SUPPLEMENTARY APPENDIX 2: Evidence Report

2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis

PICO 1a. Should patients with MTX-naïve and non-MTX csDMARDs naïve RA and low disease activity receive MTX monotherapy or an alternative csDMARD monotherapy?

P - Patients with MTX-naïve and non-MTX csDMARDs naïve RA and low disease activity
I - MTX monotherapy
C - HCQ
C - SSZ
C – LEF

Comparison 1: MTX monotherapy **versus** HCQ. No eligible RCT, NRS, or indirect evidence were identified.
Comparison 2: MTX monotherapy **versus** SSZ. See below Table.
Comparison 3: MTX monotherapy **versus** LEF. See below Table.
Comparison 4: SSZ **versus** HCQ. See below Table.

Comparison 2: MTX monotherapy **versus** SSZ. Data based on **indirect** RCT evidence.
Overall certainty of evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX monotherapy	SSZ	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 1 year; assessed with: DAS28-ESR (Lower values –> benefit) (MCID -1.17)												
2 (1, 2)	randomised trials	serious [a]	not serious [b]	serious [c]	serious [d]	none	104	102	-	MD **0.14 higher** (0.18 lower to 0.47 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Disability (follow up: 1 year; assessed with: HAQ-DI (Lower values –> benefit) (MCID -0.22)												
2 (1, 2)	randomised trials	serious [a]	not serious	serious [c]	serious [d]	none	104	102	-	MD **0.04 lower** (0.2 lower to 0.13 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Pain (follow up: 1 year; assessed with: VAS 0-100 (Lower values – > benefit) (MCID -11.9)												
1 (2)	randomised trials	not serious	not serious	serious [c]	very serious [e]	none	35	34	-	MD **0.1 higher** (13.46 lower to 13.66 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX monotherapy	SSZ	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events (follow up: 1 year)												
1 (2)	randomised trials	not serious	not serious	serious [c]	very serious [e]	none	0/35 (0.0%)	3/34 (8.8%)	**RR 0.14** (0.01 to 2.59)	**76 fewer per 1,000** (from 87 fewer to 140 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Withdrawal due to lack of efficacy (follow up: 1 year)												
2 (1, 2)	randomised trials	serious [a]	not serious	serious [c]	very serious [f]	none	5/104 (4.8%)	10/102 (9.8%)	**RR 0.51** (0.19 to 1.39)	**48 fewer per 1,000** (from 79 fewer to 38 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX monotherapy	SSZ	Relative (95% CI)	Absolute (95% CI)		
Withdrawal due to adverse events (follow up: 1 year)												
2 (1, 2)	randomised trials	serious [a]	not serious [g]	serious [c]	serious [h]	none	9/104 (8.7%)	19/102 (18.6%)	**RR 0.46** (0.22 to 0.98)	**101 fewer per 1,000** (from 145 fewer to 4 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. Downgraded by one level due to serious risk of bias. Lack of allocation and lack of blinding of outcome assessors of non-radiographic outcomes in the study with the higher weight,
b. I2= 41%
c. Downgraded by one level due to serious indirectness. The evidence is based on a population with moderate to high disease activity.
d. Downgraded by one level due to serious imprecision. Small sample size.
e. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm. Very small sample size.
f. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm. Small sample size and low number of events.
g. I2= 44%
h. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting no effect. Small sample size.

Comparison 3: MTX monotherapy **versus** LEF. Data based on **indirect** RCT evidence.
Overall certainty of evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX monotherapy	LEF	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 6 months; assessed with: DAS28-ESR (Lower values –> benefit) (MCID -1.17)												
1 (3)	randomised trials	very serious [a]	not serious	serious [b]	not serious	none	147	147	-	MD **0.1 lower** (0.27 lower to 0.07 higher)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Downgraded by one level due to serious risk of bias. Lack of allocation concealment and lack of blinding of patients, personnel, and outcome assessors.
b. Downgraded by one level due to serious indirectness. The evidence is based on a population with moderate to high disease activity.

Comparison 4: SSZ **versus** HCQ. Data based on **indirect** RCT evidence.
Overall certainty of evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SSZ	HCQ	Relative (95% CI)	Absolute (95% CI)		
Pain (follow up: 11 months; assessed with: VAS 0-10 (Lower values – > benefit) (MCID 0.5)												
1 (4)	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	28	29	-	MD **0.02 lower** (1.36 lower to 1.32 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Withdrawal due to lack of efficacy (follow up: 11 months)												
1 (4)	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	3/28 (10.7%)	9/29 (31.0%)	**RR 0.35** (0.10 to 1.15)	**202 fewer per 1,000** (from 279 fewer to 47 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SSZ	HCQ	Relative (95% CI)	Absolute (95% CI)		
Withdrawal due to adverse events (follow up: 11 months)												
1 (4)	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	4/28 (14.3%)	1/29 (3.4%)	**RR 4.14** (0.49 to 34.82)	**108 more per 1,000** (from 18 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. Downgraded by one level due to serious risk of bias. Lack of allocation concealment.

b. Downgraded by one level due to serious indirectness. The evidence is based on a population with moderate to high disease activity.

c. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting harm and values suggesting benefit. Small sample size.

Cost-effectiveness

No cost-effectiveness data identified.

References

1. Dougados M. Combination therapy in early rheumatoid arthritis: a randomised, controlled, double blind 52 week clinical trial of sulphasalazine and methotrexate compared with the single components. Annals of the Rheumatic Diseases. 1999;58(4):220.
2. Haagsma C, van Riel P, de Jong A, van de Putte L. Combination of sulphasalazine and methotrexate versus the single components in early rheumatoid arthritis: a randomized, controlled, double-blind, 52 week clinical trial. British Journal of Rheumatology. 1997;36(10):1082.
3. Zeb S. Comparison of short-term efficacy of leflunomide and methotrexate in active rheumatoid arthritis. Journal of Postgraduate Medical Institute. 2016;30(2):177.
4. Nuver Zwart IH, van Riel PL, van de Putte LB, Gribnau FW. A double blind comparative study of sulphasalazine and hydroxychloroquine in rheumatoid arthritis: evidence of an earlier effect of sulphasalazine. Annals of the Rheumatic Diseases. 1989;48(5):389.

PICO 1b. Should patients with MTX-naïve and non-MTX csDMARDs exposed and low disease activity receive MTX monotherapy or an alternative csDMARD monotherapy?

P - Patients with MTX-naïve and non-MTX csDMARDs exposed RA and low disease activity
I - MTX monotherapy
C - HCQ
C - SSZ
C - LEF

Comparison 1: MTX monotherapy **versus** HCQ. No eligible RCT, NRS, or indirect evidence were identified.
Comparison 2: MTX monotherapy **versus** SSZ. No eligible RCT, NRS, or indirect evidence were identified.
Comparison 3: MTX monotherapy **versus** LEF. See below Table.

Comparison 3: MTX monotherapy **versus** LEF. Data based on **indirect** RCT evidence.
Overall certainty of evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX monotherapy	LEF	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 4 months; assessed with: ACR 20)												
1 (5)	randomised trials	not serious	not serious	serious [a]	very serious [b]	none	88/180 (48.9%)	95/182 (52.2%)	**RR 0.94** (0.76 to 1.15)	**31 fewer per 1,000** (from 125 fewer to 78 more)	⨁◯◯◯ VERY LOW	CRITICAL
Disease activity (follow up: 4 months; assessed with: DAS28-ESR (Lower values – > benefit) (MCID -1.17)												
1 (6)	randomised trials	serious [c]	not serious	serious [a]	very serious [d]	none	21	19	-	MD **0.67 lower** (1.5 lower to 0.16 higher)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Downgraded by one level due to serious indirectness. The evidence is based on a population with moderate to high disease activity.
b. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm.
c. Downgraded by one level due to serious risk of bias. Lack of blinding of patients, personnel, and outcome assessors.
d. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting no effect. Small sample size.

Cost-effectiveness

No cost-effectiveness data identified.

References

1. Strand V, Cohen S, Schiff M, Weaver A, Fleischmann R, Cannon G, et al. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. Leflunomide Rheumatoid Arthritis Investigators Group. Archives of Internal Medicine. 1999;159(21):2542.

2. Fiehn C, Jacki S, Heilig B, Lampe M, Wiesmullerr G, Richter C, et al. Eight versus 16-week re-evaluation period in rheumatoid arthritis patients treated with leflunomide or methotrexate accompanied by moderate dose prednisone. Rheumatology International. 2007;27(10):975.

PICO 2a. Should patients with MTX-naïve and non-MTX csDMARDs naïve RA and moderate to high disease activity receive MTX monotherapy or an alternative csDMARD monotherapy?

P - Patients with MTX-naïve and non-MTX csDMARDs naïve RA and moderate to high disease activity
I - MTX monotherapy
C - HCQ
C - SSZ
C - LEF

Comparison 1: MTX monotherapy **versus** HCQ. No eligible RCT, NRS, or indirect evidence were identified.
Comparison 2: MTX monotherapy **versus** SSZ. See below Table.
Comparison 3: MTX monotherapy **versus** LEF. See below Table.
Comparison 4: SSZ **versus** HCQ. See below Table.

Comparison 2: MTX monotherapy **versus** SSZ. Data based on **direct** RCT evidence.
Overall certainty of evidence: Low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX monotherapy	SSZ	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 1 year; assessed with: DAS28-ESR (Lower values – > benefit) (MCID -1.17)												
2 (1, 2)	randomised trials	serious [a]	not serious [b]	not serious	serious [c]	none	104	102	-	MD **0.14 higher** (0.18 lower to 0.47 higher)	⨁⨁◯◯ LOW	CRITICAL
Disability (follow up: 1 year; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
2 (1, 2)	randomised trials	serious [a]	not serious	not serious	serious [c]	none	104	102	-	MD **0.04 lower** (0.2 lower to 0.13 higher)	⨁⨁◯◯ LOW	IMPORTANT
Pain (follow up: 1 year; assessed with: VAS 0-100 (Lower values – > benefit) (MCID -11.9)												
1 (2)	randomised trials	not serious	not serious	not serious	very serious [d]	none	35	34	-	MD **0.1 higher** (13.46 lower to 13.66 higher)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX monotherapy	SSZ	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events (follow up: 1 year)												
1 (2)	randomised trials	not serious	not serious	not serious	very serious [d]	none	0/35 (0.0%)	3/34 (8.8%)	**RR 0.14** (0.01 to 2.59)	**76 fewer per 1,000** (from 87 fewer to 140 more)	⨁⨁◯◯ LOW	IMPORTANT
Withdrawal due to lack of efficacy (follow up: 1 year)												
2 (1, 2)	randomised trials	serious [a]	not serious	not serious	very serious [e]	none	5/104 (4.8%)	10/102 (9.8%)	**RR 0.51** (0.19 to 1.39)	**48 fewer per 1,000** (from 79 fewer to 38 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX monotherapy	SSZ	Relative (95% CI)	Absolute (95% CI)		
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CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. Downgraded by one level due to serious risk of bias. Lack of allocation and lack of blinding of outcome assessors of non-radiographic outcomes in the study with the higher weight

b. I2= 41%

c. Downgraded by one level due to serious imprecision. Small sample size.

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Comparison 3: MTX monotherapy **versus** LEF. Data based on **direct** RCT evidence.
Overall certainty of evidence: Low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX monotherapy	LEF	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 6 months; assessed with: DAS28-ESR (Lower values – > benefit) (MCID -1.17)												
1 (3)	randomised trials	very serious [a]	not serious	not serious	not serious	none	147	147	-	MD **0.1 lower** (0.27 lower to 0.07 higher)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Downgraded by one level due to serious risk of bias. Lack of allocation concealment and lack of blinding of patients, personnel, and outcome assessors.

Comparison 4: SSZ **versus** HCQ. Data based on **direct** RCT evidence.
Overall certainty of evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SSZ	HCQ	Relative (95% CI)	Absolute (95% CI)		
Pain (follow up: 11 months; assessed with: VAS 0-10 (Lower values – > benefit) (MCID 0.5)												
1 (4)	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	28	29	-	MD **0.02 lower** (1.36 lower to 1.32 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Withdrawal due to lack of efficacy (follow up: 11 months)												
1 (4)	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	3/28 (10.7%)	9/29 (31.0%)	**RR 0.35** (0.10 to 1.15)	**202 fewer per 1,000** (from 279 fewer to 47 more)	⨁◯◯◯ VERY LOW	IMPORTANT

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№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SSZ	HCQ	Relative (95% CI)	Absolute (95% CI)		
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1 (4)	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	4/28 (14.3%)	1/29 (3.4%)	**RR 4.14** (0.49 to 34.82)	**108 more per 1,000** (from 18 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. Downgraded by one level due to serious risk of bias. Lack of allocation concealment.

b. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting harm and values suggesting benefit. Small sample size.

Cost-effectiveness

The economic analysis RefID 9358 (7) conducted in USA, societal perspective compared etanercept, leflunomide, MTX, sulfasalazine and no second line agent.

The study reported: I. SSZ increased the probability of achieving ACR 20 by 1 percentage point and increased total costs by $101 compared with the MTX option, resulting in an incremental CE ratio of $11,500 per patient with ACR 20 response over a 6-month period. **II.** Using the outcome of ACR 70WR, SSZ cost more but was less efficacious than MTX therapy (i.e., ruled out by simple dominance). **III.** Leflunomide was also dominated by MTX under base case assumptions.

Author's conclusion: Based on currently available data, the relative CE between SSZ and MTX cannot be determined with reasonable certainty and SSZ therapy appears to be as cost effective as MTX (cost saving compared with no second line agent) in achieving ACR outcomes over a 6-month period.

References

1. Dougados M. Combination therapy in early rheumatoid arthritis: a randomised, controlled, double blind 52 week clinical trial of sulphasalazine and methotrexate compared with the single components. Annals of the Rheumatic Diseases. 1999;58(4):220.
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5. Choi H, Seeger J, Kuntz K. A cost effectiveness analysis of treatment options for methotrexate-naive rheumatoid arthritis. Journal of Rheumatology. 2002;29(6):1156.

PICO 2b. Should patients with MTX-naïve and non-MTX csDMARDs exposed RA and moderate to high disease activity receive MTX monotherapy or an alternative csDMARD monotherapy?

P - Patients with MTX-naïve and non-MTX csDMARDs exposed RA and moderate to high disease activity
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C - SSZ
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CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. Downgraded by one level due to serious risk of bias. Lack of allocation and lack of blinding of outcome assessors of non-radiographic outcomes in the study with the higher weight

b. I2= 41%

c. Downgraded by one level due to serious indirectness. The evidence is based on a population who are non-MTX csDMARD naive.

d. Downgraded by one level due to serious imprecision. Small sample size.

e. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm. Very small sample size.

f. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm. Small sample size and low number of events.

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Comparison 3: MTX monotherapy **versus** LEF. Data based on **direct** RCT evidence.
Overall certainty of evidence: Low

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CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm.
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Comparison 4: SSZ **versus** HCQ. Data based on **indirect** RCT evidence.
Overall certainty of evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SSZ	HCQ	Relative (95% CI)	Absolute (95% CI)		
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1 (4)	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	28	29	-	MD **0.02 lower** (1.36 lower to 1.32 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Withdrawal due to lack of efficacy (follow up: 11 months)												
1 (4)	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	3/28 (10.7%)	9/29 (31.0%)	**RR 0.35** (0.10 to 1.15)	**202 fewer per 1,000** (from 279 fewer to 47 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SSZ	HCQ	Relative (95% CI)	Absolute (95% CI)		
Withdrawal due to adverse events (follow up: 11 months)												
1 (4)	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	4/28 (14.3%)	1/29 (3.4%)	**RR 4.14** (0.49 to 34.82)	**108 more per 1,000** (from 18 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. Downgraded by one level due to serious risk of bias. Lack of allocation concealment.
b. Downgraded by one level due to serious indirectness. The evidence is based on a non-MTX csDMARD-naive population.
c. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting harm and values suggesting benefit. Small sample size.

Cost-effectiveness

The economic analysis RefID 9432 (8) based on Leflunomide Rheumatoid Arthritis Investigators Group trial conducted in Canada, societal perspective compared LEF (20 mg/day) vs placebo vs MTX (up to 15 mg/week).

The study reported: I. Statistical analyses of the annualized total costs, representing the societal perspective, revealed no statistically significant differences between leflunomide and methotrexate. **II.** Analysis of direct medical costs only, representing the perspective of the Provincial Health Insurance Plan, also revealed an absence of a statistically significant difference between leflunomide and methotrexate. **III.** Leflunomide was statistically significantly more costly than methotrexate and placebo in statistical comparisons of all costs when including monitoring and drug acquisition costs ($p < 0.0001$).

Author's conclusion: leflunomide has an economic profile similar to that of methotrexate, and that the extra costs associated with its use are fixed treatment costs that, however, are higher than those of generic drugs such as methotrexate. From an economic perspective, leflunomide is positioned as an alternative once methotrexate fails, because of its equally high efficacy. But leflunomide might also be a drug of first choice, provided that drug acquisition costs are covered.

References

1. Dougados M. Combination therapy in early rheumatoid arthritis: a randomised, controlled, double blind 52 week clinical trial of sulphasalazine and methotrexate compared with the single components. Annals of the Rheumatic Diseases. 1999;58(4):220.
2. Haagsma C, van Riel P, de Jong A, van de Putte L. Combination of sulphasalazine and methotrexate versus the single components in early rheumatoid arthritis: a randomized, controlled, double-blind, 52 week clinical trial. British Journal of Rheumatology. 1997;36(10):1082.
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8. Maetzel A. Economic Comparison of Leflunomide and Methotrexate in Patients with Rheumatoid Arthritis. Pharmacoeconomics. 2002;20(1):61-70.

PICO 3a. Should patients with MTX-naïve and non-MTX csDMARDs naïve RA and low disease activity receive csDMARD monotherapy or csDMARD combination (double or triple) therapy?

P - Patients with MTX-naïve and non-MTX csDMARDs naïve RA and low disease activity
I - csDMARD monotherapy
C - csDMARD double combination therapy
C - csDMARD triple combination therapy

Comparison 1: csDMARD double combination therapy **versus** csDMARD monotherapy. See below Table.
Comparison 2: csDMARD triple combination therapy **versus** csDMARD monotherapy. See below Table.

Comparison 1: csDMARD double combination therapy **versus** csDMARD monotherapy. Data based on **indirect** RCT evidence.
Overall certainty of evidence: Low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	csDMARD double therapy	csDMARD monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 1 year; assessed with: DAS 44 (Lower values – > benefit) (MCID -1.2 based on the EULAR criteria)												
2 (1, 2)	randomised trials	serious [a]	not serious	serious [b]	not serious	none	104 [c]	206 [d]	-	MD 0.3 lower (0.57 lower to 0.02 lower)	⨁⨁◯◯ LOW	CRITICAL
Disability (follow up: 1 year; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
2 (1, 2)	randomised trials	serious [a]	not serious	serious [b]	not serious	none	104 [c]	206 [d]	-	MD 0.01 lower (0.16 lower to 0.14 higher)	⨁⨁◯◯ LOW	IMPORTANT
Pain (follow up: 1 year; assessed with: VAS 0-100 (Lower values – > benefit) (MCID -11.9)												
1 (2)	randomised trials	serious [e]	not serious	serious [b]	serious [f]	none	36 [c]	69 [d]	-	MD 0.05 higher (10.89 lower to 10.99 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	csDMARD double therapy	csDMARD monotherapy	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events (follow up: 1 year)												
1 (2)	randomised trials	serious [e]	not serious	serious [b]	very serious [g]	none	0/36 (0.0%) [c]	3/69 (4.3%) [d]	**RR 0.27** (0.01 to 5.09)	**32 fewer per 1,000** (from 43 fewer to 178 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Withdrawal due to lack of efficacy (follow up: 1 year)												
2 (1, 2)	randomised trials	serious [a]	not serious	serious [b]	very serious [g]	none	4/104 (3.8%) [c]	15/206 (7.3%) [d]	**RR 0.53** (0.18 to 1.56)	**34 fewer per 1,000** (from 60 fewer to 41 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	csDMARD double therapy	csDMARD monotherapy	Relative (95% CI)	Absolute (95% CI)		
Withdrawal due to adverse events (follow up: 1 year)												
2 (1, 2)	randomised trials	serious [a]	not serious	serious [b]	very serious [g]	none	14/104 (13.5%) [c]	28/206 (13.6%) [d]	**RR 0.99** (0.54 to 1.79)	**1 fewer per 1,000** (from 63 fewer to 107 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. Downgraded by one level due to serious risk of bias. Lack of allocation concealment in both studies, high risk of attrition bias in one of the two studies.
b. Downgraded by one level due to serious indirectness. The evidence is based on a population with moderate to high disease activity.
c. csDMARD double therapy includes: MTZ+SSZ
d. csDMARD monotherapy includes: MTX or SSZ
e. Downgraded by one level due to serious risk of bias. Lack of allocation concealment.
f. Downgraded by one level due to serious imprecision. Low sample size.
g. Downgraded by two levels due to very serious imprecision. Confidence intervals includes both values suggesting benefit and values suggesting harm. Small sample size, very low number of events.

Comparison 2: csDMARD triple combination therapy vs csDMARD monotherapy. Data based on **direct** RCT evidence.
Overall certainty of evidence: Low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	csDMARD triple therapy	csDMARD monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 3 months; assessed with: DAS 44 (Lower values --> benefit)												
1 (3)	randomised trials	not serious	not serious	not serious	serious [a]	none	89 [b]	90 [c]	-	MD **0.35 lower** (0.64 lower to 0.06 lower)	⨁⨁⨁◯ MODERATE	CRITICAL
Remission (follow up: 3 months; assessed with: DAS 44 <1.6)												
1 (3)	randomised trials	not serious	not serious	not serious	very serious [d]	none	38/89 (42.7%) [b]	28/90 (31.1%) [c]	**RR 1.37** (0.93 to 2.03)	**115 more per 1,000** (from 22 fewer to 320 more)	⨁⨁◯◯ LOW	CRITICAL
Disability (follow up: 3 months; assessed with: HAQ-DI (Lower values --> benefit) (MCID -0.22)												
1 (3)	randomised trials	not serious	not serious	not serious	serious [e]	none	78 [b]	78 [c]	-	MD **0.03 lower** (0.2 lower to 0.14 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	csDMARD triple therapy	csDMARD monotherapy	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events (follow up: 3 months)												
1 (3)	randomised trials	not serious	not serious	not serious	very serious [d]	none	4/89 (4.5%) [b]	6/90 (6.7%) [c]	**RR 0.67** (0.20 to 2.31)	**22 fewer per 1,000** (from 53 fewer to 87 more)	⨁⨁◯◯ LOW	IMPORTANT
Withdrawal due to Adverse events (follow up: 3 months)												
1 (3)	randomised trials	not serious	not serious	not serious	very serious [d]	none	0/93 (0.0%) [b]	3/97 (3.1%) [c]	**RR 0.15** (0.01 to 2.84)	**26 fewer per 1,000** (from 31 fewer to 57 more)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. Downgraded by one level due to serous imprecision. Small sample size.
b. csDMARD triple therapy includes: MTX+SSZ+HCQ
c. csDMARD monotherapy includes: MTX
d. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm. Small sample size.
e. Downgraded by one level due to serious imprecision. Small sample size.

Cost-effectiveness

The economic analysis RefID 1942 (4) based on tREACH trial conducted in 8 rheumatology centers, Netherlands compared (A) initial triple DMARD therapy (iTDT) with glucocorticoids (GCs) intramuscular (n = 91); (B) iTDT with an oral GC tapering scheme (n = 93); and (C) initial MTX monotherapy (iMM) with GCs similar to B (n = 97).

The study reported: I. direct as well as indirect costs were higher with iMM (strategy C) compared with iTDT (strategy B). **II.** iTDT was>95% cost-effective across all willingness to-pay thresholds compared with iMM.

Author's conclusion: iTDT (B) was more cost-effective and had better worker productivity compared with iMM.

References

1. Dougados M. Combination therapy in early rheumatoid arthritis: a randomised, controlled, double blind 52 week clinical trial of sulphasalazine and methotrexate compared with the single components. Annals of the Rheumatic Diseases. 1999;58(4):220.
2. Haagsma C, van Riel P, de Jong A, van de Putte L. Combination of sulphasalazine and methotrexate versus the single components in early rheumatoid arthritis: a randomized, controlled, double-blind, 52 week clinical trial. British Journal of Rheumatology. 1997;36(10):1082.
3. de Jong PHP, Hazes JM, Barendregt PJ, Huisman M, van Zeben D, van der Lubbe PA, et al. Induction therapy with a combination of DMARDs is better than methotrexate monotherapy: first results of the tREACH trial. Annals of the Rheumatic Diseases. 2013;72(1):72.
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PICO 3b. Should patients with MTX-naïve and non-MTX csDMARDs exposed RA and low disease activity receive csDMARD monotherapy or csDMARD combination (double or triple) therapy?

P - Patients with MTX-naïve and non-MTX csDMARDs exposed RA and low disease activity
I - csDMARD monotherapy
C - csDMARD double combination therapy
C - csDMARD triple combination therapy

Comparison 1: csDMARD double combination therapy **versus** csDMARD monotherapy. No eligible RCT, NRS, or indirect evidence were identified.
Comparison 2: csDMARD triple combination therapy **versus** csDMARD monotherapy. See below Table.

Comparison 2: csDMARD triple combination therapy **versus** csDMARD monotherapy. Data based on **indirect** RCT evidence.
Overall certainty of evidence: Moderate

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	csDMARD triple therapy	csDMARD monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 6 months; assessed with: DAS 28-ESR (Lower values – > benefit) (MCID -1.17)												
1 (1)	randomised trials	not serious	not serious	serious [a]	not serious	none	132	379	-	MD **0.64 lower** (0.95 lower to 0.33 lower)	⨁⨁⨁◯ MODERATE	CRITICAL
Disease activity (follow up: 6 months; assessed with: ACR 20)												
1 (1)	randomised trials	not serious	not serious	serious [a]	not serious	none	73/132 (55.3%) [b]	150/379 (39.6%) [c]	**RR 1.40** (1.15 to 1.70)	**158 more per 1,000** (from 59 more to 277 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Disease activity (follow up: 6 months; assessed with: ACR 50)												
1 (1)	randomised trials	not serious	not serious	serious [a]	not serious	none	41/132 (31.1%) [b]	73/379 (19.3%) [c]	**RR 1.61** (1.16 to 2.24)	**117 more per 1,000** (from 31 more to 239 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	csDMARD triple therapy	csDMARD monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 6 months; assessed with: ACR 70)												
1 (1)	randomised trials	not serious	not serious	serious [a]	serious [d]	none	11/132 (8.3%) [b]	13/379 (3.4%) [c]	**RR 2.43** (1.12 to 5.29)	**49 more per 1,000** (from 4 more to 147 more)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. Downgraded by one level due to serious indirecteness. The population has moderate disease activity.
b. csDMARD triple therapy includes MTX + SSZ + HCQ.
c. csDMARD monotherapy includes MTX.
d. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting harm. Low number of events.

Cost-effectiveness

No cost-effectiveness data identified.

References

1. Moreland LW, Zhang J. A randomized comparative effectiveness study of oral triple therapy versus etanercept plus methotrexate in early aggressive rheumatoid arthritis: The treatment of early aggressive rheumatoid arthritis trial. Arthritis and Rheumatism. 2012;64(9):2824.

PICO 4a. Should patients with MTX-naïve and non-MTX csDMARDs naïve RA and moderate to high disease activity receive csDMARD monotherapy or combination (double or triple) therapy?

P - Patients with MTX-naïve and non-MTX csDMARDs naïve RA who have moderate to high disease activity
I - csDMARD monotherapy
C - csDMARD double combination therapy
C - csDMARD triple combination therapy

Comparison 1: csDMARD double combination therapy vs csDMARD monotherapy. See below Table.
Comparison 2: csDMARD triple combination therapy vs csDMARD monotherapy. See below Table.

Comparison 1: csDMARD double combination therapy **versus** csDMARD monotherapy. Data based on **direct** RCT evidence.
Overall certainty of evidence: Moderate

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	csDMARD double therapy	csDMARD monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 1 year; assessed with: DAS 44 (Lower values – > benefit) (MCID -1.2 based on the EULAR criteria)												
2 (1, 2)	randomised trials	serious [a]	not serious	not serious	not serious	none	104 [b]	206 [c]	-	MD **0.3 lower** (0.57 lower to 0.02 lower)	⨁⨁⨁◯ MODERATE	CRITICAL
Disability (follow up: 1 year; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
2 (1, 2)	randomised trials	serious [a]	not serious	not serious	not serious	none	104 [b]	206 [c]	-	MD **0.01 lower** (0.16 lower to 0.14 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Pain (follow up: 1 year; assessed with: VAS 0-100 (Lower values – > benefit) (MCID -11.9)												
1 (2)	randomised trials	serious [d]	not serious	not serious	serious [e]	none	36 [b]	69 [c]	-	MD **0.05 higher** (10.89 lower to 10.99 higher)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	csDMARD double therapy	csDMARD monotherapy	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events (follow up: 1 year)												
1 (2)	randomised trials	serious [d]	not serious	not serious	very serious [f]	none	0/36 (0.0%) [b]	3/69 (4.3%) [c]	**RR 0.27** (0.01 to 5.09)	**32 fewer per 1,000** (from 43 fewer to 178 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Withdrawal due to lack of efficacy (follow up: 1 year)												
2 (1, 2)	randomised trials	serious [a]	not serious	not serious	very serious [f]	none	4/104 (3.8%) [b]	15/206 (7.3%) [c]	**RR 0.53** (0.18 to 1.56)	**34 fewer per 1,000** (from 60 fewer to 41 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	csDMARD double therapy	csDMARD monotherapy	Relative (95% CI)	Absolute (95% CI)		
Withdrawal due to Adverse events (follow up: 1 year)												
2 (1, 2)	randomised trials	serious [a]	not serious	not serious	very serious [f]	none	14/104 (13.5%) [b]	28/206 (13.6%) [c]	**RR 0.99** (0.54 to 1.79)	**1 fewer per 1,000** (from 63 fewer to 107 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. Downgraded by one level due to serious risk of bias. Lack of allocation concealment in both studies, high risk of attrition bias in one of the two studies.
b. csDMARD double therapy includes: MTZ+SSZ
c. csDMARD monotherapy includes: MTX or SSZ
d. Downgraded by one level due to serious risk of bias. Lack of allocation concealment.
e. Downgraded by one level due to serious imprecision. Low sample size.
f. Downgraded by two levels due to very serious imprecision. Confidence intervals includes both values suggesting benefit and values suggesting harm. Small sample size, very low number of events.

Comparison 2: csDMARD triple combination therapy vs csDMARD monotherapy. Data based on **direct** RCT evidence.
Overall certainty of evidence: Moderate

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	csDMARD triple therapy	csDMARD monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 3 months; assessed with: DAS 44 (Lower values – > benefit) (MCID -1.2)												
1 (3)	randomised trials	not serious	not serious	not serious	serious [a]	none	89 [b]	90 [c]	-	MD **0.35 lower** (0.64 lower to 0.06 lower)	⨁⨁⨁◯ MODERATE	CRITICAL
Remission (follow up: 3 months; assessed with: DAS 44 < 1.6)												
1 (3)	randomised trials	not serious	not serious	not serious	serious [d]	none	38/89 (42.7%) [b]	28/90 (31.1%) [c]	**RR 1.37** (0.93 to 2.03)	**115 more per 1,000** (from 22 fewer to 320 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Disability (follow up: 3 months; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
1 (3)	randomised trials	not serious	not serious	not serious	serious [a]	none	89 [b]	90 [c]	-	MD **0.03 lower** (0.19 lower to 0.13 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	csDMARD triple therapy	csDMARD monotherapy	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events (follow up: 3 months)												
1 (3)	randomised trials	not serious	not serious	not serious	very serious [e]	none	4/89 (4.5%) [b]	6/90 (6.7%) [c]	**RR 0.67** (0.20 to 2.31)	**22 fewer per 1,000** (from 53 fewer to 87 more)	⨁⨁◯◯ LOW	IMPORTANT
Withdrawal due to adverse events (follow up: 3 months)												
1 (3)	randomised trials	not serious	not serious	not serious	very serious [e]	none	0/93 (0.0%) [b]	3/97 (3.1%) [c]	**RR 0.15** (0.01 to 2.84)	**26 fewer per 1,000** (from 31 fewer to 57 more)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. Downgraded by one level due to serious imprecision. Small sample size.
b. csDMARD triple therapy includes: MTX+SSZ+HCQ
c. csDMARD monotherapy includes: MTX
d. Downgraded by one level due to serious imprecision. Confidence interval includes both values of no effect and benefit. Small sample size.
e. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm. Small sample size.

Cost-effectiveness

The economic analysis RefID 1942 (4) based on tREACH trial conducted in 8 rheumatology centers, Netherlands compared (A) initial triple DMARD therapy (iTDT) with glucocorticoids (GCs) intramuscular; (B) iTDT with an oral GC tapering scheme; and (C) initial MTX monotherapy (iMM) with GCs similar to B.

The study reported: I. direct as well as indirect costs were higher with iMM (strategy C) compared with iTDT (strategy B). **II.** iTDT was>95% cost-effective across all willingness to-pay thresholds compared with iMM.

Author's conclusion: iTDT (B) was more cost-effective and had better worker productivity compared with iMM.

References

1. Dougados M. Combination therapy in early rheumatoid arthritis: a randomised, controlled, double blind 52 week clinical trial of sulphasalazine and methotrexate compared with the single components. Annals of the Rheumatic Diseases. 1999;58(4):220.
2. Haagsma C, van Riel P, de Jong A, van de Putte L. Combination of sulphasalazine and methotrexate versus the single components in early rheumatoid arthritis: a randomized, controlled, double-blind, 52 week clinical trial. British Journal of Rheumatology. 1997;36(10):1082.
3. de Jong PHP. Induction therapy with a combination of DMARDs is better than methotrexate monotherapy: First results of the tREACH trial. Annals of the Rheumatic Diseases. 2013;72(1):72.
4. de Jong PHP, Hazes JM, Buisman LR, Barendregt PJ, van Zeben D, van der Lubbe PA, et al. Best cost-effectiveness and worker productivity with initial triple DMARD therapy compared with methotrexate monotherapy in early rheumatoid arthritis: cost-utility analysis of the tREACH trial. Rheumatology. 2016;55(12):2138.

PICO 4b. Should patients with MTX-naïve and non-MTX csDMARDs exposed RA and moderate to high disease activity receive csDMARD monotherapy or combination (double or triple) therapy?

P - Patients with MTX-naïve and non-MTX csDMARDs exposed RA who have moderate to high disease activity
I - csDMARD monotherapy
C - csDMARD double combination therapy
C - csDMARD triple combination therapy

Comparison 1: csDMARD double combination therapy **versus** csDMARD monotherapy. See below Table.
Comparison 2: csDMARD triple combination therapy **versus** csDMARD monotherapy. See below Table.

Comparison 1: csDMARD double combination therapy **versus** csDMARD monotherapy. Data based on **indirect** RCT evidence.
Overall certainty of evidence: Low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	csDMARD double therapy	csDMARD monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 1 year; assessed with: DAS 44 (Lower values – > benefit) (MCID -1.2 based on the EULAR criteria)												
2 (1, 2)	randomised trials	serious [a]	not serious	serious [b]	not serious	none	104 [c]	206 [d]	-	MD **0.3 lower** (0.57 lower to 0.02 lower)	⨁⨁◯◯ LOW	CRITICAL
Disability (follow up: 1 year; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
2 (1, 2)	randomised trials	serious [a]	not serious	serious [b]	not serious	none	104 [c]	206 [d]	-	MD **0.01 lower** (0.16 lower to 0.14 higher)	⨁⨁◯◯ LOW	IMPORTANT
Pain (follow up: 1 year; assessed with: VAS 0-100 (Lower values – > benefit) (MCID -11.9)												
1 (2)	randomised trials	serious [e]	not serious	serious [b]	serious [f]	none	36 [c]	69 [d]	-	MD **0.05 higher** (10.89 lower to 10.99 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	csDMARD double therapy	csDMARD monotherapy	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events (follow up: 1 year)												
1 (2)	randomised trials	serious [e]	not serious	serious [b]	very serious [g]	none	0/36 (0.0%) [c]	3/69 (4.3%) [d]	**RR 0.27** (0.01 to 5.09)	**32 fewer per 1,000** (from 43 fewer to 178 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Withdrawal due to lack of efficacy (follow up: 1 year)												
2 (1, 2)	randomised trials	serious [a]	not serious	serious [b]	very serious [g]	none	4/104 (3.8%) [c]	15/206 (7.3%) [d]	**RR 0.53** (0.18 to 1.56)	**34 fewer per 1,000** (from 60 fewer to 41 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	csDMARD double therapy	csDMARD monotherapy	Relative (95% CI)	Absolute (95% CI)		
Withdrawal due to adverse events (follow up: 1 year)												
2 (1, 2)	randomised trials	serious [a]	not serious	serious [b]	very serious [g]	none	14/104 (13.5%) [c]	28/206 (13.6%) [d]	**RR 0.99** (0.54 to 1.79)	**1 fewer per 1,000** (from 63 fewer to 107 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. Downgraded by one level due to serious risk of bias. Lack of allocation concealment in both studies, high risk of attrition bias in one of the two studies.
b. Downgraded by one level due to serious indirectness. The evidence is based on a population who are non-MTX csDMARD naive.
c. csDMARD double therapy includes: MTZ+SSZ
d. csDMARD monotherapy includes: MTX or SSZ
e. Downgraded by one level due to serious risk of bias. Lack of allocation concealment.
f. Downgraded by one level due to serious imprecision. Low sample size.
g. Downgraded by two levels due to very serious imprecision. Confidence intervals includes both values suggesting benefit and values suggesting harm. Small sample size, very low number of events.

Comparison 2: csDMARD triple combination therapy **versus** csDMARD monotherapy. Data based on **direct** RCT evidence.
Overall certainty of evidence: High

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	csDMARD triple therapy	csDMARD monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 6 months; assessed with: DAS 28-ESR (Lower values – > benefit) (MCID -1.17)												
1 (3)	randomised trials	not serious	not serious	not serious	not serious	none	132 [a]	379 [b]	-	MD **0.64 lower** (0.95 lower to 0.33 lower)	⨁⨁⨁⨁ HIGH	CRITICAL
Disease activity (follow up: 6 months; assessed with: ACR 20)												
1 (3)	randomised trials	not serious	not serious	not serious	not serious	none	73/132 (55.3%) [a]	150/379 (39.6%) [b]	**RR 1.40** (1.15 to 1.70)	**158 more per 1,000** (from 59 more to 277 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Disease activity (follow up: 6 months; assessed with: ACR 50)												
1 (3)	randomised trials	not serious	not serious	not serious	not serious	none	41/132 (31.1%) [a]	73/379 (19.3%) [b]	**RR 1.61** (1.16 to 2.24)	**117 more per 1,000** (from 31 more to 239 more)	⨁⨁⨁⨁ HIGH	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	csDMARD triple therapy	csDMARD monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 6 months; assessed with: ACR 70)												
1 (3)	randomised trials	not serious	not serious	not serious	serious [c]	none	11/132 (8.3%) [a]	13/379 (3.4%) [b]	**RR 2.43** (1.12 to 5.29)	**49 more per 1,000** (from 4 more to 147 more)	⨁⨁⨁◯ MODERATE	CRITICAL

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. csDMARD triple therapy includes MTX + SSZ + HCQ.
b. csDMARD monotherapy includes MTX.
c. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting harm. Low number of events.

Cost-effectiveness

No cost-effectiveness data identified.

References

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2. Haagsma C. Combination of sulphasalazine and methotrexate versus the single components in early rheumatoid arthritis: a randomized, controlled, double-blind, 52 week clinical trial. British Journal of Rheumatology. 1997;36(10):1082.
3. Moreland LW, Zhang J. A randomized comparative effectiveness study of oral triple therapy versus etanercept plus methotrexate in early aggressive rheumatoid arthritis: The treatment of early aggressive rheumatoid arthritis trial. Arthritis and Rheumatism. 2012;64(9):2824.

PICO 5a. Should patients with MTX-naïve and non-MTX csDMARDs naïve RA and moderate to high disease activity receive MTX monotherapy or boDMARD monotherapy or tsDMARD monotherapy?

P - Patients with MTX-naïve and non-MTX csDMARDs naïve RA and moderate to high disease activity
I - MTX monotherapy
C - TNF Inhibitor
C - Abatacept
C - Rituximab
C - IL-6 Receptor Inhibitor
C - JAK Inhibitor

Comparison 1: TNF Inhibitor **versus** MTX monotherapy. See below Table.
Comparison 2: Abatacept **versus** MTX monotherapy. See below Table.
Comparison 3: Rituximab **versus** MTX monotherapy. No eligible RCT, NRS, or indirect evidence were identified.
Comparison 4: IL-6 Receptor Inhibitor **versus** MTX monotherapy. See below Table.
Comparison 5: JAK Inhibitor **versus** MTX monotherapy. See below Table.

Comparison 1: TNF Inhibitor **versus** MTX monotherapy. Data based on **indirect** RCT evidence.
Overall certainty of evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNF inhibitor	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 2 years; assessed with: ACR 20)												
2 (1, 2)	randomised trials	serious [a]	serious [b]	serious [c]	very serious [d]	none	207/467 (44.3%) [e]	205/459 (44.7%)	**RR 0.99** (0.86 to 1.15)	**4 fewer per 1,000** (from 63 fewer to 67 more)	⨁◯◯◯ VERY LOW	CRITICAL
Disease activity (follow up: 2 years; assessed with: ACR 50)												
2 (1, 2)	randomised trials	serious [a]	serious [f]	serious [c]	very serious [d]	none	188/451 (41.7%) [e]	182/426 (42.7%)	**RR 0.98** (0.84 to 1.14)	**9 fewer per 1,000** (from 68 fewer to 60 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNF inhibitor	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 2 years; assessed with: ACR 70)												
2 (1, 2)	randomised trials	serious [a]	not serious	serious [c]	very serious [d]	none	128/451 (28.4%) [e]	113/426 (26.5%)	**RR 1.07** (0.86 to 1.33)	**19 more per 1,000** (from 37 fewer to 88 more)	⨁◯◯◯ VERY LOW	CRITICAL
Remission (follow up: 2 years; assessed with: DAS28-ESR <2.6)												
1 (2)	randomised trials	serious [a]	not serious	serious [c]	very serious [d]	none	69/274 (25.2%) [e]	64/257 (24.9%)	**RR 1.01** (0.75 to 1.36)	**2 more per 1,000** (from 62 fewer to 90 more)	⨁◯◯◯ VERY LOW	CRITICAL
Radiographic progression (follow up: 2 years; assessed with: mTSS (Lower values – > benefit) (MCID 4.6)												
1 (1)	randomised trials	serious [a]	not serious	serious [c]	not serious	none	177 [e]	169	-	MD **1.9 lower** (3.19 lower to 0.61 lower) [g]	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNF inhibitor	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disability (follow up: range 1 year to 2 years; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
2 (2, 3)	randomised trials	serious [a]	not serious	serious [c]	not serious	none	481 [e]	474	-	MD **0.01 higher** (0.07 lower to 0.1 higher) [h]	⨁⨁◯◯ LOW	IMPORTANT
Fatigue (follow up: 2 years; assessed with: FACIT-F (Higher values – > benefit) (MCID 15.9)												
1 (4)	randomised trials	serious [a]	not serious	serious [c]	not serious	none	272 [e]	254	-	MD **1.7 lower** (3.09 lower to 0.31 lower)	⨁⨁◯◯ LOW	IMPORTANT
Pain (follow up: 2 years; assessed with: VAS 0-100 (Lower values – > benefit) (MCID -11.9)												
1 (5)	randomised trials	serious [a]	not serious	serious [c]	not serious	none	273 [e]	256	-	MD **7.1 higher** (4.34 higher to 9.86 higher)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNF inhibitor	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Quality of life (follow up: range 1 year to 2 years; assessed with: SF-36 PCS (Higher values – > benefit) (MCID 4.4)												
2 (3, 5)	randomised trials	serious [a]	serious [i]	serious [c]	not serious	none	471	464	-	MD **0.56 lower** (1.73 lower to 0.6 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Quality of life (follow up: range 1 year to 2 years; assessed with: SF-36 MCS (Higher values – > benefit) (MCID 3.1)												
2 (3, 5)	randomised trials	serious [a]	not serious [j]	serious [c]	serious [k]	none	471	464	-	MD **1.98 lower** (3.18 lower to 0.78 lower)	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events (follow up: 2 years)												
1 (2)	randomised trials	serious [a]	not serious	serious [c]	serious [k]	none	92/274 (33.6%) [e]	68/257 (26.5%)	**RR 1.27** (0.98 to 1.65)	**71 more per 1,000** (from 5 fewer to 172 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNF inhibitor	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Withdrawal due to lack of efficacy (2 years)												
2 (1, 2)	randomised trials	serious [a]	not serious	serious [c]	very serious [d]	none	68/481 (14.1%) [e]	69/474 (14.6%)	**RR 0.95** (0.70 to 1.30)	**7 fewer per 1,000** (from 44 fewer to 44 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Withdrawal due to adverse events (follow up: 2 years)												
2 (1, 2)	randomised trials	serious [a]	serious [l]	serious [c]	very serious [d]	none	41/481 (8.5%) [e]	46/474 (9.7%)	**RR 0.88** (0.59 to 1.32)	**12 fewer per 1,000** (from 40 fewer to 31 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Death (follow up: 2 years)												
1 (2)	randomised trials	serious [a]	not serious	serious [c]	serious [m]	none	4/274 (1.5%) [e]	1/257 (0.4%)	**RR 3.75** (0.42 to 33.35)	**11 more per 1,000** (from 2 fewer to 126 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNF inhibitor	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Malignancy (follow up: 2 years)												
2 (1, 2)	randomised trials	serious [a]	not serious	serious [c]	serious [m]	none	8/481 (1.7%) [e]	7/474 (1.5%)	**RR 1.13** (0.41 to 3.08)	**2 more per 1,000** (from 9 fewer to 31 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Malignancy (from SRs on harms)												
0 (6)							The systematic review RefID=3394, 2014 (RCTs=28, n=11741) comparing any TNFi vs placebo + MTX among RA showed that for cancer, the result was OR=1.30 (95% CI 0.80,2.14 Modified ITT model) [OR=1.06 (95% CI 0.64,1.75; p=0.82) Per protocol model]				-	
Cardiovascular disease (from SRs on harms)												
0 (7)							The systematic review RefID=1105, 2017 (NRS=7, n=49003) comparing any TNFi vs csDMARDs among RA showed that for Cardiovascular disease, the result was RR = 0.62 (95% CI 0.44–0.88), p=0.007				-	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNF inhibitor	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Death (from SRs on harms)												
0 (7)							The systematic review RefID=1105, 2017 (NRS=5, n=41579) comparing any TNFi vs csDMARD among RA showed that for Death, the result was RR = 0.60 (95% CI 0.38–0.94), p=0.03				-	

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Downgraded by one level due to serious risk of bias. Lack of allocation concealment.
b. Downgraded by one level due to serious inconsistency. Unexplained heterogeneity I2=65%.
c. Downgraded by one level due to serious indirectness. The evidence is based on a non-MTX csDMARD exposed population.
d. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm.
e. TNFi includes ETN or ADA.
f. Downgraded by one level due to serious inconsistency. Unexplained heterogeneity I2=75%.
g. The study PREMIER found that the RR of developing no radiographic progression (change in mTSS ≤0.5) was 1.33 (95%CI 1.07 to 1.65), absolute risk increase 112 more per 1000 (95%CI 24 more to 220 more).
h. The study PREMIER found that the RR of improvement in HAQ-DI (≥0.22 change from baseline) was 0.92 (95%CI 0.80 to 1.06), absolute risk reduction 50 fewer per 1000 (95%CI 126 fewer to 38 more).
i. Downgraded by one level due to serious inconsistency. I2=67%. Question whether heterogeneity might be related to the use of different TNFis.
j. Indication of serious inconsistency I2=59% (taken into consideration when downgrading for imprecision). Question whether heterogeneity might be related to the use of different TNFis.
k. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting harm.
l. Downgraded by one level due to serious inconsistency. Unexplained heterogeneity I2=72%.
m. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting harm. Low number of events.

Comparison 2: Abatacept **versus** MTX monotherapy. Data based on **direct** RCT evidence.
Overall certainty of evidence: Low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ABA	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Remission (follow up: 1 year; assessed with: DAS28-CRP < 2.6)												
1 (8)	randomised trials	not serious	not serious	not serious	very serious [a]	none	48/113 (42.5%)	52/115 (45.2%)	**RR 0.94** (0.70 to 1.26)	**27 fewer per 1,000** (from 136 fewer to 118 more)	⨁⨁◯◯ LOW	CRITICAL
Disability (follow up: 1 year; assessed with: HAQ-DI ≥ 0.3)												
1 (8)	randomised trials	not serious	not serious	not serious	very serious [a]	none	61/113 (54.0%)	51/115 (44.3%)	**RR 1.22** (0.93 to 1.59)	**98 more per 1,000** (from 31 fewer to 262 more)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ABA	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events (1 year)												
1 (8)	randomised trials	not serious	not serious	not serious	very serious [a]	none	14/116 (12.1%)	9/116 (7.8%)	**RR 1.56** (0.70 to 3.45)	**43 more per 1,000** (from 23 fewer to 190 more)	⨁⨁◯◯ LOW	IMPORTANT
Withdrawal due to adverse events (follow up: 1 year)												
1 (8)	randomised trials	not serious	not serious	not serious	very serious [a]	none	8/116 (6.9%)	5/116 (4.3%)	**RR 1.60** (0.54 to 4.75)	**26 more per 1,000** (from 20 fewer to 162 more)	⨁⨁◯◯ LOW	IMPORTANT
Withdrawal due to lack of efficacy (follow up: 1 year)												
1 (8)	randomised trials	not serious	not serious	not serious	very serious [a]	none	6/116 (5.2%)	11/116 (9.5%)	**RR 0.55** (0.21 to 1.43)	**43 fewer per 1,000** (from 75 fewer to 41 more)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ABA	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Death (follow up: 1 year)												
1 (8)	randomised trials	not serious	not serious	not serious	very serious [b]	none	0/116 (0.0%)	0/116 (0.0%)	not estimable		⨁⨁◯◯ LOW	IMPORTANT
Malignancy (follow up: 1 year)												
1 (8)	randomised trials	not serious	not serious	not serious	very serious [b]	none	2/116 (1.7%)	1/116 (0.9%)	**RR 2.00** (0.18 to 21.75)	**9 more per 1,000** (from 7 fewer to 179 more)	⨁⨁◯◯ LOW	IMPORTANT
Malignancy (from SR of harms) ABA vs MTX												
0 (9)							The Systematic Review RefID=1220, 2017 (RCTs=4, n=Not provided) comparing Abatacept vs Placebo + csDMARD among RA and showed that for Cancer, the result was Peto OR=1.12 (0.33, 3.81)				-	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm. Small sample size.
b. Downgraded by two levels due to very serious imprecision. Small sample size and very low number of events.

Comparison 4: IL-6 Receptor Inhibitor **versus** MTX monotherapy. Data based on **indirect** RCT evidence.
Overall certainty of evidence: Low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-6i	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 1 year; assessed with: ACR 20)												
1 (4)	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	184/292 (63.0%) [d]	164/287 (57.1%)	**RR 1.10** (0.97 to 1.26)	**57 more per 1,000** (from 17 fewer to 149 more)	⨁◯◯◯ VERY LOW	CRITICAL
Disease activity (follow up: 1 year; assessed with: ACR 50)												
1 (4)	randomised trials	serious [a]	not serious	serious [b]	not serious	none	145/292 (49.7%) [d]	117/287 (40.8%)	**RR 1.22** (1.02 to 1.46)	**90 more per 1,000** (from 8 more to 188 more)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-6i	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 1 year; assessed with: ACR 70)												
1 (4)	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	107/292 (36.6%) [d]	84/287 (29.3%)	**RR 1.25** (0.99 to 1.58)	**73 more per 1,000** (from 3 fewer to 170 more)	⨁◯◯◯ VERY LOW	CRITICAL
Disease activity (follow up: 1 year; assessed with: DAS28-ESR (Lower values –> benefit) (MCID -1.17)												
1 (4)	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	292 [d]	287	-	MD **0.96 lower** (1.24 lower to 0.68 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Remission (follow up: 1 year; assessed with: DAS28-ESR <2.6)												
1 (4)	randomised trials	serious [a]	not serious	serious [b]	not serious	none	115/292 (39.4%) [d]	56/287 (19.5%)	**RR 2.02** (1.53 to 2.66)	**199 more per 1,000** (from 103 more to 324 more)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-6i	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Radiographic progression (follow up: 1 year; assessed with: mTSS (Lower values –> benefit) (MCID 4.6)												
1 (4)	randomised trials	serious [a]	not serious	serious [b]	not serious	none	275 [d]	267	-	MD **0.88 lower** (1.44 lower to 0.32 lower)	⨁⨁◯◯ LOW	IMPORTANT
Disability (follow up: 1 year; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
1 (4)	randomised trials	serious [a]	not serious	serious [b]	not serious	none	0 [d]	0	-	MD **0.03 lower** (0.15 lower to 0.09 higher)	⨁⨁◯◯ LOW	IMPORTANT
Quality of life (follow up: 1 year; assessed with: SF-36 PCS (Higher values – > benefit) (MCID 4.4)												
1 (4)	randomised trials	serious [a]	not serious	serious [b]	not serious	none	0 [d]	0	-	MD **0.14 higher** (0.13 lower to 0.41 higher)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-6i	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Quality of life (1 year) (follow up: 1 year; assessed with: SF-36 MCS (Higher values – > benefit) (MCID 3.1)												
1 (4)	randomised trials	serious [a]	not serious	serious [b]	not serious	none	0 [d]	0	-	MD **0.34 higher** (0.68 lower to 1.36 higher)	⨁⨁◯◯ LOW	IMPORTANT
Serious adverse events (follow up: 1 year)												
1 (4)	randomised trials	serious [a]	not serious	serious [b]	very serious [e]	none	25/292 (8.6%) [d]	24/282 (8.5%)	**RR 1.01** (0.59 to 1.72)	**1 more per 1,000** (from 35 fewer to 61 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Withdrawal due to lack of efficacy (follow up: 1 year)												
1 (4)	randomised trials	serious [a]	not serious	serious [b]	serious [f]	none	34/292 (11.6%) [d]	21/282 (7.4%)	**RR 1.56** (0.93 to 2.63)	**42 more per 1,000** (from 5 fewer to 121 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-6i	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Death (follow up: 1 year)												
1 (4)	randomised trials	serious [a]	not serious	serious [b]	very serious [e]	none	1/292 (0.3%) [d]	2/282 (0.7%)	**RR 0.48** (0.04 to 5.30)	**4 fewer per 1,000** (from 7 fewer to 30 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Malignancy (follow up: 1 year)												
1 (4)	randomised trials	serious [a]	not serious	serious [b]	very serious [e]	none	2/292 (0.7%) [d]	3/282 (1.1%)	**RR 0.64** (0.11 to 3.82)	**4 fewer per 1,000** (from 9 fewer to 30 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Myocardial infarction (follow up: 1 year)												
1 (4)	randomised trials	serious [a]	not serious	serious [b]	serious [g]	none	1/292 (0.3%) [d]	0/282 (0.0%)	**RR 2.90** (0.12 to 70.83)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-6i	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Malignancy (from SRs of harms)												
0 (10)							The Systematic Review RefID=4638, 2012 (RCTs=1, n=302) comparing IL-6 Receptor Inhibitors vs Placebo + MTX among RA showed that for Cancer, the result was RR=6.5 (0.34-124.2) at 1 year and RR=0.33 (0.01-8.0) at 6 months (RCTs=2, n=697 at 6 months)				-	
Serious adverse events (from SRs of harms)												
0 (11)							The systematic review RefID=18, 2018 (RCTs=2, n=785) comparing IL-6 inhibitors vs MTX among TCZ naïve RA patients showed that for serious adverse events, the result was RR=2.57 (95% 0.61-10.93, p=0.2).				-	

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Downgraded by one level due to serious risk of bias. Lack of allocation concealment.
b. Downgraded by one level due to serious indirectness. The evidence is based on a population exposed to non-MTX csDMARDs.
c. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting benefit.
d. IL-6i includes TCZ.
e. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm.
f. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting harm.
g. Downgraded by one level due to serious imprecision. Low number of events.

Comparison 5: JAK Inhibitor **versus** MTX monotherapy. Data based on **indirect** RCT evidence.
Overall certainty of evidence: Moderate

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JAKi (Tofa)	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 2 years; assessed with: ACR 20)												
1 (12)	randomised trials	not serious	not serious	serious [a]	not serious	none	239/373 (64.1%) [b]	79/186 (42.5%)	**RR 1.51** (1.26 to 1.81)	**217 more per 1,000** (from 110 more to 344 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Disease activity (follow up: 2 years; assessed with: ACR 50)												
1 (12)	randomised trials	not serious	not serious	serious [a]	not serious	none	184/373 (49.3%) [b]	53/186 (28.5%)	**RR 1.73** (1.35 to 2.22)	**208 more per 1,000** (from 100 more to 348 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JAKi (Tofa)	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 2 years; assessed with: ACR 70)												
1 (12)	randomised trials	not serious	not serious	serious [a]	not serious	none	128/373 (34.3%) [b]	28/186 (15.1%)	**RR 2.28** (1.58 to 3.30)	**193 more per 1,000** (from 87 more to 346 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Disease activity (follow up: 2 years; assessed with: DAS28-ESR (Lower values – > benefit) (MCID -1.17)												
1 (12)	randomised trials	not serious	not serious	serious [a]	not serious	none	373 [b]	186	-	MD **0.6 lower** (0.88 lower to 0.32 lower)	⨁⨁⨁◯ MODERATE	CRITICAL
Remission (follow up: 2 years; assessed with: DAS28-ESR < 2.6)												
1 (12)	randomised trials	not serious	not serious	serious [a]	not serious	none	78/373 (20.9%) [b]	18/186 (9.7%)	**RR 2.16** (1.34 to 3.50)	**112 more per 1,000** (from 33 more to 242 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JAKi (Tofa)	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Radiographic progression (follow up: 2 years; assessed with: mTSS (Lower values – > benefit) (MCID 4.6)												
1 (12)	randomised trials	not serious	not serious	serious [a]	not serious	none	373 [b]	186	-	MD **1.53 lower** (2.36 lower to 0.7 lower)	⨁⨁⨁◯ MODERATE	IMPORTANT
Disability (follow up: 2 years; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
1 (12)	randomised trials	not serious	not serious	serious [a]	serious [c]	none	373 [b]	186	-	MD **0.2 lower** (0.31 lower to 0.09 lower)	⨁⨁◯◯ LOW	IMPORTANT
Serious adverse events (follow up: 2 years)												
1 (12)	randomised trials	not serious	not serious	serious [a]	very serious [d]	none	40/373 (10.7%) [b]	22/186 (11.8%)	**RR 0.91** (0.56 to 1.48)	**11 fewer per 1,000** (from 52 fewer to 57 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JAKi (Tofa)	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Withdrawal due to adverse events (follow up: 2 years)												
1 (12)	randomised trials	not serious	not serious	serious [a]	very serious [d]	none	40/373 (10.7%) [b]	25/186 (13.4%)	**RR 0.80** (0.50 to 1.27)	**27 fewer per 1,000** (from 67 fewer to 36 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Death (follow up: 2 years)												
1 (12)	randomised trials	not serious	not serious	serious [a]	very serious [e]	none	3/373 (0.8%) [b]	0/186 (0.0%)	**RR 3.50** (0.18 to 67.41)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT
Malignancy (follow up: 2 years)												
1 (12)	randomised trials	not serious	not serious	serious [a]	very serious [c]	none	2/373 (0.5%) [b]	1/186 (0.5%)	**RR 1.00** (0.09 to 10.93)	**0 fewer per 1,000** (from 5 fewer to 53 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JAKi (Tofa)	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Malignancy (from SRs on harms)												
0 (9)							The systematic review RefID=1220, 2017 (RCTs=3) comparing tofacitinib 5mg vs placebo + csDMARD among RA showed that for cancer, the result was Peto OR=2.39 (0.50, 11.50)				-	

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Downgraded by one level due to serious indirectness. The evidence is based on a population exposed to non-MTX csDMARDs.
b. JAKi include TOFA.
c. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting no effect.
d. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm.
e. Downgraded by two levels due to very serious imprecision. Very low number of events.

Cost-effectiveness

No cost-effectiveness data identified.

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PICO 5b. Should patients with MTX-naïve and non-MTX csDMARDs exposed RA and moderate to high disease activity receive MTX monotherapy or boDMARD monotherapy or tsDMARD monotherapy?

P - Patients with MTX-naïve and non-MTX csDMARDs exposed RA and moderate to high disease activity
I - MTX monotherapy
C - TNF Inhibitor
C - Abatacept
C - Rituximab
C - IL-6 Receptor Inhibitor
C - JAK Inhibitor

Comparison 1: TNF Inhibitor **versus** MTX monotherapy. See below Table.
Comparison 2: Abatacept **versus** MTX monotherapy. See below Table.
Comparison 3: Rituximab **versus** MTX monotherapy. No RCT, NRS and indirect evidence were identified.
Comparison 4: IL-6 Receptor Inhibitor **versus** MTX monotherapy. See below Table.
Comparison 5: JAK Inhibitor **versus** MTX monotherapy. See below Table.

Comparison 1: TNF Inhibitor **versus** MTX monotherapy. Data based on **direct** RCT evidence.
Overall certainty of evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNFi	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 2 years; assessed with: ACR 20)												
2 (1, 2)	randomised trials	serious [a]	serious [b]	not serious	very serious [c]	none	207/467 (44.3%) [d]	205/459 (44.7%)	**RR 0.99** (0.86 to 1.15)	**4 fewer per 1,000** (from 63 fewer to 67 more)	⨁◯◯◯ VERY LOW	CRITICAL
Disease activity (follow up: 2 years; assessed with: ACR 50)												
2 (1, 2)	randomised trials	serious [a]	serious [e]	not serious	very serious [c]	none	188/451 (41.7%) [d]	182/426 (42.7%)	**RR 0.98** (0.84 to 1.14)	**9 fewer per 1,000** (from 68 fewer to 60 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNFi	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 2 years; assessed with: ACR 70)												
2 (1, 2)	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	128/451 (28.4%) [d]	113/426 (26.5%)	**RR 1.07** (0.86 to 1.33)	**19 more per 1,000** (from 37 fewer to 88 more)	⨁◯◯◯ VERY LOW	CRITICAL
Remission (follow up: 2 years; assessed with: DAS28-ESR <2.6)												
1 (2)	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	69/274 (25.2%) [d]	64/257 (24.9%)	**RR 1.01** (0.75 to 1.36)	**2 more per 1,000** (from 62 fewer to 90 more)	⨁◯◯◯ VERY LOW	CRITICAL
Radiographic progression (follow up: 2 years; assessed with: mTSS (Lower values – > benefit) (MCID 4.6)												
1 (1)	randomised trials	serious [a]	not serious	not serious	not serious	none	177 [d]	169	-	MD **1.9 lower** (3.19 lower to 0.61 lower) [f]	⨁⨁⨁◯ MODERATE	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNFi	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disability (follow up: range 1 year to 2 years; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
2 (2, 3)	randomised trials	serious [a]	not serious	not serious	not serious	none	481 [d]	474	-	MD **0.01 higher** (0.07 lower to 0.1 higher) [g]	⨁⨁⨁◯ MODERATE	IMPORTANT
Fatigue (follow up: 2 years; assessed with: FACIT-F (Higher values – > benefit) (MCID 15.9)												
1 (4)	randomised trials	serious [a]	not serious	not serious	not serious	none	272 [d]	254	-	MD **1.7 lower** (3.09 lower to 0.31 lower)	⨁⨁⨁◯ MODERATE	IMPORTANT
Pain (follow up: 2 years; assessed with: VAS 0-100 (Lower values – > benefit) (MCID -11.9)												
1 (4)	randomised trials	serious [a]	not serious	not serious	not serious	none	273 [d]	256	-	MD **7.1 higher** (4.34 higher to 9.86 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNFi	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Quality of life (follow up: range 1 year to 2 years; assessed with: SF-36 PCS (Higher values – > benefit) (MCID 4.4)												
2 (3, 4)	randomised trials	serious [a]	serious [h]	not serious	not serious	none	471	464	-	MD **0.56 lower** (1.73 lower to 0.6 higher)	⨁⨁◯◯ LOW	IMPORTANT
Quality of life (follow up: range 1 year to 2 years; assessed with: SF-36 MCS (Higher values – > benefit) (MCID 3.1)												
2 (3, 4)	randomised trials	serious [a]	not serious [i]	not serious	serious [j]	none	471	464	-	MD **1.98 lower** (3.18 lower to 0.78 lower)	⨁⨁◯◯ LOW	IMPORTANT
Serious adverse events (follow up: 2 years)												
1 (2)	randomised trials	serious [a]	not serious	not serious	serious [j]	none	92/274 (33.6%) [d]	68/257 (26.5%)	**RR 1.27** (0.98 to 1.65)	**71 more per 1,000** (from 5 fewer to 172 more)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNFi	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Withdrawal due to lack of efficacy (2 years)												
2 (1, 2)	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	68/481 (14.1%) [d]	69/474 (14.6%)	**RR 0.95** (0.70 to 1.30)	**7 fewer per 1,000** (from 44 fewer to 44 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Withdrawal due to adverse events (follow up: 2 years)												
2 (1, 2)	randomised trials	serious [a]	serious [k]	not serious	very serious [c]	none	41/481 (8.5%) [d]	46/474 (9.7%)	**RR 0.88** (0.59 to 1.32)	**12 fewer per 1,000** (from 40 fewer to 31 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Death (follow up: 2 years)												
1 (2)	randomised trials	serious [a]	not serious	not serious	serious [l]	none	4/274 (1.5%) [d]	1/257 (0.4%)	**RR 3.75** (0.42 to 33.35)	**11 more per 1,000** (from 2 fewer to 126 more)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNFi	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Malignancy (follow up: 2 years)												
2 (1, 2)	randomised trials	serious [a]	not serious	not serious	serious [l]	none	8/481 (1.7%) [d]	7/474 (1.5%)	**RR 1.13** (0.41 to 3.08)	**2 more per 1,000** (from 9 fewer to 31 more)	⨁⨁◯◯ LOW	IMPORTANT
Malignancy (from SRs on harms)												
0 (5)							The systematic review RefID=3394, 2014 (RCTs=28, n=11741) comparing any TNFi vs placebo + MTX among RA showed that for cancer, the result was OR=1.30 (95% CI 0.80,2.14 Modified ITT model) [OR=1.06 (95% CI 0.64,1.75; p=0.82) Per protocol model]				-	
Cardiovascular disease (from SRs on harms)												
0 (6)							The systematic review RefID=1105, 2017 (NRS=7, n=49003) comparing any TNFi vs csDMARDs among RA showed that for Cardiovascular disease, the result was RR = 0.62 (95% CI 0.44–0.88), p=0.007				-	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNFi	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Death (from SRs on harms)												
0 (6)							The systematic review RefID=1105, 2017 (NRS=5, n=41579) comparing any TNFi vs csDMARD among RA showed that for Death, the result was RR = 0.60 (95% CI 0.38–0.94), p=0.03				-	

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Downgraded by one level due to serious risk of bias. Lack of allocation concealment.
b. Downgraded by one level due to serious inconsistency. Unexplained heterogeneity I2=65%.
c. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm.
d. TNFi includes ETN or ADA.
e. Downgraded by one level due to serious inconsistency. Unexplained heterogeneity I2=75%.
f. The study PREMIER found that the RR of developing no radiographic progression (change in mTSS ≤0.5) was 1.33 (95%CI 1.07 to 1.65), absolute risk increase 112 more per 1000 (95%CI 24 more to 220 more).
g. The study PREMIER found that the RR of improvement in HAQ-DI (≥0.22 change from baseline) was 0.92 (95%CI 0.80 to 1.06), absolute risk reduction 50 fewer per 1000 (95%CI 126 fewer to 38 more).
h. Downgraded by one level due to serious inconsistency. I2=67%. Question whether heterogeneity might be related to the use of different TNFis.
i. Indication of serious inconsistency I2=59% (taken into consideration when downgrading for imprecision). Question whether heterogeneity might be related to the use of different TNFis.
j. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting harm.
k. Downgraded by one level due to serious inconsistency. Unexplained heterogeneity I2=72%.
l. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting harm. Low number of events.

Comparison 2: Abatacept **versus** MTX monotherapy. Data based on **indirect** RCT evidence.
Overall certainty of evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ABA	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Remission (follow up: 1 year; assessed with: DAS28-CRP < 2.6)												
1 (7)	randomised trials	not serious	not serious	serious [a]	very serious [b]	none	48/113 (42.5%)	52/115 (45.2%)	**RR 0.94** (0.70 to 1.26)	**27 fewer per 1,000** (from 136 fewer to 118 more)	⨁◯◯◯ VERY LOW	CRITICAL
Disability (follow up: 1 year; assessed with: HAQ-DI (≥ 0.3)												
1 (7)	randomised trials	not serious	not serious	serious [a]	very serious [b]	none	61/113 (54.0%)	51/115 (44.3%)	**RR 1.22** (0.93 to 1.59)	**98 more per 1,000** (from 31 fewer to 262 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ABA	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events (1 year)												
1 (7)	randomised trials	not serious	not serious	serious [a]	very serious [b]	none	14/116 (12.1%)	9/116 (7.8%)	**RR 1.56** (0.70 to 3.45)	**43 more per 1,000** (from 23 fewer to 190 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Withdrawal due to adverse events (follow up: 1 year)												
1 (7)	randomised trials	not serious	not serious	serious [a]	very serious [b]	none	8/116 (6.9%)	5/116 (4.3%)	**RR 1.60** (0.54 to 4.75)	**26 more per 1,000** (from 20 fewer to 162 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Withdrawal due to lack of efficacy (follow up: 1 year)												
1 (7)	randomised trials	not serious	not serious	serious [a]	very serious [b]	none	6/116 (5.2%)	11/116 (9.5%)	**RR 0.55** (0.21 to 1.43)	**43 fewer per 1,000** (from 75 fewer to 41 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ABA	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Death (follow up: 1 year)												
1 (7)	randomised trials	not serious	not serious	serious [a]	very serious [c]	none	0/116 (0.0%)	0/116 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	IMPORTANT
Malignancy (follow up: 1 year)												
1 (7)	randomised trials	not serious	not serious	serious [a]	very serious [c]	none	2/116 (1.7%)	1/116 (0.9%)	**RR 2.00** (0.18 to 21.75)	**9 more per 1,000** (from 7 fewer to 179 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Malignancy (from SR of harms) ABA vs MTX												
0 (8)							The Systematic Review RefID=1220, 2017 (RCTs=4, n=Not provided) comparing Abatacept vs Placebo + csDMARD among RA and showed that for Cancer, the result was Peto OR=1.12 (0.33, 3.81)				-	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Downgraded by one level due to serious indirectness. The evidence is based on a population naive to non-MTX csDMARDs.
b. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm. Small sample size.
c. Downgraded by two levels due to very serious imprecision. Small sample size and very low number of events.

Comparison 4: IL-6 Receptor Inhibitor **versus** MTX monotherapy. Data based on **direct** RCT evidence.
Overall certainty of evidence: Moderate

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-6i	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 1 year; assessed with: ACR 20)												
1 (9)	randomised trials	serious [a]	not serious	not serious	serious [b]	none	184/292 (63.0%) [c]	164/287 (57.1%)	**RR 1.10** (0.97 to 1.26)	**57 more per 1,000** (from 17 fewer to 149 more)	⨁⨁◯◯ LOW	CRITICAL
Disease activity (follow up: 1 year; assessed with: ACR 50)												
1 (9)	randomised trials	serious [a]	not serious	not serious	not serious	none	145/292 (49.7%) [c]	117/287 (40.8%)	**RR 1.22** (1.02 to 1.46)	**90 more per 1,000** (from 8 more to 188 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-6i	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 1 year; assessed with: ACR 70)												
1 (9)	randomised trials	serious [a]	not serious	not serious	serious [b]	none	107/292 (36.6%) [c]	84/287 (29.3%)	**RR 1.25** (0.99 to 1.58)	**73 more per 1,000** (from 3 fewer to 170 more)	⨁⨁◯◯ LOW	CRITICAL
Disease activity (follow up: 1 year; assessed with: DAS28-ESR (Lower values –> benefit) (MCID -1.17)												
1 (9)	randomised trials	serious [a]	not serious	not serious	serious [b]	none	292 [c]	287	-	MD **0.96 lower** (1.24 lower to 0.68 lower)	⨁⨁◯◯ LOW	CRITICAL
Remission (follow up: 1 year; assessed with: DAS28-ESR <2.6)												
1 (9)	randomised trials	serious [a]	not serious	not serious	not serious	none	115/292 (39.4%) [c]	56/287 (19.5%)	**RR 2.02** (1.53 to 2.66)	**199 more per 1,000** (from 103 more to 324 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-6i	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Radiographic progression (follow up: 1 year; assessed with: mTSS (Lower values –> benefit) (MCID 4.6)												
1 (9)	randomised trials	serious [a]	not serious	not serious	not serious	none	275 [c]	267	-	MD **0.88 lower** (1.44 lower to 0.32 lower)	⨁⨁⨁◯ MODERATE	IMPORTANT
Disability (follow up: 1 year; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
1 (9)	randomised trials	serious [a]	not serious	not serious	not serious	none	0 [c]	0	-	MD **0.03 lower** (0.15 lower to 0.09 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Quality of life (follow up: 1 year; assessed with: SF-36 PCS (Higher values – > benefit) (MCID 4.4)												
1 (9)	randomised trials	serious [a]	not serious	not serious	not serious	none	0 [c]	0	-	MD **0.14 higher** (0.13 lower to 0.41 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-6i	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Quality of life (1 year) (follow up: 1 year; assessed with: SF-36 MCS (Higher values – > benefit) (MCID 3.1)												
1 (9)	randomised trials	serious [a]	not serious	not serious	not serious	none	0 [c]	0	-	MD **0.34 higher** (0.68 lower to 1.36 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Serious adverse events (follow up: 1 year)												
1 (9)	randomised trials	serious [a]	not serious	not serious	very serious [d]	none	25/292 (8.6%) [c]	24/282 (8.5%)	**RR 1.01** (0.59 to 1.72)	**1 more per 1,000** (from 35 fewer to 61 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Withdrawal due to lack of efficacy (follow up: 1 year)												
1 (9)	randomised trials	serious [a]	not serious	not serious	serious [e]	none	34/292 (11.6%) [c]	21/282 (7.4%)	**RR 1.56** (0.93 to 2.63)	**42 more per 1,000** (from 5 fewer to 121 more)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-6i	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Death (follow up: 1 year)												
1 (9)	randomised trials	serious [a]	not serious	not serious	very serious [d]	none	1/292 (0.3%) [c]	2/282 (0.7%)	**RR 0.48** (0.04 to 5.30)	**4 fewer per 1,000** (from 7 fewer to 30 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Malignancy (follow up: 1 year)												
1 (9)	randomised trials	serious [a]	not serious	not serious	very serious [d]	none	2/292 (0.7%) [c]	3/282 (1.1%)	**RR 0.64** (0.11 to 3.82)	**4 fewer per 1,000** (from 9 fewer to 30 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Myocardial infarction (follow up: 1 year)												
1 (9)	randomised trials	serious [a]	not serious	not serious	serious [f]	none	1/292 (0.3%) [c]	0/282 (0.0%)	**RR 2.90** (0.12 to 70.83)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-6i	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Malignancy (from SRs of harms)												
0 (8)							The Systematic Review RefID=1220, 2017 (RCTs=4) comparing abatacept vs placebo +csDMARD among RA showed that for cancer, the result was OR=1.12 (0.33, 3.81).				-	
Serious adverse events (from SRs of harms)												
0 (10)							The systematic review RefID=18, 2018 (RCTs=2, n=785) comparing IL-6 inhibitors vs MTX among TCZ naïve RA patients showed that for serious adverse events, the result was RR=2.57 (95% 0.61-10.93, p=0.2).				-	

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Downgraded by one level due to serious risk of bias. Lack of allocation concealment.
b. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting benefit.
c. IL-6i includes TCZ.
d. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm.
e. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting harm.
f. Downgraded by one level due to serious imprecision. Low number of events.

Comparison 5: JAK Inhibitor **versus** MTX monotherapy. Data based on **direct** RCT evidence.
Overall certainty of evidence: High

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JAKi (Tofa)	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 2 years; assessed with: ACR 20)												
1 (11)	randomised trials	not serious	not serious	not serious	not serious	none	239/373 (64.1%) [a]	79/186 (42.5%)	**RR 1.51** (1.26 to 1.81)	**217 more per 1,000** (from 110 more to 344 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Disease activity (follow up: 2 years; assessed with: ACR 50)												
1 (11)	randomised trials	not serious	not serious	not serious	not serious	none	184/373 (49.3%) [a]	53/186 (28.5%)	**RR 1.73** (1.35 to 2.22)	**208 more per 1,000** (from 100 more to 348 more)	⨁⨁⨁⨁ HIGH	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JAKi (Tofa)	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 2 years; assessed with: ACR 70)												
1 (11)	randomised trials	not serious	not serious	not serious	not serious	none	128/373 (34.3%) [a]	28/186 (15.1%)	**RR 2.28** (1.58 to 3.30)	**193 more per 1,000** (from 87 more to 346 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Disease activity (follow up: 2 years; assessed with: DAS28-ESR (Lower values – > benefit) (MCID -1.17)												
1 (11)	randomised trials	not serious	not serious	not serious	not serious	none	373 [a]	186	-	MD **0.6 lower** (0.88 lower to 0.32 lower)	⨁⨁⨁⨁ HIGH	CRITICAL
Remission (follow up: 2 years; assessed with: DAS28-ESR < 2.6)												
1 (11)	randomised trials	not serious	not serious	not serious	not serious	none	78/373 (20.9%) [a]	18/186 (9.7%)	**RR 2.16** (1.34 to 3.50)	**112 more per 1,000** (from 33 more to 242 more)	⨁⨁⨁⨁ HIGH	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JAKi (Tofa)	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Radiographic progression (follow up: 2 years; assessed with: mTSS (Lower values – > benefit) (MCID 4.6)												
1 (11)	randomised trials	not serious	not serious	not serious	not serious	none	373 [a]	186	-	MD **1.53 lower** (2.36 lower to 0.7 lower)	⨁⨁⨁⨁ HIGH	IMPORTANT
Disability (follow up: 2 years; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
1 (11)	randomised trials	not serious	not serious	not serious	serious [b]	none	373 [a]	186	-	MD **0.2 lower** (0.31 lower to 0.09 lower)	⨁⨁⨁◯ MODERATE	IMPORTANT
Serious adverse events (follow up: 2 years)												
1 (11)	randomised trials	not serious	not serious	not serious	very serious [c]	none	40/373 (10.7%) [a]	22/186 (11.8%)	**RR 0.91** (0.56 to 1.48)	**11 fewer per 1,000** (from 52 fewer to 57 more)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JAKi (Tofa)	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Withdrawal due to adverse events (follow up: 2 years)												
1 (11)	randomised trials	not serious	not serious	not serious	very serious [c]	none	40/373 (10.7%) [a]	25/186 (13.4%)	**RR 0.80** (0.50 to 1.27)	**27 fewer per 1,000** (from 67 fewer to 36 more)	⨁⨁◯◯ LOW	IMPORTANT
Death (follow up: 2 years)												
1 (11)	randomised trials	not serious	not serious	not serious	very serious [d]	none	3/373 (0.8%) [a]	0/186 (0.0%)	**RR 3.50** (0.18 to 67.41)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	IMPORTANT
Malignancy (follow up: 2 years)												
1 (11)	randomised trials	not serious	not serious	not serious	very serious [b]	none	2/373 (0.5%) [a]	1/186 (0.5%)	**RR 1.00** (0.09 to 10.93)	**0 fewer per 1,000** (from 5 fewer to 53 more)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JAKi (Tofa)	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Malignancy (from SRs on harms)												
(8)							The systematic review RefID=1220, 2017 (RCTs=3) comparing tofacitinib 5mg vs placebo + csDMARD among RA showed that for cancer, the result was Peto OR=2.39 (0.50, 11.50)				-	

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. JAKi include TOFA.
b. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting no effect.
c. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm.
d. Downgraded by two levels due to very serious imprecision. Very low number of events.

Cost-effectiveness

The economic analysis RefID 6163 (12) based on the PREMIER trial conducted in Europe (54%), North America (40%), or Australia (6%) compared adalimumab + MTX vs adalimumab alone vs MTX alone.

The study reported (1) Over 2 years, patients who received combination therapy missed approximately half as many days as patients who received methotrexate (17.4 versus 36.9 days for employed workers; 7.9 versus 18.6 days for homemakers). (2) Presenteeism was lower (reflecting better productivity) for combination therapy than methotrexate monotherapy. (3) The likelihood of gaining/ retaining employment over 2 years was greater for combination therapy than methotrexate monotherapy (odds ratio 1.530, 95% confidence interval 1.038–2.255; P 0.0318).

Authors conclusion: Compared with methotrexate monotherapy, combination therapy was associated with more positive work outcomes: less absenteeism, less presenteeism, and greater likelihood of gaining/retaining employment.

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PICO 6a. Should patients with MTX-naïve and non-MTX csDMARDs naïve RA and moderate to high disease activity receive MTX monotherapy or boDMARD with MTX or tsDMARD with MTX?

P -Patients with MTX-naïve and non-MTX csDMARDs naïve RA and moderate to high disease activity
I - MTX monotherapy
C - TNF Inhibitor + MTX
C - Abatacept+ MTX
C - Rituximab+ MTX
C - IL-6 Receptor Inhibitor+ MTX
C - JAK Inhibitor + MTX

Comparison 1: TNF Inhibitor + MTX **versus** MTX monotherapy. See below Table.
Comparison 2: Abatacept + MTX **versus** MTX monotherapy. See below Table.
Comparison 3: Rituximab + MTX **versus** MTX monotherapy. See below Table.
Comparison 4: IL-6 Receptor Inhibitor + MTX **versus** MTX monotherapy. See below Table.
Comparison 5: JAK Inhibitor + MTX **versus** MTX monotherapy. No RCT, NRS, or indirect evidence were identified.

Comparison 1: TNF Inhibitor + MTX **versus** MTX monotherapy. Data based on **direct** RCT evidence.
Overall certainty of evidence: Low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNFi + MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: range 6 months to 1 year; assessed with: ACR 20)												
2 (1, 2)	randomised trials	not serious [a]	not serious	not serious	serious [b]	none	521/742 (70.2%) [c]	188/298 (63.1%)	**RR 1.14** (1.03 to 1.26)	**88 more per 1,000** (from 19 more to 164 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Disease activity (follow up: 6 months; assessed with: ACR 50)												
2 (1, 2)	randomised trials	not serious [a]	not serious	not serious	serious [b]	none	426/742 (57.4%)	148/298 (49.7%)	**RR 1.17** (1.02 to 1.33)	**84 more per 1,000** (from 10 more to 164 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNFi + MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: range 6 months to 12 months; assessed with: ACR 70)												
2 (1, 2)	randomised trials	not serious [d]	serious [e]	not serious	not serious	none	378/742 (50.9%)	108/298 (36.2%)	**RR 1.36** (1.15 to 1.61)	**130 more per 1,000** (from 54 more to 221 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Disease activity (follow up: range 6 months to 12 months; assessed with: DAS28 or DAS44 (Lower values -> benefit) (values>0.2 are considered clinically important)												
2 (2, 3)	randomised trials	serious [f]	serious [g]	not serious	serious [b]	none	0 [c]	0	-	SMD **0.21 lower** (0.37 lower to 0.05 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Remission (follow up: range 6 months to 12 months; assessed with: DAS28<2.6)												
3 (1-3)	randomised trials	serious [f]	serious [h]	not serious	not serious	none	359/797 (45.0%) [c]	116/353 (32.9%)	**RR 1.49** (1.25 to 1.77)	**161 more per 1,000** (from 82 more to 253 more)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNFi + MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Radiographic progression (follow up: 1 year; assessed with: mTSS (Lower values – > benefit) (MCID 4.6)												
1 (3)	randomised trials	serious [i]	not serious	not serious	not serious	none	0 [c]	0	-	MD **0** (0.64 lower to 0.64 higher) [j]	⨁⨁⨁◯ MODERATE	IMPORTANT
Fatigue (follow up: 1 year; assessed with: VAS fatigue (Lower values – > benefit) (MCID -1.12 to -0.82))												
1 (3)	randomised trials	not serious [k]	not serious	not serious	very serious [l]	none	55 [c]	55	-	MD **5.2 lower** (17.17 lower to 6.77 higher)	⨁⨁◯◯ LOW	IMPORTANT
Pain (follow up: 1 year; assessed with: VAS pain (Lower values – > benefit) (MCID -11.9)												
1 (3)	randomised trials	not serious [k]	not serious	not serious	serious [b]	none	55 [c]	55	-	MD **18.4 lower** (30.88 lower to 5.92 lower)	⨁⨁⨁◯ MODERATE	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNFi + MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disability (follow up: range 6 months to 12 months; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
3 (1-3)	randomised trials	serious [f]	not serious	not serious	serious [b]	none	0 [c]	0	-	MD **0.18 lower** (0.25 lower to 0.1 lower) [m]	⨁⨁◯◯ LOW	IMPORTANT
Quality of Life (follow up: range 6 months to 12 months; assessed with: SF-36 PCS (Higher values – > benefit) (MCID 4.4)												
2 (2, 3)	randomised trials	serious [f]	not serious	not serious	serious [b]	none	0 [c]	0	-	MD **3.21 higher** (0.63 higher to 5.79 higher)	⨁⨁◯◯ LOW	IMPORTANT
Quality of Life (follow up: range 6 months to 12 months; assessed with: SF-36 MCS (Higher values – > benefit) (MCID 3.1)												
2 (2, 3)	randomised trials	serious [f]	not serious	not serious	not serious	none	0 [c]	0	-	MD **0.54 lower** (2.98 lower to 1.89 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNFi + MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Withdrawal due to lack of efficacy (follow up: range 6 months to 12 months)												
3 (1-3)	randomised trials	serious [f]	not serious	not serious	not serious	none	21/802 (2.6%) [c]	24/359 (6.7%)	**RR 0.38** (0.21 to 0.69)	**41 fewer per 1,000** (from 53 fewer to 21 fewer)	⨁⨁⨁◯ MODERATE	IMPORTANT
Withdrawal due to adverse events (follow up: range 6 months to 12 months)												
3 (1-3)	randomised trials	serious [f]	not serious	not serious	serious [n]	none	61/801 (7.6%) [c]	24/357 (6.7%)	**RR 0.94** (0.60 to 1.49)	**4 fewer per 1,000** (from 27 fewer to 33 more)	⨁⨁◯◯ LOW	IMPORTANT
Serious adverse events (follow up: range 6 months to 12 months)												
3 (1-3)	randomised trials	not serious [o]	serious [p]	not serious	very serious [n]	none	91/801 (11.4%) [c]	45/357 (12.6%)	**RR 1.00** (0.71 to 1.43)	**0 fewer per 1,000** (from 37 fewer to 54 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNFi + MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Death (follow up: range 6 months to 12 months)												
2 (1, 2)	randomised trials	serious [q]	not serious	not serious	serious [n]	none	2/746 (0.3%) [c]	1/302 (0.3%)	**RR 0.66** (0.06 to 7.23)	**1 fewer per 1,000** (from 3 fewer to 21 more)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNFi + MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Malignancy (from SRs on harms)												
0 (4)							The Systematic Review RefID=4638, 2012 (RCTs=3, n=1842) comparing certolizumab + MTX vs placebo + MTX among RA showed that for cancer, the result was RR=2.8 (0.36-21.6) at 1 year and RR=1.3 (0.24-7.3) at all time points.				-	

CI: Confidence interval; **RR:** Risk ratio; **SMD:** Standardised mean difference; **MD:** Mean difference

Explanations

a. Concern about risk of bias associated with lack of allocation concealment and incomplete outcome data in one study is taken into account when rating down for imprecision.
b. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting benefit. According to the Cochrane's handbook, Cohen suggested that SMD=0.2 be considered a 'small' effect size, 0.5 represents a 'medium' effect size and 0.8 a 'large' effect size. This means that if two groups' means do not differ by 0.2 standard deviations or more, the difference is trivial, even if it is statistically significant.
c. TNFis include etanercept (ETN), certolizumab (CZP) and adalimumab (ADA).
d. Concern about risk of bias associated with lack of allocation concealment and incomplete outcome data in one study is taken into account when rating down for inconsistency.
e. Downgraded by one level due to serious inconsistency. Unexplained heterogeneity I2=51%.
f. Downgraded by one level due to serious risk of bias. Lack of allocation concealment in 2 studies.
g. Downgraded by one level due to serious inconsistency. Unexplained heterogeneity I2=78%.
h. Downgraded by one level due to serious inconsistency. Unexplained heterogeneity I2=58%.
i. Downgraded by one level due to serious risk of bias. Lack of allocation concealment.
j. The study EMPIRE found that the RR of developing no radiographic progression (change in mTSS ≤0.5) was 0.86 (95%CI 0.57 to 1.3), absolute risk reduction 77 fewer per 1000 (95%CI 237 fewer to 165 more).
k. Concern about risk of bias associated with lack of allocation concealment taken into account when rating down for imprecision.
l. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm.
m. The study C-EARLY found that the RR of having HAQ-DI ≤0.5 at 1 year was 1.35 (95%CI 1.11 to 1.64), absolute risk increase 125 more per 1000 (95%CI 39 more to 228 more).
n. Downgraded by one level due to serious imprecision. Low number of events.
o. Concern about risk of bias associated with lack of allocation concealment in two studies taken into account when rating down for inconsistency and imprecision.
p. Downgraded by one level due to serious inconsistency. Unexplained heterogeneity I2=72%.
q. Downgraded by one level due to serious risk of bias. Lack of allocation concealment and incomplete outcome data in one study.

Comparison 2: Abatacept + MTX **versus** MTX monotherapy. Data based on **indirect** RCT evidence.
Overall certainty of evidence: Low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ABA+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 1 year; assessed with: ACR 70)												
1 (5)	randomised trials	serious [a]	not serious	serious [b]	not serious	none	109/256 (42.6%)	69/253 (27.3%)	**RR 1.56** (1.22 to 2.00)	**153 more per 1,000** (from 60 more to 273 more)	⨁⨁◯◯ LOW	CRITICAL
Disease activity (follow up: 1 year; assessed with: DAS28 CRP (Lower values – > benefit) (MCID -1.02)												
1 (5)	randomised trials	serious [a]	not serious	serious [b]	not serious	none	256	253	-	MD **0.73 lower** (0.98 lower to 0.48 lower)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ABA+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Remission (follow up: 1 year; assessed with: DAS28-ESR remission <2.6)												
2 (5, 6)	randomised trials	serious [a]	not serious	serious [b]	not serious	none	176/371 (47.4%)	109/368 (29.6%)	**RR 1.60** (1.33 to 1.93)	**178 more per 1,000** (from 98 more to 275 more)	⨁⨁◯◯ LOW	CRITICAL
Radiographic progression (follow up: 1 year; assessed with: mTSS (Lower values – > benefit) (MCID 4.6)												
1 (5)	randomised trials	serious [a]	not serious	serious [b]	not serious	none	0 [c]	0	-	MD **0.43 lower** (0.91 lower to 0.05 higher)	⨁⨁◯◯ LOW	IMPORTANT
Disability (follow up: 1 year; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
1 (5)	randomised trials	serious [a]	not serious	serious [b]	serious [d]	none	256 [e]	253	-	MD **0.2 lower** (0.31 lower to 0.09 lower)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ABA+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Quality of Life (follow up: 1 year; assessed with: SF-36 PCS (Higher values – > benefit) (MCID 4.4)												
1 (5)	randomised trials	serious [a]	not serious	serious [b]	serious [d]	none	256	253	-	MD **2.5 higher** (0.77 higher to 4.23 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Quality of Life (follow up: 1 year; assessed with: SF-36 MCS (Higher values – > benefit) (MCID 3.1)												
1 (5)	randomised trials	serious [a]	not serious	serious [b]	serious [f]	none	256	253	-	MD **1.81 lower** (3.58 lower to 0.04 lower)	⨁◯◯◯ VERY LOW	IMPORTANT
Withdrawal due to lack of efficacy (follow up: 1 year)												
1 (6)	randomised trials	not serious	not serious	serious [b]	serious [f]	none	5/115 (4.3%)	11/115 (9.6%)	**RR 0.45** (0.16 to 1.27)	**53 fewer per 1,000** (from 80 fewer to 26 more)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ABA+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Withdrawal due to adverse events (follow up: 1 year)												
2 (5, 6)	randomised trials	serious [a]	not serious	serious [b]	serious [g]	none	13/375 (3.5%)	16/369 (4.3%)	**RR 0.80** (0.39 to 1.64)	**9 fewer per 1,000** (from 26 fewer to 28 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events (follow up: 1 year)												
1 (5)	randomised trials	serious [a]	not serious	serious [b]	serious [h]	none	20/256 (7.8%)	20/253 (7.9%)	**RR 0.99** (0.55 to 1.79)	**1 fewer per 1,000** (from 36 fewer to 62 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Malignancy (follow up: 1 year)												
2 (5, 6)	randomised trials	serious [a]	not serious	serious [b]	serious [f]	none	1/371 (0.3%)	2/368 (0.5%)	**RR 0.60** (0.08 to 4.48)	**2 fewer per 1,000** (from 5 fewer to 19 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ABA+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Death (follow up: 1 year)												
2 (5, 6)	randomised trials	serious [a]	not serious	serious [b]	serious [g]	none	2/371 (0.5%)	4/368 (1.1%)	**RR 0.49** (0.09 to 2.67)	**6 fewer per 1,000** (from 10 fewer to 18 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Malignancy (from SRs on harms)												
0 (4)							The Systematic Review RefID=4638, 2012 (RCTs=3, n=2435) comparing Abatacept + csDMARD vs Placebo + csDMARD among RA showed that for Cancer, the result was RR=0.65 (0.25-1.7) at 1 year.				-	

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Downgraded by one level due to serious risk of bias. Lack of allocation concealment and lack of blinding of non-radiographic outcome assessors.
b. Downgraded by one level due to serious indirectness. The evidence is based on a non-MTX csDMARD exposed population.
c. The study AGREE found that the RR of developing no radiographic progression (change in mTSS ≤0) was 1.6 (95%CI 0.99 to 1.36), absolute risk increase 84 more per 1000 (95%CI 5 fewer to 190 more).
d. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting benefit.
e. The studies AGREE and AVERT found that the RR of improvement in HAQ-DI (≥0.3 change from baseline) was 1.25 (95%CI 1.12 to 1.39), absolute risk increase 141 more per 1000 (95%CI 668 more to 220 more).
f. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting harm.
g. Downgraded by two levels due to serious imprecision. Confidence interval includes both values suggesting harm and values suggesting benefit. Low number of events.
h. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting harm and values suggesting benefit.

Comparison 3: Rituximab + MTX **versus** MTX monotherapy. Data based on **indirect** RCT evidence.
Overall certainty of evidence: Low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RTX+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 2 years; assessed with: ACR 20)												
1 (7)	randomised trials	serious [a]	not serious	serious [b]	not serious	none	185/250 (74.0%)	137/249 (55.0%)	**RR 1.34** (1.18 to 1.54)	**187 more per 1,000** (from 99 more to 297 more)	⨁⨁◯◯ LOW	CRITICAL
Disease activity (follow up: 2 years; assessed with: ACR 50)												
1 (7)	randomised trials	serious [a]	not serious	serious [b]	not serious	none	155/250 (62.0%)	102/249 (41.0%)	**RR 1.51** (1.27 to 1.81)	**209 more per 1,000** (from 111 more to 332 more)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RTX+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 2 years; assessed with: ACR 70)												
1 (7)	randomised trials	serious [a]	not serious	serious [b]	not serious	none	115/250 (46.0%)	67/249 (26.9%)	**RR 1.71** (1.34 to 2.18)	**191 more per 1,000** (from 91 more to 318 more)	⨁⨁◯◯ LOW	CRITICAL
Disease activity (follow up: 2 years; assessed with: DAS28 ESR (Lower values – > benefit) (MCID -1.17)												
1 (7)	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	250	249	-	MD **1.19 lower** (1.5 lower to 0.88 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Remission (follow up: 2 years; assessed with: DAS28-ESR remission <2.6)												
1 (7)	randomised trials	serious [a]	not serious	serious [b]	not serious	none	80/250 (32.0%)	32/249 (12.9%)	**RR 2.49** (1.72 to 3.61)	**191 more per 1,000** (from 93 more to 335 more)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RTX+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Radiographic progression (follow up: 2 years; assessed with: mTSS (Lower values – > benefit) (MCID 4.6)												
1 (7)	randomised trials	serious [a]	not serious	serious [b]	not serious	none	244	233	-	MD **1.54 lower** (2.3 lower to 0.78 lower)	⨁⨁◯◯ LOW	IMPORTANT
Pain (follow up: 1 year; assessed with: VAS pain (Lower values – > benefit) (MCID -11.9)												
1 (7)	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	0	0	-	MD **12.2 lower** (16.15 lower to 8.25 lower)	⨁◯◯◯ VERY LOW	IMPORTANT
Fatigue (follow up: 1 year; assessed with: FACIT-F (Higher values – > benefit) (MCID 15.9)												
1 (7)	randomised trials	serious [a]	not serious	serious [b]	not serious	none	0	0	-	MD **3.45 higher** (1.77 higher to 5.13 higher)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RTX+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disability (follow up: 2 years; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
1 (7)	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	250 [d]	249	-	MD **0.25 lower** (0.4 lower to 0.1 lower)	⨁◯◯◯ VERY LOW	IMPORTANT
Quality of Life (follow up: 1 year; assessed with: SF-36 PCS (Higher values – > benefit) (MCID 4.4)												
1 (7)	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	0	0	-	MD **3.53 higher** (2.04 higher to 5.02 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Quality of Life (follow up: 1 year; assessed with: SF-36 MCS (Higher values – > benefit) (MCID 3.1)												
1 (7)	randomised trials	serious [a]	not serious	serious [b]	not serious	none	0	0	-	MD **0.81 higher** (1.03 lower to 2.66 higher)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RTX+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Withdrawal due to adverse events (follow up: 2 years)												
1 (7)	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	7/250 (2.8%)	17/249 (6.8%)	**RR 0.41** (0.17 to 0.97)	**40 fewer per 1,000** (from 57 fewer to 2 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events (follow up: 2 years)												
1 (7)	randomised trials	serious [a]	not serious	serious [b]	very serious [e]	none	33/250 (13.2%)	42/249 (16.9%)	**RR 0.78** (0.51 to 1.19)	**37 fewer per 1,000** (from 83 fewer to 32 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Malignancy (follow up: 2 years)												
1 (7)	randomised trials	serious [a]	not serious	serious [b]	very serious [e]	none	3/250 (1.2%)	7/249 (2.8%)	**RR 0.43** (0.11 to 1.63)	**16 fewer per 1,000** (from 25 fewer to 18 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RTX+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Death (follow up: 2 years)												
1 (7)	randomised trials	serious [a]	not serious	serious [b]	very serious [e]	none	1/250 (0.4%)	3/249 (1.2%)	**RR 0.33** (0.03 to 3.17)	**8 fewer per 1,000** (from 12 fewer to 26 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Malignancy (from SRs on harms)												
0 (4)							The Systematic Review RefID=4638, 2012 (RCTs=5, n=2066) comparing Rituximab + csDMARD vs Placebo + MTX among RA and showed that for Cancer, the result was RR=1.5 (0.38-6.1) at 24 weeks and RR=0.65 (0.24-1.7) at 2 years (RCT= 1, n=748)				-	

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Downgraded by one level due to serious risk of bias. Lack of allocation concealment.
b. Downgraded by one level due to serious indirectness. The evidence is based on a non-MTX csDMARD exposed population.
c. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting benefit.
d. The study IMAGE found that the RR of improvement in HAQ-DI (≥0.22 change from baseline) was 1.12 (95%CI 1.03 to 1.21), absolute risk increase 93 more per 1000 (95%CI 23 more to 162 more).
e. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm.

Comparison 4: IL-6 Receptor Inhibitor + MTX **versus** MTX monotherapy. Data based on **indirect** RCT evidence.
Overall certainty of evidence: Low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCZ+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 1 year; assessed with: ACR 20)												
1 (8)	randomised trials	serious [a]	not serious	serious [b]	not serious	none	374/578 (64.7%)	164/287 (57.1%)	**RR 1.13** (1.01 to 1.27)	**74 more per 1,000** (from 6 more to 154 more)	⨁⨁◯◯ LOW	CRITICAL
Disease activity (follow up: 1 year; assessed with: ACR 50)												
1 (8)	randomised trials	serious [a]	not serious	serious [b]	not serious	none	314/578 (54.3%)	117/287 (40.8%)	**RR 1.33** (1.14 to 1.56)	**135 more per 1,000** (from 57 more to 228 more)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCZ+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 1 year; assessed with: ACR 70)												
1 (8)	randomised trials	serious [a]	not serious	serious [b]	not serious	none	234/578 (40.5%)	84/287 (29.3%)	**RR 1.38** (1.13 to 1.70)	**111 more per 1,000** (from 38 more to 205 more)	⨁⨁◯◯ LOW	CRITICAL
Disease activity (follow up: 1 year; assessed with: DAS28-ESR (Lower values – > benefit) (MCID -1.17)												
1 (8)	randomised trials	serious [a]	not serious	serious [b]	not serious	none	578	287	-	MD **0.83 lower** (1.09 lower to 0.57 lower)	⨁⨁◯◯ LOW	CRITICAL
Remission (follow up: 1 year; assessed with: DAS28-ESR remission <2.6)												
1 (8)	randomised trials	serious [a]	not serious	serious [b]	not serious	none	240/578 (41.5%)	56/287 (19.5%)	**RR 2.13** (1.65 to 2.74)	**220 more per 1,000** (from 127 more to 340 more)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCZ+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Radiographic progression (follow up: 1 year; assessed with: mTSS (Lower values – > benefit) (MCID 4.6)												
1 (8)	randomised trials	serious [a]	not serious	serious [b]	not serious	none	540	267	-	MD **0.89 lower** (1.45 lower to 0.33 lower)	⨁⨁◯◯ LOW	IMPORTANT
Disability (follow up: 1 year; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
1 (8)	randomised trials	serious [a]	not serious	serious [b]	not serious	none	0	0	-	MD **0.14 lower** (0.22 lower to 0.06 lower)	⨁⨁◯◯ LOW	IMPORTANT
Quality of Life (follow up: 1 year; assessed with: SF-36 PCS (Higher values – > benefit) (MCID 4.4)												
1 (8)	randomised trials	serious [a]	not serious	serious [b]	not serious	none	0	0	-	MD **1.99 higher** (0.41 higher to 3.57 higher)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCZ+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Quality of Life (follow up: 1 year; assessed with: SF-36 MCS (Higher values – > benefit) (MCID 3.1)												
1 (8)	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	0	0	-	MD **1.25 higher** (1.58 lower to 4.08 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Withdrawal due to adverse events (follow up: 1 year)												
1 (8)	randomised trials	serious [a]	not serious	serious [b]	not serious	none	94/579 (16.2%)	21/282 (7.4%)	**RR 2.18** (1.39 to 3.42)	**88 more per 1,000** (from 29 more to 180 more)	⨁⨁◯◯ LOW	IMPORTANT
Serious adverse events (follow up: 1 year)												
1 (8)	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	60/579 (10.4%)	24/282 (8.5%)	**RR 1.22** (0.78 to 1.91)	**19 more per 1,000** (from 19 fewer to 77 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCZ+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Malignancy (follow up: 1 year)												
1 (8)	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	5/579 (0.9%)	3/282 (1.1%)	**RR 0.81** (0.20 to 3.37)	**2 fewer per 1,000** (from 9 fewer to 25 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Myocardial infarction (follow up: 1 year)												
1 (8)	randomised trials	serious [a]	not serious	serious [b]	very serious [d]	none	4/579 (0.7%)	0/282 (0.0%)	**RR 4.39** (0.24 to 81.28)	**7 fewer per 1,000** (from 480 fewer to 160 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Death (follow up: 1 year)												
1 (8)	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	6/579 (1.0%)	2/282 (0.7%)	**RR 1.46** (0.30 to 7.19)	**3 more per 1,000** (from 5 fewer to 44 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCZ+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events (from SRs on harms)												
0 (9)							The Systematic Review RefID=5712, 2011 (RCTs=4, n=2701) comparing Tocilizumab + MTX vs Placebo + MTX among MTX naïve RA showed that for Serious adverse events, the result was OR=0.78 (0.45, 1.33)				-	
Malignancy (from SRs on harms)												
0 (9)							The Systematic Review RefID=4638, 2012 (RCTs=1, n=1190) comparing Tocilizumab + MTX vs Placebo + MTX among RA showed that for Cancer, the result was RR=4.4 (0.56-34.8) at 1 year and RR=0.41 (0.14-1.2) at 6 months (RCT=4, n=2950)				-	

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Rated down by one level for lack of allocation concealment
b. Downgraded by one level due to serious indirectness. The evidence is based on a non-MTX csDMARD exposed population.
c. Rated down by one level for imprecision as the CI includes both values suggesting no effect and values suggesting harm
d. Rated down by two levels for imprecision as the CI includes both values suggesting benefit and values suggesting harm

Cost-effectiveness

The economic analysis RefID 7858 (10) randomized-control study compared ADA, ADA+MTX, ETN, ETN+MTX and MTX.

The study reported (1) adalimumab plus methotrexate and infliximab plus methotrexate had incremental cost-effectiveness ratios (ICERs) versus methotrexate monotherapy of $US63 769, $US89 772, $US194 589 and $US409 523 per QALY, respectively.

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PICO 6b. Should patients with MTX-naïve and non-MTX csDMARDs exposed RA and moderate to high disease activity receive MTX monotherapy or boDMARD with MTX or tsDMARD with MTX?

P -Patients with MTX-naïve and non-MTX csDMARDs exposed RA and moderate to high disease activity
I - MTX monotherapy
C - TNF Inhibitor + MTX
C - Abatacept+ MTX
C - Rituximab+ MTX
C - IL-6 Receptor Inhibitor+ MTX
C - JAK Inhibitor + MTX

Comparison 1: TNF Inhibitor + MTX **versus** MTX monotherapy. See below Table.
Comparison 2: Abatacept + MTX **versus** MTX monotherapy. See below Table.
Comparison 3: Rituximab + MTX **versus** MTX monotherapy. See below Table.
Comparison 4: IL-6 Receptor Inhibitor + MTX **versus** MTX monotherapy. See below Table.
Comparison 5: JAK Inhibitor + MTX versus MTX monotherapy. No eligible RCT, NRS, or indirect evidence were identified.

Comparison 1: TNF Inhibitor + MTX versus MTX monotherapy. Data based on **direct** RCT evidence.
Overall certainty of evidence: High

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNFi+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: range 6 months to 2 years; assessed with: ACR 20)												
9 (1-9)	randomised trials	not serious	not serious	not serious	not serious	none	1414/2051 (68.9%) [a]	1134/2094 (54.2%)	**RR 1.25** (1.19 to 1.31)	**135 more per 1,000** (from 103 more to 168 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Disease activity (follow up: 1 year; assessed with: ACR50)												
5 (4-6, 8, 9)	randomised trials	not serious	not serious	not serious	not serious	none	559/974 (57.4%) [a]	363/881 (41.2%)	**RR 1.42** (1.29 to 1.56)	**173 more per 1,000** (from 119 more to 231 more)	⨁⨁⨁⨁ HIGH	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNFi+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: range 6 months to 2 years; assessed with: ACR 70)												
9 (1-9)	randomised trials	not serious	not serious [b]	not serious	not serious	none	733/2051 (35.7%) [a]	401/2094 (19.1%)	**RR 1.74** (1.55 to 1.96)	**142 more per 1,000** (from 105 more to 184 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Disease activity (follow up: range 6 months to 1 year; assessed with: DAS28ESR/CRP (Lower values – > benefit) (values>0.2 are considered clinically significant)												
5 (2, 4, 6, 7, 9)	randomised trials	not serious	not serious	not serious	not serious [c]	none	1133 [a]	1200	-	SMD **0.39 lower** (0.47 lower to 0.31 lower)	⨁⨁⨁⨁ HIGH	CRITICAL
Remission (follow up: range 6 months to 2 years; assessed with: DAS28-ESR remission <2.6)												
7 (1-5, 8, 9)	randomised trials	not serious	not serious	not serious	not serious	none	662/1743 (38.0%) [a]	353/1667 (21.2%)	**RR 1.80** (1.62 to 2.01)	**169 more per 1,000** (from 131 more to 214 more)	⨁⨁⨁⨁ HIGH	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNFi+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Radiographic progression (follow up: range 6 months to 1 year; assessed with: mTSS (Lower values – > benefit) (MCID 4.6)												
3 (1, 5, 9)	randomised trials	not serious	very serious [d]	not serious	not serious	none	782 [a]	702	-	MD **1.94 lower** (3.61 lower to 0.28 lower)	⨁⨁◯◯ LOW	IMPORTANT
Fatigue (follow up: range 1 year to 2 years; assessed with: VAS-F or FACIT-F (Higher values –> benefit) (values >0.2 are considered clinically significant)												
2 (10, 11)	randomised trials	not serious	serious [e]	not serious	serious [f]	none	530 [a]	520	-	SMD **0.15 higher** (0.03 higher to 0.28 higher)	⨁⨁◯◯ LOW	IMPORTANT
Pain (follow up: range 1 year to 2 years; assessed with: VAS pain (0-100) (Lower values – > benefit) (MCID -11.9)												
2 (10, 11)	randomised trials	not serious	very serious [g]	not serious	not serious	none	530 [a]	519	-	MD **4.66 lower** (6.93 lower to 2.39 lower)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNFi+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disability (follow up: range 6 months to 24 months; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
5 (2, 4, 6, 7, 9)	randomised trials	not serious	very serious [h]	not serious	serious [f]	none	1135 [a,i]	1119	-	MD **0.19 lower** (0.25 lower to 0.14 lower)	⨁◯◯◯ VERY LOW	IMPORTANT
Quality of life (follow up: range 1 year to 2 years; assessed with: SF-36 PCS (Higher values – > benefit) (MCID 4.4)												
3 (9-11)	randomised trials	not serious	serious [j]	not serious	not serious	none	880 [a]	792	-	MD **1.39 higher** (1.42 lower to 4.2 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Quality of Life (follow up: range 1 year to 2 years; assessed with: SF-36 MCS (Higher values – > benefit) (MCID 3.1)												
2 (10, 11)	randomised trials	not serious	not serious	not serious	not serious	none	521 [a]	510	-	MD **0.15 lower** (1.35 lower to 1.04 higher)	⨁⨁⨁⨁ HIGH	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNFi+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Withdrawal due to lack of efficacy (follow up: range 1 year to 2 years)												
3 (2, 4, 9)	randomised trials	not serious	not serious [k]	not serious	not serious	none	33/716 (4.6%) [a]	99/628 (15.8%)	**RR 0.32** (0.19 to 0.52)	**107 fewer per 1,000** (from 128 fewer to 76 fewer)	⨁⨁⨁⨁ HIGH	IMPORTANT
Withdrawal due to adverse events (follow up: range 6 months to 2 years)												
5 (2-4, 8, 9)	randomised trials	not serious	not serious	not serious	not serious	none	109/1389 (7.8%) [a]	53/1305 (4.1%)	**RR 1.88** (1.36 to 2.59)	**36 more per 1,000** (from 15 more to 65 more)	⨁⨁⨁⨁ HIGH	IMPORTANT
Serious adverse events (follow up: range 6 months to 2 years)												
7 (2-6, 8, 9)	randomised trials	not serious	not serious	not serious	serious [l]	none	235/1677 (14.0%) [a]	188/1580 (11.9%)	**RR 1.17** (0.99 to 1.40)	**20 more per 1,000** (from 1 fewer to 48 more)	⨁⨁⨁◯ MODERATE	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNFi+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Cardiovascular disease (follow up: 1 year)												
3 (4, 5, 9)	randomised trials	not serious	not serious	not serious	very serious [m]	none	4/721 (0.6%) [a]	6/632 (0.9%)	**RR 0.62** (0.17 to 2.21)	**4 fewer per 1,000** (from 8 fewer to 11 more)	⨁⨁◯◯ LOW	IMPORTANT
Malignancy (follow up: range 1 year to 2 years)												
2 (3, 5)	randomised trials	not serious	not serious	not serious	very serious [m]	none	6/542 (1.1%) [a]	8/525 (1.5%)	**RR 0.74** (0.25 to 2.14)	**4 fewer per 1,000** (from 11 fewer to 17 more)	⨁⨁◯◯ LOW	IMPORTANT
Death (follow up: range 6 months to 2 years)												
5 (2, 3, 8, 9, 12)	randomised trials	not serious	not serious	not serious	serious [l]	none	10/1587 (0.6%) [a]	4/1493 (0.3%)	**RR 1.85** (0.57 to 6.00)	**2 more per 1,000** (from 1 fewer to 13 more)	⨁⨁⨁◯ MODERATE	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNFi+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Malignancy (from SRs on harms)												
0 (13)							The Systematic Review RefID=4638, 2012 (RCTs=6, n=1890) comparing any TNFi + csDMARD vs csDMARD among RA showed that for Cancer, the result was RR=0.85 (0.30-2.4) at 2 years and RR=1.3 (0.77-2.1) at all time points combined (6 months, 1 year, 2 years, 2.5 years, RCT=29, n=11144)				-	

CI: Confidence interval; **RR:** Risk ratio; **SMD:** Standardised mean difference; **MD:** Mean difference

Explanations

a. TNFis includes Etanercept, Adalimumab, Certolizumab, Golimumab and Infliximab.
b. I2=17%
c. According to the Cochrane's handbook, Cohen suggested that SMD=0.2 be considered a 'small' effect size, 0.5 represents a 'medium' effect size and 0.8 a 'large' effect size. This means that if two groups' means do not differ by 0.2 standard deviations or more, the difference is trivial, even if it is statistically significant.
d. Downgraded by two levels due to very serious inconsistency. I2=90%.
e. I2=55%
f. Rated down by one level for imprecision, as CI includes both values suggesting benefits and values suggesting no effect. According to the Cochrane's handbook, Cohen suggested that SMD=0.2 be considered a 'small' effect size, 0.5 represents a 'medium' effect size and 0.8 a 'large' effect size. This means that if two groups' means do not differ by 0.2 standard deviations or more, the difference is trivial, even if it is statistically significant.
g. Downgraded by two levels due to very serious inconsistency. I2=85%
h. Downgraded by two levels due to very serious inconsistency. I2=92%
i. The studies PREMIER, COMET and ASPIRE found that the RR of improvement in HAQ-DI (≥0.22 change from baseline) at 1-2 years was 1.05 (95%CI 0.87 to 1.28), absolute risk increase 36 more per 1000 (95%CI 94 fewer to 201 more).
j. Downgraded by two levels due to very serious inconsistency. I2=88%
k. I2=42%
l. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting harm.
m. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm. Low number of events.

Comparison 2: Abatacept + MTX **versus** MTX monotherapy. Data based on **direct** RCT evidence.
Overall certainty of evidence: Moderate

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ABA+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 1 year; assessed with: ACR 70)												
1 (14)	randomised trials	serious [a]	not serious	not serious	not serious	none	109/256 (42.6%)	69/253 (27.3%)	**RR 1.56** (1.22 to 2.00)	**153 more per 1,000** (from 60 more to 273 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Disease activity (follow up: 1 year; assessed with: DAS28 CRP (Lower values – > benefit) (MCID -1.02)												
1 (14)	randomised trials	serious [a]	not serious	not serious	not serious	none	256	253	-	MD **0.73 lower** (0.98 lower to 0.48 lower)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ABA+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Remission (follow up: 1 year; assessed with: DAS28-ESR remission <2.6)												
2 (14, 15)	randomised trials	serious [a]	not serious	not serious	not serious	none	176/371 (47.4%)	109/368 (29.6%)	**RR 1.60** (1.33 to 1.93)	**178 more per 1,000** (from 98 more to 275 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Radiographic progression (follow up: 1 year; assessed with: mTSS (Lower values – > benefit) (MCID 4.6)												
1 (14)	randomised trials	serious [a]	not serious	not serious	not serious	none	0 [b]	0	-	MD **0.43 lower** (0.91 lower to 0.05 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Disability (follow up: 1 year; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
1 (14)	randomised trials	serious [a]	not serious	not serious	serious [c]	none	256 [d]	253	-	MD **0.2 lower** (0.31 lower to 0.09 lower)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ABA+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Quality of Life (follow up: 1 year; assessed with: SF-36 PCS (Higher values – > benefit) (MCID 4.4)												
1 (14)	randomised trials	serious [a]	not serious	not serious	serious [c]	none	256	253	-	MD **2.5 higher** (0.77 higher to 4.23 higher)	⨁⨁◯◯ LOW	IMPORTANT
Quality of Life (follow up: 1 year; assessed with: SF-36 MCS (Higher values – > benefit) (MCID 3.1)												
1 (14)	randomised trials	serious [a]	not serious	not serious	serious [e]	none	256	253	-	MD **1.81 lower** (3.58 lower to 0.04 lower)	⨁⨁◯◯ LOW	IMPORTANT
Withdrawal due to lack of efficacy (follow up: 1 year)												
1 (15)	randomised trials	not serious	not serious	not serious	serious [e]	none	5/115 (4.3%)	11/115 (9.6%)	**RR 0.45** (0.16 to 1.27)	**53 fewer per 1,000** (from 80 fewer to 26 more)	⨁⨁⨁◯ MODERATE	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ABA+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Withdrawal due to adverse events (follow up: 1 year)												
2 (14, 15)	randomised trials	serious [a]	not serious	not serious	serious [f]	none	13/375 (3.5%)	16/369 (4.3%)	**RR 0.80** (0.39 to 1.64)	**9 fewer per 1,000** (from 26 fewer to 28 more)	⨁⨁◯◯ LOW	IMPORTANT
Serious adverse events (follow up: 1 year)												
1 (14)	randomised trials	serious [a]	not serious	not serious	serious [g]	none	20/256 (7.8%)	20/253 (7.9%)	**RR 0.99** (0.55 to 1.79)	**1 fewer per 1,000** (from 36 fewer to 62 more)	⨁⨁◯◯ LOW	IMPORTANT
Malignancy (follow up: 1 year)												
2 (14, 15)	randomised trials	serious [a]	not serious	not serious	serious [e]	none	1/371 (0.3%)	2/368 (0.5%)	**RR 0.60** (0.08 to 4.48)	**2 fewer per 1,000** (from 5 fewer to 19 more)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ABA+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Death (follow up: 1 year)												
2 (14, 15)	randomised trials	serious [a]	not serious	not serious	serious [f]	none	2/371 (0.5%)	4/368 (1.1%)	**RR 0.49** (0.09 to 2.67)	**6 fewer per 1,000** (from 10 fewer to 18 more)	⨁⨁◯◯ LOW	IMPORTANT
Malignancy (from SRs on harms)												
(13)							The Systematic Review RefID=4638, 2012 (RCTs=3, n=2435) comparing Abatacept + csDMARD vs Placebo + csDMARD among RA showed that for Cancer, the result was RR=0.65 (0.25-1.7) at 1 year.				-	

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Downgraded by one level due to serious risk of bias. Lack of allocation concealment and lack of blinding of non-radiographic outcome assessors.
b. The study AGREE found that the RR of developing no radiographic progression (change in mTSS ≤0) was 1.6 (95%CI 0.99 to 1.36), absolute risk increase 84 more per 1000 (95%CI 5 fewer to 190 more).
c. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting benefit.
d. The studies AGREE and AVERT found that the RR of improvement in HAQ-DI (≥0.3 change from baseline) was 1.25 (95%CI 1.12 to 1.39), absolute risk increase 141 more per 1000 (95%CI 668 more to 220 more).
e. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting harm.
f. Downgraded by two levels due to serious imprecision. Confidence interval includes both values suggesting harm and values suggesting benefit. Low number of events.
g. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting harm and values suggesting benefit.

Comparison 3: Rituximab + MTX versus MTX monotherapy. Data based on **direct** RCT evidence.
Overall certainty of evidence: Moderate

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RTX+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 2 years; assessed with: ACR 20)												
1 (16)	randomised trials	serious [a]	not serious	not serious	not serious	none	185/250 (74.0%)	137/249 (55.0%)	**RR 1.34** (1.18 to 1.54)	**187 more per 1,000** (from 99 more to 297 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Disease activity (follow up: 2 years; assessed with: ACR 50)												
1 (16)	randomised trials	serious [a]	not serious	not serious	not serious	none	155/250 (62.0%)	102/249 (41.0%)	**RR 1.51** (1.27 to 1.81)	**209 more per 1,000** (from 111 more to 332 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RTX+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 2 years; assessed with: ACR 70)												
1 (16)	randomised trials	serious [a]	not serious	not serious	not serious	none	115/250 (46.0%)	67/249 (26.9%)	**RR 1.71** (1.34 to 2.18)	**191 more per 1,000** (from 91 more to 318 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Disease activity (follow up: 2 years; assessed with: DAS28 ESR (Lower values – > benefit) (MCID -1.17)												
1 (16)	randomised trials	serious [a]	not serious	not serious	serious [b]	none	250	249	-	MD **1.19 lower** (1.5 lower to 0.88 lower)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RTX+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Remission (follow up: 2 years; assessed with: DAS28-ESR remission <2.6)												
1 (16)	randomised trials	serious [a]	not serious	not serious	not serious	none	80/250 (32.0%)	32/249 (12.9%)	**RR 2.49** (1.72 to 3.61)	**191 more per 1,000** (from 93 more to 335 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Radiographic progression (follow up: 2 years; assessed with: mTSS (Lower values – > benefit) (MCID 4.6)												
1 (16)	randomised trials	serious [a]	not serious	not serious	not serious	none	244	233	-	MD **1.54 lower** (2.3 lower to 0.78 lower)	⨁⨁⨁◯ MODERATE	IMPORTANT
Pain (follow up: 1 year; assessed with: VAS pain (Lower values – > benefit) (MCID -11.9)												
1 (17)	randomised trials	serious [a]	not serious	not serious	serious [b]	none	0	0	-	MD **12.2 lower** (16.15 lower to 8.25 lower)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RTX+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Fatigue (follow up: 1 year; assessed with: FACIT-F (Higher values – > benefit) (MCID 15.9)												
1 (17)	randomised trials	serious [a]	not serious	not serious	not serious	none	0	0	-	MD **3.45 higher** (1.77 higher to 5.13 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Disability (follow up: 2 years; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
1 (16)	randomised trials	serious [a]	not serious	not serious	serious [b]	none	250 [c]	249	-	MD **0.25 lower** (0.4 lower to 0.1 lower)	⨁⨁◯◯ LOW	IMPORTANT
Quality of Life (follow up: 1 year; assessed with: SF-36 PCS (Higher values – > benefit) (MCID 4.4)												
1 (17)	randomised trials	serious [a]	not serious	not serious	serious [b]	none	0	0	-	MD **3.53 higher** (2.04 higher to 5.02 higher)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RTX+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Quality of Life (follow up: 1 year; assessed with: SF-36 MCS (Higher values – > benefit) (MCID 3.1)												
1 (17)	randomised trials	serious [a]	not serious	not serious	not serious	none	0	0	-	MD **0.81 higher** (1.03 lower to 2.66 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Withdrawal due to adverse events (follow up: 2 years)												
1 (16)	randomised trials	serious [a]	not serious	not serious	serious [b]	none	7/250 (2.8%)	17/249 (6.8%)	**RR 0.41** (0.17 to 0.97)	**40 fewer per 1,000** (from 57 fewer to 2 fewer)	⨁⨁◯◯ LOW	IMPORTANT
Serious adverse events (follow up: 2 years)												
1 (16)	randomised trials	serious [a]	not serious	not serious	very serious [d]	none	33/250 (13.2%)	42/249 (16.9%)	**RR 0.78** (0.51 to 1.19)	**37 fewer per 1,000** (from 83 fewer to 32 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RTX+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Malignancy (follow up: 2 years)												
1 (16)	randomised trials	serious [a]	not serious	not serious	very serious [d]	none	3/250 (1.2%)	7/249 (2.8%)	**RR 0.43** (0.11 to 1.63)	**16 fewer per 1,000** (from 25 fewer to 18 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Death (follow up: 2 years)												
1 (16)	randomised trials	serious [a]	not serious	not serious	very serious [d]	none	1/250 (0.4%)	3/249 (1.2%)	**RR 0.33** (0.03 to 3.17)	**8 fewer per 1,000** (from 12 fewer to 26 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RTX+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Malignancy (from SRs on harms)												
(13)							The Systematic Review RefID=4638, 2012 (RCTs=5, n=2066) comparing Rituximab + csDMARD vs Placebo + MTX among RA and showed that for Cancer, the result was RR=1.5 (0.38-6.1) at 24 weeks and RR=0.65 (0.24-1.7) at 2 years (RCT= 1, n=748)				-	

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Downgraded by one level due to serious risk of bias. Lack of allocation concealment.

b. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting benefit.

c. The study IMAGE found that the RR of improvement in HAQ-DI (≥0.22 change from baseline) was 1.12 (95%CI 1.03 to 1.21), absolute risk increase 93 more per 1000 (95%CI 23 more to 162 more).

d. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm.

Comparison 4: IL-6 Receptor Inhibitor + MTX **versus** MTX monotherapy. Data based on **direct** RCT evidence.
Overall certainty of evidence: Moderate

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCZ+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 1 year; assessed with: ACR 20)												
1 (18)	randomised trials	serious [a]	not serious	not serious	not serious	none	374/578 (64.7%)	164/287 (57.1%)	**RR 1.13** (1.01 to 1.27)	**74 more per 1,000** (from 6 more to 154 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Disease activity (follow up: 1 year; assessed with: ACR 50)												
1 (18)	randomised trials	serious [a]	not serious	not serious	not serious	none	314/578 (54.3%)	117/287 (40.8%)	**RR 1.33** (1.14 to 1.56)	**135 more per 1,000** (from 57 more to 228 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCZ+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 1 year; assessed with: ACR 70)												
1 (18)	randomised trials	serious [a]	not serious	not serious	not serious	none	234/578 (40.5%)	84/287 (29.3%)	**RR 1.38** (1.13 to 1.70)	**111 more per 1,000** (from 38 more to 205 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Disease activity (follow up: 1 year; assessed with: DAS28-ESR (Lower values – > benefit) (MCID -1.17)												
1 (18)	randomised trials	serious [a]	not serious	not serious	not serious	none	578	287	-	MD **0.83 lower** (1.09 lower to 0.57 lower)	⨁⨁⨁◯ MODERATE	CRITICAL
Remission (follow up: 1 year; assessed with: DAS28-ESR remission <2.6)												
1 (18)	randomised trials	serious [a]	not serious	not serious	not serious	none	240/578 (41.5%)	56/287 (19.5%)	**RR 2.13** (1.65 to 2.74)	**220 more per 1,000** (from 127 more to 340 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCZ+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Radiographic progression (follow up: 1 year; assessed with: mTSS (Lower values – > benefit) (MCID 4.6)												
1 (18)	randomised trials	serious [a]	not serious	not serious	not serious	none	540	267	-	MD **0.89 lower** (1.45 lower to 0.33 lower)	⨁⨁⨁◯ MODERATE	IMPORTANT
Disability (follow up: 1 year; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
1 (18)	randomised trials	serious [a]	not serious	not serious	not serious	none	0	0	-	MD **0.14 lower** (0.22 lower to 0.06 lower)	⨁⨁⨁◯ MODERATE	IMPORTANT
Quality of Life (follow up: 1 year; assessed with: SF-36 PCS (Higher values – > benefit) (MCID 4.4)												
1 (18)	randomised trials	serious [a]	not serious	not serious	not serious	none	0	0	-	MD **1.99 higher** (0.41 higher to 3.57 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCZ+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Quality of Life (follow up: 1 year; assessed with: SF-36 MCS (Higher values – > benefit) (MCID 3.1)												
1 (18)	randomised trials	serious [a]	not serious	not serious	serious [b]	none	0	0	-	MD **1.25 higher** (1.58 lower to 4.08 higher)	⨁⨁◯◯ LOW	IMPORTANT
Withdrawal due to adverse events (follow up: 1 year)												
1 (18)	randomised trials	serious [a]	not serious	not serious	not serious	none	94/579 (16.2%)	21/282 (7.4%)	**RR 2.18** (1.39 to 3.42)	**88 more per 1,000** (from 29 more to 180 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Serious adverse events (follow up: 1 year)												
1 (18)	randomised trials	serious [a]	not serious	not serious	serious [b]	none	60/579 (10.4%)	24/282 (8.5%)	**RR 1.22** (0.78 to 1.91)	**19 more per 1,000** (from 19 fewer to 77 more)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCZ+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Malignancy (follow up: 1 year)												
1 (18)	randomised trials	serious [a]	not serious	not serious	serious [b]	none	5/579 (0.9%)	3/282 (1.1%)	**RR 0.81** (0.20 to 3.37)	**2 fewer per 1,000** (from 9 fewer to 25 more)	⨁⨁◯◯ LOW	IMPORTANT
Myocardial infarction (follow up: 1 year)												
1 (18)	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	4/579 (0.7%)	0/282 (0.0%)	**RR 4.39** (0.24 to 81.28)	**7 fewer per 1,000** (from 480 fewer to 160 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Death (follow up: 1 year)												
1 (18)	randomised trials	serious [a]	not serious	not serious	serious [b]	none	6/579 (1.0%)	2/282 (0.7%)	**RR 1.46** (0.30 to 7.19)	**3 more per 1,000** (from 5 fewer to 44 more)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCZ+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events (from SRs on harms)												
(19)	randomised trials	serious	not serious				The Systematic Review RefID=5712, 2011 (RCTs=4, n=2701) comparing Tocilizumab + MTX vs Placebo + MTX among MTX naïve RA showed that for Serious adverse events, the result was OR=0.78 (0.45, 1.33)				-	
Malignancy (from SRs on harms)												
(13)			not serious				The Systematic Review RefID=4638, 2012 (RCTs=1, n=1190) comparing Tocilizumab + MTX vs Placebo + MTX among RA showed that for Cancer, the result was RR=4.4 (0.56-34.8) at 1 year and RR=0.41 (0.14-1.2) at 6 months (RCT=4, n=2950)				-	

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Rated down by one level for lack of allocation concealment
b. Rated down by one level for imprecision as the CI includes both values suggesting no effect and values suggesting harm
c. Rated down by two levels for imprecision as the CI includes both values suggesting benefit and values suggesting harm

Cost-effectiveness

The economic analysis RefID 1591 (20) based on the OPTIMA and PROWD trials compared ADA + MTX vs MTX monotherapy.

The study reported (1) In OPTIMA, those patients receiving ADA + MTX had significantly greater improvements in the total RA-WIS score compared with MTX monotherapy, with a mean change of -7.22 vs -5.23, respectively (P = 0.0069). In PROWD, patients receiving ADA + MTX had a large improvement, although not significant, in the RA-WIS compared with MTX alone (mean change of -8.14 vs -6.49, respectively). (2) From baseline to 26 or 24 weeks for OPTIMA and PROWD, respectively, there was not a large change in employment status for patients who were employed and had a baseline WIS 510. In OPTIMA, 91 and 86% of patients who were treated with ADA + MTX or PBO + MTX, respectively, were still employed at week 26, while 9 and 14% of patients with ADA + MTX or PBO + MTX treatment, respectively, had lost employment by 26 weeks. In PROWD, 94 and 98% of patients treated with ADA + MTX or PBO + MTX, respectively, remained employed at 24 weeks, whereas 6% of patients treated with ADA + MTX had lost employment at week 24 compared with 2% treated with PBO + MTX. (3) Over the 24 and 26 weeks of follow-up, patients in both treatment groups experienced a decreased risk of work instability as measured by the WIS in both OPTIMA and PROWD. Compared with patients in the PBO + MTX group in OPTIMA, a significantly higher percentage of patients in the ADA + MTX group experienced improvements of one or more risk category, referring to the low, medium or high risk of premature work cessation (47% vs 58%, respectively; P = 0.0479). (4) The percentage of patients achieving clinically meaningful improvements in WIS of 55, 57 and 59 points at week 26 in OPTIMA was 55, 47 and 42%, respectively, for those treated with ADA + MTX, and clinically meaningful changes were significantly higher in the ADA + MTX treatment group compared with the PBO + MTX group. (5) the percentage of patients with improvement of one or more risk category and a WIS improvement of55 points was 53 and 50% for ADA + MTX treatment and 41 and 42% for MTX monotherapy at week 26 in OPTIMA (P = 0.0315) and week 24 in PROWD (P = 0.3879), respectively. (5) At week 26 in OPTIMA, the mean change from baseline in the WPAI subdomain for work-related activity impairment was significantly higher in patients on ADA + MTX therapy vs MTX monotherapy (P = 0.0071). There was also a significant difference in the change from baseline in presenteeism, defined as performance at work owing to RA, and overall work impairment (P = 0.0253, and 0.0105, respectively) between combination therapy with ADA + MTX and PBO + MTX. For both treatment groups in OPTIMA, there was very little change from baseline in absenteeism, or the days/hours of work missed owing to RA, and differences were not significant (P = 0.5640).

Author's conclusion: (1) In OPTIMA, treatment with ADA + MTX showed a clinically meaningful and statistically significant reduction in work instability in patients with early RA at medium to high risk of job loss compared with MTX monotherapy. (2) In addition, in OPTIMA, patients on ADA + MTX therapy showed a statistically significant change in percentage points from baseline vs MTX monotherapy in activity impairment, presenteeism and overall work impairment. (3) Taken together, these results provide evidence that, compared with MTX monotherapy, ADA + MTX does in fact reduce the work-related disability in RA patients at elevated risk of job loss.

The economic analysis RefID 2636 (21) based on PREMIER trial conducted in UK compared ADA+MTX vs MTX.
The study reported (1) Discounted life expectancy was estimated to be 12.62 versus 9.94 for combination therapy versus MTX monotherapy, respectively, an incremental gain of 2.68 life years in the combination treatment arm. (2) Discounted QALYs were 6.83 versus 3.79, respectively, a gain of 3.04 QALYs in the combination treatment arm. (3) The associated discounted cost of medication was estimated to be £108 805 and £2 589, respectively, corresponding to a net cost of £106 217 favoring MTX. (4) However, the more effective combination therapy was also associated with savings in terms of hospitalizations and GP visits, such that the total net cost for combination therapy was estimated to be £98 558. (5) the ICER excluding indirect costs was estimated to be £32 425. When indirect costs were included in the analysis, the ICER decreased to £27 238.
Author's conclusion: the results of this new modelling approach, which sought to integrate explicitly into a single unifying framework the reversible and irreversible effects of RA, suggest that starting with combination therapy in early, aggressive RA is not only effective, but is also associated with an acceptable balance between costs and effects.

The economic analysis RefID 6163 (22) based on PREMIER trial conducted in patients were from Europe (54%), North America (40%), or Australia (6%) compared adalimumab + MTX vs adalimumab alone vs MTX alone.
The study reported (1) patients who received combination therapy missed approximately half as many days as patients who received methotrexate (17.4 versus 36.9 days for employed workers; 7.9 versus 18.6 days for homemakers). (2) Presenteeism was lower (reflecting better productivity) for combination therapy than methotrexate monotherapy. (3) The likelihood of gaining/ retaining employment over 2 years was greater for combination therapy than methotrexate monotherapy (odds ratio 1.530, 95% confidence interval 1.038–2.255; P= 0.0318).
Author's conclusion: Compared with methotrexate monotherapy, combination therapy was associated with more positive work outcomes: less absenteeism, less presenteeism, and greater likelihood of gaining/retaining employments of missed workdays and job gain/retainment.

The economic analysis RefID 6492 (23) based on COMET trial conducted in UK compared ETN + MTX vs MTX alone.
The study reported (1) compared with the MTX group, the ETN + MTX group had a maximum of 37 fewer missed workdays or at minimum 22 fewer missed workdays. (2) The associated productivity gain equaled £2586 and £1555, respectively. (3) When additionally accounting for presenteeism, the total improvement could be as high as 42 (95% CI 16, 69) fewer lost workdays representing a productivity gain of £2968. **Author's conclusion:** Our results demonstrated that early treatment with ETN + MTX led to a significant attenuation of absenteeism among patients with early active RA.

The economic analysis RefID 6964 (4) compared adalimumab + MTX or placebo + MTX.

The study reported (1) although job loss during the 56-week study was significantly lower with adalimumab MTX (14 of 75 patients) compared with MTX alone (29 of 73 patients; P 0.005), the primary end point was not met (12 of 75 versus 20 of 73 patients; P = 0.092), likely owing to early drop out in the MTX group. (2) There were significant improvements in the working time lost in the adalimumab + MTX group.

Author's conclusion: adalimumab + MTX reduced job loss and improved productivity in early RA when compared with MTX alone, which supports the early use of anti–tumor necrosis factor therapy and suggests its cost efficacy.

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PICO 7a. Should patients with MTX-naïve and non-MTX csDMARDs naïve RA and moderate to high disease activity receive mono- or combination csDMARDs and *short-term (< 3 months)* GCs or mono or combination csDMARDs alone?

P - Patients with MTX-naïve and non-MTX csDMARDs naïve RA and moderate to high disease activity

I - Mono or combination csDMARDs with short-term (< 3 months) GCs

C - Mono or combination csDMARDs alone (i.e., without short-term GCs)

No eligible RCT, NRS, or indirect evidence were identified.

PICO 7b. Should patients with MTX-naïve and non-MTX csDMARDs exposed RA and moderate to high disease activity receive mono- or combination csDMARDs and *short-term (< 3 months)* GCs or mono or combination csDMARDs alone?

P - Patients with MTX-naïve and non-MTX csDMARDs exposed RA and moderate to high disease activity

I - Mono or combination csDMARDs with short-term (< 3 months) GCs

C - Mono or combination csDMARDs alone (i.e., without short-term GCs)

No eligible RCT, NRS, or indirect evidence were identified.

PICO 8a. Should patients with MTX-naïve and non-MTX csDMARDs naïve RA and moderate to high disease activity, receive *long-term (≥ 3 months)* low dose (≤ 10mg per day) GCs and mono- or combination csDMARDs or mono or combination csDMARDs alone?

P - Patients with MTX-naïve and non-MTX csDMARDs naïve RA and moderate to high disease activity

I - Mono or combination csDMARDs with long-term (**≥** 3 months) low dose (≤ 10mg per day) GCs

C - Mono or combination csDMARDs alone (i.e. without long-term GCs)

Comparison 1: Mono or combination csDMARDs with long-term (**≥** 3 months) low dose (≤ 10mg per day) GCs **versus** mono or combination csDMARDs alone (i.e. without long-term GCs). See below Table.

Comparison 1: Mono or combination csDMARDs with long-term (≥ 3 months) low dose (≤ 10mg per day) GCs **versus** mono or combination csDMARDs alone (i.e. without long-term GCs). Data based on **direct** RCT evidence.
Overall certainty of evidence: Moderate

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	csDMARDs + long-term low-dose GCs	csDMARDs monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 2 years; assessed with: DAS28-ESR (Lower values – > benefit) (MCID -1.17)												
1 (1)	randomised trials	serious [a]	not serious	not serious	not serious	none	116 [b]	126 [c]	-	MD **0.5 lower** (0.84 lower to 0.16 lower)	⨁⨁⨁◯ MODERATE	CRITICAL
Remission (follow up: 2 years; assessed with: DAS28-ESR<2.6)												
1 (1)	randomised trials	serious [a]	not serious	not serious	not serious	none	64/116 (55.2%) [b]	41/126 (32.5%) [c]	**RR 1.70** (1.26 to 2.29)	**228 more per 1,000** (from 85 more to 420 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Radiographic progression (follow up: 2 years; assessed with: Sharp/van der Heijde score (Lower values – > benefit) (MCID 4.6)												
1 (1)	randomised trials	not serious [a]	not serious	not serious	serious [d]	none	108 [b]	117 [c]	-	MD **3.9 lower** (7 lower to 0.8 lower)	⨁⨁⨁◯ MODERATE	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	csDMARDs + long-term low-dose GCs	csDMARDs monotherapy	Relative (95% CI)	Absolute (95% CI)		
Disability (follow up: 2 years; assessed with: HAQ swedish version (Lower values – > benefit) (MCID -0.22)												
1 (1)	randomised trials	serious [a]	not serious	not serious	serious [d]	none	116 [b]	126 [c]	-	MD **0.2 lower** (0.34 lower to 0.06 lower)	⨁⨁◯◯ LOW	IMPORTANT
Withdrawal due to adverse events (follow up: 2 years)												
1 (1)	randomised trials	serious [a]	not serious	not serious	very serious [e]	none	26/116 (22.4%) [b]	24/126 (19.0%) [c]	**RR 1.18** (0.72 to 1.93)	**34 more per 1,000** (from 53 fewer to 177 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Death (follow up: 2 years)												
1 (1)	randomised trials	serious [a]	not serious	not serious	very serious [f]	none	1/116 (0.9%) [b]	0/126 (0.0%) [c]	**RR 3.26** (0.13 to 79.15)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	csDMARDs + long-term low-dose GCs	csDMARDs monotherapy	Relative (95% CI)	Absolute (95% CI)		
Death (age-adjusted) (follow up: 10 years)												
1 (2)	randomised trials	serious [a]	not serious	not serious	very serious [e]	none	119 participants [b]	111 participants [c]	**HR 1.60** (0.61 to 4.18) [Death (age-adjusted)]	**45 more per 1,000** (from 31 fewer to 216 more)	⨁◯◯◯ VERY LOW	IMPORTANT
							-	8.1%		**45 more per 1,000** (from 31 fewer to 216 more)		

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	csDMARDs + long-term low-dose GCs	csDMARDs monotherapy	Relative (95% CI)	Absolute (95% CI)		
Composite CardioVascular events (age-adjusted) (follow up: 10 years)												
1 (2)	randomised trials	serious [a]	not serious	not serious	serious [e]	none	119 participants [b]	111 participants [c]	**HR 1.8** (0.9 to 3.6) [Composite CardioVascular events (age-adjusted)]	**95 more per 1,000** (from 13 fewer to 272 more)	⨁⨁◯◯ LOW	IMPORTANT
							-	13.5%		**95 more per 1,000** (from 13 fewer to 272 more)		

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio; **HR:** Hazard Ratio

Explanations

a. Downgraded by one level due to serious risk of bias. Patients, personnel, and outcome assessors of non-radiographic outcomes were not blinded. Patients, personnel, and outcome assessors of radiographic outcomes were blinded

b. csDMARD (51% started with MTX and 32% with SSZ, 8% with antimalarials, 8% with gold) + long-term (>= 3 months) prednisolone (7.5mg/day).

c. csDMARD (55% started with MTX and 34% with SSZ, 4% with antimalarials, 7% with gold).

d. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting no effect.

e. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm.

f. Downgraded by two levels due to very serious imprecision. Very low number of events.

Cost-effectiveness

No cost-effectiveness data identified.

References

1. Svensson B, Boonen A, Albertsson K, Heijde Dvd, Keller C, Hafstrom I. Low-dose prednisolone in addition to the initial disease-modifying antirheumatic drug in patients with early active rheumatoid arthritis reduces joint destruction and increases the remission rate: a two-year randomized trial. Arthritis & Rheumatism. 2005;52(11):3360.
2. Ajeganova S, Svensson B, Hafstrom I. Low-dose prednisolone treatment of early rheumatoid arthritis and late cardiovascular outcome and survival: 10-year follow-up of a 2-year randomised trial. BMJ Open. 2014;4(4).

PICO 8b. Should patients with MTX-naïve and non-MTX csDMARDs exposed RA and moderate to high disease activity, receive *long-term (≥ 3 months)* low dose (≤ 10mg per day) GCs and mono- or combination csDMARDs or mono or combination csDMARDs alone?

P - Patients with MTX-naïve and non-MTX csDMARDs exposed RA and moderate to high disease activity

I - Mono or combination csDMARDs with long-term (**≥** 3 months) low dose (≤ 10mg per day) GCs

C - Mono or combination csDMARDs alone (i.e. without long-term GCs)

Comparison 1: Mono or combination csDMARDs with long-term (**≥** 3 months) low dose (≤ 10mg per day) GCs **versus** mono or combination csDMARDs alone (i.e. without long-term GCs). See below Table.

Comparison 1: Mono or combination csDMARDs with long-term (**≥** 3 months) low dose (≤ 10mg per day) GCs **versus** mono or combination csDMARDs alone (i.e. without long-term GCs). Data based on **direct** RCT evidence.
Overall certainty of evidence: Low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**csDMARDs + long-term low-dose GCs**	**csDMARDs monotherapy**	**Relative (95% CI)**	**Absolute (95% CI)**		
Disability (follow up: 2 years; assessed with: HAQ (Lower values – > benefit) (MCID -0.22)												
1 (1)	randomised trials	not serious	not serious	not serious	very serious [a]	none	77 [b]	74 [c]	-	MD **0.22 higher** (0.02 lower to 0.46 higher)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting harm. Small sample size.
b. csDMARD includes SSZ with long-term (>=3 months) prednisone (7mg/day).
c. csDMARD monotherapy includes SSZ.

Cost-effectiveness

No cost-effectiveness data identified.

References

1. Capell HA, Madhok R, Hunter JA, Porter D, Morrison E, Larkin J, et al. Lack of radiological and clinical benefit over two years of low dose prednisolone for rheumatoid arthritis: results of a randomised controlled trial. Annals of the Rheumatic Diseases. 2004;63(7):797.

PICO 9. Should patients with RA initiating MTX receive oral MTX or subcutaneous (SC) MTX?
P - Patients with RA initiating MTX
I - Oral MTX
C - SC MTX

Comparison 1: SC MTX **versus** Oral MTX. See below Table.

Comparison 1: SC MTX **versus** Oral MTX. Data based on **direct** RCT evidence.
Overall certainty of evidence: Moderate

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SC MTX	Oral MTX	Relative (95% CI)	Absolute (95% CI)		
Disease Activity (follow up: 4 months; assessed with: ACR 20)												
1 (1)	randomised trials	not serious [a]	not serious	not serious	serious [b]	none	160/188 (85.1%)	144/187 (77.0%)	**RR 1.11** (1.00 to 1.22)	**85 more per 1,000** (from 0 fewer to 169 more)	⨁⨁⨁◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. The study did not report on whether allocation was concealed.
b. Downgraded by one level due to serious imprecision. Confidence intervals includes both values suggesting no effect and values suggesting benefit.

Cost-effectiveness

No cost-effectiveness data identified.

References

1. Braun J. Comparison of the clinical efficacy and safety of subcutaneous versus oral administration of methotrexate in patients with active rheumatoid arthritis: results of a six-month, multicenter, randomized, double-blind, controlled, phase IV trial. Arthritis & Rheumatism. 2008;58(1):73.

PICO 10. Should patients with RA initiating MTX receive MTX at 15mg or more per week (includes up-titrating to 15mg over the first month) or less than 15mg per week as the initial dose?

P - Patients with RA initiating MTX
I - MTX < 15mg per week
C - MTX 15mg per week
C - MTX 20 mg per week
C - MTX 25mg per week

Comparison 1: MTX 15mg per week **versus** MTX < 15mg per week. See below Table.
Comparison 2: MTX 20 mg per week **versus** MTX < 15mg per week. No eligible RCT, NRS, or ineligible evidence were identified.
Comparison 3: MTX 25mg per week **versus** MTX < 15mg per week. No eligible RCT, NRS, or ineligible evidence were identified.

Comparison 1: MTX 15mg per week **versus** MTX < 15mg per week. Data based on **direct** RCT evidence.
Overall certainty of evidence: Moderate

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX 15 mg/week	<MTX 15mg/week as initial dose	Relative (95% CI)	Absolute (95% CI)		
Disease Activity (follow up: 3 months; assessed with: DAS 28-ESR (Lower values – > benefit) (MCID -1.17)												
1 (1)	randomised trials	not serious	not serious	not serious	serious [a]	none	53	47 [b]	-	MD **0.08 lower** (0.41 lower to 0.25 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Disability (follow up: 3 months; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
1 (1)	randomised trials	not serious	not serious	not serious	very serious [c]	none	53	47 [b]	-	MD **0.11 lower** (0.29 lower to 0.07 higher)	⨁⨁◯◯ LOW	IMPORTANT
Withdrawal due to lack of efficacy (follow up: 3 months)												
1 (1)	randomised trials	not serious	not serious	not serious	very serious [d]	none	0/53 (0.0%)	2/47 (4.3%) [b]	**RR 0.18** (0.01 to 3.61)	**35 fewer per 1,000** (from 42 fewer to 111 more)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX 15 mg/week	<MTX 15mg/week as initial dose	Relative (95% CI)	Absolute (95% CI)		
Withdrawal due to adverse events (follow up: 3 months)												
1 (1)	randomised trials	not serious	not serious	not serious	very serious [d]	none	2/53 (3.8%)	2/47 (4.3%) [b]	**RR 0.89** (0.13 to 6.05)	**5 fewer per 1,000** (from 37 fewer to 215 more)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. Downgraded by one level due to serious imprecision. Small sample size.
b. 7.5mg/week MTX
c. Downgraded by two levels due to very serious imprecision. Confidence interval including both values suggesting benefit and values suggesting no effect. Very small sample size.
d. Downgraded by two levels due to very serious imprecision. Confidence interval including both values suggesting benefit and values suggesting harm. Very small sample size and low number of events.

Cost-effectiveness

No cost-effectiveness data identified.

References

1. Dhir V, Singla M, Gupta N, Goyal P, Sagar V, Sharma A, et al. Randomized controlled trial comparing 2 different starting doses of methotrexate in rheumatoid arthritis. Clinical Therapeutics. 2014;36(7):1005.

PICO 11. Should patients with RA initiating oral MTX receive MTX as a single or split dose (over < 24 hours)?

P - Patients with RA initiating oral MTX

I - MTX single dose

C - MTX split dose

No eligible RCT, NRS, or indirect evidence were identified.

PICO 12.a. Should patients with RA who have not been previously treated with boDMARD and tsDAMRD receive T2T strategies or usual care?

P - Patients with RA who have not been previously treated with boDMARD and tsDAMRD
I - T2T strategy
C - Usual care

Comparison: T2T strategy **versus** usual care. See below Table.

Comparison: T2T strategy **versus** usual care. Data based on **direct** RCT evidence.
Overall certainty of evidence: Low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	T2T	Usual care	Relative (95% CI)	Absolute (95% CI)		
Remission (follow up: range 6 months to 1.5 years; assessed with: DAS 44 <1.4 and DAS28 ESR <2.6)												
3 (1-3)	randomised trials	serious [a]	not serious	not serious	not serious	none	88/176 (50.0%)	32/186 (17.2%)	**RR 2.89** (2.04 to 4.09)	**325 more per 1,000** (from 179 more to 532 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Disease activity (follow up: range 6 months to 1.5 years; assessed with: ACR 20)												
2 (1,2)	randomised trials	serious [a]	not serious	not serious	serious [b]	none	69/76 (90.8%)	48/77 (62.3%)	**RR 1.46** (1.21 to 1.76)	**287 more per 1,000** (from 131 more to 474 more)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	T2T	Usual care	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: range 6 months to 1.5 years; assessed with: ACR 50)												
2 (1,2)	randomised trials	serious [a]	not serious	not serious	serious [b]	none	62/76 (81.6%)	30/77 (39.0%)	**RR 2.09** (1.55 to 2.82)	**425 more per 1,000** (from 214 more to 709 more)	⨁⨁◯◯ LOW	CRITICAL
Disease activity (follow up: range 6 months to 1.5 years; assessed with: ACR 70)												
2 (1,2)	randomised trials	serious [a]	not serious	not serious	serious [b]	none	54/76 (71.1%)	16/77 (20.8%)	**RR 3.43** (2.16 to 5.43)	**505 more per 1,000** (from 241 more to 921 more)	⨁⨁◯◯ LOW	CRITICAL
Disease activity (follow up: range 6 months to 1.5 years; assessed with: DAS 44/DAS28 ESR (Lower values - > benefit) (values>0.2 are considered clinically important)												
3 (1-3)	randomised trials	serious [a]	very serious [c]	not serious	not serious	none	174	181	-	SMD **0.43 lower** (0.65 lower to 0.21 lower)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	T2T	Usual care	Relative (95% CI)	Absolute (95% CI)		
Radiographic progression (follow up: range 1 years to 1.5 years; assessed with: modified Sharp score (Lower values – > benefit) (MCID 4.6)												
2 (2,4)	randomised trials	very serious [d]	serious [e]	not serious	not serious	none	143	159	-	MD **0.6 lower** (1.68 lower to 0.47 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Disability (follow up: range 1.5 years to 2 years; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
4 (1-4)	randomised trials	very serious [d]	serious [f]	not serious	serious [g]	none	323	328	-	MD **0.13 lower** (0.3 lower to 0.05 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Quality of life (follow up: 1.5 years; assessed with: SF-12 PCS (Higher values – > benefit) (MCID 4.4)												
1 (2)	randomised trials	serious [a]	not serious	not serious	serious [h]	none	53	50	-	MD **5.3 higher** (0.86 higher to 9.74 higher)	⨁⨁◯◯ LOW	IMPORTANT
Quality of life (follow up: 1.5 years; assessed with: SF-12 MCS (Higher values – > benefit) (MCID 3.1)												
1 (2)	randomised trials	serious [a]	not serious	not serious	serious [h]	none	53	50	-	MD **4.9 higher** (1.69 lower to 11.49 higher)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	T2T	Usual care	Relative (95% CI)	Absolute (95% CI)		
Pain (follow up: range 1.5 years to 2 years; assessed with: VAS 0-100 (Lower values – > benefit) (MCID -11.9)												
3 (1,2,4)	randomised trials	very serious [d]	serious [i]	not serious	serious [g]	none	225	220	-	MD **12.15 lower** (17.76 lower to 6.54 lower)	⨁◯◯◯ VERY LOW	IMPORTANT
Withdrawal due to lack of efficacy (follow up: range 1.5 years to 2 years)												
3 (1,3,4)	randomised trials	very serious [d]	serious [j]	not serious	very serious [k]	none	17/272 (6.3%)	25/279 (9.0%)	**RR 0.71** (0.39 to 1.29)	**26 fewer per 1,000** (from 55 fewer to 26 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Withdrawal due to adverse events (follow up: range 6 months to 1.5 years)												
3 (1,3,5)	randomised trials	very serious [l]	not serious [m]	not serious	very serious [n]	none	16/326 (4.9%)	19/310 (6.1%)	**RR 0.86** (0.46 to 1.59)	**9 fewer per 1,000** (from 33 fewer to 36 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	T2T	Usual care	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events (follow up: 6 months)												
1 (1)	randomised trials	serious [o]	not serious	not serious	very serious [n]	none	2/21 (9.5%)	1/22 (4.5%)	**RR 2.10** (0.20 to 21.42)	**50 more per 1,000** (from 36 fewer to 928 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Cardiovascular disease (follow up: 2 years)												
1 (6)	randomised trials	very serious [d]	not serious	not serious	very serious [p]	none	4/149 (2.7%)	0/140 (0.0%)	**RR 8.46** (0.46 to 155.72)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT
Death (follow up: mean 1.5 years)												
1 (2)	randomised trials	serious [a]	not serious	not serious	very serious [n]	none	1/55 (1.8%)	3/55 (5.5%)	**RR 0.33** (0.04 to 3.11)	**37 fewer per 1,000** (from 52 fewer to 115 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **SMD:** Standardised mean difference; **MD:** Mean difference

Explanations

a. Downgraded by one level due to serious risk of bias. Lack of allocation concealment and lack of blinding.
b. Downgraded by one level due to serious imprecision. Small sample size.
c. Downgraded by two levels due to very serious inconsistency. I2= 96%.
d. Downgraded by two levels due to very serious risk of bias. Lack of allocation concealment, lack of blinding, and attrition bias.
e. Downgraded by one level due to serious inconsistency. I2= 78%.
f. Downgraded by one level due to serious inconsistency. I2= 71%.
g. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting no effect.
h. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting no effect. Small sample size.
i. Downgraded by one level due to serious inconsistency. I2= 74%.
j. Downgraded by one level due to serious inconsistency. I2= 75%.
k. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm. Low number of events.
l. Downgraded by two levels due to very serious risk of bias. Two studies consisting of 97% of the weight have high risk of bias due to lack of allocation concealment, lack of blinding of outcome assessors, and reporting incomplete outcome data.
m. I2=55%
n. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm. Low number of events.
o. Downgraded by one level due to serious risk of bias. Lack of blinding.
p. Downgraded by two levels due to very serious imprecision. Very small number of events.

Cost-effectiveness

The economic analysis RefID 1138 (7) compared Treat-to-target vs usual care.

The study reported (1) that TTT was associated with an incremental cost of €3591 per remission at 2 years and after 3 years was dominant (cost saving and more patients in remission). (2) Similarly, at 2 years the cost per QALY for TTT compared with usual care was €19,410 and it was dominant at 3 years (more QALYs, cost saving). (3) This suggests that TTT has higher costs in the short term (as the strategy requires more intensive drug therapy and more frequent assessment of patients), but it is more effective and, in the longer term, this greater effectiveness offsets some of the initial extra costs and may more than offset them.

Author's conclusion: There is also evidence to suggest that, in early RA, the components of care that together constitute TTT are likely to form a cost-effective approach. Studies indicated that TTT would be considered cost-effective other than when the TTT strategy included the use of bDMARDs in early disease. No conclusions could be made in relation to TTT in established disease.

References

1. Mueller RBea. Superiority of a Treat-to-Target Strategy over Conventional Treatment with Fixed csDMARD and Corticosteroids: A Multi-Center Randomized Controlled Trial in RA Patients with an Inadequate Response to Conventional Synthetic DMARDs, and New Therapy with Certolizumab Pegol. Journal of Clinical Medicine. 2019;8.
2. Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet. 2004;364(9430):263.
3. Pope JE, Haraoui B, Rampakakis E, Psaradellis E, Thorne C, Sampalis JS. Treating to a target in established active rheumatoid arthritis patients receiving a tumor necrosis factor inhibitor: results from a real-world cluster-randomized adalimumab trial. Arthritis care & research. 2013;65(9):1401.
4. Verstappen SM, Jacobs JW, Veen MJVD, Heurkens AH, Schenk Y, Borg EJt, et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). Annals of the Rheumatic Diseases. 2007;66(11):1443.
5. Fransen J. Effectiveness of systematic monitoring of rheumatoid arthritis disease activity in daily practice: a multicentre, cluster randomised controlled trial. Ann Rheum Dis BMJ. 2005; 64:1294–1298.
6. Verstappen SMB, M. F.; et. al. Adverse events and factors associated with toxicity in patients with early rheumatoid arthritis treated with methotrexate tight control therapy: the CAMERA study. Ann Rheum Dis BMJ. 2010;69(6):1044-8.
7. Wailoo A. The clinical effectiveness and cost-effectiveness of treat-to-target strategies in rheumatoid arthritis: a systematic review and cost-effectiveness analysis. [Review]. Health Technology Assessment (Winchester, England). 2017;21(71):1.

PICO 12.b. Should patients with RA who have had an inadequate response to 1 or more bDMARD or tsDAMRD receive T2T strategies or usual care?

P - Patients with RA who have had an inadequate response to 1 or more bDMARD or tsDAMRD
I - T2T strategy
C - Usual care

No eligible RCT, NRS, or indirect evidence were identified.

PICO 13. In patients with RA receiving T2T, should the treatment goal be low disease activity or remission?
P - Patients with RA
I - Treat to low disease activity
C - Treat to remission

Comparison 1: Treat to low disease activity **versus** treat to remission. See below Table.

Comparison 1: Treat to low disease activity **versus** treat to remission. Data based on **direct** NRS evidence.
Overall certainty of evidence: Low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a treatment goal of low disease activity	a treatment goal of remission	Relative (95% CI)	Absolute (95% CI)		
DAS remission (follow up: 1 year; assessed with DAS44 ≤ 1.6)												
1 (1)	observational studies	not serious [a,b]	not serious	not serious	not serious	none	40/133 (30.1%)	89/175 (50.9%)	**RR 0.59** (0.44 to 0.80)	**209 fewer per 1,000** (from 285 fewer to 102 fewer)	⨁⨁◯◯ LOW	CRITICAL
Disease activity (follow up: 1 year; assessed with DAS-44 (Lower values – > benefit) (MCID -1.2)												
1 (1)	observational studies	not serious [a]	not serious	not serious	not serious	none	133	175	-	MD **0.1 lower** (0.35 lower to 0.15 higher)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Unclear risk of bias related to missing data as rate of those data not reported
b. In the remission goal group (DAS <1.6), baseline DAS was lower than in the low disease activity goal group (DAS ≤2.4) targeted group; symptom duration was shorter and baseline radiological damage was less often present. The investigators adjusted for these differences in their analyses, but this could have still favored the remission goal group

Cost-effectiveness

No cost-effectiveness data identified.

References

1. Akdemir G. Comparison between low disease activity or das remission as treatment target in patients with early active rheumatoid arthritis. RMD Open. 2018;4(1).

PICO 14. In patients with RA planning to receive T2T, should the interval for treatment escalation be 3 months versus less than 3 months after the last DMARD change?

P - Patients with RA planning to receive T2T

I - Escalate treatment 3 months or later after the last DMARD change

C - Escalate treatment less than 3 months after the last DMARD change

No eligible RCT, NRS, or indirect evidence were identified.

PICO 15. Should patients with RA not tolerating MTX, on folic acid 1 mg/day, increase the dose of folic acid?

P - Patients with RA not tolerating MTX on 1mg of folic acid

I - Increase dose of folic acid to > 1mg per day

C - Remain on folic acid 1 mg per day

Comparison: Remain on folic acid 1 mg per day **versus** increase dose of folic acid to > 1mg per day. See below Table.

Comparison: Remain on folic acid 1 mg per day **versus** increase dose of folic acid to > 1mg per day. Data based on **indirect** RCT evidence.

Overall certainty of evidence: Low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Remain on folic acid 1 mg per day	Increase dose of folic acid to > 1mg per day	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 6 months; assessed with: DAS28-ESR (Lower values – > benefit) (MCID -1.17)												
1 (1)	randomised trials	not serious [a]	not serious	serious [b]	serious [c]	none	51 [d]	49 [e]	-	MD **0.28 higher** (0.1 higher to 0.46 higher)	⨁⨁◯◯ LOW	CRITICAL
Disability (follow up: range 6 months to 12 months; assessed with: HAQ-DI or modified HAQ (Lower values – > benefit) (values>0.2 are considered clinically significant)												
2 (1, 2)	randomised trials	not serious [a]	serious [f]	serious [g]	serious [h,i]	none	76 [d]	75 [e]	-	SMD **0.49 SD higher** (0.16 higher to 0.82 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Remain on folic acid 1 mg per day	Increase dose of folic acid to > 1mg per day	Relative (95% CI)	Absolute (95% CI)		
Withdrawal due to adverse events (follow up: range 6 months to 12 months)												
2 (1, 2)	randomised trials	not serious [a]	not serious	serious [g]	very serious [j]	none	3/76 (3.9%) [d]	2/75 (2.7%) [e]	**RR 1.42** (0.29 to 6.92)	**11 more per 1,000** (from 19 fewer to 158 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **SMD:** Standardised mean difference; **RR:** Risk ratio

Explanations

a. Concern about risk of bias associated with handling of incomplete outcome data.
b. Downgraded by one level due to serious indirectness. The evidence is based on a population who are starting MTX treatment (MTX-naive and not on folic acid) with different folic acid doses (10 mg/week vs 30 mg/week).
c. Downgraded by one level due to serious imprecision. Small sample size.
d. Folic acid dose is 5-10 mg/week.
e. Folic acid dose is 27.5-30mg/week.
f. Downgraded by one level due to serious inconsistency. I2=79%.
g. Downgraded by one level due to serious indirectness. The evidence is based on a population who are starting MTX treatment (MTX-naive and not on folic acid) with different folic acid doses (5-10 mg/week vs 27.5-30 mg/week).
h. According to the Cochrane's handbook, Cohen suggested that SMD=0.2 be considered a 'small' effect size, 0.5 represents a 'medium' effect size and 0.8 a 'large' effect size. This means that if two groups' means do not differ by 0.2 standard deviations or more, the difference is trivial, even if it is statistically significant.
i. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting harm.
j. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting harm. Very low number of events.

Cost-effectiveness

No cost-effectiveness data were identified.

References

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PICO 16. Should patients with RA not tolerating oral MTX receive a split dose (over < 24 hours) or subcutaneous (SC) MTX?
P - Patients with RA not tolerating oral MTX
I - Split oral MTX
C - SC MTX

No eligible RCT, NRS, or indirect evidence were identified.

PICO 17a. Should patients with RA not tolerating MTX, switch to alternative mono or combination csDMARDs, to a boDMARD, or to a tsDMARD?

P - Patients with RA not tolerating MTX monotherapy (either oral or SC)
I - Switch to non-MTX mono or combination csDMARDs
C - Switch to TNF Inhibitor
C - Switch to Abatacept
C - Switch to Rituximab
C - Switch to IL-6 Receptor Inhibitor
C - Switch to JAK Inhibitor
C- Continue same management

Comparison 1: Switch to non-MTX mono or combination csDMARDs **versus** switch to TNF Inhibitor. No eligible RCT, NRS, or indirect evidence were identified.
Comparison 2: Switch to non-MTX mono or combination csDMARDs **versus** switch to Abatacept**.** No eligible RCT, NRS, or indirect evidence were identified.
Comparison 3: Switch to non-MTX mono or combination csDMARDs **versus** switch to Rituximab**.** No eligible RCT, NRS, or indirect evidence were identified.
Comparison 4: Switch to non-MTX mono or combination csDMARDs **versus** switch to IL-6 Receptor Inhibitor**.** No eligible RCT, NRS, or indirect evidence were identified.
Comparison 5: Switch to non-MTX mono or combination csDMARDs **versus** switch to JAK Inhibitor**.** No eligible RCT, NRS, or indirect evidence were identified.
Comparison 6: Switch to non-MTX mono or combination csDMARDs **versus** Continue same management**.** No eligible RCT, NRS, or indirect evidence were identified.
Comparison 7: Switch to TNF Inhibitor **versus** switch to JAK Inhibitor. See below Table.
Comparison 8: Switch to IL-6 Receptor Inhibitor **versus** switch to TNF Inhibitor. See below Table.

Comparison 7: Switch to TNF Inhibitor **versus** switch to JAK Inhibitor. Data based on **indirect** RCT evidence.
Overall certainty of evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to TNFi	Switch to JAKi	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 3 months; assessed with: ACR 20)												
1 (1)	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	19/53 (35.8%)	29/49 (59.2%)	**RR 0.61** (0.39 to 0.93)	**231 fewer per 1,000** (from 361 fewer to 41 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Disease activity (follow up: 3 months; assessed with: ACR 50)												
1 (1)	randomised trials	serious [a]	not serious	serious [b]	very serious [d]	none	10/53 (18.9%)	17/49 (34.7%)	**RR 0.54** (0.28 to 1.07)	**160 fewer per 1,000** (from 250 fewer to 24 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to TNFi	Switch to JAKi	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 3 months; assessed with: ACR 70)												
1 (1)	randomised trials	serious [a]	not serious	serious [b]	very serious [d]	none	2/53 (3.8%)	6/49 (12.2%)	**RR 0.31** (0.07 to 1.46)	**84 fewer per 1,000** (from 114 fewer to 56 more)	⨁◯◯◯ VERY LOW	CRITICAL
Disability (follow up: 3 months; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
1 (1)	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	49	53	-	MD **0.16 higher** (0.13 higher to 0.19 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to TNFi	Switch to JAKi	Relative (95% CI)	Absolute (95% CI)		
Pain (follow up: 3 months; assessed with: VAS 0-100 (Lower values – > benefit) (MCID -11.9)												
1 (1)	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	53	49	-	MD **9.91 higher** (8.64 higher to 11.18 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Downgraded by one level due to serious risk of bias. Lack of allocation concealment.
b. Downgraded by one level due to serious indirectness. The evidence is based on a population on a maximally tolerated dose of MTX monotherapy.
c. Downgraded by one level due to serious imprecision. Small sample size.
d. Downgraded by two level due to very serious imprecision. Confidence interval includes both values suggesting harm and values suggesting benefit. Small sample size and low number of events.

Comparison 8: Switch to IL-6 Receptor Inhibitor **versus** switch to TNF Inhibitor. Data based on **indirect** RCT evidence.
Overall certainty of evidence: Low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to IL6i	Switch to TNFi	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 6 months; assessed with: ACR 20)												
1 (2)	randomised trials	serious [a]	not serious	serious [b]	not serious	none	132/184 (71.7%)	108/185 (58.4%)	**RR 1.23** (1.06 to 1.43)	**134 more per 1,000** (from 35 more to 251 more)	⨁⨁◯◯ LOW	CRITICAL
Disease activity (follow up: 6 months; assessed with: ACR 50)												
1 (2)	randomised trials	serious [a]	not serious	serious [b]	not serious	none	84/184 (45.7%)	55/185 (29.7%)	**RR 1.54** (1.17 to 2.02)	**161 more per 1,000** (from 51 more to 303 more)	⨁⨁◯◯ LOW	CRITICAL
Disease activity (follow up: 6 months; assessed with: ACR 70)												
1 (2)	randomised trials	serious [a]	not serious	serious [b]	not serious	none	43/184 (23.4%)	22/185 (11.9%)	**RR 1.97** (1.23 to 3.15)	**115 more per 1,000** (from 27 more to 256 more)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to IL6i	Switch to TNFi	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: range 4 months to 6 months; assessed with: DAS28-ESR (Lower values – > benefit) (MCID -1.17)												
2 (2, 3)	randomised trials	serious [c]	not serious	serious [b]	serious [d]	none	347	347	-	MD **1.11 lower** (1.34 lower to 0.87 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Remission (follow up: 6 months; assessed with: DAS28 ESR <2.6)												
1 (2)	randomised trials	serious [a]	not serious	serious [b]	not serious	none	49/184 (26.6%)	13/185 (7.0%)	**RR 3.79** (2.13 to 6.74)	**196 more per 1,000** (from 79 more to 403 more)	⨁⨁◯◯ LOW	CRITICAL
Disability (follow up: range 4 months to 6 months; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
2 (2, 3)	randomised trials	serious [c]	not serious	serious [b]	serious [d]	none	347	347	-	MD **0.16 lower** (0.27 lower to 0.05 lower) [e]	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to IL6i	Switch to TNFi	Relative (95% CI)	Absolute (95% CI)		
Quality of life (follow up: 6 months; assessed with: SF-36 PCS (Higher values – > benefit) (MCID 4.4)												
1 (2)	randomised trials	serious [a]	not serious	serious [b]	not serious	none	184	185	-	MD **2.6 higher** (0.94 higher to 4.26 higher) [f]	⨁⨁◯◯ LOW	IMPORTANT
Quality of life (follow up: 6 months; assessed with: SF-36 MCS (Higher values – > benefit) (MCID 3.1)												
1 (2)	randomised trials	serious [a]	not serious	serious [b]	serious [d]	none	184	185	-	MD **1.1 higher** (1.12 lower to 3.32 higher) [g]	⨁◯◯◯ VERY LOW	IMPORTANT
Fatigue (follow up: 6 months; assessed with: FACIT-F (Higher values – > benefit) (MCID 15.9)												
1 (2)	randomised trials	serious [a]	not serious	serious [b]	not serious	none	184	185	-	MD **1.8 higher** (0.14 lower to 3.74 higher)	⨁⨁◯◯ LOW	IMPORTANT
Death (follow up: 6 months)												
1 (2)	randomised trials	serious [a]	not serious	serious [b]	very serious [h]	none	1/184 (0.5%)	0/184 (0.0%)	**RR 3.00** (0.12 to 73.17)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to IL6i	Switch to TNFi	Relative (95% CI)	Absolute (95% CI)		
Pain (follow up: 6 months; assessed with: VAS 0-100 (Lower values – > benefit) (MCID -11.9)												
1 (4)	randomised trials	serious [a]	not serious	serious [b]	not serious	none	184	185	-	MD **8.78 lower** (9.15 lower to 8.41 lower)	⨁⨁◯◯ LOW	IMPORTANT
Serious adverse events (follow up: 6 months)												
1 (2)	randomised trials	serious [a]	not serious	serious [b]	very serious [i]	none	9/184 (4.9%)	12/184 (6.5%)	**RR 0.75** (0.32 to 1.74)	**16 fewer per 1,000** (from 44 fewer to 48 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Withdrawal lack of effect (follow up: 6 months)												
1 (2)	randomised trials	serious [a]	not serious	serious [b]	very serious [i]	none	2/184 (1.1%)	4/185 (2.2%)	**RR 0.50** (0.09 to 2.71)	**11 fewer per 1,000** (from 20 fewer to 37 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to IL6i	Switch to TNFi	Relative (95% CI)	Absolute (95% CI)		
Withdrawal adverse events (follow up: 6 months)												
1 (2)	randomised trials	serious [a]	not serious	serious [b]	very serious [i]	none	11/184 (6.0%)	15/184 (8.2%)	**RR 0.73** (0.35 to 1.55)	**22 fewer per 1,000** (from 53 fewer to 45 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Downgraded by one level due to serious risk of bias. Lack of allocation concealment.
b. Downgraded by one level due to serious indirectness. The evidence is based on a population on a maximally tolerated dose of MTX monotherapy.
c. Downgraded by one level due to serious risk of bias. Lack of allocation concealment in the MONARCH, the study with the larger weight.
d. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting no effect.
e. The study MONARCH found that the RR of improvement in HAQ-DI (≥0.22 change from baseline) was 1.25 (95%CI 1.06 to 1.47), absolute risk increase 135 more per 1000 (95%CI 32 more to 254 more).
f. The study MONARCH found that the RR of improvement in quality of life- SF-36 PCS (≥2.5 change from baseline) was 1.27 (95%CI 1.07 to 1.49), absolute risk increase 146 more per 1000 (95%CI 38 more to 265 more).
g. The study MONARCH found that the RR of improvement in quality of life- SF-36 MCS (≥2.5 change from baseline) was 1.18 (95%CI 1.00 to 1.39), absolute risk increase 100 more per 1000 (95%CI 0 fewer to 217 more).
h. Downgraded by two levels due to very serious imprecision. Low number of events.
i. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm. Low number of events.

Cost-effectiveness

No cost-effectiveness data were identified.

References

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3. Gabay C, Emery P, Vollenhoven Rv, Dikranian A, Alten R, Pavelka K, et al. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial.[Erratum appears in Lancet. 2013 May 4;381(9877):1540 Note: Dosage error in article text], [Erratum appears in Lancet. 2013 Dec 7;382(9908):1878]. Lancet. 2013;381(9877):1541.
4. Strand V. Patient-reported outcomes from a randomized phase III trial of sarilumab monotherapy versus adalimumab monotherapy in patients with rheumatoid arthritis. Arthritis Research and Therapy. 2018;20(1).

PICO 17b. Should patients with RA on maximally tolerated dose of MTX monotherapy who are NOT at target, switch to alternative mono or combination csDMARDs, to a boDMARD, or to a tsDMARD?

P - Patients with RA on maximally tolerated dose of MTX monotherapy (either oral or SC) who are not at target
I - Switch to non-MTX mono or combination csDMARDs
C - Switch to TNF Inhibitor
C - Switch to Abatacept
C - Switch to Rituximab
C - Switch to IL-6 Receptor Inhibitor
C - Switch to JAK Inhibitor
C- Continue same management

Comparison 1: Switch to non-MTX mono or combination csDMARDs **versus** switch to TNF Inhibitor. See below evidence.
Comparison 2: Switch to non-MTX mono or combination csDMARDs **versus** switch to Abatacept**.** No eligible RCT, NRS, or indirect evidence were identified.
Comparison 3: Switch to non-MTX mono or combination csDMARDs **versus** switch to Rituximab**.** No eligible RCT, NRS, or indirect evidence were identified.
Comparison 4: Switch to non-MTX mono or combination csDMARDs **versus** switch to IL-6 Receptor Inhibitor**.** No eligible RCT, NRS, or indirect evidence were identified.
Comparison 5: Switch to non-MTX mono or combination csDMARDs **versus** switch to JAK Inhibitor**.** No eligible RCT, NRS, or indirect evidence were identified.
Comparison 6: Switch to non-MTX mono or combination csDMARDs **versus** Continue same management **.** No eligible RCT, NRS, or indirect evidence were identified.
Comparison 7: Switch to TNF Inhibitor **versus** switch to JAK Inhibitor. See below Table.
Comparison 8: Switch to IL-6 Receptor Inhibitor **versus** switch to TNF Inhibitor. See below Table.

Comparison 1: Switch to non-MTX mono or combination csDMARDs **versus** switch to TNF Inhibitor. Data based on **direct** NRS evidence.
Overall certainty of evidence: Low

Evidence identified: Zink 2005 [RefID: 8554] (1) was a prospective cohort study based on the German biologics register RABBIT. Patients with RA who had failed at least one previous therapy between May 2001 and September 2003 were included. Relevant patient groups include Leflunomide monotherapy (n=120) and TNFi monotherapy (Etanercept n=511 and Infliximab n=343)
Findings

- Patients in the Leflunomide subgroup had lower treatment continuation rates (64% after six months, 51% after 12 months) than patients receiving TNF inhibitors (fig 2, p=0.058).
- There was a significantly increased hazard ratio of 1.7 (p=0.025) for treatment termination with Leflunomide in comparison with infliximab/etanercept

Low certainty evidence due to NRS design.

Harms data: The Systematic Review RefID=1220, 2017 (RCTs=33) comparing TNFi vs Placebo + csDMARD among RA showed that for cancer, the result was Peto OR=1.01 (0.72, 1.42)

Comparison 7: Switch to TNF Inhibitor **versus** switch to JAK Inhibitor. Data based on **direct** RCT evidence.
Overall certainty of evidence: Low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to TNFi	Switch to JAKi	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 3 months; assessed with: ACR 20)												
1 (2)	randomised trials	serious [a]	not serious	not serious	serious [b]	none	19/53 (35.8%)	29/49 (59.2%)	**RR 0.61** (0.39 to 0.93)	**231 fewer per 1,000** (from 361 fewer to 41 fewer)	⨁⨁◯◯ LOW	CRITICAL
Disease activity (follow up: 3 months; assessed with: ACR 50)												
1 (2)	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	10/53 (18.9%)	17/49 (34.7%)	**RR 0.54** (0.28 to 1.07)	**160 fewer per 1,000** (from 250 fewer to 24 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to TNFi	Switch to JAKi	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 3 months; assessed with: ACR 70)												
1 (2)	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	2/53 (3.8%)	6/49 (12.2%)	**RR 0.31** (0.07 to 1.46)	**84 fewer per 1,000** (from 114 fewer to 56 more)	⨁◯◯◯ VERY LOW	CRITICAL
Disability (follow up: 3 months; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
1 (2)	randomised trials	serious [a]	not serious	not serious	serious [b]	none	49	53	-	MD **0.16 higher** (0.13 higher to 0.19 higher)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to TNFi	Switch to JAKi	Relative (95% CI)	Absolute (95% CI)		
Pain (follow up: 3 months; assessed with: VAS 0-100 (Lower values – > benefit) (MCID -11.9)												
1 (2)	randomised trials	serious [a]	not serious	not serious	serious [b]	none	53	49	-	MD **9.91 higher** (8.64 higher to 11.18 higher)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Downgraded by one level due to serious risk of bias. Lack of allocation concealment.
b. Downgraded by one level due to serious imprecision. Small sample size.
c. Downgraded by two level due to very serious imprecision. Confidence interval includes both values suggesting harm and values suggesting benefit. Small sample size and low number of events.

Comparison 8: Switch to IL-6 Receptor Inhibitor **versus** switch to TNF Inhibitor. Data based on **direct** RCT evidence.
Overall certainty of evidence: Moderate

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to IL6i	Switch to TNFi	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 6 months; assessed with: ACR 20)												
1 (3)	randomised trials	serious [a]	not serious	not serious	not serious	none	132/184 (71.7%)	108/185 (58.4%)	**RR 1.23** (1.06 to 1.43)	**134 more per 1,000** (from 35 more to 251 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Disease activity (follow up: 6 months; assessed with: ACR 50)												
1 (3)	randomised trials	serious [a]	not serious	not serious	not serious	none	84/184 (45.7%)	55/185 (29.7%)	**RR 1.54** (1.17 to 2.02)	**161 more per 1,000** (from 51 more to 303 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Disease activity (follow up: 6 months; assessed with: ACR 70)												
1 (3)	randomised trials	serious [a]	not serious	not serious	not serious	none	43/184 (23.4%)	22/185 (11.9%)	**RR 1.97** (1.23 to 3.15)	**115 more per 1,000** (from 27 more to 256 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to IL6i	Switch to TNFi	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: range 4 months to 6 months; assessed with: DAS28-ESR (Lower values – > benefit) (MCID -1.17)												
2 (3, 4)	randomised trials	serious [b]	not serious	not serious	serious [c]	none	347	347	-	MD **1.11 lower** (1.34 lower to 0.87 lower)	⨁⨁◯◯ LOW	CRITICAL
Remission (follow up: 6 months; assessed with: DAS28 ESR <2.6)												
1 (3)	randomised trials	serious [a]	not serious	not serious	not serious	none	49/184 (26.6%)	13/185 (7.0%)	**RR 3.79** (2.13 to 6.74)	**196 more per 1,000** (from 79 more to 403 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Disability (follow up: range 4 months to 6 months; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
2 (3, 4)	randomised trials	serious [b]	not serious	not serious	serious [c]	none	347	347	-	MD **0.16 lower** (0.27 lower to 0.05 lower) [d]	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to IL6i	Switch to TNFi	Relative (95% CI)	Absolute (95% CI)		
Quality of life (follow up: 6 months; assessed with: SF-36 PCS (Higher values – > benefit) (MCID 4.4)												
1 (3)	randomised trials	serious [a]	not serious	not serious	not serious	none	184	185	-	MD **2.6 higher** (0.94 higher to 4.26 higher) [e]	⨁⨁⨁◯ MODERATE	IMPORTANT
Quality of life (follow up: 6 months; assessed with: SF-36 MCS (Higher values – > benefit) (MCID 3.1)												
1 (3)	randomised trials	serious [a]	not serious	not serious	serious [c]	none	184	185	-	MD **1.1 higher** (1.12 lower to 3.32 higher) [f]	⨁⨁◯◯ LOW	IMPORTANT
Fatigue (follow up: 6 months; assessed with: FACIT-F (Higher values – > benefit) (MCID 15.9)												
1 (3)	randomised trials	serious [a]	not serious	not serious	not serious	none	184	185	-	MD **1.8 higher** (0.14 lower to 3.74 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Death (follow up: 6 months)												
1 (3)	randomised trials	serious [a]	not serious	not serious	very serious [g]	none	1/184 (0.5%)	0/184 (0.0%)	**RR 3.00** (0.12 to 73.17)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to IL6i	Switch to TNFi	Relative (95% CI)	Absolute (95% CI)		
Pain (follow up: 6 months; assessed with: VAS 0-100 (Lower values – > benefit) (MCID -11.9)												
1 (5)	randomised trials	serious [a]	not serious	not serious	not serious	none	184	185	-	MD **8.78 lower** (9.15 lower to 8.41 lower)	⨁⨁⨁◯ MODERATE	IMPORTANT
Serious adverse events (follow up: 6 months)												
1 (3)	randomised trials	serious [a]	not serious	not serious	very serious [h]	none	9/184 (4.9%)	12/184 (6.5%)	**RR 0.75** (0.32 to 1.74)	**16 fewer per 1,000** (from 44 fewer to 48 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Withdrawal due to lack of effect (follow up: 6 months)												
1 (3)	randomised trials	serious [a]	not serious	not serious	very serious [h]	none	2/184 (1.1%)	4/185 (2.2%)	**RR 0.50** (0.09 to 2.71)	**11 fewer per 1,000** (from 20 fewer to 37 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to IL6i	Switch to TNFi	Relative (95% CI)	Absolute (95% CI)		
Withdrawal due to adverse events (follow up: 6 months)												
1 (3)	randomised trials	serious [a]	not serious	not serious	very serious [h]	none	11/184 (6.0%)	15/184 (8.2%)	**RR 0.73** (0.35 to 1.55)	**22 fewer per 1,000** (from 53 fewer to 45 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Downgraded by one level due to serious risk of bias. Lack of allocation concealment.
b. Downgraded by one level due to serious risk of bias. Lack of allocation concealment in the MONARCH, the study with the larger weight.
c. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting no effect.
d. The study MONARCH found that the RR of improvement in HAQ-DI (≥0.22 change from baseline) was 1.25 (95%CI 1.06 to 1.47), absolute risk increase 135 more per 1000 (95%CI 32 more to 254 more).
e. The study MONARCH found that the RR of improvement in quality of life- SF-36 PCS (≥2.5 change from baseline) was 1.27 (95%CI 1.07 to 1.49), absolute risk increase 146 more per 1000 (95%CI 38 more to 265 more).
f. The study MONARCH found that the RR of improvement in quality of life- SF-36 MCS (≥2.5 change from baseline) was 1.18 (95%CI 1.00 to 1.39), absolute risk increase 100 more per 1000 (95%CI 0 fewer to 217 more).
g. Downgraded by two levels due to very serious imprecision. Low number of events.
h. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm. Low number of events.

Cost-effectiveness

No cost-effectiveness data were identified.

References

1. Zink A. Treatment continuation in patients receiving biological agents or conventional DMARD therapy. Annals of the Rheumatic Diseases. 2005;64(9):1274.
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4. Gabay C, Emery P, Vollenhoven Rv, Dikranian A, Alten R, Pavelka K, et al. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial.[Erratum appears in Lancet. 2013 May 4;381(9877):1540 Note: Dosage error in article text], [Erratum appears in Lancet. 2013 Dec 7;382(9908):1878]. Lancet. 2013;381(9877):1541.
5. Strand V. Patient-reported outcomes from a randomized phase III trial of sarilumab monotherapy versus adalimumab monotherapy in patients with rheumatoid arthritis. Arthritis Research and Therapy. 2018;20(1).

PICO 18. Should patients with RA on oral MTX monotherapy 15 mg per week who are NOT at target increase the dose of oral MTX or switch to SC MTX?

P - Patients with RA on oral MTX monotherapy 15 mg per week who are not at target

I - Increase the dose of oral MTX

C - Switch to SC MTX

Comparison: Switch to SC MTX **versus** Increase the dose of oral MTX. See below Table.

Comparison: Switch to SC MTX **versus** Increase the dose of oral MTX. Data based on **direct** RCT evidence.
Overall certainty of evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to SC MTX	increase dose of oral MTX	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 6 months; assessed with: ACR 20)												
1 (1)	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	43/46 (93.5%) [c]	36/46 (78.3%) [d]	**RR 1.19** (1.01 to 1.42)	**149 more per 1,000** (from 8 more to 329 more)	⨁◯◯◯ VERY LOW	CRITICAL
Disease activity (follow up: 6 months; assessed with: ACR 50)												
1 (1)	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	41/46 (89.1%) [c]	33/46 (71.7%) [d]	**RR 1.24** (1.01 to 1.53)	**172 more per 1,000** (from 7 more to 380 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to SC MTX	increase dose of oral MTX	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 6 months; assessed with: ACR 70)												
1 (1)	randomised trials	very serious [a]	not serious	not serious	very serious [e]	none	5/46 (10.9%) [c]	4/46 (8.7%) [d]	**RR 1.25** (0.36 to 4.36)	**22 more per 1,000** (from 56 fewer to 292 more)	⨁◯◯◯ VERY LOW	CRITICAL
Disability (follow up: 6 months; assessed with: HAQ (Lower values – > benefit) (MCID -0.22)												
1 (1)	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	46 [c]	46 [d]	-	MD **2.3 lower** (4.06 lower to 0.54 lower)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to SC MTX	increase dose of oral MTX	Relative (95% CI)	Absolute (95% CI)		
Pain (6 months) (follow up: 6 months; assessed with: VAS 0-10 (Lower values – > benefit) (MCID 0.5)												
1 (1)	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	46 [c]	46 [d]	-	MD **1.43 lower** (2.05 lower to 0.81 lower)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Downgraded by two levels due to very serious risk of bias. Lack of blinding and lack of allocation concealment.
b. Downgraded by one level due to serious imprecision. Very small sample size.
c. SC 20mg MTX for 4 weeks, then 25mg MTX for 8 weeks.
d. PO 20mg MTX for 4 weeks, then 25mg MTX for 8 weeks.
e. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm. Very small sample size.

Cost-effectiveness

No cost-effectiveness data identified.

References

1. Islam MS, Haq SA, Islam MN, Azad AK, Islam MA, Barua. Comparative efficacy of subcutaneous versus oral methotrexate in active rheumatoid arthritis. Mymensingh Medical Journal: MMJ. 2013;22(3):483.

PICO 19. Should patients with RA on maximally tolerated dose of MTX monotherapy who are NOT at target add SSZ and HCQ, add LEF, add a boDMARD, or add a tsDMARD?

P - Patients with RA on maximally tolerated dose of MTX monotherapy (either oral or SC) who are not at target
I - Add SSZ and HCQ
C - Add LEF
C - Add TNF Inhibitor
C - Add Abatacept
C - Add Rituximab
C - Add IL-6 Receptor Inhibitor
C - Add JAK Inhibitor
C- Continue same management

Comparison 1: Add SSZ and HCQ **versus** add LEF. No eligible RCT, NRS, or indirect evidence were identified.
Comparison 2: Add SSZ and HCQ **versus** add TNF Inhibitor. See below Table.
Comparison 3: Add SSZ and HCQ **versus** add Abatacept. No eligible RCT, NRS, or indirect evidence were identified.
Comparison 4: Add SSZ and HCQ **versus** add Rituximab. No eligible RCT, NRS, or indirect evidence were identified.
Comparison 5: Add SSZ and HCQ **versus** add IL-6 Receptor Inhibitor. No eligible RCT, NRS, or indirect evidence were identified.
Comparison 6: Add SSZ and HCQ **versus** add JAK Inhibitor. No eligible RCT, NRS, or indirect evidence were identified.
Comparison 7: Add SSZ and HCQ **versus** continue same management. No eligible RCT, NRS, or indirect evidence were identified.
Comparison 8: Add TNF Inhibitor **versus** add JAK Inhibitor. See below Table.
Comparison 9: Add Abatacept **versus** add TNF Inhibitor. See below Table.

Comparison 2: Add SSZ and HCQ **versus** add TNF Inhibitor. Data based on **direct** RCT evidence.
Overall certainty of evidence: Low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add SSZ+HCQ	Add TNFi	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 6 months; assessed with: ACR20)												
1 (1)	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	89/159 (56.0%)	90/163 (55.2%)	**RR 1.01** (0.83 to 1.23)	**6 more per 1,000** (from 94 fewer to 127 more)	⨁◯◯◯ VERY LOW	CRITICAL
Disease activity (follow up: 6 months; assessed with: ACR50)												
1 (1)	randomised trials	serious [a]	not serious	not serious	serious [c]	none	41/159 (25.8%)	58/163 (35.6%)	**RR 0.72** (0.52 to 1.01)	**100 fewer per 1,000** (from 171 fewer to 4 more)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add SSZ+HCQ	Add TNFi	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 6 months; assessed with: ACR70)												
1 (1)	randomised trials	serious [a]	not serious	not serious	not serious	none	8/159 (5.0%)	26/163 (16.0%)	**RR 0.32** (0.15 to 0.68)	**108 fewer per 1,000** (from 136 fewer to 51 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Disease activity (follow up: 6 months; assessed with: DAS28-ESR (Lower values – > benefit) (MCID -1.17)												
1 (1)	randomised trials	serious [a]	not serious	not serious	not serious	none	157	161	-	MD **0.27 higher** (0.01 lower to 0.55 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Remission (follow up: 6 months; assessed with: DAS28-CRP < 2.6)												
1 (1)	randomised trials	serious [a]	not serious	not serious	serious [c]	none	20/157 (12.7%)	35/161 (21.7%)	**RR 0.59** (0.35 to 0.97)	**89 fewer per 1,000** (from 141 fewer to 7 fewer)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add SSZ+HCQ	Add TNFi	Relative (95% CI)	Absolute (95% CI)		
Radiographic progression (follow up: 6 months; assessed with: mTSS (Lower values – > benefit) (MCID 4.6)												
1 (1)	randomised trials	serious [a]	not serious	not serious	not serious	none	158	160	-	MD **0.42 higher** (0.22 lower to 1.05 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Disability (follow up: 6 months; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
1 (1)	randomised trials	serious [a]	not serious	not serious	serious [c]	none	155	160	-	MD **0.07 higher** (0.11 lower to 0.25 higher)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add SSZ+HCQ	Add TNFi	Relative (95% CI)	Absolute (95% CI)		
Malignancy (from SRs of harms)												
1 (2)							The Systematic Review RefID=4638, 2012 (RCTs=9, n=3712) comparing csDMARD + placebo vs infliximab + MTX among RA showed that for cancer, the result was RR=0.83 (0.22-3.13) at 2 years and RR=0.56(0.22-1.47) at all time points (6 months, 1 year and 2 years combined)				-	

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Downgraded by one level due to serious risk of bias. Lack of allocation concealment.

b. Downgraded by two levels due to very serious imprecision. Confidence intervals includes both values suggesting benefit and values suggesting harm. Concern about risk of bias associated with lack of allocation concealment taken into account when rating down for imprecision.

c. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting harm and values suggesting no effect.

Comparison 8: Add TNF Inhibitor **versus** add JAK Inhibitor. Data **based** on direct RCT evidence.
Overall certainty of evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add TNFi	Add JAKi	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: range 3 months to 1 year; assessed with: ACR20)												
3 (3-5)	randomised trials	not serious	not serious	not serious	serious [a]	none	581/917 (63.4%)	849/1231 (69.0%)	**RR 0.93** (0.87 to 0.99)	**48 fewer per 1,000** (from 90 fewer to 7 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Disease activity (follow up: range 3 months to 1 year; assessed with: ACR50)												
3 (3-5)	randomised trials	not serious	serious [b]	not serious	serious [a]	none	317/917 (34.6%)	539/1231 (43.8%)	**RR 0.76** (0.56 to 1.02)	**105 fewer per 1,000** (from 193 fewer to 9 more)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add TNFi	Add JAKi	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: range 3 months to 1 year; assessed with: ACR70)												
3 (3-5)	randomised trials	not serious	serious [c]	not serious	serious [a]	none	160/917 (17.4%)	297/1231 (24.1%)	**RR 0.69** (0.47 to 1.02)	**75 fewer per 1,000** (from 128 fewer to 5 more)	⨁⨁◯◯ LOW	CRITICAL
Disease activity (follow up: 3 months; assessed with: DAS28-ESR (Lower values – > benefit) (MCID -1.17)												
1 (3)	randomised trials	serious [d]	not serious	not serious	not serious	none	204	204	-	MD **0.11 lower** (0.27 lower to 0.05 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Remission (follow up: range 3 months to 1 year; assessed with: DAS28-CRP<2.6)												
2 (4, 5)	randomised trials	not serious	very serious [e]	not serious	very serious [f]	none	195/713 (27.3%)	303/1027 (29.5%)	**RR 0.85** (0.46 to 1.59)	**44 fewer per 1,000** (from 159 fewer to 174 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add TNFi	Add JAKi	Relative (95% CI)	Absolute (95% CI)		
Disability (follow up: 3 months; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
2 (5, 6)	randomised trials	not serious	not serious	not serious	not serious	none	526	849	-	MD **0.08 higher** (0.01 higher to 0.15 higher)	⨁⨁⨁⨁ HIGH	IMPORTANT
Quality of life (follow up: range 3 months to 12 months; assessed with: SF-36 PCS (Higher values – > benefit) (MCID 4.4)												
3 (5-7)	randomised trials	not serious	not serious	not serious	not serious	none	912	1225	-	MD **1.09 lower** (1.82 lower to 0.35 lower) [g]	⨁⨁⨁⨁ HIGH	IMPORTANT
Quality of life (follow up: range 3 months to 12 months; assessed with: SF-36 MCS (Higher values – > benefit) (MCID 3.1)												
2 (6, 7)	randomised trials	not serious	not serious	not serious	not serious	none	585	574	-	MD **0.2 lower** (1.26 lower to 0.86 higher) [h]	⨁⨁⨁⨁ HIGH	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add TNFi	Add JAKi	Relative (95% CI)	Absolute (95% CI)		
Pain (follow up: range 3 months to 12 months; assessed with: VAS 100 (Lower values – > benefit) (MCID -11.9)												
3 (5-7)	randomised trials	not serious	not serious	not serious	not serious	none	912	1225	-	MD **4 higher** (1.66 higher to 6.35 higher) [i]	⨁⨁⨁⨁ HIGH	IMPORTANT
Fatigue (follow up: range 3 months to 12 months; assessed with: FACIT-F (Higher values – > benefit) (MCID 15.9)												
3 (5-7)	randomised trials	not serious	not serious	not serious	not serious	none	912	1225	-	MD **1.15 lower** (2.02 lower to 0.27 lower) [j]	⨁⨁⨁⨁ HIGH	IMPORTANT
Serious adverse events (follow up: range 3 months to 12 months)												
2 (3, 4)	randomised trials	not serious	not serious	not serious	very serious [f]	none	29/590 (4.9%)	39/580 (6.7%)	**RR 0.69** (0.35 to 1.34)	**21 fewer per 1,000** (from 44 fewer to 23 more)	⨁⨁◯◯ LOW	IMPORTANT
Withdrawal due to lack of efficacy (follow up: 3 months)												
1 (5)	randomised trials	not serious	not serious	not serious	very serious [k]	none	0/327 (0.0%)	0/651 (0.0%)	not estimable		⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add TNFi	Add JAKi	Relative (95% CI)	Absolute (95% CI)		
Withdrawal due to adverse events (follow up: range 3 months to 12 months)												
3 (3-5)	randomised trials	not serious	not serious	not serious	serious [a]	none	62/917 (6.8%)	55/1231 (4.5%)	**RR 1.30** (0.78 to 2.15)	**13 more per 1,000** (from 10 fewer to 51 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Death (follow up: 1 year)												
1 (4)	randomised trials	not serious	not serious	not serious	very serious [k]	none	0/386 (0.0%)	0/376 (0.0%)	not estimable		⨁⨁◯◯ LOW	IMPORTANT
Malignancy (follow up: 1 year)												
1 (4)	randomised trials	not serious	not serious	not serious	very serious [k]	none	1/386 (0.3%)	0/376 (0.0%)	**RR 2.92** (0.12 to 71.51)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add TNFi	Add JAKi	Relative (95% CI)	Absolute (95% CI)		
Major adverse cardiovascular event (follow up: 1 year)												
1 (4)	randomised trials	not serious	not serious	not serious	very serious [k]	none	2/386 (0.5%)	0/376 (0.0%)	**RR 4.87** (0.23 to 101.12)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting harm and values suggesting no effect.
b. Downgraded by one level due to serious inconsistency. Unexplained heterogeneity I2=83%.
c. Downgraded by one level due to serious inconsistency. Unexplained heterogeneity I2=73%.
d. Downgraded by one level due to serious risk of bias. Lack of blinding of outcome assessors.
e. Downgraded by two levels due to very serious inconsistency. Unexplained heterogeneity I2=93%.
f. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting harm and values suggesting benefit.
g. The study ORAL Standard and ORAL Strategy found that the RR of improvement in SF-36 PCS ≥ 2.5 was 0.98 (95% CI 0.92 to 1.05), absolute risk reduction 15 fewer per 1000 (95%CI 61 fewer to 38 more).
h. The study ORAL Standard and ORAL Strategy found that the RR of improvement in SF-36 MCS ≥ 2.5 was 0.93 (95% CI 0.78 to 1.11), absolute risk reduction 43 fewer per 1000 (95%CI 134 fewer to 67 more).
i. The study ORAL Standard and ORAL Strategy found that the RR of improvement in VAS-pain ≥ 10 was 0.97 (95% CI 0.9 to 1.04), absolute risk reduction 22 fewer per 1000 (95%CI 75 fewer to 30 more).
j. The study ORAL Standard and ORAL Strategy found that the RR of improvement in FACIT-F≥ 4 was 0.96 (95% CI 0.87 to 1.05), absolute risk reduction 26 fewer per 1000 (95%CI 85 fewer to 33 more).
k. Downgraded by two levels due to very serious imprecision. Very low number of events.

Comparison 9: Add Abatacept **versus** add TNF Inhibitor. Data based on **direct** evidence.
Overall certainty of evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add ABA	Add TNFi	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: range 1 year to 2 years; assessed with: ACR 20)												
2 (8, 9)	randomised trials	serious [a]	serious [b]	not serious	serious [c]	none	303/474 (63.9%)	289/493 (58.6%)	**RR 1.09** (0.99 to 1.21)	**53 more per 1,000** (from 6 fewer to 123 more)	⨁◯◯◯ VERY LOW	CRITICAL
Disease activity (follow up: range 1 year to 2 years; assessed with: ACR 50)												
2 (8, 9)	randomised trials	serious [a]	serious [d]	not serious	very serious [e]	none	213/474 (44.9%)	213/493 (43.2%)	**RR 1.04** (0.90 to 1.20)	**17 more per 1,000** (from 43 fewer to 86 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add ABA	Add TNFi	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: range 1 year to 2 years; assessed with: ACR 70)												
2 (8, 9)	randomised trials	serious [a]	not serious	not serious	very serious [e]	none	140/474 (29.5%)	130/493 (26.4%)	**RR 1.12** (0.91 to 1.37)	**32 more per 1,000** (from 24 fewer to 98 more)	⨁◯◯◯ VERY LOW	CRITICAL
Disease activity (follow up: range 1 year to 2 years; assessed with: DAS28 ESR/CRP (Lower values – > benefit) (values>0.2 are considered clinically significant)												
2 (8, 9)	randomised trials	serious [a]	serious [f]	not serious	not serious [g]	none	474	493	-	SMD **0.14 lower** (0.27 lower to 0.02 lower)	⨁⨁◯◯ LOW	CRITICAL
Remission (follow up: range 1 year to 2 years; assessed with: DAS28ESR/CRP <2.6)												
2 (8, 9)	randomised trials	serious [a]	serious [h]	not serious	very serious [e]	none	190/474 (40.1%)	195/493 (39.6%)	**RR 1.01** (0.87 to 1.17)	**4 more per 1,000** (from 51 fewer to 67 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add ABA	Add TNFi	Relative (95% CI)	Absolute (95% CI)		
Radiographic progression (follow up: 2 years; assessed with: mTSS (Lower values – > benefit) (MCID 4.6)												
1 (8)	randomised trials	serious [i]	not serious	not serious	not serious	none	257	260	-	MD **0.24 lower** (1.41 lower to 0.93 higher) [j]	⨁⨁⨁◯ MODERATE	IMPORTANT
Disability (follow up: 2 years; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
1 (8)	randomised trials	serious [i]	not serious	not serious	not serious	none	318	328	-	MD **0.02 lower** (0.13 lower to 0.09 higher) [k]	⨁⨁⨁◯ MODERATE	IMPORTANT
Quality of life (follow up: 1 year; assessed with: SF-36 PCS (Higher values – > benefit) (MCID 4.4)												
1 (9)	randomised trials	not serious	not serious	not serious	serious [c]	none	156	165	-	MD **1.92 higher** (2.03 lower to 5.87 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add ABA	Add TNFi	Relative (95% CI)	Absolute (95% CI)		
Quality of life (follow up: 1 year; assessed with: SF-36 MCS (Higher values – > benefit) (MCID 3.1)												
1 (9)	randomised trials	not serious	not serious	not serious	serious [c]	none	156	165	-	MD **2.72 higher** (0.99 lower to 6.43 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Fatigue (follow up: 2 years; assessed with: VAS (MCID range -1.12, -0.82)												
1 (10)	randomised trials	serious [i]	not serious	not serious	very serious [e]	none	310	315	-	MD **1.9 lower** (6.06 lower to 2.26 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Withdrawal due to AE (follow up: range 1 year to 2 years)												
2 (8, 9)	randomised trials	serious [a]	not serious	not serious	not serious	none	16/474 (3.4%)	42/493 (8.5%)	**RR 0.40** (0.23 to 0.69)	**51 fewer per 1,000** (from 66 fewer to 26 fewer)	⨁⨁⨁◯ MODERATE	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add ABA	Add TNFi	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events (follow up: range 1 year to 2 years)												
2 (8, 9)	randomised trials	serious [a]	not serious	not serious	serious [c]	none	59/474 (12.4%)	84/493 (17.0%)	**RR 0.73** (0.54 to 0.99)	**46 fewer per 1,000** (from 78 fewer to 2 fewer)	⨁⨁◯◯ LOW	IMPORTANT
Withdrawal due to lack of efficacy (follow up: range 1 year to 2 years)												
2 (8, 9)	randomised trials	serious [a]	not serious	not serious	very serious [e]	none	23/474 (4.9%)	22/493 (4.5%)	**RR 1.08** (0.61 to 1.92)	**4 more per 1,000** (from 17 fewer to 41 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Death (follow up: range 1 year to 2 years)												
2 (8, 9)	randomised trials	serious [a]	not serious	not serious	very serious [l]	none	2/474 (0.4%)	3/493 (0.6%)	**RR 0.70** (0.12 to 4.16)	**2 fewer per 1,000** (from 5 fewer to 19 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add ABA	Add TNFi	Relative (95% CI)	Absolute (95% CI)		
Malignancy (follow up: range 1 year to 2 years)												
2 (8, 9)	randomised trials	serious [a]	not serious	not serious	very serious [e]	none	8/474 (1.7%)	9/493 (1.8%)	**RR 0.92** (0.36 to 2.37)	**1 fewer per 1,000** (from 12 fewer to 25 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **SMD:** Standardised mean difference; **MD:** Mean difference

Explanations

a. Downgraded by two levels due to very serious risk of bias. Lack of allocation concealment and lack of blinding in the study contributing with the bigger weight.
b. Downgraded by one level due to serious inconsistency. I2=84%
c. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting benefit.
d. Downgraded by one level due to serious inconsistency. I2=64%
e. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting harm and values suggesting benefit.
f. Downgraded by one level due to serious inconsistency. I2=88%
g. According to the Cochrane's handbook, Cohen suggested that SMD=0.2 be considered a 'small' effect size, 0.5 represents a 'medium' effect size and 0.8 a 'large' effect size. This means that if two groups' means do not differ by 0.2 standard deviations or more, the difference is trivial, even if it is statistically significant. CI suggesting some imprecision, taken into consideration when rating down for inconsistency and risk of bias.
h. Downgraded by one level due to serious inconsistency. I2=68%
i. Downgraded by two levels due to very serious risk of bias. Lack of allocation concealment and lack of blinding.
j. The study AMPLE found that the RR of developing radiographic non-progression (change in mTSS ≤0.5) was 0.97 (95%CI 0.87to 1.08), absolute risk reduction 22 fewer per 1000 (95%CI 95 fewer to 58 more).
k. The studies AMPLE and ATTEST found that the RR of improvement in disability (change in HAQ-DI ≥ 0.3) was 1.10 (95%CI 0.98 to 124), absolute risk increase 50 more per 1000 (95%CI 10 fewer to 120 more).
l. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting harm. Low number of events.

Cost-effectiveness

No cost-effectiveness data were identified.

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PICO 20. Should patients with RA on maximally tolerated dose of LEF monotherapy who are NOT at target, and have previously failed MTX (due to an inadequate response or adverse events), add SSZ and HCQ, or add a boDMARD, or add tsDMARD?

P - Patients with RA on maximally tolerated dose of LEF monotherapy who are not at target, and have previously failed MTX (due to an inadequate response or adverse events)
I - Add SSZ and HCQ
C - Add TNF Inhibitor
C - Add Abatacept
C - Add Rituximab
C - Add IL-6 Receptor Inhibitor
C - Add JAK Inhibitor

Comparison 1: Add SSZ and HCQ **versus** add TNF Inhibitor. See below Table.
Comparison 2: Add SSZ and HCQ **versus** add Abatacept. No eligible RCT, NRS, or indirect evidence were identified.
Comparison 3: Add SSZ and HCQ **versus** add Rituximab. No eligible RCT, NRS, or indirect evidence were identified.
Comparison 4: Add SSZ and HCQ **versus** add IL-6 Receptor Inhibitor. No eligible RCT, NRS, or indirect evidence were identified.
Comparison 5: Add SSZ and HCQ **versus** add JAK Inhibitor. No eligible RCT, NRS, or indirect evidence were identified.
Comparison 6: Add TNF Inhibitor **versus** add JAK Inhibitor. See below Table.
Comparison 7: Add Abatacept **versus** add TNF Inhibitor. See below Table.

Comparison 1: Add SSZ and HCQ **versus** add TNF Inhibitor. Data based on **indirect** RCT evidence.
Overall certainty of evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add SSZ+HCQ	Add TNFi	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 6 months; assessed with: ACR20)												
1 (1)	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	89/159 (56.0%)	90/163 (55.2%)	**RR 1.01** (0.83 to 1.23)	**6 more per 1,000** (from 94 fewer to 127 more)	⨁◯◯◯ VERY LOW	CRITICAL
Disease activity (follow up: 6 months; assessed with: ACR50)												
1 (1)	randomised trials	serious [a]	not serious	serious [b]	serious [d]	none	41/159 (25.8%)	58/163 (35.6%)	**RR 0.72** (0.52 to 1.01)	**100 fewer per 1,000** (from 171 fewer to 4 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add SSZ+HCQ	Add TNFi	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 6 months; assessed with: ACR70)												
1 (1)	randomised trials	serious [a]	not serious	serious [b]	not serious	none	8/159 (5.0%)	26/163 (16.0%)	**RR 0.32** (0.15 to 0.68)	**108 fewer per 1,000** (from 136 fewer to 51 fewer)	⨁⨁◯◯ LOW	CRITICAL
Disease activity (follow up: 6 months; assessed with: DAS28-ESR (Lower values – > benefit) (MCID -1.17)												
1 (1)	randomised trials	serious [a]	not serious	serious [b]	not serious	none	157	161	-	MD **0.27 higher** (0.01 lower to 0.55 higher)	⨁⨁◯◯ LOW	CRITICAL
Remission (follow up: 6 months; assessed with: DAS28-CRP < 2.6)												
1 (1)	randomised trials	serious [a]	not serious	serious [b]	serious [d]	none	20/157 (12.7%)	35/161 (21.7%)	**RR 0.59** (0.35 to 0.97)	**89 fewer per 1,000** (from 141 fewer to 7 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add SSZ+HCQ	Add TNFi	Relative (95% CI)	Absolute (95% CI)		
Radiographic progression (follow up: 6 months; assessed with: mTSS (Lower values – > benefit) (MCID 4.6)												
1 (1)	randomised trials	serious [a]	not serious	serious [b]	not serious	none	158	160	-	MD **0.42 higher** (0.22 lower to 1.05 higher)	⨁⨁◯◯ LOW	IMPORTANT
Disability (follow up: 6 months; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
1 (1)	randomised trials	serious [a]	not serious	serious [b]	serious [d]	none	155	160	-	MD **0.07 higher** (0.11 lower to 0.25 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add SSZ+HCQ	Add TNFi	Relative (95% CI)	Absolute (95% CI)		
Malignancy (from SRs of harms)												
1 (2)							The Systematic Review RefID=4638, 2012 (RCTs=9, n=3712) comparing csDMARD + placebo vs infliximab + MTX among RA showed that for cancer, the result was RR=0.83 (0.22-3.13) at 2 years and RR=0.56(0.22-1.47) at all time points (6 months, 1 year and 2 years combined)				-	

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Downgraded by one level due to serious risk of bias. Lack of allocation concealment.
b. Downgraded by one level due to serious indirectness. The evidence is based on a population on maximally tolerated dose of MTX monotherapy and not LEF.
c. Downgraded by two levels due to very serious imprecision. Confidence intervals includes both values suggesting benefit and values suggesting harm. Concern about risk of bias associated with lack of allocation concealment taken into account when rating down for imprecision.
d. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting harm and values suggesting no effect.

Comparison 6: Add TNF Inhibitor **versus** add JAK Inhibitor. Data based on **indirect** RCT evidence.
Overall certainty of evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add TNFi	Add JAKi	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: range 3 months to 1 year; assessed with: ACR20)												
3 (3-5)	randomised trials	not serious	not serious	serious [a]	serious [b]	none	581/917 (63.4%)	849/1231 (69.0%)	**RR 0.93** (0.87 to 0.99)	**48 fewer per 1,000** (from 90 fewer to 7 fewer)	⨁⨁◯◯ LOW	CRITICAL
Disease activity (follow up: range 3 months to 1 year; assessed with: ACR50)												
3 (3-5)	randomised trials	not serious	serious [c]	serious [a]	serious [b]	none	317/917 (34.6%)	539/1231 (43.8%)	**RR 0.76** (0.56 to 1.02)	**105 fewer per 1,000** (from 193 fewer to 9 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add TNFi	Add JAKi	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: range 3 months to 1 year; assessed with: ACR70)												
3 (3-5)	randomised trials	not serious	serious [d]	serious [a]	serious [b]	none	160/917 (17.4%)	297/1231 (24.1%)	**RR 0.69** (0.47 to 1.02)	**75 fewer per 1,000** (from 128 fewer to 5 more)	⨁◯◯◯ VERY LOW	CRITICAL
Disease activity (follow up: 3 months; assessed with: DAS28-ESR (Lower values – > benefit) (MCID -1.17)												
1 (3)	randomised trials	serious [e]	not serious	serious [a]	not serious	none	204	204	-	MD **0.11 lower** (0.27 lower to 0.05 higher)	⨁⨁◯◯ LOW	CRITICAL
Remission (follow up: range 3 months to 1 year; assessed with: DAS28-CRP<2.6)												
2 (4, 5)	randomised trials	not serious	very serious [f]	serious [a]	very serious [g]	none	195/713 (27.3%)	303/1027 (29.5%)	**RR 0.85** (0.46 to 1.59)	**44 fewer per 1,000** (from 159 fewer to 174 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add TNFi	Add JAKi	Relative (95% CI)	Absolute (95% CI)		
Disability (follow up: 3 months; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
2 (5, 6)	randomised trials	not serious	not serious	serious [a]	not serious	none	526	849	-	MD **0.08 higher** (0.01 higher to 0.15 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Quality of life (follow up: range 3 months to 12 months; assessed with: SF-36 PCS (Higher values – > benefit) (MCID 4.4)												
3 (5-7)	randomised trials	not serious	not serious	serious [a]	not serious	none	912	1225	-	MD **1.09 lower** (1.82 lower to 0.35 lower) [h]	⨁⨁⨁◯ MODERATE	IMPORTANT
Quality of life (follow up: range 3 months to 12 months; assessed with: SF-36 MCS (Higher values – > benefit) (MCID 3.1)												
2 (6, 7)	randomised trials	not serious	not serious	serious [a]	not serious	none	585	574	-	MD **0.2 lower** (1.26 lower to 0.86 higher) [i]	⨁⨁⨁◯ MODERATE	IMPORTANT
Pain (follow up: range 3 months to 12 months; assessed with: VAS 100 (Lower values – > benefit) (MCID -11.9)												
3 (5-7)	randomised trials	not serious	not serious	serious [a]	not serious	none	912	1225	-	MD **4 higher** (1.66 higher to 6.35 higher) [j]	⨁⨁⨁◯ MODERATE	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add TNFi	Add JAKi	Relative (95% CI)	Absolute (95% CI)		
Fatigue (follow up: range 3 months to 12 months; assessed with: FACIT-F (Higher values – > benefit) (MCID 15.9)												
3 (5-7)	randomised trials	not serious	not serious	serious [a]	not serious	none	912	1225	-	MD **1.15 lower** (2.02 lower to 0.27 lower) [k]	⨁⨁⨁◯ MODERATE	IMPORTANT
Serious adverse events (follow up: range 3 months to 12 months)												
2 (3, 4)	randomised trials	not serious	not serious	serious [a]	very serious [g]	none	29/590 (4.9%)	39/580 (6.7%)	**RR 0.69** (0.35 to 1.34)	**21 fewer per 1,000** (from 44 fewer to 23 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Withdrawal due to lack of efficacy (follow up: 3 months)												
1 (5)	randomised trials	not serious	not serious	serious [a]	very serious [l]	none	0/327 (0.0%)	0/651 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add TNFi	Add JAKi	Relative (95% CI)	Absolute (95% CI)		
Withdrawal due to adverse events (follow up: range 3 months to 12 months)												
3 (3-5)	randomised trials	not serious	not serious	serious [a]	serious [b]	none	62/917 (6.8%)	55/1231 (4.5%)	**RR 1.30** (0.78 to 2.15)	**13 more per 1,000** (from 10 fewer to 51 more)	⨁⨁◯◯ LOW	IMPORTANT
Death (follow up: 1 year)												
1 (4)	randomised trials	not serious	not serious	serious [a]	very serious [l]	none	0/386 (0.0%)	0/376 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	IMPORTANT
Malignancy (follow up: 1 year)												
1 (4)	randomised trials	not serious	not serious	serious [a]	very serious [l]	none	1/386 (0.3%)	0/376 (0.0%)	**RR 2.92** (0.12 to 71.51)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add TNFi	Add JAKi	Relative (95% CI)	Absolute (95% CI)		
Major adverse cardiovascular event (follow up: 1 year)												
1 (4)	randomised trials	not serious	not serious	serious [a]	very serious [l]	none	2/386 (0.5%)	0/376 (0.0%)	**RR 4.87** (0.23 to 101.12)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Downgraded by one level due to serious indirectness. The evidence is based on a population on maximally tolerated dose of MTX monotherapy and not LEF.
b. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting harm and values suggesting no effect.
c. Downgraded by one level due to serious inconsistency. Unexplained heterogeneity I2=83%.
d. Downgraded by one level due to serious inconsistency. Unexplained heterogeneity I2=73%.
e. Downgraded by one level due to serious risk of bias. Lack of blinding of outcome assessors.
f. Downgraded by two levels due to very serious inconsistency. Unexplained heterogeneity I2=93%.
g. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting harm and values suggesting benefit.
h. The study ORAL Standard and ORAL Strategy found that the RR of improvement in SF-36 PCS ≥ 2.5 was 0.98 (95% CI 0.92 to 1.05), absolute risk reduction 15 fewer per 1000 (95%CI 61 fewer to 38 more).
i. The study ORAL Standard and ORAL Strategy found that the RR of improvement in SF-36 MCS ≥ 2.5 was 0.93 (95% CI 0.78 to 1.11), absolute risk reduction 43 fewer per 1000 (95%CI 134 fewer to 67 more).
j. The study ORAL Standard and ORAL Strategy found that the RR of improvement in VAS-pain ≥ 10 was 0.97 (95% CI 0.9 to 1.04), absolute risk reduction 22 fewer per 1000 (95%CI 75 fewer to 30 more).
k. The study ORAL Standard and ORAL Strategy found that the RR of improvement in FACIT-F≥ 4 was 0.96 (95% CI 0.87 to 1.05), absolute risk reduction 26 fewer per 1000 (95%CI 85 fewer to 33 more).
l. Downgraded by two levels due to very serious imprecision. Very low number of events.

Comparison 7: Add Abatacept **versus** add TNF Inhibitor. Data based on **indirect** RCT evidence.
Overall certainty of evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add ABA	Add TNFi	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: range 1 year to 2 years; assessed with: ACR 20)												
2 (8, 9)	randomised trials	serious [a]	serious [b]	serious [c]	serious [d]	none	303/474 (63.9%)	289/493 (58.6%)	**RR 1.09** (0.99 to 1.21)	**53 more per 1,000** (from 6 fewer to 123 more)	⨁◯◯◯ VERY LOW	CRITICAL
Disease activity (follow up: range 1 year to 2 years; assessed with: ACR 50)												
2 (8, 9)	randomised trials	serious [a]	serious [e]	serious [c]	very serious [f]	none	213/474 (44.9%)	213/493 (43.2%)	**RR 1.04** (0.90 to 1.20)	**17 more per 1,000** (from 43 fewer to 86 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add ABA	Add TNFi	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: range 1 year to 2 years; assessed with: ACR 70)												
2 (8, 9)	randomised trials	serious [a]	not serious	serious [c]	very serious [f]	none	140/474 (29.5%)	130/493 (26.4%)	**RR 1.12** (0.91 to 1.37)	**32 more per 1,000** (from 24 fewer to 98 more)	⨁◯◯◯ VERY LOW	CRITICAL
Disease activity (follow up: range 1 year to 2 years; assessed with: DAS28 ESR/CRP (Lower values – > benefit) (values>0.2 are considered clinically significant)												
2 (8, 9)	randomised trials	serious [a]	serious [g]	serious [c]	not serious [h]	none	474	493	-	SMD **0.14 lower** (0.27 lower to 0.02 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Remission (follow up: range 1 year to 2 years; assessed with: DAS28ESR/CRP <2.6)												
2 (8, 9)	randomised trials	serious [a]	serious [i]	serious [c]	very serious [f]	none	190/474 (40.1%)	195/493 (39.6%)	**RR 1.01** (0.87 to 1.17)	**4 more per 1,000** (from 51 fewer to 67 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add ABA	Add TNFi	Relative (95% CI)	Absolute (95% CI)		
Radiographic progression (follow up: 2 years; assessed with: mTSS (Lower values – > benefit) (MCID 4.6)												
1 (8)	randomised trials	serious [j]	not serious	serious [c]	not serious	none	257	260	-	MD **0.24 lower** (1.41 lower to 0.93 higher) [k]	⨁⨁◯◯ LOW	IMPORTANT
Disability (follow up: 2 years; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
1 (8)	randomised trials	serious [j]	not serious	serious [c]	not serious	none	318	328	-	MD **0.02 lower** (0.13 lower to 0.09 higher) [l]	⨁⨁◯◯ LOW	IMPORTANT
Quality of life (follow up: 1 year; assessed with: SF-36 PCS (Higher values – > benefit) (MCID 4.4)												
1 (9)	randomised trials	not serious	not serious	serious [c]	serious [d]	none	156	165	-	MD **1.92 higher** (2.03 lower to 5.87 higher)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add ABA	Add TNFi	Relative (95% CI)	Absolute (95% CI)		
Quality of life (follow up: 1 year; assessed with: SF-36 MCS (Higher values – > benefit) (MCID 3.1)												
1 (9)	randomised trials	not serious	not serious	serious [c]	serious [d]	none	156	165	-	MD **2.72 higher** (0.99 lower to 6.43 higher)	⨁⨁◯◯ LOW	IMPORTANT
Fatigue (follow up: 2 years; assessed with: VAS (MCID range -1.12, -0.82)												
1 (10)	randomised trials	serious [j]	not serious	serious [c]	very serious [f]	none	310	315	-	MD **1.9 lower** (6.06 lower to 2.26 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Withdrawal due to AE (follow up: range 1 year to 2 years)												
2 (8, 9)	randomised trials	serious [a]	not serious	serious [c]	not serious	none	16/474 (3.4%)	42/493 (8.5%)	**RR 0.40** (0.23 to 0.69)	**51 fewer per 1,000** (from 66 fewer to 26 fewer)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add ABA	Add TNFi	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events (follow up: range 1 year to 2 years)												
2 (8, 9)	randomised trials	serious [a]	not serious	serious [c]	serious [d]	none	59/474 (12.4%)	84/493 (17.0%)	**RR 0.73** (0.54 to 0.99)	**46 fewer per 1,000** (from 78 fewer to 2 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT
Withdrawal due to lack of efficacy (follow up: range 1 year to 2 years)												
2 (8, 9)	randomised trials	serious [a]	not serious	serious [c]	very serious [f]	none	23/474 (4.9%)	22/493 (4.5%)	**RR 1.08** (0.61 to 1.92)	**4 more per 1,000** (from 17 fewer to 41 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Death (follow up: range 1 year to 2 years)												
2 (8, 9)	randomised trials	serious [a]	not serious	serious [c]	very serious [m]	none	2/474 (0.4%)	3/493 (0.6%)	**RR 0.70** (0.12 to 4.16)	**2 fewer per 1,000** (from 5 fewer to 19 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add ABA	Add TNFi	Relative (95% CI)	Absolute (95% CI)		
Malignancy (follow up: range 1 year to 2 years)												
2 (8, 9)	randomised trials	serious [a]	not serious	serious [c]	very serious [f]	none	8/474 (1.7%)	9/493 (1.8%)	**RR 0.92** (0.36 to 2.37)	**1 fewer per 1,000** (from 12 fewer to 25 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **SMD:** Standardised mean difference; **MD:** Mean difference

Explanations

a. Downgraded by two levels due to very serious risk of bias. Lack of allocation concealment and lack of blinding in the study contributing with the bigger weight.
b. Downgraded by one level due to serious inconsistency. I2=84%
c. Downgraded by one level due to serious indirectness. The evidence is based on a population on maximally tolerated dose of MTX monotherapy and not LEF.
d. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting benefit.
e. Downgraded by one level due to serious inconsistency. I2=64%
f. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting harm and values suggesting benefit.
g. Downgraded by one level due to serious inconsistency. I2=88%
h. According to the Cochrane's handbook, Cohen suggested that SMD=0.2 be considered a 'small' effect size, 0.5 represents a 'medium' effect size and 0.8 a 'large' effect size. This means that if two groups' means do not differ by 0.2 standard deviations or more, the difference is trivial, even if it is statistically significant. CI suggesting some imprecision, taken into consideration when rating down for inconsistency and risk of bias.
i. Downgraded by one level due to serious inconsistency. I2=68%
j. Downgraded by two levels due to very serious risk of bias. Lack of allocation concealment and lack of blinding.
k. The study AMPLE found that the RR of developing radiographic non-progression (change in mTSS ≤0.5) was 0.97 (95%CI 0.87to 1.08), absolute risk reduction 22 fewer per 1000 (95%CI 95 fewer to 58 more).
l. The studies AMPLE and ATTEST found that the RR of improvement in disability (change in HAQ-DI ≥ 0.3) was 1.10 (95%CI 0.98 to 124), absolute risk increase 50 more per 1000 (95%CI 10 fewer to 120 more).
m. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting harm. Low number of events.

Cost-effectiveness

No cost-effectiveness data were identified.

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PICO 21a. Should patients with RA on DMARD(s) who are NOT at target switch to another DMARD versus add a 2nd DMARD?
P - Patients with RA on non-biologic DMARD(s) who are not at target
I - Switch to another DMARD
C - Add another DMARD

Comparison: Add another DMARD **versus** Switch to another DMARD. See below Table.

Comparison: Add another DMARD **versus** switch to another DMARD. Data based on **direct** RCT evidence.
Overall certainty of evidence: Moderate

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch DMARDs	Add DMARDs	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: range 4 months to 2 years; assessed with: ACR 20)												
9 (1-9)	randomised trials	not serious [a]	not serious	not serious	serious [b]	none	795/1279 (62.2%)	1112/1658 (67.1%)	**RR 0.93** (0.86 to 1.02)	**47 fewer per 1,000** (from 94 fewer to 13 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Disease activity (follow up: range 4 months to 2 years; assessed with: ACR 50)												
9 (1-9)	randomised trials	not serious [a]	not serious	not serious	not serious	none	491/1279 (38.4%)	744/1658 (44.9%)	**RR 0.87** (0.79 to 0.97)	**58 fewer per 1,000** (from 94 fewer to 13 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch DMARDs	Add DMARDs	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: range 4 months to 2 years; assessed with: ACR 70)												
9 (1-9)	randomised trials	not serious [a]	not serious	not serious	not serious	none	266/1263 (21.1%)	422/1658 (25.5%)	**RR 0.84** (0.73 to 0.97)	**41 fewer per 1,000** (from 69 fewer to 8 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Disease activity (follow up: range 4 months to 2 years; assessed with: DAS28 or DAS44 (lower values --> benefit) (values>0.2 are considered clinically important)												
7 (2-5, 7-9)	randomised trials	not serious [a]	not serious	not serious	serious [c]	none	0	0	-	SMD **0.24 SD higher** (0.1 higher to 0.38 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Remission (follow up: range 4 months to 1 year; assessed with: DAS remission < 2.6)												
6 (1-3, 5-7)	randomised trials	not serious	not serious	not serious	serious [d]	none	250/998 (25.1%)	356/1367 (26.0%)	**RR 0.85** (0.70 to 1.02)	**39 fewer per 1,000** (from 78 fewer to 5 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch DMARDs	Add DMARDs	Relative (95% CI)	Absolute (95% CI)		
Flare (follow up: 1 months)												
1 (7)	randomised trials	serious [e]	not serious	not serious	serious [b]	none	0/155 (0.0%)	1/152 (0.7%)	**RR 0.33** (0.01 to 7.96)	**4 fewer per 1,000** (from 7 fewer to 46 more)	⨁⨁◯◯ LOW	IMPORTANT
Radiographic progression (follow up: 6 months; assessed with: mTSS (Lower values – > benefit) (MCID 4.6)												
1 (3)	randomised trials	not serious	not serious	not serious	not serious	none	276	277	-	MD **0.17 higher** (0.14 higher to 0.2 higher) [f]	⨁⨁⨁⨁ HIGH	IMPORTANT
Pain (follow up: range 4 months to 12 months; assessed with: VAS pain (0-100) (Lower values – > benefit) (MCID -11.9)												
5 (2, 3, 5, 10, 11)	randomised trials	not serious	not serious	not serious	not serious	none	949	1328	-	MD **1.9 higher** (0.3 lower to 4.1 higher) [g]	⨁⨁⨁⨁ HIGH	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch DMARDs	Add DMARDs	Relative (95% CI)	Absolute (95% CI)		
Disability (follow up: range 4 months to 2 years; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
5 (2-5, 10)	randomised trials	serious [h]	not serious	not serious	not serious	none	670	673	-	MD **0** (0.06 lower to 0.07 higher) [i]	⨁⨁⨁◯ MODERATE	IMPORTANT
Fatigue (follow up: 1 year; assessed with: FACIT-F (Higher values – > benefit) (MCID 15.9)												
1 (11)	randomised trials	not serious	not serious	not serious	not serious	none	384	762	-	MD **0.62 lower** (1.84 lower to 0.6 higher) [j]	⨁⨁⨁⨁ HIGH	IMPORTANT
Quality of Life (follow up: 1 year; assessed with: SF-36 MCS (Higher values – > benefit) (MCID 3.1)												
1 (11)	randomised trials	not serious	not serious	not serious	not serious	none	384	762	-	MD **0.97 lower** (2.1 lower to 0.16 higher) [k]	⨁⨁⨁⨁ HIGH	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch DMARDs	Add DMARDs	Relative (95% CI)	Absolute (95% CI)		
Quality of Life (follow up: 1 year; assessed with: SF-36 PCS (Higher values – > benefit) (MCID 4.4)												
1 (11)	randomised trials	not serious	not serious	not serious	not serious	none	384	762	-	MD **0.87 lower** (1.9 lower to 0.16 higher) [l]	⨁⨁⨁⨁ HIGH	IMPORTANT
Quality of Life (follow up: range 4 months to 2 years; assessed with: RAQol or EQ-5D VAS (lower values --> benefit) (values>0.2 are considered clinically important)												
3 (3, 4, 10)	randomised trials	not serious	not serious	not serious	serious [m]	none	533	529	-	SMD **0.13 lower** (0.25 lower to 0.01 lower)	⨁⨁⨁◯ MODERATE	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch DMARDs	Add DMARDs	Relative (95% CI)	Absolute (95% CI)		
Withdrawal due to lack of efficacy (follow up: range 4 months to 1 year)												
6 (4-9)	randomised trials	not serious	not serious	not serious	serious [c]	none	32/591 (5.4%)	16/446 (3.6%)	**RR 1.18** (0.59 to 2.36)	**6 more per 1,000** (from 15 fewer to 49 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Withdrawal due to adverse events (follow up: range 3 months to 2 years)												
9 (1, 2, 4-8, 12, 13)	randomised trials	not serious [n]	not serious	not serious	very serious [o]	none	101/1017 (9.9%)	145/1392 (10.4%)	**RR 0.91** (0.66 to 1.25)	**9 fewer per 1,000** (from 35 fewer to 26 more)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch DMARDs	Add DMARDs	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events (follow up: range 3 months to 2 years)												
6 (1, 2, 4, 6, 7, 9)	randomised trials	serious [e]	not serious	not serious	serious [c]	none	94/1009 (9.3%)	113/1371 (8.2%)	**RR 1.10** (0.85 to 1.42)	**8 more per 1,000** (from 12 fewer to 35 more)	⨁⨁◯◯ LOW	IMPORTANT
Malignancy (follow up: range 4 months to 2 years)												
3 (1, 2, 4)	randomised trials	serious [e]	not serious	not serious	serious [p]	none	3/598 (0.5%)	6/978 (0.6%)	**RR 0.65** (0.11 to 3.70)	**2 fewer per 1,000** (from 5 fewer to 17 more)	⨁⨁◯◯ LOW	IMPORTANT
Death (follow up: range 4 months to 2 years)												
4 (1, 2, 4, 7)	randomised trials	serious [e]	not serious	not serious	serious [p]	none	3/757 (0.4%)	4/1133 (0.4%)	**RR 0.92** (0.17 to 4.88)	**0 fewer per 1,000** (from 3 fewer to 14 more)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **SMD:** Standardised mean difference; **MD:** Mean difference

Explanations

a. Three studies at low risk of bias represent 60% of the weight.
b. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting harm.
c. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting harm. According to the Cochrane's handbook, Cohen suggested that SMD=0.2 be considered a 'small' effect size, 0.5 represents a 'medium' effect size and 0.8 a 'large' effect size. This means that if two groups' means do not differ by 0.2 standard deviations or more, the difference is trivial, even if it is statistically significant.
d. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting benefit.
e. Downgraded by one level due to serious risk of bias. Lack of allocation concealment and blinding.
f. The studies ACT-RAY and SURPRISE found that the RR of developing no radiographic progression (change in mTSS ≤0.5) was 0.96 (95%CI 0.91 to 1.02), absolute risk reduction 34 fewer per 1000 (95%CI 76 fewer to 17 more).
g. The study ORAL Strategy found that the RR of improvement in pain VAS (0-100) ≥ 10 was 0.99 (95% CI 0.92 to 1.07), absolute risk reduction 8 fewer per 1000 (95%CI 62 fewer to 54 more).
h. Downgraded by one level due to serious risk of bias in three studies representing 55% of the weight.
i. The studies ADORE, ORAL strategy and Strand 2006, found that the RR of improvement in HAQ-DI (≥0.22 or ≥0.25 change from baseline) was 0.94 (95%CI 0.83 to 1.07), absolute risk reduction 39 fewer per 1000 (95%CI 112 fewer to 46 more).
j. The study ORAL Strategy found that the RR of improvement in FACIT-F≥ 4 was 0.92 (95% CI 0.83 to 1.01), absolute risk reduction 55 fewer per 1000 (95%CI 117 fewer to 7 more).
k. The study ORAL Strategy found that the RR of improvement in SF-36 MCS ≥ 2.5 was 0.94 (95% CI 0.84 to 1.05), absolute risk reduction 37 fewer per 1000 (95%CI 100 fewer to 31 more).
l. The study ORAL Strategy found that the RR of improvement in SF-36 PCS ≥ 2.5 was 0.92 (95% CI 0.85 to 0.99), absolute risk reduction 65 fewer per 1000 (95%CI 121 fewer to 8 fewer).
m. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting benefit. According to the Cochrane's handbook, Cohen suggested that SMD=0.2 be considered a 'small' effect size, 0.5 represents a 'medium' effect size and 0.8 a 'large' effect size. This means that if two groups' means do not differ by 0.2 standard deviations or more, the difference is trivial, even if it is statistically significant.
n. Four studies at high risk of bias represent 40% of the weight. This is accounted for when downgrading for imprecision.
o. Downgraded by two levels due to serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm.
p. Downgraded by one level due serious imprecision. Low number of events.

Cost-effectiveness

No cost-effectiveness data identified.

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PICO 21b. Should patients with RA on DMARD(s) who are NOT at target and who are being switched to a second DMARD, have *short-term* GCs *(≤ 3 months) added, long-term* GCs *(> 3 months) added* versus no GCs added?

P - Patients with RA on DMARD(s) who are not at target and who are being switched to a second DMARD

I – Add short-term GCs (≤ 3 months)

C – Add long-term GCs (> 3 months)

C – No GCs added

No eligible RCT, NRS, or indirect evidence were identified.

PICO 21c. Should patients with RA on DMARD(s) who are NOT at target and whom a second DMARD is being added, have *short-term* GCs *(≤ 3 months) added, long-term* GCs *(> 3 months) added* versus no GCs added?

P - Patients with RA on DMARD(s) who are not at target and whom a second DMARD is being added

I – Add short-term GCs (≤ 3 months)

C – Add long-term GCs (> 3 months)

C – No GCs added

No eligible RCT, NRS, or indirect evidence were identified.

PICO 23. Should patients with RA on DMARD(s) requiring GCs to remain at target, add a 2nd DMARD or switch to another DMARD to enable tapering off of GCs?

P - Patients with RA on DMARD(s) requiring GCs to remain at target
I - No change to management
C - Switch to another DMARD
C - Add a 2nd DMARD

No eligible RCT, NRS, or indirect evidence were identified.

PICO 24. Should patients with RA on their first TNF Inhibitor who are NOT at target, switch to a 2nd TNF Inhibitor or switch to a boDMARD targeting a different molecule or to a tsDMARD?

P - Patients with RA on their first TNF Inhibitor who are not at target
I - Switch to a 2nd TNF Inhibitor
C - Switch to Abatacept
C - Switch to Rituximab
C - Switch to IL-6 Receptor Inhibitor
C - Switch to JAK Inhibitor
C- Continue same management

Comparison 1: Switch to Abatacept **versus** switch to a 2nd TNF Inhibitor. See below Table.
Comparison 2: Switch to Rituximab **versus** switch to a 2nd TNF Inhibitor. See below Table.
Comparison 3: Switch to IL-6 Receptor Inhibitor **versus** switch to a 2nd TNF Inhibitor. See below Table.
Comparison 4: Switch to JAK Inhibitor **versus** switch to a 2nd TNF Inhibitor. No eligible RCT, NRS, or indirect evidence were identified.
Comparison 5: Switch to a 2nd TNF Inhibitor **versus** continue same management. See below Table.
Comparison 6: Switch to IL-6 Receptor Inhibitor **versus** switch to Abatacept. See below Table.
Comparison 7: Switch to Rituximab **versus s**witch to IL-6 Receptor Inhibitor. See below Table.

Comparison 1: Switch to Abatacept **versus** switch to a 2nd TNF Inhibitor. Data based on **direct** RCT evidence.
Overall certainty of evidence: Low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to ABA	switch to a 2nd TNFi	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 1 year; assessed with: ACR 20)												
1 (1)	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	11/31 (35.5%)	17/31 (54.8%)	**RR 0.65** (0.37 to 1.15)	**192 fewer per 1,000** (from 345 fewer to 82 more)	⨁◯◯◯ VERY LOW	CRITICAL
Disease activity (follow up: 1 year; assessed with: ACR 50)												
1 (1)	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	6/32 (18.8%)	9/31 (29.0%)	**RR 0.65** (0.26 to 1.60)	**102 fewer per 1,000** (from 215 fewer to 174 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to ABA	switch to a 2nd TNFi	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 1 year; assessed with: ACR 70)												
1 (1)	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	3/32 (9.4%)	5/31 (16.1%)	**RR 0.58** (0.15 to 2.23)	**68 fewer per 1,000** (from 137 fewer to 198 more)	⨁◯◯◯ VERY LOW	CRITICAL
Remission (follow up: 1 year; assessed with: DAS28-ESR <2.6)												
2 (1, 2)	randomised trials	serious [c]	not serious	not serious	serious [d]	none	6/76 (7.9%)	17/80 (21.3%)	**RR 0.38** (0.16 to 0.91)	**132 fewer per 1,000** (from 179 fewer to 19 fewer)	⨁⨁◯◯ LOW	CRITICAL
Disease activity (follow up: 1 year; assessed with: DAS28-ESR (Lower values – > benefit) (MCID -1.17)												
2 (1, 2)	randomised trials	serious [c]	not serious	not serious	serious [e]	none	76	80	-	MD **0.45 higher** (0.02 higher to 0.88 higher)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to ABA	switch to a 2nd TNFi	Relative (95% CI)	Absolute (95% CI)		
Disability (follow up: 1 year; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
2 (1, 2)	randomised trials	serious [c]	not serious	not serious	very serious [f]	none	77	81	-	MD **0.04 higher** (0.17 lower to 0.25 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Quality of life (follow up: 1 year; assessed with: RAQol (Lower values – > benefit) (MCID 2)												
1 (1)	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	34	30	-	MD **1.5 lower** (6.36 lower to 3.36 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Pain (follow up: 1 year; assessed with: VAS 0-100 (Lower values – > benefit) (MCID -11.9)												
1 (1)	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	34	31	-	MD **2.5 higher** (14.99 lower to 19.99 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to ABA	switch to a 2nd TNFi	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events (follow up: 1 year)												
2 (1, 2)	randomised trials	serious [c]	not serious	not serious	very serious [g]	none	5/63 (7.9%)	1/65 (1.5%)	**RR 3.75** (0.64 to 22.11)	**42 more per 1,000** (from 6 fewer to 325 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Withdrawal due to lack of efficacy (follow up: 1 year)												
1 (1)	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	3/41 (7.3%)	2/41 (4.9%)	**RR 1.50** (0.26 to 8.51)	**24 more per 1,000** (from 36 fewer to 366 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Withdrawal due to adverse events (follow up: 1 year)												
1 (1)	randomised trials	serious [a]	not serious	not serious	very serious [d]	none	1/41 (2.4%)	0/41 (0.0%)	**RR 3.00** (0.13 to 71.56)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to ABA	switch to a 2nd TNFi	Relative (95% CI)	Absolute (95% CI)		
Malignancy (follow up: 1 year)												
1 (2)	randomised trials	serious [c]	not serious	not serious	very serious [d]	none	0/22 (0.0%)	0/24 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	IMPORTANT
Cardiovascular disease (follow up: 1 year)												
1 (2)	randomised trials	serious [c]	not serious	not serious	very serious [b]	none	1/22 (4.5%)	2/24 (8.3%)	**RR 0.55** (0.05 to 5.60)	**37 fewer per 1,000** (from 79 fewer to 383 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to ABA	switch to a 2nd TNFi	Relative (95% CI)	Absolute (95% CI)		
Death (follow up: 1 year)												
1 (1)	randomised trials	serious [a]	not serious	not serious	very serious [d]	none	1/41 (2.4%)	0/41 (0.0%)	**RR 3.00** (0.13 to 71.56)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Downgraded by one level due to serious risk of bias. Lack of blinding.
b. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm. Very small sample size, low number of events.
c. Downgraded by one level due to serious risk of bias. Lack of blinding and lack of allocation concealment.
d. Downgraded by two levels due to very serious imprecision. Very small sample size, low number of events.
e. Downgraded by one level due to serious imprecision. Very small sample size.
f. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting harm. Very small sample size.
g. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting harm. Very small sample size, low number of events.

Comparison 2: Switch to Rituximab **versus** switch to a 2nd TNF Inhibitor. Data based on **direct** RCT evidence.
Overall certainty of evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to RTX	switch to a 2nd TNFi	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 1 year; assessed with: ACR 20)												
1 (1)	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	12/28 (42.9%)	17/31 (54.8%)	**RR 0.78** (0.46 to 1.33)	**121 fewer per 1,000** (from 296 fewer to 181 more)	⨁◯◯◯ VERY LOW	CRITICAL
Disease activity (follow up: 1 year; assessed with: ACR 50)												
1 (1)	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	6/29 (20.7%)	9/31 (29.0%)	**RR 0.71** (0.29 to 1.75)	**84 fewer per 1,000** (from 206 fewer to 218 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to RTX	switch to a 2nd TNFi	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 1 year; assessed with: ACR 70)												
1 (1)	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	3/30 (10.0%)	5/31 (16.1%)	**RR 0.62** (0.16 to 2.37)	**61 fewer per 1,000** (from 135 fewer to 221 more)	⨁◯◯◯ VERY LOW	CRITICAL
Disease activity (follow up: 1 year; assessed with: DAS28 ESR (Lower values – > benefit) (MCID -1.17)												
2 (1, 2)	randomised trials	serious [c]	not serious	not serious	very serious [d]	none	73	80	-	MD **0.13 higher** (0.44 lower to 0.7 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Remission (follow up: 1 year; assessed with: DAS28-ESR <2.6)												
2 (1, 2)	randomised trials	serious [c]	not serious	not serious	very serious [b]	none	16/73 (21.9%)	17/80 (21.3%)	**RR 0.96** (0.38 to 2.40)	**9 fewer per 1,000** (from 132 fewer to 298 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to RTX	switch to a 2nd TNFi	Relative (95% CI)	Absolute (95% CI)		
Disability (follow up: 1 year; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
2 (1, 2)	randomised trials	serious [c]	not serious	not serious	very serious [e]	none	76	81	-	MD **0.08 higher** (0.13 lower to 0.29 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Quality of life (follow up: 1 year; assessed with: RAQol (Lower values – > benefit) (MCID 2)												
1 (1)	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	30	30	-	MD **0.5 higher** (4.56 lower to 5.56 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Pain (follow up: 1 year; assessed with: VAS 0-100 (Lower values – > benefit) (MCID -11.9)												
1 (1)	randomised trials	serious [a]	not serious	not serious	very serious [f]	none	30	31	-	MD **8 higher** (6.43 lower to 22.43 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to RTX	switch to a 2nd TNFi	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events (follow up: 1 year)												
2 (1, 2)	randomised trials	serious [c]	not serious	not serious	very serious [b]	none	4/74 (5.4%)	1/65 (1.5%)	**RR 4.10** (0.48 to 35.11)	**48 more per 1,000** (from 8 fewer to 525 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events												
(3)							The Systematic Review RefID=1403, 2017 comparing Rituximab vs Etanercept, Adalimumab, Certolizumab, Golimumab, and Infliximab among RA showed that for Serious adverse events, the result was RR=1.13 (0.79 to 1.62) [Low certainty], RR=1.24 (0.89 to 1.73) [Low certainty], RR=1.56 (1.03 to 2.37) [Moderate certainty], RR=1.15 (0.71 to 1.86) [Very low certainty], and RR=1.20 (0.082 to 1.74) [Low certainty] respectively. All are Indirect evidence.				-	IMPORTANT
Withdrawal due to lack of efficacy (follow up: 1 year)												
1 (1)	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	0/40 (0.0%)	2/41 (4.9%)	**RR 0.20** (0.01 to 4.14)	**39 fewer per 1,000** (from 48 fewer to 153 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to RTX	switch to a 2nd TNFi	Relative (95% CI)	Absolute (95% CI)		
Withdrawal due to adverse events (follow up: 1 year)												
1 (1)	randomised trials	serious [a]	not serious	not serious	very serious [g]	none	0/40 (0.0%)	0/41 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	IMPORTANT
Death (follow up: 1 year)												
1 (1)	randomised trials	serious [a]	not serious	not serious	very serious [g]	none	1/40 (2.5%)	0/41 (0.0%)	**RR 3.07** (0.13 to 73.28)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT
CVD (follow up: 1 year)												
1 (2)	randomised trials	serious [c]	not serious	not serious	very serious [b]	none	2/34 (5.9%)	2/24 (8.3%)	**RR 0.71** (0.11 to 4.67)	**24 fewer per 1,000** (from 74 fewer to 306 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to RTX	switch to a 2nd TNFi	Relative (95% CI)	Absolute (95% CI)		
Malignancy (1 year) (follow up: 1 year)												
1 (2)	randomised trials	serious [c]	not serious	not serious	very serious [g]	none	3/34 (8.8%)	0/24 (0.0%)	**RR 5.00** (0.27 to 92.56)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Downgraded by one level due to serious risk of bias. Lack of blinding.
b. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm. Very small sample size, low number of events.
c. Downgraded by one level due to serious risk of bias. Lack of blinding and lack of allocation concealment.
d. Downgraded by one level due to serious imprecision. Small sample size.
e. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting harm. Very small sample size.
f. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting harm. Very small sample size, low number of events.
g. Downgraded by two levels due to very serious imprecision. Very small sample size, very low number of events

Comparison 3: Switch to a 2nd TNF Inhibitor **versus** switch to IL-6 Receptor Inhibitor. Data based on **direct** NRS evidence.
Overall certainty of evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to 2nd TNFi	switch to IL-6 inhibitor	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 6 months; assessed with: DAS 28-ESR (Lower values – > benefit) (MCID -1.17)												
1 (4)	observational studies	not serious	not serious	not serious	serious [a]	none	390	147	-	MD **1.3 lower** (1.63 lower to 0.97 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Low disease activity (follow up: 6 months; assessed with: DAS28-ESR <3.2)												
1 (4)	observational studies	not serious	not serious	not serious	not serious	none	43/103 (41.7%)	29/44 (65.9%)	**RR 0.63** (0.46 to 0.87)	**244 fewer per 1,000** (from 356 fewer to 86 fewer) [b]	⨁⨁◯◯ LOW	IMPORTANT
Pain (follow up: 6 months; assessed with: VAS 100 (Lower values – > benefit) (MCID -11.9)												
1 (4)	observational studies	not serious	not serious	not serious	not serious	none	185	74	-	MD **1.1 lower** (7.52 lower to 5.32 higher)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to 2nd TNFi	switch to IL-6 inhibitor	Relative (95% CI)	Absolute (95% CI)		
Disability (follow up: 6 months; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
1 (4)	observational studies	not serious	not serious	not serious	serious [a]	none	185	74	-	MD **0.2 lower** (0.4 lower to 0)	⨁◯◯◯ VERY LOW	IMPORTANT
Withdrawal due to adverse events (follow up: 1 year)												
1 (4)	observational studies	not serious	not serious	not serious	not serious	none	49/217 (22.6%)	19/35 (54.3%)	**RR 0.42** (0.28 to 0.62)	**315 fewer per 1,000** (from 391 fewer to 206 fewer)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to 2nd TNFi	switch to IL-6 inhibitor	Relative (95% CI)	Absolute (95% CI)		
Withdrawal due to lack of efficacy (follow up: 6 months)												
1 (4)	observational studies	not serious	not serious	not serious	not serious	none	137/217 (63.1%)	11/35 (31.4%)	**RR 2.01** (1.22 to 3.31)	**317 more per 1,000** (from 69 more to 726 more)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting benefit.

b. The study Santos-Faria 2019 found that the RR of low disease activity assessed with Simplified Disease Activity Index ≤ 11 was 0.9 (95%CI 0.68 to 1.17), absolute risk reduction 69 per 1000 (95%CI 222 fewer to 118 more). The RR of low disease activity assessed with Clinical Disease Activity Index ≤ 10 was 0.88 (95%CI 0.68 to 1.15), absolute risk reduction 83 per 1000 (95%CI 222 fewer to 104 more).

Comparison 5: Switch to a 2nd TNF Inhibitor **versus** continue same management. Data based on **direct** RCT evidence.
Overall certainty of evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to a 2nd TNFi	continue 1st TNFi	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 4 months; assessed with: ACR 20)												
1 (5)	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	8/13 (61.5%) [c]	4/14 (28.6%) [d]	**RR 2.15** (0.85 to 5.48)	**329 more per 1,000** (from 43 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL
Disease activity (follow up: 4 months; assessed with: ACR 50)												
1 (5)	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	4/13 (30.8%) [c]	2/14 (14.3%) [d]	**RR 2.15** (0.47 to 9.85)	**164 more per 1,000** (from 76 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL
Disease activity (follow up: 4 months; assessed with: DAS28-ESR (Lower values – > benefit) (MCID -1.17)												
1 (5)	randomised trials	very serious [a]	not serious	not serious	very serious [e]	none	13 [c]	14 [d]	-	MD **1.2 lower** (2.37 lower to 0.03 lower)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to a 2nd TNFi	continue 1st TNFi	Relative (95% CI)	Absolute (95% CI)		
Remission (follow up: 4 months; assessed with: DAS28-ESR <2.6)												
1 (5)	randomised trials	very serious [a]	not serious	not serious	very serious [f]	none	8/13 (61.5%) [c]	2/14 (14.3%) [d]	**RR 4.31** (1.11 to 16.67)	**473 more per 1,000** (from 16 more to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL
Radiographic progression (follow up: 4 months; assessed with: Sharp/ van der Heijde (Lower values – > benefit) (MCID 4.6)												
1 (5)	randomised trials	serious [g]	not serious	not serious	very serious [h]	none	12 [c]	12 [d]	-	MD **0.6 higher** (1.78 lower to 2.98 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events (follow up: 4 months)												
1 (5)	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	0/13 (0.0%) [c]	2/14 (14.3%) [d]	**RR 0.21** (0.01 to 4.08)	**113 fewer per 1,000** (from 141 fewer to 440 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to a 2nd TNFi	continue 1st TNFi	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events (from SR of harms)												
(3, 6)							The Systematic Review RefID=5595, 2011 comparing Infliximab vs Etanercept among RA and AS, Psoriasis, PsA, IBD, Cancer showed that for Serious adverse events, the result was OR=0.93 (0.60 to 1.42). The Systematic Review RefID=1403, 2017 comparing Infliximab vs Etanercept among RA showed that for Serious adverse events, the result was RR=4.90 (0.23 to 104) [Direct Evidence, Low certainty].				-	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to a 2nd TNFi	continue 1st TNFi	Relative (95% CI)	Absolute (95% CI)		
Withdrawal due to adverse events (follow up: 4 months)												
1 (5)	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	2/13 (15.4%) [c]	1/14 (7.1%) [d]	**RR 2.15** (0.22 to 21.03)	**82 more per 1,000** (from 56 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Downgraded by two levels due to serious risk of bias. Lack of blinding (except for radiographic outcomes) and lack of allocation concealment.
b. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm. Very small sample size, very low number of events.
c. Switch to IFX.
d. Continue ETN.
e. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting no effect. Very small sample size.
f. Downgraded by two levels due to very serious imprecision. Very small sample size, very low number of events.
g. Downgraded by one level due to serious risk of bias. Lack of blinding of patients and personnel and lack of allocation concealment. Outcome assessors for radiographic outcomes were blinded.
h. Downgraded by two levels due to very serious imprecision. Very small sample size.

Comparison 6: Switch to IL-6 Receptor Inhibitor **versus** switch to Abatacept. Data based on **direct** RCT evidence.
Overall certainty of evidence: Low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to IL-6 (TCZ)	Switch to ABA	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 6 months; assessed with: DAS28-ESR (Lower values – > benefit) (MCID -1.17)												
1 (7)	randomised trials	serious [a]	not serious	not serious	serious [b]	none	58	60	-	MD **0.4 lower** (0.69 lower to 0.11 lower)	⨁⨁◯◯ LOW	CRITICAL
Disability (follow up: 6 months; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
1 (7)	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	58	60	-	MD **0.12 lower** (0.55 lower to 0.31 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Withdrawal due to adverse events (follow up: 6 months)												
1 (7)	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	10/68 (14.7%)	4/64 (6.3%)	**RR 2.35** (0.78 to 7.13)	**84 more per 1,000** (from 14 fewer to 383 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to IL-6 (TCZ)	Switch to ABA	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events (follow up: 6 months)												
1 (7)	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	10/68 (14.7%)	4/64 (6.3%)	**RR 2.35** (0.78 to 7.13)	**84 more per 1,000** (from 14 fewer to 383 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. Downgraded by one level due to serious risk of bias. Lack of allocation concealment and lack of blinding.
b. Downgraded by one level due to serious imprecision. Low sample size.
c. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm. Low sample size.

Comparison 7: Switch to Rituximab **versus s**witch to IL-6 Receptor Inhibitor. Data based on **direct** NRS evidence.
Overall certainty of evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to RTX	switch to IL6-inhibitor	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 6 months; assessed with: DAS 28-ESR (Lower values – > benefit) (MCID -1.17)												
1 (4)	observational studies	not serious	not serious	not serious	serious [a]	none	106	147	-	MD **1.4 lower** (1.76 lower to 1.04 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Low disease activity (follow up: 6 months; assessed with: DAS28-ESR <3.2)												
1 (4)	observational studies	not serious	not serious	not serious	not serious	none	13/44 (29.5%)	29/44 (65.9%)	**RR 0.45** (0.27 to 0.74)	**363 fewer per 1,000** (from 481 fewer to 171 fewer) [b]	⨁⨁◯◯ LOW	IMPORTANT
Disability (follow up: 6 months; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
1 (4)	observational studies	not serious	not serious	not serious	serious [a]	none	73	74	-	MD **0.2 lower** (0.43 lower to 0.03 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to RTX	switch to IL6-inhibitor	Relative (95% CI)	Absolute (95% CI)		
Pain (follow up: 6 months; assessed with: VAS 100 (Lower values – > benefit) (MCID -11.9)												
1 (4)	observational studies	not serious	not serious	not serious	not serious	none	73	74	-	MD **2.5 higher** (4.97 lower to 9.97 higher)	⨁⨁◯◯ LOW	IMPORTANT
Withdrawal due to adverse events (follow up: 1 year)												
1 (4)	observational studies	not serious	not serious	not serious	not serious	none	7/38 (18.4%)	19/35 (54.3%)	**RR 0.34** (0.16 to 0.71)	**358 fewer per 1,000** (from 456 fewer to 157 fewer)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to RTX	switch to IL6-inhibitor	Relative (95% CI)	Absolute (95% CI)		
Withdrawal due to lack of efficacy (follow up: 6 months)												
1 (4)	observational studies	not serious	not serious	not serious	very serious [c]	none	17/38 (44.7%)	11/35 (31.4%)	**RR 1.42** (0.78 to 2.60)	**132 more per 1,000** (from 69 fewer to 503 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting benefit.

b. The study Santos-Faria 2019 found that the RR of low disease activity assessed with Simplified Disease Activity Index ≤ 11 was 0.72 (95%CI 0.49 to 1.06), absolute risk reduction 194 per 1000 (95%CI 354 fewer to 42 more). The RR of low disease activity assessed with Clinical Disease Activity Index ≤ 10 was 0.72 (95%CI 0.5 to 1.05), absolute risk reduction 194 per 1000 (95%CI 346 fewer to 35 more).

c. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm.

Cost-effectiveness

The economic analysis RefID 263 (1) based on SWITCH trial conducted in outpatient rheumatology departments in 35 hospitals, UK, patient and payer perspective compared switching to etanercept vs switching to abatacept vs rituximab (control).

The study reported (1) that switching to alternative TNFi would be cost-effective compared with rituximab, as QALY gains are higher and costs are only slightly higher, leading to an ICER value of £5332.02 per QALY gained. This is well below the NICE acceptance threshold (λ = £20,000), which indicates that switching to alternative TNFi would be a cost-effective treatment option. (2) Conversely, the abatacept group has much higher costs and only marginal gains in QALYs compared with the alternative TNFi treatment group. This results in an ICER value of £253,967.96 per QALY gained, indicating that switching to abatacept compared with switching to alternative TNFi drug would not be cost-effective, as this ICER value is well above the NICE cost/QALY threshold.

Author's conclusion: The analysis shows that switching to alternative TNFi following an initial TNFi failure may be a cost-effective option compared with rituximab, although switching to abatacept is unlikely to be cost-effective.

The economic analysis RefID 709 (8) based on ROC trial conducted in Italy compared non-TNFi vs second TNFi.

The study reported (1) total costs in the two tocilizumab arms were higher than those resulting from the anti-TNF-α (Euro 38,948 and Euro 40,374 for tocilizumab IV and SC vs. Euro 26,621–36,565 for the anti-TNF-α). (2) The cost-consequence ratios of tocilizumab iv was Euro 174.3/day in remission and Euro 112.8/day in LDA. The same values were Euro 180.7/day in remission and Euro 116.9/day in LDA for tocilizumab sc. These ratios were lower than those related to anti-TNF-α comparators. (3) The incremental cost-consequence ratio of the comparison tocilizumab iv versus infliximab biosimilar was Euro 112.97/day in remission gained and Euro 80.78/day in LDA gained.

Author's conclusion: the switch to a drug characterized by a different mechanism of action, namely tocilizumab, after the failure of a first anti-TNF-α may be considered an effective and cost-effective strategy in RA.

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PICO 25. Should patients with RA on their 2nd TNF Inhibitor who are NOT at target, switch to a 3rd TNF Inhibitor or switch to a boDMARD targeting a different molecule or to a tsDMARD?

P - Patients with RA on their 2nd TNF Inhibitor who are not at target
I - Switching to a 3rd TNF Inhibitor
C - Switch to Abatacept
C - Switch to Rituximab
C - Switch to IL-6 Receptor Inhibitor
C - Switch to JAK Inhibitor
C- Continue same management

Comparison 1: Switch to Abatacept **versus** switch to a 3rd TNF Inhibitor. See below Table.
Comparison 2: Switch to Rituximab **versus** switch to a 3rd TNF Inhibitor. See below Table.
Comparison 3: Switch to IL-6 Receptor Inhibitor **versus** switch to a 3rd TNF Inhibitor. No eligible RCT, NRS, or indirect evidence were identified.
Comparison 4: Switch to JAK Inhibitor **versus** switch to a 3rd TNF Inhibitor. No eligible RCT, NRS, or indirect evidence were identified.
Comparison 5: Switch to a 3rd TNF Inhibitor **versus** continue same management. See below Table.
Comparison 6: Switch to IL-6 Receptor Inhibitor **versus** switch to Abatacept. See below Table.

Comparison 1: Switch to Abatacept **versus** switch to a 3rd TNF Inhibitor. Data based on **indirect** RCT evidence.
Overall certainty of evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to ABA	switch to a 3rd TNFi	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 1 year; assessed with: ACR 20)												
1 (1)	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	11/31 (35.5%)	17/31 (54.8%)	**RR 0.65** (0.37 to 1.15)	**192 fewer per 1,000** (from 345 fewer to 82 more)	⨁◯◯◯ VERY LOW	CRITICAL
Disease activity (follow up: 1 year; assessed with: ACR 50)												
1 (1)	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	6/32 (18.8%)	9/31 (29.0%)	**RR 0.65** (0.26 to 1.60)	**102 fewer per 1,000** (from 215 fewer to 174 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to ABA	switch to a 3rd TNFi	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 1 year; assessed with: ACR 70)												
1 (1)	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	3/32 (9.4%)	5/31 (16.1%)	**RR 0.58** (0.15 to 2.23)	**68 fewer per 1,000** (from 137 fewer to 198 more)	⨁◯◯◯ VERY LOW	CRITICAL
Remission (follow up: 1 year; assessed with: DAS28-ESR <2.6)												
2 (1, 2)	randomised trials	serious [d]	not serious	serious [b]	serious [e]	none	6/76 (7.9%)	17/80 (21.3%)	**RR 0.38** (0.16 to 0.91)	**132 fewer per 1,000** (from 179 fewer to 19 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Disease activity (follow up: 1 year; assessed with: DAS28-ESR (Lower values – > benefit) (MCID -1.17)												
2 (1, 2)	randomised trials	serious [d]	not serious	serious [b]	serious [f]	none	76	80	-	MD **0.45 higher** (0.02 higher to 0.88 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to ABA	switch to a 3rd TNFi	Relative (95% CI)	Absolute (95% CI)		
Disability (follow up: 1 year; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
2 (1, 2)	randomised trials	serious [d]	not serious	serious [b]	very serious [g]	none	77	81	-	MD **0.04 higher** (0.17 lower to 0.25 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Quality of life (follow up: 1 year; assessed with: RAQol (Lower values – > benefit) (MCID 2)												
1 (1)	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	34	30	-	MD **1.5 lower** (6.36 lower to 3.36 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Pain (follow up: 1 year; assessed with: VAS 0-100 (Lower values – > benefit) (MCID -11.9)												
1 (1)	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	34	31	-	MD **2.5 higher** (14.99 lower to 19.99 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to ABA	switch to a 3rd TNFi	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events (follow up: 1 year)												
2 (1, 2)	randomised trials	serious [d]	not serious	serious [b]	very serious [h]	none	5/63 (7.9%)	1/65 (1.5%)	**RR 3.75** (0.64 to 22.11)	**42 more per 1,000** (from 6 fewer to 325 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Withdrawal due to lack of efficacy (follow up: 1 year)												
1 (1)	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	3/41 (7.3%)	2/41 (4.9%)	**RR 1.50** (0.26 to 8.51)	**24 more per 1,000** (from 36 fewer to 366 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Withdrawal due to adverse events (follow up: 1 year)												
1 (1)	randomised trials	serious [a]	not serious	serious [b]	very serious [e]	none	1/41 (2.4%)	0/41 (0.0%)	**RR 3.00** (0.13 to 71.56)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to ABA	switch to a 3rd TNFi	Relative (95% CI)	Absolute (95% CI)		
Death (follow up: 1 year)												
1 (1)	randomised trials	serious [a]	not serious	serious [b]	very serious [e]	none	1/41 (2.4%)	0/41 (0.0%)	**RR 3.00** (0.13 to 71.56)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT
Malignancy (follow up: 1 year)												
1 (2)	randomised trials	serious [d]	not serious	serious [b]	very serious [e]	none	0/22 (0.0%)	0/24 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	IMPORTANT
Cardiovascular disease (follow up: 1 year)												
1 (2)	randomised trials	serious [d]	not serious	serious [b]	very serious [c]	none	1/22 (4.5%)	2/24 (8.3%)	**RR 0.55** (0.05 to 5.60)	**37 fewer per 1,000** (from 79 fewer to 383 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to ABA	switch to a 3rd TNFi	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events (from SR of harms)												
0 (3)							The Systematic Review RefID=1403, 2017 comparing Rituximab vs Etanercept, Adalimumab, Certolizumab, Golimumab, and Infliximab among RA showed that for Serious adverse events, the result was RR=1.13 (0.79 to 1.62) [Low certainty], RR=1.24 (0.89 to 1.73) [Low certainty], RR=1.56 (1.03 to 2.37) [Moderate certainty], RR=1.15 (0.71 to 1.86) [Very low certainty], and RR=1.20 (0.082 to 1.74) [Low certainty] respectively. All are Indirect evidence.				-	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Downgraded by one level due to serious risk of bias. Lack of blinding.
b. Downgraded by one level due to serious indirectness. The evidence is based on a population on their first TNF Inhibitor who are NOT at target and the intervention is second TNFi rather than third TNFi.
c. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm. Very small sample size, low number of events.
d. Downgraded by one level due to serious risk of bias. Lack of blinding and lack of allocation concealment.
e. Downgraded by two levels due to very serious imprecision. Very small sample size, low number of events.
f. Downgraded by one level due to serious imprecision. Very small sample size.
g. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting harm. Very small sample size.
h. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting harm. Very small sample size, low number of events.

Comparison 2: Switch to a 3rd TNF Inhibitor **versus** switch to Rituximab. Data based on **direct** NRS evidence.
Overall certainty of evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switching to a 3rd TNF Inhibitor	switching to rituximab	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 6 months; assessed with DAS 28-ESR (Lower values – > benefit) (MCID -1.17)												
1 (4)	observational studies	serious [a]	not serious	not serious	serious [b]	none	43	58	-	MD **0.35 lower** (1.82 lower to 1.12 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Low disease activity (follow up: 6 months; assessed with DAS28 ≤ 3.2)												
1 (4)	observational studies	serious [a]	not serious	not serious	very serious [c]	none	6/35 (17.1%)	20/69 (29.0%)	**RR 0.59** (0.26 to 1.34)	**119 fewer per 1,000** (from 214 fewer to 99 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Disability (follow up: 1 year; assessed with HAQ-DI (Lower values – > benefit) (MCID -0.22)												
1 (4)	observational studies	serious [a]	not serious	not serious	very serious [c]	none	35	54	-	MD **0** (0.53 lower to 0.53 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switching to a 3rd TNF Inhibitor	switching to rituximab	Relative (95% CI)	Absolute (95% CI)		
Withdrawal due to lack of efficacy (follow up: 1 year)												
1 (4)	observational studies	serious [a]	not serious	not serious	serious [d]	none	15/64 (23.4%)	10/90 (11.1%)	**RR 2.11** (1.01 to 4.39)	**123 more per 1,000** (from 1 more to 377 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Withdrawal due to adverse events (follow up: 1 year)												
1 (4)	observational studies	serious [a]	not serious	not serious	serious [d]	none	14/64 (21.9%)	1/90 (1.1%)	**RR 19.69** (2.66 to 145.95)	**208 more per 1,000** (from 18 more to 1,000 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. 'Other limitations of this observational study are the relative low numbers of patients and the high number of missing data.'
b. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting no effect. Small sample size.
c. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm. Small sample size.
d. Downgraded by one level due to very serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting harm. Small sample size.

Comparison 5: Switch to a 3rd TNF Inhibitor **versus** continue same management. Data based on **indirect RCT** evidence.
Overall certainty of evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to a 3rd TNFi	continue same management	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 4 months; assessed with: ACR 20)												
1 (5)	randomised trials	very serious [a]	not serious	serious [b]	very serious [c]	none	8/13 (61.5%) [d]	4/14 (28.6%) [e]	**RR 2.15** (0.85 to 5.48)	**329 more per 1,000** (from 43 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL
Disease activity (follow up: 4 months; assessed with: ACR 50)												
1 (5)	randomised trials	very serious [a]	not serious	serious [b]	very serious [c]	none	4/13 (30.8%) [d]	2/14 (14.3%) [e]	**RR 2.15** (0.47 to 9.85)	**164 more per 1,000** (from 76 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to a 3rd TNFi	continue same management	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 4 months; assessed with: DAS28-ESR (Lower values – > benefit) (MCID -1.17)												
1 (5)	randomised trials	very serious [a]	not serious	serious [b]	very serious [f]	none	13 [d]	14 [e]	-	MD **1.2 lower** (2.37 lower to 0.03 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Remission (follow up: 4 months; assessed with: DAS28-ESR <2.6)												
1 (5)	randomised trials	very serious [a]	not serious	serious [b]	very serious [g]	none	8/13 (61.5%) [d]	2/14 (14.3%) [e]	**RR 4.31** (1.11 to 16.67)	**473 more per 1,000** (from 16 more to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL
Radiographic progression (follow up: 4 months; assessed with: Sharp/ van der Heijde (Lower values – > benefit) (MCID 4.6)												
1 (5)	randomised trials	serious [h]	not serious	serious [b]	very serious [i]	none	12 [d]	12 [e]	-	MD **0.6 higher** (1.78 lower to 2.98 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to a 3rd TNFi	continue same management	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events (follow up: 4 months)												
1 (5)	randomised trials	very serious [a]	not serious	serious [b]	very serious [c]	none	0/13 (0.0%) [d]	2/14 (14.3%) [e]	**RR 0.21** (0.01 to 4.08)	**113 fewer per 1,000** (from 141 fewer to 440 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Withdrawal due to adverse events (follow up: 4 months)												
1 (5)	randomised trials	very serious [a]	not serious	serious [b]	very serious [c]	none	2/13 (15.4%) [d]	1/14 (7.1%) [e]	**RR 2.15** (0.22 to 21.03)	**82 more per 1,000** (from 56 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to a 3rd TNFi	continue same management	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events (from SR of harms)												
0 (3, 6)							The Systematic Review RefID=5595, 2011 comparing Infliximab vs Etanercept among RA and AS, Psoriasis, PsA, IBD, Cancer showed that for Serious adverse events, the result was OR=0.93 (0.60 to 1.42). The Systematic Review RefID=1403, 2017 comparing Infliximab vs Etanercept among RA showed that for Serious adverse events, the result was RR=4.90 (0.23 to 104) [Direct Evidence, Low certainty].		-	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Downgraded by two levels due to serious risk of bias. Lack of blinding (except for radiographic outcomes) and lack of allocation concealment.
b. Downgraded by one level due to serious indirectness. The evidence is based on a population on their first TNF Inhibitor who are NOT at target and the intervention is second TNFi rather than third TNFi.
c. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm. Very small sample size, very low number of events.
d. Switch to IFX.
e. Continue ETN.
f. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting no effect. Very small sample size.
g. Downgraded by two levels due to very serious imprecision. Very small sample size, very low number of events.
h. Downgraded by one level due to serious risk of bias. Lack of blinding of patients and personnel and lack of allocation concealment. Outcome assessors for radiographic outcomes were blinded.
i. Downgraded by two levels due to very serious imprecision. Very small sample size.

Comparison 6: Switch to IL-6 Receptor Inhibitor **versus** switch to Abatacept. Data based on **indirect** RCT evidence.
Overall certainty of evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to IL-6 (TCZ)	Switch to ABA	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 6 months; assessed with: DAS28-ESR (Lower values – > benefit) (MCID -1.17)												
1 (7)	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	58	60	-	MD **0.4 lower** (0.69 lower to 0.11 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Disability (follow up: 6 months; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
1 (7)	randomised trials	serious [a]	not serious	serious [b]	very serious [d]	none	58	60	-	MD **0.12 lower** (0.55 lower to 0.31 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Withdrawal due to adverse events (follow up: 6 months)												
1 (7)	randomised trials	serious [a]	not serious	serious [b]	very serious [d]	none	10/68 (14.7%)	4/64 (6.3%)	**RR 2.35** (0.78 to 7.13)	**84 more per 1,000** (from 14 fewer to 383 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to IL-6 (TCZ)	Switch to ABA	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events (follow up: 6 months)												
1 (7)	randomised trials	serious [a]	not serious	serious [b]	very serious [d]	none	10/68 (14.7%)	4/64 (6.3%)	**RR 2.35** (0.78 to 7.13)	**84 more per 1,000** (from 14 fewer to 383 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. Downgraded by one level due to serious risk of bias. Lack of allocation concealment and lack of blinding.
b. Downgraded by one level due to serious indirectness. The evidence is based on a population on their first TNF Inhibitor who are NOT at target.
c. Downgraded by one level due to serious imprecision. Low sample size.
d. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm. Low sample size.

Cost-effectiveness

The economic analysis RefID 4215 (8) based on trial conducted in Germany, German public payer's perspective compared abatacept or rituximab versus use after 1st, 2nd and 3rd anti-TNFO agents.

The study reported: using a 3rd anti-TNF agent was less effective and cost effective than the same sequence using abatacept (€2,000 vs. €1,067/day in LDAS and €6,623 vs. €3,592/day in remission). Differences were statistically significant ($p<0.01$).

Author's conclusion: The results suggest that in patients with an IR to at least one anti-TNF agent, biologic sequences including abatacept appear more efficacious and cost-effective than similar sequences including rituximab or only cycled anti-TNF agents.

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PICO 26. Should patients with RA on their first IL-6 Receptor Inhibitor who are NOT at target, switch to a 2nd IL-6 Receptor Inhibitor or switch to a boDMARD targeting a different molecule or to a tsDMARD?

P - Patients with RA on their first IL-6 Receptor Inhibitor who are not at target
I - Switch to a 2nd IL-6 Receptor Inhibitor
C - Switch to Abatacept
C - Switch to Rituximab
C - Switch to TNF Inhibitor
C - Switch to JAK Inhibitor
C- Continue same management

No eligible RCT, NRS, or indirect evidence were identified.

PICO 27. Should patients with RA on their first JAK Inhibitor who are NOT at target, switch to a 2nd JAK Inhibitor or switch to a boDMARD?

P - Patients with RA on their first JAK Inhibitor who are not at target
I - Switch to a 2nd JAK Inhibitor
C - Switch to Abatacept
C - Switch to Rituximab
C - Switch to TNF Inhibitor
C - Switch to IL-6 Receptor Inhibitor
C- Continue same management

No eligible RCT, NRS, or indirect evidence were identified.

PICO 28. Should patients with RA on DMARDs who are NOT at target receive IA corticosteroids alone or add/switch DMARDs or IA corticosteroids and add/switch DMARD(s)?

P - Patients with RA on DMARDs who are not at target
I - IA steroids
C – Add/Switch DMARD(s)
C - IA steroids and add/switch DMARD(s)

Comparison 1: IA steroids **versus** add/Switch DMARD(s). See below Table.
Comparison 2: IA steroids **versus** IA steroids and add/switch DMARD(s). No eligible RCT, NRS, or indirect evidence were identified.

Comparison 1: IA steroids **versus** add/Switch DMARD(s). Data based on **indirect** RCT evidence.
Overall certainty of evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IA corticosteroids alone	Add/Switch DMARD(s)	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 3 months; assessed with: ACR 20)												
1 (1)	randomised trials	very serious [a]	not serious	serious [b]	very serious [c]	none	25/25 (100.0%)	21/25 (84.0%)	**RR 1.19** (0.99 to 1.43)	**160 more per 1,000** (from 8 fewer to 361 more)	⨁◯◯◯ VERY LOW	CRITICAL
Disease activity (follow up: 3 months; assessed with: ACR 50)												
1 (1)	randomised trials	serious [a]	not serious	serious [b]	serious [d]	none	15/25 (60.0%)	5/25 (20.0%)	**RR 3.00** (1.29 to 7.00)	**400 more per 1,000** (from 58 more to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IA corticosteroids alone	Add/Switch DMARD(s)	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 3 months; assessed with: ACR 70)												
1 (1)	randomised trials	very serious [a]	not serious	serious [b]	very serious [e]	none	9/25 (36.0%)	0/25 (0.0%)	**RR 19.00** (1.17 to 309.77)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Disease activity (follow up: 3 months; assessed with: DAS28-ESR (Lower values – > benefit) (MCID -1.17)												
1 (1)	randomised trials	very serious [a]	not serious	serious [b]	very serious [f]	none	25	25	-	MD **1.6 lower** (2.21 lower to 0.99 lower)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IA corticosteroids alone	Add/Switch DMARD(s)	Relative (95% CI)	Absolute (95% CI)		
Disability (follow up: 3 months; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
1 (1)	randomised trials	very serious [a]	not serious	serious [b]	very serious [f]	none	25	25	-	MD **0.24 lower** (0.42 lower to 0.06 lower)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Downgraded by two levels due to very serious risk of bias. Lack of allocation concealment, lack of blinding, and selective reporting.
b. Downgraded by one level due to serious indirectness. Study compared IA GCs + csDMARD to csDMARDs.
c. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting no effect and value suggesting harm. Very small sample size.
d. Downgraded by one level due to serious imprecision. Very small sample size.
e. Downgraded by two levels due to very serious imprecision. Very small sample size and low number of events.
f. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting no effect. Very small sample size.

Cost-effectiveness

No cost-effectiveness data identified.

References

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PICO 52. Should patients with RA on DMARDs who are <u>in low disease activity</u> gradually taper off DMARDs, abruptly withdraw DMARDs, or continue DMARDS at the same doses?

P - Patients with RA on DMARDs who are in low disease activity
I - Taper off DMARDs (as long as the patient remains on at least one DMARD)
C- Abruptly withdraw DMARDs (as long as the patient remains on at least one DMARD)
C - Continue DMARDs at same doses

Comparison 1: Taper off DMARDs **versus** abruptly withdraw DMARDs. See below Table.
Comparison 2: Continue DMARDs at same doses **versus** taper off DMARDs. See below Table.
Comparison 3: Continue DMARDs at same doses **versus** abruptly withdraw DMARDs. See below Table.

Comparison 1: Taper off DMARDs **versus** abruptly withdraw DMARDs. Data based on **direct** RCT evidence.
Overall certainty of evidence: Low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Taper off DMARDs	Abruptly withdraw DMARDs	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: range 9 months to 12 months; assessed with: DAS28-ESR (Lower values – > benefit) (MCID -1.17)												
2 (1, 2)	randomised trials	not serious	not serious	not serious	serious [e]	none	264	262	-	MD **0.95 lower** (1.18 lower to 0.72 lower)	⨁⨁⨁◯ MODERATE	CRITICAL
Flare (follow up: range 6 months to 12 months)												
2 (3, 4)	randomised trials	not serious	serious [f]	not serious	serious [g]	none	18/153 (11.8%)	30/102 (29.4%)	**RR 0.48** (0.32 to 0.71)	**153 fewer per 1,000** (from 200 fewer to 85 fewer)	⨁⨁◯◯ LOW	CRITICAL
Radiographic progression (follow up: range 9 months to 12 months; assessed with: mTSS (Lower values – > benefit) (MCID 4.6)												
2 (1, 2)	randomised trials	serious [c]	not serious	not serious	not serious	none	247	232	-	MD **0.09 higher** (0.34 lower to 0.53 higher) [h]	⨁⨁⨁◯ MODERATE	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Taper off DMARDs	Abruptly withdraw DMARDs	Relative (95% CI)	Absolute (95% CI)		
Fatigue (follow up: range 9 months to 12 months; assessed with: FACIT-F (Higher values – > benefit) (MCID 15.9)												
2 (5, 6)	randomised trials	not serious	not serious [i]	not serious	not serious	none	264	262	-	MD **3.19 higher** (1.53 higher to 4.85 higher)	⨁⨁⨁⨁ HIGH	IMPORTANT
Quality of Life (follow up: 9 months; assessed with: SF-36 PCS (Higher values – > benefit) (MCID 4.4)												
1 (6)	randomised trials	serious [j]	not serious	not serious	serious [e]	none	63	65	-	MD **2.3 higher** (0.47 lower to 5.07 higher) [k]	⨁⨁◯◯ LOW	IMPORTANT
Quality of Life (follow up: 9 months; assessed with: SF-36 MCS (Higher values – > benefit) (MCID 3.1)												
1 (6)	randomised trials	serious [j]	not serious	not serious	serious [e]	none	63	65	-	MD **1.8 higher** (0.97 lower to 4.57 higher) [l]	⨁⨁◯◯ LOW	IMPORTANT
Disability (follow up: 12 months; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
1 (1)	randomised trials	not serious	not serious	not serious	serious [e]	none	201	197	-	MD **0.2 lower** (0.31 lower to 0.09 lower) [m]	⨁⨁⨁◯ MODERATE	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Taper off DMARDs	Abruptly withdraw DMARDs	Relative (95% CI)	Absolute (95% CI)		
Pain (follow up: 12 months; assessed with: VAS Pain (0-100) (Lower values – > benefit) (MCID -11.9)												
1 (1)	randomised trials	not serious	not serious	not serious	serious [e]	none	201	197	-	MD **12.6 lower** (17.05 lower to 8.15 lower)	⨁⨁⨁◯ MODERATE	IMPORTANT
Withdrawal due to lack of efficacy (follow up: 12 months)												
1 (1)	randomised trials	not serious	not serious	not serious	serious [g]	none	11/202 (5.4%)	43/200 (21.5%)	**RR 0.25** (0.13 to 0.48)	**161 fewer per 1,000** (from 187 fewer to 112 fewer)	⨁⨁⨁◯ MODERATE	IMPORTANT
Withdrawal due to adverse events (follow up: range 9 months to 12 months)												
2 (1, 2)	randomised trials	not serious	not serious	not serious	very serious [g,n]	none	4/267 (1.5%)	6/265 (2.3%)	**RR 0.69** (0.21 to 2.26)	**7 fewer per 1,000** (from 18 fewer to 29 more)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Taper off DMARDs	Abruptly withdraw DMARDs	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events (follow up: range 9 months to 12 months)												
2 (1, 2)	randomised trials	not serious	not serious	not serious	very serious [g,n]	none	9/267 (3.4%)	17/265 (6.4%)	**RR 0.53** (0.24 to 1.16)	**30 fewer per 1,000** (from 49 fewer to 10 more)	⨁⨁◯◯ LOW	IMPORTANT
Malignancy (follow up: range 9 months to 12 months)												
2 (1, 2)	randomised trials	not serious	not serious	not serious	very serious [g,o]	none	4/267 (1.5%)	1/265 (0.4%)	**RR 3.96** (0.45 to 35.12)	**11 more per 1,000** (from 2 fewer to 129 more)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Taper off DMARDs	Abruptly withdraw DMARDs	Relative (95% CI)	Absolute (95% CI)		
Death (follow up: 12 months)												
1 (1)	randomised trials	not serious	not serious	not serious	very serious [g]	none	0/202 (0.0%)	0/200 (0.0%)	not estimable		⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Downgraded by two levels due to very serious inconsistency. Unexplained heterogeneity I2=84%
b. Downgraded by two levels due to very serious inconsistency. Unexplained heterogeneity I2=95%
c. Study contributing most of the weight is at risk of bias associated with missing data and selective outcome reporting
d. Downgraded by two levels due to very serious inconsistency. Unexplained heterogeneity I2=93%
e. CI includes both values suggesting benefit and values suggesting no effect
f. Downgraded by one level due to serious inconsistency. Unexplained heterogeneity I2=78%
g. Small number of events
h. The study PRESERVE found that the RR of developing no radiographic progression (change in mTSS ≤0.5) was 1.07 (95%CI 0.98 to 1.17), absolute risk increase 58 more per 1000 (95%CI 17 fewer to 140 more).
i. I2=16%
j. Risk of bias associated with missing data and selective outcome reporting
k. The study PRIZE found that the RR of improvement in SF-36 PCS (≥5 change from baseline) was 1.03 (95%CI 0.86 to 1.24), absolute risk increase 23 more per 1000 (95%CI 108 fewer to 185 more)
l. The study PRIZE found that the RR of improvement in SF-36 MCS (≥5 change from baseline) was 1.27 (95%CI 0.91 to 1.78), absolute risk increase 125 more per 1000 (95%CI 42 fewer to 360 more)
m. The study PRESERVE found that the RR of improvement in HAQ-DI (≥0.22 change from baseline) was 1.41 (95%CI 1.21 to 1.67), absolute risk increase 214 more per 1000 (95%CI 107 more to 342 more).
n. CI includes both values suggesting benefit and values suggesting harm
o. CI includes both values suggesting harm and values suggesting no effect

Comparison 2: Continue DMARDs at same doses **versus** taper off DMARDs. Data based on **direct** RCT evidence.
Overall certainty of evidence: Low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continue DMARDs at same doses	Taper off DMARDs	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 1 year; assessed with: DAS28-ESR (Lower values – > benefit) (MCID -1.17)												
1 (1)	randomised trials	not serious	not serious	not serious	not serious	none	200	201	-	MD **0.1 lower** (0.31 lower to 0.11 higher)	⨁⨁⨁⨁ HIGH	CRITICAL
Flare (follow up: range 11 months to 18 months)												
2 (4, 7) [b]	randomised trials	serious [c,d]	serious [e]	not serious	not serious	none	82 participants	148 participants	**HR 0.46** (0.31 to 0.67) [Flare]	**275 fewer per 1,000** (from 388 fewer to 146 fewer)	⨁⨁◯◯ LOW	CRITICAL
							-	69.9%		**275 fewer per 1,000** (from 388 fewer to 146 fewer)		

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continue DMARDs at same doses	Taper off DMARDs	Relative (95% CI)	Absolute (95% CI)		
Radiographic progression (follow up: 1 year; assessed with: mTSS (Lower values – > benefit) (MCID 4.6)												
1 (1)	randomised trials	not serious	not serious	not serious	very serious [a]	none	184	184	-	MD **3.7 higher** (8.42 lower to 15.82 higher) [f]	⨁⨁◯◯ LOW	IMPORTANT
Fatigue (follow up: 1 year; assessed with: FACIT-F (Higher values – > benefit) (MCID 15.9)												
1 (5)	randomised trials	not serious	not serious	not serious	not serious	none	201	201	-	MD **0.1 higher** (1.63 lower to 1.83 higher)	⨁⨁⨁⨁ HIGH	IMPORTANT
Pain (follow up: 1 year; assessed with: VAS pain (0-100) (Lower values – > benefit) (MCID -11.9)												
1 (1)	randomised trials	not serious	not serious	not serious	not serious	none	200	201	-	MD **2.8 lower** (6.6 lower to 1 higher)	⨁⨁⨁⨁ HIGH	IMPORTANT
Disability (follow up: 1 year; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
1 (1)	randomised trials	not serious	not serious	not serious	not serious	none	201	201	-	MD **0.1 lower** (0.2 lower to 0) [g]	⨁⨁⨁⨁ HIGH	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continue DMARDs at same doses	Taper off DMARDs	Relative (95% CI)	Absolute (95% CI)		
Withdrawal due to lack of efficacy (follow up: 1 year)												
1 (1)	randomised trials	not serious	not serious	not serious	very serious [a]	none	4/202 (2.0%)	11/202 (5.4%)	**RR 0.36** (0.12 to 1.12)	**35 fewer per 1,000** (from 48 fewer to 7 more)	⨁⨁◯◯ LOW	IMPORTANT
Withdrawal due to adverse events (follow up: 1 year)												
1 (1)	randomised trials	not serious	not serious	not serious	very serious [h,i]	none	7/202 (3.5%)	4/202 (2.0%)	**RR 1.75** (0.52 to 5.89)	**15 more per 1,000** (from 10 fewer to 97 more)	⨁⨁◯◯ LOW	IMPORTANT
Serious adverse events (follow up: 1 year)												
1 (1)	randomised trials	not serious	not serious	not serious	very serious [h,i]	none	12/202 (5.9%)	7/202 (3.5%)	**RR 1.71** (0.69 to 4.27)	**25 more per 1,000** (from 11 fewer to 113 more)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continue DMARDs at same doses	Taper off DMARDs	Relative (95% CI)	Absolute (95% CI)		
Malignancy (follow up: 1 year)												
1 (1)	randomised trials	not serious	not serious	not serious	very serious [a,h]	none	2/202 (1.0%)	4/202 (2.0%)	**RR 0.50** (0.09 to 2.70)	**10 fewer per 1,000** (from 18 fewer to 34 more)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continue DMARDs at same doses	Taper off DMARDs	Relative (95% CI)	Absolute (95% CI)		
Death (follow up: 1 year)												
1 (1)	randomised trials	not serious	not serious	not serious	very serious [a,h]	none	2/202 (1.0%)	0/202 (0.0%)	**RR 5.00** (0.24 to 103.50)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **HR:** Hazard Ratio

Explanations

a. CI includes both values suggesting benefit and values suggesting harm
b. Pooled results reported as HR and RR in the 2 respective studies
c. Downgraded for risk of bias associated with lack of blinding of participants, providers and outcome assessors
d. Downgraded for risk of bias associated with lack of allocation concealment
e. Downgraded by one level due to serious inconsistency. I2= 77%
f. The study PRESERVE found that the RR of developing no radiographic progression (change in mTSS ≤0.5) was 1.01 (95%CI 0.94 to 1.08), absolute risk increase 9 more per 1000 (95%CI 53 fewer to 71 more).
g. The study PRESERVE found that the RR of improvement in HAQ-DI (≥0.22 change from baseline) was 1.00 (95%CI 0.88 to 1.13), absolute risk reduction 0 fewer per 1000 (95%CI 87 fewer to 94 more).
h. Small number of events
i. CI includes both values suggesting harm and values suggesting no effect

Comparison 3: Continue DMARDs at same doses **versus** abruptly withdraw DMARDs. Data based on **direct** RCT evidence.
Overall certainty of evidence: Low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continue DMARDs at same dose	Abruptly withdraw DMARDs	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: range 3 months to 1 year; assessed with: DAS28 ESR or CRP (Lower values – > benefit) (values>0.2 are considered clinically important)												
3 (1, 8, 9)	randomised trials	not serious [d]	very serious [c]	not serious	not serious [e]	none	385	377	-	SMD **0.88 lower** (1.03 lower to 0.73 lower)	⨁⨁◯◯ LOW	CRITICAL
Flare (follow up: range 11 months to 18 months)												
3 (4, 10, 11)[f]	randomised trials	not serious	very serious [g]	not serious	not serious	none	472 participants	722 participants	**HR 0.53** (0.46 to 0.61) [Flare]	**213 fewer per 1,000** (from 254 fewer to 170 fewer)	⨁⨁◯◯ LOW	CRITICAL
							-	59.0%		**213 fewer per 1,000** (from 254 fewer to 170 fewer)		

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continue DMARDs at same dose	Abruptly withdraw DMARDs	Relative (95% CI)	Absolute (95% CI)		
Disability (follow up: 1 year; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
3 (1, 8, 9)	randomised trials	not serious	very serious [h]	not serious	serious [i]	none	388	381	-	MD **0.17 lower** (0.26 lower to 0.09 lower) [j]	⨁◯◯◯ VERY LOW	IMPORTANT
Radiographic progression (follow up: 1 year; assessed with: mTSS (Lower values – > benefit) (MCID 4.6)												
2 (1, 8)	randomised trials	serious [k]	not serious	not serious	not serious	none	289	269	-	MD **0.17 lower** (0.79 lower to 0.45 higher) [l]	⨁⨁⨁◯ MODERATE	IMPORTANT
Pain (follow up: 1 year; assessed with: VAS pain (0-100) (Lower values – > benefit) (MCID -11.9)												
2 (1, 8)	randomised trials	not serious	very serious [m]	not serious	serious [i]	none	305	299	-	MD **9.29 lower** (12.44 lower to 6.15 lower)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continue DMARDs at same dose	Abruptly withdraw DMARDs	Relative (95% CI)	Absolute (95% CI)		
Fatigue (follow up: 1 year; assessed with: FACIT-F (Higher values – > benefit) (MCID 15.9)												
1 (5)	randomised trials	not serious	not serious	not serious	not serious	none	201	197	-	MD **3.9 higher** (1.9 higher to 5.9 higher)	⨁⨁⨁⨁ HIGH	IMPORTANT
Quality of life (follow up: 3 months; assessed with: SF-36 PCS (Higher values – > benefit) (MCID 4.4)												
1 (9)	randomised trials	serious [n]	not serious	not serious	serious [o]	none	82	82	-	MD **3.38 higher** (0.69 higher to 6.07 higher)	⨁⨁◯◯ LOW	IMPORTANT
Quality of life (follow up: 3 months; assessed with: SF-36 MCS (Higher values – > benefit) (MCID 3.1)												
1 (9)	randomised trials	serious [n]	not serious	not serious	serious [p]	none	82	82	-	MD **1.88 lower** (4.78 lower to 1.02 higher)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continue DMARDs at same dose	Abruptly withdraw DMARDs	Relative (95% CI)	Absolute (95% CI)		
Withdrawal due to lack of efficacy (follow up: range 3 months to 1 year)												
2 (1, 9)	randomised trials	not serious	not serious	not serious	serious [q]	none	4/285 (1.4%)	44/282 (15.6%)	**RR 0.10** (0.04 to 0.26)	**140 fewer per 1,000** (from 150 fewer to 115 fewer)	⨁⨁⨁◯ MODERATE	IMPORTANT
Withdrawal due to adverse events (follow up: range 3 months to 1 year)												
3 (1, 8, 9)	randomised trials	not serious [d]	not serious [r]	not serious	very serious [s]	none	13/390 (3.3%)	13/384 (3.4%)	**RR 0.98** (0.46 to 2.09)	**1 fewer per 1,000** (from 18 fewer to 37 more)	⨁⨁◯◯ LOW	IMPORTANT
Serious adverse events (follow up: range 3 months to 1 year)												
3 (1, 8, 9)	randomised trials	not serious [d]	not serious	not serious	very serious [s]	none	25/390 (6.4%)	30/384 (7.8%)	**RR 0.82** (0.49 to 1.36)	**14 fewer per 1,000** (from 40 fewer to 28 more)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continue DMARDs at same dose	Abruptly withdraw DMARDs	Relative (95% CI)	Absolute (95% CI)		
Malignancy (follow up: 1 year)												
2 (1, 8)	randomised trials	serious [a]	not serious	not serious	very serious [t]	none	2/307 (0.7%)	2/302 (0.7%)	**RR 0.98** (0.17 to 5.62)	**0 fewer per 1,000** (from 5 fewer to 31 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Congestive Heart Failure (1 year)												
1 (8)	randomised trials	serious [a]	not serious	not serious	very serious [u]	none	0/105 (0.0%)	0/102 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	IMPORTANT
Death (follow up: range 3 months to 1 year)												
3 (1, 8, 9)	randomised trials	not serious	not serious	not serious	very serious [t]	none	2/390 (0.5%)	0/384 (0.0%)	**RR 4.95** (0.24 to 102.48)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **SMD:** Standardised mean difference; **HR:** Hazard Ratio; **MD:** Mean difference

Explanations

a. Concern about risk of bias associated with incomplete outcome data (48% drop-out) in a study contributing to a large percentage of the weight.
b. Downgraded by two levels due to very serious inconsistency. Unexplained heterogeneity I2=98%.
c. Downgraded by two levels due to very serious inconsistency. Unexplained heterogeneity I2=96%.
d. Concern about risk of bias associated with incomplete outcome data (48% drop-out and inappropriate handling of missing data) in two studies contributing to a large percentage of the weight. However, a study with no risk of bias contributes a large proportion of the weight, and sensitivity analysis removing studies with incomplete outcome data do not change the results substantively.
e. According to the Cochrane's handbook, Cohen suggested that SMD=0.2 be considered a 'small' effect size, 0.5 represents a 'medium' effect size and 0.8 a 'large' effect size. This means that if two groups' means do not differ by 0.2 standard deviations or more, the difference is trivial, even if it is statistically significant.
f. Pooled results reported as HR and RR in the 2 respective studies
g. Downgraded by two levels due to very serious inconsistency. Unexplained heterogeneity I2=89%.
h. Downgraded by one level due to serious inconsistency. Unexplained heterogeneity I2=88%.
i. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting benefit.
j. The study PRESERVE found that the RR of improvement in HAQ-DI (≥0.22 change from baseline) was 1.42 (95%CI 1.21 to 1.67), absolute risk increase 214 more per 1000 (95%CI 107 more to 342 more).
k. Concern about risk of bias associated with incomplete outcome data (48% drop-out) in a study contributing to a 99.7% of the weight.
l. The studies OPTIMA and PRESERVE found that the RR of developing no radiographic progression (change in mTSS ≤0.5) was 1.09 (95%CI 1.02 to 1.17), absolute risk increase 74 more per 1000 (95%CI 16 more to 139 more).
m. Downgraded by two levels due to very serious inconsistency. Unexplained heterogeneity I2=94%.
n. Concern about risk of bias associated with incomplete outcome data (inappropriate handling of missing data).
o. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting benefit. Low sample size
p. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting harm. Low sample size
q. Low number of events
r. I2=31%
s. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm. Low number of events.
t. Downgraded by two levels due to very serious imprecision. Low number of events.
u. Downgraded by two levels due to very serious imprecision. Very low number of events.

Cost-effectiveness

The economic analysis RefID 2215 (12) based on DRESS trial conducted in 2 rheumatology outpatient clinics, Netherlands compared dose optimization of TNFi (increasing intervals between injections of ETN or ADA) plus csDMARD and/or CS vs usual care.

The study reported (1) the dose optimization strategy resulted in a mean cost saving of −€12 280 (95 percentiles − €10 502; −€14 104) per patient per 18 months. (2) there is an 84% chance that the dose optimization strategy results in a QALY loss with a mean QALY loss of −0.02 (−0.07 to 0.02). (3) The decremental cost-effectiveness ratio (DCER) was €390 493 (€5 085 184; dominant) of savings per QALY lost. The mean iNMB was €10 467 (€6553–€14037).

Author's conclusion: Disease activity-guided dose optimization of TNFi results in considerable cost savings while no relevant loss of quality of life was observed.

The economic analysis RefID 11363 (13) based on POET trial conducted in Netherlands, a societal perspective compared TNFi stopped vs TNFi continued.

The study reported (1) withdrawal of TNFi treatment resulted in a >60% reduction of the total drug cost but led to an increase of 30% in other health care expenditures. (2) Compared to continuation, stopping TNFi resulted in a mean yearly cost saving of €7,133 (95% confidence interval [95% CI] €6,071, €8,234]) and was associated with a mean loss of QALYs of 0.02 (95% CI 0.002, 0.040). (3) Mean saved cost per QALY lost and per extra flare incurred in the stop group compared to the continuation group was €368,269 (95% CI €155,132, €1,675,909) and €17,670 (95% CI €13,650, €22,721), respectively. (4) At a WTA of €98,438 per QALY lost, the probability that stopping TNFi treatment is cost-effective was 100%. **Author's conclusion:** Although an official WTA is not defined, the mean saved cost of €368,269 per QALY lost seems acceptable in The Netherlands, given existing data on willingness to pay.

The economic analysis RefID 13902 (5) based on PRESERVE trial conducted in USA compared ETN 25mg+MTX vs ETN50mg+MTX vs Placebo+MTX.

The study reported (1) At week 88, the percentage of patients employed changed slightly from period one (open label) baseline to 43.3, 46.3 and 45.2% for the E50/MTX, E25/MTX and PBO/MTX groups, respectively, which was not significantly different among groups. (2) Absenteeism (4.2 [-0.7, 9.1]), presenteeism (5.9 [2.2, 9.7]) and overall work impairment (8.1 [3.7, 12.5]) worsened (increased) in the E25/MTX group, significant for presenteeism and overall work impairment ($p < 0.01$ vs week 36). (3) In patients who received PBO/MTX, absenteeism (8.1, [3.6, 12.6]), presenteeism (11.9 [7.2, 16.5]) and overall work impairment (13.0 [7.8, 18.2]) significantly worsened (increased) versus week 36 ($p < 0.001$). (4) Across treatment groups, activity impairment, presenteeism and overall work impairment were statistically significant for the E50/MTX group compared with PBO/MTX at week 88 ($p < 0.05$), whereas absenteeism was borderline significant ($p = 0.051$). (5) Activity impairment and presenteeism were significant at week 88 in the E25/MTX group versus PBO/MTX ($p < 0.0001$; adjusted mean treatment difference [95% CI] -10.28 [-14.2, -6.3] and $p < 0.05$; -

5.31 [-10.3, -0.3], respectively) but not for absenteeism or work impairment (p = 0.27; -3.40 [-9.4, 2.6]) and p = 0.12; -4.53 [-10.3, 1.2], respectively). (6) No significant differences were observed between the two etanercept dose groups for activity impairment or absenteeism (p = 0.72; adjusted mean treatment difference [95% CI] -0.72 [-4.7, 3.2] and p = 0.37; -2.8 [-9.1, 3.4], respectively), although differences were significant for presenteeism (p < 0.05; -5.27 [-10.4, 0.1]) and work impairment (p < 0.01; -7.92 [-13.9, -1.9]).
Author's conclusion: In conclusion, E50/MTX maintained significant improvements in absenteeism, presenteeism and overall work impairment to week 88 in the first RCT in patients with RA to assess the effects of maintenance, dose reduction or withdrawal of a biologic agent after sustained LDA.

The economic analysis RefID 32468 (14) based on PRESERVE trial conducted in Sweden compared ETA 50 mg or ETA 25 mg weekly both with MTX background therapy, or MTX alone.
The study reported (1) The cost per QALY for the half-ETA strategy versus MTX varies between €14,000 and €29,000, depending on the time frame: Longer durations of the simulations increase the incremental cost-effectiveness ratio (ICER), as incremental costs of the ETA strategies versus MTX become higher. (2) Half ETA technically dominates full ETA (i.e., it has lower costs and slightly better effectiveness) although differences are small. (3) the ICER for half ETA compared with MTX decreases, while the ICER for full ETA compared with MTX increases, reinforcing the dominance of the half ETA strategy. (4) Total costs over 5 years are €100,500 in the MTX arm and €103,200 in the half-ETA arm. Treatment costs were €49,700 anD €56,800, respectively, but direct healthcare costs decreased from
€13,300 to €8,500 with half ETA.
Author's conclusion: Although ultimately all three strategies explored achieve a similar outcome as all three continuously manage patients to maintain remission, it appears that a dose reduction is the most advantageous strategy in patients with moderate disease activity.

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PICO 53. Should patients with RA on DMARDs who are <u>in remission</u> gradually taper off DMARDs, abruptly withdraw DMARDs, or continue DMARDS at the same doses? P - Patients with RA on DMARDs in remission
I - Taper off DMARDs (as long as the patient remains on at least one DMARD)
C- Abruptly withdraw DMARDs (as long as the patient remains on at least one DMARD)
C - Continue DMARDs at same doses

Comparison 1: Taper off DMARDs **versus** abruptly withdraw DMARDs. See below Table.
Comparison 2: Continue DMARDs at same doses **versus** taper off DMARDs. See below Table.
Comparison 3: Continue DMARDs at same doses **versus** abruptly withdraw DMARDs. See below Table.

Comparison 1: Taper off DMARDs **versus** abruptly withdraw DMARDs. Data based on **direct** RCT evidence.
Overall certainty of evidence: Low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Taper off DMARDs	Abruptly withdraw DMARDs	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 9 months; assessed with: ACR 20)												
1 (1)	randomised trials	serious [a]	not serious	not serious	serious [b]	none	56/63 (88.9%)	48/63 (76.2%)	**RR 1.17** (0.99 to 1.37)	**130 more per 1,000** (from 8 fewer to 282 more)	⨁⨁◯◯ LOW	CRITICAL
Disease activity (follow up: 9 months; assessed with: ACR 50)												
1 (1)	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	49/63 (77.8%)	45/63 (71.4%)	**RR 1.09** (0.89 to 1.34)	**64 more per 1,000** (from 79 fewer to 243 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Taper off DMARDs	Abruptly withdraw DMARDs	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 9 months; assessed with: ACR 70)												
1 (1)	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	45/63 (71.4%)	39/63 (61.9%)	**RR 1.15** (0.90 to 1.48)	**93 more per 1,000** (from 62 fewer to 297 more)	⨁◯◯◯ VERY LOW	CRITICAL
Disease activity (follow up: 9 months; assessed with: DAS28-ESR (Lower values – > benefit) (MCID -1.17)												
1 (1)	randomised trials	serious [a]	not serious	not serious	serious [b]	none	63	65	-	MD **0.7 lower** (1.25 lower to 0.15 lower)	⨁⨁◯◯ LOW	CRITICAL
Remission (follow up: 9 months; assessed with: DAS28ESR < 2.6)												
1 (1)	randomised trials	serious [a]	not serious	not serious	not serious	none	50/63 (79.4%)	35/65 (53.8%)	**RR 1.47** (1.14 to 1.91)	**253 more per 1,000** (from 75 more to 490 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Taper off DMARDs	Abruptly withdraw DMARDs	Relative (95% CI)	Absolute (95% CI)		
Flare (follow up: 12 months)												
1 (2)	randomised trials	not serious	not serious	not serious	very serious [d]	none	3/126 (2.4%)	10/79 (12.7%)	**RR 0.19** (0.05 to 0.66)	**103 fewer per 1,000** (from 120 fewer to 43 fewer)	⨁⨁◯◯ LOW	CRITICAL
Radiographic progression (follow up: 9 months; assessed with: mTSS (Lower values – > benefit) (MCID 4.6)												
1 (1)	randomised trials	serious [a]	not serious	not serious	not serious	none	63	65	-	MD **0.1 higher** (0.34 lower to 0.54 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Quality of Life (follow up: 9 months; assessed with: SF-36 PCS (Higher values – > benefit) (MCID 4.4)												
1 (3)	randomised trials	serious [a]	not serious	not serious	serious [b]	none	63	65	-	MD **2.3 higher** (0.47 lower to 5.07 higher) [e]	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Taper off DMARDs	Abruptly withdraw DMARDs	Relative (95% CI)	Absolute (95% CI)		
Quality of Life (follow up: 9 months; assessed with: SF-36 MCS (Higher values – > benefit) (MCID 3.1)												
1 (3)	randomised trials	serious [a]	not serious	not serious	serious [b]	none	63	65	-	MD **1.8 higher** (0.97 lower to 4.57 higher) [f]	⨁⨁◯◯ LOW	IMPORTANT
Fatigue (follow up: 9 months; assessed with: FACIT-F (Higher values – > benefit) (MCID 15.9)												
1 (3)	randomised trials	serious [a]	not serious	not serious	not serious	none	63	65	-	MD **1.8 higher** (1.25 lower to 4.85 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Withdrawal due to adverse events (follow up: 9 months)												
1 (1)	randomised trials	serious [a]	not serious	not serious	very serious [d]	none	3/63 (4.8%)	0/65 (0.0%)	**RR 7.22** (0.38 to 136.98)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Taper off DMARDs	Abruptly withdraw DMARDs	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events (follow up: 9 months)												
1 (1)	randomised trials	serious [a]	not serious	not serious	very serious [d]	none	3/63 (4.8%)	2/65 (3.1%)	**RR 1.55** (0.27 to 8.95)	**17 more per 1,000** (from 22 fewer to 245 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Downgraded by one level due to serious risk of bias. Lack of allocation concealment, incomplete outcome data and selective reporting.
b. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting benefit.
c. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm.
d. Downgraded by two levels due to very serious imprecision. Very low number of events.
e. The study PRIZE found that the RR of improvement in SF-36 PCS (≥ 5 change from baseline) was 1.03 (95%CI 0.86 to 1.24), absolute risk increase 23 more per 1000 (95%CI 108 fewer to 185 more).
f. The study PRIZE found that the RR of improvement in SF-36 MCS (≥ 5 change from baseline) was 1.27 (95%CI 0.91 to 1.78), absolute risk increase 125 more per 1000 (95%CI 42 fewer to 360 more).

Comparison 2: Continue DMARDs at same doses **versus** taper off DMARDs. Data based on **direct** RCT evidence.
Overall certainty of evidence: Low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continue DMARDs at same dose	Taper off DMARDs	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 6 months; assessed with: ACR 20)												
1 (4)	randomised trials	serious [a]	not serious	not serious	serious [b]	none	85/89 (95.5%)	79/90 (87.8%)	**RR 1.09** (1.00 to 1.19)	**79 more per 1,000** (from 0 fewer to 167 more)	⨁⨁◯◯ LOW	CRITICAL
Disease activity (follow up: 6 months; assessed with: ACR 50)												
1 (4)	randomised trials	serious [a]	not serious	not serious	serious [c]	none	75/89 (84.3%)	71/90 (78.9%)	**RR 1.07** (0.93 to 1.23)	**55 more per 1,000** (from 55 fewer to 181 more)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continue DMARDs at same dose	Taper off DMARDs	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 6 months; assessed with: ACR 70)												
1 (4)	randomised trials	serious [a]	not serious	not serious	serious [c]	none	61/89 (68.5%)	58/90 (64.4%)	**RR 1.06** (0.86 to 1.31)	**39 more per 1,000** (from 90 fewer to 200 more)	⨁⨁◯◯ LOW	CRITICAL
Disease activity (follow up: range 3 months to 6 months; assessed with: DAS28-ESR (Lower values – > benefit) (MCID -1.17)												
2 (4, 5)	randomised trials	serious [a]	not serious	not serious	not serious	none	162	154	-	MD **0.33 lower** (0.72 lower to 0.52 higher)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continue DMARDs at same dose	Taper off DMARDs	Relative (95% CI)	Absolute (95% CI)		
Flare (follow up: range 12 months to 18 months)												
3(4-6) [d]	randomised trials	serious [a]	serious [e]	not serious	not serious	none	105 participants	95 participants	**HR 0.56** (0.40 to 0.77) [Flare]	**204 fewer per 1,000** (from 303 fewer to 95 fewer)	⨁⨁◯◯ LOW	CRITICAL
							-	63.5%		**204 fewer per 1,000** (from 303 fewer to 95 fewer)		
Disability (follow up: 3 months; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
2 (4, 5)	randomised trials	serious [a]	not serious	not serious	not serious	none	162	154	-	MD **0.02 lower** (0.18 lower to 0.14 higher) [f]	⨁⨁⨁◯ MODERATE	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continue DMARDs at same dose	Taper off DMARDs	Relative (95% CI)	Absolute (95% CI)		
Withdrawal due to lack of efficacy (follow up: 6 months)												
1 (4)	randomised trials	serious [a]	not serious	not serious	very serious [g]	none	1/89 (1.1%)	0/90 (0.0%)	**RR 3.03** (0.13 to 73.48)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT
Withdrawal due to adverse events (follow up: 6 months)												
1 (4)	randomised trials	serious [a]	not serious	not serious	very serious [g]	none	1/89 (1.1%)	2/90 (2.2%)	**RR 0.51** (0.05 to 5.48)	**11 fewer per 1,000** (from 21 fewer to 100 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continue DMARDs at same dose	Taper off DMARDs	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events (follow up: 6 months)												
1 (4)	randomised trials	serious [a]	not serious	not serious	very serious [g]	none	2/89 (2.2%)	1/90 (1.1%)	**RR 2.02** (0.19 to 21.91)	**11 more per 1,000** (from 9 fewer to 232 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **HR:** Hazard Ratio

Explanations

a. Downgraded by one level due to serious risk of bias. Lack of blinding of participants and personnel.
b. Downloaded by two levels due to very serious imprecision. Confidence interval includes both values suggesting no effect and benefit. Small sample size.
c. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm.
d. Pooled results reported as HR and RR in the 2 respective studies
e. Downgraded by one level due to serious inconsistency. Unexplained heterogeneity I2=76%
f. The study Sanmarti 2019 found that the RR of improvement in HAQ-DI (≥0.5 change from baseline) was 0.97 (95%CI 0.75 to 1.26), absolute risk reduction 17 fewer per 1000 (95%CI 142 fewer to 147 more).
g. Downgraded by two levels due to very serious imprecision. Very low number of events and small sample size.

Comparison 3: Continue DMARDs at same doses **versus** abruptly withdraw DMARDs. Data based on **direct** RCT evidence.
Overall certainty of evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continue DMARDs at same dose	Abruptly withdraw DMARDs	Relative (95% CI)	Absolute (95% CI)		
Flare (follow up: 7 months)												
1 (7)	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	8/16 (50.0%)	12/15 (80.0%)	**RR 0.63** (0.36 to 1.08)	**296 fewer per 1,000** (from 512 fewer to 64 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Downgraded by two levels due to very serious risk of bias. Lack of allocation concealment and lacking of blinding of participants, personnel, and radiographic and non-radiographic outcome assessors.
b. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm.

Cost-effectiveness

The economic analysis RefID 32057 (8) compared TNFi dose tapering or withdrawal.

The study reported (1) anti-TNF withdrawal and tapering incurred comparable 5-year total costs (€37,900–€59,700 vs €47,500–€59,200), which were lower than those incurred by anti-TNF maintenance (€67,100–€72,100). (2) Maintenance was associated with the longest time to loss of disease control (range, 27.3–47.1 months), while withdrawal had the shortest (range, 6.9–30.5 months).

Author's conclusion: Dose tapering or withdrawal of anti-TNFs results in similar reduction of health care costs but less time in sustained disease control compared to maintaining therapy. Future research is needed to understand the long-term clinical consequences of these strategies and patient preferences for treatment withdrawals.

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2. Weinblatt ME. A Phase III Study Evaluating Continuation, Tapering, and Withdrawal of Certolizumab Pegol After One Year of Therapy in Patients With Early Rheumatoid Arthritis. Arthritis & Rheumatology. 2017;69(10):1937.
3. Wiland P, Dudler J, Veale D, Tahir H, Pedersen R, Bukowski J, et al. The Effect of Reduced or Withdrawn Etanercept-methotrexate Therapy on Patient-reported Outcomes in Patients with Early Rheumatoid Arthritis. Journal of Rheumatology. 2016;43(7):1268.
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6. Miedany Y. Optimizing therapy in inflammatory arthritis: prediction of relapse after tapering or stopping treatment for rheumatoid arthritis patients achieving clinical and radiological remission. Clin Rheumatol. 2016;35:2915–23.
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PICO 54a. Should patients with RA on two or more DMARDs who are at target for less than six months withdraw DMARDs or continue DMARDs?

P - Patients with RA on two or more DMARDs at target for less than six months

I - Withdraw one DMARD (or more than one DMARD as long as the patient remains on at least one DMARD)

C – Continue current therapy

Comparison 1: Withdraw one DMARD **versus** continue current therapy. See below Table.

Comparison 1: Withdraw one DMARD **versus** continue current therapy. Data based on **direct** RCT evidence.
Overall certainty of evidence: Moderate

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Withdraw one DMARD	Continue current therapy	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 1 year; assessed with: DAS28-ESR (Lower values – > benefit) (MCID -1.17)												
1 (1)	randomised trials	not serious	not serious	not serious	not serious	none	398	201	-	MD **0.59 higher** (0.4 higher to 0.78 higher)	⨁⨁⨁⨁ HIGH	CRITICAL
Remission (follow up: 1 year; assessed with: DAS28-ESR <2.6)												
1 (1)	randomised trials	not serious	not serious	not serious	not serious	none	179/398 (45.0%)	134/201 (66.7%)	**RR 0.67** (0.58 to 0.78)	**220 fewer per 1,000** (from 280 fewer to 147 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Withdraw one DMARD	Continue current therapy	Relative (95% CI)	Absolute (95% CI)		
Flare (follow up: range 7 months to 12 months)												
2 (2, 3)	randomised trials	serious [a]	not serious [b]	not serious	not serious	none	100/136 (73.5%)	24/75 (32.0%)	**RR 2.40** (1.68 to 3.42)	**448 more per 1,000** (from 218 more to 774 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Radiographic progression (follow up: 1 year; assessed with: mTSS (Lower values – > benefit) (MCID 4.6)												
1 (1)	randomised trials	not serious	not serious	not serious	very serious [c]	none	351	184	-	MD **1.77 lower** (11.99 lower to 8.45 higher) [d]	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Withdraw one DMARD	Continue current therapy	Relative (95% CI)	Absolute (95% CI)		
Fatigue (follow up: 1 year; assessed with: FACIT-F (Higher values – > benefit) (MCID 15.9)												
1 (4)	randomised trials	not serious	not serious	not serious	not serious	none	398	201	-	MD **1.98 lower** (3.57 lower to 0.39 lower)	⨁⨁⨁⨁ HIGH	IMPORTANT
Pain (follow up: 1 year; assessed with: VAS pain (0-100) (Lower values – > benefit) (MCID -11.9)												
1 (1)	randomised trials	not serious	not serious	not serious	serious [e]	none	398	201	-	MD **9.04 higher** (5.62 higher to 12.46 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Withdraw one DMARD	Continue current therapy	Relative (95% CI)	Absolute (95% CI)		
Disability (follow up: 1 year; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
1 (1)	randomised trials	not serious	not serious	not serious	serious [e]	none	398	201	-	MD **0.2 higher** (0.11 higher to 0.29 higher) [f]	⨁⨁⨁◯ MODERATE	IMPORTANT
Quality of Life (follow up: 1 year; assessed with: EuroQol-5 (Higher values – > benefit) (MCID 0.1)												
1 (1)	randomised trials	not serious	not serious	not serious	not serious	none	398	201	-	MD **0.05 lower** (0.09 lower to 0.01 lower)	⨁⨁⨁⨁ HIGH	IMPORTANT
Withdrawal due to lack of efficacy (follow up: 1 year)												
1 (1)	randomised trials	not serious	not serious	not serious	serious [g]	none	54/402 (13.4%)	4/202 (2.0%)	**RR 6.78** (2.49 to 18.47)	**114 more per 1,000** (from 30 more to 346 more)	⨁⨁⨁◯ MODERATE	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Withdraw one DMARD	Continue current therapy	Relative (95% CI)	Absolute (95% CI)		
Withdrawal due to adverse events (follow up: 1 year)												
1 (1)	randomised trials	not serious	not serious	not serious	very serious [c]	none	9/402 (2.2%)	7/202 (3.5%)	**RR 0.65** (0.24 to 1.71)	**12 fewer per 1,000** (from 26 fewer to 25 more)	⨁⨁◯◯ LOW	IMPORTANT
Serious adverse events (follow up: 1 year)												
1 (1)	randomised trials	not serious	not serious	not serious	very serious [e]	none	22/402 (5.5%)	12/202 (5.9%)	**RR 0.92** (0.47 to 1.82)	**5 fewer per 1,000** (from 31 fewer to 49 more)	⨁⨁◯◯ LOW	IMPORTANT
Malignancy (follow up: 1 year)												
1 (1)	randomised trials	not serious	not serious	not serious	very serious [e,g]	none	5/402 (1.2%)	2/202 (1.0%)	**RR 1.26** (0.25 to 6.42)	**3 more per 1,000** (from 7 fewer to 54 more)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Withdraw one DMARD	Continue current therapy	Relative (95% CI)	Absolute (95% CI)		
Death (follow up: 1 year)												
1 (1)	randomised trials	not serious	not serious	not serious	very serious [g]	none	0/402 (0.0%)	2/202 (1.0%)	**RR 0.10** (0.00 to 2.09)	**9 fewer per 1,000** (from -- to 11 more)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. A study contributing 27% of the weight is at very serious risk of bias, while the other study is at risk of bias due to the lack of blinding of participants and personnel.
b. I2=57%
c. CI interval includes both values suggesting benefit and values suggesting harm
d. The study PRESERVE found that the RR of developing no radiographic progression (change in mTSS ≤0.5) was 0.96 (95%CI 0.9 to 1.03), absolute risk reduction per 1000 36 fewer (95%CI 89 fewer to 27 more).
e. CI interval includes both values suggesting harm and values suggesting no effect
f. The study PRESERVE found that the RR of improvement in HAQ-DI (≥0.22 change from baseline) was 0.85 (95%CI 0.76 to 0.96), absolute risk reduction 109 fewer per 1000 (95%CI 174 fewer to 29 fewer).
g. Very small number of events

Cost-effectiveness

No cost-effectiveness data identified.

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PICO 54b. Should patients with RA on two or more DMARDs who are at target for six months and longer withdraw DMARDs or continue DMARDs?

P - Patients with RA on two or more DMARDs at target for six months and longer

I - Withdraw one DMARD (or more than one DMARD as long as the patient remains on at least one DMARD)

C – Continue current therapy

Comparison 1: Withdraw one DMARD **versus** continue current therapy. See below Table.

Comparison 1: Withdraw one DMARD **versus** continue current therapy. Data based on **direct** RCT evidence.
Overall certainty of evidence: Low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Withdraw one DMARD	Continue current therapy	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 3 months; assessed with: DAS28-ESR (Lower values – > benefit) (MCID -1.17)												
1 (1)	randomised trials	serious [a]	not serious	not serious	not serious	none	64	73	-	MD **0.1 higher** (0.02 higher to 0.18 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Flare (follow up: range 11 months to 18 months)												
3 (1-3) [b]	randomised trials	serious [c]	serious [d]	not serious	not serious	none	645 participants	382 participants	**HR 2.61** (2.11 to 3.23) [Flare]	**281 more per 1,000** (from 207 more to 358 more)	⨁⨁◯◯ LOW	CRITICAL
							-	25.4%		**281 more per 1,000** (from 207 more to 358 more)		

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Withdraw one DMARD	Continue current therapy	Relative (95% CI)	Absolute (95% CI)		
Disability (follow up: 3 months; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
1 (1)	randomised trials	serious [a]	not serious	not serious	serious [e]	none	64	73	-	MD **0.09 higher** (0.11 lower to 0.29 higher)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **HR:** Hazard Ratio

Explanations

a. Concern about the lack of blinding of participants and providers
b. Pooled results reported as HR and RR in the 2 respective studies
c. All included studies are at risk of bias
d. I2=55%
e. CI includes both values suggesting harms and values suggesting no effect

Cost-effectiveness

No cost-effectiveness data identified.

References

1. Fautrel B, Pham T, Alfaiate T, Gandjbakhch F, Foltz V, Morel J, et al. Step-down strategy of spacing TNF-blocker injections for established rheumatoid arthritis in remission: Results of the multicentre non-inferiority randomised open-label controlled trial (STRASS: Spacing of TNF-blocker injections in Rheumatoid ArthritiS Study). Annals of the Rheumatic Diseases. 2016;75(1):59.
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PICO 55. Should patients with RA on DMARDs and low dose GCs (≤ 10mg per day) who are at target taper off or continue low dose GCs?

P - Patients with RA on DMARDs and low dose GCs (≤ 10mg per day) who are at target

I - Taper off low dose GCs

C - Continue low dose GCs

No eligible RCT, NRS, or indirect evidence were identified.

PICO 56. Should patients with RA on DMARD monotherapy who are in remission gradually taper off DMARD, abruptly withdraw DMARD, or continue DMARD at the same dose?

P - Patients with RA on DMARD monotherapy who are in remission
I - Taper off DMARD
C- Abruptly withdraw DMARD
C - Continue DMARD at same dose

No eligible RCT, NRS, or indirect evidence were identified.

PICO 57. Should patients with RA on DMARD monotherapy who are in low disease activity gradually taper off DMARD, abruptly withdraw DMARD, or continue DMARD at the same dose?

P - Patients with RA on DMARD monotherapy who are in low disease activity
I - Taper off DMARD
C- Abruptly withdraw DMARD
C - Continue DMARD at same dose

Comparison 1: Abruptly withdraw DMARD **versus** taper off DMARD. No eligible RCT, NRS, or indirect evidence were identified.
Comparison 2: Continue DMARD at same dose **versus** taper off DMARD. No eligible RCT, NRS, or indirect evidence were identified.
Comparison 3: Abruptly withdraw DMARD **versus** continue DMARD at same dose. See below Table.

Comparison 3: Abruptly withdraw DMARD **versus** taper off DMARD. Data providing **direct** NRS evidence.
Overall certainty of evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Abruptly withdraw DMARD	continue DMARD at same dose	Relative (95% CI)	Absolute (95% CI)		
Relapse (follow up: 1 year; assessed with DAS28 CRP>2.7)												
1 (1)	observational studies	serious [a]	not serious	not serious	serious [b]	none	8/16 (50.0%)	2/20 (10.0%)	**RR 5.00** (1.23 to 20.34)	**400 more per 1,000** (from 23 more to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Study did not report on handling confounding; also high rate of missing data
b. Very low number of participants and number of events

Cost-effectiveness

No cost-effectiveness data were identified.

References

1. Harigai M. Discontinuation of adalimumab treatment in rheumatoid arthritis patients after achieving low disease activity. Modern Rheumatology. 2012;22:814-22.

PICO 58. Should patients with RA on triple therapy (MTX + SSZ + HCQ) who are at target withdraw (taper off or abruptly stop) MTX or withdraw (taper off or abruptly stop) alternative csDMARDs?

P - Patients with RA on triple therapy who are at target

I - Withdraw (taper off or abruptly stop) MTX

C - Withdraw (taper off or abruptly stop) alternative csDMARDs

C- Continue same management

No eligible RCT, NRS, or indirect evidence were identified.

PICO 59. Should patients with RA on MTX + boDMARD or MTX + tsDMARD who are at target withdraw (taper off or abruptly stop) MTX or withdraw (taper off or abruptly stop) the boDMARD or the tsDMARD?

P - Patients with RA on MTX + boDMARD or MTX + tsDMARD who are at target

I - Withdraw (taper off or abruptly stop) MTX

C - Withdraw (taper off or abruptly stop) the boDMARD or the tsDMARD

C- Continue same management

Comparison 1: Withdraw (taper off or abruptly stop) the boDMARD or the tsDMARD **versus** withdraw (taper off or abruptly stop) MTX. No RCT, NRS or indirect evidence were identified.

Comparison 2: Continue same management **versus** withdraw (taper off or abruptly stop) MTX. See below Table.

Comparison 3: Continue same management **versus** withdraw (taper off or abruptly stop) the boDMARD or the tsDMARD. See below Table.

Comparison 2: Continue same management **versus** withdraw (taper off or abruptly stop) MTX. Data based on **direct** RCT evidence.
Overall certainty of evidence: Moderate

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continue	Withdraw (Taper/Stop) MTX	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 3 months; assessed with: DAS28-ESR (Lower values – > benefit) (MCID -1.17)												
1 (1)	randomised trials	not serious [a]	not serious	not serious	serious [b]	none	80	79	-	MD **0.07 lower** (0.4 lower to 0.27 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Disability (follow up: 3 months; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
1 (1)	randomised trials	not serious [a]	not serious	not serious	serious [b]	none	82	82	-	MD **0.04 higher** (0.11 lower to 0.19 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Quality of life (follow up: 3 months; assessed with: SF-36 PCS (Higher values – > benefit) (MCID 4.4)												
1 (1)	randomised trials	not serious [a]	not serious	not serious	serious [c]	none	82	82	-	MD **3.38 higher** (0.69 higher to 6.07 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continue	Withdraw (Taper/Stop) MTX	Relative (95% CI)	Absolute (95% CI)		
Quality of life (follow up: 3 months; assessed with: SF-36 MCS (Higher values – > benefit) (MCID 3.1)												
1 (1)	randomised trials	not serious [a]	not serious	not serious	serious [d]	none	82	82	-	MD **1.88 lower** (4.78 lower to 1.02 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Serious adverse events (follow up: 3 months)												
1 (1)	randomised trials	not serious [a]	not serious	not serious	very serious [e]	none	1/83 (1.2%)	4/82 (4.9%)	**RR 0.25** (0.03 to 2.16)	**37 fewer per 1,000** (from 47 fewer to 57 more)	⨁⨁◯◯ LOW	IMPORTANT
Withdrawal due to lack of efficacy (follow up: 3 months)												
1 (1)	randomised trials	not serious [a]	not serious	not serious	very serious [e]	none	0/83 (0.0%)	1/82 (1.2%)	**RR 0.33** (0.01 to 7.97)	**8 fewer per 1,000** (from 12 fewer to 85 more)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continue	Withdraw (Taper/Stop) MTX	Relative (95% CI)	Absolute (95% CI)		
Withdrawal due to adverse events (follow up: 3 months)												
1 (1)	randomised trials	not serious [a]	not serious	not serious	serious [f]	none	3/83 (3.6%)	1/82 (1.2%)	**RR 2.96** (0.31 to 27.91)	**24 more per 1,000** (from 8 fewer to 328 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Death (follow up: 3 months)												
1 (1)	randomised trials	not serious [a]	not serious	not serious	very serious [g]	none	0/83 (0.0%)	0/82 (0.0%)	not estimable		⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. Concern with risk of bias. Missing data was not appropriately handled in the trial.
b. Downgraded by one level due to serious imprecision. Very small sample size.
c. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting benefit. Very small sample size.
d. Downgraded by one level due to very serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting harm. Very small sample size.
e. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm. Very small sample size, and low number of events.
f. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting no effect and values suggesting benefit. Very small sample size, and low number of events.
g. Downgraded by two levels due to very serious imprecision. Very small sample size, and very low number of events.

Comparison 3: Continue same management **versus** withdraw (taper off or abruptly stop) the boDMARD or the tsDMARD. Data based on **direct** RCT evidence.
Overall certainty of evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continue	Withdraw (Taper/Stop boDMARD or tsDMARD)	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 1 year; assessed with: DAS28-ESR/CRP)												
2 (2, 3)	randomised trials	not serious	not serious	not serious	not serious	none	305	499 [b]	-	SMD **0.45 lower** (0.6 lower to 0.3 lower)	⨁⨁⨁⨁ HIGH	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continue	Withdraw (Taper/Stop boDMARD or tsDMARD)	Relative (95% CI)	Absolute (95% CI)		
Flare (follow up: range 7 months to 11 months)												
2 (4, 5) [e]	randomised trials	very serious [f]	serious [g]	not serious	not serious	none	39 participants	65 participants	**HR 0.57** (0.38 to 0.85) [Flare]	**152 fewer per 1,000** (from 231 fewer to 49 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
							-	41.5%		**152 fewer per 1,000** (from 231 fewer to 49 fewer)		
Radiographic progression (follow up: 1; assessed with: mTSS (Lower values – > benefit) (MCID 4.6)												
1 (3)	randomised trials	not serious	not serious	not serious	very serious [h]	none	184	351 [b]	-	MD **1.84 higher** (8.4 lower to 12.08 higher)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continue	Withdraw (Taper/Stop boDMARD or tsDMARD)	Relative (95% CI)	Absolute (95% CI)		
Disability (follow up: 1 year; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
2 (2, 3)	randomised trials	not serious	serious [i]	not serious	serious [j]	none	306	500 [b]	-	MD **0.16 lower** (0.23 lower to 0.08 lower)	⨁⨁◯◯ LOW	IMPORTANT
Quality of life (follow up: 1 year; assessed with: EQ-5D (Higher values – > benefit) (MCID 0.1)												
1 (3)	randomised trials	not serious	not serious	not serious	not serious	none	201	398 [b]	-	MD **0** (0.04 lower to 0.04 higher)	⨁⨁⨁⨁ HIGH	IMPORTANT
Withdrawal due to adverse events (follow up: 1 year)												
1 (2)	randomised trials	serious [k]	not serious	not serious	very serious [h]	none	3/105 (2.9%)	7/102 (6.9%) [b]	**RR 0.42** (0.11 to 1.57)	**40 fewer per 1,000** (from 61 fewer to 39 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continue	Withdraw (Taper/Stop boDMARD or tsDMARD)	Relative (95% CI)	Absolute (95% CI)		
Pain (follow up: 1 year; assessed with: VAS 0-100 (Lower values – > benefit) (MCID -11.9)												
2 (2, 3)	randomised trials	not serious	serious [l]	not serious	not serious	none	305	500 [b]	-	MD **6.56 lower** (9.32 lower to 3.81 lower)	⨁⨁⨁◯ MODERATE	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continue	Withdraw (Taper/Stop boDMARD or tsDMARD)	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events (follow up: 1 year)												
2 (2, 3)	randomised trials	not serious	not serious	not serious	very serious [h]	none	24/307 (7.8%)	33/504 (6.5%) [b]	**RR 1.07** (0.64 to 1.79)	**5 more per 1,000** (from 24 fewer to 52 more)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **SMD:** Standardised mean difference; **HR:** Hazard Ratio; **MD:** Mean difference

Explanations

a. Downgraded by two levels due to very serious inconsistency. I2=97%.
b. Withdraw boDMARD or tsDMARD include withdraw boDMARDs (TNFis: adalimumab and etanercept)
c. Downgraded by two levels due to very serious inconsistency. I2=92%.
d. Downgraded by one level due to serious inconsistency. I2=80%.
e. Pooled results reported as HR and RR in the 2 respective studies
f. Downgraded by two levels due to very serious risk of bias. Lack of allocation concealment and lack of blinding.
g. Downgraded by one level due to serious inconsistency. Unexplained heterogeneity I2=65%
h. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm.
i. Downgraded by one level due to serious inconsistency. I2=70%.
j. Downgraded by one level due to serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting no effect.
k. Downgraded by one level due to serious risk of bias. Incomplete outcome data (Overall loss to follow-up rate is 48)
l. Downgraded by one level due to serious inconsistency. I2=82%.

Cost-effectiveness

No cost-effectiveness data were identified.

References

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PICO 60. Should patients with RA on DMARD monotherapy who are at target lower the dose or increase the interval between doses or continue the DMARD at the same dose?

P - Patients with RA on DMARD monotherapy in remission
I - Continue DMARD at the same dose
C - Lower the dose of the DMARD
C - Increase the interval between DMARD doses

No eligible RCT, NRS, or indirect evidence were identified.

PICO 61. Should patients with RA on MTX + boDMARD or tsDMARD who are at target continue MTX at the same dose or lower the dose of MTX? (boDMARD or tsDMARD continued at same dose)

P - Patients with RA on MTX + boDMARD or tsDMARD who are at target

I - Continue MTX at the same dose

C - Lower the dose of MTX

No eligible RCT, NRS, or indirect evidence were identified.

PICO 62. Should patients with RA on MTX + boDMARD or tsDMARD who are at target continue the boDMARD or tsDMARD at the same dose or lower the dose or increase the interval between doses of the boDMARD or tsDMARD (MTX continued at same dose)?

P - Patients with RA on MTX + boDMARD or tsDMARD who are at target
I - Continue the same dose of the boDMARD or tsDMARD
C - Lower the dose of the boDMARD or tsDMARD
C - Increase the interval between the doses of the boDMARD or tsDMARD

Comparison 1: Continue the same dose of the boDMARD or tsDMARD **versus** lower the dose of the boDMARD or tsDMARD. See below Table.
Comparison 2: Continue the same dose of the boDMARD or tsDMARD **versus** increase the interval between the doses of the boDMARD or tsDMARD. See below Table.

Comparison 1: Continue the same dose of the boDMARD or tsDMARD versus lower the dose of the boDMARD or tsDMARD. Data based on **direct** RCT evidence.
Overall certainty of evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continue the same dose of the boDMARD or tsDMARD	Lower the dose of the boDMARD or tsDMARD	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: range 6 months to 12 months; assessed with: DAS28-ESR (Lower values – > benefit) (MCID -1.17)												
2 (1, 2)	randomised trials	not serious [b]	not serious	not serious	not serious	none	250	248	-	MD **0.06 lower** (0.24 lower to 0.12 higher)	⨁⨁⨁⨁ HIGH	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continue the same dose of the boDMARD or tsDMARD	Lower the dose of the boDMARD or tsDMARD	Relative (95% CI)	Absolute (95% CI)		
Flare (follow up: range 6 months to 12 months)												
3 (2-4)[c]	randomised trials	serious [d]	serious [e]	not serious	very serious [a]	none	105 participants	105 participants	**HR 0.68** (0.39 to 1.19) [Flare]	**97 fewer per 1,000** (from 196 fewer to 51 more)	⨁◯◯◯ VERY LOW	CRITICAL
							-	35.2%		**97 fewer per 1,000** (from 196 fewer to 51 more)		
Radiographic progression (follow up: range 6 months to 12 months; assessed with: Larsen/Sharp (Lower values – > benefit) (values>0.2 are considered clinically important)												
2 (1, 2)	randomised trials	not serious	not serious [f]	not serious	serious [g]	none	234	231	-	SMD **0.13 higher** (0.06 lower to 0.31 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continue the same dose of the boDMARD or tsDMARD	Lower the dose of the boDMARD or tsDMARD	Relative (95% CI)	Absolute (95% CI)		
Fatigue (follow up: range 6 months to 12 months; assessed with: FACIT-F (Higher values – > benefit) (MCID 15.9)												
2 (1, 2)	randomised trials	not serious	not serious	not serious	not serious	none	250	248	-	MD **0.79 lower** (2.01 lower to 0.44 higher)	⨁⨁⨁⨁ HIGH	IMPORTANT
Pain (follow up: range 6 months to 12 months; assessed with: VAS pain (0-100) (Lower values – > benefit) (MCID -11.9)												
2 (1, 2)	randomised trials	not serious	not serious	not serious	not serious	none	250	248	-	MD **2.92 lower** (6.34 lower to 0.5 higher)	⨁⨁⨁⨁ HIGH	IMPORTANT
Disability (follow up: range 6 months to 12 months; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
2 (1, 2)	randomised trials	not serious	not serious	not serious	not serious	none	251	248	-	MD **0.09 lower** (0.19 lower to 0) [h]	⨁⨁⨁⨁ HIGH	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continue the same dose of the boDMARD or tsDMARD	Lower the dose of the boDMARD or tsDMARD	Relative (95% CI)	Absolute (95% CI)		
Quality of Life (follow up: range 6 months to 12 months; assessed with: EQ-5D (Higher values – > benefit) (MCID 0.1)												
2 (1, 2)	randomised trials	not serious	not serious	not serious	not serious	none	251	248	-	MD **0** (0.03 lower to 0.04 higher)	⨁⨁⨁⨁ HIGH	IMPORTANT
Withdrawal due to adverse events (follow up: 1 year)												
1 (1)	randomised trials	not serious	not serious	not serious	very serious [g,i]	none	7/202 (3.5%)	4/202 (2.0%)	**RR 1.75** (0.52 to 5.89)	**15 more per 1,000** (from 10 fewer to 97 more)	⨁⨁◯◯ LOW	IMPORTANT
Serious adverse events (follow up: range 6 months to 12 months)												
2 (1, 2)	randomised trials	not serious	not serious [j]	not serious	very serious [i,k]	none	12/221 (5.4%)	10/230 (4.3%)	**RR 1.28** (0.56 to 2.91)	**12 more per 1,000** (from 19 fewer to 83 more)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continue the same dose of the boDMARD or tsDMARD	Lower the dose of the boDMARD or tsDMARD	Relative (95% CI)	Absolute (95% CI)		
Cardiovascular disease (follow up: 6 months)												
1 (2)	randomised trials	serious [l]	not serious	not serious	very serious [i,k]	none	3/19 (15.8%)	4/28 (14.3%)	**RR 1.11** (0.28 to 4.39)	**16 more per 1,000** (from 103 fewer to 484 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Malignancy (follow up: 1 year)												
1 (1)	randomised trials	not serious	not serious	not serious	very serious [i,k]	none	2/202 (1.0%)	4/202 (2.0%)	**RR 0.50** (0.09 to 2.70)	**10 fewer per 1,000** (from 18 fewer to 34 more)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continue the same dose of the boDMARD or tsDMARD	Lower the dose of the boDMARD or tsDMARD	Relative (95% CI)	Absolute (95% CI)		
Death (follow up: 1 year)												
1 (1)	randomised trials	not serious	not serious	not serious	very serious [i]	none	2/202 (1.0%)	0/202 (0.0%)	**RR 5.00** (0.24 to 103.50)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **HR:** Hazard Ratio; **SMD:** Standardised mean difference

Explanations

a. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting harm.
b. We did not downgrade due to risk of bias. The one study that contributed 76% of the weight is at low risk of bias; the other study suffers from lLack of blinding of participants and personnel and lack of blinding of outcome assessment for non-radiographic outcomes.
c. Pooled results reported as HR and RR in the 2 respective studies
d. Downgraded by one level due to serious risk of bias. Lack of allocation concealment in one study and lack of blinding of participants and personnel in both studies.
e. Downgraded by one level due to serious inconsistency. Unexplained heterogeneity I2=65%
f. I2=43%
g. CI includes both values suggesting harm and values suggesting no effect. According to the Cochrane's handbook, Cohen suggested that SMD=0.2 be considered a 'small' effect size, 0.5 represents a 'medium' effect size and 0.8 a 'large' effect size. This means that if two groups' means do not differ by 0.2 standard deviations or more, the difference is trivial, even if it is statistically significant.
h. The study PRESERVE found that the RR of improvement in HAQ-DI (≥0.22 change from baseline) at 1 year was 1 (95%CI 0.88 to 1.13), absolute risk reduction 0 fewer per 1000 (95%CI 87 fewer to 94 more).
i. Very small number of events
j. I2=47%
k. CI includes both values suggesting benefit and values suggesting harm
l. Downgraded for risk of bias as the one included study did not blind participants, providers, or outcome assessors

Comparison 2: Continue the same dose of the boDMARD or tsDMARD **versus** increase the interval between the doses of the boDMARD or tsDMARD. Data based on **direct** RCT evidence.
Overall certainty of evidence: Low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continue the same dose of the boDMARD or tsDMARD	Increase the interval between the doses of the boDMARD or tsDMARD	Relative (95% CI)	Absolute (95% CI)		
Disease activity (follow up: 3 months; assessed with: DAS28-ESR (Lower values – > benefit) (MCID -1.17)												
1 (5)	randomised trials	serious [a]	not serious	not serious	not serious	none	73	64	-	MD **0.2 lower** (0.56 lower to 0.16 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Flare (follow up: 18 months)												
2 (5, 6)	randomised trials	serious [b]	serious [c]	not serious	not serious	none	50/132 (37.9%)	137/185 (74.1%)	**RR 0.48** (0.38 to 0.62)	**385 fewer per 1,000** (from 459 fewer to 281 fewer)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continue the same dose of the boDMARD or tsDMARD	Increase the interval between the doses of the boDMARD or tsDMARD	Relative (95% CI)	Absolute (95% CI)		
Disability (follow up: 3 months; assessed with: HAQ-DI (Lower values – > benefit) (MCID -0.22)												
1 (5)	randomised trials	serious [a]	not serious	not serious	serious [d]	none	73	64	-	MD **0.09 lower** (0.41 lower to 0.23 higher)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. Downgraded by one level due to serious risk of bias. Lack of blinding of participants and personnel.
b. Downgraded by one level due to serious risk of bias. Lack of blinding of participants and personnel in both studies and lack of blinding of non-radiographic outcome assessors in one study.
c. Downgraded by one level due to serious inconsistency. I2=75%.
d. Downgraded by two levels due to very serious imprecision. Confidence interval includes both values suggesting benefit and values suggesting no effect.

Cost-effectiveness

The economic analysis RefID 13902 (7) based on PRESERVE trial conducted in USA compared ETN 25mg + MTX vs ETN 50mg + MTX vs Placebo + MTX.

The study reported (1) At week 88, the percentage of patients employed changed slightly from period one (open-label) baseline to 43.3, 46.3 and 45.2% for the E50/MTX, E25/MTX and PBO/MTX groups, respectively, which was not significantly different among groups. (2) Absenteeism (4.2 [-0.7, 9.1]), presenteeism (5.9 [2.2, 9.7]) and overall work impairment (8.1 [3.7, 12.5]) worsened (increased) in the E25/MTX group, significant for presenteeism and overall work impairment ($p < 0.01$ vs week 36). (3) In patients who received PBO/MTX, absenteeism (8.1, [3.6, 12.6]), presenteeism (11.9 [7.2, 16.5]) and overall work impairment (13.0 [7.8, 18.2]) significantly worsened (increased) versus week 36 ($p < 0.001$). (4) Across treatment groups, activity impairment, presenteeism and overall work impairment were statistically significant for the E50/MTX group compared with PBO/MTX at week 88 ($p < 0.05$), whereas absenteeism was borderline significant ($p = 0.051$). (5) Activity impairment and presenteeism were significant at week 88 in the E25/MTX group versus PBO/MTX ($p < 0.0001$; adjusted mean treatment difference [95% CI] -10.28 [-14.2, -6.3] and $p < 0.05$; -5.31 [-10.3, -0.3], respectively) but not for absenteeism or work impairment ($p = 0.27$; -3.40 [-9.4, 2.6]) and $p = 0.12$; -4.53 [-10.3, 1.2], respectively). (6) No significant differences were observed between the two etanercept dose groups for activity impairment or absenteeism ($p = 0.72$; adjusted mean treatment difference [95% CI] -0.72 [-4.7, 3.2] and $p = 0.37$; -2.8 [-9.1, 3.4], respectively), although differences were significant for presenteeism ($p < 0.05$; -5.27 [-10.4, 0.1]) and work impairment ($p < 0.01$; -7.92 [-13.9, -1.9]).

Author's conclusion: In conclusion, E50/MTX maintained significant improvements in absenteeism, presenteeism and overall work impairment to week 88 in the first RCT in patients with RA to assess the effects of maintenance, dose reduction or withdrawal of a biologic agent after sustained LDA.

The economic analysis RefID 32468 (8) based on PRESERVE trial conducted in Sweden compared ETA 50 mg or ETA 25 mg weekly both with MTX background therapy, or MTX alone.

The study reported (1) The cost per QALY for the half-ETA strategy versus MTX varies between €14,000 and €29,000, depending on the time frame: Longer durations of the simulations increase the incremental cost-effectiveness ratio (ICER), as incremental costs of the ETA strategies versus MTX become higher. (2) Half ETA technically dominates full ETA (i.e., it has lower costs and slightly better effectiveness) although differences are small. (3) the ICER for half ETA compared with MTX decreases, while the ICER for full ETA compared with MTX increases, reinforcing the dominance of the half ETA strategy. (4) Total costs over 5 years are €100,500 in the MTX arm and €103,200 in the half-ETA arm. Treatment costs were €49,700 anD €56,800, respectively, but direct healthcare costs decreased from €13,300 to €8,500 with half ETA.

Author's conclusion: Although ultimately all three strategies explored achieve a similar outcome as all three continuously manage patients to maintain remission, it appears that a dose reduction is the most advantageous strategy in patients with moderate disease activity.

References

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PICO 63. Should patients with RA on MTX + boDMARD or tsDMARD who are at target lower the dose of MTX or lower the dose or increase the interval between doses of the boDMARD or tsDMARD?

P - Patients with RA on MTX + boDMARD or tsDMARD who are at target

I - Lower the dose of MTX

C - Lower the dose of the boDMARD or tsDMARD

C - Increase the interval between doses of boDMARD or tsDMARD

No eligible RCT, NRS, or indirect evidence were identified.

PICO 64. Should patients with RA with (progressive) subcutaneous nodules, who are NOT at target and are not on MTX, start MTX or alternative DMARDs?

P - Patients with RA and (progressive) subcutaneous nodules, who are not at target, are not on MTX
I - Start MTX
C - Start alternative csDMARD mono or combination therapy
C - Start TNF Inhibitor
C - Start Abatacept
C - Start Rituximab
C - Start IL-6 Receptor Inhibitor
C - Start JAK Inhibitor

No eligible RCT, NRS, or indirect evidence were identified.

PICO 65. Should patients with RA with (progressive) subcutaneous nodules, who are at target and are on MTX, continue MTX or switch to alternative DMARD(s)?

P - Patients with RA and (progressive) subcutaneous nodules who are at target and are on MTX
I - Continue MTX
C - Switch to alternative csDMARD mono or combination therapy
C - Switch to TNF Inhibitor
C - Switch to Abatacept
C - Switch to Rituximab
C - Switch to IL-6 Receptor Inhibitor
C - Switch to JAK Inhibitor

No eligible RCT, NRS, or indirect evidence were identified.

PICO 66. Should patients with RA who have persistent hypogammaglobulinemia after RTX treatment continue RTX or switch to csDMARD mono or combination therapy or to a boDMARD targeting a different molecule or to a tsDMARD?

P - Patients with RA who have persistent hypogammaglobulinemia after RTX treatment
I - Continue RTX
C - Switch to csDMARD mono or combination therapy
C - Switch to TNF Inhibitor
C - Switch to Abatacept
C - Switch to IL-6 Receptor Inhibitor
C - Switch to JAK Inhibitor

No eligible RCT, NRS, or indirect evidence were identified.

PICO 67. Should patients with RA who have clinical parenchymal lung disease receive MTX or alternative DMARD(s) for treatment of joint disease?

P - Patients with RA and parenchymal lung disease
I - MTX
C - Alternative csDMARD mono or combination therapy
C - TNF Inhibitor
C - Abatacept
C - Rituximab
C - IL-6 Receptor Inhibitor
C - JAK Inhibitor

No direct evidence identified. See below for indirect evidence.

Evidence identified 1: Rojas-Serrano 2017 [RefID: 978] (1) was a retrospective cohort study conducted in an ILD/Rheumatology unit, single center in Mexico City covering the 2004-2015 period

Findings (Follow up 25 months):

- "Patients treated with methotrexate and leflunomide had no difference in survival compared to those treated with methotrexate alone."
- Methotrexate treatment was associated with survival: adjusted HR: 0.063 (0.15–0.47)
- Patients who died were less likely than those who survived to have been on MTX treatment throughout follow-up (not clear what the comparator is): 4/17 (23.5%) vs. 48/61 (79%) with a HR of 0.16 (0.05-0.52).

Very low certainty evidence due to NRS design and low number of participants

Evidence identified 2: Curtis 2015 [RefID: 2440] (2) was a retrospective cohort study based on claims data base covering 2010-2012 claim for new biologics. It included 419 patients with ILD.

Findings

- In Cox models, recent methotrexate exposure was associated with reduced ILD hospitalization (HR 0.16; 95 % CI 0.06–0.46); ABA, RTX and TCZ were not associated with reduced ILD hospitalization.
- "Although methotrexate may in fact have a protective effect with respect to ILD exacerbation, these results are perhaps more likely to reflect channeling of patients with aggressive or severe ILD away from methotrexate because these patients have less pulmonary reserve were they to develop methotrexate-associated pneumonitis."

Low certainty evidence due to NRS design.

Cost-effectiveness

No cost-effectiveness data were identified.

References

1. Rojas-Serrano J. Rheumatoid arthritis-related interstitial lung disease (RA-ILD): methotrexate and the severity of lung disease are associated to prognosis. Clin Rheumatol. 2017;36:1493–500.
2. Curtis. Incidence and complications of interstitiallung disease in users of tocilizumab,rituximab, abatacept and anti-tumornecrosis factorαagents, a retrospectivecohort study. Arthritis Research & Therapy - BMC. 2015;17:319.

PICO 70. Should patients with RA with CHF NYHA class III or IV with inadequate response to csDMARDs add a TNF Inhibitor or a boDMARD targeting a different molecule or a tsDMARD?

P - Patients with RA with CHF class III or IV with inadequate response to csDMARDs
I - Add TNF Inhibitor
C - Add Abatacept
C - Add Rituximab
C - Add IL-6 Receptor Inhibitor
C - Add JAK Inhibitor

No eligible RCT, NRS, or indirect evidence were identified.

PICO 71. Should patients with RA who are at target on a TNF Inhibitor and who develop CHF continue the TNF Inhibitor or switch to a boDMARD targeting a different molecule or to a tsDMARD?

P - Patients with RA who are at target on TNF Inhibitor and who develop CHF
I - Continue TNF Inhibitor
C - Switch to Abatacept
C - Switch to Rituximab
C - Switch to IL-6 Receptor Inhibitor
C - Switch to JAK Inhibitor

No eligible RCT, NRS, or indirect evidence were identified.

PICO 72. Should patients with RA with an inadequate response to csDMARDs, who have had non-melanoma skin cancer, receive a TNF Inhibitor or a boDMARD targeting a different molecule or a tsDMARD?

P - Patients with RA with inadequate response to csDMARDs, who have had non-melanoma skin cancer
I - TNF Inhibitor
C - Abatacept
C - Rituximab
C - IL-6 Receptor Inhibitor
C - JAK Inhibitor

No direct evidence identified. See below for indirect evidence.

Evidence identified 1: Silva-Fernandez 2016 [RefID: 103] (1) was a retrospective cohort study of patients with prior malignancy based on the British registry for biologic use (2001-2013 period). The 2 relevant comparison groups:

- 234 patients on TNFi (percentage with NMSC not reported, likely 0%; average of 11.5 years from most recent prior malignancy)
- 23 patients on RTX (percentage with NMSC not reported, likely 0%; average of 5.4 years from most recent prior malignancy)

Rate per 1000-person year over a 5 year follow up was:

- 26.8 (17.5, 39.2) in the TNFi group;
- 24.7 (3.0, 89.3) in the RTX group;
- no p value reported, but should be non-significant

Very low certainty of evidence due to NRS design, indirectness, and imprecision

Cost-effectiveness

No cost-effectiveness data were identified.

References

1. Silva-Fernandez L. The incidence of cancer in patients with rheumatoid arthritis and a prior malignancy who receive TNF inhibitors or rituximab: results from the British Society for Rheumatology Biologics Register-Rheumatoid Arthritis. Rheumatology. 2016;55(11):2033.

PICO 73. Should patients with RA with inadequate response to csDMARDs, who have had melanoma, receive a TNF Inhibitor or a boDMARD targeting a different molecule or a tsDMARD?

P - Patients with RA with inadequate response to csDMARDs, who have had melanoma
I - TNF Inhibitor
C - Abatacept
C - Rituximab
C - IL-6 Receptor Inhibitor
C - JAK Inhibitor

No direct evidence identified. See below for indirect evidence.

Evidence identified 1: Silva-Fernandez 2016 [RefID: 103] (1) was a retrospective cohort study of patients with prior malignancy based on the British registry for biologic use (2001-2013 period). The 2 relevant comparison groups:

- 234 patients on TNFi (of which 213, 88% had solid cancer; average of 11.5 years from most recent prior malignancy)
- 23 patients on RTX (of which 19, 83% had solid cancer; average of 5.4 years from most recent prior malignancy)

Rate per 1000-person year over a 5 year follow up was:

- 26.8 (17.5, 39.2) in the TNFi group;
- 24.7 (3.0, 89.3) in the RTX group;
- no p value reported, but should be non-significant

Very low certainty of evidence due to NRS design, indirectness, and imprecision.

Cost-effectiveness

No cost-effectiveness data were identified.

References

1. Silva-Fernandez L. The incidence of cancer in patients with rheumatoid arthritis and a prior malignancy who receive TNF inhibitors or rituximab: results from the British Society for Rheumatology Biologics Register-Rheumatoid Arthritis. Rheumatology. 2016;55(11):2033.

PICO 74. Should patients with DMARD-naïve RA with a previously treated lymphoproliferative disorder, who have low disease activity, receive csDMARDs or RTX?

P - Patients with DMARD-naïve RA with a previously treated lymphoproliferative disorder, who have low disease activity
I - csDMARDs
C – RTX

No eligible RCT, NRS, or indirect evidence were identified.

PICO 75. Should patients with DMARD-naïve RA who have moderate to high disease activity and a previously treated lymphoproliferative disorder receive csDMARDs or RTX?

P - Patients with DMARD-naïve RA with a previously treated lymphoproliferative disorder who have moderate to high disease activity

I - csDMARDs

C – RTX

No eligible RCT, NRS, or indirect evidence were identified.

PICO 76. Should patients with RA with inadequate response to csDMARDs and a previously treated lymphoproliferative disorder receive RTX or a boDMARD targeting a different molecule or a tsDMARD?

P - Patients with RA with inadequate response to csDMARDs and a previously treated lymphoproliferative disorder
I - RTX
C - Abatacept
C - TNF Inhibitor
C - IL-6 Receptor Inhibitor
C - JAK Inhibitor

No eligible RCT, NRS, or indirect evidence were identified.

PICO 77. Should patients with RA with inadequate response to csDMARDs and a previously treated lymphoproliferative disorder, who are NOT eligible for RTX, receive a boDMARD targeting a different molecule or a tsDMARD?

P - Patients with RA with inadequate response to csDMARDs and a previously treated lymphoproliferative disorder, and who are NOT eligible for RTX

I - JAK Inhibitor

C - Abatacept

C - TNF Inhibitor

C - IL-6 Receptor Inhibitor

No eligible RCT, NRS, or indirect evidence were identified.

PICO 78. Should patients with RA with inadequate response to csDMARD monotherapy and a *remote history (≥ 5 years)* of solid organ cancer and no known residual disease receive triple therapy (MTX or LEF + SSZ + HCQ) or a boDMARD or tsDMARD?

P - Patients with RA with inadequate response to csDMARD monotherapy and a remote history of solid organ cancer
I - Triple therapy (MTX or LEF + SSZ + HCQ)
C - TNF Inhibitor
C - Abatacept
C - Rituximab
C - IL-6 Receptor Inhibitor
C - JAK Inhibitor

No direct evidence identified. See below for indirect evidence.

Evidence identified 1: Silva-Fernandez 2016 [RefID: 103] (1)was a retrospective cohort study of patients with prior malignancy based on the British registry for biologic use (2001-2013 period). The 2 relevant comparison groups:

- 234 patients on TNFi (of which 23, 9.4% had melanoma)
- 23 patients on RTX (none of which had melanoma)

Rate per 1000-person year over a 5 year follow up was:

- 26.8 (17.5, 39.2) in the TNFi group;
- 24.7 (3.0, 89.3) in the RTX group;
- no p value reported, but should be non-significant

Very low certainty of evidence due to NRS design, indirectness, and imprecision.

Cost-effectiveness

No cost-effectiveness data were identified.

References

1. Silva-Fernandez L. The incidence of cancer in patients with rheumatoid arthritis and a prior malignancy who receive TNF inhibitors or rituximab: results from the British Society for Rheumatology Biologics Register-Rheumatoid Arthritis. Rheumatology. 2016;55(11):2033.

PICO 79. Should patients with RA with inadequate response to csDMARD monotherapy with *recently treated (< 5 years)* solid organ cancer receive triple therapy (MTX or LEF + SSZ + HCQ) or a boDMARD or tsDMARD?

P - Patients with RA with inadequate response to csDMARD monotherapy and recently treated (< 5 years) solid organ cancer
I - Triple therapy
C - TNF Inhibitor
C - Abatacept
C - Rituximab
C - IL-6 Receptor Inhibitor
C - JAK Inhibitor

No direct evidence identified. See below for indirect evidence.

Evidence identified 1: Silva-Fernandez 2016 [RefID: 103] (1) was a retrospective cohort study of patients with prior malignancy based on the British registry for biologic use (2001-2013 period). The 2 relevant comparison groups:

- 234 patients on TNFi (of which 213, 88% had solid cancer; average of 11.5 years from most recent prior malignancy)
- 23 patients on RTX (of which 19, 83% had solid cancer; average of 5.4 years from most recent prior malignancy)

Rate per 1000-person year over a 5 year follow up was:

- 26.8 (17.5, 39.2) in the TNFi group;
- 24.7 (3.0, 89.3) in the RTX group;
- no p value reported, but should be non-significant

Very low certainty of evidence due to NRS design, indirectness, and imprecision.

Cost-effectiveness

No cost-effectiveness data were identified.

References

1. Silva-Fernandez L. The incidence of cancer in patients with rheumatoid arthritis and a prior malignancy who receive TNF inhibitors or rituximab: results from the British Society for Rheumatology Biologics Register-Rheumatoid Arthritis. Rheumatology. 2016;55(11):2033.

PICO 80. Should patients with RA in low disease activity or remission, who are on DMARD(s) and are being treated with a check-point Inhibitor for cancer, stop or continue DMARDs?

P - Patients with RA in low disease activity or remission on DMARD(s), receiving a check-point Inhibitor for cancer

I - Stop DMARDs

C - Continue DMARDs

No eligible RCT, NRS, or indirect evidence were identified.

PICO 81. Should patients with RA with moderate to high disease activity, who are being treated with a check-point Inhibitor for cancer, receive GCs or DMARDs?

P - Patients with RA with moderate to high disease activity receiving a check-point Inhibitor for cancer
I - GCs
C - csDMARDs
C - TNF Inhibitor
C - Abatacept
C - Rituximab
C - IL-6 Receptor Inhibitor
C - JAK Inhibitor

No eligible RCT, NRS, or indirect evidence were identified.

PICO 82. Should patients with RA and low or very low risk of reactivation of Hepatitis B, who are initiating RTX, undergo frequent monitoring or start prophylactic anti-viral therapy?

P - Patients with RA and low or very low risk of reactivation of Hepatitis B, who are initiating RTX

I - Frequent monitoring

C - Prophylactic anti-viral therapy

No direct evidence identified. See below for indirect evidence.

Evidence identified 1: Papalopoulos 2018 [RefID: 913] (1) was retrospective cohort conducted in a single center in Greece (2001-2016 period) that recruited patients with:

- serologic evidence of previous exposure to HBV (serologic evidence of previous exposure to HBV, i.e., HBsAg(-), anti-HBc(+), anti-HBs(±) at baseline. Majority had anti-HBs(+), i.e., resolved infection; minority had anti-HBs(-), i.e., chronic active HBV infection).
- rheumatological diseases (vast majority RA; no further details about RA disease provided). Followed up for 24 months.

Findings:

- 30 RA patients received RTX. 5/30 received anti-viral prophylaxis. 0/30 patient experienced HBV reactivation
- Notes:
    - 69 RA patients received **non-TNFi** (ABA, RTX and TCZ); 7 received antiviral prophylaxis; 1 patient receiving ABA experienced HBV reactivation; successfully treated with entecavir
    - One patient with Cryoglobulinemic vasculitis receiving RTX and prior exposure to cyclophosphamide died

Certainty of evidence very low due to NRS design, serious risk of bias.

Evidence identified 2: Varisco 2016 [RefID: 1546] (2) was a retrospective cohort study conducted in 5 Italian rheumatology departments (time period 2006-2011) and recruited 33 patients with:

- HBsAg-negative/anti-HBc–positive outpatients with undetectable HBV DNA by sensitive PCR assay [85% anti-HBs pos, 37% with antihepatitis B envelope antigen pos]
- RA with a median of 3 cycles of RTX (range1–8) over 34 months (range 0–80) combined with disease-modifying antirheumatic drugs (DMARD) without prophylaxis.

Findings:

- "None of the patients seroreverted to HBsAg during RTX treatment, but 6/28 (21%) showed a > 50% decrease in protective anti-HBs levels, including 2 who became anti-HBs–negative.
- One patient (3%) who became HBV DNA-positive (44 IU/ml) after 6 months of RTX treatment was effectively rescued with lamivudine before any hepatitis flare occurred.
- Among the 14 patients monitored for 18 months (range 0–70) after RTX discontinuation, no HBV reactivation was observed."

Certainty of evidence very low due to NRS design, serious risk of bias.

Cost-effectiveness

No cost-effectiveness data was identified.

References

1. Papalopoulos I. Liver safety of non-tumour necrosis factor inhibitors in rheumatic patients with past hepatitis B virus infection: an observational, controlled, long-term study. Clinical & Experimental Rheumatology. 2018;36(1):102.
2. Varisco V. Low Risk of Hepatitis B Virus Reactivation in HBsAg-negative/Anti-HBc-positive Carriers Receiving Rituximab for Rheumatoid Arthritis: A Retrospective Multicenter Italian Study. Journal of Rheumatology. 2016;43(5):869.

PICO 83. Should patients with RA and low or very low risk of reactivation of Hepatitis B, who are initiating boDMARD or tsDMARD other than RTX, undergo frequent monitoring or start prophylactic anti-viral therapy?

P - Patients with RA and low or very low risk of reactivation of Hepatitis B, who are initiating boDMARD or tsDMARD *other than RTX*

I - Frequent monitoring

C - Prophylactic anti-viral therapy

No direct evidence identified. See below for indirect evidence.

Evidence identified 1: Chen 2017 [RefID: 906] (1) was a cohort study conducted in a single center in China (2013-2016 period), that recruited 7 patients with:

- chronic HBV infection
- RA (moderate to high disease activity, with at least one feature of poor prognosis and inadequate response to conventional synthetic disease-modifying antirheumatic drugs (csDMARDs)).
- Patients received 3 consecutive doses of intravenous **TCZ** were given combined with csDMARDs. Follow up average of 60 weeks.

Findings (Follow up ~ 60 weeks):

- 0 of 2 patients receiving antiviral prophylaxis developed HBV reactivation after TCZ.
- 3 of 5 patients not receiving antiviral prophylaxis developed HBV reactivation after TCZ; reactivation was asymptomatic with normal aminotransferases; their HBV-DNA became undetectable after therapeutic antiviral therapy.

Certainty of evidence very low due to NRS design, very low number of participants

Evidence identified 2: Padovan 2016 [RefID: 1349] (2) was retrospective cohort study conducted in 11 Italian centers, that recruited 72 patients with:

- HBV infection: 47 inactive carriers, 21 occult carriers, and 4 chronic active carriers for HBV.
- RA disease (mean SD DAS28 score 6.44+/-1.5).
- All patients treated with **abatacept**. 17/47 received antiviral prophylaxis.

Findings (follow up 24 months).

- No patients experienced reactivation of hepatitis B. Follow up 24 months.
- Treatment Withdrawal (23 patients) were due to lack of efficacy, subject decision/lost at follow-up, or adverse events not related to HBV infection.

Certainty of evidence very low due to NRS design, serious risk of bias.

Evidence identified 3: Papalopoulos 2018 [RefID: 913] (3) was retrospective cohort conducted in a single center in Greece (2001-2016 period) that recruited patients with:

- serologic evidence of previous exposure to HBV (serologic evidence of previous exposure to HBV, i.e., HBsAg(-), anti-HBc(+), anti-HBs(±) at baseline. Majority had anti-HBs(+), i.e., resolved infection; minority had anti-HBs(-), i.e., chronic active HBV infection).
- rheumatological diseases (vast majority RA; no further details about RA disease provided). Followed up for 24 months.

Findings:

- 59 RA patients received **TNFi** treatment; 1 received antiviral prophylaxis; 0/59 patient experienced HBV reactivation
- 69 RA patients received **non-TNFi** (ABA, RTX and TCZ); 7 received antiviral prophylaxis; 1 patient receiving ABA experienced HBV reactivation; successfully treated with entecavir.
    - 30 RA patients received **RTX**. 5/30 received anti-viral prophylaxis. 0/30 patient experienced HBV reactivation
- Note: One patient with Cryoglobulinemic vasculitis receiving RTX and prior exposure to cyclophosphamide died

Certainty of evidence very low due to NRS design, serious risk of bias.

Evidence Identified 4: Lan 2011 [RefID: 5384] (4) was a retrospective cohort study conducted in a single center in Taiwan (2006-2009 period) that recruited 88 patients with:

- HBcAb-positive, 18 of whom were HBsAg-positive
- RA receiving **anti-TNFα therapy**,

Findings (Follow-up 1year):

- 0/10 patients receiving antiviral prophylaxis developed HBV reactivation
- 5/8 patients not receiving antiviral prophylaxis developed HBV reactivation

Certainty of evidence very low due to NRS design, very low number of participants

Cost-effectiveness

No cost-effectiveness data was identified.

References

1. Chen LF, Mo YQ, Jing. Short-course tocilizumab increases risk of hepatitis B virus reactivation in patients with rheumatoid arthritis: a prospective clinical observation. International Journal of Rheumatic Diseases. 2017;20(7):859.
2. Padovan M. Safety of Abatacept in Rheumatoid Arthritis With Serologic Evidence of Past or Present Hepatitis B Virus Infection. Arthritis care & research. 2016;68(6):738.
3. Papalopoulos I. Liver safety of non-tumour necrosis factor inhibitors in rheumatic patients with past hepatitis B virus infection: an observational, controlled, long-term study. Clinical & Experimental Rheumatology. 2018;36(1):102.
4. Lan JL. Kinetics of viral loads and risk of hepatitis B virus reactivation in hepatitis B core antibody-positive rheumatoid arthritis patients undergoing anti-tumour necrosis factor alpha therapy. Ann Rheum Dis BMJ. 2011;70:1701.

PICO 84. Should patients with RA and moderate to very high risk of reactivation of Hepatitis B, who are initiating boDMARD or tsDMARDs, undergo frequent monitoring or start prophylactic anti-viral therapy?

P - Patients with RA and moderate to very high risk of reactivation of Hepatitis B, who are initiating boDMARD or tsDMARDs

I - Frequent monitoring

C - Prophylactic anti-viral therapy

No direct evidence identified. See below for indirect evidence.

Evidence identified 1: Chen 2017 [RefID: 906] (1) was a cohort study conducted in a single center in China (2013-2016 period), that recruited 7 patients with:

- chronic HBV infection
- RA (moderate to high disease activity, with at least one feature of poor prognosis and inadequate response to conventional synthetic disease-modifying antirheumatic drugs (csDMARDs)).
- Patients received 3 consecutive doses of intravenous **TCZ** were given combined with csDMARDs.

Findings (Follow up ~ 60 weeks):

- 0 of 2 patients receiving antiviral prophylaxis developed HBV reactivation after TCZ.
- 3 of 5 patients not receiving antiviral prophylaxis developed HBV reactivation after TCZ; reactivation was asymptomatic with normal aminotransferases; their HBV-DNA became undetectable after therapeutic antiviral therapy.

Certainty of evidence very low due to NRS design, very low number of participants.

Evidence identified 2: Padovan 2016 [RefID: 1349] (2) was retrospective cohort study conducted in 11 Italian centers, that recruited 72 patients with:

- HBV infection: 47 inactive carriers, 21 occult carriers, and 4 chronic active carriers for HBV.
- RA disease (mean SD DAS28 score 6.44+/-1.5).
- All patients treated with **abatacept**. 17/47 received antiviral prophylaxis.

Findings (follow up 24 months).

- No patients experienced reactivation of hepatitis B.
- Treatment withdrawals (23 patients) were due to lack of efficacy, subject decision/lost at follow-up, or adverse events not related to HBV infection.

Certainty of evidence very low due to NRS design, serious risk of bias.

Evidence identified 3: Lan 2011 [RefID: 5384] (3) was a retrospective cohort study conducted in a single center in Taiwan (2006-2009 period) that recruited 88 patients with:

- HBcAb-positive, 18 of whom were HBsAg-positive
- RA receiving **anti-TNFα therapy**,

Findings (Follow-up 1year):

- 0/10 patients receiving antiviral prophylaxis developed HBV reactivation
- 5/8 patients not receiving antiviral prophylaxis developed HBV reactivation

Certainty of evidence very low due to NRS design, very low number of participants.

Guide to interpreting HBV serology

Test	Result	Interpretation
HBsAg anti-HBc anti-HBs	negative negative negative	Susceptible (vaccinate)
HBsAg anti-HBc anti-HBs	negative positive positive	Resolved HBV infection
HBsAg anti-HBc anti-HBs	negative negative positive	Vaccinated
HBsAg anti-HBc anti-HBs	positive positive negative	Active HBV infection (usually chronic) *If anti-HBc IgM present, may represent acute infection.
HBsAg HBcAb HBsAb	negative positive negative	Various possibilities: distant resolved infection (most common) recovering from acute infection false positive occult hepatitis B

Cost effectiveness

No cost-effectiveness data was identified.

References

1. Chen LF, Mo YQ, Jing. Short-course tocilizumab increases risk of hepatitis B virus reactivation in patients with rheumatoid arthritis: a prospective clinical observation. International Journal of Rheumatic Diseases. 2017;20(7):859.
2. Padovan M. Safety of Abatacept in Rheumatoid Arthritis With Serologic Evidence of Past or Present Hepatitis B Virus Infection. Arthritis care & research. 2016;68(6):738.
3. Lan JL. Kinetics of viral loads and risk of hepatitis B virus reactivation in hepatitis B core antibody-positive rheumatoid arthritis patients undergoing anti-tumour necrosis factor alpha therapy. Ann Rheum Dis BMJ. 2011;70:1701.

PICO 85. Should patients with DMARD-naïve RA and chronic untreated Hepatitis C receive MTX or alternative DMARDs?

P - Patients with DMARD-naïve RA and chronic untreated Hepatitis C
I - MTX
C - Alternative csDMARD mono or combination therapy
C - TNF Inhibitor
C - Abatacept
C - Rituximab
C - IL-6 Receptor Inhibitor
C - JAK Inhibitor

No direct evidence identified. See below for indirect evidence.

Evidence Identified 1: Burton 2017 [RefID: 1199] **(1)** was a retrospective cohort study conducted using the US Veteran's administration electronic health data (1997-2011 time period). The study included 748 unique patients who:

- Had concomitant HCV and RA.
- Could contribute > 1 treatment episode, provided they initiated a new DMARD/biologic or reinitiated a previously prescribed DMARD/biologic with no exposure within 1 year of the index date.
- Contributed 1097 treatment episodes as follows: 156 with MTX, 91 with leflunomide, 393 with sulfasalazine/hydroxychloroquine, 22 with Abatacept, 407 with TNF, 28 with Rituximab.

Findings:

- The third column of the following tables shows the rate of hepatoxic events (increase in serum ALT to > 100 IU/l) per treatment episode:

- Biologic vs. non-biologic 4.8% vs. 2.3%, p = 0.03
- No significant difference among biologic agents
- No significant difference among non-biologics
- No treatment episodes involved an increase of serum HCV RNA of > 1 log IU/l within 12 months of index date

Authors conclusion: In US veterans with HCV and RA receiving biologic and non-biologic DMARD, the frequency of hepatotoxicity (ALT ≥ 100 IU/l) was low, with a higher frequency observed in treatment episodes with current biologic use.

Certainty of the evidence very low given NRS design and high risk of bias

Table 2. Surveillance for hepatotoxicity during followup period among treatment episodes[1]. Values are n (%) unless otherwise specified.

Drug	Treatment Episodes, n	Cumulative Events Within 12 Mos[2]	Episodes in Which Any ALT Testing Occurred During Followup Period			Event Rates for Hepatotoxicity		
			0–3 Mos[3]	3–6 Mos[3]	6–12 Mos[3]	0–3 Mos Events[4]	3–6 Mos Events[4]	6–12 Mos Events[4]
Biologic agents	457	22 (4.8)	398 (87.1)	362 (79.2)	425 (93.0)	8 (1.8)	10 (2.2)	4 (0.9)
ABA	22	1 (4.5)	19 (86.4)	19 (86.4)	21 (95.5)	0 (0)	1 (4.6)	0 (0)
ADA	180	8 (4.4)	151 (83.9)	146 (81.1)	168 (93.3)	3 (1.7)	4 (2.2)	1 (0.6)
ETN	179	10 (5.6)	156 (87.2)	138 (77.1)	167 (93.3)	4 (2.2)	3 (1.7)	3 (1.7)
IFX	48	2 (4.2)	45 (93.8)	37 (77.1)	44 (91.7)	0 (0)	2 (4.2)	0 (0)
RTX	28	1 (3.6)	27 (96.4)	22 (78.6)	25 (89.3)	1 (3.6)	0 (0)	0 (0)
Nonbiologic agents	640	15 (2.3)	540 (84.4)	482 (75.3)	568 (88.8)	6 (0.9)	5 (0.8)	4 (0.6)
LEF	91	2 (2.2)	80 (87.9)	79 (86.8)	80 (87.9)	1 (1.1)	1 (1.1)	0 (0)
MTX	156	6 (3.8)	140 (89.7)	120 (76.9)	138 (88.5)	0 (0)	4 (2.6)	2 (1.3)
SSZ-HCQ	393	7 (1.8)	320 (81.4)	283 (72.0)	350 (89.1)	5 (1.3)	0 (0)	2 (0.5)
Total	1097	37 (3.4)	938 (85.5)	844 (76.9)	993 (90.5)	14 (1.5)	15 (1.8)	8 (0.8)

[1] No episodes met the HCV RNA definition for hepatotoxicity within the 12-month followup period. [2] Hepatotoxic events in time period divided by treatment episodes for drug listed in row. [3] Represents episodes that had at least 1 ALT test performed in given followup time period. Summation of 3 columns will exceed the total episodes because an ALT could be performed in all 3 followup periods, unless censoring occurred (failure or end of followup period). [4] Event rate % equals the number of hepatotoxicity events in time period divided by the number of ALT tests performed in same time period for drug row. ALT: alanine aminotransferase; ABA: abatacept; ADA: adalimumab; ETN: etanercept; IFX: infliximab; RTX: rituximab; LEF: leflunomide; MTX: methotrexate; SSZ-HCQ: sulfasalazine/hydroxychloroquine; COPD: chronic obstructive pulmonary disease; HCV: hepatitis C virus.

Cost-effectiveness

No cost-effectiveness data was identified.

References

1. Burton MJ, J.R. C, Yang S, Chen. Safety of Biologic and Nonbiologic Disease-modifying Antirheumatic Drug Therapy in Veterans with Rheumatoid Arthritis and Hepatitis C Virus Infection. Journal of Rheumatology. 2017;44(5):565.

PICO 86. Should patients with RA with an inadequate response to csDMARDs, and who have chronic untreated Hepatitis C, receive a TNF Inhibitor or a boDMARD targeting a different molecule or a tsDMARD?

P - Patients with RA with inadequate response to csDMARDs, and who have chronic untreated Hepatitis
I - TNF Inhibitor
C - Abatacept
C - Rituximab
C - IL-6 Receptor Inhibitor
C - JAK Inhibitor

No direct evidence identified. See below for indirect evidence.

Evidence Identified 1: Burton 2017 [RefID: 1199] **(1)** was a retrospective cohort study conducted using the US Veteran's administration electronic health data (1997-2011 time period). The study included 748 unique patients who:

- Had concomitant HCV and RA.
- Could contribute > 1 treatment episode, provided they initiated a new DMARD/biologic or reinitiated a previously prescribed DMARD/biologic with no exposure within 1 year of the index date.
- Contributed 1097 treatment episodes as follows: 156 with MTX, 91 with leflunomide, 393 with sulfasalazine/hydroxychloroquine, 22 with Abatacept, 407 with TNF, 28 with Rituximab.

Findings:

- The third column of the following tables shows the rate of hepatoxic events (increase in serum ALT to > 100 IU/l) per treatment episode:
  - Biologic vs. non-biologic 4.8% vs. 2.3%, p = 0.03
  - No significant difference among biologic agents
  - No significant difference among non-biologics
  - No treatment episodes involved an increase of serum HCV RNA of > 1 log IU/l within 12 months of index date

Authors conclusion: In US veterans with HCV and RA receiving biologic and non-biologic DMARD, the frequency of hepatotoxicity (ALT ≥ 100 IU/l) was low, with a higher frequency observed in treatment episodes with current biologic use.

Certainty of the evidence very low given NRS design and high risk of bias.

Table 2. Surveillance for hepatotoxicity during followup period among treatment episodes[1]. Values are n (%) unless otherwise specified.

Drug	Treatment Episodes, n	Cumulative Events Within 12 Mos[2]	Episodes in Which Any ALT Testing Occurred During Followup Period			Event Rates for Hepatotoxicity		
			0–3 Mos[3]	3–6 Mos[3]	6–12 Mos[3]	0–3 Mos Events[4]	3–6 Mos Events[4]	6–12 Mos Events[4]
Biologic agents	457	22 (4.8)	398 (87.1)	362 (79.2)	425 (93.0)	8 (1.8)	10 (2.2)	4 (0.9)
ABA	22	1 (4.5)	19 (86.4)	19 (86.4)	21 (95.5)	0 (0)	1 (4.6)	0 (0)
ADA	180	8 (4.4)	151 (83.9)	146 (81.1)	168 (93.3)	3 (1.7)	4 (2.2)	1 (0.6)
ETN	179	10 (5.6)	156 (87.2)	138 (77.1)	167 (93.3)	4 (2.2)	3 (1.7)	3 (1.7)
IFX	48	2 (4.2)	45 (93.8)	37 (77.1)	44 (91.7)	0 (0)	2 (4.2)	0 (0)
RTX	28	1 (3.6)	27 (96.4)	22 (78.6)	25 (89.3)	1 (3.6)	0 (0)	0 (0)
Nonbiologic agents	640	15 (2.3)	540 (84.4)	482 (75.3)	568 (88.8)	6 (0.9)	5 (0.8)	4 (0.6)
LEF	91	2 (2.2)	80 (87.9)	79 (86.8)	80 (87.9)	1 (1.1)	1 (1.1)	0 (0)
MTX	156	6 (3.8)	140 (89.7)	120 (76.9)	138 (88.5)	0 (0)	4 (2.6)	2 (1.3)
SSZ-HCQ	393	7 (1.8)	320 (81.4)	283 (72.0)	350 (89.1)	5 (1.3)	0 (0)	2 (0.5)
Total	1097	37 (3.4)	938 (85.5)	844 (76.9)	993 (90.5)	14 (1.5)	15 (1.8)	8 (0.8)

[1] No episodes met the HCV RNA definition for hepatotoxicity within the 12-month followup period. [2] Hepatotoxic events in time period divided by treatment episodes for drug listed in row. [3] Represents episodes that had at least 1 ALT test performed in given followup time period. Summation of 3 columns will exceed the total episodes because an ALT could be performed in all 3 followup periods, unless censoring occurred (failure or end of followup period). [4] Event rate % equals the number of hepatotoxicity events in time period divided by the number of ALT tests performed in same time period for drug row. ALT: alanine aminotransferase; ABA: abatacept; ADA: adalimumab; ETN: etanercept; IFX: infliximab; RTX: rituximab; LEF: leflunomide; MTX: methotrexate; SSZ-HCQ: sulfasalazine/hydroxychloroquine; COPD: chronic obstructive pulmonary disease; HCV: hepatitis C virus.

Evidence identified 2: Chen 2015 [RefID: 2939] **(2)** was a retrospective cohort study (1997-2011 time period).
Included participants who:

- Had concomitant HCV infection and RA
- Treated with anti-TNF-α (n= 20 patients: etanercept n=12; adalimumab n=6; and golimumab n=2), or RTX (n=6).

Findings:
Authors reported a statistically significant difference in changes of HCV viral load between anti-TNF-α treatment and RTX therapy (figure 1C, p=0.003), where the HCV viral load increased after RTX therapy but not after anti-TNF-α treatment.

Certainty of evidence very low due to NRS design, risk of bias, and imprecision.

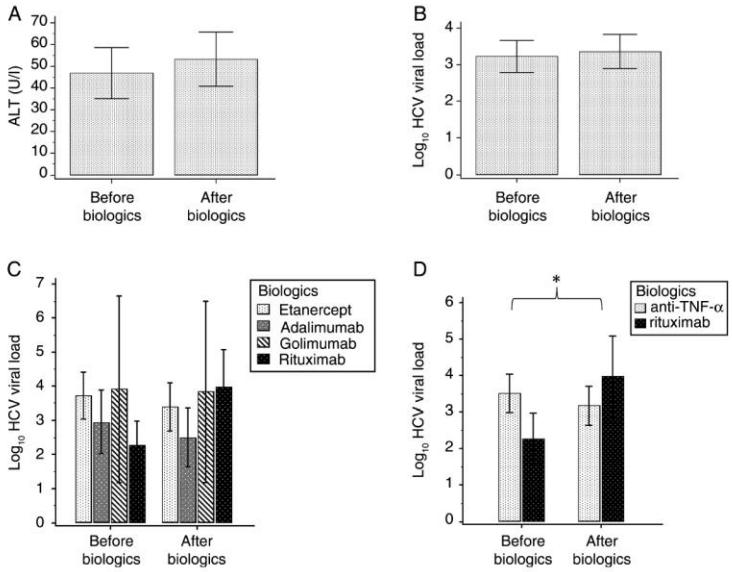


Figure 1 Comparisons of (A) serum alanine aminotransferase (ALT) and (B) hepatitis C virus (HCV) viral load before and after biological therapy by Wilcoxon signed-rank test. Biological treatments were categorised by (C) individual biologics and (D) mechanism of action. Data are mean±1 SEM. HCV viral loads were expressed as $\log_{10}$ of the detected values. *p=0.003 by generalised estimating equation.

Cost-effectiveness

No cost-effectiveness data identified.

References

1. Burton MJ, J.R. C, Yang S, Chen. Safety of Biologic and Nonbiologic Disease-modifying Antirheumatic Drug Therapy in Veterans with Rheumatoid Arthritis and Hepatitis C Virus Infection. Journal of Rheumatology. 2017;44(5):565.
2. Chen YM. A comparison of safety profiles of tumour necrosis factor α inhibitors and rituximab therapy in patients with rheumatoid arthritis and chronic hepatitis C. Ann Rheum Dis BMJ. 2015;74(3):626-7.

PICO 87. Should patients with RA and NAFLD or NASH receive MTX or alternative DMARDs?

P - patients with DMARD-naïve RA and NAFLD or NASH
I - MTX
C - Alternative DMARDs
C - TNF Inhibitor
C - Abatacept
C - Rituximab
C - IL-6 Receptor Inhibitor
C - JAK Inhibitor

No eligible RCT, NRS, or indirect evidence were identified.

PIOC 88. Should patients with RA with inadequate response to MTX and/or LEF, who have moderate to high disease activity and a prior serious infection within 3 years, add HCQ and SSZ or a boDMARD or tsDMARD?

P - Patients with RA with inadequate response to MTX and/or LEF, moderate to high disease activity, and a prior serious infection within 3 years
I - Add SSZ and HCQ
C - Add TNF Inhibitor
C - Add Abatacept
C - Add Rituximab
C - Add IL-6 Receptor Inhibitor
C - Add JAK Inhibitor

No eligible RCT, NRS, or indirect evidence were identified.

PICO 89. Should patients with RA with inadequate response to csDMARDs, who have moderate to high disease activity and a prior serious infection within 3 years, receive abatacept or a boDMARD targeting a different molecule or a tsDMARD?

P - Patients with RA with inadequate response to csDMARDs, moderate to high disease activity, and a prior serious infection within 3 years

I - Abatacept

C - TNF Inhibitor

C - Rituximab

C - IL-6 Receptor Inhibitor

C - JAK Inhibitor

No direct evidence identified. See below for indirect evidence.

Evidence identified 1: Accortt 2016 [RefID: 2324] (1) was a retrospective cohort was conducted based on a US database (2006-2011 period). It included 21,699 patients who had experienced a serious infection, the majority of whom (84%) had RA.

Follow up was up to 18 months post-index infection, starting 60 days post-index.

The authors concluded that there was no observed "increased risk of subsequent infection in patients who received TNF inhibitor treatment following a serious infection. The risk of a subsequent serious infection was lower in patients treated with both a TNF inhibitor and a non-biologic DMARD compared with that in patients treated with a non-biologic DMARD alone."
Very low certainty evidence due to NRS design, and indirectness.

Table 2. Rates of subsequent infection according to drug class level and drug level*

	Without 1-month exposure extension		
	Patient-years	No. of recurrent infections	Subsequent infection rate per 100 patient-years
Drug class level			
No current systemic treatment	5,045.9	845	16.7
Nonbiologic DMARD alone	10,640.3	2,274	21.4
TNF inhibitor alone	4,029.9	731	18.1
TNF inhibitor + nonbiologic DMARD	3,660.8	633	17.3
Other biologic agent alone	422.3	73	17.3
Other biologic agent + nonbiologic DMARD	464.9	102	21.9
Drug level			
Nonbiologic DMARD alone	10,640.3	2,274	21.4
Etanercept + nonbiologic DMARD	1,426.2	235	16.5
Etanercept alone	2,210.3	365	16.5
Adalimumab + nonbiologic DMARD	1,224.7	215	17.6
Adalimumab alone	986.9	187	18.9
Infliximab + nonbiologic DMARD	900.6	161	17.9
Infliximab alone	730.6	162	22.2
Golimumab + nonbiologic DMARD	68.5	8	11.7
Golimumab alone	63.3	10	15.8
Certolizumab + nonbiologic DMARD	40.9	14	34.2
Certolizumab alone	38.9	7	18.0
Abatacept + nonbiologic DMARD	297.0	64	21.5
Abatacept alone	214.1	43	20.1
Rituximab + nonbiologic DMARD	123.1	33	26.8
Rituximab alone	104.8	20	19.1
Tocilizumab + nonbiologic DMARD	43.3	5	11.6
Tocilizumab alone	32.7	5	15.3
Ustekinumab	72.3	5	6.9

* DMARD = disease-modifying antirheumatic drug; TNF = tumor necrosis factor.

Evidence identified 2: Yun 2015 [RefID: 3086] (2) was a retrospective cohort based on Medicare data (2006-2010 period). Included RA patients hospitalized with an infection while on anti-TNF agents. There were 10,794 eligible hospitalized infections. Follow up started 61 days after hospital discharge to assess the subsequent risk of hospitalized infections.

Findings:

- "After multivariable adjustment, abatacept (hazard ratio (HR): 0.80, 95% CI: 0.64-0.99) and etanercept (HR: 0.83, 95% CI: 0.72-0.96) users had significantly lower risks of a subsequent infection compared to infliximab users."
- Absolute incidence rates (IRs) and pairwise comparison of each biologic* to every other for subsequent hospitalized infection. Values in the cross cells provide adjusted hazard ratios with 95% CI.

Very low certainty evidence due to NRS design, and indirectness.

Biologies	**Referent Group**				
	Infliximab	**Adalimumab**	**Etanercept**	**Rituximab**	**Abatacept**
Crude IR Per 100 years (n/pys†)	**33.8 (1,382/4,087)**	**34.9 (497/1,423)**	**36.1 (661/1,831)**	**28.5 (38/133)**	**26.5 (88/333)**
Adjusted HR (95% CI) ‡					
Abatacept	**0.80 (0.64-0.99)**	0.88 (0.68-1.12)	0.97 (0.76-1.23)	0.93 (0.64-1.36)	1.0 (Ref)
Rituximab	0.87 (0.63-1.20)	0.94 (0.67-1.32)	1.04 (0.74-1.46)	1.0 (Ref)	
Etanercept	**0.83 (0.72-0.97)**	0.91 (0.76-1.08)	1.0 (Ref)		
Adalimumab	0.92 (0.79-1.09)	1.0 (Ref)			
Infliximab	1.0 (Ref)				

Cost-effectiveness

No cost-effectiveness data was identified.

References

1. Accortt NA. Risk of Subsequent Infection Among Patients Receiving Tumor Necrosis Factor Inhibitors and Other Disease-Modifying Antirheumatic Drugs. ARTHRITIS & RHEUMATOLOGY. 2016;68(1):67-76.
2. Yun H. Risk of Hospitalized Infection in Rheumatoid Arthritis Patients Receiving Biologics Following a Previous Infection While on Treatment with Anti-TNF Therapy. Ann Rheum Dis. 2015;74(6):1965-071.

PICO 90. Should patients with RA with inadequate response to csDMARDs, who have moderate to high disease activity and a prior serious infection within 3 years, receive low dose GCs (≤ 10mg per day) or a boDMARD or tsDMARD?

P - Patients with RA with inadequate response to csDMARDs, moderate to high disease activity, and a prior serious infection within 3 years

I - Low dose GCs (≤ 10mg/day)

C -TNF Inhibitor

C - Abatacept

C - Rituximab

C - IL-6 Receptor Inhibitor

C - JAK Inhibitor

No eligible RCT, NRS, or indirect evidence were identified.

PICO 91. Should patients with RA with inadequate response to csDMARDs, who have moderate to high disease activity and a prior serious infection within 3 years, on low dose GCs (≤ 10mg per day), receive GCs 11-20mg per day or a boDMARD or tsDMARD?

P - Patients with RA with inadequate response to csDMARDs, moderate to high disease activity, a prior serious infection within 3 years, and on low dose GCs (≤10mg per day)
I - GCs 11-20mg per day
C - TNF Inhibitor
C - Abatacept
C - Rituximab
C - IL-6 Receptor Inhibitor
C - JAK Inhibitor

No eligible RCT, NRS, or indirect evidence were identified.

PICO 92. Should patients with RA with inadequate response to MTX and/or LEF, who have moderate to high disease activity and are on treatment for MAC, add HCQ and SSZ or a boDMARD or tsDMARD?

P - Patients with RA with inadequate response to MTX and/or LEF, moderate to high disease activity, on treatment for MAC
I - Add SSZ and HCQ
C - TNF Inhibitor
C - Abatacept
C - Rituximab
C - IL-6 Receptor Inhibitor
C - JAK Inhibitor

No eligible RCT, NRS, or indirect evidence were identified.

PICO 93. Should patients with RA with inadequate response to csDMARDs, who have moderate to high disease activity and are on treatment for MAC, receive a TNF Inhibitor or a boDMARD targeting a different molecule or a tsDMARD?

P - Patients with RA with inadequate response to csDMARDs, moderate to high disease activity, on treatment for MAC
I - TNF Inhibitor
C - Abatacept
C - Rituximab
C - IL-6 Receptor Inhibitor
C - JAK Inhibitor

No eligible RCT, NRS, or indirect evidence were identified.

PICO 94. Should patients with RA with inadequate response to csDMARDs, who have moderate to high disease activity and are on treatment for MAC, receive low dose GCs (≤ 10mg per day) or a boDMARD or tsDMARD?

P - Patients with RA with inadequate response to csDMARDs, moderate to high disease activity, on treatment for MAC
I - GCs ≤ 10mg per day
C - TNF Inhibitor
C - Abatacept
C - Rituximab
C - IL-6 Receptor Inhibitor
C - JAK Inhibitor

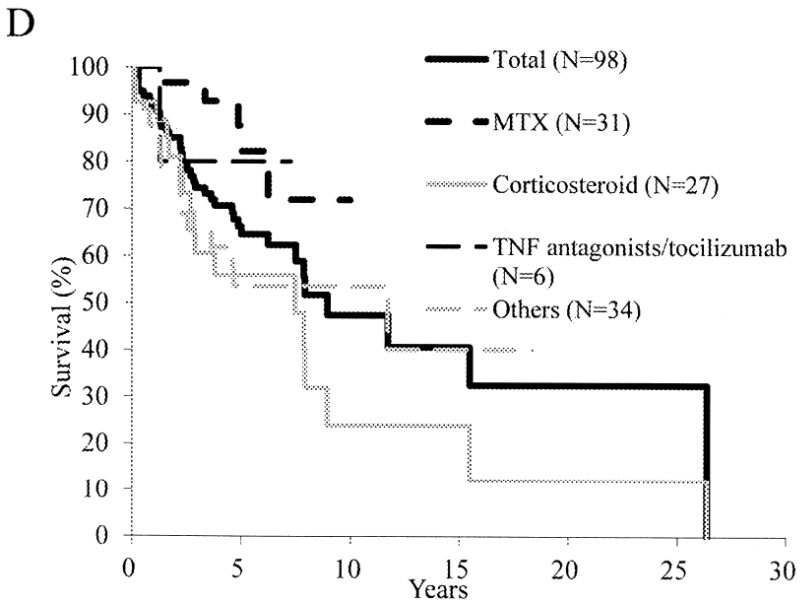
No direct evidence identified. See below for indirect evidence.

Evidence identified 1: Yamakawa 2013 [RefID: 15641] (1) was a retrospective cohort study conducted in a single center in Japan (1993-2011 time period) and included 98 patients HIV-negative with RA and nontuberculous mycobacterial (NTM) lung disease.

Findings:

Table 3. Factors associated with risk of all-cause mortality in the s

Variable	Univariate Cox Regression Crude HR (95% CI)	p
Sex		
Female	Reference	—
Male	1.975 (1.032–3.780)	0.040
Age		
< 70 yrs	Reference	—
≥ 70 yrs	2.561 (1.302–5.040)	0.006
Smoking status		
Never smoker	Reference	—
Ex/current smoker	1.501 (0.775–2.907)	0.229
Respiratory comorbidity		
None	Reference	< 0.001††
UIP	8.013 (3.176–20.216)	< 0.001
Pulmonary emphysema	5.812 (2.091–16.154)	< 0.001
Previous pulmonary tuberculosis	1.960 (0.506–7.602)	0.330
Bronchiolitis	2.090 (0.441–9.911)	0.353
Others	3.372 (1.096–10.380)	0.034
Systemic comorbidity		
None	Reference	—
Some	1.192 (0.624–2.279)	0.595
Antirheumatic drugs		
MTX	Reference	0.090††
Corticosteroid	3.597 (1.303–9.926)	0.013
TNF antagonists/ tocilizumab	1.383 (0.161–11.859)	0.767
Others	2.700 (0.965–7.551)	0.058



(D) patients who received methotrexate (MTX) at NTM diagnosis (MST) not reached) or who received corticosteroid (MST 7.48 yrs; p = 0.022) or other drugs (MST 11.70 yrs; p = 0.024). MST: median survival time

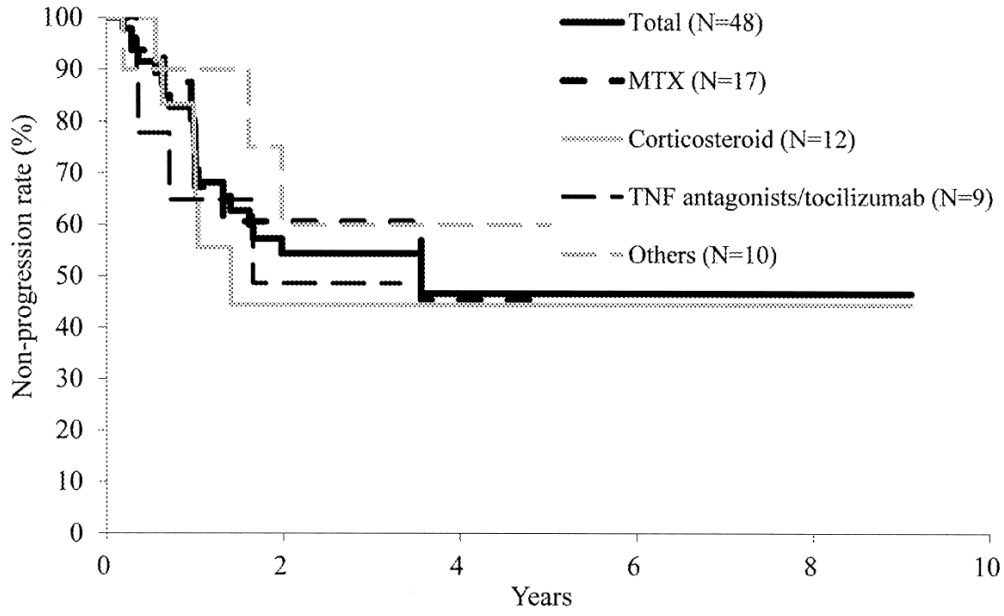


Figure 2. Kaplan-Meier survival curves for time to radiologic progression stratified by antirheumatic drugs. There were no significant differences in time to radiologic progression according to the antirheumatic drugs received during the nontuberculous mycobacteriosis followup period; median times to progression were 3.56, 1.40, and 1.66 years in the methotrexate (MTX), corticosteroid, and tumor necrosis factor (TNF) antagonists/tocilizumab groups, respectively.

Authors conclusion: The difference in survival curves between patients receiving MTX and corticosteroid was significant and may be because patients receiving MTX had nodular/bronchiectatic (NB) disease more frequently than did patients receiving corticosteroids.

Certainty of evidence very low due to NRS, risk of bias, imprecision.

Cost-effectiveness

No cost-effectiveness data was identified.

References

1. Yamakawa H. Prognostic factors and radiographic outcomes of nontuberculous mycobacterial lung disease in rheumatoid arthritis. Journal of Rheumatology. 2013;40(8):1307.

PICO 95. Should patients with RA with inadequate response to csDMARDs, on low dose GCs (≤ 10mg per day) who have moderate to high disease activity and are on treatment for MAC, receive GCs 11-20mg/day, boDMARD or tsDMARD?

P - Patients with RA with inadequate response to csDMARDs, on low dose GCs (≤ 10mg per day), moderate to high disease activity, on treatment for MAC
I - GCs 11-20mg/day
C - TNF Inhibitor
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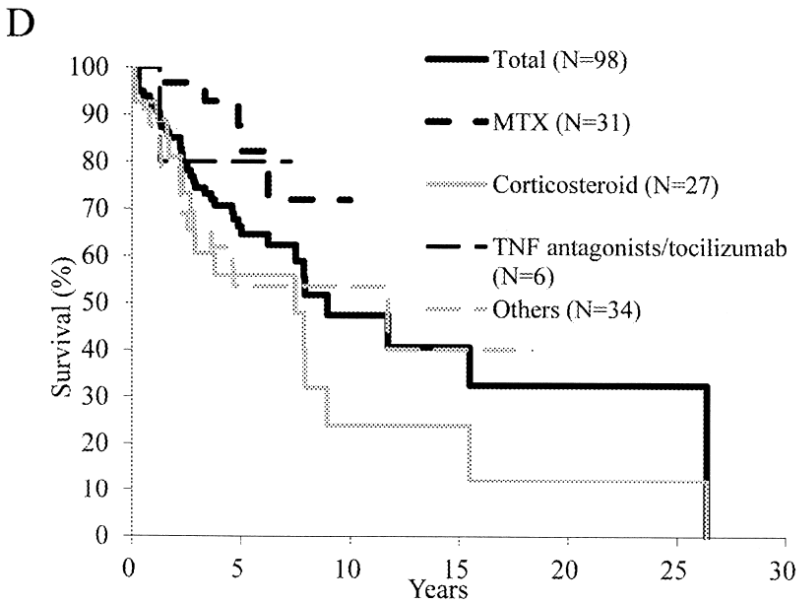

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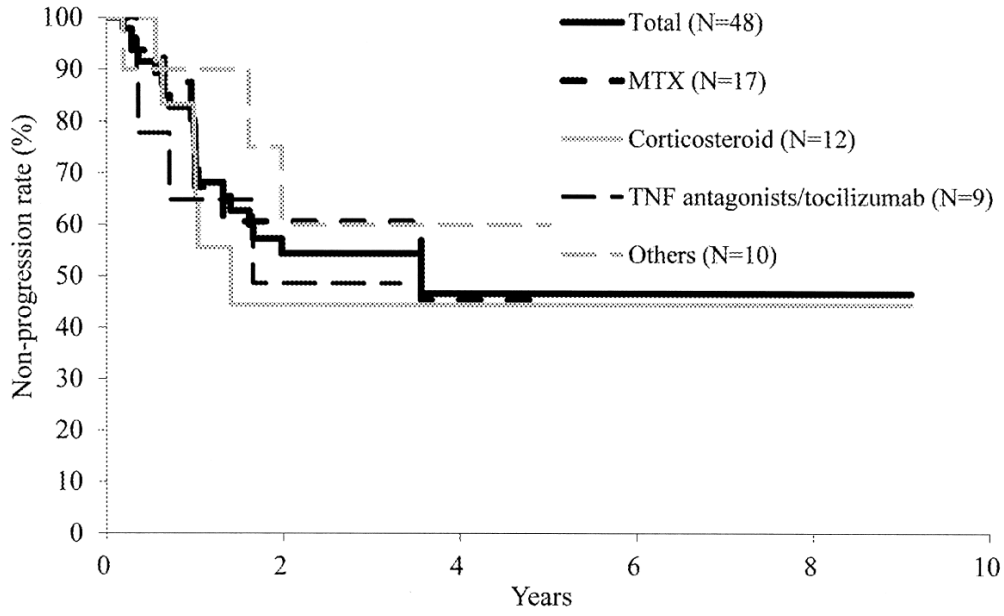

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