PICO 3 - ARE tsDMARD (JAK INHIBITORS) EFFECTIVE AND SAFE FOR THE TREATMENT OF RA PATIENTS AFTER bDMARD FAILURE?

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

Medline/PubMed: (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 Protein Kinase Inhibitors OR Tofacitinib OR Baricitinib OR Upadacitinib) AND (inadequate response OR insufficient response OR unacceptable side effects OR bDMARD-IR) AND (tumor necrosis factor inhibitors OR TNFis OR biologic DMARDs OR bDMARDs OR adalimimab OR certolizumabe pegol OR etanercept OR golimumab OR Infliximab OR Rituximab OR anti-CD20 OR Tocilizumab OR anti-IL6 OR abatacept OR anti-CTL4Ig) AND Random*

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) AND (JAK inhibitor OR JAK inhibitors OR Janus Kinases Inhibitors OR Protein Kinase Inhibitors OR Tofacitinib OR Baricitinib OR Upadacitinib OR Filgotinib) AND (tumor necrosis factor inhibitors OR TNFis OR biologic DMARDs OR bDMARDs OR adalimimab OR certolizumabe pegol OR etanercept OR golimumab OR Infliximab OR Rituximab OR anti-CD20 OR Tocilizumab OR anti-IL6 OR abatacept OR anti-CTL4Ig) (inadequate response OR unsuccessfully)

EMBASE: ('arthritis, rheumatoid'/exp OR 'arthritis, rheumatoid' OR (arthritis, AND rheumatoid) OR 'rheumatoid arthritis'/exp OR 'rheumatoid arthritis' OR (rheumatoid AND ('arthritis'/exp OR arthritis)) OR 'sjogren syndrome'/exp OR 'sjogren syndrome' OR (sjogren AND ('syndrome'/exp OR syndrome)) OR 'caplan syndrome'/exp OR 'caplan syndrome' OR (caplan AND ('syndrome'/exp OR syndrome)) OR 'felty syndrome'/exp OR 'felty syndrome' OR (felty AND ('syndrome'/exp OR syndrome)) OR 'rheumatoid nodule'/exp OR 'rheumatoid nodule' OR (rheumatoid AND ('nodule'/exp OR nodule)) OR 'rheumatoid vasculitis'/exp OR 'rheumatoid vasculitis' OR (rheumatoid AND ('vasculitis'/exp OR vasculitis)) OR 'still disease'/exp OR 'still disease' OR (still AND ('disease'/exp OR disease)) OR 'arthritis, juvenile'/exp OR 'arthritis, juvenile' OR (arthritis, AND ('juvenile'/exp OR juvenile)) OR 'juvenile arthritis'/exp OR 'juvenile arthritis' OR (('juvenile'/exp OR juvenile) AND ('arthritis'/exp OR arthritis)) OR 'polyarthritis, juvenile' OR (polyarthritis, AND ('juvenile'/exp OR juvenile))) AND ('jak inhibitor'/exp OR 'jak inhibitor' OR (jak AND ('inhibitor'/exp OR inhibitor)) OR 'jak inhibitors' OR (jak AND ('inhibitors'/exp OR inhibitors)) OR 'janus kinases inhibitors' OR (janus AND kinases AND ('inhibitors'/exp OR inhibitors)) OR 'janus kinase inhibitors upadacitinib' OR (janus AND ('kinase'/exp OR kinase) AND ('inhibitors'/exp OR inhibitors) AND ('upadacitinib'/exp OR upadacitinib)) OR 'protein kinase inhibitors'/exp OR 'protein kinase inhibitors' 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) AND [randomized controlled trial]/lim

The data-based search was carried out until the month of April 2020, with a systematic review being carried out as recommended by the *Preferred Reporting Items for Systematic reviews and Meta-Analyses* (PRISMA)[5].

RESULTS

Figure 01 - FLOW DIAGRAM

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

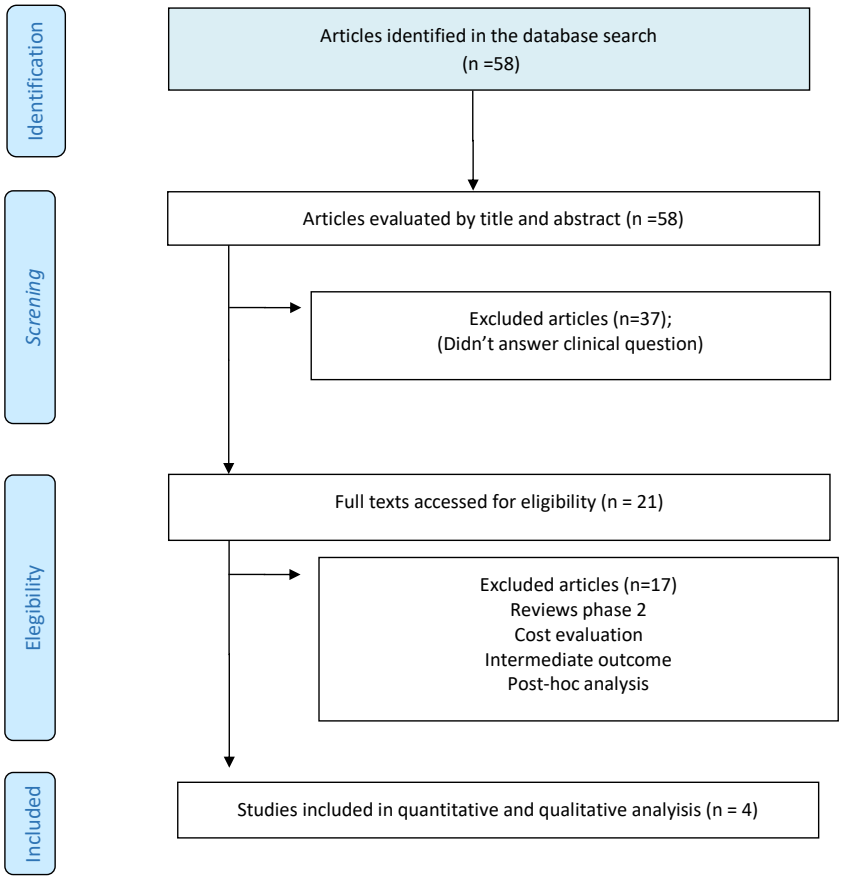

Table 1. Characteristics of the included studies and results of primary outcomes

Study	Population	Follow up	Intervention (N)	Number of patients with with outcome				
				ACR20	**ACR50**	**ACR 70**	**DAS28 - ESR ≥ 2.6- < 3.2** (low RA activity)	**DAS28 -ESR <2.6** (RA remission)
Burmester GR 2013[8]	Moderate to severe RA, inadequate response to anti-TNFs	3 months	TOFA 5 mg BID + MTX (n= 133)	55 / 132	35 / 132	18 / 132	17 /119	8 / 119
			TOFA 10 mg BID + MTX (n=134)	64 / 133	37 / 133	14 / 133	26 / 125	11/ 125
			Placebo + MTX (n=132)	32 / 131	11 / 131	2 / 131	6 / 120	2 / 120
Genovese MC 2016[9]	Moderate to severe RA, inadequate response or toxicity/intolerance to bDMARD	3 months	BARI 2 mg QD + csDMARD n= 174	85 / 174	35 /174	22 /174	23 / 174	10 / 174
			BARI 4 mg QD + csDMARD n= 177	98 / 177	50 / 177	20 / 177	21 / 177	11 / 177
			Placebo QD + csDMARD n= 176	48 / 176	14 / 176	4 / 176	7 /176	2 / 176

Genovese MC 2018[10]	Moderate to severe RA, inadequate response or toxicity/intolerance to bDMARD	3 months	UPA 15 mg QD + csDMARDs (n=164)	106 /164	56 / 164	19 / 164	DAS28 (CRP) ≤3.2 (baixa atividade da doença)
							71 / 164
			UPA 30 mg QD + csDMARDs (n=165)	93 / 165	59 / 165	38 / 165	70 / 165
			Placebo + csDMARDs (n= 169)	48 / 169	20 / 169	11 / 169	24 / 169
Genovese MC 2019[11]	Moderate to severe RA, inadequate response or toxicity/intolerance to bDMARD	3 months	FILGO 200 mg QD (n = 147)	97 /147	74 / 147	37 / 147	60 / 147
			FILGO 100 mg QD (n = 153)	88 / 153	54 / 153	34 / 153	57 / 153
			Placebo QD (n = 148)	46 / 148	25 / 148	10 / 148	23 / 148

Table 2. Description of the biases of the included studies

JAK inhibitors after bDMARD failure									
STUDY	RANDOM	ALOCATION	DOUBLE BIND	LOSSES	PROGNOSTIC FACTORS	OUTCOME	SAMPLE CALCULATION	ITA	EARLY INTERRUPTION
Burmester GR 2013									
Genovese MC 2016									
Genovese MC 2018									
Genovese MC 2019									

ITA = Intention-to-treat analysis Low risk of bias Presence of bias Uncertain risk of bias

The ORAL-STEP study(8) included patients who had an inadequate response or intolerance to at least one anti-TNF drug and compared tofacitinib at 5 mg or 10 mg twice a day with placebo for 12 weeks, followed by twice a day daily 5 mg tofacitinib or 10 mg for 12 weeks, in combination with methotrexate.

The RA-BEACON study(9) was carried out in patients in whom at least one anti-TNF had failed (although they could have also received other MMCDb) and compared, once a day, placebo with baricitinib 2 mg or 4 mg in combination with conventional synthetic DMARDs (csDMARDs), for a period of 24 weeks.

The SELECT-BEYOND study(10) included patients who had an inadequate response or intolerance to any DMARDs, not just anti-TNF drugs, therefore differing from ORAL-STEP and RA-BEACON in inclusion of a broader population of refractory patients. In SELECT-BEYOND, 89% had lack of efficacy with at least one previous MMCDb and 25% were treated with at least three MMCDb.

The FINCH 2 study(11) was performed in patients with moderately to severely active RA and previously inadequate response or intolerance to one or more bDMARDs. Patients were randomized to filgotinib 200 mg; filgotinib 100mg; or placebo once a day. All patients continued with concomitant DMARDsc.

For this review, the results of outcomes involving the conventional doses reported in the JAK studies will be considered.

EFFICACY

The ACR20 response rate was considered the primary outcome in the four RCTs included in this review. There was a higher proportion of patients who achieved, within three months, ACR20 (20% improvement on the American College of Rheumatology scale) as well as ACR50 and ACR70 in all groups using JAK compared to placebo.

This increase with the use of BARICITINIB (BARI) was 28% for ACR20 (95%CI 18 - 38%); 4 patients need to be treated for one to reach ACR20 (NNT = 4, 95%CI 3 - 5)]; 20% for ACR 50 [95% CI 12 - 28%; NNT = 5 (95%CI 4 - 8)] and 14% for ACR70 [95%CI 4 - 14%; NNT = 11 (95%CI 7 - 26)], Figure 2.With the use of TOFACITINIB (TOFA) the increase was 17% for ACR20 (95%CI 28 - 6; NNT = 6, 95%CI 4 - 16); 18% for ACR 50 (95%CI 9 - 27; NNT = 6, 95%CI 4 - 11) and 12% for ACR 70 (95%CI 6 - 18; NNT =8, 95%CI 5 - 17), Figure 2.With UPDACITINIBE (UPA) the increase was 36% for ACR20 (95%CI 26 - 46, NNT = 3, 95%CI 2 - 4); 22% for ACR50 (95%CI 14 - 31; NNT = 4, 95%CI 3 - 7) and there was no difference for ACR70 compared to placebo (95%CI −1 - 11; NNT = NS), Figure 2.

Therapy with FILGOTINIB (FILGO), also compared to placebo, showed a 35% increase for ACR20 (95%CI 24 - 46, NNT = 3 95%CI 2 - 4); 33% for ACR50 (95%CI 23 - 44; NNT = 3, 95%CI 2 -4) and 18% for ACR70 (95%CI 10 - 27; NNT = 5, IC95 4 - 10)**Figure 2.**

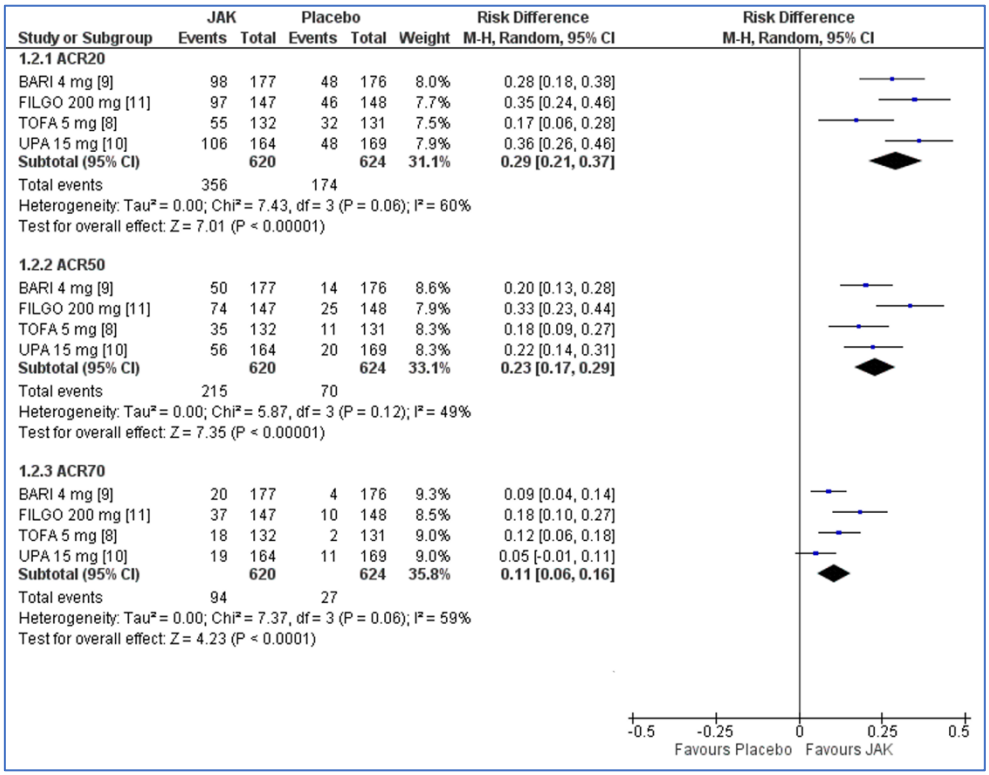

Figure 2. Forest plot of comparison: 1 Janus Kinase inhibitors versus Placebo, outcome: 1.2 Degree of response to ACR20/50/70 treatment, within three months of follow-up**.**

Two studies evaluated the number of patients in disease remission, as well as patients with low activity, comparing JAKi with placebo in a 3-month follow-up, according to the DAS28-ESR disease activity score, considering a value < 2.6 for remission and ≥ 2.6 – < 3.2 for low activity. The 5% increase in the number of patients in RA remission using TOFA 5mg was not statistically significant (95%CI 0 to 10; NNT =NS), but there was an increase in patients with low activity in 9% [95%CI 2 – 17%; NNT = 11 (95%CI 5 – 53)], compared to placebo. BARI 4 mg increased by 5% (95%CI 1 – 9%) the number of patients with RA remission (NNT = 20, 95%CI 11 – 81), as well as patients with low activity by 8% [95%CI 2 – 13%; NNT = 13 (95%CI 7 - 43)], compared to placebo, Figure 3.

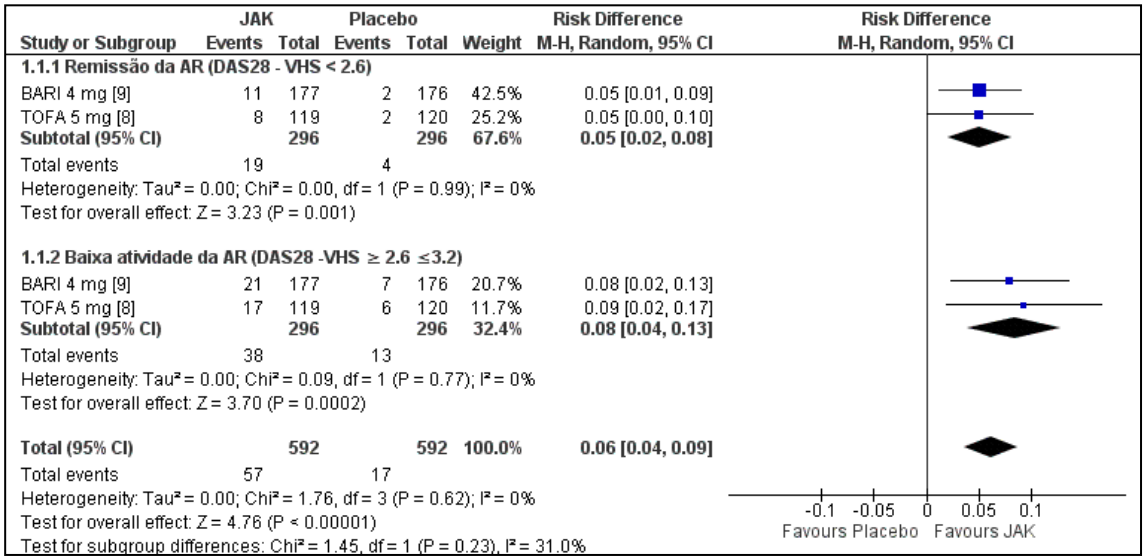

Figure 3. Forest plot: 1 Janus Kinase inhibitors versus Placebo, outcome: 1.1 AR - DAS28 - ESR activity at 3 months.

Two studies evaluated the number of patients with low RA activity, comparing JAKi with placebo in a three-month follow-up, according to the DAS28 (CRP) score, considering a value ≤ 3.2 for low disease activity. FILGO 200 mg increased by 25% (95%CI 15 - 35%) the number of patients with low RA activity (NNT = 4, 95%CI 3 - 6), compared to placebo and UPA 15 mg increased by 29% (95%CI 20 - 38) with an NNT = 3, (95%CI 3 - 5), Figure 4.

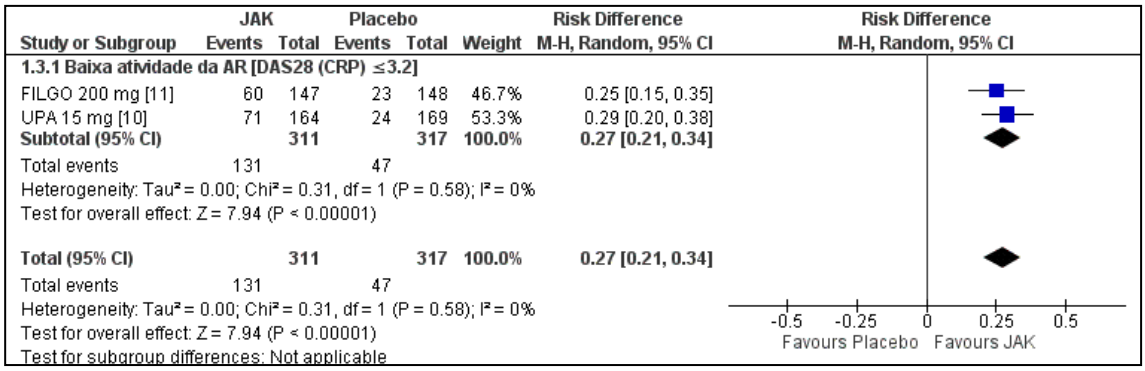

Figure 4. Forest plot of comparison: 1 Janus Kinase inhibitors versus Placebo, outcome: 1.3 AR activity - DAS28 (CRP) at 3 months.

The four studies evaluated the functional capacity outcome, assessed by the "Health Assessment Questionnaire-Disability Index" (HAQ-DI) questionnaire. Clinically significant improvement in HAQ-DI is considered a change of ≥0.22 units from baseline in HAQ to <0.68 and no improvement of <0.22(12). In comparison with placebo, the four JAKi (TOFA, BARI, UPA and FILGO) increased by 14% to 24% the number of patients who achieved HAQ-DI ≥ 0.22.

Table 3 . Efficacy Results (HAQ) of JAKs in RA patients, up to 3 months

Study	**Outcome**	**TOFA 5 mg BID + MTX**	**TOFA 10 mg BID + MTX**	**Placebo + MTX**
Burmester GR 2013	Improvement HAQ-DI ≥ 0.22	71 / 131	----------	53 / 131
Study	**Outcome**	**BARI 4 mg**	**BARI 2 mg**	**Placebo**
Genovese MC 2016	Improvement HAQ-DI ≥ 0.22	118 / 177	----------	75 / 176
Study	**Outcome**	**UPA 15 mg**	**UPA 30 mg**	**Placebo**
Genovese MC 2018	Improvement HAQ-DI ≥ 0.22	102 /164	----------	64 / 169
Study	**Outcome**	**FILGO 200 mg**	**FILGO 100mg**	**Placebo**

Genovese MC 2019	Improvement HAQ-DI ≥ 0.22	96 / 144	98 / 148	64 / 144

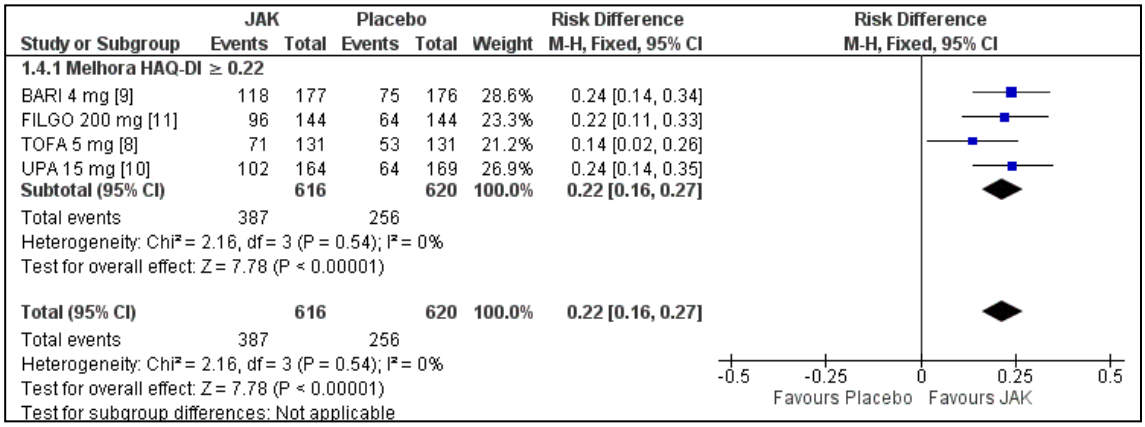

Figure 5. Forest plot of comparison: 1 Janus Kinase inhibitors versus Placebo, outcome: 1.4 Functional capacity assessed by HAQ-DI ≥0.22.

SAFETY

Regarding serious adverse effects, there was no statistically significant difference when comparing the different JAKi evaluated in this review, compared to placebo, Figure 6.

Table 4. Results of serious adverse events of JAKs in patients with RA, up to 3 months

Study	Outcome	TOFA 5 mg BID = MTX	TOFA 10 mg BID = MTX	Placebo + MTX
Burmester GR 2013	Serious adverse events	2 / 133	----------	6 /132
Study	**Outcome**	**BARI 4 mg**	**BARI 2 mg**	**Placebo**
Genovese MC 2016	Serious adverse events	11 / 177	----------	7 / 176
Study	**Outcome**	**UPA 15 mg**	**UPA 30 mg**	**Placebo**
Genovese MC 2018	Serious adverse events	8 /164	12 /165	0 /169
Study	**Outcome**	**FILGO 200 mg**	**FILGO 100mg**	**Placebo**
Genovese MC 2019	Serious adverse events	6 / 147	8 / 153	5 / 148

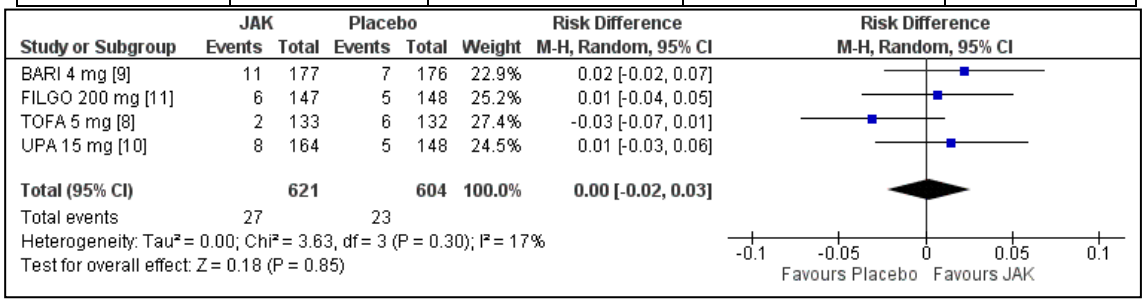

Figure 6. Forest plot of comparison: 1 Janus Kinase inhibitors versus Placebo, outcome: 1.5 Serious adverse events.

Table 5. Certainty assessment - tsDMARD effectiveness after bDMARD failure

Outcome	Potential absolute effects * (95% CI)		Relative Effect (95% CI)	№ (studies)	Certainty of the evidence (GRADE)
	PBO risk	JAKi risk			
(DAS28 - VHS < 2.6)	14 per 1.000	64 per 1.000 (22 to 185)	RR 4.71 (1.62 to 13.71)	592 (2 RCT)	⊕⊕⊕⊕ HIGH

Outcome	Potential absolute effects * (95% CI)		Relative Effect (95% CI)	№ (studies)	Certainty of the evidence (GRADE)
	PBO risk	JAKi risk			
(DAS28 -VHS ≥ 2.6 ≤3.2)	44 per 1.000	128 per 1.000 (70 to 236)	RR 2.92 (1.59 to 5.37)	592 (2 RCT)	⊕⊕⊕⊕ HIGH
ACR20/50/70 - ACR20	279 per 1.000	577 per 1.000 (499 for 666)	RR 2.07 (1.79 to 2.39)	1244 (4 RCT)	⊕⊕⊕⊕ HIGH
ACR20/50/70 - ACR50	112 per 1.000	346 per 1.000 (271 for 441)	RR 3.08 (2.42 to 3.93)	1244 (4 RCT)	⊕⊕⊕⊕ HIGH
ACR20/50/70 - ACR70	43 per 1.000	153 per 1.000 (83 for 281)	RR 3.53 (1.91 to 6.49)	1244 (4 RCT)	⊕⊕⊕⊕ HIGH
[DAS28 (CRP) ≤3.2]	148 per 1.000	421 per 1.000 (313 for 565)	RR 2.84 (2.11 to 3.81)	628 (2 RCT)	⊕⊕⊕⊕ HIGH
Improvement of HAQ-DI ≥ 0.22	413 per 1.000	628 per 1.000 (562 for 702)	RR 1.52 (1.36 to 1.70)	1236 (4 RCT)	⊕⊕⊕⊕ HIGH
Serious adverse events	38 per 1.000	45 per 1.000 (26 for 79)	RR 1.18 (0.67 to 2.08)	1225 (4 RCT)	⊕⊕⊕⊕ HIGH

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