PICO 4 - ARE tsDMARD (JAK INHIBITORS) MORE EFFECTIVE FOR THE TREATMENT OF PATIENTS WITH RA COMPARED TO csDMARD?

The search for evidence was carried out in the virtual scientific information bases using the search strategies:

1. Medline/PubMed:

(((Methotrexate OR Immunosuppressive Agents OR Antirheumatic Agents OR Leflunomide OR Sulfasalazine OR Sulfasalazin OR Sulphasalazine OR Chloroquine OR Chlorochin OR Hydroxychloroquine))) AND ((((Arthritis, Rheumatoid OR Rheumatoid Arthritis OR Sjogren's Syndrome OR Caplan Syndrome OR Felty Syndrome OR Rheumatoid Nodule OR Rheumatoid Vasculitis OR Still Disease OR Arthritis, Juvenile OR Juvenile Arthritis OR Polyarthritis, Juvenile) AND (JAK inhibitor OR JAK inhibitors OR Janus Kinases Inhibitors OR Janus Kinase Inhibitors OR Upadacitinib OR Protein Kinase Inhibitors OR Tofacitinib OR Baricitinib))))

2. CENTRAL (Cochrane):

(Methotrexate OR Immunosuppressive Agents OR Antirheumatic Agents OR Leflunomide OR Sulfasalazine OR Sulfasalazin OR Sulphasalazine OR Chloroquine OR Chlorochin OR Hydroxychloroquine) AND (Arthritis, Rheumatoid OR Rheumatoid Arthritis OR Sjogren's Syndrome OR Caplan Syndrome OR Felty Syndrome OR Rheumatoid Nodule OR Rheumatoid Vasculitis OR Still Disease OR Arthritis, Juvenile OR Juvenile Arthritis OR Polyarthritis, Juvenile) AND (JAK inhibitor OR JAK inhibitors OR Janus Kinases Inhibitors OR Janus Kinase Inhibitors OR Upadacitinib OR Protein Kinase Inhibitors OR Tofacitinib OR Baricitinib)

3. EMBASE:

#5. #4 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)

#4. #1 AND #2 AND #3

#3. ((((jak AND inhibitor OR jak) AND inhibitors OR janus) AND kinases AND inhibitors OR janus) AND kinase AND inhibitors OR upadacitinib OR protein) AND kinase AND inhibitors OR tofacitinib OR baricitinib

#2. ((((((((((arthritis, AND rheumatoid OR rheumatoid) AND arthritis OR sjogrens) AND syndrome OR caplan) AND syndrome OR felty) AND syndrome OR rheumatoid) AND nodule OR rheumatoid) AND vasculitis OR still) AND disease OR arthritis,) AND juvenile OR juvenile) AND arthritis OR polyarthritis,) AND juvenile

#1. (('methotrexate'/exp OR methotrexate OR immunosuppressive) AND agents OR 'antirheumatic'/exp OR antirheumatic) AND agents OR 'leflunomide'/exp OR leflunomide OR 'sulfasalazine'/exp OR sulfasalazine OR sulfasalazin OR 'sulphasalazine'/exp OR sulphasalazine OR 'chloroquine'/exp OR chloroquine OR 'chlorochin'/exp OR chlorochin OR 'hydroxychloroquine'/exp OR hydroxychloroquine

Searches ended on January 11, 2020.

RESULTS

Figure 1 shows the selection of retrieved papers. The included studies are in Table 1.

Figure 01 - FLOW DIAGRAM

The selection of works retrieved from the virtual databases of scientific information is detailed in the flowchart below:

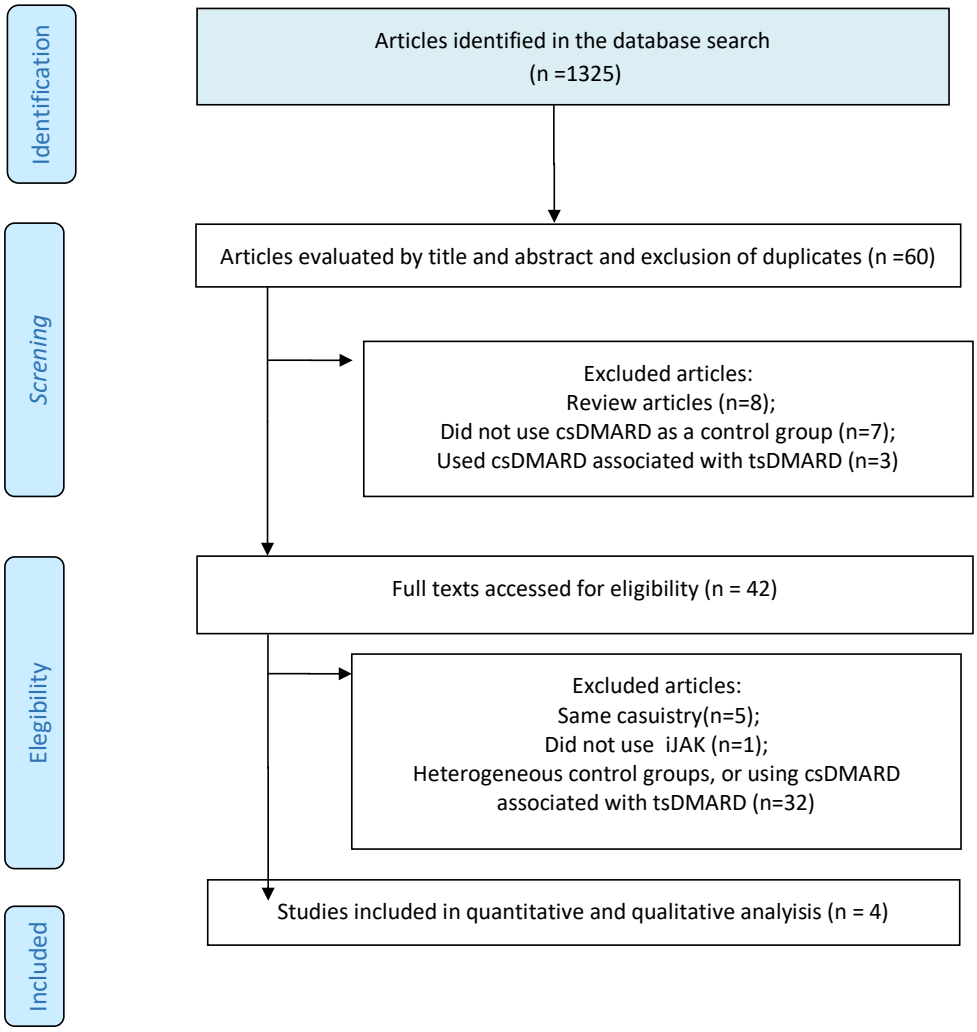


Table 1. Characteristics of the included studies

Study	Design	Follow up	Intervention / dose (mg) / N	Control / N
Conaghan PG, 2016	RCT	12 months	Tofacitinib 10 /36	MTX/ 37
Lee EB, 2014	RCT	24 months	Tofacitinib 5 - 10/373	MTX/ 186
Fleischmann R, 2017	RCT	12 months	Baricitinib 4 /159	MTX/ 210
van Vollenhoven R, 2020	RCT	6 months	Upadacitinib 15- 30 /317-314	MTX/ 314

Risk of bias

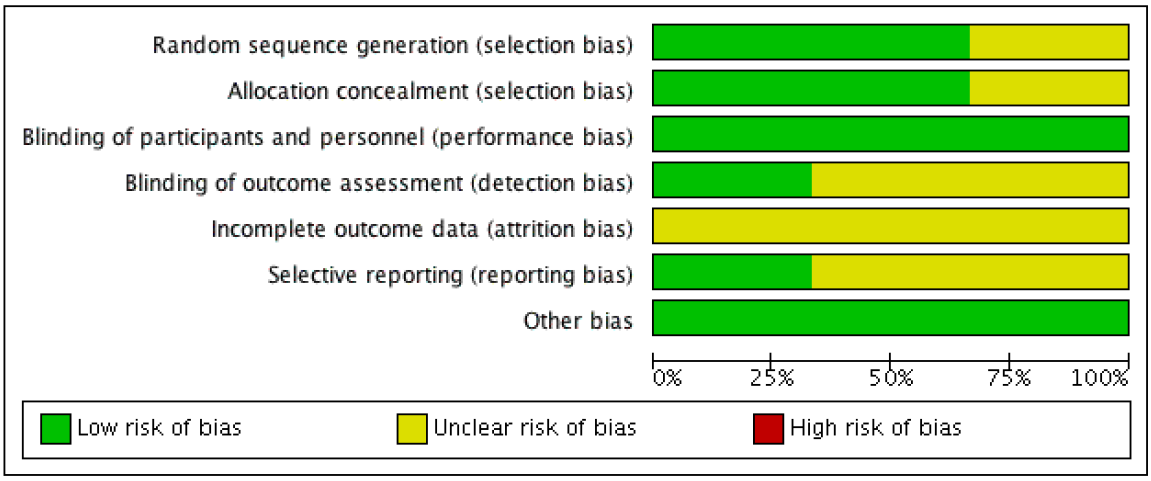
Regarding the risk of bias of the 4 included studies, the studies generally presented a low risk of bias. The 4 studies showed loss of follow-up of a small portion of the studied population (<20%). The certainty rating is high (Table 2 and Figure 2).

Table 2. Certainty assessment **(GRADE)-** tsDMARD effectiveness in comparison with csDMARD**.**

Certainty assessment						
N (Studies)	Bias risk	Inconsistencies	Indirect evidence	Imprecision	Publication Bias	

Certainty assessment						
						Certainty of the evidence (GRADE)
1946 (4 RCT)	Non serious	Non serious	Non serious	Non serious	None	⊕⊕⊕⊕ HIGH

Figure 2. Description of the biases of the included studies



Efficacy

Tofacitinib vs. MTX

The efficacy of Tofacitinib was compared with MTX in 2 ECR3, 4, demonstrating superiority for the clinical outcomes ACR 20, ACR 50, ACR 70, DAS 28 (<2.6 and ≤ 3.2). See table 3.

For Tofacitinib 5 mg twice daily3, the clinical response assessed by the ACR 20 at 6 and 12 months was 71.3 and 67.8%, respectively (p<0.001 compared to MTX of 50.5 and 51.1%, respectively). The clinical response assessed using the ACR 50 at 6 and 12 months was 46.6 and 49.9%, respectively (p<0.001 compared to MTX of 26.6 and 33.7%, respectively). The clinical response assessed using the ACR 70 at 6 and 12 months was 25.5 and 28.7%, respectively (p<0.001 compared to MTX of 12 and 15.2%, respectively). The proportion of patients with low disease activity (DAS28≤3.2) was higher with Tofacitinib 5 mg twice daily at 6 and 12 months, 27.8 and 33.3%, respectively (p<0.001 compared to MTX of 14 and 18.7%, respectively). The proportion of patients with disease remission (DAS28<2.6) was higher with Tofacitinib 5 mg twice daily at 6 and 12 months, 14.6 and 18.7%, respectively (p≤0.05 compared to MTX of 7.6 and 11.7%, respectively).The group of patients using Tofacitinib (10 mg twice a day) compared to MTX had a higher proportion of ACR 20 in 6 months (Hazard difference: 0.25; 95% CI: 0.17 to 0.32; p<0.001; fixed model ; I2: 0) and in 12 months (Difference in risk: 0.24; 95% CI: 0.16 to 0.31; p<0.001; fixed model; I2: 40%). See figures 3 and 4.

Figure 3. Efficacy. Tofacitinib vs. MTX. ACR 20 (6 months)

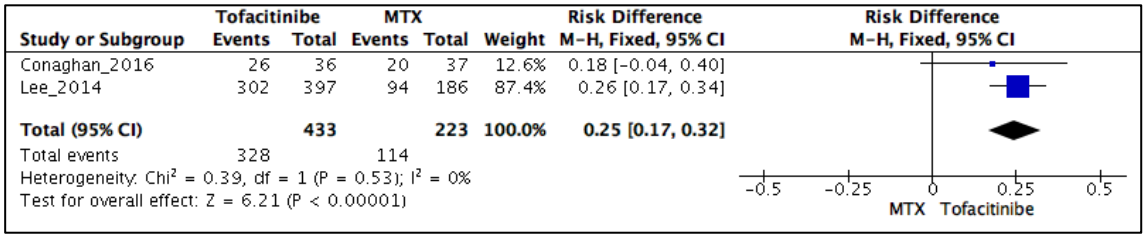
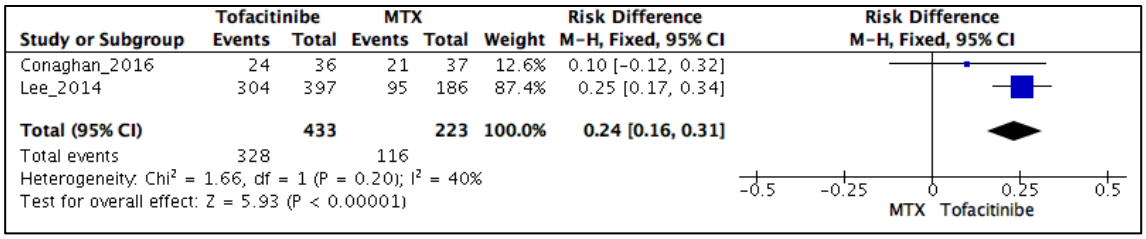


Figure 4. Efficacy. Tofacitinib vs. MTX. ACR 20 (12 months)



The group of patients using Tofacitinib (10 mg twice a day) compared to MTX had a higher proportion of ACR 50 in 6 months (Hazard difference: 0.30; 95% CI: 0.22 to 0.37; p<0.001; fixed model ; I2: 0) and in 12 months (Difference in risk: 0.21; 95% CI: 0.13 to 0.29; p<0.001; fixed model; I2: 0). See figures 5 and 6.

Figure 5. Efficacy. Tofacitinib vs. MTX. ACR 50 (6 months)

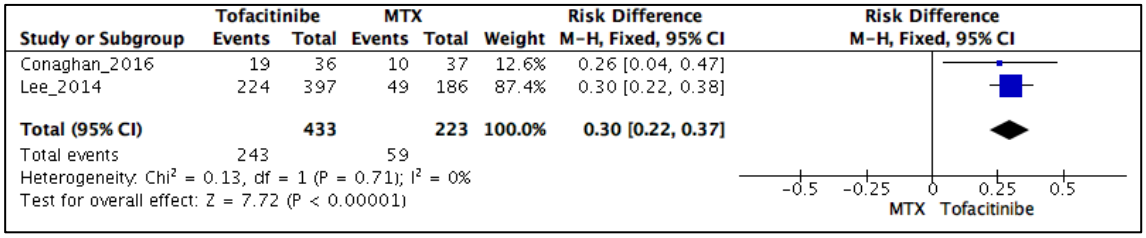
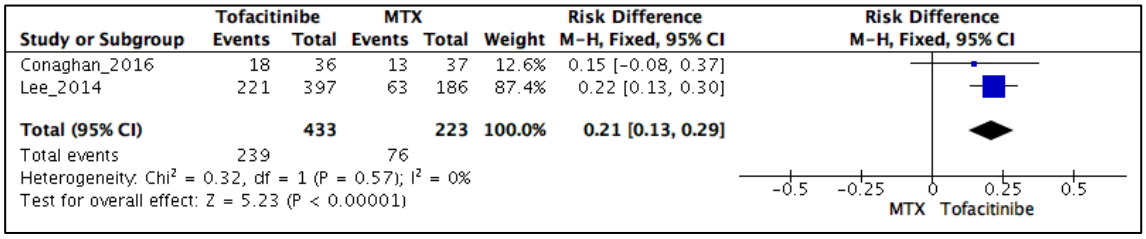


Figure 6. Efficacy. Tofacitinib vs. MTX. ACR 50 (12 months)



The group of patients using Tofacitinib (10 mg twice a day) compared to MTX had a similar proportion of ACR 70 at 6 months (Hazard difference: 0.19; 95% CI: -0.00 to 0.37; p=0.05; model random; I2: 69%), but at 12 months the proportion in patients in the Tofacitinib group was higher (Difference in risk: 0.21; 95% CI: 0.15 to 0.28; p<0.001; fixed model; I2: 37%). See figures 7 and 8.

Figure 7. Efficacy. Tofacitinib vs. MTX. ACR 70 (06 months)

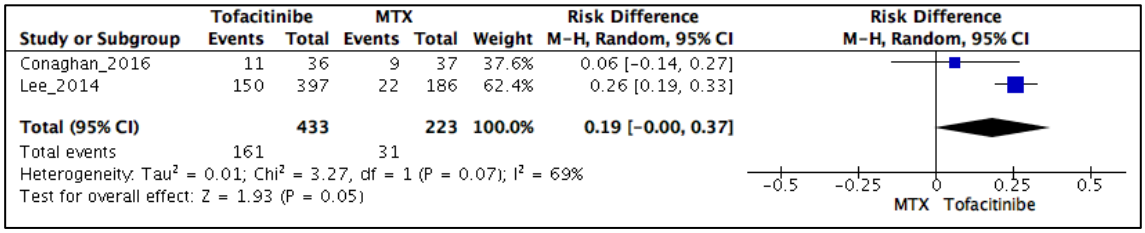
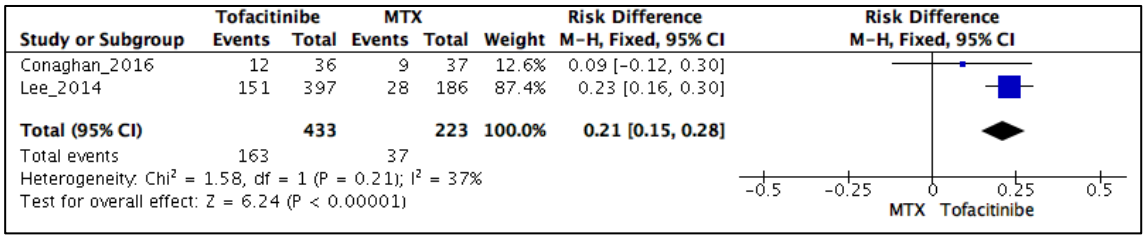


Figure 8. Efficacy. Tofacitinib vs. MTX. ACR 70 (12 months)



The group of patients using Tofacitinib (10 mg twice a day) compared to MTX had a higher proportion of patients with low disease activity (DAS28≤3.2) at 6 months (risk difference: 0.18; 95% CI: 0.01 a 0.35; p=0.04; random model; I2: 66%); and also in 12 months (Difference in risk: 0.21; 95% CI: 0.14 to 0.28; p<0.001; fixed model; I2: 0). See figures 9 and 10.

Figure 09. Efficacy. Tofacitinib vs. MTX. DAS28≤3.2 (06 months)

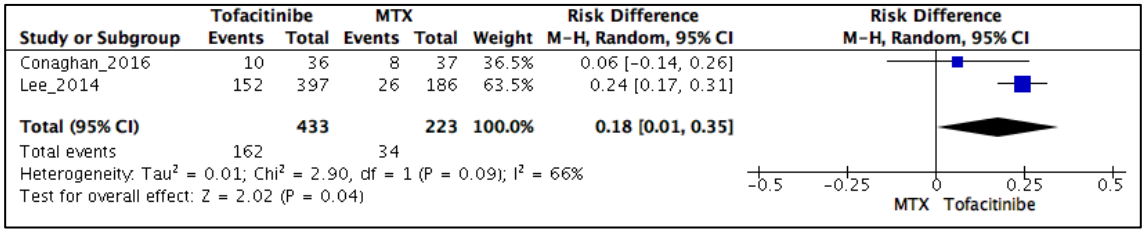
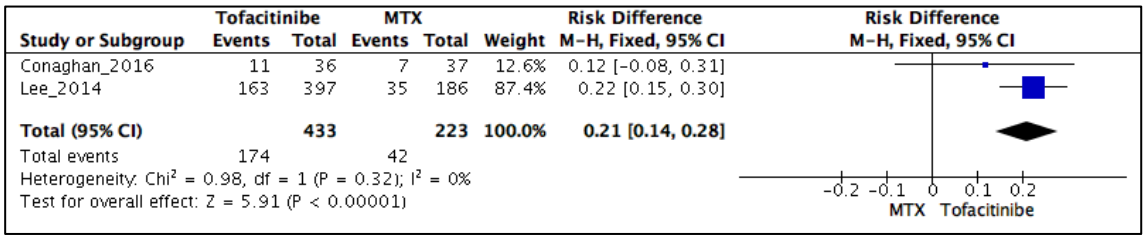


Figure 10. Efficacy. Tofacitinib vs. MTX. DAS28≤3.2 (12 months)



The group of patients using Tofacitinib (10 mg twice daily) compared to MTX had a similar proportion of patients in disease remission (DAS28<2.6) at 6 months (Hazard difference: 0.09; 95% CI: -0.04 a 0.23; p=0.16; random model; I2: 63%); but higher when evaluated at 12 months (risk difference: 0.11; 95% CI: 0.05 to 0.17; p<0.001; fixed model; I2: 0). See figures 11 and 12.

Figure 11. Efficacy. Tofacitinib vs. MTX. DAS28<2.6 (06 months)

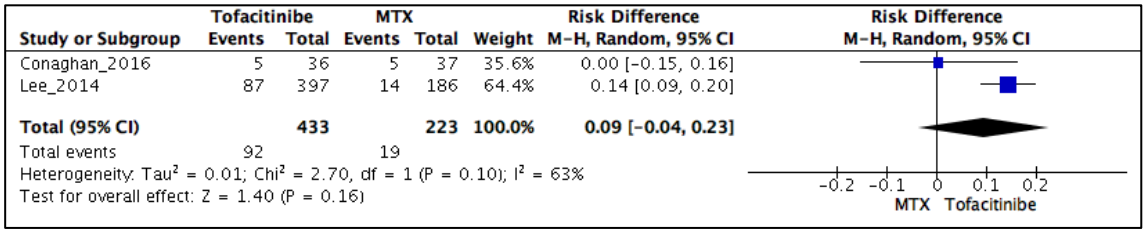


Figure 12. Efficacy. Tofacitinib vs. MTX. DAS28<2.6 (12 months)

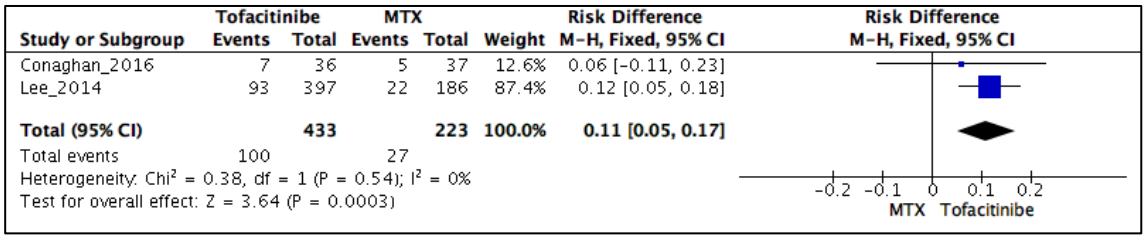


Table 3. Tofacitinib vs. MTX. Clinical outcomes.

	6 months				12 months			
	Risk difference	IC 95%		*p value*	Risk difference	IC 95%		*p value*
		Inf.	Sup.			Inf.	Sup.	
ACR 20	0.25	0.17	0.32	<0.001	0.24	0.16	0.31	<0.001
ACR 50	0.30	0.22	0.37	<0.001	0.21	0.13	0.29	<0.001
ACR 70	0.19	-0.00	0.37	0.05	0.21	0.15	0.28	<0.001
DAS28≤3.2	0.18	0.01	0.35	0.04	0.21	0.14	0.28	<0.001
DAS28<2.6	0.09	-0.04	0.23	0.16	0.11	0.05	0.17	<0.001

For radiographic outcomes, when Tofacitinib 5 mg was used twice a day, compared to MTX, it was evaluated through the outcome variation in relation to the base condition of the van der Heijde mTSS score, indicating less structural joint damage in patients with Tofacitinib group (p≤0.05). The 6-month variation in mTSS score was 0.18 (SE: 0.12) for Tofacitinib and 0.84 (SE: 0.16) for MTX; in 12 months it was 0.36 (SE: 0.14) and 1.18 (SE: 0.20).3 See table 4.

Comparing Tofacitinib (10 mg, twice daily) with MTX, there is a lower risk of structural joint damage determined by the outcome variation from baseline in the van der Heijde mTSS score. At 6 months, mean difference of -0.91 (95% CI: -1.17 to -0.65; p<0.001; random model; I2: 80%). In 12 months, mean difference of -1.25 (95% CI: -1.73 to -0.77; p<0.001; random model; I2: 93%). See figures 13 and 14.

Figure 13. Effectiveness. Tofacitinib vs. MTX. van der Heijde mTSS score (6 months)

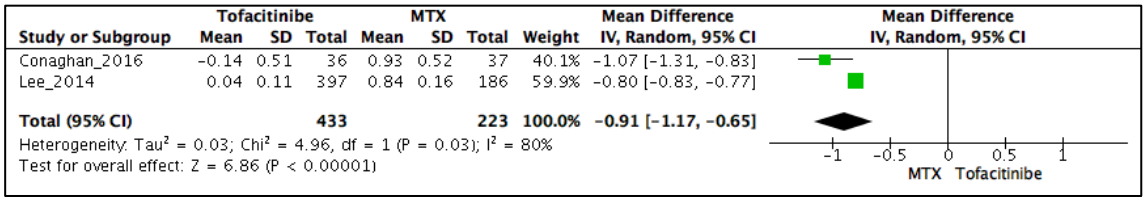


Figure 14. Effectiveness. Tofacitinib vs. MTX. van der Heijde mTSS score (12 months)

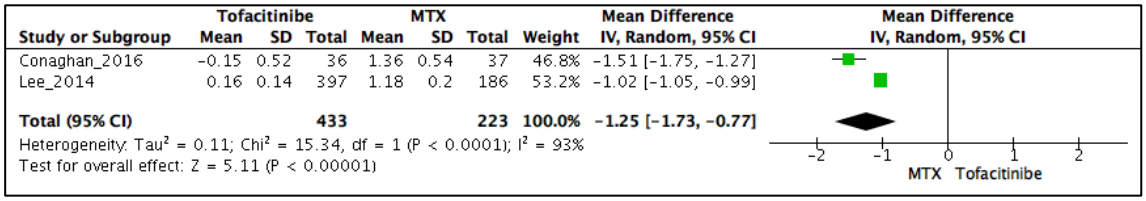


Table 4. Tofacitinib vs. MTX. Radiographic outcomes.

	6 months				12 months			
	Average difference	IC 95%		*p value*	Average difference	IC 95%		*p value*
		Inf.	Sup.			Inf.	Sup.	
mTSS	-0.91	-1.17	-0.65	**<0.001**	-1.25	-1.73	-0.77	**<0.001**

For MRI outcomes, the study by Conaghan et al.4, comparing Tofacitinib (10 mg, twice daily) with MTX reported less bone deterioration in the Tofacitinib group in the RAMRIS (bone erosion) score. The difference between treatments in RAMRIS score (bone erosion) at 6 months was −0.71 (90% CI: −1.29 to −0.08; p = 0.06). At 12 months, the difference between the forms of treatment was -1.26 (CI 90%; -1.87 to -0.65; p <0.001).

Baricitinib vs. MTX

The efficacy of Baricitinib, 4 mg once daily, was compared with MTX in an ECR5, demonstrating superiority of the former in relation to this one for the clinical outcomes ACR 20, ACR 50, ACR 70, DAS 28 (<2.6 and □ 3.2). See table 5.

The group of patients using Baricitinib (4 mg, once a day) compared to MTX had a higher proportion of ACR 20 in 6 months (Hazard difference: 0.15; 95% CI: 0.06 to 0.24; p=0.002; fixed model) and in 12 months (Hazard difference: 0.17; 95% CI: 0.08 to 0.27; p<0.001; fixed model).

The group of patients using Baricitinib (4 mg, once a day) compared to MTX had a higher proportion of ACR 50 in 6 months (Hazard difference: 0.16; 95% CI: 0.06 to 0.27; p=0.002; fixed model) and in 12 months (Difference in risk: 0.20; 95% CI: 0.10 to 0.30; p<0.001; fixed model).

The group of patients using Baricitinib (4 mg, once a day) compared to MTX had a higher proportion of ACR 70 in 6 months (Hazard difference: 0.21; 95% CI: 0.11 to 0.30; p<0.001; fixed model) and in 12 months (Hazard difference: 0.17; 95% CI: 0.07 to 0.27; p<0.001; fixed model).

The group of patients using Baricitinib (4 mg, once a day) compared to MTX had a higher proportion of DAS28≤3.2 in 6 months (Hazard difference: 0.19; 95% CI: 0.09 to 0.29; p<0.001; model fixed) and in 12 months (Difference in risk: 0.20; 95% CI: 0.10 to 0.30; p<0.001; fixed model).

The group of patients using Baricitinib (4 mg, once a day) compared to MTX had a higher proportion of DAS28<2.6 in 6 months (Hazard difference: 0.16; 95% CI: 0.07 to 0.26; p<0.001; model fixed) and in 12 months (Difference in risk: 0.20; 95% CI: 0.11 to 0.30; p<0.001; fixed model). See figures 22 and 23.

Table 5. Baricitinib vs. MTX. Clinical outcomes.

	6 months				12 months			
	Risk difference	IC 95%		*p value*	Risk difference	IC 95%		*p value*
		Inf.	Sup.			Inf.	Sup.	
ACR 20	0.15	0.06	0.24	0.002	0.17	0.08	0.27	<0.001
ACR 50	0.16	0.06	0.27	0.002	0.20	0.1	0.30	<0.001
ACR 70	0.21	0.11	0.30	<0.001	0.17	0.07	0.27	<0.001
DAS28≤3.2	0.19	0.09	0.29	<0.001	0.20	0.10	0.30	<0.001
DAS28<2.6	0.16	0.07	0.26	<0.001	0.20	0.11	0.30	<0.001

For radiological outcomes, comparing Baricitinib (4 mg, once daily) with MTX, there is no difference in structural joint damage determined by the outcome variation in relation to the base condition of the van der Heijde mTSS score. At 6 months, mean difference of -0.22 (95% CI: -0.53 to 0.09; p=0.16; fixed model). In 12 months, mean difference of -0.70 (95% CI: -0.70 to -0.26; p=0.37; fixed model). See table 6.

Table 6. Baricitinib vs. MTX. Radiographic outcomes.

	6 months				12 months			
	Average difference	IC 95%		*p value*	Average difference	IC 95%		*p value*
		Inf.	Sup.			Inf.	Sup.	
mTSS	-0.22	-0.53	0.09	0.16	-0.22	-0.70	0.26	0.37

Upadacitinib versus Methotrexate

An RCT (SELECT-EARLY)(6) evaluated upadacitinib at dosages of 15 and 30 mg as monotherapy versus MTX in 947 patients with active RA and no previous treatment with csDMARDs [no or limited exposure to MTX (≤ 3 doses)] or biological DMARDs (bDMARDs). MTX started at 10 mg/week and titrated to a maximum of 20 mg/week at week 8 as tolerated. The methotrexate dose increment was 5 mg / 4 weeks with a minimum of 15 mg / week as the final dose if intolerance to 20 mg / week was documented.

Upadacitinib 15 mg increased the rate of patients achieving ACR50 and ACR20 within 3 months compared to methotrexate. This increase was 24% (95%CI 17 - 31%) for ACR50 (NNT = 4, 95%CI 3 -6)] and 23% (95%CI 15 - 30%) for ACR20 (NNT = 4, 95%CI 3 - 7)].

Upadacitinib 30 mg also increased the rate of patients achieving ACR50 and ACR20 within 3 months compared to methotrexate. This increase was 28% (95%CI 21 - 35%) for ACR50 (NNT = 4, 95%CI 3 -5)] and 24% (95%CI 17 - 31%) for ACR20 (NNT = 4, 95%CI 3 - 6)].

Upadacitinib at dosages of 15 and 30 mg increased by 30% (95%CI 23 – 37%; NNT = 3, 95%CI 2 – 4) and 32% (95%CI 25 − 39; NNT = 3, 95%CI 2 − 4), respectively, the number of patients with clinical RA remission (DAS28[CRP] <2.6) compared to methotrexate, at a 6-month follow-up.

Upadacitinib, within 6 months, reduced the risk of radiological progression of active RA at dosages of 15 and 30 mg by 10% (95%CI 3 − 16%; NNT = 10, 95%CI 6 - 33) and 11% (95%CI) 5 − 17%; NNT = 9, 95%CI 6 - 20), respectively, compared to methotrexate. Radiological progression was assessed by mTSS which is calculated as the sum of the total joint erosion score and the total joint space narrowing score (JSN), and ranging from 0 (normal) to 448 (worst). A change from baseline greater than 0 indicates progression.

Safety

Tofacitinib vs. MTX

The most commonly reported adverse events3, 4 were anemia, abominal pain, constipation, diarrhea, dyspepsia, nausea and vomiting, peripalpebral edema, bronchitis, nasopharyngitis, herpes zoster, respiratory infections, urinary infections, weight gain, hypercholesterolemia, arthralgia, low back pain, headache, skin rash, hypertension, elevated liver enzymes.The safety of Tofacitinib 10 mg twice daily was compared with MTX, equivalent to that for the probability of adverse events (Difference in risk: 0.05; 95% CI: -0.01 to 0.11; p=0.12; fixed model; I2: 0).Only Lee et al.3 evaluated the safety of Tofacitinib 5 mg twice daily and compared it with MTX, equivalent to that for the probability of adverse events (Difference in risk: 0.01; 95% CI: -0.07 to 0.08; p=0.87; fixed model).

Baricitinib vs. MTX

The adverse events reported were gastrointestinal, cardiovascular, herpes zoster infection, tuberculosis infection, malignancy (5).There was no difference in risk for adverse events between Baricitinib, 4 mg once daily, compared to MTX (Hazard difference: -0.10; 95% CI: -0.10 to 0.08; p=0.86; fixed model).

Upadacitinib vs. MTX

In the SELECT-EARLY(6) study over the 6-month period, the frequencies of treatment-emergent adverse events were similar with methotrexate (65%) and upadacitinib 15 mg (64%), but higher with upadacitinib 30 mg (71%), but without statistical significance in comparison with methotrexate. A similar trend was observed in the frequency of severe AEs, but also without statistical significance.

REFERENCES

1. Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.
2. GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University, 2015 (developed by Evidence Prime, Inc.). Available from gradepro.org.
3. Lee EB, Fleischmann R, Hall S, Wilkinson B, Bradley JD, Gruben D, et al. Tofacitinib versus methotrexate in rheumatoid arthritis. N Engl J Med 2014 19;370:2377-86. PMID:24941177
4. Conaghan PG, Østergaard M, Bowes MA, Wu C, Fuerst T, van der Heijde D, Irazoque-Palazuelos F, Soto-Raices O, Hrycaj P, Xie Z, Zhang R. Comparing the effects of tofacitinib, methotrexate and the combination, on bone marrow oedema, synovitis and bone erosion in methotrexate-naive, early active rheumatoid arthritis: results of an exploratory randomised MRI study incorporating semiquantitative and quantitative techniques. Annals of the rheumatic diseases. 2016 Jun 1;75(6):1024-33.
5. Fleischmann R, Schiff M, van der Heijde D, Ramos-Remus C, Spindler A, Stanislav M, Zerbini CA, Gurbuz S, Dickson C, de Bono S, Schlichting D. Baricitinib, methotrexate, or combination in patients with rheumatoid arthritis and no or limited prior disease-modifying antirheumatic drug treatment. Arthritis & Rheumatology. 2017 Mar;69(3):506-17.
6. van Vollenhoven R, Takeuchi T, Pangan AL, et al. Efficacy and Safety of Upadacitinib Monotherapy in Methotrexate-naïve Patients with Moderately to Severely Active Rheumatoid Arthritis (SELECT-EARLY): A Randomized, Double-blind, Active-comparator, Multi-center, Multi-country Trial [published online ahead of print, 2020 Jul 8]. *Arthritis Rheumatol*. 2020;10.1002/art.41384. doi:10.1002/art.41384