PICO 5 - ARE tsDMARD (JAK INHIBITORS) MORE EFFECTIVE FOR THE TREATMENT OF PATIENTS WITH RA COMPARED TO bDMARD?

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

1. **Medline/PubMed:**

#1 – (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) – 315.767

#2 – (JAK inhibitor OR JAK inhibitors OR Janus Kinases Inhibitors OR Janus Kinase Inhibitors OR Upadacitinib OR Protein Kinase Inhibitors OR Tofacitinib OR Baricitinib) – 203.592

#3 – (Anti-CD20 OR Veltuzumab OR Obinutuzumab OR Antibodies, Monoclonal, Humanized OR Ocrelizumab OR Ofatumumab OR Antibodies, Monoclonal OR Rituximab OR Belimumab OR Rilonacept OR Interleukin-1 OR IL-1 OR Canakinumab OR Interleukin-6 OR IL-6 OR Tocilizumab OR Anti-TNF-alpha OR tumor necrosis factor inhibitors OR Anti TNF-alpha OR Etanercept OR Infliximab OR Adalimumab OR Golimumab OR Certolizumab OR Abatacept OR CTLA-4 OR Secukinumab OR Interleukin-17 OR IL-17 OR Ixekizumab OR Brodalumab OR Ustekinumab OR Interleukin-12 OR IL-12 OR Interleukin-23 OR IL-23 OR Risankizumab OR Guselkumab OR bDMARDs) – 574.004

2. **CENTRAL (Cochrane):**

(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) in All Text AND (JAK inhibitor OR JAK inhibitors OR Janus Kinases Inhibitors OR Janus Kinase Inhibitors OR Upadacitinib OR Protein Kinase Inhibitors OR Tofacitinib OR Baricitinib) in Title Abstract Keyword AND (Anti-CD20 OR Veltuzumab OR Obinutuzumab OR Antibodies, Monoclonal, Humanized OR Ocrelizumab OR Ofatumumab OR Antibodies, Monoclonal OR Rituximab OR Belimumab OR Rilonacept OR Interleukin-1 OR IL-1 OR Canakinumab OR Interleukin-6 OR IL-6 OR Tocilizumab OR Anti-TNF-alpha OR tumor necrosis factor inhibitors OR Anti TNF-alpha OR Etanercept OR Infliximab OR Adalimumab OR Golimumab OR Certolizumab OR Abatacept OR CTLA-4 OR Secukinumab OR Interleukin-17 OR IL-17 OR Ixekizumab OR Brodalumab OR Ustekinumab OR Interleukin-12 OR IL-12 OR Interleukin-23 OR IL-23 OR Risankizumab OR Guselkumab OR bDMARDs)

3. **EMBASE:**

#1. ((((((((((arthritis, AND rheumatoid OR rheumatoid) AND ('arthritis'/exp OR arthritis) OR sjogrens) AND ('syndrome'/exp OR syndrome) OR caplan) AND ('syndrome'/exp OR syndrome) OR felty) AND ('syndrome'/exp OR syndrome) OR rheumatoid) AND ('nodule'/exp OR nodule) OR rheumatoid) AND ('vasculitis'/exp OR vasculitis) OR still) AND ('disease'/exp OR disease) OR arthritis,) AND ('juvenile'/exp OR juvenile) OR 'juvenile'/exp OR juvenile) AND ('arthritis'/exp OR arthritis) OR polyarthritis,) AND ('juvenile'/exp OR juvenile) - 58,441

#2. ((((jak AND ('inhibitor'/exp OR inhibitor) OR jak) AND ('inhibitors'/exp OR inhibitors) OR janus) AND kinases AND ('inhibitors'/exp OR inhibitors) OR janus) AND ('kinase'/exp OR kinase) AND ('inhibitors'/exp OR inhibitors) OR 'upadacitinib'/exp OR upadacitinib OR 'protein'/exp OR protein) AND ('kinase'/exp OR kinase) AND ('inhibitors'/exp OR inhibitors) OR 'tofacitinib'/exp OR tofacitinib OR 'baricitinib'/exp OR Baricitinib - 128,207

#3. ((((('anti cd20' OR 'veltuzumab'/exp OR veltuzumab OR 'obinutuzumab'/exp OR obinutuzumab OR

antibodies,) AND monoclonal, AND humanized OR 'ocrelizumab'/exp OR ocrelizumab OR 'ofatumumab'/exp OR ofatumumab OR antibodies,) AND monoclonal OR 'rituximab'/exp OR rituximab OR 'belimumab'/exp OR belimumab OR 'rilonacept'/exp OR rilonacept OR 'interleukin 1'/exp OR 'interleukin 1' OR 'il 1'/exp OR 'il 1' OR 'canakinumab'/exp OR canakinumab OR 'interleukin 6'/exp OR 'interleukin 6' OR 'il 6'/exp OR 'il 6' OR 'tocilizumab'/exp OR tocilizumab OR 'anti tnf alpha' OR 'tumor'/exp OR tumor) AND ('necrosis'/exp OR necrosis) AND factor AND ('inhibitors'/exp OR inhibitors) OR anti) AND ('tnf alpha'/exp OR 'tnf alpha') OR 'etanercept'/exp OR etanercept OR 'infliximab'/exp OR infliximab OR 'adalimumab'/exp OR adalimumab OR 'golimumab'/exp OR golimumab OR 'certolizumab'/exp OR certolizumab OR 'abatacept'/exp OR abatacept OR 'ctla 4'/exp OR 'ctla 4' OR 'secukinumab'/exp OR secukinumab OR 'interleukin 17'/exp OR interleukin 17' OR 'il 17'/exp OR 'il 17' OR 'ixekizumab'/exp OR ixekizumab OR 'brodalumab'/exp OR brodalumab OR 'ustekinumab'/exp OR ustekinumab OR 'interleukin 12'/exp OR 'interleukin 12' OR 'il 12'/exp OR 'il 12' OR 'interleukin 23'/exp OR 'interleukin 23' OR 'il 23'/exp OR 'il 23' OR 'risankizumab'/exp OR risankizumab OR 'guselkumab'/exp OR guselkumab OR bdmards - 268,507

#4. #1 AND #2 AND #3 - 111

#5. #4 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) – 43

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

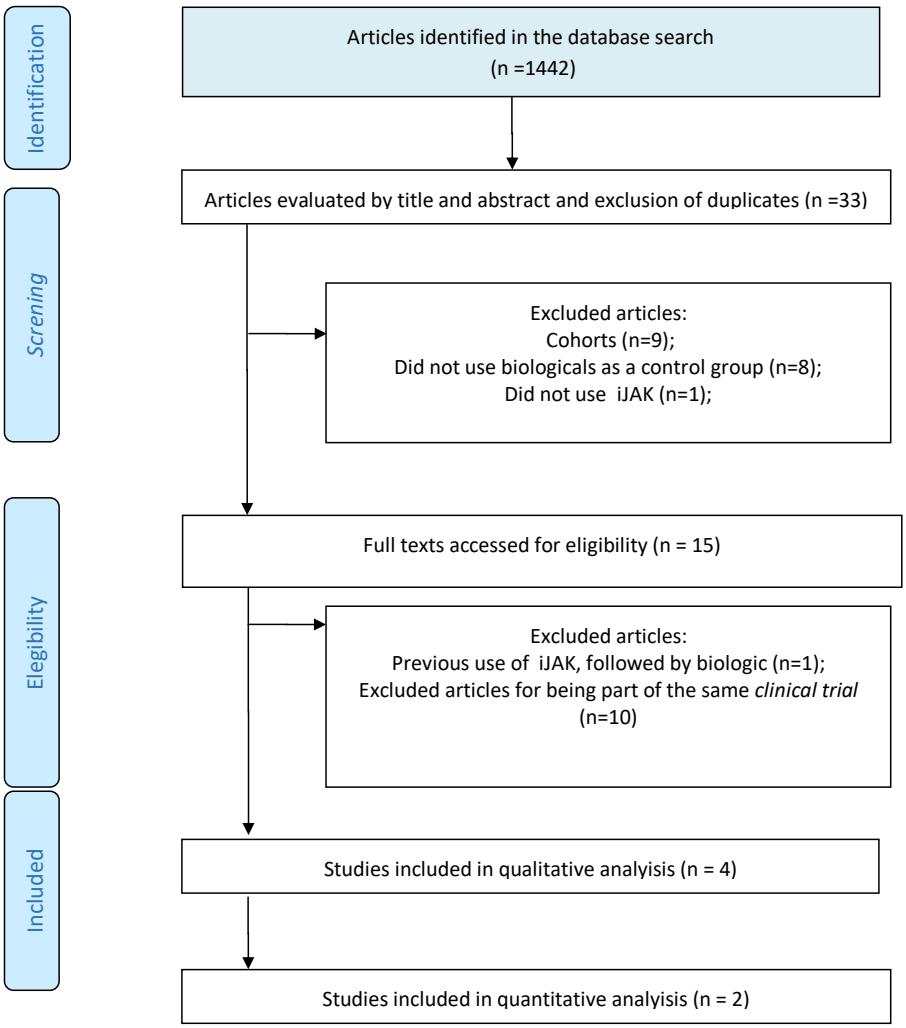


Table 1. Characteristics of the included studies

Study	Design	Follow up	Intervention			Control	
			JAKi	mg	N	bDMARD	N
Fleischmann_2017	RCT	12 months	Tofacitinib	5	384	Adalimumab + MTX	386
Fleischmann_2019	RCT	6 months	Upadacitinib + MTX	15	651	Adalimumab + MTX	327
Hall_2018	RCT	6 months	Tofacitinib	5 or 10	91	Adalimumab + MTX	7
Taylor_2017	RCT	12 months	Baricitinib + MTX	4	487	Adalimumab + MTX	330

Risk of bias

Regarding the risk of bias of the 4 included studies, the studies generally presented a low risk of bias. The certainty rating is moderate (Table 2 and Figure 2).

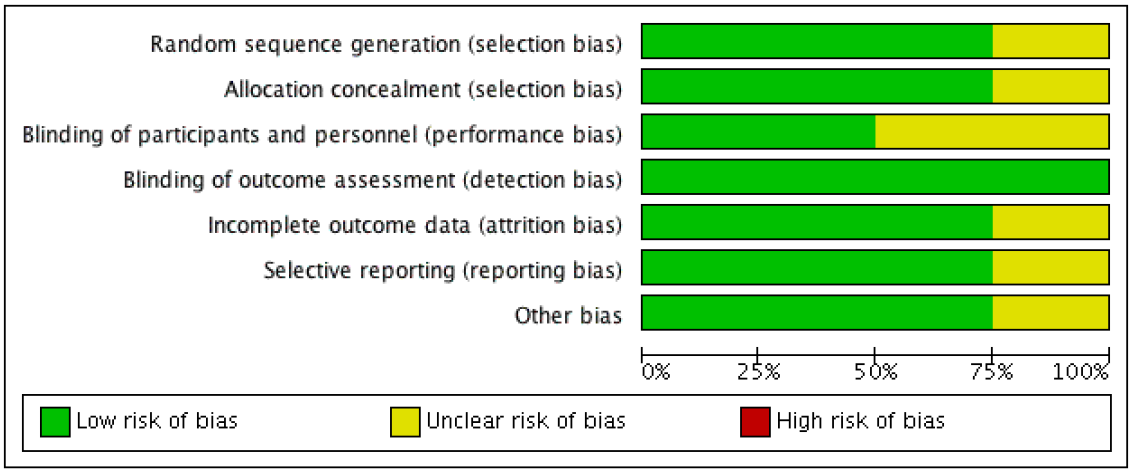
Table 2. Certainty assessment **(GRADE)**

Certainty assessment						
N (Studies)	Bias risk	Inconsistencies	Indirect evidence	Imprecision	Publication Bias	Certainty of the evidence (GRADE)
2663 (4 RCT)	Serious[a,b]	Non Serious [b]	Non Serious	Non Serious [b]	None	⊕⊕⊕◯ MODERATE

[a.] Studies use Tofacitinib, Upadacitinib or Baricitinib as iJAK, with or without associated MTX

[b.] Only two studies were submitted to quantitative analysis.

Figure 2. Description of the biases of the included studies



Efficacy

Tofacitinib vs. Adalimumab + MTX

The efficacy of Tofacitinib was compared with Adalimumab plus Metrotexate (MTX) in 2 randomized clinical trials [4, 6]. The clinical outcomes evaluated were ACR 20, ACR 50, ACR 70, DAS 28 (<2.6 and ≤ 3.2) at 6 and 12 months , with a dose of Tofacitinib of 5 or 10 mg twice a day (See table 3 and 4 and figures 3 to 17).

Both regimens were equivalent for the clinical outcomes evaluated, except for ACR 70 at 6 months, which favored the use of Tofacitinib 10 mg twice daily over Adalimumab (risk difference=0.21; 95% CI 0.01 to 0.42; p=0.04); for the DAS outcome 28≤3.2 (low disease activity), which favored the use of Adalimumab over Tofacitinib 5 mg twice daily (risk difference at 6 months of follow-up = -0.06; 95% CI -0.12 to -0.00; p =0.03; risk difference at 12 months of follow-up = -0.11; 95% CI -0.17 to -0.04; p=0.001); and for the outcome DAS 28<2.6 (disease remission), which favored the use of Adalimumab over Tofacitinib 5 mg twice daily (risk difference at 6 months of follow-up = -0.06; 95% CI -0.11 to -0.01; p =0.02).

Figure 3. Efficacy. Tofacitinib 10 mg vs. Adalimumab + MTX. ACR 20 (6 months)

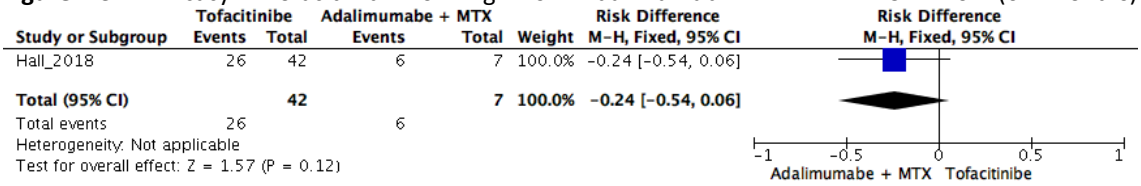


Figure 4. Efficacy. Tofacitinib 10 mg vs. Adalimumab + MTX. ACR 50 (6 months)

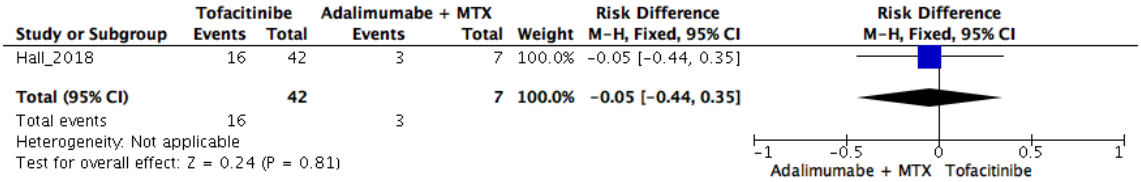


Figure 5. Efficacy. Tofacitinib 10 mg vs. Adalimumab + MTX. ACR 70 (6 months)

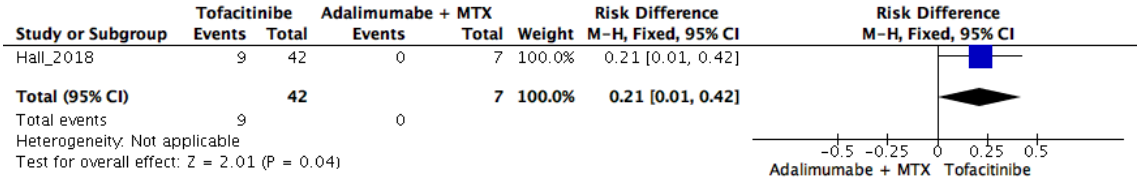


Figure 6. Efficacy. Tofacitinib 10 mg vs. Adalimumab + MTX. DAS 28<2.6 (6 months)

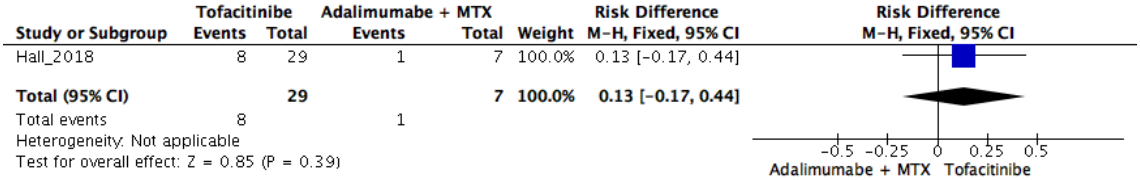


Figure 7. Efficacy. Tofacitinib 10 mg vs. Adalimumab + MTX. DAS 28≤3.2 (6 months)

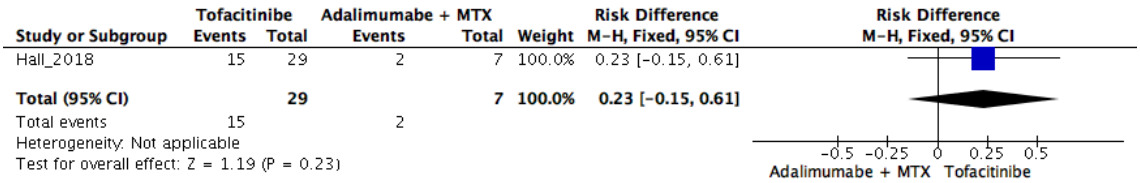


Figure 8. Efficacy. Tofacitinib 5 mg vs. Adalimumab + MTX. ACR 20 (6 months)

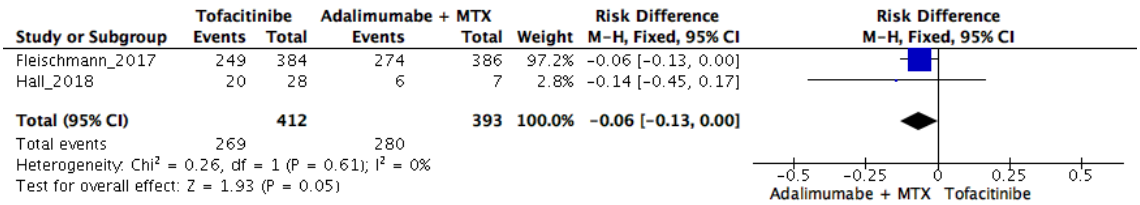


Figure 9. Efficacy. Tofacitinib 5 mg vs. Adalimumab + MTX. ACR 50 (6 months)

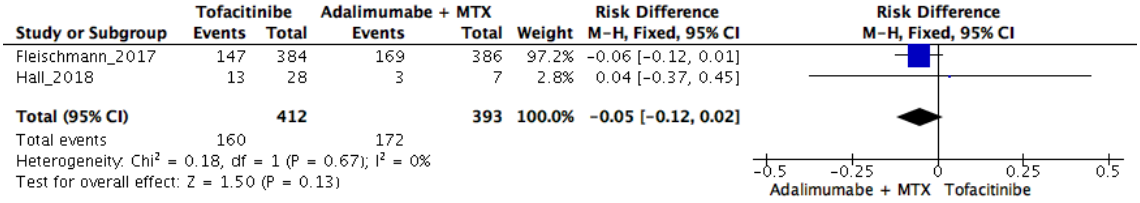


Figure 10. Efficacy. Tofacitinib 5 mg vs. Adalimumab + MTX. ACR 70 (6 months)

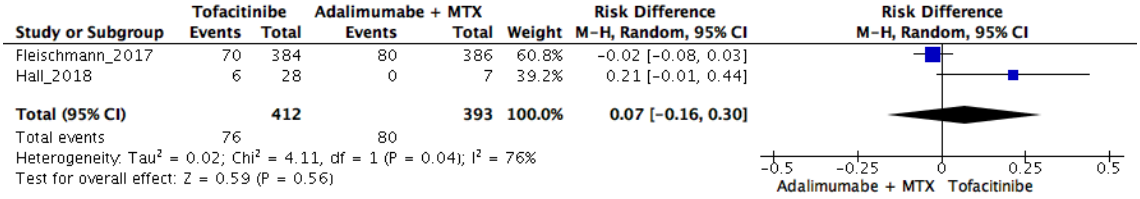


Figure 11. Efficacy. Tofacitinib 5 mg vs. Adalimumab + MTX. DAS 28<2.6 (6 months)

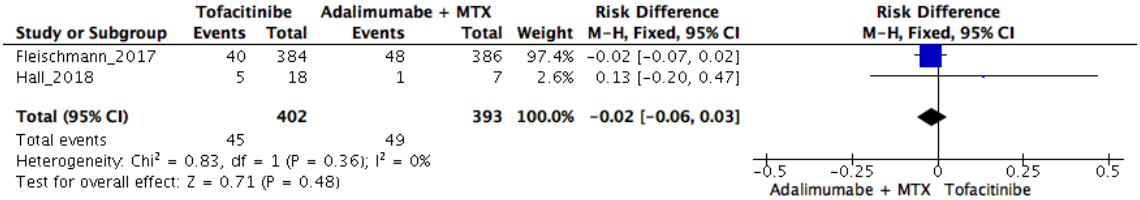


Figure 12. Efficacy. Tofacitinib 5 mg vs. Adalimumab + MTX. DAS 28≤3.2 (6 months)

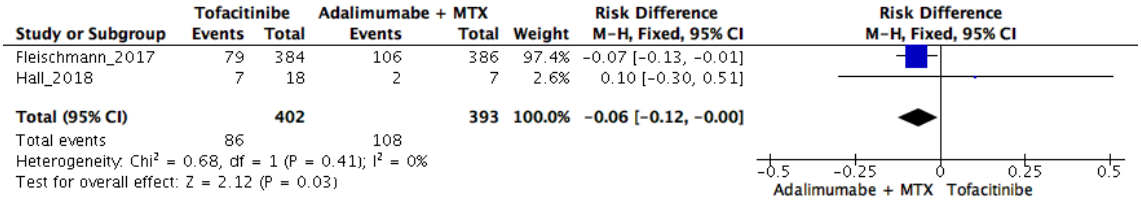


Figure 13. Efficacy. Tofacitinib 5 mg vs. Adalimumab + MTX. ACR 20 (12 months)

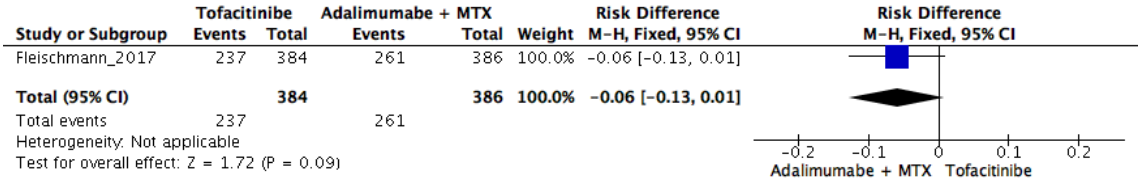


Figure 14. Efficacy. Tofacitinib 5 mg vs. Adalimumab + MTX. ACR 50 (12 months)

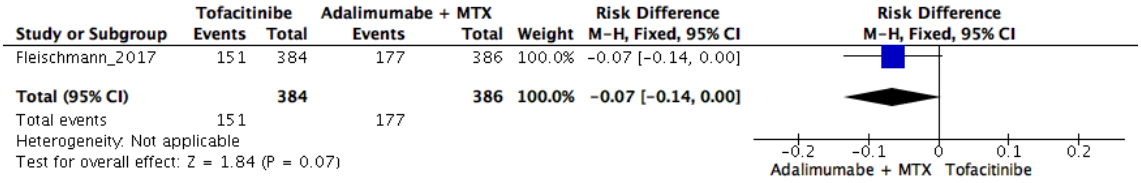


Figure 15. Efficacy. Tofacitinib 5 mg vs. Adalimumab + MTX. ACR 70 (12 months)

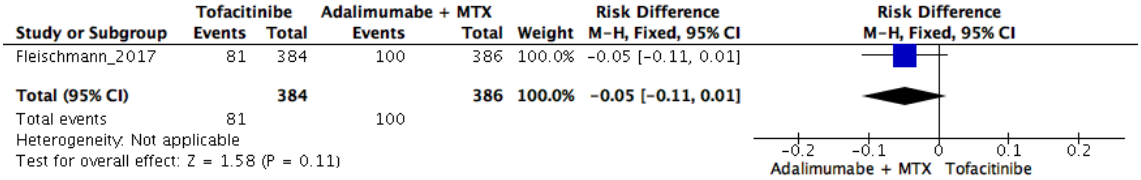


Figure 16. Efficacy. Tofacitinib 5 mg vs. Adalimumab + MTX. DAS 28<2.6 (12 months)

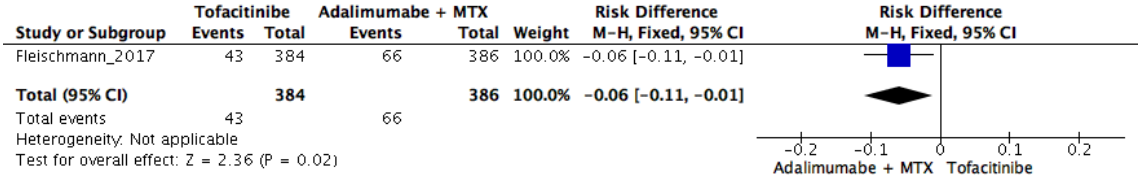


Figure 17. Efficacy. Tofacitinib 5 mg vs. Adalimumab + MTX. DAS 28≤3.2 (12 months)

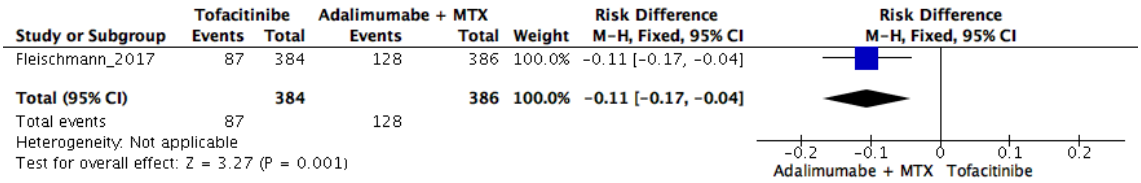


Table 3. Tofacitinib 5 mg vs. Adalimumab + MTX. Clinical Outcomes

	6 months				12 months			
	Risk difference	IC 95%		*p value*	Risk difference	IC 95%		*p value*
		Inf.	Sup.			Inf.	Sup.	
ACR 20	-0.06	-0.13	0.00	0.05	-0.06	-0.13	0.01	0.09
ACR 50	-0.05	-0.12	0.02	0.13	-0.07	-0.14	0.00	0.07
ACR 70	0.07	-0.16	0.30	0.56	-0.05	-0.11	0.01	0.11
DAS28≤3.2	-0.02	-0.12	-0.00	**0.03**	-0.11	-0.17	-0.04	**0.001**
DAS28<2.6	-0.06	-0.06	0.03	0.48	-0.06	-0.11	-0.01	**0.02**

Table 4. Tofacitinib 10 mg vs. Adalimumab + MTX. Clinical Outcomes

	6 months			
	Risk difference	IC 95%		*p value*
		Inf.	Sup.	
ACR 20	-0.24	-0.54	0.06	0.12
ACR 50	-0.05	-0.44	0.35	0.81
ACR 70	0.21	0.01	0.42	**0.04**
DAS28≤3.2	0.23	-0.15	0.61	0.23
DAS28<2.6	0.13	-0.17	0.44	0.39

Baricitinib + MTX vs. Adalimumab + MTX

The efficacy of Baricitinib, 4 mg once a day, was compared with Adalimumab, associated with MTX, in an ECR[7], demonstrating superiority in relation to this one for the clinical outcomes ACR 20, ACR 50, ACR 70, and equivalent for the outcomes DAS 28 (<2.6 and ≤ 3.2). See table 5 and figures 18 to 27.

Figure 18. Efficacy. Baricitinib 5 mg+ MTX vs. Adalimumab + MTX. ACR 20 (6 months)

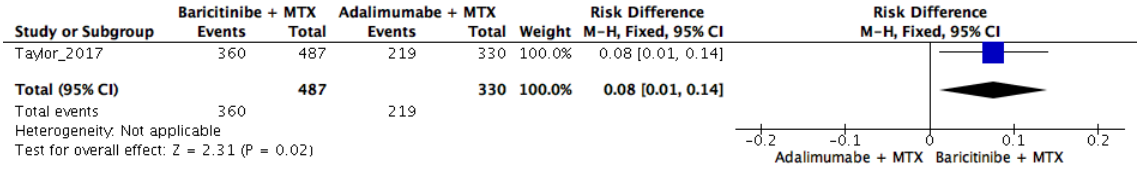


Figure 19. Efficacy. Baricitinib 5 mg+ MTX vs. Adalimumab + MTX. ACR 20 (12 months)

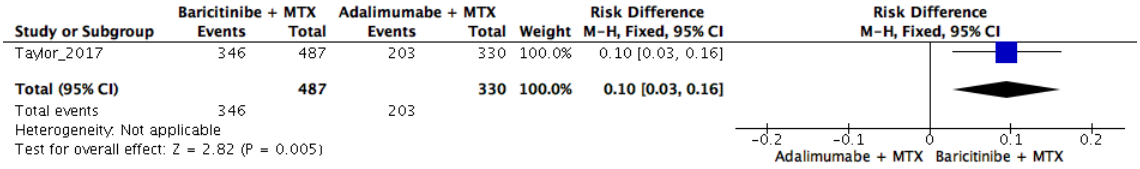


Figure 20. Efficacy. Baricitinib 5 mg + MTX vs. Adalimumab + MTX. ACR 50 (6 months)

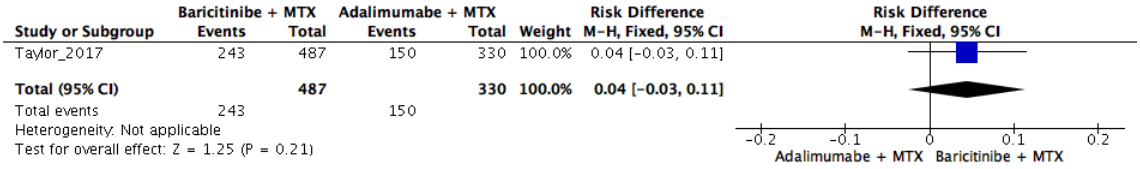


Figure 21. Efficacy. Baricitinib 5 mg+ MTX vs. Adalimumab + MTX. ACR 50 (12 months)

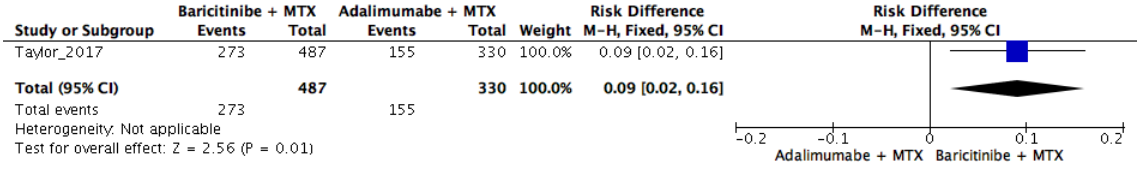


Figure 22. Efficacy. Baricitinib 5 mg+ MTX vs. Adalimumab + MTX. ACR 70 (6 months)

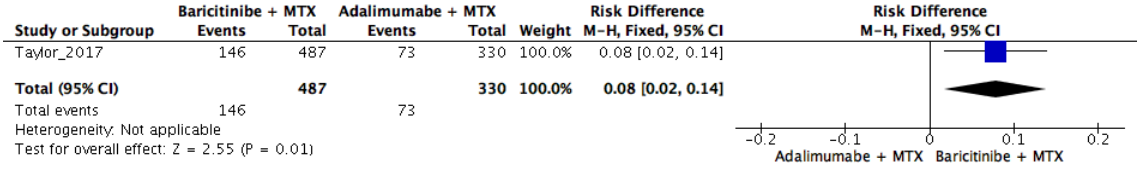


Figure 23. Efficacy. Baricitinib 5 mg+ MTX vs. Adalimumab + MTX. ACR 70 (12 months)

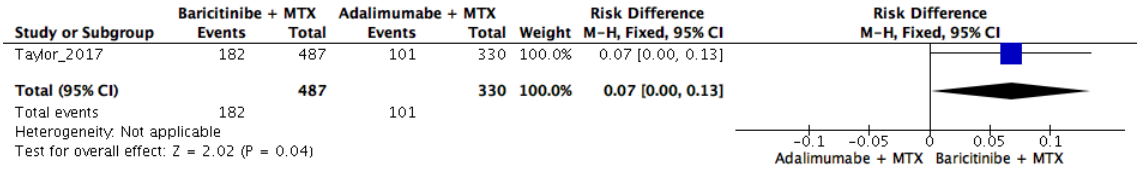


Figure 24. Efficacy. Baricitinib 5 mg + MTX vs. Adalimumab + MTX. DAS 28<2.6 (6 months)

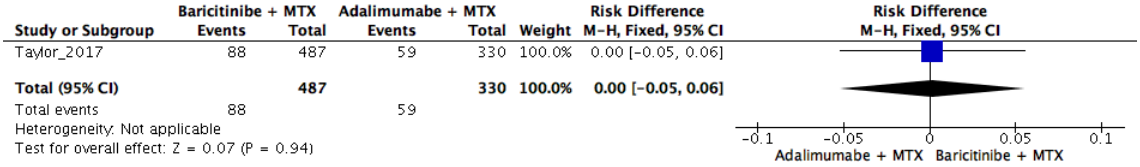


Figure 25. Efficacy. Baricitinib 5 mg+ MTX vs. Adalimumab + MTX. DAS 28<2.6 (12 months)

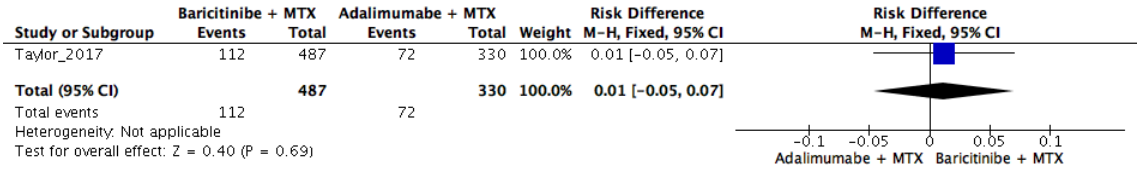


Figure 26. Efficacy. Baricitinib 5 mg+ MTX vs. Adalimumab + MTX. DAS 28≤3.2 (6 months)

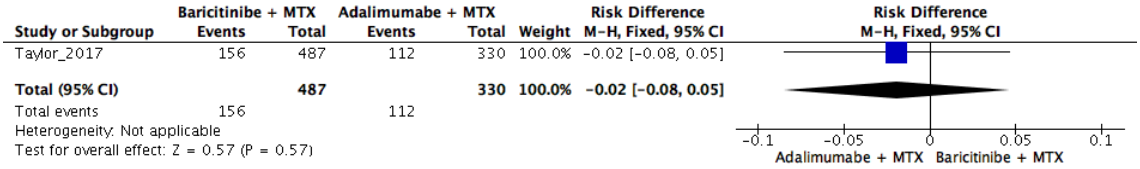


Figure 27. Efficacy. Baricitinib 5 mg + MTX vs. Adalimumab + MTX. DAS 28≤3.2 (12 months)

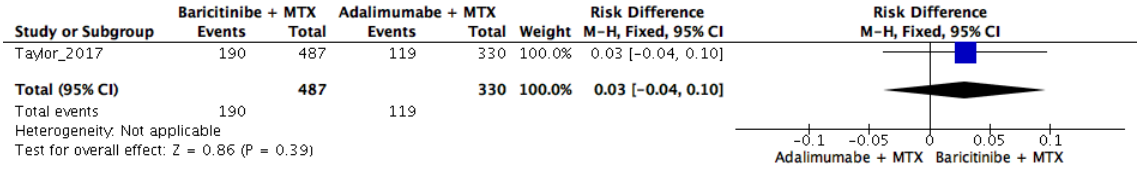


Table 5. Baricitinib 10 mg vs. Adalimumab, both associated with MTX. Clinical Outcomes

	6 months				12 months			
	Risk difference	IC 95%		*p value*	Risk difference	IC 95%		*p value*
		Inf.	Sup.			Inf.	Sup.	
ACR 20	0.08	0.01	0.14	**0.02**	0.10	0.03	0.16	**0.005**
ACR 50	0.04	-0.03	0.11	0.21	0.09	0.12	0.16	**0.01**
ACR 70	0.08	0.12	0.14	**0.01**	0.07	0.00	0.13	**0.04**
DAS28≤3.2	-0.02	-0.08	0.05	0.57	0.03	-0.04	0.10	0.39
DAS28<2.6	0.00	-0.05	0.06	0.94	0.01	-0.05	0.07	0.69

For radiological outcomes, comparing Baricitinib (4 mg, once a day) with Adalimumab 40 mg subcutaneously once every two weeks, associated with MTX, the use of Baricitinib was associated with greater radiographic progression determined by van der Heijde mTSS score. At 6 months, mean difference of 0.07 (95% CI: 0.06 to 0.08; p<0.001). At 12 months, mean difference of 0.11 (95% CI: 0.09 to 0.13; p<0.001). See figures 28 and 29 and table 6.

Figure 28. Efficacy. Baricitinib + MTX vs. Adalimumab + MTX. van der Heijde mTSS (6 months)

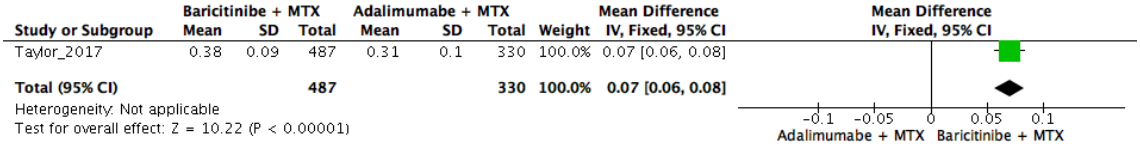


Figure 29. Efficacy. Baricitinib + MTX vs. Adalimumab + MTX. van der Heijde mTSS (12 months)

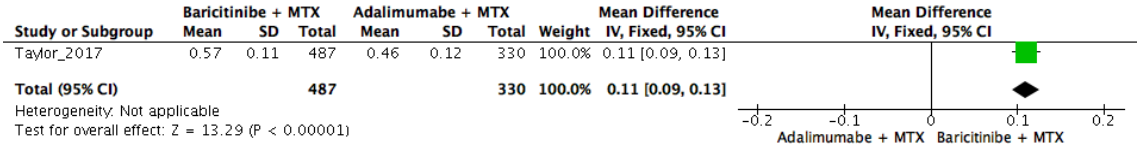


Table 6. Efficacy: Baricitinib 10 mg vs. Adalimumab, both associated with MTX. Radiological Outcomes.

	6 months				12 months			
	Average difference	IC 95%		*p value*	Average difference	IC 95%		*p value*
		Inf.	Sup.			Inf.	Sup.	
mTSS	0.07	0.06	0.08	**<0.001**	0.11	0.09	0.13	**<0.001**

Upadacitinib + MTX vs. Adalimumab + MTX

The efficacy of Upadacitinib, 15 mg once a day, was compared with Adalimumab, 40 mg subcutaneously every 2 weeks, both associated with MTX, in an ECR5, demonstrating superiority in relation to this one for the clinical outcomes ACR 20 and ACR 50 within 6 months of follow-up. See figures 30 and 31 and table 7.

Figure 30. Efficacy. Upadacitinib + MTX vs. Adalimumab + MTX. ACR 20 (6 months)

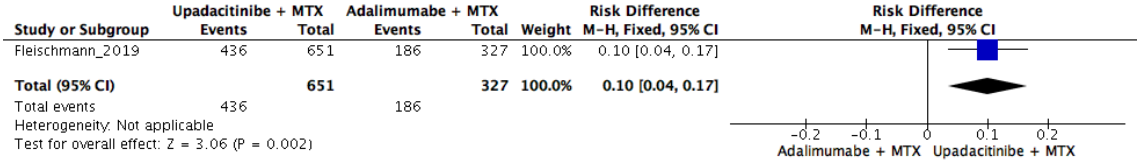


Figure 31. Efficacy. Upadacitinib + MTX vs. Adalimumab + MTX. ACR 50 (6 months)

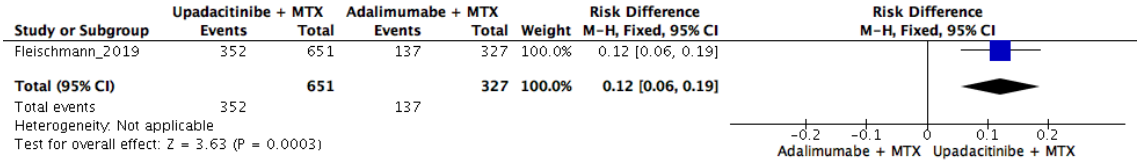


Table 7. Upadacitinibe vs. Adalimumab, both associated with MTX. Clinical Outcomes

	6 months			
	Risk difference	IC 95%		*p value*
		Inf.	Sup.	
ACR 20	0.10	0.04	0.16	**0.002**
ACR 50	0.12	0.06	0.19	**<0.001**

For radiological outcomes, comparing Upadacitinib (15 mg, once a day) with Adalimumab 40 mg subcutaneously once every two weeks, associated with MTX, there was no difference in radiographic progression determined by the outcome variation in relation to the baseline van der Heijde mTSS score at 6 months (nominal p<0.448).

Safety

Tofacitinib vs. Adalimumab + MTX

Two clinical trials[4, 6] evaluated the risk for adverse events comparing the use of Tofacitinib versus Adalimumab 40 mg subcutaneously once every 2 weeks (see Figures 32 to 35). Rates of adverse events (including infections) associated with tofacitinib and adalimumab were similar at 6 months of follow-up. For Tofacitinib 5 mg twice daily, the difference in risk for adverse events was 0.02; 95% CI: -0.24 to 0.29; p=0.87; random model; I2: 57%)[4, 6]. For Tofacitinib 10 mg twice daily, the difference in risk for adverse events was 0.02; 95% CI: -0.16 to 0.56; p=0.29)[6].For serious adverse events, there was also no difference between the studied groups at 6 months. For Tofacitinib 5 mg twice daily, the difference in risk for serious adverse events was 0.00; 95% CI: -0.03 to 0.04; p=0.92; fixed model; I2: 0)4, 6. For Tofacitinib 10 mg twice daily, the difference in risk for serious adverse events was -0.12; 95% CI: -0.39 to 0.14; p=0.35)[6].The most frequent complications were infections such as pneumonia, herpes zoster infection, tuberculosis and other opportunistic infections, development of neoplasms, nausea, diarrhea, skin rash, low back pain, hematological alterations, renal failure, and hypercholesterolemia.

Figure 32. Security. Risk of adverse events. Tofacitinib 5 mg twice daily vs. Adalimumab + MTX.

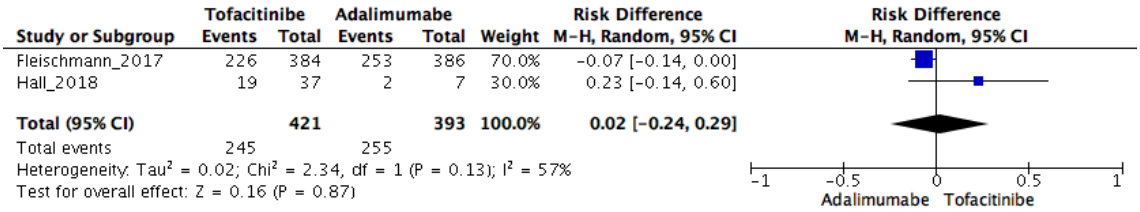


Figure 33. Security. Risk of adverse events. Tofacitinib 10 mg twice daily vs. Adalimumab + MTX.

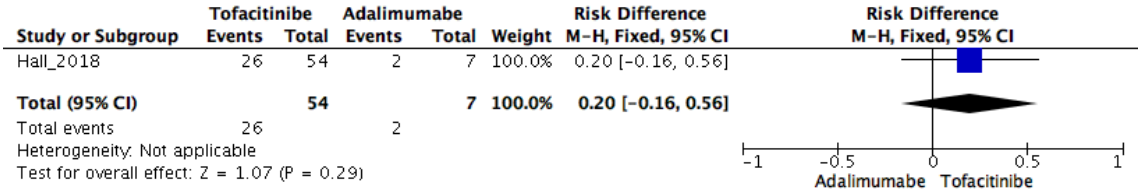


Figure 34. Security. Risk of serious adverse events. Tofacitinib 5 mg twice daily vs. Adalimumab + MTX.

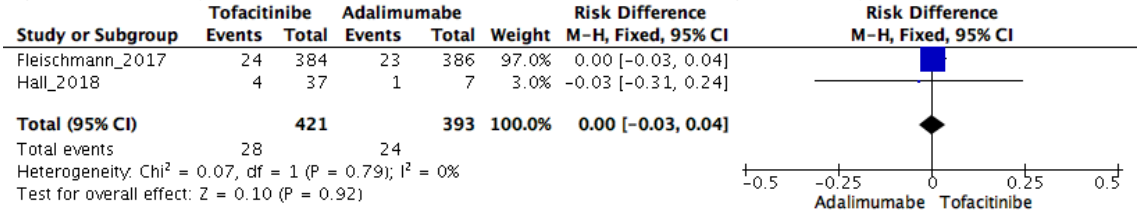
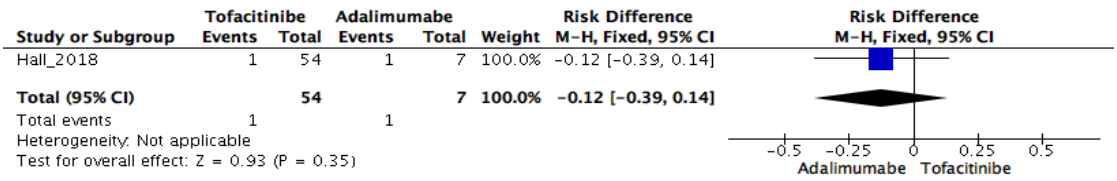


Figure 35. Security. Risk of serious adverse events. Tofacitinib 10 mg twice daily vs. Adalimumab + MTX.



Baricitinib + MTX vs. Adalimumab + MTX

A clinical trial[7] evaluated the risk for adverse events comparing the use of Baricitinib 4 mg daily against Adalimumab 40 mg subcutaneous every 2 weeks, both associated with MTX (see Figures 36 to 40). Rates of adverse events (including infections) associated with Baricitinib and Adalimumab were similar at 6 (risk difference=0.03; 95% CI -0.03 to 0.10; p=0.30) and 12 (risk difference= 0.02; 95% CI -0.04 to 0.08; p=0.46) months of follow-up. However, for serious adverse events, the regimen with Baricitinib had the worst results in 6 (risk difference=0.03; 95% CI 0.01 to 0.05; p=0.02) and 12 months (risk difference=0.04; 95% CI 0.01 to 0.07; p=0.02). Infection rates were similar with Baricinib and Adalimumab at 6 (risk difference=0.03; 95% CI -0.04 to 0.09; p=0.41) and 12 months (risk difference=0.04; 95% CI -0.03 to 0.11; p =0.27). The most frequent complications were infections such as herpes zoster infection, development of neoplasms, cardiovascular events, hematological alterations, renal failure, and hypercholesterolemia.

Figure 36. Security. Risk of adverse events (6 months of follow-up). Baricitinib 4 mg once daily vs. Adalimumab, both associated with MTX.

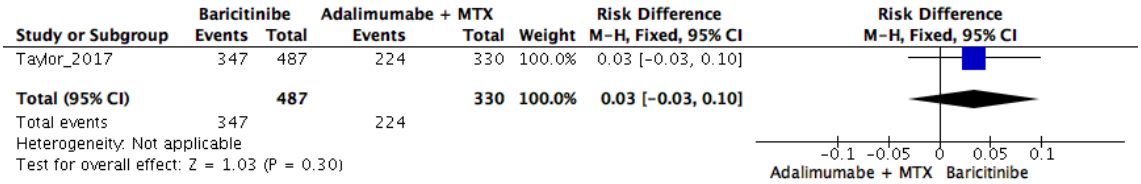


Figure 37. Security. Risk of adverse events (12 months of follow-up). Baricitinib 4 mg once daily vs. Adalimumab, both associated with MTX.

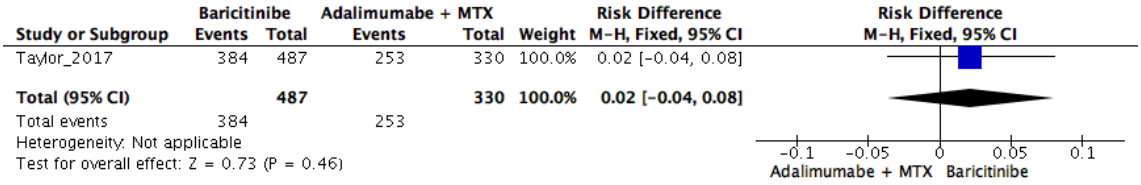


Figure 38. Security. Risk of serious adverse events (06 months of follow-up). Baricitinib 4 mg once daily vs. Adalimumab, both associated with MTX.

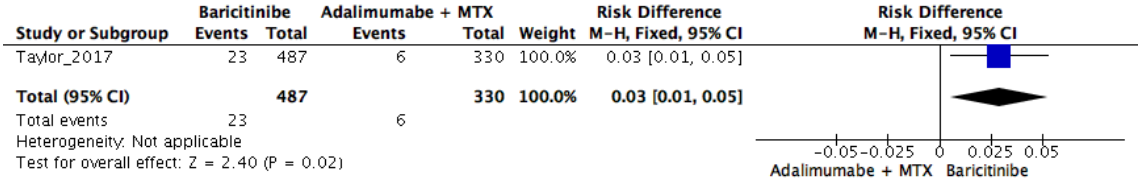


Figure 39. Security. Risk of serious adverse events (12 months of follow-up). Baricitinib 4 mg once daily vs. Adalimumab, both associated with MTX.

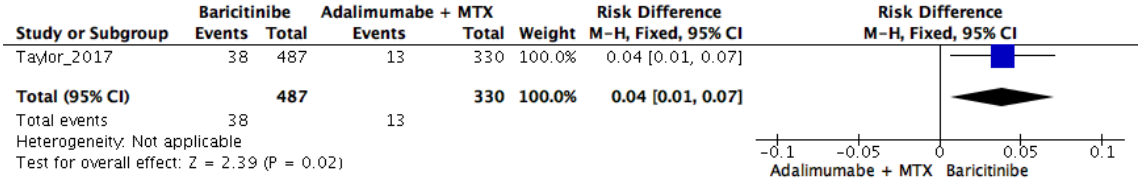


Figure 40. Security. Risk of infections (06 months of follow-up). Baricitinib 4 mg once daily vs. Adalimumab, both associated with MTX.

Upadacitinib + MTX vs. Adalimumab + MTX

A clinical trial[5] evaluated the risk for adverse events comparing the use of Upadacitinib 15 mg daily associated with MTX, against Adalimumab 40 mg subcutaneously every 2 weeks, associated with MTX (see Figures 41 to 43). Rates of adverse events (including infections) associated with the adalimumab regimen were higher at 6 months of follow-up (risk difference=-0.07; 95% CI -0.13 to -0.00; p=0.04). However, for serious adverse events, both regimens were equivalent at 6 months (risk difference=-0.01; 95% CI -0.03 to 0.02; p=0.66). Infection rates were similar between regimens at 6 months (risk difference=0.06; 95% CI -0.00 to 0.12; p=0.07). The most frequent complications were infections, such as herpes zoster infection, opportunistic infections, development of neoplasms, liver changes, gastrointestinal perforations, hematological changes, renal failure, and hypercholesterolemia.

Figure 41. Security. Risk of adverse events (06 months of follow-up). Upadacitinib 15mg once daily vs. Adalimumab, both associated with MTX.

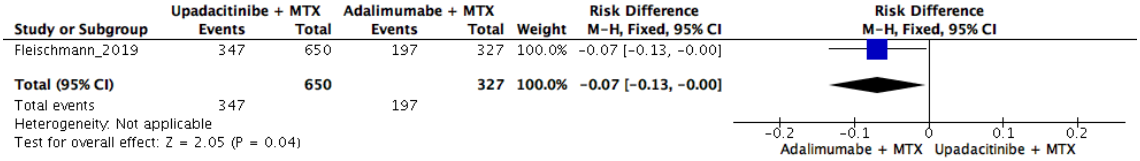


Figure 42. Security. Risk of serious adverse events (06 months of follow-up). Upadacitinib 15mg once daily vs. Adalimumab, both associated with MTX.

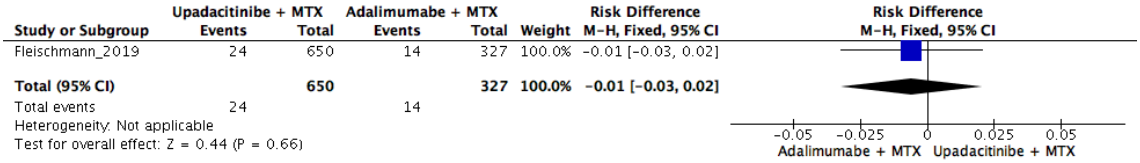
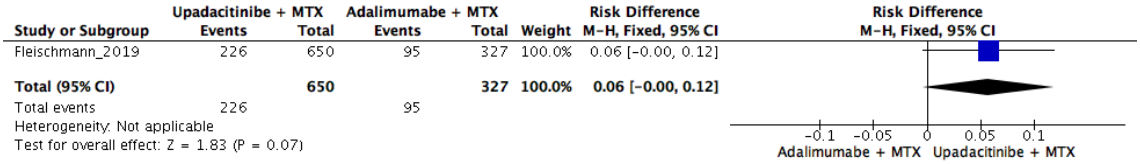


Figure 43. Security. Risk of infeccions (06 months of follow-up). Upadacitinib 15mg once daily vs. Adalimumab, both associated with MTX.



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