Comparison of the efficacy of Janus kinase inhibitors and adalimumab in rheumatoid arthritis: a meta-analysis

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Abstract

Objective

Rheumatoid arthritis (RA) is a prevalent autoimmune disorder. This study examines the comparative efficacy of Janus kinase inhibitors (JAKi) and adalimumab (ADA) in managing RA.

Methods

As of May 2024, four electronic databases were systematically reviewed: PubMed, Web of Science, Embase, and the Cochrane Library. Data were analysed using Review Manager (RevMan) software. The risk ratio (RR) and its 95% confidence interval (CI) represented dichotomous outcomes. Evaluated outcome measures included ACR20, ACR50, ACR70, Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI), and Disease Activity Score 28-4 (C-reactive protein) (DAS28-4(CRP)).

Results

The analysis encompassed 6 studies, totalling 4048 patients with RA. There was no statistically significant difference in efficacy between JAKi and ADA when assessing ACR20 (p=0.25) and DAS28-4(CRP) (p=0.57). However, JAKi demonstrated superior efficacy compared to ADA for ACR50 (RR=1.20; p=0.02), ACR70 (RR=1.24; p=0.03), CDAI (RR=1.17; p=0.01), and SDAI (RR=1.19; p=0.006) outcomes. Longitudinal analysis revealed that over a 52-week period, JAKi did not exhibit superior efficacy to ADA for ACR50 (RR=1.16; p=0.19) and ACR70 (RR=1.10; p=0.26). Specifically, the tofacitinib subgroup outperformed ADA (RR=1.49; p=0.003), while other JAKi treatments did not show a significant difference (RR=1.19; p=0.11) compared to ADA.

Conclusion

JAKi generally offers better efficacy than ADA in the treatment of RA, though this advantage appears to be influenced by the duration of treatment.

Key words

rheumatoid arthritis, Janus kinase inhibitors, adalimumab, efficacy, meta-analysis.

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Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease that primarily affects the joints, including those in the hands, wrists, feet, ankles, knees, shoulders, and elbows (1). As of 2019, RA afflicted approximately 18 million individuals globally, with women constituting about 70% of this demographic (2). RA has emerged as the sixth leading cause of long-term mobility impairments or disabilities worldwide (3).

The primary therapeutic agents for RA include non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs), glucocorticoids, biological agents, and targeted therapies. The efficacy of these treatments is often limited by adverse drug reactions and varying patient response rates, prompting ongoing research into novel RA medications. Traditional treatments such as NSAIDs, DMARDs, and glucocorticoids are associated with several adverse effects, including gastrointestinal distress, liver damage, and diabetes mellitus (4).

In recent years, advances in biological and targeted therapies have been significant. Biological DMARDs (bDMARDs), such as tumour necrosis factor inhibitors-α (TNFi-α), with adalimumab (ADA) being a prominent example, have shown efficacy in combination with methotrexate (MTX) in slowing joint damage progression (as evidenced by x-ray) and enhancing physical function (5). However, ADA use can lead to complications, including infections, pain, abnormal blood markers, neurological effects, and certain lymphoid malignancies (5).

Janus kinase inhibitors (JAKi) represent a newer class of small molecule targeted oral drugs for RA treatment. JAKis, such as tofacitinib – the first approved JAKi – have demonstrated efficacy in phase III trials among patients who were either untreated with conventional synthetic DMARDs (csDMARDs) or had inadequate responses to csDMARDs and bDMARDs (6, 7). Although previous meta-analyses comparing JAKi with ADA suggested that JAKis are more effective, these analyses were limited to four articles and lacked extensive subgroup analyses.

Given recent publications of new randomised controlled trials (RCTs) and the need for more comprehensive assessments, this study aims to conduct an updated meta-analysis to explore the differences in efficacy between JAKi and ADA for treating RA.

Methods

Literature retrieval strategy

This meta-analysis systematically searched four databases: PubMed, Cochrane Library, Web of Science, and Embase, up to May 2024. We employed a combination of Medical Subject Headings (MeSH) and free-text terms in English, including "Adalimumab," "Tumor Necrosis Factor Inhibitors-α," "Janus Kinase Inhibitor," and "Rheumatoid Arthritis." The search strategy was structured as follows: (((((Adalimumab) OR (TNFi-α)) OR (Tumor Necrosis Factor Inhibitors-α)) AND ((Rheumatoid Arthritis) OR (RA))) AND ((((((Tofacitinib) OR (Baricitinib)) OR (Filgotinib)) OR (Upadacitinib)) OR (JAKi)) OR (Janus Kinase Inhibitor)). Searches were conducted using full-text filters, and manual screening was performed to select relevant literature. References of the articles were reviewed to ensure thoroughness.

EndNote X7 (Thomson Reuters, Toronto, ON, Canada) was utilised to manage and remove duplicates among retrieved records. We focused on identifying randomised controlled trials (RCTs) comparing JAK inhibitors (JAKi) and ADA for the treatment of RA, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines for transparent reporting (8). This study is registered with PROSPERO, an international database for registered systematic reviews in health and social care. Detailed meta-analysis protocol can be accessed via PROSPERO at ID: CRD42024553279.

Literature screening was independently conducted by two researchers based on predefined inclusion and exclusion criteria. Discrepancies were resolved through discussion with a third-party arbitrator when necessary.

Inclusion and exclusion criteria

The criteria for including studies in this

meta-analysis were based on the PICOS (Population, Intervention, Comparator, Outcomes, Study Design) framework, which was predetermined by the authors. The specific criteria are as follows:

Population (P): Studies must include participants diagnosed with rheumatoid arthritis (RA), aged 18 years or older, with no restrictions based on ethnicity or nationality.

Intervention (I): Participants in the trial group must have received JAKis, including, but not limited to, tofacitinib, baricitinib, filgotinib, and upadacitinib.

Comparator (C): The control group must have been treated with ADA.

Outcomes (O): Primary outcome measures include, but are not limited to, ACR20, ACR50, ACR70, Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI), and Disease Activity Score 28-4 (C-reactive protein) (DAS28-4(CRP)).

Study Design (S): Only randomised controlled trials (RCTs) were considered for inclusion.

The exclusion criteria for this study encompass non-English literature; only the most comprehensive or recent research is included to ensure relevance and currency. Studies where full texts or essential data are unavailable are also excluded.

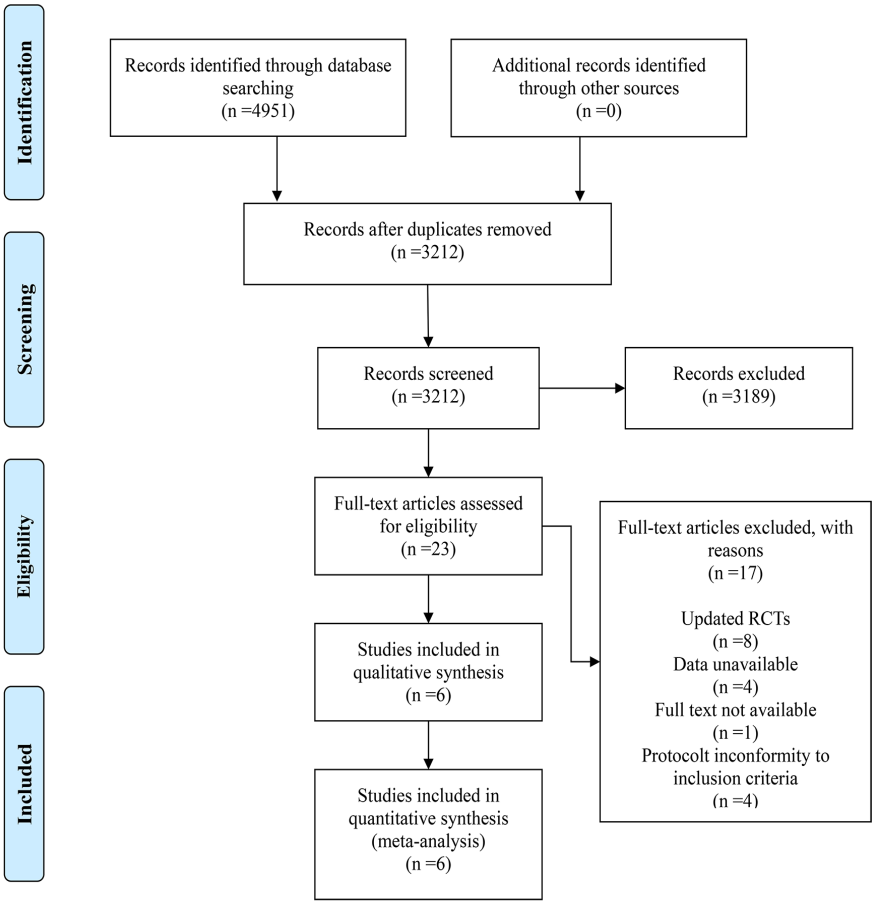

Fig. 1. Flow diagram of the selection process.

Data extraction and outcomes of interest

Data for this meta-analysis were extracted based on a structured protocol predefined by the authors. The extracted variables from each study included the authors, country, year of publication, treatment ratio, follow-up duration, outcome assessment, and efficacy. The efficacy outcomes considered were ACR20, ACR50, ACR70, Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI), and Disease Activity Score 28-4 (CRP) (DAS28-4(CRP)).

- ACR20 is defined as a reduction of at least 20% in both swollen and tender joint counts, accompanied by a minimum 20% improvement in three or more of the following five core measures: global assessment of disease activity (*e.g.* Visual Analogue Scale (VAS)), global disease activity assessed by healthcare providers (*e.g.* Health Services Administration), patient pain assessment (*e.g.* VAS), functional disability (*e.g.* provided by health assistance agencies), and acute phase reactants (erythrocyte sedimentation rate - ESR) or C-reactive protein - CRP) (9).
- ACR50 denotes a reduction of at least 50% in swollen and tender joint counts, along with a 50% - improvement in at least three of the five core measures.
- ACR70 signifies a reduction of at least 70% in swollen and tender joint counts, with a corresponding 70% improvement in at least three of the five core measures.
- CDAI is utilised to evaluate the clinical disease activity in RA. This index includes: 1. number of tender joints out of 28; 2. number of swollen joints out of 28; 3. patient's assessment of disease activity on a scale from 0 to 10; 4. physician's global assessment of disease activity on a scale from 0 to 10 (10).
- SDAI extends the CDAI by incorporating the serum hypersensitive CRP level (mg/L) and is employed to assess treatment efficacy in RA. It comprises the number of tender joints out of 28, number of swollen joints out of 28, patient's assessment of disease activity (0–10 points), physician's overall assessment (0–10 points), and serum hypersensitive CRP level (10).
- DAS28-4 (CRP) provides a quantifiable measure of RA disease activity based on hypersensitive CRP levels, including 1. CRP level in serum (mg/L); 2. number of tender joints out of 28; 3. number of swollen joints out of 28; 4. patient's assessment of disease activity (0–10 points) (11).

Literature quality evaluation

The quality of the included literature was assessed using the bias assessment tool recommended by the Cochrane Handbook for Systematic Reviews of Interventions, version 5.3.5. This evaluation covered several domains: method of randomisation, allocation concealment, blinding of participants,

Table I. Characteristics of all the studies included in the meta-analysis.

Author	Year	Clinicaltrials.gov number	Treatment regimens		Number of patients		Follow-up (week)	Staging of clinical trials	Outcome measures
			Experiment	Control	Experiment	Control			
Fleischmann R.M.	2019	NCT02629159	upadacitinib 15 mg + MTX	ADA 40 mg + MTX	651	327	52	phase III	ACR20, ACR50, ACR70, CDAI, SDAI, DAS28-4 (CRP)
Keystone E.C.	2017	NCT01710358	baricitinib 4 mg + MTX	ADA 40 mg + MTX	487	330	52	phase III	ACR20, ACR50, ACR70, CDAI, SDAI, DAS28-4 (CRP)
Strand V.	2019	NCT02187055	tofacitinib 5 mg + MTX	ADA 40 mg + MTX	384	386	52	phase IIIB/IV	ACR20, ACR50, ACR70, CDAI, SDAI, DAS28-4 (CRP)
Combe B.	2021	NCT02889796	filgotinib 200 mg + MTX	ADA 40 mg + MTX	477	352	52	phase III	ACR20, ACR50, ACR70, CDAI, SDAI, DAS28-4 (CRP)
			filgotinib 100 mg + MTX		480				
van Vollenhoven R.F.	2012	NCT00853385	tofacitinib 5 mg + MTX	ADA 40 mg + MTX	204	204	52	phase III	ACR20, ACR50, ACR70
			tofacitinib 10 mg + MTX		201				
Fleischmann R.M.	2012	NCT00550446	tofacitinib 1 mg	ADA	54	53	24	phase IIb	ACR20, ACR50, ACR70
			tofacitinib 3 mg	40 mg	51				
			tofacitinib 5 mg		49				
			tofacitinib 10 mg		61				
			tofacitinib 15 mg		57				

MTX: methotrexate; ADA: adalimumab; ACR20: American College of Rheumatology 20; ACR50: American College of Rheumatology 50; ACR70: American College of Rheumatology 70; CDAI: Crohn's disease activity index; SDAI: Simplified disease activity index; DAS28-4 (CRP): 28 joint disease activity scores based on erythrocyte sedimentation rate.

personnel and outcome assessors, completeness of outcome data, selective reporting, and other potential biases. Each domain was judged as presenting a low risk of bias, high risk of bias, or unclear risk of bias.

Statistical analysis

Statistical analyses were conducted using Review Manager (RevMan, The Cochrane Collaboration; v. 5.3.5). Dichotomous outcomes were expressed as risk ratios (RR) with their 95% confidence intervals (CI). Study heterogeneity was assessed using the chi-square (χ^2) test and quantified by the I^2 statistic. A threshold of $p<0.05$ and $I^2>50\%$ was interpreted as indicating substantial heterogeneity, whereas $p\geq0.05$ and $I^2\leq50\%$ suggested low heterogeneity (12).

Results favouring the experimental group were indicated by an RR >1, while an RR <1 suggested outcomes favouring the control group. Given the potential and inevitable variability among the included studies, such as differences in population ethnicity and drug regimens, a random-effects model was employed to provide a more reliable interpretation of the data.

Publication bias was assessed using funnel plots. All statistical tests were two-sided, with a significance threshold set at $p<0.05$.

Results

Study selection

Through systematic searches of PubMed, the Cochrane Library, Web of Science, and Embase, a total of 4951 records were retrieved. After removing duplicates, 3212 records remained. Screening by titles and abstracts resulted in the exclusion of 3189 records, leaving 23 articles for full-text assessment. Of these, 17 were excluded for various reasons: 8 were updated randomised controlled trials (RCTs), 4 lacked necessary data, 1 was unavailable in full-text, and 4 did not meet the inclusion criteria. Ultimately, 6 studies were included in the analysis (13-18). The detailed selection process is depicted in the PRISMA flowchart (Fig. 1).

Study characteristics

The included studies were published between 2010 and 2020, encompassing a total of 4048 RA patients. Of these, 3156 were treated with JAK inhibitors (JAKi) and 1652 with ADA (13-18). In the JAKi group, 1061 patients were treated with tofacitinib, 651 with upadacitinib, 487 with baricitinib, and 957 with filgotinib. Five of the six studies utilised MTX concomitantly (13-16, 18), while one study did not involve MTX (17). The follow-up durations ranged from 24 to 52 weeks. Four studies were phase III (13, 14, 16, 18), one was phase IIIB/IV (15), and one was phase IIb (17). Outcomes measured included ACR20, ACR50, ACR70, Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI), and Disease Activity Score 28-4 (C-reactive protein) (DAS28-4(CRP)). Specific characteristics of each study are detailed in Table I. Additional recruitment details and inclusion criteria for subjects, requiring active RA with tenderness in at least 6 out of 68 joints and swelling in at least 6 out of 66 joints, are included in Supplementary Table S1.

Quality assessment of included studies

The quality of the included studies was assessed using the bias assessment tool recommended in the Cochrane Handbook for Systematic Reviews of Interventions, version 5.3.5. The risk of selection bias was deemed low due

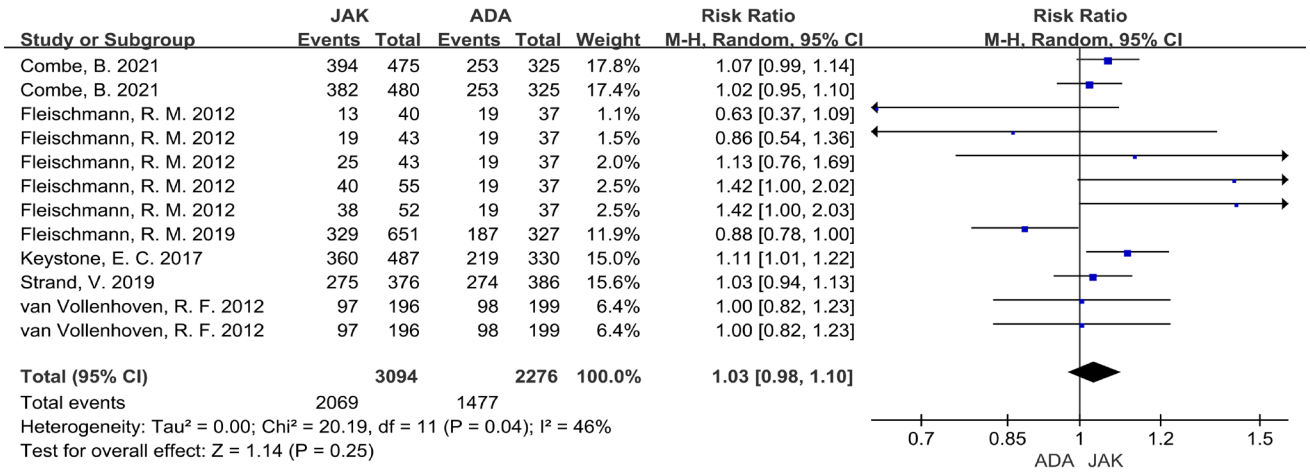

Fig. 2. Forest plot of a meta-analysis assessing differences in efficacy of JAKi and ADA in RA using ACR20 as an outcome measure.

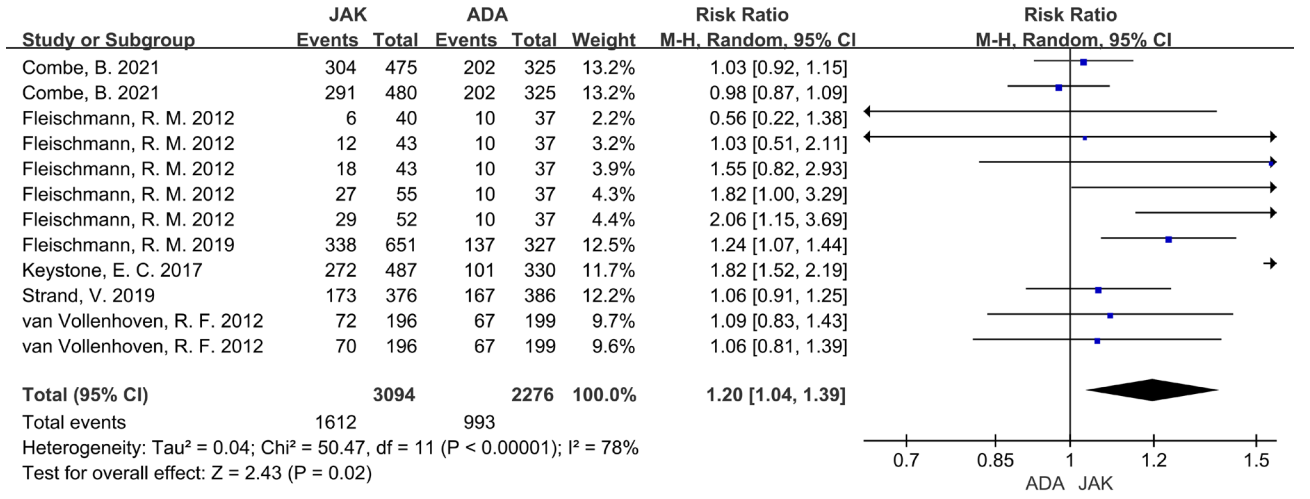

Fig. 3. Forest plot of a meta-analysis assessing differences in efficacy of JAKi and ADA in RA using ACR50 as an outcome measure.

to well-documented random sequence generation and patient randomisation methods. Adequate descriptions within the studies ensured clear delineation of blinding methods, minimising performance and detection biases. The risk of attrition and reporting biases was also considered low, as the criteria for measuring outcomes were well-defined, and the reporting of data was comprehensive. However, the risk of other potential biases remains unclear due to insufficient information to make a definitive assessment (Suppl. Fig. S1-S2).

Meta-analysis and subgroup analyses - ACR analysis

A total of six studies reported ACR20 outcomes. The pooled analysis revealed no significant difference in ACR20 response rates between the JAK inhibitor (JAKi) group and the ADA group (RR=1.03, p=0.25; Fig. 2). Similarly, subgroup analyses stratified by follow-up duration demonstrated no significant difference between the two groups at both 24 weeks (RR=1.04, p=0.47) and 52 weeks (RR=1.04, p=0.11). There was also no significant difference observed in subgroups combining JAKi or ADA with MTX (RR=1.03, p=0.30). When stratified by specific JAKi, the tofacitinib group showed no significant difference compared to the ADA group (RR=1.16, p=0.08), and similar results were obtained for the other JAKi subgroup *versus* the ADA group (RR=1.22, p=0.11).

When ACR50 was used as the outcome measure, the pooled analysis indicated that the ACR50 response rate was significantly higher in the JAKi group compared to the ADA group, albeit with a high degree of heterogeneity (RR=1.20; 95% CI: 1.04–1.39; p=0.02; I^2=78%; Fig. 3). Subgroup analysis revealed that at 24 weeks of follow-up, the JAKi group exhibited a significantly higher ACR50 response compared to the ADA group (RR=1.24; 95% CI: 1.02–1.50; p=0.03; I^2=46%). However, this difference was not significant at 52 weeks (RR=1.16, p=0.19). No significant differences were found in the MTX combination subgroup (RR=1.16, p=0.07). Furthermore, there was no significant difference in ACR50 response between the tofacitinib group and the ADA group (RR=1.16, p=0.08), nor between the other JAKi subgroup and the ADA group (RR=1.22, p=0.11).

Six studies provided data on ACR70. The pooled analysis indicated that the JAK inhibitor (JAKi) group had a significantly higher response rate compared to the ADA group (RR=1.30;

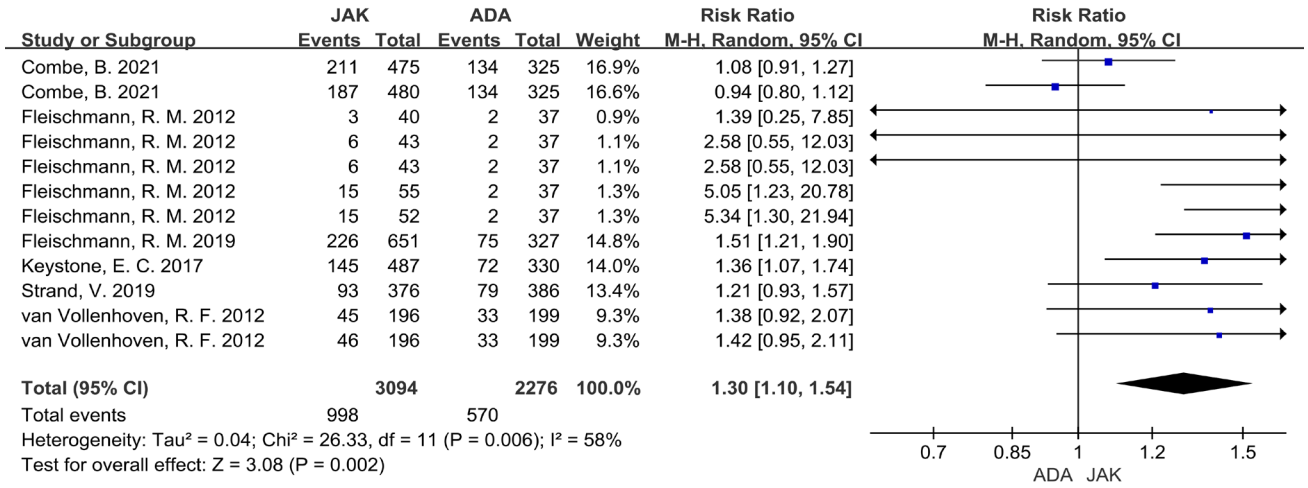

Fig. 4. Forest plot of a meta-analysis assessing differences in efficacy of JAKi and ADA in RA using ACR70 as an outcome measure.

95% CI: 1.10–1.54; p=0.002; I^2=58%; Fig. 4). Subgroup analysis based on follow-up duration revealed that the JAKi group performed significantly better than the ADA group at the 24-week follow-up (RR=1.47; 95% CI: 1.20–1.79; p<0.001; I^2=27%), but no significant difference was observed at the 52-week follow-up (RR=1.10, p=0.26). The combined MTX subgroup analysis showed no significant difference between the two groups (RR=1.22, p=0.08). Further subgroup analysis by JAKi type indicated that the tofacitinib group outperformed the ADA group (RR=1.49; 95% CI: 1.15–1.94; p=0.003; I^2=24%), whereas no significant difference was observed between the other JAKi subgroup and the ADA group (RR=1.19, p=0.11).

When Clinical Disease Activity Index (CDAI) was used as the outcome measure, the pooled analysis demonstrated that the JAKi group was superior to the ADA group (RR=1.17; 95% CI: 1.03–1.33; p=0.01; I^2=0%; Suppl. Fig. S3). Similarly, when Simplified Disease Activity Index (SDAI) was used as the outcome measure, the pooled results also favoured the JAKi group over the ADA group (RR=1.19; 95% CI: 1.05–1.35; p=0.006; I^2=0%; Suppl. Fig. S4). However, no significant difference between the two groups was observed when Disease Activity Score in 28 joints using C-reactive protein (DAS28-4 [CRP]) was used as the outcome measure (RR=1.04, p=0.57; Suppl. Fig. S5).

- Publication bias

Funnel plots were generated to assess publication bias for ACR20, ACR50, and ACR70 outcomes. The results indicated that all funnel plots were approximately symmetric, suggesting no significant publication bias. Detailed funnel plots can be found in Supplementary Figures S6, S7, and S8.

Discussion

In this study, six randomised controlled trials (RCTs) were included to compare the efficacy of JAKis and ADA in the treatment of rheumatoid arthritis (RA) (13-18). Five of the studies involved new patients on biotherapy. The results indicated that there was no significant difference in efficacy between JAKi and ADA based on ACR20 and DAS28-4 (CRP) outcomes. However, JAKi demonstrated superior efficacy in achieving ACR50, ACR70, Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI) responses. Notably, the superiority of JAKi over ADA diminished with prolonged treatment duration.

RA is a common chronic autoimmune disease characterised by the infiltration of various immune cells, such as B cells, T cells, and macrophages, into synovial tissues, which perpetuates local inflammation (1). Pro-inflammatory cytokines and chemokines released from synovial inflammatory tissues further recruit and activate immune cells, promoting a cycle of inflammation through multiple signalling pathways, including the JAK pathway (19, 20). This cascade leads to the amplification of the inflammatory response and ultimately results in chronic joint damage (19).

ADA is a recombinant, fully human IgG1 monoclonal antibody that specifically binds to tumour necrosis factor-α (TNF-α), thereby blocking its interaction with TNF-α receptors (p55 and p75) on the surface of cells and neutralising its biological function (5). Additionally, ADA modulates other TNF-mediated biological effects, such as the regulation of adhesion molecule levels crucial for leukocyte migration (5). Treatment with ADA has been shown to rapidly reduce levels of acute-phase inflammatory markers, including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), as well as serum cytokine levels (*e.g.* interleukin-6) in RA patients compared to baseline (21). Moreover, serum concentrations of matrix metalloproteinases (*e.g*, matrix metallopeptidase 1 and matrix metallopeptidase 3), which contribute to tissue remodelling and cartilage destruction, are also significantly decreased following ADA treatment, ultimately leading to disease control (21).

Unlike traditional biologic agents that target a single molecule, JAK inhibitors (JAKi) can simultaneously block the signal transduction of multiple cytokines. JAKi selectively inhibit JAK phosphorylation by mimicking the structure of adenosine triphosphate (ATP) without the phosphate group, thereby disrupting the recruitment and

Table II. Subgroup analysis of ACR20, ACR50 and ACR70.

Subgroup	no. of studies	RR	95%CI	*p*	Heterogeneity	
					I^2	*p*
Duration of follow-up (ACR20)						
24 weeks	4	1.04	0.93, 1.17	0.47	46%	0.007
52 weeks	2	1.04	0.99, 1.09	0.11	0%	0.82
Basic treatment (ACR20)						
MTX	5	1.03	0.98, 1.08	0.30	41%	0.12
JAK (ACR20)						
Tofacitinib	3	1.05	0.94, 1.17	0.37	32%	0.18
Other JAK	3	1.03	0.95, 1.11	0.53	70%	0.02
Duration of follow-up (ACR50)						
24 weeks	3	1.24	1.02, 1.50	0.03	46%	0.08
52 weeks	3	1.16	0.93, 1.46	0.19	89%	<0.001
Basic treatment (ACR50)						
MTX	5	1.16	0.99, 1.35	0.07	85%	<0.001
JAK (ACR50)						
Tofacitinib	3	1.16	0.98, 1.38	0.08	35%	0.15
Other JAK	3	1.22	0.95, 1.55	0.11	93%	<0.001
Duration of follow-up (ACR70)						
24 weeks	4	1.47	1.20, 1.79	<0.001	27%	0.21
52 weeks	2	1.10	0.93, 1.30	0.26	46%	0.14
Basic treatment (ACR70)						
MTX	5	1.22	1.05, 1.42	0.08	61%	0.02
JAK (ACR70)						
Tofacitinib	3	1.49	1.15, 1.94	0.003	24%	0.24
Other JAK	3	1.19	0.96, 1.47	0.11	78%	0.004

ACR20: American College of Rheumatology 20; ACR50: American College of Rheumatology 50; ACR70: American College of Rheumatology 70; MTX: methotrexate; JAK: Janus kinase; RR: relative risk; 95%CI: 95% confidence interval.

phosphorylation of cytokine receptors and preventing the activation of signal transducer and activator of transcription (STAT). As a result, STAT cannot be activated or translocate to the nucleus to initiate the transcription of inflammation-related genes (22, 23). Tofacitinib, a selective inhibitor of JAK-1, JAK-2, and JAK-3, directly inhibits the effects of various inflammatory cytokines, such as interleukin (IL)-6, IL-7, and IL-15, and indirectly inhibits the effects of tumour necrosis factor-α (TNF-α) and IL-1 by suppressing the activation of immune cells, including dendritic cells and B cells (23). In summary, tofacitinib disrupts the inflammatory cascade, leading to a marked reduction in pro-inflammatory cytokine levels in RA patients and ultimately achieving disease control (23). It is important to note that intracellular pathways involving JAKs (JAK-1, JAK-2, JAK-3) and tyrosine kinase 2 (Tyk2) play a critical role in immune cell activation, pro-inflammatory cytokine synthesis, and cytokine signalling (22).

The findings of this study indicate that there is no significant difference in efficacy between JAKi and ADA when ACR20 and DAS28-4 (CRP) are used as outcome measures. This may be attributed to the relatively low therapeutic threshold of these measures, where most therapeutic agents, such as MTX and IL-6 receptor antagonists, can achieve comparable efficacy. Patients treated with either JAKi or ADA can reach ACR20 and DAS28-4 (CRP) response levels (7). The stability of ACR20 across subgroup analyses, which included variations in treatment follow-up duration, background therapies, and different types of JAKi, further supports this observation.

When ACR 50 and ACR 70 are used as outcome measures, due to the high heterogeneity of JAKi, we cannot claim that all JAKi are better than ADA, but only to show that the average efficacy of all JAKi in the included study had somewhat advantage over ADA. This may be due to the higher therapeutic thresholds of ACR50 and ACR70, which result in fewer patients meeting these criteria, thereby highlighting the greater effectiveness of JAKi. As described in the previous mechanistic explanation, JAKi competitively block ATP binding sites in the JAK homology 1 (JH1) domain through non-covalent interactions (22). This binding site, along with active domains of other tyrosine kinases (Tyk), binds specifically to JAKi, enabling JAKi to selectively inhibit JAKs without off-target effects (9). This mechanism is inherently more effective than ADA's antigen-antibody binding approach (5). By blocking the molecular signal transduction at the source of the signalling pathway, JAKi are more effective in inhibiting downstream cytokines compared to ADA (22). Consequently, JAKi offer a faster, more precise, and less resistance-prone therapeutic option (22).

Additionally, considering the confounding nature of including JAKi, we can only consider that the average efficacy of all JAKi has a certain advantage over ADA in achieving CDAI and SDAI responses. This is likely due to the higher therapeutic thresholds of CDAI and SDAI, which result in a reduced number of patients reaching the target levels (10). These findings further confirm the superiority of all JAKi average efficacy in the study.

The efficacy of JAKis diminishes over time. The underlying mechanism involves the gradually decreasing intensity of anti-drug antibodies (ADA), which requires time to accumulate to achieve optimal efficacy (5). Over an extended treatment period, ADAs in the serum can significantly neutralise related cytokines, thus exerting potent biological effects and enhancing therapeutic efficacy (5). Ultimately, this leads to higher disease remission rates among patients (5). In summary, while the effects of JAKi are more immediate, ADA-based treatments can eventually attain comparable efficacy levels.

When evaluating efficacy using ACR50 and ACR70 as benchmarks, subgroup analyses of JAKi demonstrate that tofacitinib offers significant advantages. This superiority can be attributed to its inhibition of JAK-1, JAK-2, and JAK-3, with functional cells predominantly favouring JAK-1 and JAK-3 (16). Conversely, baricitinib inhibits JAK-1 and JAK-2 but lacks inhibitory effects on JAK-3 and Tyk2 (24). Upadacitinib

and filgotinib primarily inhibit JAK-1, with lesser effects on Tyk2, JAK-2, and JAK-3 (25). Thus the broader spectrum of inhibition of tofacitinib, particularly targeting the JAK-1 and JAK-3 pathways preferred by functional cells, outperforms other JAKis (16). Additionally, the larger body of research focusing on tofacitinib facilitates the achievement of statistically significant differences (15-17).

Notably, when both the JAKi and ADA groups used the same drug, MTX, the effect of MTX as a single variable could be controlled to more accurately assess the effect of other treatments. This approach helps to reduce confounders and makes the results more reliable.

RA has a longer disease duration, and this study did not cover the full period of RA, but the long-term use of JAKi still has superior aspects over ADA. First, JAKi are oral drugs, compared to ADA requiring injection, JAKi provides more convenience and helps to improve patient compliance (26). Second, the continuous long-term extension study of the SELECT-COMPARE study evaluates the long-term efficacy of upadacitinib and ADA in RA patients, it shows that the proportion of patients who reached CDAI ≤10, CDAI ≤2.8, DAS28-CRP<3.2, DAS28-CRP <2.6 at week 26, week 48, week 72, week 120 and week 156 is higher in upadacitinib combined with MTX group than in ADA combined with MTX group (27). In addition, ADA decreases the activity of the immune system by inhibiting TNF-α, which may lead to excessive suppression of the immune system and increase the risk of infection, especially in severe bacterial, viral or fungal infections (5). JAKi has shown better safety in some studies, especially low-dose filgotinib has emerged as a safety marker for adverse events (26).

The strength of this study lies in its systematic comparison of the efficacy of JAKi *versus* ADA in treating rheumatoid arthritis, supplemented by detailed subgroup analyses. However, the study is limited by the small number of included studies, restricting the ability to conduct extensive subgroup analyses. Moreover, due to the excessive variety of JAKi included in this study, with great heterogeneity, we cannot prove that the efficacy of JAKi in all included studies is better than ADA, we can only think that the average efficacy of JAKi included in the study is superior to ADA to some extent; meanwhile, ADA is a widely used TNFi, but ADA cannot represent all TNFi, and this study cannot indicate that all TNFi is inferior to RA than JAKi. In addition, the patients included in this study are patients with moderate to severe RA, which led to the fact that our study population did not have a realistic universal value, and the majority of patients had a good response to JAKi and ADA, a small proportion of moderate to severe RA patients will show the difference between JAKi and ADA.

Conclusion

This study demonstrates that the average efficacy of the 5 JAKi in the included studies is more effective than ADA across various outcomes – ACR50, ACR70, CDAI, and SDAI – particularly in RA patients treated with tofacitinib. Notably, the superiority of JAKi diminishes with longer treatment durations. To substantiate these findings, further research involving larger, high-quality, multi-centre RCTs is required.

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