga ME, Shishov M, Boteanu AL, Henrickson M, Bass D, Clark K, Hammer A, Ji BN, Nino A, Roth DA, Struemper H, Wang ML, Martini A, Lovell D, Ruperto N; Paediatric Rheumatology International Trials Organisation (PRINTO) and the Pediatric Rheumatology Collaborative Study Group (PRCSG). Safety and efficacy of intravenous belimumab in children with systemic lupus erythematosus: results from a randomised, placebo-controlled trial. Ann Rheum Dis. 2020 Oct;79(10):1340-1348. doi: 10.1136/annrheumdis-2020-217101. Epub 2020 Jul 22. PMID: 32699034; PMCID: PMC7509523.
4. Kneeland R, Montes D, Endo J, Shields B, Bartels CM, Garg S. Improvement in Cutaneous Lupus Erythematosus After Twenty Weeks of Belimumab Use: A Systematic Review and Meta-Analysis. Arthritis Care Res (Hoboken). 2023 Aug;75(8):1838-1848. doi: 10.1002/acr.25058. Epub 2023 Feb 3. PMID: 36358025.

P50.4.f. Among SLE patients with active acute cutaneous lupus despite treatment with topical steroid and HCQ, does additional therapy, compared to no additional therapy, improve clinical outcomes?

P51.7.i. Among SLE patients with active SCLE or DLE on HCQ and topical steroid therapy, does the addition of listed therapies, compared to no additional therapy, improve clinical outcomes?

P53.5.m. In SLE patients with chilblains, does addition of the listed medical treatments compared to symptomatic measures (with or without topical therapies) lead to improved clinical outcomes?

Population: SLE patients with mucocutaneous

Interventions:

- Belimumab

Comparator:

- Standard of Care

Outcomes:

- SLEDAI improvement

Table 1.

Study	Design	Population	Intervention	Comparator	Outcomes
Manzi 2012	Post hoc analysis for BLISS 52 and BLISS 72	Patients with active SLE	Belimumab 10 mg	Standard of care (immunosuppressive therapy, or/and steroids, or/and HCQ)	SLEDAI improvement

Evidence summary: Improvement of SLEDAI-2K (mucocutaneous) were higher in belimumab arm compared to standard of care, with an absolute effect (CI) of104 more per 1,000(from 28 more to 192 more) These results are based on low certainty of evidence due to risk of bias (in the post hoc analysis without randomization) and imprecision in the RCT (wide CI in absolute effect).
Safety profile: For adverse events, serious adverse events, infections, adverse events leading to discontinuation, were comparable between both arms (CI between the borders of minimally importance difference) with moderate-high certainty of the evidence.

Evidence profile:

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Belimumab	standard of care	Relative (95% CI)	Absolute (95% CI)	
SELENA-SLEDAI 2K-Rash											
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	151/362 (41.7%)	114/363 (31.4%)	**RR 1.33** (1.09 to 1.61)	**104 more per 1,000** (from 28 more to 192 more)	⨁⨁◯◯ Low[a,b]
Adverse events											

5	randomised trials	not serious	not serious	not serious	not serious	none	1597/1920 (83.2%)	1074/1242 (86.5%)	**RR 0.99** (0.96 to 1.02)	**9 fewer per 1,000** (from 35 fewer to 17 more)	⊕⊕⊕⊕ High

Adverse events leading to discontinuation (Dichotomous)

5	randomised trials	not serious	not serious	not serious	not serious	none	129/1754 (7.4%)	101/1242 (8.1%)	**RR 0.90** (0.70 to 1.16)	**8 fewer per 1,000** (from 24 fewer to 13 more)	⊕⊕⊕⊕ High

Serious adverse events

5	randomised trials	not serious	not serious	not serious	not serious	none	256/1920 (13.3%)	208/1242 (16.7%)	**RR 0.83** (0.70 to 0.98)	**28 fewer per 1,000** (from 50 fewer to 3 fewer)	⊕⊕⊕⊕ High

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

Explanations

a. Non-randomized study (Post hoc analysis)
b. Wide CI in absolute effect

References: Randomized clinical trial (1 post hoc analysis)

1. Manzi S, Sánchez-Guerrero J, Merrill JT, et al. Effects of belimumab, a B lymphocyte stimulator-specific inhibitor, on disease activity across multiple organ domains in patients with systemic lupus erythematosus: combined results from two phase III trials. *Ann Rheum Dis*. 2012;71(11):1833-1838. doi:10.1136/annrheumdis-2011-200831

i) MTX vs Chloroquine:

P50.3.c. Among SLE patients with active acute cutaneous lupus despite treatment with topical steroid and HCQ, does additional therapy, compared to no additional therapy, improve clinical outcomes?
P51.5.e. Among SLE patients with active SCLE or DLE on HCQ and topical steroid therapy, does the addition of listed therapies, compared to no additional therapy, improve clinical outcomes?

Population: SLE patients with active ACLE on HCQ and topical steroid therapy

Interventions: Continued HCQ and topical steroid therapy with addition of

- MTX

Comparator:

- Chloroquine+steroids

Outcomes:

- Persistence of skin lesions

Table 1.

Study	Design	Population	Intervention	Comparator	Outcomes
Islam 2012	RCT	Patients with active SLE	MTX	Chloroquine+steroids	• Persistence of skin lesions

Evidence summary: 1 RCT addressed MTX use in patients with cutaneous involvement. In Islam et al, it was MTX versus chloroquine, and both arms were taking background steroids. The absolute effect was 93 fewer per 1,000
(from 124 fewer to 449 more). This was based on low certainty evidence due to a high risk of bias (although it was randomized, the study was not blinded) and imprecision (small number of events and sample size, leading to wide confidence interval).

Evidence profile:

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	Chloroquine	Relative (95% CI)	Absolute (95% CI)	
Persistence of Cutaneous lesions											
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	0/13 (0.0 %)	3/24 (12.5%)	**RR 0.26** (0.01 to 4.59)	**93 fewer per 1,000** (from 124 fewer to 449 more)	⨁◯◯◯ Very low[a,b]

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

Explanations

a. No blinding even though there was randomization.
b. Wide CI in absolute risk.

References: 1 Randomized clinical trial

- Islam MN, Hossain M, Haq SA, Alam MN, Ten Klooster PM, Rasker JJ. Efficacy and safety of methotrexate in articular and cutaneous manifestations of systemic lupus erythematosus. Int J Rheum Dis. 2012 Feb;15(1):62-8. doi: 10.1111/j.1756-185X.2011.01665.x. Epub 2011 Sep 21. PMID: 22324948.

ii) MTX vs SOC:

P50.3.c. Among SLE patients with active acute cutaneous lupus despite treatment with topical steroid and HCQ, does additional therapy, compared to no additional therapy, improve clinical outcomes?
P51.5.e. Among SLE patients with active SCLE or DLE on HCQ and topical steroid therapy, does the addition of listed therapies, compared to no additional therapy, improve clinical outcomes?

Population: SLE patients with active ACLE on HCQ and topical steroid therapy

Interventions: Continued HCQ and topical steroid therapy with addition of
- MTX

Comparator:
- Steroids

Outcomes:
- Persistence of skin lesions

Table 1.

Study	Design	Population	Intervention	Comparator	Outcomes
Carneiro 1999	RCT	Patients with active SLE	MTX	Standard of care (steroids)	• Persistence of skin lesions

Evidence summary: 1 RCT addressed MTX use in patients with cutaneous involvement. In Carneiro et al, they compared MTX to a placebo, and all patients were taking background steroids. The absolute effect 720 fewer per 1,000
(from 890 fewer to 320 fewer). This was based on low certainty evidence due to a high risk of bias (although it was randomized, there were differences in baseline characteristics) and imprecision (small number of events and sample size, leading to wide confidence interval).

Evidence profile:

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	standard of care	Relative (95% CI)	Absolute (95% CI)	
Persistance of Cutaneous lesions- MTX vs SOC											
1	randomised trials	serious[a]	not serious	not serious	Very serious[b,c]	none	3/12 (25.0 %)	16/16 (100.0 %)	**RR 0.28** (0.11 to 0.68)	**720 fewer per 1,000** (from 890 fewer to 320 fewer)	⨁⨁⨁◯ Very Low[a,b,c]

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

Explanations

a. Differences in baseline characteristics.
b. Wide CI in the absolute effect.
c.Small Sample Size

References: 1 Randomized clinical trial

- Carneiro JR, Sato EI. Double blind, randomized, placebo controlled clinical trial of methotrexate in systemic lupus erythematosus. J Rheumatol. 1999;26(6):1275-1279.

iii) MMF vs SOC:

P50.3.e Among SLE patients with active acute cutaneous lupus despite treatment with topical steroid and HCQ, does additional therapy, compared to no additional therapy, improve clinical outcomes?
P51.5.g Among SLE patients with active SCLE or DLE on HCQ and topical steroid therapy, does the addition of listed therapies, compared to no additional therapy, improve clinical outcomes?

Population: Patients with SLE and rash

Interventions:

- MMF

Comparator:

- Standard of Care

Outcomes:

- New or worsening symptoms
- Adverse events

Table 1.

Study	Design	Population	Intervention	Comparator	Outcomes
You 2024	RCT	Patients with active SLE	oral prednisone (0.5 mg/kg/d) and hydroxychloroquine sulfate (5 mg/kg/d) and MMF (500 mg twice daily) (MMF group) for 96 weeks	oral prednisone (0.5 mg/kg/d) and hydroxychloroquine sulfate (5 mg/kg/d)	-New or Worsening symptoms -Adverse Events

Evidence summary: One study was included however, it was not specific for patients with mucocutaneous SLE.Instead in had patients with SLE with only 5/65 from the control group and 8/65 from the MMF group having oral ulcers at baseline. Patients were followed up at 96 weeks. The new or worsening symptoms were later on calculated out of the whole populations not just those having symptoms at baseline. There was 0 fewer patients per 1,000(from 0 fewer to 0 fewer) in the MMF group having new or worsening symptoms of oral ulcers. However, those in the MMF group had 106 more per 1,000(from 50 fewer to 350 more) risk of adverse events (infection, GI, bone fracture, osteonecrosis of the femoral head or other events). Infections included URTI, pneumonia,UTI, herpes zoster, candida or tuberculosis.

Evidence report:

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**MMF with Prednisone and HCQ**	**Prednisone with HCQ**	**Relative (95% CI)**	**Absolute (95% CI)**	
New or worsening symptoms-Rash											
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	3/65 (4.6%)	1/65 (1.5%)	**RR 3.00** (0.32 to 28.09)	**31 more per 1,000** (from 10 fewer to 417 more)	⨁◯◯◯ Very low[a,b]

Any adverse event

1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	30/65 (46.2%)	23/65 (35.4%)	**RR 1.30** (0.86 to 1.99)	**106 more per 1,000** (from 50 fewer to 350 more)	⊕◯◯◯ Very low[a,b]

Adverse event-Infection

1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	22/65 (33.8%)	23/65 (35.4%)	**RR 0.96** (0.60 to 1.53)	**14 fewer per 1,000** (from 142 fewer to 188 more)	⊕◯◯◯ Very low[a,b]

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

Explanations

a. Study was an open label observer blinded study
b. Wide absolute CI

Reference:

1. You Y, Zhou Z, Wang F, et al. Mycophenolate Mofetil and New-Onset Systemic Lupus Erythematosus: A Randomized Clinical Trial. JAMA Netw Open. 2024;7(9):e2432131. doi:10.1001/jamanetworkopen.2024.32131

Non-Comparative:

i) Anifrolumab vs SOC:

P50.4.g. Among SLE patients with active acute cutaneous lupus despite treatment with topical steroid and HCQ, does additional therapy, compared to no additional therapy, improve clinical outcomes?
P51.7.j. Among SLE patients with active SCLE or DLE on HCQ and topical steroid therapy, does the addition of listed therapies, compared to no additional therapy, improve clinical outcomes?
P53.5.n. In SLE patients with chilblains, does addition of the listed medical treatments compared to symptomatic measures (with or without topical therapies) lead to improved clinical outcomes?
P54.5.q. In SLE patients with cutaneous vasculitis, what is the impact of listed medical treatments compared to topical steroids alone or other standard therapy on clinical outcomes?

Population:

- SLE patients with active cutaneous lupus, SCLE, DLE, chilblains or cutaneous vasculitis

Intervention:

- Anifrolumab300 mg

Comparator:

- Standard of care

Outcomes:

- BILAG (mucocutaneous),
- Change in baseline SLEDAI-2K (mucocutaneous),
- >50% improvement in CLASI

Table 1.

Study	Design	Population	Intervention	Comparator	Outcomes
Furie 2017 MUSE trial	RCT	Patients with active SLE	Anifrolumab 300 mg	Standard of care (immunosuppressive therapy, or/and steroids, or/and HCQ)	>50% improvement in CLASI in patients who had a score>10 at baseline to week 52
Furie 2019 TULIP 1	RCT	Patients with active SLE	Anifrolumab 300 mg	Standard of care (immunosuppressive therapy, or/and steroids, or/and HCQ)	≥50% reduction in CLASI activity score from baseline to week 12
Morand 2020 TULIP 2	RCT	Patients with active SLE	Anifrolumab 300 mg	Standard of care (immunosuppressive therapy, or/and steroids, or/and HCQ)	≥50% reduction in CLASI activity score from baseline to week 12
Morand 2022	Posthoc analysis (TULIP 1 and 2)	Patients with active SLE	Anifrolumab 300 mg	Standard of care (immunosuppressive therapy, or/and steroids, or/and HCQ)	BILAG (mucocutaneous), Change in baseline SLEDAI-2K (mucocutaneous)
Merill 2018	Posthoc analysis (MUSE)	Patients with active SLE	Anifrolumab 300 mg	Standard of care (immunosuppressive therapy, or/and	BILAG (mucocutaneous), Change in baseline

				steroids, or/and HCQ)	SLEDAI-2K (mucocutaneous), >50% improvement in CLASI in patients who had a score>0 at baseline to week 52

Evidence summary: 3 randomized clinical trials (MUSE, TULIP 1, TULIP 2) addressed Anifrolumab versus standard of care (SOC). For SLEDAI-2K, 2 studies showed that 173 more per 1000 (from 97 more to 263 more) had an improvement in SLEDAI-2K in the Anifrolumab arm. For BILAG, the same 2 studies (which are post hoc analyses) had 213 more SLEDAI-2K improvement per 1,000 (from 130 more to 310 more) also in the Anofrolumab arm. For the CLASI activity score, measurements varied in which the MUSE trial assessed ≥50% reduction in CLASI activity score>10 from baseline to week 52 with a result of 323 more per 1,000(from 22 more to 892 more) while the MUSE post hoc analyses assessed ≥50% reduction in CLASI activity score>0 from baseline to week 52 with a result of 283 more per 1,000(from 108 more to 526 more). Two other studies (TULIP-1 and TULIP-2) assessed efficacy ≥50% reduction in CLASI activity score>10 from baseline to week 12 in which the result was 191 more per 1,000 (from 43 more to 416 more). All these studies did not specify the mucocutaneous symptoms, except for the post hoc analyses of MUSE (Merril 2018) in which they specified that mCLASI was defined as the activity portions of CLASI that describe skin erythema, scale/hypertrophy and inflammation of the scalp and that damage, oral ulcers and alopecia without scalp inflammation were excluded from the mCLASI analysis. However, PICOs related to alopecia and oral ulcers did not have Anifrolumab as an intervention of interest.
Adverse events (AE) were comparable between both arms but serious AE and AE led to discontinuation were 48 fewer per 1,000 (from 86 fewer to 5 more) 16 fewer per 1,000 (from 43 fewer to 75 more) in the Anifrolumab compared to SOC.

Evidence Profile:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Anifrolumab**	**Standard of care**	**Relative (95% CI)**	**Absolute (95% CI)**		
Efficacy-SLEDAI-2K												
2[1,2]	randomised trials	serious[a]	not serious	not serious	serious[b]	none	229/436 (52.5%)	151/419 (36.0%)	**RR 1.48** (1.27 to 1.73)	**173 more per 1,000** (from 97 more	⊕⊕◯◯ Low[a,b]	

										to 263 more)		

Efficacy- BILAG

2[1,2]	randomised trials	serious[a]	not serious	not serious	serious[b]	none	216/377 (57.3%)	143/397 (36.0%)	**RR 1.59** (1.36 to 1.86)	**213 more per 1,000** (from 130 more to 310 more)	⊕⊕◯◯ Low[a,b]	

Efficacy- ≥50% reduction in CLASI activity score>0 from baseline to week 52

1[2]	randomised trials	serious[a]	not serious	not serious	serious[b]	none	57/92 (62.0%)	30/89 (33.7%)	**RR 1.84** (1.32 to 2.56)	**283 more per 1,000** (from 108 more to 526 more)	⊕⊕◯◯ Low[a,b]	

Efficacy- ≥50% reduction in CLASI activity score>10 from baseline to week 52

1[3]	randomised trials	not serious	not serious	not serious	very serious[b,c]	none	17/27 (63.0%)	8/26 (30.8%)	**RR 2.05** (1.07 to 3.90)	**323 more per 1,000** (from 22 more to 892 more)	⊕⊕◯◯ Low[b,c]	

Efficacy-≥50% reduction in CLASI activity score>10 from baseline to week 12

1[4,5]	randomised trials	not serious	not serious	not serious	serious[b]	none	48/107 (44.9%)	24/94 (25.5%)	**RR 1.75** (1.17 to 2.63)	**191 more per 1,000** (from	⊕⊕⊕◯ Moderate[b]	

										43 more to 416 more)		

Serious adverse events

3	randomised trials	serious	not serious	not serious	serious	none	56/459 (12.2%)	80/467 (17.1%)	**RR 0.72** (0.50 to 1.03)	**48 fewer per 1,000** (from 86 fewer to 5 more)	⊕⊕◯◯ Low	

Adverse events

3	randomised trials	not serious	not serious	not serious	serious	none	404/459 (88.0%)	375/467 (80.3%)	**RR 1.09** (1.03 to 1.16)	**72 more per 1,000** (from 24 more to 128 more)	⊕⊕⊕◯ Moderate	

Adverse events leading to discontinuation

3	randomised trials	serious	not serious	not serious	serious	none	19/459 (4.1%)	26/468 (5.6%)	**RR 0.71** (0.22 to 2.35)	**16 fewer per 1,000** (from 43 fewer to 75 more)	⊕⊕◯◯ Low	

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

Explanations

a. Studies are post hoc.
b. Wide range of CI in absolute risk.
c. Very low sample size.

References: 3 RCTs, 2 post hoc analyses of the RCTs

1.Morand, Eric F, Furie, Richard A, Bruce, Ian N, Vital, Edward M, Dall'Era, Maria, Maho, Emmanuelle, Pineda, Lilia, Tummala, Raj. Efficacy of anifrolumab across organ domains in patients with moderate-to-severe systemic lupus erythematosus: a post-hoc analysis of pooled data from the TULIP-1 and TULIP-2 trials.The Lancet Rheumatology; 2022.
2.Merrill, Joan T, Furie, Richard, Werth, Victoria P, Khamashta, Munther, Drappa, Jorn, Wang, Liangwei, Illei, Gabor, Tummala, Raj. Anifrolumab effects on rash and arthritis: impact of the type I interferon gene signature in the phase IIb MUSE study in patients with systemic lupus erythematosus.Lupus Science & Medicine; 2018.
3.Furie, Richard, Khamashta, Munther, Merrill, Joan T, Werth, Victoria P, Kalunian, Kenneth, Brohawn, Philip, Illei, Gabor G, Drappa, Jorn, Wang, Liangwei, Yoo, Stephen, Investigators, CD1013,Study. Anifrolumab, an Anti-Interferon-α Receptor Monoclonal Antibody, in .Arthritis & rheumatology (Hoboken, N.J.); 2017.

4.Morand, Eric F, Furie, Richard, Tanaka, Yoshiya, Bruce, Ian N, Askanase, Anca D, Richez, Christophe, Bae, Sang-Cheol, Brohawn, Philip Z, Pineda, Lilia, Berglind, Anna, Tummala, Raj, Investigators, TULIP-2,Trial. Trial of Anifrolumab in Active Systemic Lupus Erythematosus..The New England journal of medicine; 2020.
5.Furie, Richard A, Morand, Eric F, Bruce, Ian N, Manzi, Susan, Kalunian, Kenneth C, Vital, Edward M, Lawrence Ford, Theresa, Gupta, Ramesh, Hiepe, Falk, Santiago, Mittermayer, Brohawn, Philip Z, Berglind, Anna, Tummala, Raj. Type I interferon inhibitor anifrolumab in active systemic lupus erythematosus (TULIP-1): a randomised, controlled, phase 3 trial.The Lancet Rheumatology; 2019.

ii) Rituximab vs SOC:

P50.4.h. Among SLE patients with active acute cutaneous lupus despite treatment with topical steroid and HCQ, does additional therapy, compared to no additional therapy, improve clinical outcomes?
P51.7.k. Among SLE patients with active SCLE or DLE on HCQ and topical steroid therapy, does the addition of listed therapies, compared to no additional therapy, improve clinical outcomes?
P52.3.g. In SLE patients with bullous lupus, what is the impact of listed medical treatments compared to steroids alone on clinical outcomes?
P54.5. In SLE patients with cutaneous vasculitis, what is the impact of listed medical treatments compared to topical steroids alone or other standard therapy on clinical outcomes?

Population: Patients with mucocutaneous SLE

Interventions:
- Rituximab

Comparator:
- Standard of Care

Outcomes:
- Partial Response
- Complete Response
- Adverse Events
- Flare rate in patients who had achieved a response of low disease activity.

Table 1.

Study	Design	Population	Intervention	Comparator	Outcomes
Merril 2010	RCT-EXPLORER Trial	Patients with active SLE	Rituximab (2 1,000-mg doses given 14 days apart)	Standard of care (immunosuppressive therapy, or/and steroids, or/and HCQ)	-Partial Response -Complete Response -Adverse Events
Merril 2011	Post hoc analysis of EXPLORER Trial	Patients with active SLE	Rituximab (2 1,000-mg doses	Standard of care (immunosuppressive therapy, or/and steroids, or/and HCQ)	- Flare rate in patients who had achieved a response of low disease activity

			given 14 days apart)		

Evidence summary:

1 RCT and 1 post hoc analysis of the RCT. These studies did not specify the type of mucocutaneous involvement; thus, they were reflected in different PICOs. The RCT mentioned that "most" patients had disease activity in the mucocutaneous domain. Therefore, we assumed that the whole patients had mucocutaneous symptoms. Outcomes were reports as partial and complete response using BILAG score being defined as:

- Major clinical response: Achieving BILAG C scores or better in all organs at week 24 without experiencing a severe flare (1 new domain with a BILAG A score or 2 new domains with a BILAG B score) from day 1 to week 24 and maintaining this response without a moderate or severe flare (≥1 new domains with a BILAG A or B score) to week 52.
- Partial clinical response:

1) achieving BILAG C scores or better at week 24 and maintaining this response without a new BILAG A or B score for 16 consecutive weeks **OR**

2) achieving no more than 1 organ with a BILAG B score at week 24 without achieving ≥1 new BILAG A or B score to week 52 **OR**

3) achieving a maximum of 2 BILAG B scores at week 24 without developing BILAG A or B scores in new domains until week 52 if the baseline BILAG score for the patient was 1 A score plus ≥2 B scores, ≥2 A scores, or ≥4 B scores.

Partial Response:

The results showed an absolute effect of 46 more per 1,000(from 35 fewer to 203 more). This outcome was based on low certainty evidence due to imprecision.

Complete Response:

The results showed an absolute effect of 35 fewer per 1,000(from 92 fewer to 73 more). This outcome was based on very low certainty evidence due to imprecision.

Adverse Events:

The results showed an absolute effect of 15 more per 1,000(from 95 fewer to 167 more). This outcome included infusion-related adverse events, infections, and deaths (4/64 Rituximab vs 1/32 placebo). It was based on very low certainty evidence due to imprecision.

Flare rate in patients who had achieved a response of low disease activity:

Patients who had a responded to Rituximab were followed up for 12 months and the results showed an absolute effect of 176 fewer per 1,000
(from 325 fewer to 4 more) flares in patients with Rituximab than in those given standard of care. This outcome was based on low certainty evidence due to imprecision and no randomization.

Evidence profile:

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab	standard of care	Relative (95% CI)	Absolute (95% CI)	
Partial Response											
1[1]	randomised trials	serious[a]	not serious	not serious	serious[b]	none	29/169 (17.2%)	11/88 (12.5%)	**RR 1.37** (0.72 to 2.62)	**46 more per 1,000** (from 35 fewer to 203 more)	⨁⨁⨁◯ Low[a,b]
Complete Response											
1[1]	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	21/169 (12.4%)	14/88 (15.9%)	**RR 0.78** (0.42 to 1.46)	**35 fewer per 1,000** (from 92 fewer to 73 more)	⨁⨁◯◯ Very Low[a]
Adverse Events											
1[1]	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	64/169 (37.9%)	32/88 (36.4%)	**RR 1.04** (0.74 to 1.46)	**15 more per 1,000** (from 95 fewer to 167 more)	⨁⨁◯◯ Very Low[a]
Flare rate in patients who had achieved a response of low disease activity (follow-up: 12 months)											
1[2]	randomised trials	serious[c]	not serious	not serious	serious[b]	none	81/127 (63.8%)	37/58 (63.8%)	**HR 0.61** (0.37 to 1.01)	**176 fewer per 1,000** (from 325 fewer to 4 more)	⨁⨁◯◯ Low[b,c]

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

Explanations

a. Missing data
b. Wide CI in absolute effect

c.Non-randomized study (Post hoc analysis)

References

1.Merrill, Joan T, Neuwelt, C Michael, Wallace, Daniel J, Shanahan, Joseph C, Latinis, Kevin M, Oates, James C, Utset, Tammy O, Gordon, Caroline, Isenberg, David A, Hsieh, Hsin-Ju, Zhang, David, Brunetta, Paul G. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus .Arthritis and rheumatism; 2010.
2.Merrill, Jt, Buyon, Jp, Furie, Ra, Latinis, Km, Gordon, C, Hsieh, H-J, Brunetta, P. Assessment of flares in lupus patients enrolled in a phase II/III study of .Lupus; 2011.

Hydroxychloroquine Therapy: (Relevant to all PICOs)

Population: SLE patients with active ACLE on HCQ and topical steroid therapy
Interventions: Continued HCQ and topical steroid therapy with addition of

- Chloroquine
- Quinacrine
- MTX
- AZA
- MMF/MPA
- Belimumab
- Anifrolumab
- Anti-CD-20 therapy

Outcomes:

- Disease activity (skin)
- Flares
- SLE disease activity
- Disease damage
- Mortality
- Quality of life
- Adverse impact of medications - for immunosuppressives including biologics: infection and cytopenias; for antimalarials: retinal toxicity and cardiac toxicity (prolonged QTc and myopathy).

Table 1. Studies included.

Author, year, RefID	Population (age, ethnicity)	Intervention	Outcome
Yokogawa 2013[1] RefID: 10023	27 patients Japanese with cutaneous SLE (**8 ACLE**) Mean age= 40.7(range: 18-58)	HCQ at dosages< 6.5mg/kg/day (max 400mg/day)	-Disease Activity (Skin) CLASI -Adverse Events
Lim		HCQ 400mg	

2022[2] 95274	Female 7 patients		Response to treatment
Pons-Estel 2020[3] 7234	SLE patients (n=580, **but only 489 were exposed to HCQ**),90% were women, age ≥16 years, 113 (19.5%) Texan-Hispanics, 97 (16.7%) Puerto Rican-Hispanics, 201 (34.7%) African Americans and 169 (29.1%) Caucasians.	HCQ 350 mg	Presence and non-presence of integument damage
Wakiya 2019[4] 9480	33 patients, but only 31 with skin involvement 33 were female Mean age : 40.7 ± 13.7	HCQ 200 mg daily for IBW<46 kg; 200 mg and 400 mg on alternate days for IBW 46 kg and<62 kg; and 400 mg daily for IBW 62 kg.	CLASI reduction

Evidence summary:

Four studies were included in which HCQ was used in patients with SLE + cutaneous lesions. The outcome reported was complete remission and the CLASI improvement was also reported. Two studies, Wakiya et al and Pons-Estel et al. did not have skin involvement as their main focus, so the results presented were more subjective, for example: "CLASI activity score decreased". Overall, there was a decrease in the CLASI activity with only 6/27 patients having non-serious adverse events.Wakiya et al also specified that CLASI activity scores decreased (values were not specified). Lim et al classified responses into good (5/7), fair (1/7) and poor (1/7) responses.

Table 2. Outcomes

Outcome	Author, year, RefID	Study Design	Follow up Duration	Population	Intervention	Result	Notes
Disease Activity (Skin) CLASI	Yokogawa 2013[1] RefID: 10023	Retrospective cohort	16 weeks	27 patients Japanese with cutaneous SLE (**8 ACLE**)	HCQ at dosages< 6.5mg/kg/day (max 400mg/day)	Decrease of CLASI score from Mean=8.8(6.9) to	

				Mean age= 40.7(range: 18-58)		Mean=4.5(3.4)	
Adverse Events	Yokogawa 2013[1] RefID: 10023	Retrospective cohort	16 weeks	27 patients Japanese with cutaneous SLE (8 ACLE) Mean age= 40.7(range: 18-58)	HCQ at dosages< 6.5mg/kg/day (max 400mg/day)	6/27 (only 8 had ACLE) 0/27 serious adverse events	3/27: ocular symptom(blurred vision,dizziness and double vision 2/27: GI symptoms 1/27: Skin eruption
Response to treatment	Lim 2022[1] 95274	Retrospective chart review	6.2 months	Female 7 patients	HCQ 400mg	Good response : 5/7 Fair response : 1 /7 Poor response : 1/7	**Good response** was defined as a controllable disease despite the intermittent use of other additional medications for flare-ups; **fair response** was defined as a moderately controlled but active disease, frequently or always requiring additional medications; and **poor response** was defined as a disease that was uncontrollable with hydroxychloroquine, requiring a change to another medication.

Presence and non-presence of integument damage	Pons-Estel 2020[2] 7234	Prospective cohort	5 years	SLE patients (n=580, but only 489 were exposed to HCQ),90 % were women, age ≥16 years, 113 (19.5%) Texan-Hispanics, 97 (16.7%) Puerto Rican-Hispanics, 201 (34.7%) African Americans and 169 (29.1%) Caucasians.	HCQ 350 mg	Exposure was more frequent among those patients who had not developed integument damage (85.8%) than in those who had developed it (66.7%) and this difference was significant p=0.0015);	
CLASI reduction	Wakiya 2019[3] 9480	Singles center retrospective study	3 months	33 patients, but only 31 with skin involvement 33 were female Mean age: 40.7 ± 13.7	HCQ 200 mg daily for IBW<46 kg; 200 mg and 400 mg on alternate days for IBW 46 kg and<62 kg; and	CLASI activity scores Decreased (values were not specified)	The study investigated the effect of HCQ on S100A8 and S100A9 serum levels in SLE patients with low disease activity receiving immunosuppressants. So, CLASI values were not the main point of the study and

					400 mg daily for IBW 62 kg.		they were not specified.

References:

1. Yokogawa, N., Tanikawa, A., Amagai, M. et al. Response to hydroxychloroquine in Japanese patients with lupus-related skin disease using the cutaneous lupus erythematosus disease area and severity index (CLASI). Mod Rheumatol 23, 318–322 (2013). https://doi.org/10.1007/s10165-012-0656-3
2. T Lim JW, Lee JH, Kim HJ. Use of hydroxychloroquine in dermatology: A multicenter retrospective study in Korea. J Dermatol. 2022 Jan;49(1):173-178. doi: 10.1111/1346-8138.16200. Epub 2021 Oct 28. PMID: 34713476.
3. Pons-Estel GJ, Alarcón GS, González LA, Zhang J, Vilá LM, Reveille JD, McGwin G Jr; Lumina Study Group. Possible protective effect of hydroxychloroquine on delaying the occurrence of integument damage in lupus: LXXI, data from a multiethnic cohort. Arthritis Care Res (Hoboken). 2010 Mar;62(3):393-400. doi: 10.1002/acr.20097. PMID: 20391486; PMCID: PMC3202433.
4. Wakiya R, Kameda T, Ueeda K, Nakashima S, Shimada H, Mansour MF, Kato M, Miyagi T, Miyatake N, Kadowaki N, Dobashi H. Hydroxychloroquine modulates elevated expression of S100 proteins in systemic lupus erythematosus. Lupus. 2019 Jun;28(7):826-833. doi: 10.1177/0961203319846391. Epub 2019 May 8. PMID: 31068068.

PICO 50

Non-comparative:

i) Quinacrine:

P50.2.b Among SLE patients with active acute cutaneous lupus despite treatment with topical steroid and HCQ, does additional therapy, compared to no additional therapy, improve clinical outcomes?

Population: SLE patients with active ACLE on HCQ and topical steroid therapy

Interventions: Continued HCQ and topical steroid therapy with addition of

- Quinacrine

Outcomes:

- Disease activity (skin)

Table 1. Studies included.

Author, year, RefID	Population (age, ethnicity)	Intervention	Outcome

Toubi 2000[1] 9083	Female 4 patients (25, 25, 32, 36 yo)	HCQ 200mg+ Quinacrine 100mg + Pred 20-30 mg	Complete remission of skin lupus lesions

Evidence summary: One study was a prospective cohort included in which Quinacrine was used in patients with SLE + cutaneous lesions. Four patients were studied and the outcome reported was complete remission in which 2/4 patients had complete remission of lesions.

Table 2. Outcomes

Outcome	Author, year, RefID	Study Design	Follow up Duration	Population	Intervention	Result	Notes
Complete remission of skin lupus lesions	Toubi 2000[1] 9083	prospective Cohort	2-3.5 years	Female 4 patients (25, 25, 32, 36 yo)	HCQ 200mg+ Quinacrine 100mg + Pred 20-30 mg	2/4	The 2 patients who did not reach SLEDAI score zero, reached SLEDAI score 1.

References:

1. Toubi E, Rosner I, Rozenbaum M, Kessel A, Golan TD. The benefit of combining hydroxychloroquine with quinacrine in the treatment of SLE patients. Lupus. 2000;9(2):92-5. doi: 10.1191/096120300678828082. PMID: 10787004.

ii) MMF/MPA:

P50.3 Among SLE patients with active acute cutaneous lupus despite treatment with topical steroid and HCQ, does additional therapy, compared to no additional therapy, improve clinical outcomes?

Population: SLE patients with active ACLE on HCQ and topical steroid therapy

Interventions: Continued HCQ and topical steroid therapy with addition of

- MMF/MPA

Outcomes:

- Disease activity (skin)

Table 1. Studies included.

Author, year, RefID	Population (age, ethnicity)	Intervention	Outcome
Pisoni 2005[1] 7177	4 patients with ACLE AGES: 22/42/29/35 yo	MMF	Complete remission of skin lupus lesions
Tselios 2016[2] 9155	27 patients with skin disease and non-renal SLE and 30 patients with skin disease and renal SLE mean age 38.6 ± 11.7 years	Any previous treatment with MMF	Absence of skin lesions

Evidence summary: Two studies were included in which MMF was used in patients with SLE + cutaneous lesions. The outcome reported was "complete remission or absence of skin lesions). The population in both studies was adults. Tselios et al. showed some skin improvement after treatment in patients with and without renal involvement. Complete remission of skin lesions was shown to be 0/4 in 1 study and 7/27 in another study.

Table 2. Outcomes

Outcome	Author, year, RefID	Study Design	Follow up Duration	Population	Intervention	Result	Notes
Complete remission of skin lupus lesions	Pisoni 2005[1] 7177	Retrospective case series	2/24/2/42 months	4 patients with ACLE age: 22/42/29/35 yo	MMF	0/4	
Absence of skin vasculitis lesions	Tselios 2016[2] 9155	Retrospective chart review	6 and 12 months	27 patients with skin disease and non renal SLE and 30 patients with skin disease	Any previous treatment with MMF	**In 6 months:** - 7/ 27 (w/o renal) -10/30 (w/ renal disease) **In 12 months:**	Improvement was defined as the absence of the initial clinical or laboratory manifestation after 6 and 12 months.

				and renal SLE mean age 38.6 ± 11.7 yrs		-11 / 27 (w/o renal) - 16/30 (w renal disease)	

References:

1. Pisoni CN, Obermoser G, Cuadrado MJ, Sanchez FJ, Karim Y, Sepp NT, Khamashta MA, Hughes GR. Skin manifestations of systemic lupus erythematosus refractory to multiple treatment modalities: poor results with mycophenolate mofetil. Clin Exp Rheumatol. 2005 May-Jun;23(3):393-6. PMID: 15971430.
2. Tselios K, Gladman DD, Su J, Urowitz MB. Mycophenolate Mofetil in Nonrenal Manifestations of Systemic Lupus Erythematosus: An Observational Cohort Study. J Rheumatol. 2016 Mar;43(3):552-8. doi: 10.3899/jrheum.150779. Epub 2016 Jan 15. PMID: 26773121.

iii) Thalidomide:

P50.4 Among SLE patients with active acute cutaneous lupus despite treatment with topical steroid and HCQ, does additional therapy, compared to no additional therapy, improve clinical outcomes?

Population: SLE patients with active ACLE on HCQ and topical steroid therapy

Interventions:

- Thalidomide

Comparator:

- HCQ and topical steroid therapy

Outcomes:

- Disease activity (skin)
- Adverse impact of medications - for immunosuppressives including biologics: infection and cytopenias; for antimalarials: retinal toxicity and cardiac toxicity (prolonged QTc and myopathy).

Table 1. Studies included.

Author, year, RefID	Population (age, ethnicity)	Intervention	Outcome

Sato 1998[1] 7975	18 SLE patients (ACR criteria) with active cutaneous lesions not responsive to chloroquine and photoprotectors. 16 were females with mean age of 34.2yo (16-57y.o.)	Thalidomide (5-100mg/dia) + mean dose of prednisone at beginning of study was 38.3 mg/d	Complete and partial remission of the skin lesions Side effects
Wang 2015 [2] no ref ID	69 SLE patients 6 male and 63 female 18 to 60 years old	Thaidomide at 25 mg daily and gradually increased administration dose once a week until erythema was markedly improved.	Skin lesions remission Side effects

Evidence summary: Two studies were included in which Thalidomide was used in patients with SLE + cutaneous lesions. The outcome reported was complete remission, and side effects. The studies focused on the adult population. In both the reduction of the thalidomide dose resolved the adverse effects. Complete remission was seen in 13/18 patients in one study and complete remission: 39/69 patients in another study. While partial response was 5/18 in one study and 28/69 in another study.

Table 2. Outcomes

Outcome	Author, year, RefID	Study Design	Follow up Duration	Population	Intervention	Result	Notes
Complete and partial remission of the skin lesions	Sato 1998[1] 7975	Prospective cohort	6-21 months (mean 8.5m)	18 SLE patients (ACR criteria) with active cutaneous lesions not responsive to chloroquine and photoprotectors. 16 were females with	Thalidomide (5-100mg/dia) + mean dose of prednisone at beginning of study was 38.3 mg/d	Complete remission of cutaneous lesions: 13/18 partial remission in 5/18	

				mean age of 34.2yo (16-57y.o.)			
Side Effects	Sato 1998[1] 7975	Prospective cohort	6-21 months (mean 8.5m)	18 SLE patients (ACR criteria) with active cutaneous lesions not responsive to chloroquine and photoprotectors 16 were females with mean age of 34.2yo (16-57y.o.)	Thalidomide (5-100mg/dia) + mean dose of prednisone at beginning of study was 38.3 mg/d	Drowsiness: 8 /18 Intestinal constipation: 5 /18 Transient oliguria: 1 /18 Paresthesia: 1/18	All side effects disappeared with reduction of thalidomide dose.
Skin lesions remission	Wang 2015 [2] no ref ID	prospective cohort study	8 weeks	69 SLE patients 6 male and 63 female 18 to 60 years old	Thalidomide at 25 mg daily and gradually increased administration dose once a week until erythema was markedly improved.	Complete remission: 56% (39/69) partial remission: 41% (28/69) no response:3 % (2/69)	The overall clinical remission rate was 97% (66/69).
Side effects	Wang 2015 [2] no ref ID	prospective cohort study	8 weeks	69 SLE patients 6 male and 63 female 18 to 60 years old	Thalidomide at 25 mg daily and gradually increased administration dose once a week until erythema was	Drowsiness: 6/69 Constipation: 4/69 Abdominal pain: 1/69	All the adverse events were resolved after appropriate treatment, and

					markedly improved.	Leukopenia: 1/69	thalidomide was continued

References:

1. Sato EI, Assis LS, Lourenzi VP, Andrade LE. Long-term thalidomide use in refractory cutaneous lesions of systemic lupus erythematosus. Rev Assoc Med Bras (1992). 1998 Oct-Dec;44(4):289-93. doi: 10.1590/s0104-42301998000400007. PMID: 9852648.
2. Wang D, Chen H, Wang S, Zou Y, Li J, Pan J, Wang X, Ren T, Zhang Y, Chen Z, Feng X, Sun L. Thalidomide treatment in cutaneous lesions of systemic lupus erythematosus: a multicenter study in China. Clin Rheumatol. 2016 Jun;35(6):1521-7. doi: 10.1007/s10067-016-3256-3. Epub 2016 Apr 21. PMID: 27097914.

iv) Belimumab:

P50.4.f Among SLE patients with active acute cutaneous lupus despite treatment with topical steroid and HCQ, does additional therapy, compared to no additional therapy, improve clinical outcomes?

Population: SLE patients with active ACLE on HCQ and topical steroid therapy

Interventions: Continued HCQ and topical steroid therapy with addition of

- Belimumab

Outcomes:

- Disease activity (skin)

Table 1. Studies included.

Author, year, RefID	Population (age, ethnicity)	Intervention	Outcome
Anjo 2019[1] 388	9 patients	Belimumab + prednisone with a mean daily dose of 10.2 ± 1.8 mg/day, hydroxychloroquine, and with one immunosuppressant	Complete remission of skin lupus lesions
Vashisht 2017[2] 9345	5 patients all female mean age 32 yo		CLASI improvement

	age range: 19-46 3 Caucasian and 2 Hispanic	Belimumab: 10 mg/kg every 2 weeks for three doses, followed by a maintenance dose of 10 mg/kg every 4 weeks + HCQ + Pred (3 patients were on MMF at the time of initiation and one was on both AZA and MMF)	
Wang 2023[3] 9568	193 patients did the study, but only 59 patients of the childhood SLE patients had skin involvement (malar rash) //The mean age was 11.9	Belimumab (10 mg/kg on weeks 0, 2, 4, and then every 4 weeks) as adjunct therapy + SOC therapy (this is a multicenter study, so SOC therapy varied, and it was not specified)	Complete remission of the malar rash
von Kempis 2019[4] 9441	53 patients (81% female), but only 16 had a rash	monthly belimumab, 10 mg/kg IV, after the three induction infusions on days 0, 14 and 28.	Physician-assessed improvement from index in clinical manifestations

Evidence summary: Four studies were included in which Belimumab was used in patients with SLE + cutaneous lesions. The outcomes reported were complete remission, CLASI improvement, and physician-assessed improvement.
Most of the studies were focused on showing SLE improvement in general; there was a small focus on skin improvement. Wang et al. focused on the children lupus population. Complete remission of skin lesions was seen in 8/9 patients in one study, and 59/59 patients in another study (malar rash). Improvement was assessed by CLASI in which belimumab showed improvement, and by physician-assessed improvement from index in clinical manifestations in which there was >50% improvement in 6/16 patients.

Table 2. Outcomes

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

			Duration				
Complete remission of skin lupus lesions	Anjo 2019[1] 388	Prospective Cohort	24 months	9 patients	Belimumab + prednisone with a mean daily dose of 10.2 ± 1.8 mg/day, hydroxychloroquine, and with one immunosuppressant	8/9	
CLASI improvement	Vashisht 2017[2] 9345	Prospective Cohort	16 weeks	5 patients all female mean age 32 yo age range: 19-46 3 Caucasian and 2 Hispanic	Belimumab: 10 mg/kg every 2 weeks for three doses, followed by a maintenance dose of 10 mg/kg every 4 weeks + HCQ + Pred (3 patients were on MMF at the time of initiation and one was on both AZA and MMF)	CLASI activity scores improved dramatically (p.0.043);	there was no worsening of the CLASI damage scores.
Complete remission of the malar rash	Wang 2023[3] 9568	multicentre, observational, prospective cohort study	12 months	193 patients did the study, but only 59 patients of the childhood SLE patients had skin involvement (malar rash) // mean age was 11.9	Belimumab (10 mg/kg on weeks 0, 2, 4, and then every 4 weeks) as adjunct therapy + SOC therapy	59/59	(this is a multicenter study so SOC therapy varied and it was not specified)

Physician-assessed improvement from index in clinical manifestations	von Kempis 2019[4] 9441	multicentre, observational retrospectivecohort study	6 months	53 patients (81% female), but only 16 had a rash	monthly belimumab, 10 mg/kg IV, after the three induction infusions on days 0, 14 and 28.	≥ 20% of improvement: 9/16 ≥50%of improvement: 6/16	

References:

1. Anjo C, Mascaró JM Jr, Espinosa G, Cervera R. Effectiveness and safety of belimumab in patients with systemic lupus erythematosus in a real-world setting. Scand J Rheumatol. 2019 Nov;48(6):469-473. doi: 10.1080/03009742.2019.1603324. Epub 2019 Jul 2. PMID: 31264525.
2. Vashisht P, Borghoff K, O'Dell JR, Hearth-Holmes M. Belimumab for the treatment of recalcitrant cutaneous lupus. Lupus. 2017 Jul;26(8):857-864. doi: 10.1177/0961203316682097. Epub 2016 Dec 13. PMID: 28121495.
3. Wang L, Liang X, Cao Z, Wang D, Luo Y, Feng Y, Luo C, Zhi S, Huang Y, Fan Z, Wang C, Liu H, Liu J, Zhang T, Cheng Q, Xie X, Shuai L, Rong Z, Zeng P, Yu H, Lu M, Sun L, Yang S, Zhao D, Zhang W, Wu X, Li Q, Wang Y, Zhang Q, Yang J, Li X, Song H, Tang X. Evaluation of belimumab in treatment of Chinese childhood-onset systemic lupus erythematosus: a prospective analysis from a multicentre study. Rheumatology (Oxford). 2024 May 2;63(5):1437-1446. doi: 10.1093/rheumatology/kead406. PMID: 37606970.
4. von Kempis J, Duetsch S, Reuschling N, Villiger R, Villiger PM, Vallelian F, Schaer DJ, Mueller RB. Clinical outcomes in patients with systemic lupus erythematosus treated with belimumab in clinical practice settings: a retrospective analysis of results from the OBSErve study in Switzerland. Swiss Med Wkly. 2019 Mar 10;149:w20022. doi: 10.4414/smw.2019.20022. PMID: 30852830.

v) Anifrolmab:

P50.4.g Among SLE patients with active acute cutaneous lupus despite treatment with topical steroid and HCQ, does additional therapy, compared to no additional therapy, improve clinical outcomes?

Population: SLE patients with active ACLE on HCQ and topical steroid therapy

Interventions:

- Anifrolumab

Outcomes:

- Disease activity (skin)

Table 1. Studies included.

Author, year, RefID	Population (age, ethnicity)	Intervention	Outcome
Fushida 2023[1] 3035	7 patients 31–68 years; median age, 48 years), included one male and six female individuals.	Anifrolumab + prednisolone (5 pat also got Cya ou mizoribine)	Complete remission of skin lupus lesions
Flouda 2024	18 patients with active skin involvement Female predominance (94%, n = 17/18), Mean age 44.7 (12.7) Mean disease duration of 11.6 (6.9) years	Anifrolumab + standard of care	Decrease ≥50% (CLASI50) from baseline values

Evidence summary: One study was included in which Anifrolumab was used in patients with SLE + cutaneous lesions. The outcome reported was complete remission and the CLASI improvement was also reported. Complete remission was 5/7 in skin lesions with CLASI improvement rates ranging from 67% to 100%. The other study was also a case series and included patients with multiple mucocutaneous lesions, however, data was not separated based non those lesions.

Table 2. Outcomes

Outcome	Author, year, RefID	Study Design	Follow up Duration	Population	Intervention	Result	Notes
Complete remission of skin lupus lesions	Fushida 2023[1] 3035	Case series	1–3 months after starting anifrolumab	7 patients 31–68 years; median age, 48 years), included one male and six female individuals.	Anifrolumab + prednisolone (5 pat also got Cya ou mizoribine)	5/7	Moreover, all five patients with skin rash showed improvement in CLASI activity scores, with improvement rates ranging from 67%–100% one patient who received anifrolumab, discontinued treatment owing to poor control

							of pericarditis and pleurisy
Decrease ≥50% (CLASI50) from baseline values	Flouda 2024	Case series	Mean follow up=8.5 (4.6) months	18 patients with active skin involvement Female predominance (94%, n = 17/18), Mean age 44.7 (12.7) Mean disease duration of 11.6 (6.9) years	Anifrolumab(Mean dose= 2550 (1368) mg) + standard of care	16/18	

References:

1. Fushida N, Horii M, Oishi K, Matsushita T. Anifrolumab for systemic lupus erythematosus: A clinical study of Japanese patients in Kanazawa University Hospital. J Dermatol. 2024 Apr;51(4):607-611. doi: 10.1111/1346-8138.17027. Epub 2023 Nov 6. PMID: 37929294.
2. Flouda S, Emmanouilidou E, Karamanakos A, et al. Anifrolumab for systemic lupus erythematosus with multi-refractory skin disease: A case series of 18 patients. Lupus. 2024;33(11):1248-1253. doi:10.1177/09612033241273023

vi) Rituximab:

P50.4.h Among SLE patients with active acute cutaneous lupus despite treatment with topical steroid and HCQ, does additional therapy, compared to no additional therapy, improve clinical outcomes?

Population: SLE patients with active ACLE on HCQ and topical steroid therapy

Interventions:

- Anti-CD-20 therapy

Outcomes:

- Disease activity (skin)

Table 1. Studies included.

Author, year, RefID	Population (age, ethnicity)	Intervention	Outcome
Chavarot 2017[1] 1609	2 patients Female- 37 yo Female 46 yo	Rituximab + systemic steroids	Complete remission of skin lupus lesions

Ashwaq 2014[2] 236	3 patients Female- 14 yo Female 15 yo Female 16 yo	Rituximab + systemic steroids+ Cyclophosphamide	Partial remission of skin lupus lesions
Freitas 2020[3] 2964	60 patients mean age = 34.79 (12.45)	systemic prednisolone followed by Rituximab	Complete remission of skin lupus lesions
Podolskaya 2007[4] 7201	7 patients with SLE-children- ages: 15 , 16.5, 13.2,13.,13.7,6.1,15.5 yo	All patients received two rituximab infusions, usually 14 days apart, at a dose of 750 mg/m^2/ infusion.	Complete remission of skin lupus lesions
Terrier 2010[5] 8971	61 patients of the entire SLE cohort had skin involvement (of the entire cohort - > Age, mean SD (range) years 39.1 14.4 (9–87))	Any treatment with Rituximab (dose and number of doses not specified)	remission of skin lupus lesions
Vital 2011[6] 9471	39 SLE patients were studied, but only 19 had mucocutaneous disease	infusions of 100 mg of methylprednisolone + 1,000 mg of rituximab on days 1 and 14 + a course of prednisolone at 60 mg daily on days 1–7 and 30 mg daily on days 8–14.	Clinical response was measured using the original BILAG index

Evidence summary: Six studies were included in which Rituximab was used in patients with SLE + cutaneous lesions. The outcome reported was complete or partial remission of the skin lesions. The studies focused on the adult population. Complete remission of skin lupus lesions was not always achieved with the Rituximab. The focus of most studies was not only the improvement of the skin lesions but the improvement of SLE in general. Complete remission was analyzed by 4 studies having results of 2/2, 9/51, 4/7 and 29/61 respectively. Whereas partial response was assessed by 2 studies having results of 3/3 and 14/61 patients respectively. Another outcome assessed was the clinical response and it was divided into: good , partial, severe persistance, moderate persistance amd moderate flare.

Table 2. Outcomes

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

			Duration				
Partial remission of skin lupus lesions	Ashwaq 2014[2] 236	Prospective Cohort	6-13 years	2 patients Female- 14 yo Female 15 yo	Rituximab + systemic steroids+ Cyclophosphamide	3/3	
Complete remission of skin lupus lesions	Chavarot 20171 1609	Retrospective Cohort	12 months	2 patients Female- 37 year old Female 46 yo	Rituximab 1g /15 days (x2) + oral steroids (5mg / day and 20mg/day respectively)	2/2	
Complete remission of skin lupus lesions	Freitas 2020[3] 2964	Retrospective chart review	6 months	60 patients mean age = 34.79 (12.45)	systemic prednisolone followed by Rituximab	9/51	p= 0.745*
Complete remission of skin lupus lesions	Podolskaya 2007[4] 7201	Retrospective single center review	18, 20, 27,21,7, 6,6 months	7 patients with SLE- children- ages: 15 , 16.5, 13.2,13.,13.7,6.1, 15.5 yo	All patients received two rituximab infusions, usually 14 days apart, at a dose of 750 mg/m2/ infusion.	4/7	
remission of skin lupus lesions	Terrier 2010[5] 8971	Retrospective single center review	6 months (+ or - 3 months)	61 patients of the entire SLE cohort had skin involvement (of the entire cohort - > Age, mean SD (range) years 39.1 14.4 (9–87))	Any treatment with Rituximab (dose and number of doses not specified)	**Complete:** 29/61 **Partial:** 14/61 **No response:** 18/61	Variation in SELENA–SLEDAI score for different categories of responders for skin involvements, mean SD: -12.1 + or - 9.0 (p=0.0001)

Clinical response was measured using the original BILAG index	Vital 2011[6] 9471	Retrospective single center review	26 weeks	39 SLE patients were studied, but only 19 had mucocutaneous disease	infusions of 100 mg of methylprednisolone + 1,000 mg of rituximab on days 1 and 14 + a course of prednisolone at 60 mg daily on days 1–7 and 30 mg daily on days 8–14	Good response: 12 Partial response: 1 Severe Persist. Disease: 2 Moderate persist. disease: 4 moderate flare: 2	A good response was defined as a change from grade A or B at baseline to grade C or D on the BILAG, index, a partial was defined as a change from grade A at baseline to grade B, severe persistent disease was defined as persistent grade A, and moderate persistent disease was defined as persistent grade B. A severe flare was defined as a new grade A (not present at baseline), and a moderate flare was defined as

							a new grade B (not present at baseline).

References:

- 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.

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PICO 51

Comparative:

i)Thalidomide vs JAK inhibitor:

P51.6.h.8.l Among SLE patients with active SCLE or DLE on HCQ and topical steroid therapy, does the addition of listed therapies, compared to no additional therapy, improve clinical outcomes?

Population: Patients with SLE and rash

Interventions: Thalidomide

Comparator: Tofacitinib

Outcomes:

- Improvement of symptoms
- Adverse Events

Table 1.

Study	Design	Population	Intervention	Comparator	Outcomes
Zhao 2024	Retrospective cohort	Patients with active SLE and rash	Thalidomide 9.88 ± 0.79 mg/day	Tofacitinib 48.37 ± 13.34 mg/day	-Improvement of rash -Adverse Events

Evidence Summary:

There was one retrospective cohort study comparing between Thalidomide and Tofacitinib. This study included SLE patients and separated improvement of different mucocutaneous effects. 37/46 in Thalidomide arm and 19/40 had Tofacitinib had rash. Side effects were not compared between the 2 groups however the study mentioned that within the tofacitinib group, 1 patient had Herpes Zoster and within the Thalidomide group, 6 patients had a total of 8 adverse reactions. These included 1 case of abdominal distension, 3 cases of dizziness, and 2 cases of constipation and alopecia.

Evidence Report:

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Thalidomide	Tofacitinib	Relative (95% CI)	Absolute (95% CI)	
Improvement of Rash											
1	non-randomised studies	serious[a]	not serious	not serious	very serious[b,c]	none	17/22 (77.3%)	14/17 (82.4%)	**RR 0.94** (0.68	**49 fewer per 1,000**	⨁◯◯◯ Very low[a,b,c]

									to 1.29)	(from 264 fewer to 239 more)	

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

Explanations

a. Confounding bias due to unadjustment.
b. Small sample size
c. Wide absolute CI.

Reference:

1. Zhao M, Ma L, Duan X, Huo Y, Liu S, Zhao C, Zheng Z, Wang Q, Tian X, Chen Y, Li M. Tofacitinib versus thalidomide for mucocutaneous lesions of systemic lupus erythematosus: A real-world CSTAR cohort study XXVII. Lupus. 2024 Sep;33(10):1109-1115. doi: 10.1177/09612033241272953. Epub 2024 Aug 8. PMID: 39118350.

iii) JAK inhibitor vs SOC:

P51.8.l Among SLE patients with active SCLE or DLE on HCQ and topical steroid therapy, does the addition of listed therapies, compared to no additional therapy, improve clinical outcomes?

Population: SLE patients with SCLE or DLE on HCQ and topical steroid therapy
Interventions: Continued HCQ and topical steroid therapy and addition of:

- JAK-I (Baricitinib)

Comparators:

- Standard of care

Outcomes:

- Disease activity (skin)

Table 1:

Study	Design	Population	Intervention	Comparator	Outcomes
SLE-BRAVE-I	RCT	Patients with active SLE	Baricitinib 4mg	Standard of care (immunosuppressive therapy, or/and steroids, or/and HCQ)	-BILAG improvement -SLEDAI-2K improvement - ≥50% reduction in CLASI activity score
SLE-BRAVE-II	RCT	Patients with active SLE	Baricitinib 4mg	Standard of care (immunosuppressive	-BILAG improvement

				therapy, or/and steroids, or/and HCQ)	-SLEDAI-2K improvement - ≥50% reduction in CLASI activity score

Evidence summary: 2 RCTs compared Baricitinib 4mg to standard of care. The overall certainty of evidence was judged as low due to concerns about risk of bias (due to loss to follow-up) and imprecision. The absolute effect (CI) of improvement in BILAG mucocutaneous domain was 29 more per 1,000 (from 39 fewer to 106 more) in patients taking Baricitinib versus standard of care. For SLEDAI-2k (remission of arthritis or rash) it was 10 more per 1000 (from 46 fewer to 77 more) in Baricitininb and for ≥50% reduction in CLASI it was 12 fewer per 1,000 (from 134 fewer to 140 more) Baricitinib. To be noted, in these 2 studies, the mucocutaneous involvement was not specifically DLE or SCLE, however, JAK-I medication was only present within this PICO.

Adverse events, infections, and adverse events leading to discontinuation were comparable between both arms, while for serious adverse events, it was 29 more per 1,000 (from 6 fewer to 80 more) in Baricitinib.

Evidence profile:

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Baricitinib	Standard of care	Relative (95% CI)	Absolute (95% CI)	
Efficacy-BILAG score											
2	randomised trials	serious[a]	not serious	not serious	serious[b]	none	217/425 (51.1%)	197/409 (48.2%)	**RR 1.06** (0.92 to 1.22)	**29 more per 1,000** (from 39 fewer to 106 more)	⨁⨁◯◯ Low[a,b]
Efficacy-SLEDAI-2K score											
2	randomised trials	serious[a]	not serious	not serious	serious[b]	none	258/492 (52.4%)	250/487 (51.3%)	**RR 1.02** (0.91 to 1.15)	**10 more per 1,000** (from 46 fewer to 77 more)	⨁⨁◯◯ Low[a,b]
Efficacy- ≥50% reduction in CLASI activity score											
2	randomised trials	serious[a]	not serious	not serious	serious[b]	none	53/93 (57.0%)	63/108 (58.3%)	**RR 0.98** (0.77 to 1.24)	**12 fewer per 1,000** (from 134 fewer to 140 more)	⨁⨁◯◯ Low[a,b]

Adverse events

2	randomised trials	serious	not serious	not serious	not serious	none	408/510 (80.0%)	409/516 (79.3%)	**RR 1.01** (0.95 to 1.07)	**8 more per 1,000** (from 40 fewer to 55 more)	⊕⊕⊕◯ Moderate

Serious adverse events

2	randomised trials	serious	not serious	not serious	serious	none	55/510 (10.8%)	40/509 (7.9%)	**RR 1.37** (0.93 to 2.02)	**29 more per 1,000** (from 6 fewer to 80 more)	⊕⊕⊕◯ low

Adverse events leading to discontinuation

2	randomised trials	serious	not serious	not serious	not serious	none	46/510 (9.0%)	44/509 (8.6%)	**RR 1.05** (0.70 to 1.55)	**4 more per 1,000** (from 26 fewer to 48 more)	⊕⊕⊕◯ Moderate

Infection

2	randomised trials	serious	not serious	not serious	not serious	none	264/510 (51.8%)	260/509 (51.1%)	**RR 1.02** (0.90 to 1.15)	**10 more per 1,000** (from 51 fewer to 77 more)	⊕⊕⊕◯ low

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

Explanations

a. Concerns about risk of bias due to loss to follow-up and missing outcomes.
b. Wide range of CI in absolute risk.

References:

1-Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 3 trial (SLE-BRAVE-I)Morand, Eric F et al.The Lancet, Volume 401, Issue 10381, 1001 – 1010
2- Petri M, Bruce IN, Dörner T, et al. Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 3 trial (SLE-BRAVE-II). *Lancet*. 2023;401(10381):1011-1019. doi:10.1016/S0140-6736(22)02546-6

P51.8.l Among SLE patients with active SCLE or DLE on HCQ and topical steroid therapy, does the addition of listed therapies, compared to no additional therapy, improve clinical outcomes?

Population: SLE patients with SCLE or DLE on HCQ and topical steroid therapy

Interventions: Continued HCQ and topical steroid therapy and addition of:

- JAK-I (Upadacitinib)

Comparators:

- Standard of care

Outcomes:

- Disease activity (skin)
- Adverse Events

Table 1:

Study	Design	Population	Intervention	Comparator	Outcomes
Merril 2024	RCT	Patients with SLE	Upadacitinib 30 mg	Standard of care (immunosuppressive therapy, or/and steroids, or/and HCQ)	- ≥50% reduction in CLASI activity score -Adverse Events

Evidence Summary: This study was a phase 2, randomized, double-blind, placebo-controlled, global, multicenter study evaluating the efficacy and safety of Upadacitinib versus those that were given placebo. The patients included were previously taking standard of care (Mycophenolate,Azathioprine,Methotrexate, Calcineurin inhibitor or Leflunomide). These patients had SLE with 30 patients having mucocutaneous symptoms in the Upadacitinib arm and 35 having mucocutaneous symptoms in the placebo arm. CLASI was assessed on week 24 and week 48 and the absolute risk was 51 fewer per 1,000 (from 300 fewer to 677 more) and 268 more per 1,000
(from 100 fewer to 1,000 more), respectively. Regarding adverse events, treatment related adverse events (TEAE) was 39 more per 1,000 (from 87 fewer to 181 more) in patients taking Upadacitinib,TEAE considered possibly related to study drug had 10 fewer per 1,000 (from 133 fewer to 190 more) in patients taking Upadacitinib, and 30 more per 1,000 (from 35 fewer to 235 more) leading to discontinuation. Some adverse events documented were serious infection 11.3% in those taking Upadacitinib versus 4% on placebo, opportunistic infection excluding TB and HZb 1.6% versus 1.3%, Herpes Zoster 6.5% versus 4% , active TB 0 % versus 1.3% anemia 3.2% versus 4%,neutropenia 1.5% versus 1.3%,lymphopenia 3.2% versus 0%, renal dysfunction 1.6% versus 0%, hepatic disorder 1.6% versus 1.3%, an adjudicated MACE 11.6% versus 1.3%.

Evidence Report:

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Upadacitinib**	**Standard of care**	**Relative (95% CI)**	**Absolute (95% CI)**	
CLASI Week 24											
1	non-randomised studies	serious[a]	not serious	not serious	very serious[b,c]	none	3/8 (37.5%)	6/14 (42.9%)	**RR 0.88** (0.30 to 2.58)	**51 fewer per 1,000** (from 300 fewer to 677 more)	⊕◯◯◯ Very low[a,b,c]
CLASI Week 48											

1	non-randomised studies	serious[a]	not serious	not serious	very serious[b,c]	none	5/8 (62.5%)	5/14 (35.7%)	**RR 1.75** (0.72 to 4.24)	**268 more per 1,000** (from 100 fewer to 1,000 more)	⊕◯◯◯ Very low[a,b,c]

Treatment emergent adverse events

1	randomised trials	not serious	not serious	not serious	very serious[b,c]	none	51/62 (82.3%)	59/75 (78.7%)	**RR 1.05** (0.89 to 1.23)	**39 more per 1,000** (from 87 fewer to 181 more)	⊕⊕◯◯ Low[b,c]

Serious treatment emergent adverse events

1	randomised trials	not serious	not serious	not serious	very serious[b,c]	none	13/62 (21.0%)	13/75 (17.3%)	**RR 1.21** (0.61 to 2.41)	**36 more per 1,000** (from 68 fewer to 244 more)	⊕⊕◯◯ Low[b,c]

TEAE leading to discontinuation

1	randomised trials	not serious	not serious	not serious	very serious[b,c]	none	6/62 (9.7%)	5/75 (6.7%)	**RR 1.45** (0.47 to 4.53)	**30 more per 1,000** (from 35 fewer to 235 more)	⊕⊕◯◯ Low[b,c]

Death

1	randomised trials	not serious	not serious	not serious	very serious[c,d]	none	0/62 (0.0%)	0/75 (0.0%)	**Risk difference 0.0** (-0.3 to 0.3)	**-- per 1,000** (from -- to --)	⊕⊕◯◯ Low[c,d]

TEAE considered possibly related to study drug

1	randomised trials	not serious	not serious	not serious	very serious[b,c]	none	20/62 (32.3%)	25/75 (33.3%)	**RR 0.97** (0.60 to 1.57)	**10 fewer per 1,000** (from 133 fewer to 190 more)	⊕⊕◯◯ Low[b,c]

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

Explanations

a. Subset of patients from the RCT that had mucocutaneous symptoms, not randomized.
b. Wide CI in absolute risk difference
c. Small sample size
d. Wide CI in risk difference

References:

1- Merrill JT, Tanaka Y, D'Cruz D, Vila-Rivera K, Siri D, Zeng X, Saxena A, Aringer M, D'Silva KM, Cheng L, Mohamed MF, Siovitz L, Bhatnagar S, Gaudreau MC, Doan TT, Friedman A. Efficacy and Safety of Upadacitinib or Elsubrutinib Alone or in Combination for Patients With Systemic Lupus Erythematosus: A Phase 2 Randomized

Controlled Trial. Arthritis Rheumatol. 2024 Oct;76(10):1518-1529. doi: 10.1002/art.42926. Epub 2024 Aug 7. PMID: 38923871.

Non-Comparative:

i) Antimalarial (Not specified):

P51.2.a Among SLE patients with active SCLE or DLE on HCQ and topical steroid therapy, does the addition of listed therapies, compared to no additional therapy, improve clinical outcomes?

Population: SLE patients with SCLE or DLE on HCQ and topical steroid therapy

Interventions: Continued HCQ and topical steroid therapy and addition of:

- Antimalarial

Outcomes:

- Disease activity (skin)
- Adverse impact of medications for immunosuppressives including biologics and small molecules: infection and cytopenias; for antimalarials: retinal toxicity and cardiac toxicity (prolonged QTc and myopathy); for thalidomide and lenalidomide: neuropathy and GI effects; for retinoids: liver toxicity

Table 1. Studies included.

Author, year, RefID	Population (age, ethnicity)	Intervention	Outcome
Fayard 2022[1] 2758	12 patients	Antimalarial only with a tapered dose	Skin Disease activity (long term remission)
Fayard 2022[1] 2758	27 patients	Antimalarial only with baseline dose	Skin Disease activity (long term remission)
Tye 1959[2] 9211	45 DLE patients and 3 SCLE patients 15 males/ 33 females 44 White/ 4 African-American 23-69 yo	two tablets with a combination of 25mg of quinacrine + 50mg of HCQ+ 65mg of Chloroquine	complete/almost (90%)/ moderate(75%)/ partial (50%) clearing
Tuffanelli 1963[3] 9185	6 DLE patients	Antimalarial Therapy-not specified	Adverse event: pigmentation due to antimalarial use

Evidence summary: Three studies were included in which Antimalarials were used in patients with CLE. The outcomes reported were complete/partial remission and adverse event. The focus of the study done by Fayard et al. was to find factors associated with long-term remission. That said, the fraction of the studied population who took antimalarial was not described as well as the antimalarials were not specified. Antimalarials were studied "as a group," and they only differentiated if the antimalarials were always used on the same dose (baseline dose) or if they

were tapered down before discontinuation. Tye et al combine different antimalarial drugs in the same capsule while Tuffanelli combined the results of different antimalarials in the same study.

Table 2. Outcomes

Outcome	Author, year, RefID	Study Design	Follow up Duration	Population	Intervention	Result	Notes
Skin Disease activity (long term remission)	Fayard 2022[1] 2758	Longitudinal cohort study	follow-up duration> 3 y	13 patients	Antimalarial only with a tapered dose	6/13	
Skin Disease activity (long term remission)	Fayard 2022[1] 2758	Longitudinal cohort study	follow-up duration> 3 y	27 patients	Antimalarial only with baseline dose	4/27	
Complete/almost (90%)/ moderate(75%)/ partial (50%) clearing	Tye 1959[2] 9211	Longitudinal cohort study	Mean follow-up = 5 months	45 DLE patients and 3 SCLE patients 15 males/ 33 females 44 White/ 4 African-American 23-69 yo	two tablets with a combination of 25mg of quinacrine + 50mg of HCQ+ 65mg of Chloroquine	**Complete:** 19 DLE and 1 SCLE / **Almost:** 9 DLE / **Moderate + Partial:** 16 DLE and 2 SCLE	
Adverse event: Pigmentation	Tuffanelli 1963[3] 9185	Retrospective chart review	4 to 70 months / mean was 25.6 months and the median 18.5 months	6 DLE patients	Antimalarial Therapy- not specified	6/6	

References:

1. Fayard D, Francès C, Amoura Z, Breillat P, Mathian A, Senet P, Barbaud A, Arnaud L, Chasset F. Prevalence and factors associated with long-term remission in cutaneous lupus: A longitudinal cohort study of 141 cases. J Am Acad Dermatol. 2022 Aug;87(2):323-332. doi: 10.1016/j.jaad.2022.03.056. Epub 2022 Apr 4. PMID: 35390427.
2. TYE MJ, WHITE H, APPEL B, ANSELL HB. Lupus erythematosus treated with a combination of quinacrine, hydroxychloroquine and chloroquine. N Engl J Med. 1959 Jan 8;260(2):63-6. doi: 10.1056/NEJM195901082600203. PMID: 13613503.

3. TUFFANELLI D, ABRAHAM RK, DUBOIS EI. PIGMENTATION FROM ANTIMALARIAL THERAPY. ITS POSSIBLE RELATIONSHIP TO THE OCULAR LESIONS. Arch Dermatol. 1963 Oct;88:419-26. doi: 10.1001/archderm.1963.01590220051006. PMID: 1405135

iii) Quinacrine:

P51.2.b Among SLE patients with active SCLE or DLE on HCQ and topical steroid therapy, does the addition of listed therapies, compared to no additional therapy, improve clinical outcomes?

Population: SLE patients with SCLE or DLE on HCQ and topical steroid therapy

Interventions: Continued HCQ and topical steroid therapy and addition of:

- Quinacrine

Outcomes:

- Disease activity (skin)
- SLE disease activity
- Adverse impact of medications

Table 1. Studies included.

Author, year, RefID	Population (age, ethnicity)	Intervention	Outcome
Cavazzana 2009[1] 1480	34 patients Mean age of 43.8 years (SD = 12.8)	Quinacrine 100 mg/qd1 in 29 patients And 50 mg/qd4 in 5 patients	-Cutaneous Disease activity(partial/complete) -Adverse Events
Ugarte 20182 9230	46 patients in the study // 91% were female mean age was 38 **but only 10 had DLE and only 10 had SCLE**	All patients were on HCQ + Pred + Quinacrine 100mg (27 patients were also taking one immunosuppressor)	- Global rate of improvement and CLASI improvement -Adverse events

Evidence summary:

Two studies were included, in which Quinacrine was used in patients with CLE+ SLE. The outcomes reported were cutaneous disease activity and adverse events. The studies presented results in the adult population. Cavazzana et al. did not specify the severe side effects reported. In these 2 studies, partial remission was observed in 14/34 and 42/46 patients respectively, while complete remission was in 11/34 and 22/46 patients. In addition, adverse events were seen in 10/34 patients.

Table 2. Outcomes

Outcome	Author, year, RefID	Study Design	Follow up Duration	Population	Intervention	Result	Notes
Skin Disease activity (Partial Remission)	Cavazzana 2009[1] 1480	Retrospective Cohort	Median 5.5 months (IQR = 10).	34 patients Mean age of 43.8 years (SD = 12.8)	Quinacrine 100 mg/qd1 in 29 patients And 50 mg/qd4 in 5 patients.	14/34	CLASI activity score decreased in those with partial/complete response from 10.8 (SD = 5.5) to 3.8 (SD = 3.4)
Skin Disease activity (Complete Remission)	Cavazzana 2009[1] 1480	Retrospective Cohort	Median 5.5 months (IQR = 10).	34 patients Mean age of 43.8 years (SD = 12.8)	Quinacrine 100 mg/qd1 in 29 patients And 50 mg/qd4 in 5 patients.	11/34	Patients with DLE (19) with an overall response rate of 84.2% and improvement of activity CLASI (P = 0.009). SCLE lesions (10) improved in 60% of cases, without significant decrease of activity.
Global reates of improvement and CLASI improvement	Ugarte 2018[2] 9230	Retrospective analysis of prospectively acquired data	12 months	46 patients in the study // 91% were female // mean age	All patients were on HCQ + Pred + Quinacrine 100mg (27 patients were also taking one immunosuppressor)	Complete remission: 22/46 Partial remissio	CLASI significantly improved at all the pre-specified

				were 38 // **but only 10 had DLE and only 10 had SCLE**		n: 42/46	points (see Figure 1): CLASI t0–CLASI t3 3.4 (95% confidence interval (CI) 1.5–5.3); CLASI t0–CLASI t6 5.8 (95% CI 2.3–9.3); CLASI t0–CLASI t12 6.1 (95% CI 2.2–10.1); CLASI t0–CLASI tend 6.5 (95% CI 2.9–10.1).
Adverse Events	Ugarte 2018[2] 9230	Retrospective analysis of prospectively acquired data	12 months	46 patients in the study // 91% were female // mean age were 38 // **but only 10 had DLE and only 10 had SCLE**	All patients were on HCQ + Pred + Quinacrine 100mg (27 patients were also taking one immunosuppressor)	Liver enzymes elevation: 1/46 Pruritus: 1/46 Dyspepsia: 1/46	

Adverse Events	Cavazzana 2009[1] 1480	Retrospective Cohort	Median 5.5 months (IQR = 10).	34 patients Mean age of 43.8 years (SD = 12.8)	Quinacrine 100 mg/qd1 in 29 patients and 50 mg/qd4 in 5 patients.	10/34	Mild yellow staining (6 patients), 2 severe side effects

References:

1. Cavazzana I, Sala R, Bazzani C, Ceribelli A, Zane C, Cattaneo R, Tincani A, Calzavara-Pinton PG, Franceschini F. Treatment of lupus skin involvement with quinacrine and hydroxychloroquine. Lupus. 2009 Jul;18(8):735-9. doi: 10.1177/0961203308101714. PMID: 19502270.
2. Ugarte A, Porta S, Ríos R, Martinez-Zapico A, Ortego-Centeno N, Agesta N, Ruiz-Irastorza G. Combined mepacrine-hydroxychloroquine treatment in patients with systemic lupus erythematosus and refractory cutaneous and articular activity. Lupus. 2018 Sep;27(10):1718-1722. doi: 10.1177/0961203318768877. Epub 2018 Apr 10. PMID: 29635998

iv) Azathioprine:

P51.5.f Among SLE patients with active SCLE or DLE on HCQ and topical steroid therapy, does the addition of listed therapies, compared to no additional therapy, improve clinical outcomes?

Population: SLE patients with SCLE or DLE on HCQ and topical steroid therapy

Interventions: Continued HCQ and topical steroid therapy and addition of:

- AZA

Outcomes:

- Disease activity (skin)
- Adverse impact of medications for immunosuppressives including biologics and small molecules: infection and cytopenias; for antimalarials: retinal toxicity and cardiac toxicity (prolonged QTc and myopathy); for thalidomide and lenalidomide: neuropathy and GI effects; for retinoids: liver toxicity

Table 1. Studies included.

Author, year, RefID	Population (age, ethnicity)	Intervention	Outcome
Callen 1991[1] No Ref ID	1 DLE patients and 5 SCLE patients 4 females, 2male 5 White, 1 African American Age range: 31-62	Azathioprine 150 mg + Pred 20-30mg	-Response to therapy - Adverse effects

Evidence summary: One study was included, in which Azathioprine was used in patients with CLE (DLE and SCLE). The outcomes reported were response to therapy (complete, partial or no response) and adverse events (leukopenia, pancreatitis and fever) . The study presented results in the adult population. Response to therapy was complete in 1/6 patients and partial in 3/6 patients. Whereas adverse events were present in 3/6 patients only.

Table 2. Outcomes

Outcome	Author, year, RefID	Study Design	Follow up Duration	Population	Intervention	Result
Response to therapy	Callen 1991[1] No Ref ID	Prospective cohort	1 year	1 DLE patients and 5 SCLE patients 4 female, 2male 5 White, 1 African American Age range: 31-62	Azathioprine 150 mg +Pred 20-30mg	Complete: 1 / 6 Partial: 3/6 No response: 2/6
Adverse effects	Callen 1991[1] No Ref ID	Prospective cohort		1 DLE patients and 5 SCLE patients 4 female, 2male 5 White, 1 African American Age range: 31-62	Azathioprine 150 mg +Pred 20-30mg	Leukopenia: 1 / 6 Pancreatitis; 1/ 6 Fever: 1/6

References:

1. Callen JP, Spencer LV, Burruss JB, Holtman J. Azathioprine. An effective, corticosteroid-sparing therapy for patients with recalcitrant cutaneous lupus erythematosus or with recalcitrant cutaneous leukocytoclastic vasculitis. Arch Dermatol. 1991 Apr;127(4):515-22. doi: 10.1001/archderm.127.4.515. PMID: 2006876.

v) MMF/MPA:

P51.5.g Among SLE patients with active SCLE or DLE on HCQ and topical steroid therapy, does the addition of listed therapies, compared to no additional therapy, improve clinical outcomes?

Population: SLE patients with SCLE or DLE on HCQ and topical steroid therapy

Interventions: Continued HCQ and topical steroid therapy and addition of:

- MMF/MPA

Outcomes:

- Disease activity (skin)

Table 1. Studies included.

Author, year, RefID	Population (age, ethnicity)	Intervention	Outcome
Pisoni 2005[1] 71771	4 patients with SLE and: DLE (3) / SCLE (1) Ages: 53/42/29/35 yo	MMF- 2 g	Response to treatment

Evidence summary: One study was included, in which MMF was used in patients with SLE + CLE (DLE and SCLE were presented). The outcome reported was a "response to treatment." No patients presented a response to treatment, except for one DLE patient who presented an initial response followed by a flare.

Table 2. Outcomes

Outcome	Author, year, RefID	Study Design	Follow up Duration	Population	Intervention	Result	Notes
Response to treatment	Pisoni 2005[1] 71771	Retrospective case review	2/24/2/42 months	4 patients with SLE and: DLE (3) / SCLE (1) Ages: 53/42/29/35 yo	MMF – 2 g	0/4	One DLE patient presented an initial response followed by a flare.

References:

1. Pisoni CN, Obermoser G, Cuadrado MJ, Sanchez FJ, Karim Y, Sepp NT, Khamashta MA, Hughes GR. Skin manifestations of systemic lupus erythematosus refractory to multiple treatment modalities: poor results with mycophenolate mofetil. Clin Exp Rheumatol. 2005 May-Jun;23(3):393-6. PMID: 15971430.

vi) Lenalidomide:

P51.6.h Among SLE patients with active SCLE or DLE on HCQ and topical steroid therapy, does the addition of listed therapies, compared to no additional therapy, improve clinical outcomes?

Population: SLE patients with SCLE or DLE on HCQ and topical steroid therapy

Interventions: Continued HCQ and topical steroid therapy and addition of:

- Lenalidomide

Outcomes:

- Disease activity (skin)

Table 1. Studies included.

Author, year, RefID	Population (age, ethnicity)	Intervention	Outcome
Wu 2017[1] 9828	10 adolescents with SLE + CLE 9 female 6 African-American, 3 White Average age was 16.9 yo (SD±3.8)	Lenalidomide 5. mg daily.	• complete remission of the skin lesions - reduction in prednisone.

Evidence summary: One study was included, in which Lenalidomide was used in patients with SLE + CLE. The outcomes reported were complete remission of the skin lesions and reduction in prednisone dose. The study presented results in the pediatric population. The study does not report any side effects. 10/10 patients had complete remission however 8/10 patients had prednisone tapering.

Table 2. Outcomes

Outcome	Author, year, RefID	Study Design	Follow up Duration	Population	Intervention	Result	Notes
complete remission of the skin lesions	Wu 2017[1] 9828	Retrospective chart review	6 months	10 adolescents with SLE + CLE 9 female 6 African-American, 3 White Average age was 16.9 yo (SD±3.8)	Lenalidomide 5-12.5 mg daily	complete remission : 10/10	No subject experienced a cutaneous flare on continued lenalidomide therapy.
-reduction in prednisone	Wu 2017[1] 9828	Retrospective chart review	6 months	10 adolescents with SLE + CLE 9 female	Lenalidomide 5-12.5 mg daily	8/10	prednisone was decreased from a mean of

				6 African-American, 3 White Average age was 16.9 yo (SD±3.8)			23.5mg (SD±13.3) to a mean of 12.25 mg (SD9.2)

References:

1. Wu EY, Schanberg LE, Wershba EC, Rabinovich CE. Lenalidomide for refractory cutaneous manifestations of pediatric systemic lupus erythematosus. Lupus. 2017 May;26(6):646-649. doi: 10.1177/0961203316676377. Epub 2016 Nov 12. PMID: 27837194; PMCID: PMC5388573.

vii) Thalidomide:

P51.6.h Among SLE patients with active SCLE or DLE on HCQ and topical steroid therapy, does the addition of listed therapies, compared to no additional therapy, improve clinical outcomes?

Population: SLE patients with SCLE or DLE on HCQ and topical steroid therapy

Interventions: Continued HCQ and topical steroid therapy and addition of:

- Thalidomide /Lenalidomide

Outcomes:

- Disease activity (skin)
- Adverse impact of medications

Table 1. Studies included.

Author, year, RefID	Population (age, ethnicity)	Intervention	Outcome
Atra 1993[1] 598	23 patients with SLE + CLE Mean age of 29 years (range = 9-52)// (3 non-White and 20 White)	Thalidomide 300 mg/day for adults and 4 mg/ kg/day for children	-Cutaneous Disease activity -Adverse events

Evidence summary: One study was included, in which Thalidomide was used in patients with SLE + CLE. The outcomes reported were complete/partial remission and adverse events. The study is very detailed (especially the adverse events), presented results in the pediatric and adult

population and as a limitation, 3 cases dropped out before the end of the study.Partial remission was seen in 2/23 patients and complete remission in 18/23 patients. Adverse events ranged from drowsiness to urticaria.

Table 2. Outcomes

Outcome	Author, year, RefID	Study Design	Follow up Duration	Population	Intervention	Result	Notes
Skin Disease activity	Atra 1993[1] 598	prospective single-center	2 - 4 months in 13 pat. / 6 months or more in 7 pat.	23 patients with SLE + CLE Mean age of 29 years (range = 9-52)// (3 non-White and 20 White)	Thalidomide 300 mg/day for adults and 4 mg/ kg/day for children	Complete remission : 18/23 Partial remission : 2/23 Drop out: 3/23	
Adverse Events (Drownsiness)	Atra 1993[1] 598	prospective single-centre	2 - 4 months in 13 pat. / 6 months or more in 7 pat.	23 patients Mean age of 29 years (range = 9-52)// (3 non-White and 20 White)	Thalidomide 300 mg/day for adults and 4 mg/ kg/day for children	12/23	In one patient this was significant enough to warrant halting the treatment after 30 days. In the other patients a reduction in thalidomide dosage was enough to relieve the symptoms

Adverse Events (abdominal distension or constipation)	Atra 1993 [1] 598	prospective single-centre	2 - 4 months in 13 pat. / 6 months or more in 7 pat.	23 patients Mean age of 29 years (range = 9-52)// (3 non-White and 20 White)	Thalidomide 300 mg/day for adults and 4 mg/ kg/day for children	5/23	A reduction in thalidomide dose was enough to decrease this side effect;
Adverse Events (depression)	Atra 1993 [1] 598	prospective single-centre	2 - 4 months in 13 pat. / 6 months or more in 7 pat.	23 patients Mean age of 29 years (range = 9-52)// (3 non-White and 20 White)	Thalidomide 300 mg/day for adults and 4 mg/ kg/day for children	3/23	three patients reported depression (13%). ln one patient a dose reduction was necessary
Adverse Events (insomnia/ anxiety)	Atra 1993 [1] 598	prospective single-centre	2 - 4 months in 13 pat. / 6 months or more in 7 pat.	23 patients Mean age of 29 years (range = 9-52)// (3 non-White and 20 White)	Thalidomide 300 mg/day for adults and 4 mg/ kg/day for children	3/23	the complaints disappeared with a reduction of the dose;
Adverse Events (urticaria)	Atra 1993 [1] 598	prospective single-centre	2 - 4 months in 13 pat. / 6 months or more in 7 pat.	23 patients Mean age of 29 years (range = 9-52)// (3 non-White and 20 White)	Thalidomide 300 mg/day for adults and 4 mg/ kg/day for children	2/23	Patients were unable to continue treatment;
Adverse Events (galactorrhea)	Atra 1993 [1] 598	prospective single-centre	2 - 4 months in 13 pat. / 6 months or more in 7 pat.	23 patients Mean age of 29 years (range = 9-52)// (3 non-White and 20 White)	Thalidomide 300 mg/day for adults and 4 mg/ kg/day for children	1/23	galactorrhea was observed on the 45th day of thalidomide administration, lasting for one month and

							disappearing with interruption of the drug.

References:

1. Atra E, Sato EI. Treatment of the cutaneous lesions of systemic lupus erythematosus with thalidomide. Clin Exp Rheumatol. 1993 Sep-Oct;11(5):487-93. PMID: 8275583.

viii) Anifrolumab:

P51.7.j Among SLE patients with active SCLE or DLE on HCQ and topical steroid therapy, does the addition of listed therapies, compared to no additional therapy, improve clinical outcomes?

Population: SLE patients with SCLE or DLE on HCQ and topical steroid therapy

Interventions: Continued HCQ and topical steroid therapy and addition of:

- Anifrolumab

Outcomes:

- Disease activity (skin)
- Quality of life
- Adverse impact of medications for immunosuppressives including biologics and small molecules: infection and cytopenias; for antimalarials: retinal toxicity and cardiac toxicity (prolonged QTc and myopathy); for thalidomide and lenalidomide: neuropathy and GI effects; for retinoids: liver toxicity

Table 1. Studies included.

Author, year, RefID	Population (age, ethnicity)	Intervention	Outcome
Carter 2023[1] 1443	7 patients, all female, with SLE + CLE Mean age of 46 years (range = 33-64) /// (DLE n = 5, chilblain lupus erythematosus n = 1, subacute CLE n = 1)	Anifrolumab (300 mg IV) monthly	-Cutaneous Disease activity - Quality of Life - Adverse Events
Flouda 2024	18 patients with active skin involvement Female predominance (94%, n = 17/18), Mean age 44.7 (12.7) Mean disease duration of 11.6 (6.9) years	Anifrolumab + standard of care	Decrease ≥50% (CLASI50) from baseline values

Evidence summary: One study was included, in which Anifrolumab was used in patients with CLE + SLE. The outcomes reported were Cutaneous Disease activity, Quality of Life, and Adverse Events. The study presented results in the adult population. One patient discontinued the treatment and did not complete the six month due to COVID followed by COVID followed by polydermatomal shingles requiring hospitalization and complicated by herpes zoster oticus with unilateral high-frequency sensorineural hearing loss (patient was also on prednisone 17 mg). The other study was also a case series and included patients with multiple mucocutaneous lesions, however, data was not separated based non those lesions.

Table 2. Outcomes

Outcome	Author, year, RefID	Study Design	Follow up Duration	Population	Intervention	Result	Notes
Skin Disease activity	Carter 2023[1] 1443	prospective single-centre	6 months	7 patients, all female, with SLE + CLE Mean age of 46 years (range = 33-64) /// (DLE n = 5, chilblain lupus erythematosus n = 1, subacute CLE n = 1)	Anifrolumab (300 mg IV) monthly	6/7	The median CLASI activity score had fallen significantly by 1 month to 6 points (range 0–13; P = 0.016) with a median decrease from baseline of 60% (19–100). By 3 months the median CLASI-A was 0 points (0–4; P < 0.001) and all patients had achieved a 50% or greater reduction from baseline score, which was sustained at 6 months (P = 0.001).
Decrease ≥50% (CLASI50) from baseline values	Flouda 2024	Case series	Mean follow up=8.5 (4.6) months	18 patients with active skin involvement Female predominan	Anifrolumab(Mean dose= 2550 (1368) mg) + standard of care	16/18	

				ce (94%, n = 17/18), Mean age 44.7 (12.7) Mean disease duration of 11.6 (6.9) years			
Global SLE disease activity	Carter 2023[1] 1443	prospective single-centre	6 months	7 patients, all female, with SLE + CLE Mean age of 46 years (range = 33-64) /// (DLE n = 5, chilblain lupus erythematosus n = 1, subacute CLE n = 1)	Anifrolumab (300 mg IV) monthly	6/7	No BILAG-2004 grade A/B flares in any domain were observed during follow-up.
Quality of life	Carter 2023[1] 1443	prospective single-centre	6 months	7 patients, all female, with SLE + CLE Mean age of 46 years (range = 33-64) /// (DLE n = 5, chilblain lupus erythematosus n = 1, subacute CLE n = 1)	Anifrolumab (300 mg IV) monthly	6/7	DLQI (0–30; showed marked and significant improvement during therapy (F = 19.3, P = 0.0002) from a median of 17 points (range 5–22) at baseline to 5 points at 3 months (0–13; P = 0.047) and improvement was maintained at 6 months (P = 0.013; LupusQoL indicated trends

							towards improvement across all domains that were statistically significant for fatigue (F = 6.87, P = 0.01), pain (F = 11.29, P = 0.002) and planning (F = 6.34, P = 0.01) between baseline and 6 months
Adverse Events	Carter 2023[1] 1443	prospective single-centre	6 months	7 patients, all female, with SLE + CLE Mean age of 46 years (range = 33-64) /// (DLE n = 5, chilblain lupus erythematosus n = 1, subacute CLE n = 1)	Anifrolumab (300 mg IV) monthly	URI: 2/7 URT: 1/7 Otitis: 1/7 Covid+Zoster: 1/7	uncomplicated urinary tract infection upper respiratory tract infection/bronchitis otitis externa COVID followed by polydermatomal shingles requiring hospitalization and complicated by herpes zoster oticus with unilateral high-frequency sensorineural hearing loss.(patient was also on pred 17 mg) (n=1)

References:

1. Lucy M Carter, Zoe Wigston, Philip Laws, Edward M Vital, Rapid efficacy of anifrolumab across multiple subtypes of recalcitrant cutaneous lupus erythematosus parallels changes in discrete subsets of blood transcriptomic and cellular

biomarkers, *British Journal of Dermatology*, Volume 189, Issue 2, August 2023, Pages 210–218, https://doi.org/10.1093/bjd/ljad089
2. Flouda S, Emmanouilidou E, Karamanakos A, et al. Anifrolumab for systemic lupus erythematosus with multi-refractory skin disease: A case series of 18 patients. Lupus. 2024;33(11):1248-1253. doi:10.1177/09612033241273023

Non-comparative:

i) Steroids:

P52. In SLE patients with bullous lupus, what is the impact of listed medical treatments compared to steroids alone on clinical outcomes?

Population: SLE patients with bullous LE

Interventions:

- Corticosteroids

Outcomes:

- Disease activity (skin)

Table 1. Studies included.

Author, year, RefID	Population (age, ethnicity)	Intervention	Outcome
Risi-Pugliesi 2018[1] 2167	10 patients with SLE and bullous lupus erythematosus Mean age: 23 years (age range 4-39) **But only 3 were treated with ctcs**	Corticosteroids (with HCQ, immunossup. or dapsone)	Complete response

Evidence summary: One study was included in which systemic corticosteroids was used in patients with SLE and bullous lupus. The outcome reported was complete response. The study was a case series and included, in total, only 3 cases.
The limitation is that only one patient used ctcs alone; all others were treated with systemic corticosteroids + HCQ, immunosuppressor (not specified), or dapsone.

Table 2. Outcomes

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

Complete response	Risi-Pugliesi 2018[1] 2167	Case series	Not specified	10 patients with SLE and bullous lupus erythematosus Mean age: 23 years (age range 4-39) **But only 3 were treated with ctcs**	Corticosteroids (with HCQ, immunossup. or dapsone)	3/6	There was not a complete resolution of the bullous lesions in the patient who was treated with corticosteroids alone

References:

1. de Risi-Pugliese T, Cohen Aubart F, Haroche J, Moguelet P, Grootenboer-Mignot S, Mathian A, Ingen-Housz-Oro S, Hie M, Wendremaire N, Aucouturier F, Lepelletier F, Miyara M, Bader-Meunier B, Rémy P, Fabien N, Francès C, Barete S, Amoura Z. Clinical, histological, immunological presentations and outcomes of bullous systemic lupus erythematosus: 10 New cases and a literature review of 118 cases. Semin Arthritis Rheum. 2018 Aug;48(1):83-89. doi: 10.1016/j.semarthrit.2017.11.003. Epub 2017 Nov 4. PMID: 29191376.

ii) Dapsone:

P52.1.a In SLE patients with bullous lupus, what is the impact of listed medical treatments compared to steroids alone on clinical outcomes?

Population: SLE patients with bullous LE

Interventions:

- Dapsone

Outcomes:

- Disease activity (skin)

Table 1. Studies included.

Author, year, RefID	Population (age, ethnicity)	Intervention	Outcome
Risi-Pugliesi 2018[1] 2167	10 patients with SLE and bullous lupus erythematosus Mean age: 23 years (age range 4-39) **But only 6 were treated with Dapsone**	Dapsone	Complete response

Hall 1982[2] 3554	4 cases: 32 year old white man 27 year old white woman 42 year old black woman 12 year old white boy	Systemic steroids + plaquenil + Dapsone	Complete response

Evidence summary: Two studies were included in which dapsone was used in patients with SLE and bullous lupus. The outcome reported was the complete response. Both studies were case series and included, in total, 10 cases. Only one patient did not present a complete response, and most patients were treated with other medications besides dapsone.

Table 2. Outcomes

Outcome	Author, year, RefID	Study Design	Follow up Duration	Population	Intervention	Result	Notes
Complete response	Risi-Pugliesi 2018[1] 2167	Case series	Not specified	10 patients with SLE and bullous lupus erythematosus Mean age: 23 years (age range 4-39) **But only 6 were treated with Dapsone**	Dapsone (dose was not specified)	5/6	Only 5 patients were treated with dapsone only.
Complete response	Hall 1982[1] 3554	Case series	3 days	4 cases	Systemic steroids + plaquenil + Dapsone	4/4	

References:

1. de Risi-Pugliese T, Cohen Aubart F, Haroche J, Moguelet P, Grootenboer-Mignot S, Mathian A, Ingen-Housz-Oro S, Hie M, Wendremaire N, Aucouturier F, Lepelletier F, Miyara M, Bader-Meunier B, Rémy P, Fabien N, Francès C, Barete S, Amoura Z. Clinical, histological, immunological presentations and outcomes of bullous systemic lupus erythematosus: 10 New cases and a literature review of 118 cases. Semin Arthritis Rheum. 2018 Aug;48(1):83-89. doi: 10.1016/j.semarthrit.2017.11.003. Epub 2017 Nov 4. PMID: 29191376.
2. Hall RP, Lawley TJ, Smith HR, Katz SI. Bullous eruption of systemic lupus erythematosus. Dramatic response to dapsone therapy. Ann Intern Med. 1982 Aug;97(2):165-70. doi: 10.7326/0003-4819-97-2-165. PMID: 7049027.

iii) Colchicine:

P52.1.b In SLE patients with bullous lupus, what is the impact of listed medical treatments compared to steroids alone on clinical outcomes?

Population: SLE patients with bullous LE

Interventions:

- Colchicine

Outcomes:

- Disease activity (skin)

Table 1. Studies included.

Author, year, RefID	Population (age, ethnicity)	Intervention	Outcome
Risi-Pugliesi 2018[1] 2167	10 SLE patients with bullous lupus erythematosus Mean age of 23 yo(age range 4-39) **But only 1 got colchicine.**	Colchicine	Complete Response

Evidence summary: One study was included in which colchicine was used in patients with SLE and bullous lupus. The outcome reported was complete response. The study was a case series and included only one case.
The limitation is that the study did not present details about the follow-up time or dose.

Table 2. Outcomes

Outcome	Author, year, RefID	Study Design	Follow up Duration	Population	Intervention	Result	Notes
Complete Response	Risi-Pugliesi 2018[1] 2167	Case series	Not specified	10 SLE patients with bullous lupus erythematosus Mean age of 23 (age range 4-39) **But only 1 got colchicine.**	Colchicine (dose was not specified)		

References:

1. de Risi-Pugliese T, Cohen Aubart F, Haroche J, Moguelet P, Grootenboer-Mignot S, Mathian A, Ingen-Housz-Oro S, Hie M, Wendremaire N, Aucouturier F, Lepelletier F, Miyara M, Bader-Meunier B, Rémy P, Fabien N, Francès C, Barete S, Amoura Z. Clinical, histological, immunological presentations and outcomes of bullous systemic

lupus erythematosus: 10 New cases and a literature review of 118 cases. Semin Arthritis Rheum. 2018 Aug;48(1):83-89. doi: 10.1016/j.semarthrit.2017.11.003. Epub 2017 Nov 4. PMID: 29191376.

iv) MMF and corticosteroids:

P52.2.f In SLE patients with bullous lupus, what is the impact of listed medical treatments compared to steroids alone on clinical outcomes?

Population: SLE patients with bullous LE

Interventions:

- Corticosteroids+MMF

Outcomes:

- Disease activity (skin)

Table 1. Studies included.

Author, year, RefID	Population (age, ethnicity)	Intervention	Outcome
Risi-Pugliesi 2018[1] 2167	10 patients with SLE and bullous lupus erythematosus Mean age: 23 yo(age range 4-39) **But only 2 were treated with steroids+ MMF**	Corticosteroids + MMF	Complete response

Evidence summary:

One study was included in which systemic corticosteroids + MMF were used in patients with SLE and bullous lupus. The outcome reported was complete response. The study was a case series and included, in total, only 2 cases.

The limitation is that only MMF was not used alone; all patients were also treated with systemic corticosteroids.

Table 2. Outcomes

Outcome	Author, year, RefID	Study Design	Follow up Duration	Population	Intervention	Result	Notes
Complete response	Risi-Pugliesi 2018[1] 2167	Case series	Not specified	10 patients with SLE and bullous lupus erythematosus Mean age: 23 yo(age range 4-39)	Corticosteroids plus MMF	1/2	

				But only 2 were treated with ctcs + MMF			

References:

1. de Risi-Pugliese T, Cohen Aubart F, Haroche J, Moguelet P, Grootenboer-Mignot S, Mathian A, Ingen-Housz-Oro S, Hie M, Wendremaire N, Aucouturier F, Lepelletier F, Miyara M, Bader-Meunier B, Rémy P, Fabien N, Francès C, Barete S, Amoura Z. Clinical, histological, immunological presentations and outcomes of bullous systemic lupus erythematosus: 10 New cases and a literature review of 118 cases. Semin Arthritis Rheum. 2018 Aug;48(1):83-89. doi: 10.1016/j.semarthrit.2017.11.003. Epub 2017 Nov 4. PMID: 29191376.

PICO 53

Non-Comparative:

i) Topical Steroids:

P53.1.a In SLE patients with chilblains, does addition of the listed medical treatments compared to symptomatic measures (with or without topical therapies) lead to improved clinical outcomes?

Population: SLE patients with chilblains

Interventions: Symptomatic therapy and

- Topical steroid
-

Outcomes:

- Disease activity (skin)

Table 1. Studies included.

Author, year, RefID	Population (age, ethnicity)	Intervention	Outcome
Millard 1978[1] 5939	6 patients with chilblain Age range: 15-52	Topical steroids (not specified)	Complete resolution

Evidence summary:

One study was included, in which not specified topicals steroids were used in patients with chilblain. The outcome reported was the complete remission of the chilblain lesions. One limitation was that there was no definition of the follow-up duration. Only 2/6 patients achieved complete remission.

Table 2. Outcomes

Outcome	Author, year, RefID	Study Design	Follow up Duration	Population	Intervention	Result	Notes
Complete resolution	Millard 1978[1] 5939	prospective single-center cohort	Not specified	6 patients with chilblain Age range: 15-52	Topical steroids (not specified)	2/6	

References:

1. Millard LG, Rowell NR. Chilblain lupus erythematosus (Hutchinson). A clinical and laboratory study of 17 patients. Br J Dermatol. 1978 May;98(5):497-506. doi: 10.1111/j.1365-2133.1978.tb01935.x. PMID: 656324.

ii) Antimalarials(Chloroquine and HCQ):

P53.2 In SLE patients with chilblains, does addition of the listed medical treatments compared to symptomatic measures (with or without topical therapies) lead to improved clinical outcomes?

Population: SLE patients with chilblains

Interventions: Symptomatic therapy and

- HCQ
- Chloroquine

Outcomes:

- Disease activity (skin)

Table 1. Studies included.

Author, year, RefID	Population (age, ethnicity)	Intervention	Outcome
Millard 1978[1] 5939	6 patients with chillblain Age range: 15-52	Both Antimalarials (chloroquine and hydroxychloroquine)	Complete resolution
Ototake 2019[2] 6779	12 patients with chillblain (age not specified)	hydroxychloroquine	Complete resolution
Su 1994[3] 8677	1 patient with chillblain (71 yo M)	Both Antimalarials (chloroquine and hydroxychloroquine) + Dapsone	Complete resolution

Su 1994[3] 8677	2 patients with chillblain (54 yo M and 64yo F)	Hydroxychloroquine 200 mg QD;	Complete resolution
Su 1994[3] 8677	1 patient with chillblain (71 yo M)	Chloroquine 250 mg QD	Complete resolution
Lim 2022[4] 5274	3 female patients with chillblain	Hydroxychloroquine 400	**Good response** or **Fair response**

Evidence summary:

Four studies were included in which antimalarials (hydroxychloroquine and chloroquine) were used in patients with chilblain.
The outcome reported was complete remission in most of the studies. Basically, only half of the patients achieved complete remission with antimalarials. Lim et al. used a different outcome, separating patients who presented good response or fair responses.

Table 2. Outcomes

Outcome	Author, year, RefID	Study Design	Follow up Duration	Population	Intervention	Result	Notes
Complete resolution	Millard 1978[1] 5939	prospective single-center cohort	Not specified	6 patients with chilblain Age range: 15-52	Antimalarials (chloroquine and hydroxychloroquine)	3/6	
Complete resolution	Ototake 2019[2] 6779	Retrospective chart review	16 weeks	12 patients with chilblain (age not specified)	hydroxychloroquine	6/12	Also, 3 patients had partial response and 3 patients had no response
Complete resolution	Su 1994[3] 8677	Retrospective chart review	Not specified	1 patients with chilblain (71 yo M)	Both Antimalarials (chloroquine and hydroxychloroquine) + Dapsone	1/1	
Complete resolution	Su 1994[3] 8677	Retrospective chart review	Not specified	2 patients with chilblain (54 yo M	Hydroxychloroquine 200 mg QD	0/2	

				and 64yo F)			
Complete resolution	Su 1994[3] 8677	Retrospective chart review	2 months	1 patients with chilblain (71 yo M)	Chloroquine 250 mg QD	1/1	
Good response or **fair response**	Lim 2022[4] 5274	Retrospective chart review	6.2 months	3 female patients with chilblain	Hydroxychloroquine 400mg	Good response: 2 (66.7) Fair response: 1 (33.3)	**Good response** = controllable disease despite the intermittent use of other additional medication **Fair response** = moderately controlled but active disease, frequently or always requiring additional medications ;

References:

1. Millard LG, Rowell NR. Chilblain lupus erythematosus (Hutchinson). A clinical and laboratory study of 17 patients. Br J Dermatol. 1978 May;98(5):497-506. doi: 10.1111/j.1365-2133.1978.tb01935.x. PMID: 656324.
2. Ototake Y, Yamaguchi Y, Kanaoka M, Akita A, Ikeda N, Aihara M. Varied responses to and efficacies of hydroxychloroquine treatment according to cutaneous lupus erythematosus subtypes in Japanese patients. J Dermatol. 2019 Apr;46(4):285-289. doi: 10.1111/1346-8138.14802. Epub 2019 Feb 5. PMID: 30719729.
3. Su WP, Perniciaro C, Rogers RS 3rd, White JW Jr. Chilblain lupus erythematosus (lupus pernio): clinical review of the Mayo Clinic experience and proposal of diagnostic criteria. Cutis. 1994 Dec;54(6):395-9. PMID: 7867381.
4. Lim JW, Lee JH, Kim HJ. Use of hydroxychloroquine in dermatology: A multicenter retrospective study in Korea. J Dermatol. 2022 Jan;49(1):173-178. doi: 10.1111/1346-8138.16200. Epub 2021 Oct 28. PMID: 34713476.

iii) MMF:

P53.4.k In SLE patients with chilblains, does addition of the listed medical treatments compared to symptomatic measures (with or without topical therapies) lead to improved clinical outcomes?

Population: SLE patients with chilblains

Interventions: Symptomatic therapy and

- MMF/MPA

Outcomes:

- Disease activity (skin)

Table 1. Studies included.

Author, year, RefID	Population (age, ethnicity)	Intervention	Outcome
Pisoni 2005[1] 71771	1 patient with chilblain 18 yo	MMF- 2 g	Complete resolution

Evidence summary:

One study included MMF in patients with SLE and chilblain. The focus of this study was to analyze the response of resistant-to-treatment lupus skin lesions to MMF. The outcome reported was complete remission. Since only one patient had chillblain, the study was limitaded.

Table 2. Outcomes

Outcome	Author, year, RefID	Study Design	Follow up Duration	Population	Intervention	Result	Notes
Complete resolution	Pisoni 2005[1] 7177	Retrospective case review	11 months	1 patient with chilblain Age: 18 yo	MMF – 2 g	0/1	

References:

1. Pisoni CN, Obermoser G, Cuadrado MJ, Sanchez FJ, Karim Y, Sepp NT, Khamashta MA, Hughes GR. Skin manifestations of systemic lupus erythematosus refractory to multiple treatment modalities: poor results with mycophenolate mofetil. Clin Exp Rheumatol. 2005 May-Jun;23(3):393-6. PMID: 15971430.

PICO 54

Non-Comparative:

i) Dapsone:

P54.3.e In SLE patients with cutaneous vasculitis, what is the impact of listed medical treatments compared to topical steroids alone or other standard therapy on clinical outcomes?

Population: SLE patients with cutaneous vasculitis

Interventions:

- Dapsone

Outcomes:

- Disease activity (skin)

Dapsone Therapy:

Table 1. Studies included.

Author, year, RefID	Population (age, ethnicity)	Intervention	Outcome
Callen 1988[1] 1358	72 patients with SCLE, the mean age was 42.4 years **But only 2 had cutaneous vasculitis And used dapsone**	Dapsone	beneficial response of the cutaneous vasculitis lesions

Evidence summary:

Only 1 study was included, in which dapsone was used in patients with SCLE and cutaneous vasculitis. The outcome reported was a "beneficial response of the cutaneous vasculitis lesions" in which 2/2 patients showed a beneficial reponse.

Table 2. Outcomes

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

beneficial response of the cutaneous vasculitis lesions	Callen 1988[1] 1358	prospective single-centre	Not specified	72 patients with SCLE, the mean age was 42.4 years **But only 2 had cutaneous vasculitis And used dapsone**	Dapsone	2/2	

References:

1. Callen JP, Klein J. Subacute cutaneous lupus erythematosus. Clinical, serologic, immunogenetic, and therapeutic considerations in seventy-two patients. Arthritis Rheum. 1988 Aug;31(8):1007-13. doi: 10.1002/art.1780310811. PMID: 3261587.

ii) Colchicine

P54.3.f In SLE patients with cutaneous vasculitis, what is the impact of listed medical treatments compared to topical steroids alone or other standard therapy on clinical outcomes?

Population: SLE patients with cutaneous vasculitis

Interventions:

- Colchicine
-

Outcomes:

- Disease activity (skin)

Table 1. Studies included.

Author, year, RefID	Population (age, ethnicity)	Intervention	Outcome
Callen 1988[1] 1358	472 patients with SCLE, the mean age was 42.4 years **But only 4 had cutaneous vasculitis And used colchicine**	Colchicine	beneficial response of the cutaneous vasculitis lesions

Evidence summary:

Only 1 study was included, in which colchicine was used in patients with SCLE and cutaneous vasculitis. The outcome reported was a "beneficial response of the cutaneous vasculitis lesions" in which it showed that none of the 4 patients had a clinical response.

Table 2. Outcomes

Outcome	Author, year, RefID	Study Design	Follow up Duration	Population	Intervention	Result	Notes
beneficial response of the cutaneous vasculitis lesions	Callen 1988[1] 1358	prospective single-center	Not specified	4 patients with SCLE and cutaneous vasculitis at the same time	Colchicine	0/4	There was no response to colchicine

References:

1. Callen JP, Klein J. Subacute cutaneous lupus erythematosus. Clinical, serologic, immunogenetic, and therapeutic considerations in seventy-two patients. Arthritis Rheum. 1988 Aug;31(8):1007-13. doi: 10.1002/art.1780310811. PMID: 3261587.

iii) MTX

P54.4.i In SLE patients with cutaneous vasculitis, what is the impact of listed medical treatments compared to topical steroids alone or other standard therapy on clinical outcomes?

Population: SLE patients with cutaneous vasculitis

Interventions:

- MTX

Outcomes:

- Disease activity (skin)

Table 1. Studies included.

Author, year, RefID	Population (age, ethnicity)	Intervention	Outcome
Gansauge 1997[1] 3079	22 patients with SLE mean age was 41 years (range 24–68)	MTX 15 mg / week	Cutaneous vasculitis complete resolution

	But only 2 patients of had cutaneous vasculitis		

Evidence summary: One study was included. The above study analyzed a cohort of moderate SLE patients. Patients with renal and central nervous system disease were excluded. Only 2 patients of his cohort had cutaneous vasculitis, and none presented complete resolution.

Table 2. Outcomes

Outcome	Author, year, RefID	Study Design	Follow up Duration	Population	Intervention	Result	Notes
Cutaneous vasculitis complete resolution	Gansauge 1997[1] 3079	prospective single-center cohort	Not specified	22 patients with SLE mean age was 41 years (range 24–68) **But only 2 patients of had cutaneous vasculitis**	MTX 15 mg	0/2	There was no response to MTX

References:

1. Gansauge S, Breitbart A, Rinaldi N, Schwarz-Eywill M. Methotrexate in patients with moderate systemic lupus erythematosus (exclusion of renal and central nervous system disease). Ann Rheum Dis. 1997 Jun;56(6):382-5. doi: 10.1136/ard.56.6.382. PMID: 9227169; PMCID: PMC1752396.

iv) MMF

P54.4.k In SLE patients with cutaneous vasculitis, what is the impact of listed medical treatments compared to topical steroids alone or other standard therapy on clinical outcomes?

Population: SLE patients with cutaneous vasculitis

Interventions:

- MMF/MPA

Outcomes:

- Disease activity (skin)

Table 1. Studies included.

Author, year, RefID	Population (age, ethnicity)	Intervention	Outcome
Pisoni 2005[1] 71771	1 patient with cutaneous vasculitis + SLE Age: 50 yo	MMF	Complete resolution
Tselios 2016[2] 9155	2 patients with skin vasculitis and non-renal SLE 6 patients with skin vasculitis and renal SLE mean age 38.6 ± 11.7 yrs	Any previous treatment with MMF	Complete resolution

Evidence summary: Two studies included mycophenolate, which was used in patients with SLE and cutaneous vasculitis. The outcome reported was cutaneous vasculitis complete.
The first study presented only one patient with cutaneous vasculitis and SLE, and this patient did not achieve complete remission.
In Tselios et al., two patients w/o concomitant renal involvement achieved cutaneous vasculitis remission at 6 months, but only one maintained remission for 12 months. While the patients with concomitant renal involvement achieved remission after 6 months and maintained it until 12 months.

Table 2. Outcomes

Outcome	Author, year, RefID	Study Design	Follow up Duration	Population	Intervention	Result	Notes
Complete resolution	Pisoni 2005[1] 7177	Retrospective case review	32 months	1 patient with cutaneous vasculitis + SLE Age: 50 yo	MMF	0/1	
Complete resolution	Tselios 2016[2] 9155	Retrospective chart review	6 and 12 months	2 patients with skin vasculitis and non-renal SLE 6 patients with skin vasculitis	Any previous treatment with MMF	**In 6 months:** - 2/2 (w/o renal)	Improvement was defined as the absence of the initial clinical manifestation after 6 and

				and renal SLE mean age 38.6 ± 11.7 yrs		-6/6 (w/ renal disease) **In 12 months:** -1/2 (w/o renal) - 6/6 (w renal disease)	12 months.

References:

1. Pisoni CN, Obermoser G, Cuadrado MJ, Sanchez FJ, Karim Y, Sepp NT, Khamashta MA, Hughes GR. Skin manifestations of systemic lupus erythematosus refractory to multiple treatment modalities: poor results with mycophenolate mofetil. Clin Exp Rheumatol. 2005 May-Jun;23(3):393-6. PMID: 15971430.
2. Tselios K, Gladman DD, Su J, Urowitz MB. Mycophenolate Mofetil in Nonrenal Manifestations of Systemic Lupus Erythematosus: An Observational Cohort Study. J Rheumatol. 2016 Mar;43(3):552-8. doi: 10.3899/jrheum.150779. Epub 2016 Jan 15. PMID: 26773121.

v) Rituximab

P54. In SLE patients with cutaneous vasculitis, what is the impact of listed medical treatments compared to topical steroids alone or other standard therapy on clinical outcomes?

Population: SLE patients with cutaneous vasculitis

Interventions:

- Anti-CD-20 therapy

Outcomes:

- Disease activity (skin)

Table 1. Studies included.

Author, year, RefID	Population (age, ethnicity)	Intervention	Outcome
Garcia-Carrasco 2010[1] 3111	52 SLE patients - median age was 36 years (range 19–72), **but only 3 patients had cutaneous vasculitis**	Rituximab	Cutaneous vasculitis complete resolution

Evidence summary: One study was included, in which Rituximab was used in patients with SLE cutaneous vasculitis. The outcome reported was complete remission with 1/3 patients who had remission.

Table 2. Outcomes

Outcome	Author, year, RefID	Study Design	Follow up Duration	Population	Intervention	Result	Notes
Cutaneous vasculitis complete resolution	Garcia-Carrasco 2010[1] 3111	prospective single-center cohort	6 months	52 SLE patients - median age was 36 years (range 19–72), **but only 3 patients had cutaneous vasculitis**	Rituximab	1/3	

References:

1. Garcia-Carrasco M, Mendoza-Pinto C, Sandoval-Cruz M, Soto-Vega E, Beltran-Castillo A, Jimenez-Hernandez M, Graillet D, Gonzalez L, Rojas-Rodriguez J, Pineda-Almazana A, Zamudio-Huerta L, Lopez-Colombo A. Anti-CD20 therapy in patients with refractory systemic lupus erythematosus: a longitudinal analysis of 52 Hispanic patients. Lupus. 2010 Feb;19(2):213-9. doi: 10.1177/0961203309351541. Epub 2009 Dec 4. PMID: 19965944.

vi) Tacrolimus

P54.5 In SLE patients with cutaneous vasculitis, what is the impact of listed medical treatments compared to topical steroids alone or other standard therapy on clinical outcomes?

Population: SLE patients with cutaneous vasculitis

Interventions:

- Tacrolimus

Outcomes:

- Disease activity (skin)

Table 1. Studies included.

Author, year, RefID	Population (age, ethnicity)	Intervention	Outcome
Tani 2018[1] 8890	1 patient with cutaneous vasculitis + SLE F, 35 yo	Systemic Tacrolimus + GC, HCQ, MMF, Belimumab	Cutaneous vasculitis remission

Evidence summary: One study was included, in which systemic tacrolimus was used in patients with SLE and cutaneous vasculitis. The outcomes reported was cutaneous vasculitis remission and this patient had no response.

Table 2. Outcomes

Outcome	Author, year, RefID	Study Design	Follow up Duration	Population	Intervention	Result	Notes
Cutaneous vasculitis remission	Tani 2018[1] 8890	retrospective multi-centre	12 months	1 patient with cutaneous vasculitis + SLE F, 35 yo	Systemic Tacrolimus + GC, HCQ, MMF, Belimumab	0/1	There was no response to tacrolimus

References:

1. Tani C, Elefante E, Martin-Cascón M, Belhocine M, Lavilla Olleros C, Vagelli R, Stagnaro C, Costedoat-Chalumeau N, Ruiz-Irastorza G, Mosca M. Tacrolimus in non-Asian patients with SLE: a real-life experience from three European centres. Lupus Sci Med. 2018 Nov 2;5(1):e000274. doi: 10.1136/lupus-2018-000274. PMID: 30538815; PMCID: PMC6257376.

PICO 55

Comparative:

i) Belimumab:

P55.1.2.a.b.c.d.e.f In SLE patients with focal active alopecia due to CLE or SLE, does the addition of topical treatment to systemic therapies, compared to no topical treatment, improve clinical outcomes?

Population: Patients with SLE and focal alopecia

Interventions:

- Belimumab

Comparator:

- Standard of Care

Outcomes:

- SLEDAI improvement

Table 1.

Study	Design	Population	Intervention	Comparator	Outcomes
Manzi 2012	Post hoc analysis for BLISS 52 and BLISS 72	Patients with active SLE	Belimumab 10 mg	Standard of care (immunosuppressive therapy, or/and steroids, or/and HCQ)	SLEDAI improvement

Evidence summary: Belimumab is not one of the interventions stated by the PICO question, however due to the lack of evidence for alopecia, this evidence report was added. Improvement of SLEDAI-2K (alopecia) were higher in belimumab arm compared to standard of care, with an absolute effect (CI) of 79 more per 1,000(from 4 fewer to 178 more). These results are based on low certainty of evidence due to risk of bias (in the post hoc analysis without randomization) and imprecision in the RCT (wide CI in absolute effect).

Safety profile: For adverse events, serious adverse events, infections, adverse events leading to discontinuation, were comparable between both arms (CI between the borders of minimally importance difference) with moderate-high certainty of the evidence.

Evidence profile:

Certainty assessment							№ of patients		Effect		
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Belimumab**	**Standard of care**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**
SELENA-SLEDAI-2K (Alopecia)											
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	130/274 (47.4%)	111/280 (39.6%)	**RR 1.20** (0.99 to 1.45)	**79 more per 1,000** (from 4 fewer to 178 more)	⨁⨁◯◯ Low[a,b]

Adverse events

5	randomised trials	not serious	not serious	not serious	not serious	none	1597/1920 (83.2%)	1074/1242 (86.5%)	**RR 0.99** (0.96 to 1.02)	**9 fewer per 1,000** (from 35 fewer to 17 more)	⊕⊕⊕⊕ High

Adverse events leading to discontinuation (Dichotomous)

5	randomised trials	not serious	not serious	not serious	not serious	none	129/1754 (7.4%)	101/1242 (8.1%)	**RR 0.90** (0.70 to 1.16)	**8 fewer per 1,000** (from 24 fewer to 13 more)	⊕⊕⊕⊕ High

Serious adverse events

5	randomised trials	not serious	not serious	not serious	not serious	none	256/1920 (13.3%)	208/1242 (16.7%)	**RR 0.83** (0.70 to 0.98)	**28 fewer per 1,000** (from 50 fewer to 3 fewer)	⊕⊕⊕⊕ High

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

Explanations

a. Non-randomized study (Post hoc analysis)
b. Wide CI in absolute effect

References: Randomized clinical trial (1 post hoc analysis)

1. Manzi S, Sánchez-Guerrero J, Merrill JT, et al. Effects of belimumab, a B lymphocyte stimulator-specific inhibitor, on disease activity across multiple organ domains in patients with systemic lupus erythematosus: combined results from two phase III trials. *Ann Rheum Dis*. 2012;71(11):1833-1838. doi:10.1136/annrheumdis-2011-200831

ii) Thalidomide vs Toraficitinib:

P55.1.2. In SLE patients with focal active alopecia due to CLE or SLE, does the addition of topical treatment to systemic therapies, compared to no topical treatment, improve clinical outcomes?

Population: Patients with SLE and alopecia

Interventions: Thalidomide

Comparator: Tofacitinib

Outcomes:

- Improvement of symptoms
- Adverse Events

Table 1.

Study	Design	Population	Intervention	Comparator	Outcomes
Zhao 2024	Retrospective cohort	Patients with active SLE and alopecia	Thalidomide 9.88 ± 0.79 mg/day	Tofacitinib 48.37 ± 13.34 mg/day	-Improvement of alopecia -Adverse Events

Evidence Summary: There was one retrospective cohort study comparing Thalidomide and Tofacitinib. This study included SLE patients and separated improvement of different mucocutaneous effects. 15/46 in Thalidomide arm and 15/40 had Tofacitinib had alopecia. Side effects were not compared between the 2 groups however the study mentioned that within the tofacitinib group, 1 patient had Herpes Zoster and within the Thalidomide group, 6 patients had a total of 8 adverse reactions. These included 1 case of abdominal distension, 3 cases of dizziness, and 2 cases of constipation and alopecia.

Evidence Report:

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Thalidomide	Tofaciitinib	Relative (95% CI)	Absolute (95% CI)	
Improvement of Alopecia											
1	non-randomised studies	serious[a]	not serious	not serious	extremely serious[b,c]	none	8/9 (88.9%)	7/8 (87.5%)	**RR 1.02** (0.72 to 1.44)	**18 more per 1,000** (from 245 fewer to 385 more)	⨁◯◯◯ Very low[a,b,c]

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

Explanations

a. Confounding bias due to unadjustment.
b. Very small sample size
c. Wide absolute CI

Reference:

1. Zhao M, Ma L, Duan X, Huo Y, Liu S, Zhao C, Zheng Z, Wang Q, Tian X, Chen Y, Li M. Tofacitinib versus thalidomide for mucocutaneous lesions of systemic lupus erythematosus: A real-world CSTAR cohort study XXVII. Lupus. 2024 Sep;33(10):1109-1115. doi: 10.1177/09612033241272953. Epub 2024 Aug 8. PMID: 39118350.

Non-comparative:

i) Anifrolumab:

P55.1.2.a.b.c.d.e.f In SLE patients with focal active alopecia due to CLE or SLE, does the addition of topical treatment to systemic therapies, compared to no topical treatment, improve clinical outcomes?

Population: SLE patients with alopecia

Interventions:

- Anifrolumab

Outcomes:

- Disease activity (skin)

Table 1. Studies included.

Author, year, RefID	Population (age, ethnicity)	Intervention	Outcome
Flouda 2024	18 patients with active skin involvement Female predominance (94%, n = 17/18), Mean age 44.7 (12.7) Mean disease duration of 11.6 (6.9) years	Anifrolumab + standard of care	Decrease ≥50% (CLASI50) from baseline values

Evidence summary: This study was a case series and included patients with multiple mucocutaneous lesions, however, data was not separated based non those lesions. The patients were followed up after a mean of 8.5 months from starting therapy and CLASI50 was measured. 16/18 patients achieved decrease in >50% from baseline of CLASI even though these patients were had refractory SLE.

Table 2. Outcomes

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

Decrease ≥50% (CLASI50) from baseline values	Flouda 2024	Case series	Mean follow up=8.5 (4.6) months	18 patients with active skin involvement Female predominance (94%, n = 17/18), Mean age 44.7 (12.7) Mean disease duration of 11.6 (6.9) years	Anifrolumab(Mean dose= 2550 (1368) mg) + standard of care	16/18	

References:

1.Flouda S, Emmanouilidou E, Karamanakos A, et al. Anifrolumab for systemic lupus erythematosus with multi-refractory skin disease: A case series of 18 patients. Lupus. 2024;33(11):1248-1253. doi:10.1177/09612033241273023

ii) Belimumab

P55.1.a.b.c.2.e.d.f In SLE patients with focal active alopecia due to CLE or SLE, does the addition of topical treatment to systemic therapies, compared to no topical treatment, improve clinical outcomes?

Population: Patients with SLE and focal alopecia on systemic therapy (HCQ and/or immunosuppressives)

Interventions: Belimumab

Outcomes: Remission and improvement in alopecia

Table 1. Studies included.

Author, year, RefID	Population (age, ethnicity)	Intervention	Outcome
Wang 2024[1] 9568	193 patients did the study, mean age was 11.9 **but only 34 patients had alopecia**	Belimumab (10 mg/kg on weeks 0, 2, 4, and then every 4 weeks) as adjunct therapy + SOC therapy (SOC therapy varied and it was not specified)	Complete remission of alopecia

Touma 2016[2] 9090	52 patients, 49 were female and mean age was 46.5 (10.8) **but only 11 had alopecia**	Belimumab 10 mg/kg + corticosteroids	Clinical Improvement of alopecia

Evidence summary: Two studies looked at alopecia improvement in SLE patients treated with belimumab. Alopecia was not the main outcome of the studies since both studies analyzed multiple outcomes in children (Wang et al.) and adults (Touma et al.) with SLE and treated with belimumab. That said, not the entire cohort studied presented alopecia, and there is no information, like age range, of this specific group. Intervention varied Wang et al. associated belimumab with SOC treatment, depending on each center analyzed in the study. Touma presents that besides belimumab, corticosteroids were added to patients' treatment. Each study presented its results differently. Wang et al. highlighted complete alopecia resolution in all "alopecia cohort". Touma et al. quantified the amount of improvement in their cohort.

Table 2. Outcomes

Outcome	Author, year, RefID	Study Design	Follow up Duration	Population	Intervention	Result
Complete remission of the alopecia	Wang 2024[1] 9568	multicentric observational, prospective cohort study	12 months	193 patients did the study, mean age was 11.9 **but only 34 patients had alopecia**	Belimumab (10 mg/kg on weeks 0, 2, 4, and then every 4 weeks) as adjunct therapy + SOC therapy (SOC therapy varied and it was not specified)	34/34
Clinical Improvement of alopecia	Touma 2016[2] 9090	Retrospective multicentric clinical chart review	6 months	52 patients, 49 were female and mean age was 46.5 (10.8) **But only 11 had alopecia**	Belimumab 10 mg/kg + corticosteroids	No improvement: 3/11 Less than 20% of improvement: 1/11 20-50% of improvement: 1/11 50-80% of improvement: 5/11 More than 80% of

						improvement: 1/11

References:

1. Wang L, Liang X, Cao Z, Wang D, Luo Y, Feng Y, Luo C, Zhi S, Huang Y, Fan Z, Wang C, Liu H, Liu J, Zhang T, Cheng Q, Xie X, Shuai L, Rong Z, Zeng P, Yu H, Lu M, Sun L, Yang S, Zhao D, Zhang W, Wu X, Li Q, Wang Y, Zhang Q, Yang J, Li X, Song H, Tang X. Evaluation of belimumab in treatment of Chinese childhood-onset systemic lupus erythematosus: a prospective analysis from a multicentre study. Rheumatology (Oxford). 2024 May 2;63(5):1437-1446. doi: 10.1093/rheumatology/kead406. PMID: 37606970.
2. Touma Z, Sayani A, Pineau CA, Fortin I, Matsos M, Ecker GA, Chow A, Iczkovitz S. Belimumab use, clinical outcomes and glucocorticoid reduction in patients with systemic lupus erythematosus receiving belimumab in clinical practice settings: results from the OBSErve Canada Study. Rheumatol Int. 2017 Jun;37(6):865-873. doi: 10.1007/s00296-017-3682-9. Epub 2017 Mar 9. PMID: 28280970; PMCID: PMC5434147.

PICO 56

Comparative:

i) Thalidomide vs Tofacitinib:

P56. In patients with oral ulcers due to SLE does the addition of targeted local therapies to standard systemic therapies, compared to no targeted local therapies, improve clinical outcomes?

Population: Patients with SLE and oral ulcers

Interventions: Thalidomide

Comparator: Tofacitinib

Outcomes:

- Improvement of symptoms
- Adverse Events

Table 1.

Study	Design	Population	Intervention	Comparator	Outcomes
Zhao 2024	Retrospective cohort	Patients with active SLE and oral ulcers	Thalidomide 9.88 ± 0.79 mg/day	Tofacitinib 48.37 ± 13.34 mg/day	-Improvement of oral ulcers -Adverse Events

Evidence Summary: There was one retrospective cohort study comparing between Thalidomide and Tofacitinib. This study included SLE patients and separated improvement of different mucocutaneous effects. 5/46 in Thalidomide arm and 2/40 had Tofacitinib had mucosal ulcers. Side effects were not compared between the 2 groups however the study mentioned that within the tofacitinib group, 1 patient had Herpes Zoster and within the Thalidomide group, 6 patients had a total of 8 adverse reactions. These included 1 case of abdominal distension, 3 cases of dizziness, and 2 cases of constipation and alopecia.

Evidence Report:

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Thalidomide	Tofaciitinib	Relative (95% CI)	Absolute (95% CI)	
Improvement of Mucosal Ulcer											
1	non-randomised studies	serious[a]	not serious	not serious	extremely serious[b,c]	none	2/2 (100.0%)	1/1 (100.0%)	**RR 1.00** (0.39 to 2.58)	**0 fewer per 1,000** (from 610 fewer to 1,000 more)	⨁◯◯◯ Very low[a,b,c]

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

Explanations

a. Confounding bias due to unadjustment.
b. Very small sample size
c. Wide absolute CI

Reference:

1. Zhao M, Ma L, Duan X, Huo Y, Liu S, Zhao C, Zheng Z, Wang Q, Tian X, Chen Y, Li M. Tofacitinib versus thalidomide for mucocutaneous lesions of systemic lupus erythematosus: A real-world CSTAR cohort study XXVII. Lupus. 2024 Sep;33(10):1109-1115. doi: 10.1177/09612033241272953. Epub 2024 Aug 8. PMID: 39118350.

ii) Belimumab:

P56.1.2.a,b,c,d,e,f In patients with oral ulcers due to SLE does the addition of targeted local therapies to standard systemic therapies, compared to no targeted local therapies, improve clinical outcomes?

Population: Patients with SLE and mucosal ulcers

Interventions:

- Belimumab

Comparator:

- Standard of Care

Outcomes:

- SLEDAI improvement

Table 1.

Study	Design	Population	Intervention	Comparator	Outcomes
Manzi 2012	Post hoc analysis for BLISS 52 and BLISS 72	Patients with active SLE	Belimumab 10 mg	Standard of care (immunosuppressive therapy, or/and steroids, or/and HCQ)	SLEDAI improvement

Evidence summary: Belimumab is not one of the interventions stated by the PICO question, however due to the lack of evidence for mucosal ulcers, this evidence report was added. Improvement of SLEDAI-2K (mucosal ulcers) were higher in belimumab arm compared to standard of care, with an absolute effect (CI) of 30 more per 1,000(from 73 fewer to 158 more). These results are based on low certainty of evidence due to risk of bias (in the post hoc analysis without randomization) and imprecision in the RCT (wide CI in absolute effect).
Safety profile: For adverse events, serious adverse events, infections, adverse events leading to discontinuation, were comparable between both arms (CI between the borders of minimally importance difference) with moderate-high certainty of the evidence.

Evidence profile:

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Belimumab	standard of care	Relative (95% CI)	Absolute (95% CI)	

SELENA-SLEDAI-2K (Mucosal Ulcers)

1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	87/136 (64.0%)	88/145 (60.7%)	**RR 1.05** (0.88 to 1.26)	**30 more per 1,000** (from 73 fewer to 158 more)	⊕⊕◯◯ Low[a,b]

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

Explanations

a. Non-randomized study (Post hoc analysis)
b. Wide CI in absolute effect

References: Randomized clinical trial (1 post hoc analysis)

1. Manzi S, Sánchez-Guerrero J, Merrill JT, et al. Effects of belimumab, a B lymphocyte stimulator-specific inhibitor, on disease activity across multiple organ domains in patients with systemic lupus erythematosus: combined results from two phase III trials. *Ann Rheum Dis*. 2012;71(11):1833-1838. doi:10.1136/annrheumdis-2011-200831

iii) MMF:

P56. In patients with oral ulcers due to SLE does the addition of targeted local therapies to standard systemic therapies, compared to no targeted local therapies, improve clinical outcomes?

Population: Patients with SLE and oral ulcers

Interventions: MMF

Comparator: standard of Care

Outcomes:

- New or worsening symptoms
- Adverse Events

Table 1.

Study	Design	Population	Intervention	Comparator	Outcomes

You 2024	RCT	Patients with active SLE	oral prednisone (0.5 mg/kg/d) and hydroxychloroquine sulfate (5 mg/kg/d) and MMF (500 mg twice daily) (MMF group) for 96 weeks	oral prednisone (0.5 mg/kg/d) and hydroxychloroquine sulfate (5 mg/kg/d)	-New or Worsening symptoms -Adverse Events

Evidence summary: One study was included however, it was not specific for patients with mucocutaneous SLE.Instead in had patients with SLE with only 5/65 from the control group and 8/65 from the MMF group having oral ulcers at baseline. Patients were followed up at 96 weeks. The new or worsening symptoms were later on calculated out of the whole populations not just those having symptoms at baseline. There was 0 fewer patients per 1,000(from 0 fewer to 0 fewer) in the MMF group having new or worsening symptoms of oral ulcers. However, those in the MMF group had 106 more per 1,000(from 50 fewer to 350 more) risk of adverse events (infection, GI, bone fracture, osteonecrosis of the femoral head or other events). Infections included URTI, pneumonia,UTI, herpes zoster, candida or tuberculosis.

Evidence report:

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**MMF with Prednisone and HCQ**	**Prednisone with HCQ**	**Relative (95% CI)**	**Absolute (95% CI)**	
New or worsening symptoms-Oral ulcers											
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	1/65 (1.5%)	0/65 (0.0%)	**RR 3.00** (0.12 to 72.31)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ Low[a,b]
Any adverse event											
1	randomised trials	serious[a]	not serious	not serious	very serious[c]	none	30/65 (46.2%)	23/65 (35.4%)	**RR 1.30** (0.86 to 1.99)	**106 more per 1,000** (from 50 fewer to 350 more)	⨁◯◯◯ Very low[a,c]
Adverse event-Infection											
1	randomised trials	serious[a]	not serious	not serious	very serious[c]	none	22/65 (33.8%)	23/65 (35.4%)	**RR 0.96** (0.60 to 1.53)	**14 fewer per 1,000** (from 142	⨁◯◯◯ Very low[a,c]

										fewer to 188 more)	

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

Explanations

a. Study was an open-label, observer blinded study
b. Wide CI in relative risk
c. Wide CI in absolute risk.

Reference:

1. You Y, Zhou Z, Wang F, et al. Mycophenolate Mofetil and New-Onset Systemic Lupus Erythematosus: A Randomized Clinical Trial. JAMA Netw Open. 2024;7(9):e2432131. doi:10.1001/jamanetworkopen.2024.32131

Non-Comparative:

i) Anifrolumab:

P56. 1.2.a.b.c.d.e.f In patients with oral ulcers due to SLE does the addition of targeted local therapies to standard systemic therapies, compared to no targeted local therapies, improve clinical outcomes?

Population: SLE patients with oral ulcers

Interventions: Anifrolumab

Outcomes:

- Disease activity (skin)

Anifrolumab Therapy:

Table 1. Studies included.

Author, year, RefID	Population (age, ethnicity)	Intervention	Outcome
Flouda 2024	18 patients with active skin involvement Female predominance (94%, n = 17/18), Mean age 44.7 (12.7) Mean disease duration of 11.6 (6.9) years	Anifrolumab + standard of care	Decrease ≥50% (CLASI50) from baseline values

Evidence summary: This study was a case series and included patients with multiple mucocutaneous lesions, however, data was not separated based non those lesions. The patients

were followed up after a mean of 8.5 months from starting therapy and CLASI50 was measured. 16/18 patients achieved decrease in >50% from baseline of CLASI even though these patients were had refractory SLE.

Table 2. Outcomes

Outcome	Author, year, RefID	Study Design	Follow up Duration	Population	Intervention	Result	Notes
Decrease ≥50% (CLASI50) from baseline values	Flouda 2024	Case series	Mean follow up=8.5 (4.6) months	18 patients with active skin involvement Female predominance (94%, n = 17/18), Mean age 44.7 (12.7) Mean disease duration of 11.6 (6.9) years	Anifrolumab(Mean dose= 2550 (1368) mg) + standard of care	16/18	

References:

1.Flouda S, Emmanouilidou E, Karamanakos A, et al. Anifrolumab for systemic lupus erythematosus with multi-refractory skin disease: A case series of 18 patients. Lupus. 2024;33(11):1248-1253. doi:10.1177/09612033241273023

ii) Belimumab

P56.1.2a,b,c,d,e,f In patients with oral ulcers due to SLE does the addition of targeted local therapies to standard systemic therapies, compared to no targeted local therapies, improve clinical outcomes?

Population: Patients with SLE and mouth ulcers on systemic therapy (HCQ and/or immunosuppressives)

Interventions: Belimumab

Outcomes:

- Remission and improvement

Table 1. Studies included.

Author, year, RefID	Population (age, ethnicity)	Intervention	Outcome
Wang 2024[1] 9568	193 patients did the study, mean age was 11.9 **but only 24 patients had oral ulcers**	Belimumab (10 mg/kg on weeks 0, 2, 4, and then every 4 weeks) + SOC therapy	Complete remission of the oral ulcers
Touma 2016[2] 9090	52 patients, 49 were female and mean age was 46.5 (10.8) **But only 9 had oral ulcers**	Belimumab 10 mg/kg + corticosteroids	Clinical improvement of the oral ulcers

Evidence summary: Two studies looked at the improvement of oral ulcers in SLE patients treated with belimumab. It was not the main outcome of the studies since both studies analyzed multiple outcomes in children (Wang et al.) and adults (Touma et al.) with SLE and treated with belimumab. That said, not the entire cohort studied presented oral ulcers, and there is no information, like age range, of this specific group. Intervention varied. Wang et al. associated belimumab with SOC treatment, which varied depending on each center analyzed in the study. Touma et al. presented that corticosteroids were added to patients' treatment besides belimumab.

Each study presented its results differently. Wang et al. highlighted complete remission of oral ulcers in 19 of the 24 patients with oral ulcers in the presented cohort. "alopecia cohort". Touma et al. quantified the improvement of the oral lesions in their cohort.

Table 2. Outcomes

Outcome	Author, year, RefID	Study Design	Follow up Duration	Population	Intervention	Result
Complete remission of the oral ulcers	Wang 2024[1] 9568	multicenter, observational, prospective cohort study	12 months	193 patients did the study, mean age was 11.9 **but only 24 patients had oral ulcers**	Belimumab (10 mg/kg on weeks 0, 2, 4, and then every 4 weeks) + SOC therapy	19/24
Clinical improvement of the oral ulcers	Touma 2016[2] 9090	Retrospective multicentric clinical chart review	6 months	52 patients, 49 were female and mean age	Belimumab 10 mg/kg + corticosteroids	No improvement: 2/9 20-50% of improvement:1/9

				was 46.5 (10.8) **But only 9 had oral ulcers**		50-80% of improvement: 1/9 More than 80% of improvement: 5/9

References:

1. Wang L, Liang X, Cao Z, Wang D, Luo Y, Feng Y, Luo C, Zhi S, Huang Y, Fan Z, Wang C, Liu H, Liu J, Zhang T, Cheng Q, Xie X, Shuai L, Rong Z, Zeng P, Yu H, Lu M, Sun L, Yang S, Zhao D, Zhang W, Wu X, Li Q, Wang Y, Zhang Q, Yang J, Li X, Song H, Tang X. Evaluation of belimumab in treatment of Chinese childhood-onset systemic lupus erythematosus: a prospective analysis from a multicentre study. Rheumatology (Oxford). 2024 May 2;63(5):1437-1446. doi: 10.1093/rheumatology/kead406. PMID: 37606970.
2. Touma Z, Sayani A, Pineau CA, Fortin I, Matsos M, Ecker GA, Chow A, Iczkovitz S. Belimumab use, clinical outcomes and glucocorticoid reduction in patients with systemic lupus erythematosus receiving belimumab in clinical practice settings: results from the OBSErve Canada Study. Rheumatol Int. 2017 Jun;37(6):865-873. doi: 10.1007/s00296-017-3682-9. Epub 2017 Mar 9. PMID: 28280970; PMCID: PMC5434147.

Pericarditis and Pleural disease

In SLE patients with pericarditis, what is the most effective therapy?

P57. In SLE patients with pericarditis what is the impact of listed medical therapies or pericardectomy versus baseline therapy alone on clinical outcomes?

Population: Patients with lupus and pericarditis

Intervention:

- NSAIDs
- Colchicine
- Glucocorticoid therapy alone
- Methotrexate
- Azathioprine
- MMF/MPA
- Cyclophosphamide
- Belimumab
- Anifrolumab
- Anti-CD20
- Anti IL-1therapy

- Pericardiectomy

Comparator:

- Hydroxychloroquine and/or NSAIDs
- Colchicine with HCQ (for all but HCQ, NSAID and colchicine)
- HCQ / NSAID / colchicine
- Corticosteroid (for MTX, AZA, MMF/MPA, CYC, biologics and pericardectomy)

Outcomes:

- Resolution of pericarditis
- Prevention of pericarditis flares
- Prevention of pericardiectomy
- Prevention of chronic pericarditis (≥6 mo)
- Improvement in quality of life
- Cumulative GC
- Adverse treatment events: immunosuppressives including biologics, infection and cytopenias; colchicine and NSAIDs: GI symptoms; steroid alone: osteoporosis and infection
- Mortality
- Disease damage

In SLE patients with pleuritic pain and/or pleural effusion, what is the most effective therapy?

P58. In patients with SLE and pleural disease what is the impact of medical therapy versus baseline therapy alone on clinical outcomes?

Population: Patients with lupus and pleural disease (pleuritic pain, effusion)

Intervention:

- NSAIDs
- Colchicine
- Glucocorticoid therapy alone
- Methotrexate
- Azathioprine
- MMF/MPA
- Cyclophosphamide
- Belimumab
- Anifrolumab
- Anti-CD20
- Anti IL-1 therapy

Comparator:

- Hydroxychloroquine and/or NSAIDs
- Colchicine with HCQ (for all but HCQ, NSAID and colchicine)
- HCQ / NSAID / colchicine
- Corticosteroid (for MTX, AZA, MMF/MPA, CYC, biologics)

Outcomes:

- Resolution of pleural disease
- Prevention of pleural disease flares
- Prevention of shrinking lung syndrome
- Prevention of fibrothorax
- Improvement in quality of life
- Cumulative GC
- Adverse treatment events: immunosuppressives including biologics, infection and cytopenias; NSAIDs and colchicine: GI effects; steroid alone: osteoporosis and infection
- Mortality
- Disease Damage

TABLE 1. included studies

Author, Year	Population (number and description, age)	Intervention	Outcomes	Notes
Anjo 2009	Active SLE patients (n=23) including those with serositis (n=5) Mean age at first infusion of belimumab was 41.5 +/- 10.5	Belimumab	Resolution of pleural disease Cumulative GC	Assessed efficacy and safety of belimumab in SLE patients in real world setting SLEDAI-2K and clinical SLEDAI-2K improved over time at 6, 12, and 24 month timepoints (does not specify serositis domain); 1 patient had belimumab withdrawn due to maintenance of pleural effusion Mean prednisone dose could be reduced from 10.4 +/- 4.8 mg/dy to 4.8 +/- 2.1 mg/day at 24 months (p=0.006) (does not specify in those with serositis alone)
Dubois 1975	Various forms of SLE (n=17)	Ibuprofen	Resolution of pleural disease	Short case series letter to the editor

	including n=1 with pleuritic pain Median age of 46 (range, 22 to 70 years)		Cumulative GC	"One patient had persistent pleuritic pain, which was benefited." In n=14 receiving concurrent steroid therapy, the dose of steroid could be reduced for only 3.
Gansauge 1997	SLE patients with refractory cutaneous rashes, active vasculitis of the skin, active pleurisy, or active arthritis (total n=19, n=4 with pleurisy) Mean age was 41 years (range 24-68)	MTX 15 mg PO weekly	Resolution of pleural disease Cumulative GC Adverse treatment events	Disappearance of symptoms was noted in 3 of 4 patients with pleuritis For the total group SLEDAI decreased significantly from 12.2 (SD 3.99) to 4 (3.75) (p=0.001), and mean (SD) corticosteroid dose was significantly reduced from 17.4 (12.8) to 8.8 (3.99) (p=0.01). n=4 suffered general malaise soon after starting MTX and n=2 had small increase in LFTs (<2x ULN); no D/C of therapy needed.
Kipen 1997	SLE patients using MTX (n=24 subjects; n=25 MTX treatment episodes), including n=15 with serositis Mean age was 43.6 +/- 14.0 years	MTX	Cumulative GC Adverse treatment events	Median (IQR) monthly steroid intake reduced from 298.1 (237.9-531.4) mg to 279.4 (193.4-492.9) mg during MTX treatment; this did not reach statistical significance (p=0.12). A total of 36% of subjects reduced their steroid dose during MTX therapy, but this reduction was not statistically significant. Two treatment cessations were due to oral ulcers and refractory nausea despite folinic acid therapy.
Man 2005	SLE patients with serositis (n=310) Mean age at SLE diagnosis in those with serositis was 31.8 +/- 13.3 years	NSAIDs, oral prednisolone, AZA, CYC, HCQ	Resolution of pleural disease Prevention of pleural disease flares Prevention of fibrothorax	N=2 patients with mild serositis responded completely to NSAIDs alone. All other prednisolone-treated patients responded with resolution of symptoms and signs of serositis on repeat physical examination and imaging

			Resolution of pericarditis Prevention of pericarditis flares Prevention of chronic pericarditis	studies within 2 months; these included the 5 patients with cardiac taponade. None had re-accumulation of pericardial fluid after drainage and immunosuppressive treatment. Nine (24%) patients had 18 episodes of serositis relapses; 11 were peritonitis, 6 were pleuritis, and 1 was pericardial effusion. All recurrences responded to either NSAIDs or short courses of small to moderate doses of prednisolone. Radiological pleural fibrosis occurred in 3 patients. No patients developed restrictive pericarditis or pericardial fibrosis.
Merrill 2010	SLE patients with polyarthritis, discoid lesions, or pleuritis and/or pericarditis (n=118); n=14 with pleuritis and/or pericarditis who received abatacept and n= 6 with pleuritis and/or pericarditis who received placebo Mean age of those who received abatacept was 39.1 +/- 12.4 years	Abatacept 10 mg/kg IV on Days 1, 15, 29, and every 4 weeks	Adverse treatment events	Proportion of patients with a new flare following steroid initiation over 12 months (primary end point) was 79.7% in abatacept group and 82.5% in placebo group (not significant). Most frequent AEs (>10%) in abatacept group were URI (20.7%), HA (20.7%), back pain (12.4%), diarrhea (11.6%), nasopharyngitis (2.5%), and UTI (10.7%).
Morel 2015	SLE patients with pericarditis receiving colchicine (n=10) Mean age at inclusion was 35 +/- 12 years	Colchicine 1 mg/day for a median duration of 39 days (range 10 days to 54 months)	Resolution of pericarditis Prevention of pericarditis flares Cumulative GC Adverse treatment events	Complete remission of symptoms was achieved after a median of 2.5 days (range 1-30 days). No patient had recurrence of pericarditis with colchicine tx. Two patients (patients 2 and 9) had recurrent pericarditis 1 and 2 months

				after tx discontinuation; no relapse occurred 3 and 19 months after colchicine was resumed. The use of colchicine avoided the use or increase in steroid dosage in 7 cases, and the increase in steroid dosage was minimal in 2. Mild GI side effects were reported in 3 cases (nausea in 1, diarrhea in 2); no SAEs reported.
Nwobi 2008	Children with active SLE and LN refractory to conventional therapies treated with RTX (n=18); n=9 had serositis Mean age at time of SLE diagnosis was 10.7 +/- 2.5 years (range 7 to 14 years)	RTX weekly for 2-4 doses; initial dose 188 mg/m^2, subsequent doses 375 mg/m^2 per dose	Adverse treatment events	All patients had improvement in SLEDAI score and corticosteroid dose decreased from 79 +/- 26 mg/m^2 per day to 13 +/- 20 mg/m^2 per day after RTX ($p<0.0001$), but data not available for relevant PICO questions related to serositis outcomes per se. AEs included one patient (#7) with lupus serositis and nephritis who developed S. aureus endocarditis, who died after open heart surgery. She had received prior CYC therapy.
Palavutitotai 2014	SLE patients (n=119) with 127 episodes of pleural effusion Mean age was 29.7 +/- 12.5 years	Corticosteroids, NSAIDs	Resolution of pleural disease, Prevention of pleural disease flares, Prevention of fibrothorax	Most patients with lupus pleuritis (93%) were treated with corticosteroids, whereas NSAIDs were initially prescribed in only 9 patients (7%). Most patients (94%) completely responded Relapse occurred in 13%, and no one progressed to fibrotic disease.
Tani 2018	29 non-Asian patients with SLE (n-2 with serositis) Mean age at enrollment was 38 +/- 9 years	Tacrolimus at increasing dosage from 2 mg/day to 0.06 mg/kg/day	Resolution of pleural disease Resolution of pericarditis Adverse treatment events	Patient #3 with serositis had complete response at 6 months. Patient #6 with serositis had complete response at 3 months. TAC was D/C'd in 9 pts (31%) due to durg intolerance in 3 cases (10%); inefficacy or

				disease relapse in 4 cases (13.8%); disease remission in 2 cases (6.9%). AEs included GI intolerance, HA and cognitive impairment. One case had recurrent mild episodes of infections (also received GC and belimumab).
Tselios 2016	SLE patients treated with MMF; n=72 nonrenal and n=105 LN; of the nonrenal group, n=8 had serositis and of the LN group, n=7 had serositis Mean age in the nonrenal group was 38.6 +/- 11.7 years Mean age in the renal group was 35.6 +/- 10.7 years	MMF	Resolution of pleural disease Resolution of pericarditis	In the serositis subgroup, 6/8 (75%) of the nonrenal group improved at 6 months and 5/8 (62.5%) at 12 months. In the serositis subgroup, 4/7 (57.1%) of the LN group improved at 6 months and 7/7 (100%) improved at 12 months. In the nonrenal group, 1 patient with serositis relapsed after 6 months.

Summary of the Evidence
23 single-arm studies were reviewed with regard to the PICO57 and PICO58 questions. Twelve were excluded due to lack of reporting on relevant PICO populations and/or outcomes. Eleven studies were included. One study evaluated pediatric patients (Nwobi 2008).

There were 7 studies that looked at resolution of pleural disease:
1-Anjo 2019 studied 23 active SLE patients being treated with belimumab, of whom 5 had serositis. Like many studies, they did not specifically delineate how many had pericarditis vs. pleuritis. Mean number of previous immunosuppressive agents used was 2.2 +/- 1.1, including HCQ, prednisone, AZA, MMA, MTX, cyclosporine, and LEF. The mean dose of prednisone at first infusion of belimumab was 10.2 +/- 1.8 mg/day. Values of both SLEDAI-2K and clinical SLEDAI-2K improved over time at all time-points, including 6, 12, and 24 months (but this did not specify how many improved in the serositis domain). One patient had belimumab withdrawn due to persistence of pleural effusion.
2-Dubois 1975 described a small case series of 17 patients with various forms of SLE, including 1 with persistent pleuritic pain, treated with ibuprofen. This patient "benefited" from addition of ibuprofen (further details were not provided).
3-Gansauge 1997 was an open prospective study of 22 patients with moderate SLE (exclusion of renal and CNS disease) who had one or more of the following: active non-destructive polyarthritis, dermatitis, vasculitis of the skin, or pleuritis. All patients received MTX at a dose of 15 mg orally weekly over 6 months. Disappearance of symptoms was noted in 3 of 4 patients with pleuritis.
4-Man 2005 was a case series looking at prevalence and outcomes of 310 patients with SLE and serositis. Two patients with mild serositis responded completely to NSAIDs alone. All other prednisolone-treated patients responded with resolution of symptoms and signs of serositis on repeat physical examination and imaging studies within 2 months.

5-Palavutitotai 2014 studied SLE patients satisfying ACR classification criteria who presented with pleuritis between 2002 and 2010. Pleuritis was defined as having 1 of 3 of the following: typical pleuritic chest pain, pleural rub, and clinical or radiological evidence of pleural effusion. Most patients with lupus pleuritis (93%) were treated with corticosteroids, whereas NSAIDs were initially prescribed in only 9 patients (7%). Most patients (94%) completely responded.
6-Tani 2018 was a retrospective analysis of a prospective cohort study evaluating the real-life use of tacrolimus (TAC) in SLE patients from three European SLE referral centers. 29 patients were included, of which 2 had serositis. Patient #3 with serositis had complete response at 6 months, and patient #6 with serositis had compete response at 3 months. Of note, this study did not report outcomes separately for pleuritis and pericarditis.
7-Tselios 2016 was an observational cohort study evaluating SLE patients treated with MMF; there were 72 nonrenal and 105 renal patients. Of the nonrenal group, 8 had serositis, and of the renal group, 7 had serositis. Specifically, in the nonrenal group, serositis consisted of pleuritis in 6 patients and pericarditis in 2. In the renal group, serositis consisted of 5 patients with pleuritis, 1 with pericarditis, and 1 with concomitant pleuritis and pericarditis. In the serositis subgroup, 6/8 (75%) of the nonrenal group improved at 6 months and 5/8 (62.5%) improved at 12 months. Likewise, 4/7 (57.1%) of the renal group improved at 6 months and 7/7 (100%) improved at 12 months. Results of MMF were not reported specifically in those with pleuritis vs. pericarditis.
In summary, based on a number of case series and observational cohort studies, the following therapies were found to be beneficial in treating pleural disease: belimumab, NSAIDs including ibuprofen, corticosteroids, MTX, TAC, and MMF.

There were 5 studies evaluating the cumulative GC dose in patients with serositis:
1-Anjo 2019 found that belimumab use allowed for mean prednisone dose to be reduced from 10.4 +/- 4.8 mg/day to 4.8 +/- 2.1 mg/day at 24 months (p=0.006). Note, this study did not specify GC dose reduction in the n=5 patients with serositis alone.
2-Dubois 1975 found that the dose of steroid could be reduced in only 3 of the 14 SLE patients receiving ibuprofen. Note, only 1 patient had persistent pleuritic pain in this study.
3-Gansauge 1997 found that MTX use allowed for mean GC dose to be significantly reduced from 17.4 (12.8) to 8.8 (3.99) (p=0.01). Note, the results of GC dose reduction were not reported specifically in only those with pleurisy.
4-Kipen 1997 found that a total of 36% of patients reduced their steroid dose during MTX therapy, but this was not statistically significant. Again, results were not available for the subgroup of patients with serositis specifically.
5-Morel 2015 found that the use of colchicine for SLE patients with pericarditis (n=10) led to avoidance of the use or increase in steroid dosage in 7 cases, and the increase in steroid dosage was minimal in 2.
In summary, belimumab and MTX use allowed for GC dose reduction in serositis. In pericarditis, colchicine was helpful in reducing GC dose as well. A small study on ibuprofen did not seem to suggest a substantial GC dose reduction effect.

There were 3 studies addressing the risk of serositis flares:
1-Man 2005 showed that use of prednisolone for SLE patients with serositis led to resolution of symptoms and signs within 2 months; these included 5 patints with cardiac tamponade. None had re-accumulation of pericardial fluid after drainage and immunosuppressive treatment. Nine (24%) patients had 18 episodes of serositis relapses; 11 were peritonitis, 6 were pleuritis, and 1 was pericardial effusion. All recurrences responded to either NSAIDs or short courses of small to moderate doses of prednisolone.
2-Morel 2015 evalauted the use of colchicine for SLE patients with pericarditis (n=10). Two patients (patients 2 and 9) had recurrent pericarditis 1 and 2 months after treatment discontinuation; no relapse occurred 3 and 19 months after colchicine was resumed.

3-Palavutitotai 2014 showed that most patients (94%) with episodes of pleural effusion responded completely to corticosteroids and/or NSAIDs, and relapse occurred in 13%.
In summary, treatment with corticosteroids, colchicine, and/or NSAIDs seem to be helpful in reducing risk of serositis flares in patients with SLE. When flares/relapses do occur, resuming these treatments usually leads to resolution of the symptoms.

There were 2 studies addressing prevention of fibrothorax or chronic pericarditis:
1-Man 2005 found that in the 310 SLE patients with serositis studied and treated with NSAIDs and/or steroids, radiological pleural fibrosis occurred in 3 patients. No patients developed restrictive pericarditis or pericardial fibrosis.
2- Palavutitotai 2014 found that in the 119 SLE patients with 127 episodes of pleural effusion treated with corticosteroids and/or NSAIDs, no one progressed to fibrotic disease.
In summary, progression to fibrothorax or chronic pericarditis was extremely rare in SLE patients with serositis treated with corticosteroids and/or NSAIDs.

There were 4 studies that looked at resoluation of pericardial disease:
1-Man 2005 found that SLE patients with serositis treated with NSAIDs and/or steroids showed resolution of signs and symptoms within 2 months, including 5 patients with cardiac tamponade. None of them had re-accumulation of pericardial fluid after drainage and immunosuppressive treatment. (Further details on type of immunosuppressive treatment were not provided.)

2-Morel 2015 evaluated 10 patients with SLE patient with pericarditis receiving colchicine. Complete remission of symptoms was achieved after a median of 2.5 days (range 1-30 days). No patient had recurrence of pericarditis with colchicine treatment.
3-Tani 2018 showed complete response of serositis in the 2 SLE patients with this feature treated with tacrolimus. It was not specified whether they had pericarditis vs. pleuritis vs. both.
4-Tselios 2016 showed MMF treatment resulted in the majority of patients with serositis improvement at 6 and 12 months. However, results were not available for subgroups of pleuritis vs. pericarditis.
In summary, NSAIDs, steroids, colchicine, tacrolimus, and MMF all seem to be helpful in treating pericardial disease in SLE.

There were 6 studies addressing adverse effects of treatments:
See Tables for outcomes of studies that addressed adverse effects of treatment. These included studies on MTX (Gansauge 1997, Kippen 1997), abatacept (Merrill 2010), colchicine (Morel 2015), RTX (Nwobi 2008), and TAC (Tani 2018).

Table of outcomes

Outcomes (Name + Summary)	Author, year, RefID	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
P58. Resolution of pleural disease, P57 and P58. Cumulative GC	Anjo C et al, 2019, RefID 388	Retrospective cohort study	June 2013 to April 2018	Active SLE patients (n=23) including those with	Belimumab	SLEDAI-2K and clinical SLEDAI-2K improved over time at 6, 12, and 24 month timepoints (does not specify serositis domain); 1	Mean number of previous immunosuppressive agents was 2.2 +/- 1.1, including HCQ, prednisone,

				serositis (n=5)		patient had belimumab withdrawn due to maintenance of pleural effusion Mean prednisone dose could be reduced from 10.4 +/- 4.8 mg/day to 4.8 +/- 2.1 mg/day at 24 months (p=0.006) (does not specify in those with serositis alone)	AZA, MMA, MTX, cyclosporine, LEF
P58. Resolution of pleural disease, Cumulative GC	Dubois EL, 1975, RefID 2456	Case series	Doesn't specify but duration of therapy was 1.5 to 33 weeks, with median of 16 weeks	Various forms of SLE (n=17) including n=1 with pleuritic pain	Ibuprofen	"One patient had persistent pleuritic pain, which was benefited." In n=14 receiving concurrent steroid therapy, the dose of steroid could be reduced for only 3.	
P58. Resolution of pleural disease, Cumulative GC, Adverse treatment events	Gansauge S et al, 1997, RefID 3079	Open prospective study	6 months	SLE patients with refractory cutaneous rashes, active vasculitis of the skin, active pleurisy, or active arthritis (total n=19, n=4 with pleurisy)	MTX 15 mg PO weekly	Disappearance of symptoms was noted in 3 of 4 patients with pleuritis; for the total group SLEDAI decreased significantly from 12.2 (SD 3.99) to 4 (3.75) (p=0.001), and mean (SD) corticosteroid dose was significantly reduced from 17.4 (12.8) to 8.8 (3.99) (p=0.01). n=4 suffered general malaise soon after starting MTX and n=2 had small increase in LFTs (<2x ULN); no D/C of therapy needed.	SLEDAI and GC dose and adverse event results not available for subgroup analysis of only those with pleurisy
P57 and P58. Cumulative GC, Adverse treatment events	Kipen Y et al, 1997, RefID 4697	Cross sectional study	14.43 months (5.10-41.59)	SLE patients using MTX (n=24 subjects;	MTX	Median (IQR) monthly steroid intake reduced from 298.1 (237.9-531.4) mg to 279.4 (193.4-492.9) mg during	Outcomes/results were not available for the subgroup of patines with serositis.

				n=25 MTX treatment episodes), including n=15 with serositis		MTX treatment; this did not reach statistical significance (p=0.12). A total of 36% of subjects reduced their steroid dose during MTX therapy, but this reduction was not statistically significant. Two treatment cessations were due to oral ulcers and refractory nausea despite folinic acid therapy.	
P58. Resolution of pleural disease, Prevention of pleural disease flares, Prevention of fibrothorax P57. Resolution of pericarditis, Prevention of pericarditis flares, Prevention of chronic pericarditis	Man BL and Mok CC, 2005, RefID 5629	Case series	Mean follow-up period of 46 +/- 40 months	SLE patients with serositis (n=310)	NSAIDs, oral prednisolone, AZA, CYC, HCQ	N=2 patients with mild serositis responded completely to NSAIDs alone. All other prednisolone-treated patients responded with resolution of symptoms and signs of serositis on repeat physical examination and imaging studies within 2 months; these included the 5 patients with cardiac taponade. None had re-accumulation of pericardial fluid after drainage and immunosuppressive treatment. Nine (24%) patients had 18 episodes of serositis relapses; 11 were peritonitis, 6 were pleuritis, and 1 was pericardial effusion. All recurrences responded to either NSAIDs or short courses of small to moderate doses of prednisolone. Radiological pleural fibrosis occurred in 3 patients. No patients developed restrictive	

						pericarditis or pericardial fibrosis.	
P57 and P58. Adverse treatment events	Merrill JT et al, 2010, RefID 5990	Phase IIb RCT	12 months	SLE patients with polyarthritis, discoid lesions, or pleuritis and/or pericarditis (n=118); n=14 with pleuritis and/or pericarditis who received abatacept and n= 6 with pleuritis and/or pericarditis who received placebo	Abatacept 10 mg/kg IV on Days 1, 15, 29, and every 4 weeks	Proportion of patients with a new flare following steroid initiation over 12 months (primary end point) was 79.7% in abatacept group and 82.5% in placebo group (not significant); most frequent AEs (>10%) in abatacept group were URI (20.7%), HA (20.7%), back pain (12.4%), diarrhea (11.6%), nasopharyngitis (2.5%), and UTI (10.7%).	Primary end point outcomes not available for subgroup with pleuritis and/or pericarditis, as that was not the design of the trial; cannot tell whether the AEs were in subjects with pleuritis and/or pericarditis per se; query exclude this trial?
P57. Resolution of pericarditis, Prevention of pericarditis flares, Cumulative GC, Adverse treatment events	Morel N et al, 2015, RefID 6277	Case series	2010 to 2014	SLE patients with pericarditis receiving colchicine (n=10)	Colchicine 1 mg/day for a median duration of 39 days (range 10 days to 54 months)	Complete remission of symptoms was achieved after a median of 2.5 days (range 1-30 days). No patient had recurrence of pericarditis with colchicine tx. Two patients (patients 2 and 9) had recurrent pericarditis 1 and 2 months after tx discontinuation; no relapse occurred 3 and 19 months after colchicine was resumed. The use of colchicine avoided the use or increase in steroid dosage in 7 cases, and the increase in steroid dosage was minimal in 2. Mild GI side effects were reported in 3 cases (nausea in 1,	

						diarrhea in 2); no SAEs reported.	
P57 and P58. Adverse treatment events	Nwobi O et al, 2008, RefID 6646	Case series	7 years	Children with active SLE and LN refractory to conventional therapies treated with RTX (n=18); n=9 had serositis	RTX weekly for 2-4 doses; initial dose 188 mg/m^2, subsequent doses 375 mg/m^2 per dose	All patients had improvement in SLEDAI score and corticosteroid dose decreased from 79 +/- 26 mg/m^2 per day to 13 +/- 20 mg/m^2 per day after RTX ($p<0.0001$), but data not available for relevant PICO questions related to serositis outcomes per se. AEs included one patient (#7) with lupus serositis and nephritis who developed S. aureus endocarditis, who died after open heart surgery. She had received prior CYC therapy.	Table 1 only shows 15 patients, even though text says there were 18.
P58. Resolution of pleural disease, Prevention of pleural disease flares, Prevention of fibrothorax	Palavutitotai N et al, 2014, RefID 6821	Case series	Unclear	SLE patients (n=119) with 127 episodes of pleural effusion	Corticosteroids, NSAIDs	Most patients with lupus pleuritis (93%) were treated with corticosteroids, whereas NSAIDs were initially prescribed in only 9 patients (7%). Most patients (94%) completely responded Relapse occurred in 13%, and no one progressed to fibrotic disease.	
P58. Resolution of pleural disease, P57. Resolution of pericarditis, Adverse treatment events	Tani C et al, 2018, RefID 8890	Retrospective analysis of prospective cohort study	12 months	29 non-Asian patients with SLE (n-2 with serositis)	Tacrolimus at increasing dosage from 2 mg/day to 0.06 mg/kg/day	Patient #3 with serositis had complete response at 6 months. Patient #6 with serositis had complete response at 3 months. TAC was D/C'd in 9 pts (31%) due to durg intolerance in 3 cases (10%); inefficacy or disease relapse in 4 cases (13.8%); disease remission in 2 cases (6.9%). AEs included GI intolerance, HA and	Did not report outcomes separately for pleuritis and pericarditis

						cognitive impairment. One case had recurrent mild episodes of infections (also received GC and belimumab).	
P58. Resolution of pleural disease, P57. Resolution of pericarditis	Tselios K et al, 2016, RefID 9155	Observational cohort study	12 months	SLE patients treated with MMF; n=72 nonrenal and n=105 LN; of the nonrenal group, n=8 had serositis and of the LN group, n=7 had serositis	MMF	In the serositis subgroup, 6/8 (75%) of the nonrenal group improved at 6 months and 5/8 (62.5%) at 12 months. In the serositis subgroup, 4/7 (57.1%) of the LN group improved at 6 months and 7/7 (100%) improved at 12 months. In the nonrenal group, 1 patient with serositis relapsed after 6 months.	In the nonrenal group, serositis consisted of pleuritis in 6 patients and pericarditis in 2. In the renal group, serositis consisted of 5 cases with pleuritis, 1 with pericarditis, and 1 with concomitant pleuritis and pericarditis. Results re: MMF were not available for subgroups of pleuritis vs. pericarditis.

References:

Randomized controlled trials:
-None (RefID 5990 was an RCT but primary outcome was proportion of patients with flare (score A/B) on BILAG index; not specific to the serositis subgroup)

Comparative observational studies:
-None

Single arm studies:

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Studies reviewed and excluded:

Author	Year	Title	Comments
Freitas S et al	2020	Why do some patients with systemic lupus erythematosus fail to respond to B-cell depletion using rituximab?	Cannot abstract data specifically for pleural or pericardial disease; just says, "Cardiorespiratory involvement." Study was comparing groups with failure to RTX vs. non-failure to RTX. In the "Cardiorespiratory involvement" subgroup, total n= 24, with n=3 in the Failure to RTX group and n=21 in the Non-failure to RTX group. The p=1.000 in terms of clinical and serological features between these groups.
Melander C et al	2009	Rituximab in severe lupus nephritis: early B-cell depletion affects long-term renal outcome	Only looked at renal outcomes. Of the 20 patients treated with RTX for LN, n=8 patients had Serositis.
Merrill JT et al	2010	Efficacy and safety of rituximab in moderately-to-	Cannot abstract data specifically for pleural or

		severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial	pericardial disease; just says, "Cardiovascular and respiratory." Study was comparing RTX in moderate to severely active SLE. Among the subgroup with "Cardiovascular and respiratory" involvement, n=6 with BILAG A score received placebo and n=8 with BILAG A score received RTX; and n=13 with BILAG B score received placebo and n=32 with BILAG B score received RTX. That means n=40 total (BILAG A or B) received RTX. Relevant outcomes and AEs were not reported for this specific subgroup.
Rosenbaum E t al	2009	The spectrum of clinical manifestations, outcome and treatment of pericardial tamponade in patients with systemic lupus erythematosus: a retrospective study and literature review	Although the paper describes a case series of 9 patients with pericarial tamponade in SLE patients at a single center, it doesn't mention the relevant PICO outcomes. It just states, "All patients were treated with at least 50 mg/day of prednisone. A pericardial window was required in 5 patients even though the patients were receiving high-dose corticosteroids and all of these effusions were exudates. None of the patients had signs of constrictive pericarditis."
Seedat YK and Pudifin D	1977	Systemic lupus erythematosus in Black and Indian patients in Natal	Case series of 17 Indian and 13 Black patients with SLE. Pericardial effusion occurred in 5 patients (17%), pleural effusion in 1 patient, and cardiomyopathy in 1 patient. No relevant PICO outcomes were reported.

Jimenez A et al	2021	Shrinking lung syndrome in pediatric systemic lupus erythematosus	No relevant PICO population or outcomes
Triboulet F et al	2023	Systemic lupus erythematosus-related acute lung disease	No relevant PICO population or outcomes
Tselios K et al	2015	The influence of therapy on CD4+CD25(high)FOXP3+ regulatory T cells in systemic lupus erythematosus patients: a prospective study	No relevant PICO population or outcomes
Vital E et al	2011	B cell biomarkers of rituximab responses in systemic lupus erythematosus	No relevant PICO population or outcomes
Wahadat MJ et al	2021	LLDAS is an attainable treat-to-target goal in childhood-onset SLE	No relevant PICO population or outcomes
Watson L et al	2015	The indications, efficacy and adverse events of rituximab in a large cohort of patients with juvenile-onset SLE	No relevant PICO population or outcomes
Weinrib L et al	1990	A long-term study of interstitial lung disease in systemic lupus erythematosus	No relevant PICO population or outcomes

P57.1a In SLE patients with pericarditis what is the impact of listed medical therapies or pericardectomy versus baseline therapy alone on clinical outcomes?

Population: Patients with lupus and pericarditis

Intervention:

- Colchicine

Comparator:

- Conventional therapy (NSAIDs or Aspirin +/- corticosteroids)

Outcomes:

- Resolution of pericarditis
- Prevention of pericarditis flares
- Prevention of pericardiectomy
- Prevention of chronic pericarditis (≥6 mo)
- Quality of life
- Adverse treatment events: immunosuppressives including biologics, infection and cytopenias; colchicine and NSAIDs: GI symptoms; steroid alone: fracture, hypertension, T2DM, infection
- Mortality
- Disease damage
- Cumulative GC dose

Table 1.

Author, year	Design	Population	Intervention	Comparison	Outcomes
Imazio 2005 (COPE trial)	RCT (open label)	A total of 120 patients (mean age 56.9±18.8 years, 54 males) with a first episode of acute pericarditis (idiopathic, viral, postpericardiotomy syndromes, and connective tissue diseases)	Colchicine	Conventional therapy (aspirin or NSAIDS)	Pericarditis recurrence, cardiac tamponade, constrictive pericarditis, AEs
Imazio 2005 (CORE trial)	RCT (open label)	84 consecutive patients with a first episode of recurrent pericarditis. Inclusion criteria were a diagnosis of recurrent peri- carditis (first episode); previous idiopathic, viral, and autoimmune etiologies (including postpericardiotomy syndromes and connective tissue diseases)	Colchicine	Conventional therapy (aspirin or NSAIDS)	Pericarditis recurrence, cardiac tamponade, constrictive pericarditis, AEs
Imazio 2011 (CORP trial)	RCT (double blinded)	Patients with first recurrent pericarditis	Colchicine	Conventional therapy (aspirin or NSAIDS)	Pericarditis recurrence, pericarditis resolution, cardiac tamponade, constrictive pericarditis, AEs, GI AEs
Imazio 2013 (ICAP trial)	RCT (double blinded)	First episode of acute pericarditis (idiopathic, viral, after cardiac injury, or associated with connective-tissue disease)	Colchicine	Conventional therapy (aspirin or NSAIDS)	Pericarditis recurrence, pericarditis resolution, cardiac tamponade, constrictive pericarditis, AEs, GI AEs
Imazio 2013 (CORP 2 trial)	RCT (double blinded)	Patients with more than 2 recurrences of pericarditis	Colchicine	Conventional therapy (aspirin or NSAIDS)	Pericarditis recurrence, pericarditis resolution, cardiac tamponade, constrictive pericarditis, AEs, GI AEs

Evidence summary: 5 RCTs assessed the efficacy and safety of colchicine in patients with (first or recurrent) pericarditis. Two were open-label, and three were double-blinded. Only a minority of the patients included in the trials had connective tissue diseases that's why we downgraded for indirectness. Colchicine is associated with higher rates of resolution of symptoms and lower rates of recurrence, constrictive pericarditis, and cardiac tamponade. The safety profile was comparable between both arms. The overall certainty of the evidence was judged as low because of concerns related to risk of bias, indirectness, and imprecision.
N.B: These studies were not part of the original search strategy and were identified manually.

Evidence profile

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Colchicine	conventional therapy (NSAIDS or Aspirin)	Relative (95% CI)	Absolute (95% CI)		
Resolution of pericarditis (at 1 week)												
3	randomised trials	serious	not serious	serious	not serious	none	251/300 (83.7%)	170/300 (56.7%)	**RR 1.47** (1.31 to 1.64)	**266 more per 1,000** (from 176 more to 363 more)	⨁⨁◯◯ Low	
recurrence of pericarditis (at 18 months)												
5	randomised trials	serious	not serious	serious	not serious	none	77/402 (19.2%)	171/402 (42.5%)	**RR 0.45** (0.37 to 0.56)	**234 fewer per 1,000** (from 268 fewer to 187 fewer)	⨁⨁◯◯ Low	
Cardiac tamponade												
5	randomised trials	serious	not serious	serious	serious	none	0/402 (0.0%)	6/402 (1.5%)	**Risk Difference -0.01** (-0.03 to 0.00)	**-- per 1,000** (from -- to --)	⨁◯◯◯ Very low	
Constrictive pericarditis												
5	randomised trials	serious	not serious	serious	serious	none	0/402 (0.0%)	6/402 (1.5%)	**Risk Difference -0.01** (-0.02 to 0.00)	**-- per 1,000** (from -- to --)	⨁◯◯◯ Very low	
Adverse events												
5	randomised trials	serious	not serious	serious	serious	none	40/402 (10.0%)	36/402 (9.0%)	**RR 1.12** (0.73 to 1.73)	**11 more per 1,000** (from 24 fewer to 65 more)	⨁◯◯◯ Very low	
Gastrointestinal AEs												
3	randomised trials	serious	not serious	serious	serious	none	24/300 (8.0%)	22/300 (7.3%)	**RR 1.09** (0.63 to 1.90)	**7 more per 1,000** (from 27 fewer to 66 more)	⨁◯◯◯ Very low	

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

References: 5 RCTs

- Imazio M, Belli R, Brucato A, Cemin R, Ferrua S, Beqaraj F, Demarie D, Ferro S, Forno D, Maestroni S, Cumetti D, Varbella F, Trinchero R, Spodick DH, Adler Y. Efficacy and safety of colchicine for treatment of multiple recurrences of pericarditis (CORP-2): a multicentre, double-blind, placebo-controlled, randomised trial. Lancet. 2014 Jun 28;383(9936):2232-7. doi: 10.1016/S0140-6736(13)62709-9. Epub 2014 Mar 30. PMID: 24694983..
- Imazio M, Bobbio M, Cecchi E, et al. Colchicine in addition to conventional therapy for acute pericarditis: results of the COlchicine for acute PEricarditis (COPE) trial. Circulation. 2005;112(13):2012-2016. doi:10.1161/CIRCULATIONAHA.105.542738.
- Imazio M, Bobbio M, Cecchi E, Demarie D, Pomari F, Moratti M, Ghisio A, Belli R, Trinchero R. Colchicine as first-choice therapy for recurrent pericarditis: results of the CORE

(COlchicine for REcurrent pericarditis) trial. Arch Intern Med. 2005 Sep 26;165(17):1987-91. doi: 10.1001/archinte.165.17.1987. PMID: 16186468..
- Imazio M, Brucato A, Cemin R, Ferrua S, Belli R, Maestroni S, Trinchero R, Spodick DH, Adler Y; CORP (COlchicine for Recurrent Pericarditis) Investigators. Colchicine for recurrent pericarditis (CORP): a randomized trial. Ann Intern Med. 2011 Oct 4;155(7):409-14. doi: 10.7326/0003-4819-155-7-201110040-00359. Epub 2011 Aug 28. PMID: 21873705..
- Massimo Imazio, M.D., Antonio Brucato, M.D., Roberto Cemin, M.D., Stefania Ferrua, M.D., Stefano Maggiolini, M.D., Federico Beqaraj, M.D., Daniela Demarie, M.D., +7, for the ICAP Investigators*Author Info & AffiliationsPublished October 17, 2013N Engl J Med 2013;369:1522-1528DOI: 10.1056/NEJMoa1208536.

P57.4 In SLE patients with pericarditis what is the impact of listed medical therapies or pericardectomy versus baseline therapy alone on clinical outcomes?

Population: Patients with lupus and pericarditis

Intervention:

- IL-inhibitors

Comparator:

- Conventional therapy (NSAIDs or Aspirin or Corticosteroids)

Outcomes:

- Resolution of pericarditis
- Prevention of pericarditis flares
- Prevention of pericardiectomy
- Prevention of chronic pericarditis (≥6 mo)
- Quality of life
- Adverse treatment events: immunosuppressives including biologics, infection and cytopenias; colchicine and NSAIDs: GI symptoms; steroid alone: fracture, hypertension, T2DM, infection
- Mortality
- Disease damage
- Cumulative GC dose

Table 1

Author, year	Study design	Population	Intervention	Comparison	Outcomes
Klein 2021 (RHAPSODY)	RCT (double blinded)	All patients eligible for inclusion in this study had recurrent idiopathic pericarditis, defined as a first episode of acute peri-carditis followed by recurrences (with ≥3 previous recurrences), and were older than 2 years and younger than 70 years at the screening visit	Rilonacept	Conventional therapy	Recurrence, adverse events
Brucato 2016 (AIRTRIP trial)	RCT (double blinded)	Adult and adolescent patients (≥12 years of age) with recurrent pericarditis were eligible	Anakinra	Conventional therapy	Recurrence, adverse events

		to participate if they presented with acute signs and symptoms of pericarditis during at least a second recurrence (having met the 2015 European Society of Cardiology criteria for pericarditis2 at least once), despite treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, or oral glucocorticoids in any combination.			

Evidence summary: 2 RCTs addressed the efficacy and safety of IL-1 inhibitors versus conventional therapy in patients with recurrent pericarditis. We downgraded for indirectness because a minority of patients had SLE. The recurrence rate was lower in the IL-1 Inhibitors with higher rates of adverse events. The overall certainty of evidence is very low because of risk of bias, indirectness, imprecision (small sample size).
N.B: These studies were not part of the original search strategy and were identified manually.

Evidence profile:

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IL-inhibitor**	**standard of care (colchicine)**	**Relative (95% CI)**	**Absolute (95% CI)**	
Recurrence											
2	randomised trials	serious	not serious	serious	serious	none	4/41 (9.8%)	32/41 (78.0%)	**RR 0.14** (0.05 to 0.35)	**671 fewer per 1,000** (from 741 fewer to 507 fewer)	⨁◯◯◯ Very low
Adverse events											
2	randomised trials	serious	not serious	serious	serious	none	25/41 (61.0%)	13/41 (31.7%)	**RR 1.92** (1.23 to 3.00)	**292 more per 1,000** (from 73 more to 634 more)	⨁◯◯◯ Very low

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

References: 2 RCTs.

- Phase 3 Trial of Interleukin-1 Trap Rilonacept in Recurrent PericarditisAuthors: Allan L. Klein, M.D., Massimo Imazio, M.D. https://orcid.org/0000-0002-5722-0245, Paul Cremer, M.D., Antonio Brucato, M.D., Antonio Abbate, M.D., Ph.D., Fang Fang, Ph.D., Antonella Insalaco, M.D., +8, for the RHAPSODY Investigators*Author Info & AffiliationsPublished November 16, 2020N Engl J Med 2021;384:31-41DOI: 10.1056/NEJMoa2027892VOL. 384 NO. 1.
- Brucato A, Imazio M, Gattorno M, Lazaros G, Maestroni S, Carraro M, Finetti M, Cumetti D, Carobbio A, Ruperto N, Marcolongo R, Lorini M, Rimini A, Valenti A, Erre GL, Sormani MP, Belli R, Gaita F, Martini A. Effect of Anakinra on Recurrent Pericarditis Among Patients With Colchicine Resistance and Corticosteroid Dependence: The AIRTRIP Randomized Clinical Trial. JAMA. 2016 Nov 8;316(18):1906-1912. doi: 10.1001/jama.2016.15826. PMID: 27825009.

P58.4 In patients with SLE and pleural disease what is the impact of medical therapy versus baseline therapy alone on clinical outcomes?

Population: Patients with lupus and pleural disease (pleuritic pain, effusion)

Intervention:

- Belimumab

Comparator:

- Standard of care

Outcomes:

- Resolution of pleural disease
- Prevention of pleural disease flares
- Prevention of shrinking lung syndrome
- Prevention of fibrothorax
- Quality of life
- Adverse treatment events: immunosuppressives including biologics, infection and cytopenias (depression/suicide for belimumab); NSAIDs and colchicine: GI effects; steroid alone: fracture, hypertension, T2DM, infection
- Mortality
- Disease Damage
- Cumulative GC dose

Table 1.

Study	Design	Population	Intervention	Comparator	Outcomes	Notes
Manzi 2012	Post hoc analysis for BLISS 52 and BLISS 72	Patients with active SLE (only Pleurisy)	Belimumab 10 mg	Standard of care (immunosuppressive therapy, or/and steroids, or/and HCQ)	SLEDIA improvement (pleurisy)	

Evidence summary: 1 posthoc analysis of the BLISS 52 and BLISS 72 trials compared Belimumab to standard of care in patients with Pleurisy. For BILAG neurological improvement, it was 408 fewer per 1,000 (from 667 fewer to 250 more) in the Belimumab arm. For SLEDIA (pleurisy) improvement, it was 164 fewer per 1,000 (from 340 fewer to 126 more) in patients taking Belimumab. The overall certainty of evidence is very low due to concerns about risk of

bias (posthoc analysis which will affect randomization) and imprecision (very small sample size and number of events leading to wide CI)

Evidence report:

Certainty assessment							№ of patients		Effect		Certainty	
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Belimumab	SOC	Relative (95% CI)	Absolute (95% CI)		
SELENA-SLEDAI (pleurisy, improvement)												
1	randomised trials	serious	not serious	not serious	very serious	none	14/30 (46.7%)	17/27 (63.0%)	**RR 0.74** (0.46 to 1.20)	**164 fewer per 1,000** (from 340 fewer to 126 more)	⨁◯◯◯ Very low	

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

References: 1 posthoc analysis of 2 RCTs (BLISS 52 and 72)

Manzi S, Sánchez-Guerrero J, Merrill JT, et al. Effects of belimumab, a B lymphocyte stimulator-specific inhibitor, on disease activity across multiple organ domains in patients with systemic lupus erythematosus: combined results from two phase III trials. *Ann Rheum Dis*. 2012;71(11):1833-1838. doi:10.1136/annrheumdis-2011-200831

Musculoskeletal

PICO 60. In patients with SLE and lupus arthritis, does treatment with listed medical therapies compared to no treatment impact clinical outcomes?

Population: SLE patients with active lupus arthritis

Intervention:

- HCQ

Comparator:

- No treatment

Outcomes

- Arthritis activity (improvement in joint pains, joint stiffness, joint swelling, and function)
- Joint damage – erosions, joint space narrowing, tendon loosening or deformity
- Functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)
- Disease activity
- SLE flares
- Disease damage
- Quality of life
- Treatment-related adverse events: immunosuppressives and biologics: infection and cytopenias (belimumab: depression/suicide; CNI: eGFR effects); steroids: fracture, hypertension, T2DM, infection; NSAIDs: GI

side effects; Antimalarials: retinal and cardiac effects (prolonged QTc and myopathy)

Table 1.

Study	Design	Population	Intervention	Comparator	Outcomes	Notes
Williams 1994	RCT	Patients with active SLE. (Arthropathy of Mild Systemic Lupus Erythematosus)	Hydroxy-chloroquine (200 mg)	Placebo	Painful joint count, Painful joint score, swollen joint count, swollen joint score, adverse events leading to discontinuation.	he patients also maintained a stable dose of aspirin and/or NSAID , which was kept constant for the duration of the 48-week trial. Phenylbuta-zone was not permitted. Prednisone 'therapy in a dosage that had been stable for one month before study entry in a dose :5 10 mg/day (or equivalent) was allowed, but changes in dosage were not permitted.
Meinao 1996	RCT	Patients with SLE without life-threatening manifestations.	Chloroquine diphosphate	Placebo	SLE flare up, prednisone dose	

Evidence summary: 2 RCTs compared the outcomes of antimalarials in patients with SLE. 1 was in patients with Arthropathy and the other was in patients with different presentations. For SLE flares it was 650 fewer per 1,000 (from 783 fewer to 183 fewer) in the antimalarial arm compared to placebo. For reducing prednisone dose treatment, it was 568 more per 1,000 (from 45 more to 1,000 more) in the antimalarial arm compared to placebo. The measure assessing the arthropathy measures (counts and scores) favors antimalarial over placebo. For AE leading to discontinuation of treatment, RR: 3.90 (0.19, 78.46), in the antimalarial arm compared to placebo. The overall certainty of the evidence was judged as very low

due to concerns about risk of bias and imprecision (very small sample size and events).

Evidence profile:

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antimalarial	No treatment	Relative (95% CI)	Absolute (95% CI)	
SLE flares											
1	randomised trials	serious	not serious	not serious	very serious	none	2/11 (18.2%)	10/12 (83.3%)	**RR 0.22** (0.06 to 0.78)	**650 fewer per 1,000** (from 783 fewer to 183 fewer)	⨁◯◯◯ very low
Reduced prednisone											
1	randomised trials	serious	not serious	not serious	very serious	none	9/11 (81.8%)	3/12 (25.0%)	**RR 3.27** (1.18 to 9.07)	**568 more per 1,000** (from 45 more to 1,000 more)	⨁◯◯◯ very low
Painful joint score											
1	randomised trials	serious	not serious	not serious	very serious	none	26	17	-	MD **6.2 lower** (13.69 lower to 1.29 higher)	⨁◯◯◯ very low
Swollen joint score											
1	randomised trials	serious	not serious	not serious	very serious	none	26	17	-	MD **1.1 lower** (5.29 lower to 3.09 higher)	⨁◯◯◯ very low
Swollen joint count (change from baseline)											
1	randomised trials	serious	not serious	not serious	very serious	none	26	17	-	MD **1.7 higher** (1.63 lower to 5.03 higher)	⨁◯◯◯ very low
Painful joint count (change from baseline)											
1	randomised trials	serious	not serious	not serious	very serious	none	26	17	-	MD **4.6 lower** (10.7 lower to 1.5 higher)	⨁◯◯◯ very low
Adverse events leading to discontinuation											
1	randomised trials	serious	not serious	not serious	very serious	none	2/40 (5.0%)	0/31 (0.0%)	**RR: 3.90** [0.19 , 78.46]	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ very low

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

References:

RCT: 2

- Williams HJ, Egger MJ, Singer JZ, et al. Comparison of hydroxychloroquine and placebo in the treatment of the arthropathy of mild systemic lupus erythematosus. J Rheumatol. 1994;21(8):1457-1462.

- Meinão IM, Sato EI, Andrade LE, Ferraz MB, Atra E. Controlled trial with chloroquine diphosphate in systemic lupus erythematosus. *Lupus*. 1996;5(3):237-241. doi:10.1177/096120339600500313

PICO 60e. In patients with SLE and lupus arthritis, does treatment with listed medical therapies compared to no treatment impact clinical outcomes?

Population: SLE patients with active lupus arthritis

Intervention:

- Immunosuppressants
  - MTX

Comparator:

- HCQ alone (for all other options)
- HCQ +steroid (for all other options)

Outcomes

- Arthritis activity (improvement in joint pains, joint stiffness, joint swelling, and function)
- Joint damage – erosions, joint space narrowing, tendon loosening or deformity
- Functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)
- Disease activity
- SLE flares
- Disease damage
- Quality of life
- Treatment-related adverse events: immunosuppressives and biologics: infection and cytopenias (belimumab: depression/suicide; CNI: eGFR effects); steroids: fracture, hypertension, T2DM, infection; NSAIDs: GI side effects; Antimalarials: retinal and cardiac effects (prolonged QTc and myopathy)

Evidence summary: 3 RCTs addressed MTX use in patients with arthritis. In Fortin et al, it was MTX versus placebo but the baseline table shows that patients in both arms received steroids and/or HCQ. In Islam et al, it was MTX versus chloroquine, and both arms were taking background steroids. In Carneiro et al, they compared MTX to a placebo, and all patients were taking background steroids. For SLAM-R, the Mean difference (CI) was 0.86 lower (1.68 lower to 0.04 lower). Compared to no MTX, SLE flare absolute values were 51 fewer per 1000 (from 151 fewer to 184 more). For Arthralgia or Arthritis (resolution of symptoms), it was 882 more per 1,000 (from 81 more to 1,000 more) in MTX arm, and the prednisone dose was at least 50% lower than the initial dose 602 more per 1,000 (from 46 more to

1,000 more) in MTX arm. Infection and adverse events were higher in MTX group but with very wide confidence interval. The overall certainty of the evidence was very low due to a high risk of bias (although they are all were randomized, there were differences in patients' baseline characteristics and one trial was not blinded) and imprecision (small number of events and sample size, leading to wide confidence interval).

Evidence profile:

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	HCQ+corticosteroids	Relative (95% CI)	Absolute (95% CI)	
SLAM-R											
1	randomised trials	serious	not serious	not serious	serious	none	41	45	-	MD **0.86 lower** (1.68 lower to 0.04 lower)	⨁⨁◯◯ low
SLE flares											
1	randomised trials	serious	not serious	not serious	very serious	none	7/41 (17.1%)	10/45 (22.2%)	**RR 0.77** (0.32 to 1.83)	**51 fewer per 1,000** (from 151 fewer to 184 more)	⨁◯◯◯ very low
SLEDAI											
2	randomised trials	serious	not serious	not serious	serious	none	54	69	-	MD **0.7 higher** (0.41 lower to 1.8 higher)	⨁⨁◯◯ low
Infections											
1	randomised trials	serious	not serious	not serious	very serious	none	2/41 (4.9%)	1/45 (2.2%)	**RR 2.20** (0.21 to 23.32)	**27 more per 1,000** (from 18 fewer to 496 more)	⨁◯◯◯ very low
Adverse events											
2	randomised trials	serious	not serious	not serious	very serious	none	41/54 (75.9%)	37/69 (53.6%)	**RR 1.96** (0.46 to 8.27)	**515 more per 1,000** (from 290 fewer to 1,000 more)	⨁◯◯◯ very low
SF-36 MCS											
1	randomised trials	serious	not serious	not serious	serious	none	41	45	-	MD **2.78 higher** (0.16 higher to 5.4 higher)	⨁⨁◯◯ low
SF-32 PCS											
1	randomised trials	serious	not serious	not serious	serious	none	41	45	-	MD **1.77 higher** (0.28 lower to 3.82 higher)	⨁⨁◯◯ low
Arthralgia or Arthritis (resolution of symptoms)											
1	randomised trials	serious	not serious	not serious	serious	none	16/17 (94.1%)	1/17 (5.9%)	**RR 16.00** (2.38 to 107.53)	**882 more per 1,000** (from 81 more to 1,000 more)	⨁⨁◯◯ low
Prednisone dose at least 50% lower than the initial dose											
1	randomised trials	serious	not serious	not serious	serious	none	13/20 (65.0%)	1/21 (4.8%)	**RR 13.65** (1.96 to 94.95)	**602 more per 1,000** (from 46 more to 1,000 more)	⨁⨁◯◯ low

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

References: 3 Randomized clinical trials

1. Fortin PR, Abrahamowicz M, Ferland D, et al. Steroid-sparing effects of methotrexate in systemic lupus erythematosus: a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum*. 2008;59(12):1796-1804. doi:10.1002/art.24068
2. Islam MN, Hossain M, Haq SA, Alam MN, Ten Klooster PM, Rasker JJ. Efficacy and safety of methotrexate in articular and cutaneous manifestations of systemic lupus erythematosus. Int J Rheum Dis. 2012 Feb;15(1):62-8. doi: 10.1111/j.1756-185X.2011.01665.x. Epub 2011 Sep 21. PMID: 22324948.
3. Carneiro JR, Sato EI. Double blind, randomized, placebo controlled clinical trial of methotrexate in systemic lupus erythematosus. J Rheumatol. 1999;26(6):1275-1279.

PICO 60.3. In patients with SLE and lupus arthritis, does treatment with listed medical therapies compared to no treatment impact clinical outcomes?

Population: SLE patients with active lupus arthritis
Intervention:
- Immunosuppressants
  - MMF

Comparator:
- HCQ +steroid (SOC)

Outcomes
- Arthritis activity (improvement in joint pains, joint stiffness, joint swelling, and function)
- Joint damage – erosions, joint space narrowing, tendon loosening or deformity
- Functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)
- Disease activity
- SLE flares
- Disease damage
- Quality of life
- Treatment-related adverse events: immunosuppressives and biologics: infection and cytopenias (belimumab: depression/suicide; CNI: eGFR effects); steroids: fracture, hypertension, T2DM, infection; NSAIDs: GI side effects; Antimalarials: retinal and cardiac effects (prolonged QTc and myopathy)

Table 1.

Author	Design	Population	Intervention	comparator	Outcomes
You 2024	RCT	Patients with new onset SLE (treatment naïve). China	MMF	Steroids or/and HCQ	New or worsening arthritis. Adverse events

Evidence summary:
1 RCT compared MMF to SOC (hydroxychloroquine or/and corticosteroids) (you 2024). Not all patients had arthritis, but for arthritis worsening or new onset, it was 46 fewer per 1,000 (from 157 fewer to 145 more) in patients taking MMF. Adverse events and infections were in MMF compared to SOC were **106 more per 1,000,** (from 50 fewer to 350 more) **and 31 more per 1,000** (from 102 fewer to 249 more), respectively. This was based on very low certainty in the evidence due to risk of bias and imprecision.

Evidence profile:

Certainty assessment							№ of patients		Effect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MMF	SOC	Relative (95% CI)	Absolute (95% CI)	Certainty
new or worsening arthritis											

1	randomised trials	serious	not serious	not serious	very serious	none	17/65 (26.2%)	20/65 (30.8%)	**RR 0.85** (0.49 to 1.47)	**46 fewer per 1,000** (from 157 fewer to 145 more)	⊕◯◯◯ Very low

Adverse events

1	randomised trials	serious	not serious	not serious	very serious	none	30/65 (46.2%)	23/65 (35.4%)	**RR 1.30** (0.86 to 1.99)	**106 more per 1,000** (from 50 fewer to 350 more)	⊕◯◯◯ Very low

Infections

1	randomised trials	serious	not serious	not serious	very serious	none	22/65 (33.8%)	20/65 (30.8%)	**RR 1.10** (0.67 to 1.81)	**31 more per 1,000** (from 102 fewer to 249 more)	⊕◯◯◯ Very low

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

References:

RCT: 1

You Y, Zhou Z, Wang F, et al. Mycophenolate Mofetil and New-Onset Systemic Lupus Erythematosus: A Randomized Clinical Trial. JAMA Netw Open. 2024;7(9):e2432131. Published 2024 Sep 3. doi:10.1001/jamanetworkopen.2024.32131

PICO 60.3 In patients with SLE and lupus arthritis, does treatment with listed MMF/MPA compared to AZA impact clinical outcomes?

Population: SLE patients with active lupus arthritis

Intervention:

- MMF

Comparator:

- AZA

Outcomes

- Arthritis activity (improvement in joint pains, joint stiffness, joint swelling, and function)
- Joint damage – erosions, joint space narrowing, tendon loosening or deformity
- Functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)
- Disease activity
- SLE flares
- Disease damage
- Quality of life
- Treatment-related adverse events: immunosuppressives and biologics: infection and cytopenias (belimumab: depression/suicide; CNI: eGFR effects); steroids: fracture, hypertension, T2DM, infection; NSAIDs: GI side effects; Antimalarials: retinal and cardiac effects (prolonged QTc and myopathy)

Evidence summary: 1 RCT compared the outcomes of MMF and AZA in patients with SLE. MMF might be associated with lower rates of new BILAG A or B flare and BILAG A flare (musculoskeletal only) with absolute effect (95%CI) of 69 fewer per 1,000 (from 165 fewer to 79 more) and 7 fewer per 1,000 (from 11 fewer to 78 more), respectively. AEs were comparable between MMF and AZA, but MMF might be associated with lower rates of serious AE and AE leading to discontinuation, with absolute effect (95%CI) of 16 fewer per 1,000 (from 66 fewer to 88 more), 50 fewer per 1,000 (from 73 fewer to 20 more), respectively. The overall certainty of evidence was judged as **low** because of concerns related to risk bias (high rates of drug discontinuation in both arms, which would impact the estimates, in addition for flare we extracted arthritis only while the initial trial was randomized for patients with SLE in general) and imprecision (CIs are crossing the minimal important difference for all outcomes)

Evidence profile:

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MMF	AZA	Relative (95% CI)	Absolute (95% CI)	
New BILAG A or B flare											
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	25/91 (27.5%)	32/93 (34.4%)	**RR 0.80** (0.52 to 1.23)	**69 fewer per 1,000** (from 165 fewer to 79 more)	⨁⨁◯◯ Low[a,b]
New BILAG A flare up											
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	0/91 (0.0%)	1/93 (1.1%)	**RR 0.34** (0.01 to 8.25)	**7 fewer per 1,000** (from 11 fewer to 78 more)	⨁⨁◯◯ Low[a,b]
Adverse events											
1	randomised trials	serious[c]	not serious	not serious	serious[b]	none	71/120 (59.2%)	69/120 (57.5%)	**RR 1.03** (0.83 to 1.27)	**17 more per 1,000** (from 98 fewer to 155 more)	⨁⨁◯◯ Low[a,c]
Serious adverse events											
1	randomised trials	randomised trials	serious[c]	not serious	not serious	serious[b]	none	13/120 (10.8%)	**RR 0.85** (0.39 to 1.81)	**16 fewer per 1,000** (from 66 fewer to 88 more)	⨁⨁◯◯ Low[a,c]
Adverse event leading to discontinuation											
1	randomised trials	randomised trials	serious[c]	not serious	not serious	serious[b]	4/120 (3.3%)	10/120 (8.3%)	**RR 0.40** (0.13 to 1.24)	**50 fewer per 1,000** (from 73 fewer to 20 more)	⨁⨁◯◯ Low[a,c]

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

Explanations

a. We only included patients with arthritis and the trial was randomized for patients with SLE. The rate of trial discontinuation was high compared to the total number of patients.

b. Wide confidence interval crossing minimal important difference.

c. The rate of discontinuation in both arms was high, which would impact the estimates

Reference: 1 RCT

Ordi-Ros J, Sáez-Comet L, Pérez-Conesa M, Vidal X, Mitjavila F, Castro Salomó A, Cuquet Pedragosa J, Ortiz-Santamaria V, Mauri Plana M, Cortés-Hernández J. Enteric-coated mycophenolate sodium versus azathioprine in patients with active systemic lupus erythematosus: a

randomised clinical trial. Ann Rheum Dis. 2017 Sep;76(9):1575-1582. doi: 10.1136/annrheumdis-2016-210882. Epub 2017 Apr 27. PMID: 28450313.

P60.4.t. P.61.2.g In patients with SLE and lupus arthritis, does treatment with listed medical therapies compared to no treatment impact clinical outcomes?

Population: SLE patients with active lupus arthritis

Intervention:

- Belimumab

Comparator:

- Standard of care

Outcomes

- Arthritis activity (improvement in joint pains, joint stiffness, joint swelling, and function)
- Joint damage – erosions, joint space narrowing, tendon loosening or deformity
- Functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)
- Disease activity
- SLE flares
- Disease damage
- Quality of life

Table 1.

Study	Design	Population	Intervention	Comparator	Outcomes	Notes
Manzi 2012	Post hoc analysis for BLISS 52 and BLISS 72	Patients with active SLE	Belimumab 10 mg	Standard of care (immunosuppressive therapy, or/and steroids, or/and HCQ)	BILAG (arthritis) improvement and SLEDIA (arthritis) improvement	
BLISS 52	RCT	Patients with active SLE	Belimumab 10 mg	Standard of care (immunosuppressive therapy, or/and steroids, or/and HCQ)	Adverse events (AE), serious AE, AE leading to discontinuation, infections	
BLISS 72	RCT	Patients with active SLE	Belimumab 10 mg	Standard of care (immunosuppressive therapy, or/and steroids, or/and HCQ)	Adverse events (AE), serious AE, AE leading to discontinuation, infections	
BLISS- NEA (Zhang 2017)	RCT	Patients with active SLE (Asians)	Belimumab 10 mg	Standard of care (immunosuppressive therapy, or/and steroids, or/and HCQ)	Adverse events (AE), serious AE, AE leading to discontinuation, infections, SLE flare up (severe)	

Ginzler 2022 (EMBRACE)	RCT	Patients with active SLE (African American)	Belimumab 10 mg	Standard of care (immunosuppressive therapy, or/and steroids, or/and HCQ)	Adverse events (AE), serious AE, AE leading to discontinuation, infections	
BLISS-SC Stohl 2017	RCT	Patients with active SLE	Belimumab SC (200 mg)	Standard of care (immunosuppressive therapy, or/and steroids, or/and HCQ)	Adverse events (AE), serious AE, AE leading to discontinuation, infections, SLE flare up (severe)	

Evidence summary: 5 RCTs addressed Belimumab use in patients with SLE. We extracted data for Belimumab 10mg and Belimumab 200 mg SC (this analysis doesn't include data for 1 mg).

For the efficacy outcomes data was derived from a posthoc analysis addressing the arthritis (musculoskeletal) domain only. (BLISS 52 and BLISS 76)
For the safety profile, we used data from all the trials regardless of organ involvement.

Efficacy: BILAG score improvement (musculoskeletal) and improvement of SLEDAI-2K (arthritis) were higher in belimumab arm compared to standard of care, with an absolute effect (CI) of 100 more per 1,000 (from 25 more to 190 more) and 74 more per 1000 (from 0 fewer to 158 more), respectively. This is based on low certainty of evidence because of risk of bias (posthoc analysis without randomization) and imprecision (CI crossing the minimally important difference). For severe SLE flare-up, it was fewer in belimumab with absolute (CI) 72 fewer per 1,000 (from 90 fewer to 50 fewer), based on high certainty evidence.
Safety profile: For adverse events, serious adverse events, infections, adverse events leading to discontinuation, were comparable between both arms (CI between the borders of minimally importance difference) with moderate certainty of the evidence.

The overall certainty of evidence is low.

SOC: The rate of concomitant medication use is comparable between belimumab and SOC arm.Daily prednisone use (77.1%), Antimalarial (aminoquinolone) use (65.5%), Mycophenolate (15.2%) Azathioprine (20.7%) Methotrexate (21.9%). (BLISS 76). These rates are comparable across different trials.

Evidence profile:

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Belimumab plus SOC	standard of care	Relative (95% CI)	Absolute (95% CI)	
BILAG improvement (musculoskeletal)											
1	randomised trials	serious	not serious	not serious	serious	none	204/339 (60.2%)	171/342 (50.0%)	**RR 1.20** (1.05 to 1.38)	**100 more per 1,000** (from 25 more to 190 more)	⨁⨁◯◯ Low
Improvement of SLEDAI-2K (arthritis)											

1	randomised trials	serious	not serious	not serious	serious	none	206/364 (56.6%)	183/371 (49.3%)	**RR 1.15** (1.00 to 1.32)	**74 more per 1,000** (from 0 fewer to 158 more)	⨁⨁◯◯ Low

Adverse events

5	randomised trials	not serious	not serious	not serious	not serious	none	1597/1920 (83.2%)	1074/1242 (86.5%)	**RR 0.99** (0.96 to 1.02)	**9 fewer per 1,000** (from 35 fewer to 17 more)	⨁⨁⨁⨁ High

Adverse events leading to discontinuation (Dichotomous)

5	randomised trials	not serious	not serious	not serious	not serious	none	129/1754 (7.4%)	101/1242 (8.1%)	**RR 0.90** (0.70 to 1.16)	**8 fewer per 1,000** (from 24 fewer to 13 more)	⨁⨁⨁⨁ High

Serious adverse events

5	randomised trials	not serious	not serious	not serious	serious	none	256/1920 (13.3%)	208/1242 (16.7%)	**RR 0.83** (0.70 to 0.98)	**28 fewer per 1,000** (from 50 fewer to 3 fewer)	⨁⨁⨁◯ Moderate

Infectious

3	randomised trials	not serious	not serious	not serious	serious	none	426/1119 (38.1%)	394/842 (46.8%)	**RR 1.05** (0.97 to 1.14)	**23 more per 1,000** (from 14 fewer to 66 more)	⨁⨁⨁◯ Moderate

SLE flare (severe)

2	randomised trials	not serious	not serious	not serious	not serious	none	109/1007 (10.8%)	76/506 (15.0%)	**HR 0.50** (0.38 to 0.65)	**72 fewer per 1,000** (from 90 fewer to 50 fewer)	⨁⨁⨁⨁ High

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

References: Randomized clinical trials (5 RCTS, and 1 posthoc analysis)

1. Manzi S, Sánchez-Guerrero J, Merrill JT, et al. Effects of belimumab, a B lymphocyte stimulator-specific inhibitor, on disease activity across multiple organ domains in patients with systemic lupus erythematosus: combined results from two phase III trials. *Ann Rheum Dis*. 2012;71(11):1833-1838. doi:10.1136/annrheumdis-2011-200831
2. Furie R, Petri M, Zamani O, et al. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. *Arthritis Rheum*. 2011;63(12):3918-3930. doi:10.1002/art.30613
3. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial
4. Zhang, Fengchun et al. “A pivotal phase III, randomised, placebo-controlled study of belimumab in patients with systemic lupus erythematosus located in China, Japan and South Korea.” *Annals of the rheumatic diseases* vol. 77,3 (2018): 355-363. doi:10.1136/annrheumdis-2017-211631
5. Stohl, William et al. “Efficacy and Safety of Subcutaneous Belimumab in Systemic Lupus Erythematosus: A Fifty-Two-Week Randomized, Double-Blind, Placebo-Controlled Study.” *Arthritis & rheumatology (Hoboken, N.J.)* vol. 69,5 (2017): 1016-1027. doi:10.1002/art.40049
6. Ginzler E, Guedes Barbosa LS, D'Cruz D, et al. Phase III/IV, Randomized, Fifty-Two-Week Study of the Efficacy and Safety of Belimumab in Patients of Black African Ancestry With

Systemic Lupus Erythematosus. *Arthritis Rheumatol*. 2022;74(1):112-123. doi:10.1002/art.41900

P60cc. In patients with SLE and lupus arthritis, does treatment with listed medical therapies compared to no treatment impact clinical outcomes?

Population: SLE patients with active lupus arthritis

Intervention:

- Jak-I (Baricitinib 4mg) or JAK-I (Upadacitinib), or JAK-I Tofacitinib (separarte evidence profiles and summary

Comparator:

- Standard of care

Outcomes

- Arthritis activity (improvement in joint pains, joint stiffness, joint swelling, and function)
- Joint damage – erosions, joint space narrowing, tendon loosening or deformity
- Functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)
- Disease activity
- SLE flares
- Disease damage
- Quality of life

Table 1:

Study	Design	Population	Intervention	Comparator	Outcomes	Notes
SLE-BRAVE-I	RCT	Patients with active SLE	Baricitinib 4mg	Standard of care (immunosuppressive therapy, or/and steroids, or/and HCQ)	BILAG improvement and SLEDIA improvement (arthritis or rash), 28 swollen joint score, 28 tender joint score, worst joint pain, Adverse events (AE), serious AE, AE leading to discontinuation, infections	

SLE-BRAVE-II	RCT	Patients with active SLE	Baricitinib 4mg	Standard of care (immunosuppressive therapy, or/and steroids, or/and HCQ)	SLEDIA improvement (arthritis or rash), 28 swollen joint score, 28 tender joint score, worst joint pain, Adverse events (AE), serious AE, AE leading to discontinuation, infections	

Evidence summary: 2 RCTs compared Baricitinib 4mg to standard of care. The overall certainty of evidence was judged as low due to concerns about risk of bias (due to loss to follow-up) and imprecision. The absolute effect (CI) of improvement in BILAG musculoskeletal domain was 106 more per 1,000 (from 24 more to 206 more) in patients taking Baricitinib versus standard of care. For SLEDAI-2k (remission of arthritis or rash) it was 54 more per 100 (from 5 fewer to 123 more) in Baricitininb and for SLE flare-up (severe) it was 18 fewer per 1,000 (from 49 fewer to 26 more) Baricitinib. The 28 swollen joint counts, 28 tender joint counts, and the worst joint score the outcomes were comparable between both arms. Adverse events, infections, and adverse events leading to discontinuation were comparable between both arms, while for serious adverse events, it was 29 more per 1,000 (from 6 fewer to 80 more) in Baricitinib. We downgraded for risk of bias (randomization was not stratified per clinical manifestation and because of loss to follow up).

SOC: it was comparable in Baricitinib and placebo arm. Glucocorticoids (77%), Antimalarials (84%), Immunosuppressants (59%), Methotrexate 24%), Azathioprine (15%), Mycophenolate mofetil (15%), non-steroidal anti-inflammatory drug (25%)

Evidence profile:

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Baricitinib 4mg plus SOC	standard of care	Relative (95% CI)	Absolute (95% CI)	
BILAG (musculoskeletal domain)											
1	randomised trials	serious	not serious	not serious	serious	none	167/239 (69.9%)	141/239 (59.0%)	**RR 1.18** (1.04 to 1.35)	**106 more per 1,000** (from 24 more to 206 more)	⨁⨁◯◯ Low
SLEDAI-2K remission of arthritis or rash											
2	randomised trials	serious	not serious	not serious	serious	none	280/510 (54.9%)	251/509 (49.3%)	**RR 1.11** (0.99 to 1.25)	**54 more per 1,000** (from 5 fewer to 123 more)	⨁⨁◯◯ Low
SLE flare ups (severe)											
2	randomised trials	serious	not serious	not serious	not serious	none	55/510 (10.8%)	64/509 (12.6%)	**RR 0.86** (0.61 to 1.21)	**18 fewer per 1,000** (from 49 fewer to 26 more)	⨁⨁⨁◯ Moderate
28 swollen joint count											

2	randomised trials	serious	not serious	not serious	not serious	none	510	509	-	MD **0.46 lower** (0.48 lower to 0.43 lower)	⨁⨁⨁◯ Moderate
28 tender joint count											
2	randomised trials	serious	not serious	not serious	serious	none	510	509	-	MD **0.65 lower** (0.69 lower to 0.62 lower)	⨁⨁⨁◯ low
Worst joint pain											
2	randomised trials	serious	not serious	not serious	not serious	none	510	509	-	MD **0.06 lower** (0.08 lower to 0.04 lower)	⨁⨁⨁◯ low
Adverse events											
2	randomised trials	serious	not serious	not serious	not serious	none	408/510 (80.0%)	409/516 (79.3%)	**RR 1.01** (0.95 to 1.07)	**8 more per 1,000** (from 40 fewer to 55 more)	⨁⨁⨁◯ Moderate
Serious adverse events											
2	randomised trials	serious	not serious	not serious	serious	none	55/510 (10.8%)	40/509 (7.9%)	**RR 1.37** (0.93 to 2.02)	**29 more per 1,000** (from 6 fewer to 80 more)	⨁⨁⨁◯ low
Adverse events leading to discontinuation											
2	randomised trials	serious	not serious	not serious	not serious	none	46/510 (9.0%)	44/509 (8.6%)	**RR 1.05** (0.70 to 1.55)	**4 more per 1,000** (from 26 fewer to 48 more)	⨁⨁⨁◯ Moderate
Infection											
2	randomised trials	serious	not serious	not serious	not serious	none	264/510 (51.8%)	260/509 (51.1%)	**RR 1.02** (0.90 to 1.15)	**10 more per 1,000** (from 51 fewer to 77 more)	⨁⨁⨁◯ low

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

Evidence for JAK-I (Upadacitinib)

Table 1:

Study	Design	Population	Intervention	Comparator	Outcomes
Merril 2024	RCT	Patients with SLE	Upadacitinib 30 mg	Standard of care (immunosuppressive therapy, or/and steroids, or/and HCQ)	- Joint count-50 -Adverse Events

Evidence Summary:

This study was a phase 2, randomized, double-blind, placebo-controlled, global, multicenter study evaluating the efficacy and safety of Upadacitinib versus those that were given placebo. The patients included were previously taking standard of care (Mycophenolate,Azathioprine,Methotrexate, Calcineurin inhibitor or Leflunomide). These patients had SLE with 59 patients having arthritis in the Upadacitinib arm and 59 having arthritis in the placebo arm. Joint count-50 at response rate at 48 weeks was 137 more per 1000 (from 40 fewer to 388 more) .Regarding adverse events, treatment related adverse events (TEAE) was 39 more per 1,000 (from 87 fewer to 181 more) in patients taking Upadacitinib,TEAE considered possibly related to study drug had 10 fewer per 1,000 (from 133 fewer to 190 more) in patients

taking Upadacitinib, and 30 more per 1,000 (from 35 fewer to 235 more) leading to discontinuation. Some adverse events documented were serious infection 11.3% in those taking Upadacitinib versus 4% on placebo, opportunistic infection excluding TB and HZb 1.6% versus 1.3%, Herpes Zoster 6.5% versus 4% , active TB 0 % versus 1.3% anemia 3.2% versus 4%,neutropenia 1.5% versus 1.3%,lymphopenia 3.2% versus 0%, renal dysfunction 1.6% versus 0%, hepatic disorder 1.6% versus 1.3%, an adjudicated MACE 11.6% versus 1.3%.

Evidence Report:

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Upadacitinib	Standard of care	Relative (95% CI)	Absolute (95% CI)	
Joint count-50 at Week 48											
1	non-randomised studies	serious[a]	not serious	not serious	very serious[b,c]	none	34/59 (57.6%)	26/59 (44.1%)	**RR 1.31 (0.91 to 1.88)**	**137 more per 1000 (from 40 fewer to 388 more)**	⨁◯◯◯ Very low[a,b,c]
Treatment emergent adverse events											
1	randomised trials	not serious	not serious	not serious	very serious[b,c]	none	51/62 (82.3%)	59/75 (78.7%)	**RR 1.05** (0.89 to 1.23)	**39 more per 1,000** (from 87 fewer to 181 more)	⨁⨁◯◯ Low[b,c]
Serious treatment emergent adverse events											
1	randomised trials	not serious	not serious	not serious	very serious[b,c]	none	13/62 (21.0%)	13/75 (17.3%)	**RR 1.21** (0.61 to 2.41)	**36 more per 1,000** (from 68 fewer to 244 more)	⨁⨁◯◯ Low[b,c]
TEAE leading to discontinuation											
1	randomised trials	not serious	not serious	not serious	very serious[b,c]	none	6/62 (9.7%)	5/75 (6.7%)	**RR 1.45** (0.47 to 4.53)	**30 more per 1,000** (from 35 fewer to 235 more)	⨁⨁◯◯ Low[b,c]
Death											
1	randomised trials	not serious	not serious	not serious	very serious[c,d]	none	0/62 (0.0%)	0/75 (0.0%)	**Risk difference 0.0** (-0.3 to 0.3)	**-- per 1,000** (from -- to --)	⨁⨁◯◯ Low[c,d]
TEAE considered possibly related to study drug											

1	randomised trials	not serious	not serious	not serious	very serious[b,c]	none	20/62 (32.3%)	25/75 (33.3%)	**RR 0.97** (0.60 to 1.57)	**10 fewer per 1,000** (from 133 fewer to 190 more)	⊕⊕◯◯ Low[b,c]

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

Explanations

a. Subset of patients from the RCT that had mucocutaneous symptoms, not randomized.
b. Wide CI in absolute risk difference
c. Small sample size
d. Wide CI in risk difference

Evidence for JAK-I (Tofacitinib):

Table 1:

Study	Design	Population	Intervention	Outcomes
Zhao 2044	Retrospective chart review	-Patients with SLE. -We included data for musculoskeletal lesions only	Tofacitinib	**-Improvement of musculoskeletal lesions**: 9/9 (100%) **-Infection (herpes zoster):** 1/40
Yan 2024	Single arm study	Patients with SLE (all have arthritis) N=22	Tofacitinib (5 mg twice a day)	**-Improvement (alleviated):** 22/22 **-Complete response:** 13/22 **-Relapse:** 2/22 **-Severe or significant AE:** 0/22 **-Infection:** 1/22

References: 3 Randomized clinical trials

1-Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 3 trial (SLE-BRAVE-I)Morand, Eric F et al.The Lancet, Volume 401, Issue 10381, 1001 – 1010

2- Petri M, Bruce IN, Dörner T, et al. Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 3 trial (SLE-BRAVE-II). *Lancet*. 2023;401(10381):1011-1019. doi:10.1016/S0140-6736(22)02546-6

3- Merrill JT, Tanaka Y, D'Cruz D, Vila-Rivera K, Siri D, Zeng X, Saxena A, Aringer M, D'Silva KM, Cheng L, Mohamed MF, Siovitz L, Bhatnagar S, Gaudreau MC, Doan TT, Friedman A. Efficacy and Safety of Upadacitinib or Elsubrutinib Alone or in Combination for Patients With Systemic Lupus Erythematosus: A Phase 2 Randomized Controlled Trial. Arthritis Rheumatol. 2024 Oct;76(10):1518-1529. doi: 10.1002/art.42926. Epub 2024 Aug 7. PMID: 38923871.

Non-comparative studies:

1- Zhao M, Ma L, Duan X, et al. Tofacitinib versus thalidomide for mucocutaneous lesions of systemic lupus erythematosus: A real-world CSTAR cohort study XXVII. Lupus. 2024;33(10):1109-1115. doi:10.1177/09612033241272953

2- Yan Q, Liu J, Long X, et al. Tofacitinib therapy in systemic lupus erythematosus with arthritis: a retrospective study. Clin Rheumatol. 2024;43(10):3139-3145. doi:10.1007/s10067-024-07103-2

P60qr. In patients with SLE and lupus arthritis, does treatment with listed medical therapies compared to no treatment impact clinical outcomes?

Population: SLE patients with active lupus arthritis

Intervention:

- Rituximab

Comparator:

- Standard of care

Outcomes

- Arthritis activity (improvement in joint pains, joint stiffness, joint swelling, and function)
- Joint damage – erosions, joint space narrowing, tendon loosening or deformity
- Functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)
- Disease activity
- SLE flares
- Disease damage
- Quality of life

Table 1.

Study	Design	Population	Intervention	Comparison	Outcomes
Merrill 2010 EXPLORER	RCT	Patients with moderate to severe SLE (multiple presentations)	Rituximab	Standard of care	Major clinical response, partial response, serious adverse events, SLE flare up
Roberts 2024	Single arm data (pediatrics)	Pediatric patients with SLE	Rituximab	NA	Infection

Evidence summary: 1 RCT compared Rituximab versus SOC in patients with extra-renal SLE (moderate to severe, not all had arthritis).
For major clinical, the absolute (CI) was 35 fewer per 1,000 (from 92 fewer to 73 more) in patients receiving Rituximab, while for partial clinical response, it was 46 more per 1,000 (from 35 fewer to 203 more) in patients receiving Rituximab. Serious adverse events and rates of SLE flare-up (moderate and severe) were comparable between both arms. For

infection rates in pediatrics (Roberts 2024), out of 1567 children with cSLE who received rituximab. 219 children were admitted with an infection within 1 year after first rituximab administration, for an incidence rate of 140 cases per 1000 patient-years. The overall certainty of the evidence was judged as low due to concerns about risk of bias (patients dropped and missed follow-up would affect our estimates) and imprecision because of the small sample size and wide confidence interval.

SOC: AZA (36.4%), MTX (27.3%), MMF(36.4%)

Evidence profile:

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab plus SOC	SOC	Relative (95% CI)	Absolute (95% CI)	
Major clinical response (defined as achieving BILAG C scores or better in all organs at week 24 without experiencing a severe flare)											
1	randomised trials	serious	not serious	not serious	serious	none	21/169 (12.4%)	14/88 (15.9%)	**RR 0.78** (0.42 to 1.46)	**35 fewer per 1,000** (from 92 fewer to 73 more)	⨁⨁◯◯ Low
Partial clinical response											
1	randomised trials	serious	not serious	not serious	serious	none	29/169 (17.2%)	11/88 (12.5%)	**RR 1.37** (0.72 to 2.62)	**46 more per 1,000** (from 35 fewer to 203 more)	⨁⨁◯◯ Low
Serious adverse events											
1	randomised trials	serious	not serious	not serious	serious	none	64/169 (37.9%)	32/88 (36.4%)	**RR 1.04** (0.74 to 1.46)	**15 more per 1,000** (from 95 fewer to 167 more)	⨁⨁◯◯ Low
SLE flare up (assessed with: Moderate or severe)											
1	randomised trials	serious	not serious	not serious	serious	none	81/127 (63.8%)	37/58 (63.8%)	**HR 0.97** (0.65 to 1.46)	**11 fewer per 1,000** (from 155 fewer to 135 more)	⨁⨁◯◯ Low

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

References:

Randomized clinical trials: 1

1-Merrill JT, Neuwelt CM, Wallace DJ, et al. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. Arthritis Rheum. 2010;62(1):222-233. doi:10.1002/art.27233

P60. P61. In patients with SLE and lupus arthritis, does treatment with listed medical therapies compared to no treatment impact clinical outcomes?

Population: SLE patients with active lupus arthritis

Intervention:

- Anifrolumab 300 mg

Comparator:

- Standard of care

Outcomes

- Arthritis activity (improvement in joint pains, joint stiffness, joint swelling, and function)
- Joint damage – erosions, joint space narrowing, tendon loosening or deformity
- Functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)
- Disease activity
- SLE flares
- Disease damage
- Quality of life

Table 1.

Study	Design	Population	Intervention	Comparator	Outcomes	Notes
Furie 2017 MUSE trial	RCT	Patients with active SLE	Anifrolumab 300 mg	Standard of care (immunosuppressive therapy, or/and steroids, or/and HCQ)	>50% improvement in joint counts. SLE flare Adverse events (AE), serious AE, AE leading to discontinuation.	
Furie 2019 TULIP 1	RCT	Patients with active SLE	Anifrolumab 300 mg	Standard of care (immunosuppressive therapy, or/and steroids, or/and HCQ)	≥50% Reduction in both swollen and tender joints, Swollen and tender joints count, Adverse events (AE), serious AE, AE leading to discontinuation, infections.	
Morand 2022 TULIP 2	RCT	Patients with active SLE	Anifrolumab 300 mg	Standard of care (immunosuppressive therapy, or/and steroids, or/and HCQ)	≥50% Reduction in both swollen and tender joints, Swollen and tender joints count, Adverse	

					events (AE), serious AE, AE leading to discontinuation, infections, SLE flare up.	
Morand 2022	Posthoc analysis (TULIP 1 and 2)	Patients with active SLE	Anifrolumab 300 mg	Standard of care (immunosuppressive therapy, or/and steroids, or/and HCQ)	BILAG (arthritis), Change in baseline SLEDAI-2K (arthritis), 50% or more reduction in tender joints, 50% or more reduction in swollen joint count	
Merill 2018	Posthoc analysis (MUSE)	Patients with active SLE	Anifrolumab 300 mg	Standard of care (immunosuppressive therapy, or/and steroids, or/and HCQ)	BILAG (arthritis), Resolution of arthritis (SLEDAI-2K), Swollen and tender joints count	

Evidence summary: 3 randomized clinical trials (MUSE, TULIP 1, TULIP 2) addressed Anifrolumab versus standard of care (SOC). For > 50% improvement in joint counts, the absolute estimate (95%CI) was 209 more per 1,000 (from 10 fewer to 535 more) in Anifrolumab compared to SOC. For the resolution of arthritis (SLEDAI-2K), SLEDAI-2K (arthritis) improvement, and BILAG improvement (arthritis), it was 144 more per 1,000 (from 0 fewer to 331 more), 92 more per 1,000 (from 16 more to 176 more), and 135 more per 1,000 (from 68 more to 217 more) in Anifrolumab compared to SOC, respectively. Adverse events (AE) were comparable between both arms but serious AE and AE led to discontinuation were 48 fewer per 1,000 (from 86 fewer to 5 more) 16 fewer per 1,000 (from 43 fewer to 75 more) in the Anifrolumab compared to SOC. The overall certainty of evidence was judged as low due to concerns about risk of bias (patients who discontinued the trials were high compared to the number of events, and because some of our outcome's data was derived from posthoc analysis (Morand 2022 and Merill 2018).

SOC: it was comparable in Anifrolumab plus SOC and placebo arm. Glucocorticoids (83%), Antimalarials (73%), Immunosuppressants (59%), Methotrexate (21%), Azathioprine (18%),

Mycophenolate mofetil (12%), non-steroidal anti-inflammatory drug (19%), this is from MUSE trial but it was also comparable between trials

Evidence summary:

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anifrolumab plus SOC	Standard of care	Relative (95% CI)	Absolute (95% CI)	
> 50% improvement in joint counts											
1	randomised trials	serious	not serious	not serious	serious	none	32/46 (69.6%)	18/37 (48.6%)	**RR 1.43** (0.98 to 2.10)	**209 more per 1,000** (from 10 fewer to 535 more)	⊕⊕◯◯ Low
Adverse events											
3	randomised trials	not serious	not serious	not serious	serious	none	404/459 (88.0%)	375/467 (80.3%)	**RR 1.09** (1.03 to 1.16)	**72 more per 1,000** (from 24 more to 128 more)	⊕⊕⊕◯ Moderate
Resolution of arthritis (SLEDAI-2K)											
1	randomised trials	serious	not serious	not serious	serious	none	55/97 (56.7%)	42/99 (42.4%)	**RR 1.34** (1.00 to 1.78)	**144 more per 1,000** (from 0 fewer to 331 more)	⊕⊕◯◯ Low
Adverse events leading to discontinuation											
3	randomised trials	serious	not serious	not serious	serious	none	19/459 (4.1%)	26/468 (5.6%)	**RR 0.71** (0.22 to 2.35)	**16 fewer per 1,000** (from 43 fewer to 75 more)	⊕⊕◯◯ Low
50% or more reduction in swollen joint count											
1	randomised trials	serious	not serious	not serious	serious	none	99/174 (56.9%)	92/200 (46.0%)	**RR 1.24** (1.01 to 1.51)	**110 more per 1,000** (from 5 more to 235 more)	⊕⊕◯◯ Low
BILAG improvement (arthritis)											
2	randomised trials	serious	not serious	not serious	serious	none	266/454 (58.6%)	208/461 (45.1%)	**RR 1.30** (1.15 to 1.48)	**135 more per 1,000** (from 68 more to 217 more)	⊕⊕◯◯ Low
SLEDAI-2K (arthritis) improvement											
1	randomised trials	serious	not serious	not serious	serious	none	176/360 (48.9%)	146/366 (39.9%)	**RR 1.23** (1.04 to 1.44)	**92 more per 1,000** (from 16 more to 176 more)	⊕⊕◯◯ Low
Serious adverse events											

3	randomised trials	serious	not serious	not serious	serious	none	56/459 (12.2%)	80/467 (17.1%)	**RR 0.72** (0.50 to 1.03)	**48 fewer per 1,000** (from 86 fewer to 5 more)	⊕⊕◯◯ Low

SLE flares

2	randomised trials	serious	not serious	not serious	serious	none	89/279 (31.9%)	133/284 (46.8%)	**RR 0.68** (0.56 to 0.82)	**150 fewer per 1,000** (from 206 fewer to 84 fewer)	⊕⊕◯◯ Low

50% or more reduction in tender joints

1	randomised trials	serious	not serious	not serious	serious	none	121/241 (50.2%)	107/251 (42.6%)	**OR 1.36** (0.95 to 1.94)	**76 more per 1,000** (from 12 fewer to 164 more)	⊕⊕◯◯ Low

>50% reduction in both swollen and tender joints

2	randomised trials	serious	not serious	not serious	serious	none	63/141 (44.7%)	56/158 (35.4%)	**OR 1.47** (0.92 to 2.35)	**92 more per 1,000** (from 19 fewer to 209 more)	⊕⊕◯◯ Low

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

References:

Included studies: 3 RCTs, 2 post hoc analysis of the RCTs

1-Merrill JT, Furie R, Werth VP, et al. Anifrolumab effects on rash and arthritis: impact of the type I interferon gene signature in the phase IIb MUSE study in patients with systemic lupus erythematosus. *Lupus Sci Med*. 2018;5(1):e000284. Published 2018 Nov 26. doi:10.1136/lupus-2018-000284

2- Morand EF, Furie R, Tanaka Y, et al. Trial of Anifrolumab in Active Systemic Lupus Erythematosus. *N Engl J Med*. 2020;382(3):211-221. doi:10.1056/NEJMoa1912196

3- Type I interferon inhibitor anifrolumab in active systemic lupus erythematosus (TULIP-1): a randomised, controlled, phase 3 trialFurie, Richard A et al.The Lancet Rheumatology, Volume 1, Issue 4, e208 - e219

4- Efficacy of anifrolumab across organ domains in patients with moderate-to-severe systemic lupus erythematosus: a post-hoc analysis of pooled data from the TULIP-1 and TULIP-2 trials Morand, Eric F et al. The Lancet Rheumatology, Volume 4, Issue 4, e282 - e292

5- Furie R, Khamashta M, Merrill JT, et al. Anifrolumab, an Anti-Interferon-α Receptor Monoclonal Antibody, in Moderate-to-Severe Systemic Lupus Erythematosus. *Arthritis Rheumatol*. 2017;69(2):376-386. doi:10.1002/art.39962

PICO 60z. In patients with SLE and lupus arthritis, does treatment with listed medical therapies compared to no treatment impact clinical outcomes?

Population: SLE patients with active lupus arthritis

Intervention:

- Abatacept

Comparator:

- HCQ +steroid (for all other options)

Outcomes

- Arthritis activity (improvement in joint pains, joint stiffness, joint swelling, and function)
- Joint damage - erosions, joint space narrowing, tendon loosening or deformity
- Functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)
- Disease activity
- SLE flares
- Disease damage
- Quality of life
- Treatment-related adverse events: immunosuppressives and biologics: infection and cytopenias (belimumab: depression/suicide; CNI: eGFR effects); steroids: fracture, hypertension, T2DM, infection; NSAIDs: Gl side effects; Antimalarials: retinal and cardiac effects (prolonged QT and myopathy)

Evidence summary: 1 RCT is comparing Abatacept to placebo (which included HCQ, corticosteroids, and immunosuppressive therapy), they included patients with non-life threatening SLE and excluded patients with lupus nephritis or CNS involvement. The rate of new flares was 67 fewer in the abatacept, but the confidence interval crossed the minimal important difference ranging from 202 fewer to 101 more. The rates of serious adverse events, adverse events leading to discontinuation, and infections were higher in the abatacept group. For the PCS and MCS scores on SF12, the change from baseline was 3.92 higher (CI: 1.24 higher to 6.6 higher) and 2.24 higher (CI: 1.17 lower to 5.65 higher). For the new flares, the data is for patients with polyarthritis only while for the other outcomes it included all patients.
The overall certainty of evidence is very low due to imprecision and risk of bias (loss to follow-up).

SOC: it was comparable in Abatacept plus SOC and placebo arm (SOC). Glucocorticoids (99%), Antimalarials (68.6%), Methotrexate (21%), Azathioprine (13.7%), Mycophenolate mofetil (5%), non-steroidal anti-inflammatory drug (54.9%).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Abatacept	Placebo (HCQ/GC/immunosuppressive therapy)	Relative (95% CI)	Absolute (95% CI)		
New flares (polyarthritis)												
1	randomised trials	serious	not serious	not serious	very serious	none	49/63 (77.8%)	27/32 (84.4%)	**RR 0.92** (0.76 to 1.12)	**67 fewer per 1,000** (from 202 fewer to 101 more)	⨁◯◯◯ very Low	
Infections												

1	randomised trials	serious	not serious	not serious	very serious	none	3/121 (2.5%)	1/59 (1.7%)	**RR 1.46** (0.16 to 13.76)	**8 more per 1,000** (from 14 fewer to 216 more)	⨁◯◯◯ very Low	

Adverse events

1	randomised trials	serious	not serious	not serious	serious	none	110/121 (90.9%)	54/59 (91.5%)	**RR 0.99** (0.90 to 1.09)	**9 fewer per 1,000** (from 92 fewer to 82 more)	⨁⨁◯◯ Low	

Adverse events leading to discontinuation

1	randomised trials	serious	not serious	not serious	very serious	none	10/121 (8.3%)	3/59 (5.1%)	**RR 1.63** (0.46 to 5.68)	**32 more per 1,000** (from 27 fewer to 238 more)	⨁◯◯◯ very Low	

Serious adverse events

1	randomised trials	serious	not serious	not serious	serious	none	24/121 (19.8%)	4/59 (6.8%)	**RR 2.93** (1.06 to 8.05)	**131 more per 1,000** (from 4 more to 478 more)	⨁⨁◯◯ Low	

Physical component summary (PCS) (SF12)

1	randomised trials	serious	not serious	not serious	serious	none	0	0	-	MD **3.92 higher** (1.24 higher to 6.6 higher)	⨁⨁◯◯ Low	

Mental component summary (PCS) (SF12)

1	randomised trials	serious	not serious	not serious	very serious	none	0	0	-	MD **2.24 higher** (1.17 lower to 5.65 higher)	⨁◯◯◯ very Low	

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

References:

Merrill JT, Burgos-Vargas R, Westhovens R, et al. The efficacy and safety of abatacept in patients with non-life-threatening manifestations of systemic lupus erythematosus: results of a twelve-month, multicenter, exploratory, phase IIb, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum*. 2010;62(10):3077-3087. doi:10.1002/art.27601

SLE

- **PICO question (please copy and paste the stem of PICO question from the project plan with its assigned number):**

P61. In patients with SLE and chronic persistent lupus arthritis on HCQ and steroid, does treatment with listed medical therapies **compared to no added treatment** impact clinical outcomes?

- **Outcomes (please list the outcomes as reported in the project plan):**
  - Arthritis activity (improvement in joint pains, joint stiffness, joint swelling, and function)
  - Joint damage- erosions, joint space narrowing, tendon loosening or deformity

- Functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)
- Disease activity
- SLE flares
- Disease damage
- Quality of life
- Treatment-related adverse events: immunosuppressives and biologics: infection and cytopenias (belimumab: depression/suicide; CNI: eGFR effects); steroids: fracture, hypertension, T2DM, infection; NSAIDs: GI side effects; Antimalarials: retinal and cardiac effects (prolonged QTc and myopathy)

Evidence Summary:

Ten single-arm study addressed thi PICO question (1-10). Treatment with Tacrolimus resulted in decrease of SLEDAI (MD (range)) from 8 (5.5-12) at baseline to 4 (2-6) at 3 months, to 4 (2-6.5) at 6 months, and to 3 (2-8) at 12 months (2). Treatment with MMF resulted in decrease of SLEDAI-2K from 5.7 ± 4.4 at baseline to 4.1± 4.1 at 6 months ($p = 0.002$) and to 4.5 ± 4.8 after 12 months (3). Treatment with Belimumab resulted in decrease of SELENA-SLEDAI score from 8.0 at index to 3.6 at six months in one study (4), and with the mean (SD) change of SLEDAI-2K/ SELENA-SLEDAI - 5.7 (4.5) in another study (7). Treatment with RTX resulted in decrease of global BILAG score from 4.5 (2.0–9.0, 0–28) at baseline to 3.0 (2.0–5.5, 0–15; $p = 0.16$) at 24 months, although this did not reach statistical significance (5), had complete remission rate 35% and partial remission rate 25% at median of 22 months of followup in one study (1), and complete response rate 19% and partial response rate 43% in six months and 39% and 37% in 20 months after treatment initiation (8). Another study reporting MEXSLEDAI, reported reduction in the mean global MEXSLEDAI score at 6 months from 4.9 (0.2) to 1.1 (0.3) (10). Treatment with ETN+MTX resulted in a significant improvement from baseline at 24 months in DAS28 (3.3±0.1 vs. 6.0±0.1 /BL), tender joint count (2.9±0.2 vs. 10.75±0.8/BL), swollen joint count (2.7±0.2 vs. 8.5±0.5/BL), VAS for pain (27.0±2.6 mm vs. 66.5±3.1 mm/BL), and SLEDAI-2K (6.30±0.36 vs. 13.7±0.48/BL) (6). Treatment with MTX resulted in SLEDAI decrease from 12.2 (SD 3.99) to 4 (3.75) (9).

Outcomes (Name + Summary)	Author, year, RefID	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
SLEDAI	Tani 2018, 8890	Retrospective multi-cetner	12 months	N =29 (89% female, mean age 38±9 years)	Oral tacrolimus, goal target level 4-6 ng/mL	Baseline SLDEAI 8 (5.5-12); 3 months SLED AI 4 (2-6); 6 months SLEDAI 4 (2-6.5); 12 months SLEDAI 3 (2-8)	Only 4 patients had arthritis
Disease activity	Tseilos 2016, 9155	Cohort study	12 months	N=72 (nonrenal manifestations) (mean age 38.6 ± 11.7 yrs, 90.3% female)	MMF 1350 ± 712.5 mg/day at baseline, 1512.5 ± 725 mg/day at 6 months, and	Improvement in clinical and lab disease at 6 months: 11 (57.9%)	

				19/72 with MSK disease	1662.5 ± 800 mg/day at 12 months	Improvement in clinical and lab disease at 12 months: 14 (73.7%) SLEDAI-2K was reduced from 5.7 ± 4.4 at baseline to 4.1± 4.1 at 6 months (p = 0.002) and to 4.5 ± 4.8 after 12 months	
PGA, SELENA-SLEDAI	Von Kempis 2019, 9441	Observational cohort retrospective analysis	6 months	N=53 Mean age 46.7 81% female 7/53 with MSK disease	Belimumab 10mg/kg IV q4 weeks after induction infusions at day 0, 14, and 28	At 6 months, majority of patients (n = 44, 83%) showed an overall clinical improvement based on a PGA-like scale. SELENA-SLEDAI scores available for 27/53 patients: decrease in mean SELENA-SLEDAI score from 8.0 at index to 3.6 at six months post index	Only 7 patients had arthritis
AEs, BILAG	Watson 2015, 9636	Retrospective cohort	n/a	N=63 Mean age 12.2 years (9.0-13.9) 79% female Bone pain/arthritis/arthralgia: 3/63 (5%)	RTX 750 mg/m2 14 days apart	Neutropenia causing delay in treatment: n=1 2% had a documented infection within 3 months of treatment BILAG disease activity data were available for 46 of the courses of RTX (46/104; 44%) in 25 patients.	Most patients had renal involvement, 67% also received CYC Only 5% of patients with MSK disease

						The global BILAG score before RTX was 4.5 (2.0–9.0, 0–28) that reduced to 3.0 (2.0–5.5, 0–15; p = 0.16) after RTX, although this did not reach statistical significance	
DAS28, SLEDAI-2K Tender swollen joint count, VAS	Yang 2018, 9921	Observational study	24 weeks	N=20 (met ACR criteria for both SLE and RA) Mean age 44.3 +/-8 Patients had never been treated with corticosteroids, DMARDs, or biologics	ETN plus MTX	At week 24, treatment with ETN plus MTX resulted in a significant improvement in DAS28 (3.3±0.1 vs. 6.0±0.1 /BL; p<0.001), tender joint count (2.9±0.2 vs. 10.75±0.8/BL; p<0.001), swollen joint count (2.7±0.2 vs. 8.5±0.5/BL; p<0.001), Visual Analog Scale for pain (27.0±2.6 mm vs. 66.5±3.1 mm/BL; p<0.001), and SLEDAI-2K (6.30±0.36 vs. 13.7±0.48/BL; p<0.001).	
Complete or partial remission	Melander, 2009, 5939	Observational study	22 months (range 10 to 51)	20 patients with an active class IV (15 cases) or class V(5 cases) LN. 12 patients with LN refractory to standard treatment, 6 with relapsing disease, 2 as first-line treatment.	20 patients received RTX weekly for 4 wk at a dosage of 375 mg/m2 of body surface area as induction treatment for an active class IV (15 cases) or class V(5 cases) lupus nephritis. RTX was given for LN refractory to	12/20 (60%)	

					standard treatment (12 cases), for relapsing disease (6 cases), or as first-line treatment (2 cases).		
Complete remission	Melander, 2009, 5939	Observational study	22 months (range 10 to 51)	20 patients with an active class IV (15 cases) or class V(5 cases) LN. 12 patients with LN refractory to standard treatment, 6 with relapsing disease, 2 as first-line treatment.	20 patients received RTX weekly for 4 wk at a dosage of 375 mg/m2 of body surface area as induction treatment for an active class IV (15 cases) or class V(5 cases) lupus nephritis. RTX was given for LN refractory to standard treatment (12 cases), for relapsing disease (6 cases), or as first-line treatment (2 cases).	7/20 (35%)	
Partial remission	Melander, 2009, 5939	Observational study	22 months (range 10 to 51)	20 patients with an active class IV (15 cases) or class V(5 cases) LN. 12 patients with LN refractory to standard treatment, 6 with relapsing disease, 2 as first-line treatment.	20 patients received rituximab weekly for 4 wk at a dosage of 375 mg/m2 of body surface area as induction treatment for an active class IV (15 cases) or class V(5 cases) lupus nephritis. RTX was given for LN refractory to standard treatment (12 cases), for relapsing disease (6 cases), or as first-line treatment (2 cases).	5/20 (25%)	

Corticosteroid-Sparing Effect	Melander, 2009, 5939	Observational study	22 months (range 10 to 51)	20 patients with an active class IV (15 cases) or class V(5 cases) LN. 12 patients with LN refractory to standard treatment, 6 with relapsing disease, 2 as first-line treatment.	20 patients received rituximab weekly for 4 wk at a dosage of 375 mg/m2 of body surface area as induction treatment for an active class IV (15 cases) or class V(5 cases) lupus nephritis. RTX was given for LN refractory to standard treatment (12 cases), for relapsing disease (6 cases), or as first-line treatment (2 cases).	Treatment enabled significant CS sparing as the median dose of oral CS decreased from 0.7 mg/kg per d (0 to 1.5) to 0.1 mg/kg per d (0 to 0.5) (P 0001).	
Infections	Melander, 2009, 5939	Observational study	22 months (range 10 to 51)	20 patients with an active class IV (15 cases) or class V(5 cases) LN. 12 patients with LN refractory to standard treatment, 6 with relapsing disease, 2 as first-line treatment.	20 patients received rituximab weekly for 4 wk at a dosage of 375 mg/m2 of body surface area as induction treatment for an active class IV (15 cases) or class V(5 cases) lupus nephritis. RTX was given for LN refractory to standard treatment (12 cases), for relapsing disease (6 cases), or as first-line treatment (2 cases).	5/20 (25%)	
Nautropenia	Melander, 2009, 5939	Observational study	22 months (range 10 to 51)	20 patients with an active class IV (15 cases) or class V(5 cases) LN. 12 patients with LN refractory to standard treatment, 6 with relapsing	20 patients received rituximab weekly for 4 wk at a dosage of 375 mg/m2 of body surface area as induction	4/20 (20%)	

				disease, 2 as first-line treatment.	treatment for an active class IV (15 cases) or class V(5 cases) lupus nephritis. RTX was given for LN refractory to standard treatment (12 cases), for relapsing disease (6 cases), or as first-line treatment (2 cases).		
Death	Melander, 2009, 5939	Observational study	22 months (range 10 to 51)	20 patients with an active class IV (15 cases) or class V(5 cases) LN. 12 patients with LN refractory to standard treatment, 6 with relapsing disease, 2 as first-line treatment.	20 patients received rituximab weekly for 4 wk at a dosage of 375 mg/m2 of body surface area as induction treatment for an active class IV (15 cases) or class V(5 cases) lupus nephritis. RTX was given for LN refractory to standard treatment (12 cases), for relapsing disease (6 cases), or as first-line treatment (2 cases).	1/20 (5%)	
SLEDAI	Collins 2020, 1850	Post-hoc pooled analysis	6 months	N=830 540/830 white Mean age 41.9 598/830 with MSK manifestations	Belimumab (dosage not specified)	Mean change from belimumab initiation in disease activity score (SLEDAI-2K/ SELENA-SLEDAI) was -5.7 (4.5; n = 344).	

SLEDAI	Conti 2014, 1882	Retrospective observational study	12 months	N=109 107/109 white Mean age 39.0 +/- 23 92/109 with MSK manifestations	MMF Mean dosage for MSK involvement 30.0 ± 11.7 mg/kg	Change in SLEDAI from MMF initiation: mean value of 2.8 ± 2.6 and 2.3 ± 2.2 at 4 and 12 months follow-up	
Complete and partial response	Fernandez-Nebro 2012, 2815	Multicenter retrospective longitudinal study	Mean follow-up of 20.0 +/- 15.2 months	N=128 42/128 with MSK manifestations	RTX (two doses of 1000mg rituximab given 14 days apart or four weekly doses of 375mg/m2)	73/116 patients achieved a response at six months (complete in 22 (19%) and partial in 51 (43%)) 97/128 (76%) achieved a response after a mean follow-up of 20.0 +- 15.2 months (complete in 50 (39%) and partial in 47 (37%)) Serious infection rate was 12.6/100 patient-years; 6 deaths (2 from infections, 4 from lupus complications)	
SLEDAI	Gansuage 1997, 3079	Open-label prospective study	6 months	N=22 19/22 female 12/22 with MSK manifestations	MTX 15mg PO qweek	SLEDAI decreased significantly from 12.2 (SD 3.99) to 4 (3.75) (p=0.001) 10/12 MSK patients with disappearance of symptoms	
MEXSLEDAI	Garcia-Carrasco 2010, 3111		6 months	N=52 Median age 36 25/52 with MSK manifestations MSK patients:	RTX (1g IV on days 1 and 15)	19/25 patients with severe musculoskeletal involvement had remission of arthritis Reduction in the mean global	

				25/25 female Mean age 37 All Hispanic patients with “refractory” disease		MEXSLEDAI score at 6 months from 4.9 (0.2) to 1.1 (0.3) (n = 49, p < 0.0001; (95% CI 3.1 to 4.4))	

References:

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

References:

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3. Tselios K, Gladman DD, Su J, Urowitz MB. Mycophenolate Mofetil in Nonrenal Manifestations of Systemic Lupus Erythematosus: An Observational Cohort Study. The Journal of rheumatology. 2016;43(3):552-8.
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9. Gansauge S, Breitbart A, Rinaldi N, Schwarz-Eywill M. Methotrexate in patients with moderate systemic lupus erythematosus (exclusion of renal and central nervous system disease). Annals of the rheumatic diseases. 1997;56(6):382-5.

10. Garcia-Carrasco M, Mendoza-Pinto C, Sandoval-Cruz M, Soto-Vega E, Beltran-Castillo A, Jimenez-Hernandez M, et al. Anti-CD20 therapy in patients with refractory systemic lupus erythematosus: a longitudinal analysis of 52 Hispanic patients. Lupus. 2010;19(2):213-9.

P62. In SLE patients with chronic Jaccoud's arthropathy, what is the impact of medical therapy or surgery vs PT/OT on clinical outcomes?

Populations: SLE patients with Jaccoud's arthropathy
Interventions:

- Hand arthroplasty
- Immunosuppressive therapy (MMF, AZA, MTX, or other standard immunosuppressives)

Comparator: PT/OT including splinting
Outcomes:

- Function of affected joints (hand function measure)
- Functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)
- Quality of life
- Treatment-related adverse events: infection and cytopenias for immunosuppressive therapies; surgical complications of hand arthroplasty for surgery adverse outcomes

Evidence summary:
A previosuly published systematic review assessed the outcome of surgery in patients with JA, it includes a total of 58 patients who underwent surgical procedures for JA (not all were SLE), all were small case series or case reports with variability in the surgical procedure, outcomes, and follow-up time, which limits our ability to draw conclusions on the outcomes of surgical approach to patients with JA.

Studies included: systematic reveiw
Santos WD, Baleeiro C, Santiago MB. Surgery for Jaccoud Arthropathy: A Systematic Review. J Clin Rheumatol. 2016 Jan;22(1):35-8. doi: 10.1097/RHU.0000000000000334. PMID: 26693624.

Studies reviewed and excluded: 4

No studies examined the impact of intervention on Jaccoud's arthropathy.

Title	Comments
Comparison of Hydroxychloroquine and Placebo in the Treatment of the Arthropathy of Mild Systemic Lupus Erythematosus	Does not include Jaccoud's arthropathy (incorrect population)
Diagnosis, Monitoring, and Treatment of Systemic Lupus Erythematosus: A Systematic Review of Clinical Practice Guidelines	Does not include Jaccoud's arthropathy (incorrect population)
Tacrolimus in non-Asian patients with SLE: a real-life experience from three European centres	Does not include Jaccoud's arthropathy (incorrect population)
Magnetic resonance imaging of Jaccoud's arthropathy in systemic lupus erythematosus	Does not include treatment or intervention for Jaccoud's arthropathy (no intervention)

Vasculitis

Non-Comparative

P63. In patients with SLE with vasculitis (not including cutaneous vasculitis) on HCQ and steroid, what is the impact of adding additional therapy versus not adding additional therapy on clinical outcomes?

Population: SLE patients with vasculitis (not including cutaneous vasculitis) on HCQ/steroid.
Interventions:

- High dose glucocorticoid-containing regimens – pulse followed by high dose
- Immunosuppressants
    - MTX
    - MMF
    - AZA
    - CNI
    - Cytoxan(Cyclophosphamide)
- Biologics
    - Anti-CD20
    - Belimumab
    - Anifrolumab
- IVIG
- Plasmapheresis

Outcomes:

- Vasculitis activity
- Disease activity
- SLE flares
- Disease damage
- Mortality
- Quality of life
- Treatment -related adverse events: steroids: fracture, hypertension, T2DM, infection; immunosuppressives including biologics and small molecules: infection and cytopenias (belimumab: depression/suicide; CNI: eGFR effects); IVIG: headache; plasmapheresis: low blood pressure

Evidence Summary:

The literature search identified 11 studies that addressed this PICO question, all of which were observational and the majority of which were noncomparative (n=10). Several other studies were excluded (n=22), mainly because they did not include the population of interest, which was SLE patients with non-cutaneous vasculitis. In some studies, outcomes were not reported separately for this patient subgroup or were not reported separately for each intervention of interest. Many of the included studies demonstrate small sample size, variability in co-interventions, and vague outcome definitions. These limitations, 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 the intervention of interest:

1. **Cyclophosphamide:** Six studies evaluated IV cyclophosphamide use in SLE patients with non-cutaneous vasculitis (Malaviya 1992, Zhu 2023, Fotis 2016, Liu 2018, Wang 2018, Yuan 2014).

   Four studies specifically included SLE patients with mesenteric vasculitis (Zhu 2023, Fotis 2016, Liu 2018, Yuan 2014), two of which specifically evaluated pediatric patients (Zhu 2023, Liu 2018).
   Yuan 2014 was a large, comparative study of 97 SLE patients with mesenteric vasculitis (mean [SD] age 31.7 [15.4] years). Patients receiving IV cyclophosphamide (in addition to hydroxychloroquine and steroids) were less likely to experience severe adverse events such as death or intestinal perforation (n=6/67; 9%) when compared to those receiving mycophenolate mofetil 2 grams daily (2/10; 20%) or those receiving hydroxychloroquine and steroids alone (12/20; 60%). Recurrence of mesenteric vasculitis during a median of 35 months of follow-up was significantly less likely to occur in patients receiving IV cyclophosphamide compared to those receiving other therapies.
   Zhu 2023 included 10 pediatric patients (mean [SD] age 12.5 [1.6] years) with mesenteric vasculitis as their initial presentation of SLE. All patients received high-dose steroids and IV cyclophosphamide 1 g/m^2 BSA monthly. Other co-interventions included hydroxychloroquine (n=9), belimumab (n=4), and rituximab (n=1), but outcomes were not reported separately for these patients. All 10 patients were reported to be in remission from their mesenteric vasculitis at one month.
   Fotis 2016 reported on a case series of 4 SLE patients (age range 15-21 years) with mesenteric vasculitis who were treated with steroids and IV cyclophosphasmide. Remission was reported in all 4 patients over a variable duration of follow-up.
   Liu 2018 reported on a case series of 3 pediatric SLE patients (ages 9-14 years) with mesenteric vasculitis who were treated with methylprednisolone and IV cyclophosphamide 0.8-1.0 g/m^2 BSA monthly. Remission was reported in all 3 patients during follow-up that ranged from 3-8 months in duration.

   Wang 2018 was a noncomparative study that included 6 SLE patients hospitalized with diffuse alveolar hemorrhage who were treated with steroids and IV cyclophosphamide (dose not specified). Survival of initial hospitalization was reported in 5/6 patients.

   Malaviya 1992 reported on 4 SLE patients with non-cutaneous vasculitis treated with IV cyclophosphamide 0.5-0.75 g/m^2 BSA and followed for variable duration (range 15-44 months). Remission was achieved in all 4 patients, though two experienced subsequent relapses at 10 and 24 months post-treatment, respectively.

2. **Azathioprine:** **Neuman 1995** evaluated azathioprine 1-2 mg/kg/day for treatment of retinal vasculitis in 4 SLE patients. All received concomitant systemic steroids and two were also taking hydroxychloroquine. Treatment response was reported in 2/4 patients, in whom subsequent flares occurred with discontinuation of azathioprine that responded to reinitiation. Treatment-related adverse events requiring discontinuation were reported in 3/4 patients, including two patients with GI intolerance and one with recurrent infections.

3. **Mycophenolate mofetil:** In addition to the comparative study of SLE patients with mesenteric vasculitis described above (Yuan 2014), one non-comparative study evaluated mycophenolate mofetil (dose not specified) for treatment of non-cutaneous vasculitis (organ not specified) in 6 SLE patients (**Tselios 2016**). All patients were receiving concomitant steroids, and some were also taking hydroxychloroquine. Resolution of vasculitis (based on the SLEDAI-2K) at 6 and 12 months occurred in all 6 patients.

4. **Methotrexate:** **Neuman 1995** reported on the use of methotrexate (7.5-15 mg weekly) for treatment of retinal vasculitis in 2 SLE patients followed for 18 and 37 months, respectively. Both were also receiving steroids, and one was receiving hydroxychloroquine. Treatment response was reported in both patients. In one patient, remission was noted 6 months after methotrexate discontinuation. The second patient flared with methotrexate discontinuation, but had a rapid response to reinitiation of therapy.

5. **Plasmapheresis:** Two noncomparative studies evaluated the use of plasmapheresis for the treatment of non-cutaneous vasculitis in SLE. **Wang 2018** reported survival of initial hospitalization in 5/7 SLE patients who received plasmapheresis for treatment of diffuse alveolar hemorrhage. **Papadaki 2006** reported improvement in visual acuity in two SLE patients with retinal vasculitis who received plasmapheresis. One of the patients had concomitant CNS vasculitis. In this study, both patients received concomitant steroids. One patient also received IV cyclophosphamide and the other received methotrexate.

6. **Rituximab:** Three noncomparative studies evaluated the use of rituximab (Freitas 2020, Vital 2011, Wang 2018).
   Freitas 2020 studied 8 SLE patients with vasculitis (organ involvement not specified) treated with rituximab (dose not specified) and followed for 6 months. No treatment failures (defined as new or persistent BILAG A/B score or death) were reported.
   Vital 2011 reported on 6 SLE patients with vasculitis (organ involvement not specified) treated with rituximab (1 gram x 2 doses on Day 1 and Day 14) and followed for 26 weeks. Major clinical response (based on the BILAG) was reported in all 6 patients. Subsequently, all 6 patients were followed for at least 12 additional months, with only one patient experiencing a relapse (moderate flare according to BILAG). **Wang 2018** reported on 4 SLE patients with diffuse alveolar hemorrhage treated with rituximab (375 mg/m^2 BSA x 2-4 fortnightly) and concomitant steroids. All 4 patients survived the initial hospitalization, with recurrence reported in 1/4 patients during a mean (SD) of 41 (21) months follow-up. Treatment-related adverse events were reported in 2/4 patients, including bronchitis (n=1) and UTI (n=1).

Azathioprine

Table 1. Studies included.

Author, year, RefID	Population (age, ethnicity)	Intervention	Outcome
Neumann 1995[1], 6524	4 SLE patients with retinal vasculitis	Azathioprine	Treatment response, adverse events

Table 2. Outcomes

Outcome	Author, year, RefID	Study Design	Follow up Duration	Population	Intervention	Result	Notes
Treatment response	Neumann 1995[1] 6524	Non-comparative	6-54 months	SLE pts with retinal vasculitis	AZA 1-2 mg/kg/day	2/4	2 patients had to stop AZA due to AEs

Treatment-related adverse events	Neumann 1995[1] 6524	Non-comparative	6-54 months	SLE pts with retinal vasculitis	AZA 1-2 mg/kg/day	3/4	2 patients: GI intolerance 1 patient: recurrent URTIs.

References:

1. Neumann R, Foster CS. Corticosteroid-sparing strategies in the treatment of retinal vasculitis in systemic lupus erythematosus. *Retina.* 1995;15:206-212.

Cyclophosphamide

Table 1. Studies included.

Author, year, RefID	Population (age, ethnicity)	Intervention	Outcome
Malaviya 1992[1], 5612	4 SLE patients	IV Cyclophosphamide	-Remission
Zhu 2023[2] 10373	10 pediatric SLE patients with lupus mesenteric vasculitis as initial presentation	IV cyclophosphamide	-Remission at one month
Fotis 2016[3]	4 SLE patients with mesenteric vasculitis	IV cyclophosphamide	Remission

Liu 2018[4]	3 cSLE patients with mesenteric vasculitis	IV cyclophosphamide	Remission
Wang 2018[5]	6 SLE patients with DAH	IV cyclophosphamide	Survival

Table 2. Outcomes

Outcome	Author, year, RefID	Study Design	Follow up Duration	Population	Intervention	Result	Notes
Remission	Malaviya 1992[1], 5612	RCT	Patients were followed up at (44,22,15 ,18 months)	SLE patients with vasculitis Median age= 44 (range 4-37)	Cyclophosphamide 0.5 to 0.75 g/m^2 body surface area over 1 hour	4/4	3/4: Gangrene-fingers 1/4: Retinal vasculitis
Remission	Zhu 2023[2] 10373	Case-control	1 mth	10 cSLE with lupus mesenteric vasculitis; mean (SD) age 12.5 (1.6) years	IV CYC 1 g/m2 once monthly for 6 months, then once every 3 months x 3 doses	10/10	All pts received high-dose steroids. Other treatments included HCQ (n=9), belimumab (n=4), and rituximab (n=1).
Remission	Fotis 2016[3]	Case series	Variable	4 pts, ages 15-21	IV CYC 750 mg/m^2 for 5-12 cycles with steroids	4/4	
Remission	Liu 2018[4]	Case series	3-8 months	3 pts, ages 9-14 years	IV CYC 0.8-1.0 g/m^2 monthly	3/3	All patients received concurrent methylprednisolone

Survival	Wang 2018[5]	Case series	Not reported	6 pts	IV CYC (dose not reported)	5/6	All patients received concurrent steroids

References:

1. Malaviya AN, Singh RR, Sindhwani R, Singh YN, Ahujà RK, Bhuyan UN, Khare SD, Kumar A, Malaviya R, Negi PC, et al. Intermittent intravenous pulse cyclophosphamide treatment in systemic lupus erythematosus. Indian J Med Res. 1992 Apr;96:101-8. PMID: 1428048.
2. Zhu J, Lai J, Liu X, Zhao X, Tao R, Kang M, Huang X, Wang L, Wu F, Pan X, Su G. Clinical characteristics and prognosis of childhood-onset lupus mesenteric vasculitis as the initial presentation – a case-control study. *Arthritis Research & Therapy.* 2023;25:248.
3. Fotis L, Baszis KW, French AR, Cooper MA, White AJ. Mesenteric vasculitis in children with systemic lupus erythematosus. *Clinical Rheumatology.* 2016;35:785-793.
4. Liu Y, Zhu J, Lai JM, Sun XF, Hou J, Zhou ZX, Yuan XY. Reports of three cases with the initial presentation of mesenteric vasculitis in children with system lupus erythematosus. *Clinical Rheumatology.* 2018;37:277-283.
5. Wang CR, Liu MF, Weng CT, Lin WC, Li WT, Tsai HW. Systemic lupus erythematosus-associated diffuse alveolar haemorrhage: a single-centre experience in Han Chinese patients. Scandinavian Journal of Rheumatology. 2018;47:392-399.

Mycophenolate Mofetil

Table 1. Studies included.

Author, year, RefID	Population (age, ethnicity)	Intervention	Outcome
Tselios 2016[1], 9155	6 SLE/LN patients with active vasculitis as per the SLEDAI-2K (organ not specified)	Mycophenolate mofetil (MMF)	Resolution of vasculitis based on SLEDAI-2K at 6 months and 12 months

Table 2. Outcomes

Outcome	Author, year, RefID	Study Design	Follow up Duration	Population	Intervention	Result	Notes
Resolution at 6 months	Tselios 2016[1] 9155	Non-comparative	6 months	SLE pts with vasculitis	MMF Dose not specified	6/6	Does not include results for 2 pts with "skin" vasculitis
Resolution at 12 months	Tselios 2016[1] 9155	Non-comparative	12 months	SLE pts with vasculitis	MMF Dose not specified	6/6	Does not include results for 2 pts with "skin" vasculitis

References:

1. Tselios K, Gladman DD, Su J, Urowitz MB. Mycophenolate mofetil in nonrenal manifestations of systemic lupus erythematosus: An observational cohort study. *The Journal of Rheumatology.* 2016;43:552-558.

Methotrexate

Table 1. Studies included.

Author, year, RefID	Population (age, ethnicity)	Intervention	Outcome

Neumann 1995[1], 6524	2 SLE patients with retinal vasculitis	Methotrexate	Treatment response

Table 2. Outcomes

Outcome	Author, year, RefID	Study Design	Follow up Duration	Population	Intervention	Result	Notes
Treatment response	Neumann 1995[1] 6524	Non-comparative	18-37 months	SLE pts with retinal vasculitis	MTX 7.5-15 mg weekly [Both patients were taking steroids and 1 was taking	2/2	1 patient in remission 6 months after MTX stopped. Second patient flared

					HCQ too].		when MTX stopped, but "quick response" to MTX reinitiation.

References:

1. Neumann R, Foster CS. Corticosteroid-sparing strategies in the treatment of retinal vasculitis in systemic lupus erythematosus. *Retina.* 1995;15:206-212.

Plasmapheresis

Table 1. Studies included.

Author, year, RefID	Population (age, ethnicity)	Intervention	Outcome
Papadaki 2006[1]	2 SLE patients with retinal vasculitis	Plasmapheresis	Visual acuity
Wang 2018[2]	7 SLE patients with DAH	Plasmapheresis	Survival

Table 2. Outcomes

Outcome	Author, year, RefID	Study Design	Follow up Duration	Population	Intervention	Result	Notes
Visual acuity	Papadaki 2006[1]	Case series	1 mth in Case #1, 10 months in Case #2	2 SLE pts with retinal vasculitis (1 with concurrent CNS vasculitis)	Plasmapheresis (x5 days in Case #1, x3 days and then once weekly for 5 weeks in Case #2)	Case #1: Improved from 20/65 OD, 20/100 OS to 20/30 OD, 20/40 OS Case #2: Improved from 20/400 OD, 20/200 OS to 20/125 OD, 20/30 OS	Both received high-dose steroids. Case #1 also received IV CYC, Case #2 also received MTX
Survival	Wang 2018[2]	Case series	Not reported	7 SLE pts with DAH	Plasmapheresis (details not reported)	5/7	

References:

1. Papadaki TG, Zacharopoulos IP, Papaliodis G, Iaccheri B, Fiore T, Foster CS. Plasmapheresis for lupus retinal vasculitis. *Archives of Ophthalmology.* 2006;124:1654-1656.
2. Wang CR, Liu MF, Weng CT, Lin WC, Li WT, Tsai HW. Systemic lupus erythematosus-associated diffuse alveolar haemorrhage: a single-centre experience in Han Chinese patients. Scandinavian Journal of Rheumatology. 2018;47:392-399.

Rituximab

Table 1. Studies included.

Author, year, RefID	Population (age, ethnicity)	Intervention	Outcome
Freitas 2020[1], 2964	8 SLE patients with vasculitis (organ not specified)	Rituximab	Treatment failure
Vital 2011[2], 9417	6 SLE patients with vasculitis according to BILAG (organ not specified)	Rituximab	Major clinical response, relapses
Wang 2018[3]	4 SLE patients with DAH	Rituximab	Survival, recurrence, treatment related adverse events

Table 2. Outcomes

Outcome	Author, year, RefID	Study Design	Follow up Duration	Population	Intervention	Result	Notes
Treatment failure	Freitas 2020[1], 2964	Non-comparative	6 months	SLE pts with vasculitis	Rituximab (dose not specified)	0/8	Failure:defined as new or persistent BILAG A/B score or death at 6 months)

Major clinical response	Vital 2011[2] 9417	Non-comparative	26 wks	SLE pts with vasculitis	IV RTX 1g x 2 doses on Day 1 and 14	6/6	(no domain rated BILAG A or B at Week 26 and no A or B flare up to Week 26)
Relapse	Vital 2011[2] 9417	Non-comparative	At least 18 months total. Exact FU time varied	SLE pts with vasculitis	IV RTX 1g x 2 doses on Day 1 and 14	1/6	Relapse was defined as: (new BILAG grade A flare or 2 grade B flares following major or partial clinical response at 26 weeks) -Moderate flare in 1/6 after major clinical remission at 26 weeks
Survival	Wang 2018[3]	Non-comparative	Mean (SD) 40.8 (21.1) months; range 12-58 months	SLE pts with DAH	IV RTX 375 mg/m^2 x 2-4 fortnightly	4/4	All patients received high-dose steroids
Recurrence	Wang 2018[3]	Non-comparative	Mean (SD) 40.8 (21.1) months; range 12-58 months	SLE pts with DAH	IV RTX 375 mg/m^2 x 2-4 fortnightly	1/4	All patients received high-dose steroids
Treatment-related adverse events	Wang 2018[3]	Non-comparative	Mean (SD) 40.8 (21.1) months; range 12-58 months	SLE pts with DAH	IV RTX 375 mg/m^2 x 2-4 fortnightly	2/4 (1 bronchitis, 1 UTI)	All patients received concurrent high-dose steroids

References:

1. Freitas S, Mozo Ruiz M, Costa Carneiro A, Isenberg DA. Why do some patients with systemic lupus erythematosus fail to respond to B-cell depletion using rituximab? *Clinical and Experimental Rheumatology.* 2020;38:262-266.

2. Vital EM, Dass S, Buch MH, Henshaw K, Pease CT, Martin MF, Ponchel F, Rawstron AC, Emery P. B cell biomarkers of rituximab responses in systemic lupus erythematosus. *Arthritis & Rheumatism.* 2011;63(10):3038-3047.
3. Wang CR, Liu MF, Weng CT, Lin WC, Li WT, Tsai HW. Systemic lupus erythematosus-associated diffuse alveolar haemorrhage: a single-centre experience in Han Chinese patients. Scandinavian Journal of Rheumatology. 2018;47:392-399.

Comparative

MMF

P63.2.d. In patients with SLE with vasculitis (not including cutaneous vasculitis) on HCQ and steroid, what is the impact of adding additional therapy versus not adding additional therapy on clinical outcomes?

Population:
- SLE patients with vasculitis (not including cutaneous vasculitis) on HCQ/steroid

Interventions:
- MMF

Comparator:
- Standard of care

Outcomes:
- Severe adverse events

Table 1.

Study	Design	Population	Intervention	Comparator	C
Yuan 2014	Retrospective Cohort	Patients with active SLE	Oral MMF 2 g/day	Standard of care (immunosuppressive therapy, or/and steroids, or/and HCQ)	-

Evidence summary: 1 retrospective cohort study assessing mesenteric vasculitis in patients with SLE. The recurrence of mesenteric vasculitis after treatment with cyclophosphamide was followed up at 2-96 months in which hazard ratio was 0.21(0.05 to 0.89).
The results for the severe adverse events (death or severe adverse event like intestinal perforation that needed surgical intervention during hospitalization) showed an absolute effect of 402 fewer per 1,000 (from 546 fewer to 126 more) in patients that used MMF. However this evidence is based on very low certainty due to risk of bias(no randomization), the small sample size and the indirectness since the comparator is not exactly as the PICO requires.

Evidence profile:

Certainty assessment	№ of patients	Effect	Certainty

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MMF	Standard of care	Relative (95% CI)	Absolute (95% CI)	
Severe Adverse Events											
1	non-randomised studies	serious[a]	not serious	serious[b]	serious[c,d]	none	2/10 (20.0%)	12/20 (60.0%)	**RR 0.33** (0.09 to 1.21)	**402 fewer per 1,000** (from 546 fewer to 126 more)	⨁◯◯◯ Very low[a,b,c,d]

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

Explanations

a. Non-randomized study.

b. Comparison arm is not only HCQ/steroid

c. Small sample size.

d. Wide CI in absolute effect.

References: 1 Retrospective Cohort Study

1.Shiwen Yuan, Yujin Ye, Dongying Chen, Qian Qiu, Zhongping Zhan, Fan Lian, Hao Li, Liuqin Liang, Hanshi Xu, Xiuyan Yang,Lupus mesenteric vasculitis: Clinical features and associated factors for the recurrence and prognosis of disease,Seminars in Arthritis and Rheumatism,Volume 43, Issue 6,2014,Pages 759-766,ISSN 0049-0172,https://doi.org/10.1016/j.semarthrit.2013.11.005.

Cyclophosphamide (High dose)

P63.2.f In patients with SLE with vasculitis (not including cutaneous vasculitis) on HCQ and steroid, what is the impact of adding additional therapy versus not adding additional therapy on clinical outcomes?

Population:

- SLE patients with vasculitis (not including cutaneous vasculitis) on HCQ/steroid

Interventions:

- Cyclophosphamide (High dose)

Comparator:

- Standard of care

Outcomes:

- Mesenteric Vasculitis Recurrence
- Severe adverse events

Table 1.

Study	Design	Population	Intervention	Comparator	Outcomes
Yuan 2014	Retrospective Cohort	Patients with active SLE	Cyclophosphamide **High dose (≥1.0 g/m2 /month)**	Standard of care (immunosuppressive therapy, or/and steroids, or/and HCQ)	-Mesenteric Vasculitis Recurrence -Severe adverse events

Evidence summary: 1 retrospective cohort study assessing mesenteric vasculitis in patients with SLE. The recurrence of mesenteric vasculitis after treatment with cyclophosphamide was followed up at 2-96 months in which hazard ratio was 0.21(0.05 to 0.89). However, there were no crude values for the exact number of patients followed up in the 2 arms. Therefore, we were not able to assess the baseline risk. This, along with risk of bias due to no randomization, the small sample size and the indirectness since the comparator is not exactly as the PICO requires lead to the study having very low certainty evidence.
The second outcome was the severe adverse events (death or severe adverse event like intestinal perforation that needed surgical intervention during hospitalization), however no separated results were reported for low and high cyclophosphamide dosing. The results showed an absolute effect of 510 fewer per 1,000 (from 564 fewer to 390 fewer) in patients that used cyclophosphamide.

Evidence profile:

Certainty assessment							№ of patients		Effect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	high dose cyclophosphamide	standard of care	Relative (95% CI)	Absolute (95% CI)	Certainty
Recurrence-High dose											
1	non-randomised studies	serious[a]	not serious	serious[b]	very serious[c,d]	none	-/0	-/0	**HR 0.21** (0.05 to 0.89)	**0 fewer per 1,000** (from 1 fewer to 0 fewer)	⨁◯◯◯ Very low[a,b,c,d]
Severe Adverse Events-Cytoxan(High and Low dose)											
1	non-randomised studies	serious[a]	not serious	serious[b]	serious[c]	none	6/67 (9.0%)	12/20 (60.0%)	**RR 0.15** (0.06 to 0.35)	**510 fewer per 1,000** (from 564 fewer to 390 fewer)	⨁◯◯◯ Very low[a,b,c]

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

Explanations

a. Non-randomized study.

b. Comparison arm is not only HCQ/steroid

c. Small sample size
d. No baseline risk information was provided.

References: 1 Retrospective Cohort Study

1.Shiwen Yuan, Yujin Ye, Dongying Chen, Qian Qiu, Zhongping Zhan, Fan Lian, Hao Li, Liuqin Liang, Hanshi Xu, Xiuyan Yang,Lupus mesenteric vasculitis: Clinical features and associated factors for the recurrence and prognosis of disease,Seminars in Arthritis and Rheumatism,Volume 43, Issue 6,2014,Pages 759-766,ISSN 0049-0172,https://doi.org/10.1016/j.semarthrit.2013.11.005.

Cyclophosphamide (low dose)

P63.2.f In patients with SLE with vasculitis (not including cutaneous vasculitis) on HCQ and steroid, what is the impact of adding additional therapy versus not adding additional therapy on clinical outcomes?

Population:
- SLE patients with vasculitis (not including cutaneous vasculitis) on HCQ/steroid

Interventions:
- Cyclophosphamide (Low dose)

Comparator:
- Standard of care

Outcomes:
- Mesenteric Vasculitis Recurrence
- Severe adverse events

Table 1.

Study	Design	Population	Intervention	Comparator	Outcomes
Yuan 2014	Retrospective Cohort	Patients with active SLE	Cyclophosphamide **Low dose (<1.0 g/m2 /month)**	Standard of care (immunosuppressive therapy, or/and steroids, or/and HCQ)	-Mesenteric Vasculitis Recurrence -Severe adverse events

Evidence summary: 1 retrospective cohort study assessing mesenteric vasculitis in patients with SLE. The recurrence of mesenteric vasculitis after treatment with cyclophosphamide was followed up at 2-96 months in which hazard ratio was 0.45 (0.15 to 1.37). However, there were no crude values for the exact number of patients followed up in the 2 arms. Therefore, we were not able to assess the baseline risk. This, along with risk of bias due to no randomization, the small sample size and the indirectness since the comparator is not exactly as the PICO requires lead to the study having very low certainty evidence. The second outcome was the severe adverse events (death or severe adverse event like intestinal perforation that needed surgical intervention during hospitalization), however no separated results were reported for low and high cyclophosphamide dosing. The results showed an absolute effect of 510 fewer per 1,000 (from 564 fewer to 390 fewer) in patients that used cyclophosphamide.

Evidence profile:

Certainty assessment							№ of patients		Effect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Low dose cyclophosphamide	standard of care	Relative (95% CI)	Absolute (95% CI)	Certainty
Relapse of Mesenteric Vasculitis											
1	non-randomised studies	serious[a]	not serious	serious[b]	very serious[c,d]	none	-/0	-/0	**HR 0.45** (0.15 to 1.37)	**0 fewer per 1,000** (from 1 fewer to 0 fewer)	⨁◯◯◯ Very low[a,b,c,d]
Severe Adverse Events (High and Low dose)											
1	non-randomised studies	serious[a]	not serious	serious[b]	serious[c]	none	6/67 (9.0%)	12/20 (60.0%)	**RR 0.15** (0.06 to 0.35)	**510 fewer per 1,000** (from 564 fewer to 390 fewer)	⨁◯◯◯ Very low[a,b,c]

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

Explanations

a. Non-randomized study.
b. Comparison arm is not only HCQ/steroid.
c. Small sample size
d. No baseline risk information was provided.

References: 1 Retrospective Cohort Study

1.Shiwen Yuan, Yujin Ye, Dongying Chen, Qian Qiu, Zhongping Zhan, Fan Lian, Hao Li, Liuqin Liang, Hanshi Xu, Xiuyan Yang,Lupus mesenteric vasculitis: Clinical features and associated factors for the recurrence and prognosis of disease,Seminars in Arthritis and Rheumatism,Volume 43, Issue 6,2014,Pages 759-766,ISSN 0049-0172,https://doi.org/10.1016/j.semarthrit.2013.11.005.

Belimumab

P63.3.h In patients with SLE with vasculitis (not including cutaneous vasculitis) on HCQ and steroid, what is the impact of adding additional therapy versus not adding additional therapy on clinical outcomes?

Population:

- SLE patients with vasculitis (not including cutaneous vasculitis) on HCQ/steroid.

Interventions:

- Belimumab

Comparator:

- Standard of care

Outcomes:

- Efficacy-Vasculitis activity

Table 1.

Study	Design	Population	Intervention	Comparator	Outcomes
Manzi 2012	Post hoc analysis for BLISS 52 and BLISS 72	Patients with active SLE	Belimumab 10 mg	Standard of care (immunosuppressive therapy, or/and steroids, or/and HCQ)	BILAG improvement and SLEDAI improvement
Zhang 2107	RCT	Patients with active SLE (Asians)	Belimumab 10 mg	Standard of care (immunosuppressive therapy, or/and steroids, or/and HCQ)	Adverse events (AE), serious AE, AE leading to discontinuation, infections, SLE flare up (severe)

Evidence summary: Improvement of SLEDAI-2K (vasculitis) were higher in belimumab arm compared to standard of care, with an absolute effect (CI) of 332 more per 1,000(from 73 more to 734 more). This is based on very low certainty of evidence because of risk of bias (posthoc analysis without randomization) and imprecision (wide CI in absolute effect and small sample size). Whereas the BILAG score showed an absolute effect of 226 more per 1,000 (from 24 more to 505 more) in the study with post hoc analysis, and an effect of 127 more per 1,000 (from 83 fewer to 430 more) in the RCT. These results are based on low certainty of evidence due to risk of bias (in the posthoc analysis without randomization) and imprecision in the RCT (wide CI in absolute effect and small sample size).

Evidence profile:

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Belimumab	Standard of care	Relative (95% CI)	Absolute (95% CI)	
Efficacy-BILAG-Post hoc analysis											
1[1]	randomised trials	serious[a]	not serious	not serious	serious[b]	none	36/51 (70.6%)	25/52 (48.1%)	**RR 1.47** (1.05 to 2.05)	**226 more per 1,000** (from 24 more to 505 more)	⊕⊕◯◯ Low[a,b]
Efficacy BILAG- RCT											
1[2]	randomised trials	not serious	not serious	not serious	very serious[b,c]	none	40/59 (67.8%)	16/29 (55.2%)	**RR 1.23** (0.85 to 1.78)	**127 more per 1,000** (from 83 fewer to 430 more)	⊕⊕◯◯ Low[b,c]
Efficacy-SELENA-SLEDAI											
1[1]	randomised trials	serious[a]	not serious	not serious	very serious[b,c]	none	28/38 (73.7%)	15/37 (40.5%)	**RR 1.82** (1.18 to 2.81)	**332 more per 1,000** (from 73 more to 734 more)	⊕◯◯◯ Very low[a,b,c]

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

Explanations

a. Post hoc analysis study.
b. Wide range of CI in absolute risk.
c. Small sample size.

References: Randomized clinical trials (1 RCT, and 1 posthoc analysis)

1. Manzi S, Sánchez-Guerrero J, Merrill JT, et al. Effects of belimumab, a B lymphocyte stimulator-specific inhibitor, on disease activity across multiple organ domains in patients with systemic lupus erythematosus: combined results from two phase III trials. *Ann Rheum Dis*. 2012;71(11):1833-1838. doi:10.1136/annrheumdis-2011-200831
2. Zhang, Fengchun et al. "A pivotal phase III, randomised, placebo-controlled study of belimumab in patients with systemic lupus erythematosus located in China, Japan and South Korea." *Annals of the rheumatic diseases* vol. 77,3 (2018): 355-363. doi:10.1136/annrheumdis-2017-211631

Myocarditis

In SLE patients with myocarditis, what is the most effective therapy?

P64.. In patients with lupus myocarditis what is the impact of listed therapies vs no therapy or HCQ alone on clinical outcomes?

Population: SLE patients with lupus myocarditis

1. Acute and worsening
2. Chronic and persistent

Interventions:

Glucocorticoid-containing regimens

Immunosuppressants

1. MMF/MPA
2. AZA
3. CYC

Biologics

1. Anti-CD20
2. Belimumab
3. Anifrolumab

IVIG

Comparator: No therapy or HCQ alone

Outcomes (please list the outcomes as reported in the project plan):

1. Reduction of myocarditis activity
2. Overall disease activity
3. SLE flares
4. Disease damage
5. Mortality
6. Quality of life
7. Cumulative glucocorticoid dose
8. Treatment -related adverse events

Evidence summary:

5 studies with non-comparative data were included in the final review. All studies were case series (1-5) and noted overall improvement in cardiac function and improved survival/outcomes with immunosuppression. However, none of the studies reported change in outcomes by treatment arm. Studies showed that survivors had better LVEF with immunosuppression (1-3) and one case series reported normal EF in patients who received immunosuppression (3). One case series specifically examined the impact of RTX on myocarditis and noted significant improvement in cardiac MRI at 1-2 mo. follow-up period (5). Given no comparator group and no outcomes reported by immunosuppression or treatment type, effect size and impact of specific immunosuppression type could not be determined or pooled.

- **Patient important outcomes (addressed in the study only):**

Outcomes (Name + Summary)	Author, year, RefID	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Du Toit et al.	2017, 2438	Case series	563 days (range 4–1740)	N=28, The majority of patients were female (92.9%) of mixed racial ethnicity (89.3%) that presented early after the onset of their lupus (median 11.5 weeks); Mean age 28 ± 11.4	19 received IV pulse steroids; 21 received CYC iv; 4 received additional meds e.g. AZA or IVIG; 14 on AZA maintenance; 1 on MMF maintenance; 2 received PLEX with other meds	Treatment-wise response and outcomes not reported. Overall outcomes: 19 patients required intensive care unit admission with ventilatory support required in 17 patients. 2 relapses after an initial improvement, 1 patient relapsed twice. One or more treatment-related complications occurred in 13/28 patients (46.4%). This included bone marrow suppression (25%), septicaemia (32%) and opportunistic infections (25%). Total mortality was high: 12 patients (42.9%) died after a median of 115 days. Mortality was	No reports on outcomes by treatment

						attributed to lupus myocarditis in five patients (17.8%),	
Law et al.	2005, 5020	Case series	median duration of four years (range: 2.5–10.1)	N=13; racial distribution was as follows: Chinese (46%), Malay (36%), and other ethnicity (18%). The mean age at diagnosis of SLE was 27 10 (range: 14–40) years	13 received high dose steroids; 9 received IV Steroids; 7 received CYC – 4 received 6 doses, 1 received 3 doses, 2 received 1 dose then died d/t infection Maintenance: 6 (67%) patients were receiving low dose prednisolone (7.5 mg/day) as well as concomitant hydroxychloroquine, three (33%) hydroxychloroquine and azathioprine, two (22%) or azathioprine one (11%); 1 on HCQ alone; 1 was on pred alone; 1 off all meds	2 out of 7 who received CYC died due to infection; All survivors had no relapses; 89% had normal LVEF on follow up ECHO	Death in 2 out 7 who received CYC
Meridor et al.	2021; 5979	Case series	Variable (3-7 days up to 2-4 years)	N=5; Age – 3 patients in 30s, 2 patients in 50s; All women	All received IVIG	All patients had significant improvement in LVEF after 3-5 days of IVIG therapy and 3/5 patients had a repeat ECHO after 2-5 years with normal EF	No comparator
Thomas et al.	2016; 9007	Case series	The median followup was 37 months.	Twenty-nine patients (3 men and 26 women) fulfilled the inclusion criteria (median age at the diagnosis of SLE: 30 yrs, range 16–57)	N=29; Patients were treated with corticosteroids (n = 28), cyclophosphamide (CYC; n = 16), intravenous immunoglobulins (n = 8), PLEX (n=4/29), and/or mycophenolate mofetil induction (n = 2). MMF maintenance 10/29	Outcomes: Not by treatment arm again. Overall outcomes: Median length of stay at hospital, days (range) 42.8 (8–227) Median followup, mos (range) 37 (4–115) Conventional unit only 4 ICU 25 Death due to LM 2 Total deaths 3 Relapse 1	No outcomes by treatment arm.
Wang et al.	2018; 9541	Case series	1-2 mos. after RTX rx course	N=13; 13 female, aged 19 to 52 years (31.9 ± 10.7)	N=13; 3 received RTX who were followed up	All 3 patients who received RTX 375 mg/m2 weekly x 4 or	

						fortnightly x 2 had improved EKG, EF, Cardiac MRI, resolved cardiomegaly at follow up (1-2 mos,)	

References:

- Randomized controlled trials:
- -None

- Comparative observational studies:
    - -None

- Single arm studies: 5

Du Toit R, Herbst PG, van Rensburg A, Snyman HW, Reuter H, Doubell AF. Speckle tracking echocardiography in acute lupus myocarditis: comparison to conventional echocardiography. Echo Res Pract. 2017 Jun;4(2):9-19. doi: 10.1530/ERP-17-0005. Epub 2017 May 10. PMID: 28490455; PMCID: PMC5510444.

Law WG, Thong BY, Lian TY, Kong KO, Chng HH. Acute lupus myocarditis: clinical features and outcome of an oriental case series. Lupus. 2005;14(10):827-31. doi: 10.1191/0961203305lu2228oa. PMID: 16302678.

Meridor K, Shoenfeld Y, Tayer-Shifman O, Levy Y. Lupus acute cardiomyopathy is highly responsive to intravenous immunoglobulin treatment: Case series and literature review. Medicine (Baltimore). 2021 May 7;100(18):e25591. doi: 10.1097/MD.0000000000025591. PMID: 33950936; PMCID: PMC8104142.

Thomas G, Cohen Aubart F, Chiche L, Haroche J, Hié M, Hervier B, Costedoat-Chalumeau N, Mazodier K, Ebbo M, Cluzel P, Cordel N, Ribes D, Chastre J, Schleinitz N, Veit V, Piette JC, Harlé JR, Combes A, Amoura Z. Lupus Myocarditis: Initial Presentation and Longterm Outcomes in a Multicentric Series of 29 Patients. J Rheumatol. 2017 Jan;44(1):24-32. doi: 10.3899/jrheum.160493. Epub 2016 Nov 15. PMID: 28042125.

Wang CR, Tsai YS, Li WT. Lupus myocarditis receiving the rituximab therapy-a monocentric retrospective study. Clin Rheumatol. 2018 Jun;37(6):1701-1707. doi: 10.1007/s10067-017-3971-4. Epub 2018 Jan 3. PMID: 29299707.

Studies reviewed and excluded: 10

Title	Comments
Treatment-free remission in severe systemic lupus erythematosus following synchronization of plasmapheresis with subsequent pulse cyclophosphamide	Does not include myocarditis or LS Endocarditis (incorrect population)
Why do some patients with systemic lupus erythematosus fail to respond to B-cell depletion using rituximab?	Does not include myocarditis or LS Endocarditis (incorrect population)
Assessment of flares in lupus patients enrolled in a phase II/III study of rituximab (EXPLORER)	Does not include myocarditis or LS Endocarditis (incorrect population)
Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial	Does not include myocarditis or LS Endocarditis (incorrect population)
The spectrum of clinical manifestations, outcome and treatment of pericardial tamponade in patients with systemic	Does not include myocarditis or LS Endocarditis (incorrect population)

lupus erythematosus: a retrospective study and literature review	
Intravenous pulse cyclophosphamide in the treatment of interstitial lung disease due to collagen vascular diseases	Does not include myocarditis or LS Endocarditis (incorrect population)
B cell biomarkers of rituximab responses in systemic lupus erythematosus	Does not specifically highlight if cardioresp group includes all myocarditis or LS Endocarditis (incorrect population)
The indications, efficacy and adverse events of rituximab in a large cohort of patients with juvenile-onset SLE	Does not specifically highlight if cardiac group includes all myocarditis or LS Endocarditis (incorrect population)
A long-term study of interstitial lung disease in systemic lupus erythematosus	Does not include myocarditis or LS Endocarditis (incorrect population)
A Contemporary 20-Year Cleveland Clinic Experience of Nonbacterial Thrombotic Endocarditis: Etiology, Echocardiographic Imaging, Management, and Outcomes.	No specific treatment, LS Endocarditis not separately evaluated

Endocarditis

In SLE patients with Libman-Sacks endocarditis, what is the most effective therapy?

P65. In SLE patients with lupus Libman-Sacks endocarditis, does treatment with listed medical therapy vs HCQ treatment alone impact clinical outcomes?

Population: SLE patients with Libman-Sacks endocarditis defined as sterile vegetations on the valve surface or a thickened valve or valvulitis with or without vegetation (with or without aPL/APS, and with or without low complement levels).

Interventions:

- Anticoagulation
- Steroids
- Traditional immunosuppressants and approved biologics (Belimumab, Anifrolumab)
- B-cell depletion (anti-CD-20 therapy)
- Surgical intervention (valvular surgery)

Comparators:

- Anticoagulation (AC) with vit K antagonists vs. no AC as comparator
- Steroid therapy vs. AC alone
- Steroid+ AC vs AC alone
- Immunosuppression + steroids vs AC
- Immunosuppression + steroids + AC vs AC
- B cell depletion therapy + steroids vs AC
- B cell depletion therapy + steroids + AC vs AC
- No surgical intervention vs (any) medical management

Outcomes:

- Size of the vegetations
- Valvular dysfunction requiring valve replacement / surgery
- Embolic disease (including stroke and TIA)

- Disease damage
- Mortality
- Quality of life
- Adverse impact of medications: bleeding for anticoagulation; fracture, hypertension, T2DM, infection; for steroid, infection and cytopenias for immunosuppressive medications (depression/suicide for belimumab).

Evidence summary:
3 studies with non-comparative data were included in the final review. One case series (1) including 14 cases noted 92% one-year survival and 74% 4-year survival and 49% 10-year survival post surgical repair of valvular disease from Libman Sacks Endocarditis, while no 30-day in-hospital deaths were noted. Two major cardiovascular events were noted in this study. Another case series (2) noted vegetations size decreased with anticoagulation and no surgery was needed. Finally, a case series with 17 patients noted significant improvement in valvular function and reduction in vegetation size with combined conventional anti-inflammatory and antithrombotic therapy in patients with Libman-Sacks endocarditis (3). Overall, surgical intervention, or anticoagulation, or combination of anticoagulation and anti-inflammatory therapies had better outcomes however there was no comparative data available.

Outcomes (Name + Summary)	Author, year, RefID	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Arif et al.	2015; 507	Case series	49 ± 32 mos.	N=15, 14 females; 53 ± 16 years; 13 with SLE; 2 primary APS; 4 had secondary APS	All underwent MVR or TVR (1 had tricuspid ds)	30-day death = 0 In-hospital death = 0 MACE = 2 Non-fatal later CV events incl. TE = 4; 1-year survival 92 ± 7.4% 4-year survival 74 ± 18 % 10-year survival 49 ± 23%	
Yoo et al.	2020, 10031	Case series	56.8 mos.	N=11 LS Endo	6 out of 11 received anticoagulation; 5 received Immunosuppression with AZA or MMF as well	No surgery needed at the end of the follow up period; vegetations decreased in all patients; one patient had CVA; one patient	

						had a new mass	
Roland et al.	2021; 7670	Case series	6 mos	N=17; age 36 ± 12 years (range, 18–57), 14 (82%) women, 53% Hispanic, with body mass index of 27.12 ± 7.5 Kg/m2, age at onset of SLE 29.31 ± 12.08, and SLE duration of 7.53 ± 6.10 years	15/17 on HCQ; 16/17 on prednisone; 9 on cytotoxics incl. cyclophosphamide, MMF, MTX, RTX; 7 on warfarin; 10 on ASA; 5 on clopidogrel	In 13 (76%) patients, valve vegetations or regurgitation resolved or improved in number and size or by >1 degree, , as compared to 4 (24%) patients in whom no changes occurred (p = 0.03). Valve vegetations decreased in number, diameter, and area (all p less than 0.01); the severity of associated valve regurgitation also improved (p = 0.04), 5 patients died – 1 stroke, 1 MI, 2 sepsis; 1 PLE	Combined conventional anti-inflammatory and antithrombotic therapy may be an effective treatment for Libman-Sacks endocarditis and its associated CVD and may obviate the need for high-risk valve surgery

References:
Randomized controlled trials:
-None
Comparative observational studies:
-None

Single arm studies: 3

- Arif R, Farag M, Seppelt P, Beller CJ, Ruhparwar A, Karck M, Kallenbach K. Patients with systemic lupus erythematosus and antiphospholipid syndrome undergoing cardiac valve surgery. J Heart Valve Dis. 2015 Mar;24(2):228-35. PMID: 26204691.
- Yoo BW, Lee SW, Song JJ, Park YB, Jung SM. Clinical characteristics and long-term outcomes of Libman-Sacks endocarditis in patients with systemic lupus erythematosus. Lupus. 2020 Aug;29(9):1115-1120. doi: 10.1177/0961203320930097. Epub 2020 Jun 14. PMID: 32536317.
- Roldan et al. Libman-Sacks endocarditis and associated cerebrovascular disease: The role of medical therapy. Published: February 16, 2021. https://doi.org/10.1371/journal.pone.0247052

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