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Original article

Efficacy and safety of Janus kinase inhibitors in patients with ankylosing spondylitis: A systematic review and meta-analysis

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ABSTRACT

Objectives: To assess the efficacy and safety of janus kinase (JAK) inhibitors in the treatment of ankylosing spondylitis (AS).

Methods: We searched the PubMed and Cochrane Central Register of Controlled Trials to Nov 1, 2021. We included all randomized controlled trials (RCTs) evaluating JAK inhibitors in the treatment of AS. Two reviewers independently selected studies, extracted data and assessed the risk of bias.

Results: Four RCT studies with 779 participants were included in the meta-analysis. Compared with placebo group, percentages of participants achieving responses of Assessment of spondyloarthritis international society (ASAS) 20, ASAS 40, ASAS 5/6, Bath AS disease activity index (BASDAI) 50 were significantly higher in JAK inhibitor group respectively; changes from baseline in AS disease activity score using C-reactive protein(ASDAS-CRP), Maastricht AS enthesitis score (MASES), AS Quality of Life (ASQoL) score, short-form-36 health survey physical component summary (SF-36 PCS) score, BASDAI, Bath AS functional index (BASFI), Bath AS metrology index (BASMI), Functional Assessment of Chronic Illness Therapy-fatigue (FACIT-F) score, SPARCC joint score and Work Productivity and Activity Impairment (WPAI) Overall Work Impairment score showed significant improvements in JAK inhibitor group. The incidence of adverse events (AEs) and severe adverse events (SAEs) showed no significant differences between the JAK inhibitor and placebo groups.

Conclusions: JAK inhibitors showed a satisfactory and promising efficacy in the treatment of active AS not only in mitigating disease activity, but also substantially improving patient's physical function, emotional well-being and social participation. The results of this meta-analysis provide solid evidence for JAK inhibitor as a novel therapeutic strategy for patients with active AS.

1. Introduction

Ankylosing spondylitis (AS), also known as radiographic axial spondyloarthritis, is the advanced disease stage of axial spondyloarthritis (axSpA) [1]. It was characterized by enthesitis involving the spine, inflammation of sacroiliac joints, and inflammatory low back pain, leading to functional impairment, irreversible structural damage and loss of quality of life and work productivity [2]. The prevalence of AS is about 0.5% worldwide and is more common in men [1,3]. Therapy options for AS are limited because conventional synthetic disease modifying antirheumatic drugs(cDMARDs) routinely used for RA are not effective in alleviating axial symptoms of AS [1]. According to the Assessment of SpondyloArthritis international Society (ASAS) and European League Against Rheumatism (EULAR) recommendations, non-steroidal antiinflammatory drugs (NSAIDs) are recommended as first-line therapy for AS [4]. For patients who have inadequate or no responses to NSAIDs, biological disease-modifying anti-rheumatic drug (bDMARD) is recommended [4]. Anti-tumor necrosis factor (TNF) agents and anti-interleukin (IL)-17 are the only two kinds of bDMARD approved for AS in the recent years. Nevertheless, loss of response to existing bDMARDs remains unsolved for some refractory AS patients [5]. Therefore, additional targeted drugs are needed. Over the past decades, Janus kinases(JAK) inhibitors have been widely used in the treatment of autoinflammatory and immune-mediated diseases, including rheumatoid arthritis(RA), psoriatic arthritis(PsA), psoriasis (Pso) and inflammatory bowel diseases (IBD) [6,7]. With the development and expanding indications of JAK inhibitors, increasing studies have demonstrated that they also provide benefits for patients with AS [6,8]. Thus, we performed a systematic review and meta-analysis of updated RCTs to evaluate the efficacy and safety of JAK inhibitors in the

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treatment of AS.

2. Materials and methods

This meta-analysis was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for conducting and reporting a meta-analysis of RCTs.

2.1. Search strategy

We searched the PubMed and Cochrane Central Register of Controlled Trials to Nov 1, 2021. Search algorithms consisted of the following terms: 'JAK inhibitor', 'Janus Kinase Inhibitor', 'Ankylosing spondylitis', 'Ankylosing Spondylarthritides', 'Ankylosing Spondylarthritis'. We also searched for potentially relevant publications in the reference lists.

2.2. Inclusion criteria

Only randomized placebo-controlled trials involving adult patients with AS were included. At least one experimental group was treated with any of the JAK inhibitors potentially under development for AS. Among a series of articles reporting the same RCT, only the most comprehensive and updated was included. Only studies published in english are considered.

2.3. Study selection and data extraction

The studies were screened and data were extracted by two authors (Shu Li and Ni Mao) independently, and disagreements were settled by the third author (Xi Xie). Clearly irrelevant studies were identified and excluded by reviewing titles or abstracts. The full text of the selected articles was analysed to identify whether it contained information of interest. And we also checked the results posted on ClinicalTrials.gov or EU Clinical Trials Register through the NCT number of each RCT to refine data collection. The following essential information was collected from the included trials: last name of first author, publication year, study design, number of patients, patient characteristics, intervention, and the outcomes of therapeutical effects. Adverse events(AEs) and severe adverse events(SAEs) were further documented. If the data reported formats cannot be used directly, they will be converted into the appropriate format applicable for meta-analysis according to the Cochrane Handbook recommendations.

2.4. Quality assessment

The methodological quality of the included studies were assessed by two authors independently according to the items of the Cochrane quality assessment tool: random sequence generation, allocation concealment, blinding of the participants and personnel, blinding of the outcome assessment, incomplete outcome data, selection reporting, and other bias.

2.5. Statistical analysis

Statistical analyses were performed using Review Manager software (RevMan 5.3, the Cochrane Collaboration, Copenhagen, Denmark). Dichotomous data were described as risk ratios (RRs) with corresponding 95% confidence intervals(CIs), and continuous data were expressed as mean differences (MDs) with 95% CIs. The heterogeneity among studies was evaluated by the I^2 test; I^2>50% indicates significant heterogeneity. Random-effects model was used to cover any heterogeneity among studies, allowing for a more conservative estimate of the effect of individual intervention. Statistical significance was defined as P <0:05. Sensitivity analysis was performed by removing one single study at a time to assess the impact of the removed study.

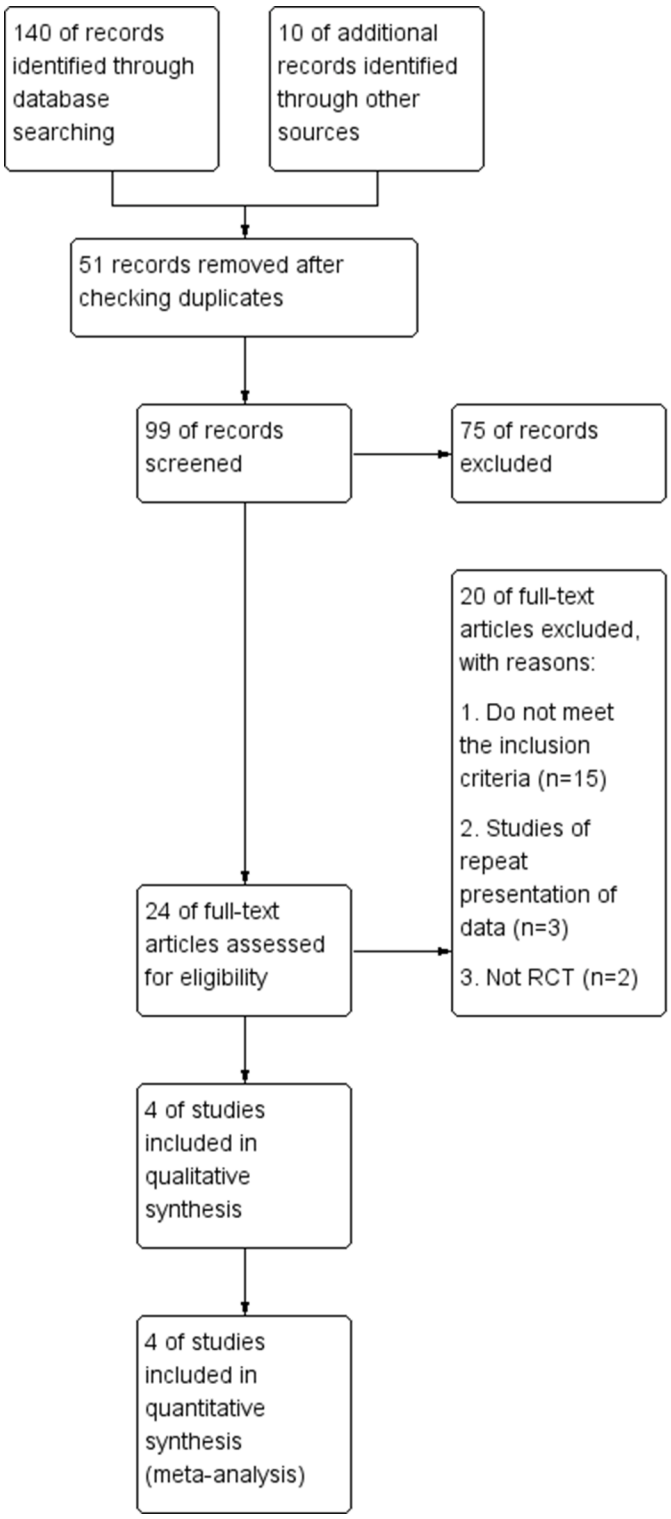

Fig. 1. Flow chart of the literature search.

3. Results

3.1. Study selection

The diagram of study selection flow were demonstrated in Fig. 1. 150 articles were initially identified at the beginning, 51 of which were removed due to duplication. And then, 75 studies were ruled out after going through the titles and abstracts. A total of 24 articles were assessed

Table 1
Characteristic of studies included in the meta-analysis.

Author,year	Clinical trial registration number, Phase	Group	Case	Age: Mean (SD) (Years)	Gender: male(%)	Time frame (weeks)	ASAS20	ASAS40	ASAS5/6	BASDAI50	ASAS Partial Remission	ASDAS Clinically Important Improvement	ASDAS Major Improvement	ASDAS inactive disease	AEs	SAEs
Deodhar,2021 [9]	NCT03502616, III	Tofacitinib 5 mg, bid	133	42.2 (11.9)	116 (87.2%)	16	56.4%	40.6%	43.6%	42.9%	15.0%	61.4%	30.1%	6.8%	54.9%	1.5%
		Placebo	136	40.0 (11.1)	108 (79.4%)	16	29.4%	12.5%	7.4%	17.7%	2.9%	19.1%	4.7%	0.0%	51.5%	0.7%
van der Heijde,2017 [10]	NCT01786668,II	Tofacitinib 2 mg, bid	52	41.8 (12.3)	34 (65.4%)	12	51.9%	42.3%	19.2%	46.2%	17.3%	52.0%	19.2%	13.5%	44.2%	0.0%
		5 mg, bid	52	41.2 (10.3)	39 (75.0%)	12	80.8%	46.2%	50.0%	42.3%	19.2%	63.5%	23.1%	13.5%	53.8%	1.9%
		10 mg, bid	52	41.6 (12.2)	38 (73.1%)	12	55.8%	38.5%	38.5%	42.3%	15.4%	55.8%	25.0%	15.0%	51.9%	1.9%
		Combined*	156	/	/	12	62.9%	42.3%	35.9%	43.6%	17.3%	57.1%	22.0%	14.0%	50.0%	1.3%
		Placebo	51	41.9 (12.9)	32 (62.7%)	12	41.2%	19.6%	15.7%	23.5%	11.8%	27.5%	11.8%	7.8%	43.1%	3.9%
van der Heijde,2019 [11]	NCT03178487,II/III	Upadacitinib 15mg, qd	93	47.0(12.8)	63 (67.7%)	14	64.5%	51.6%	/	45.2%	19.4%	53.0%	32.0%	16.0%	62.0%	1.0%
		Placebo	94	43.7 (12.1)	69 (73.4%)	14	40.4%	25.5%	/	23.4%	1.1%	18.0%	5.0%	0.0%	55.0%	1.1%
van der Heijde,2018 [12]	NCT03117270, II	Filgotinib 200mg,qd	58	41.0(11.6)	45 (78%)	12	75.9%	37.9%	58.6%	24.1%	12.1%	65.5%	32.8%	5.2%	31.0%	1.7%
		Placebo	58	42.0(9.0)	41 (71%)	12	39.7%	19.0%	20.7%	13.8%	3.4%	25.9%	1.7%	0.0%	31.0%	0.0%

* Calculated from the extracted data given according to the Cochrane Handbook recommendations.
ASAS 20: defined as an improvement of $\geq$ 20% and an absolute improvement of $\geq$ 1 unit from Baseline in at least 3 of the 4 domains(PGA, total back pain, BASFI, BASDAI), with no deterioration (defined as a worsening of $\geq$ 20% and a net worsening of $\geq$ 1 units) in the remaining domain; ASAS 40: defined as improvement of $\geq$ 40% relative to Baseline and absolute improvement of $\geq$ 2 units in $\geq$ 3 of the 4 domains(PGA, total back pain, BASFI, BASDAI) with no deterioration (defined as a net worsening of $>$ 0 units) in the potential remaining domain; ASAS 5/6: defined as $\geq$20% improvement in at least 5 of 6 domains (PGA, total back pain, BASFI, BASDAI, CRP and spinal mobility) ; ASAS partial remission: defined as a score of 2 or less in each of the 4 domains in ASAS (PGA, total back pain, BASFI, BASDAI); BASDAI50: defined as decrease of $\geq$50% from Baseline in BASDAI score at specified time points; ASDAS clinically important improvement; defined as change (decrease) from baseline of $\geq$1.1 units; ASDAS major improvement: defined as a response if improvement (decrease) from baseline in ASDAS-CRP of $\geq$2.0 units; ASDAS inactive disease: defined as a response if actual ASDAS-CRP was $<$1.3 units.

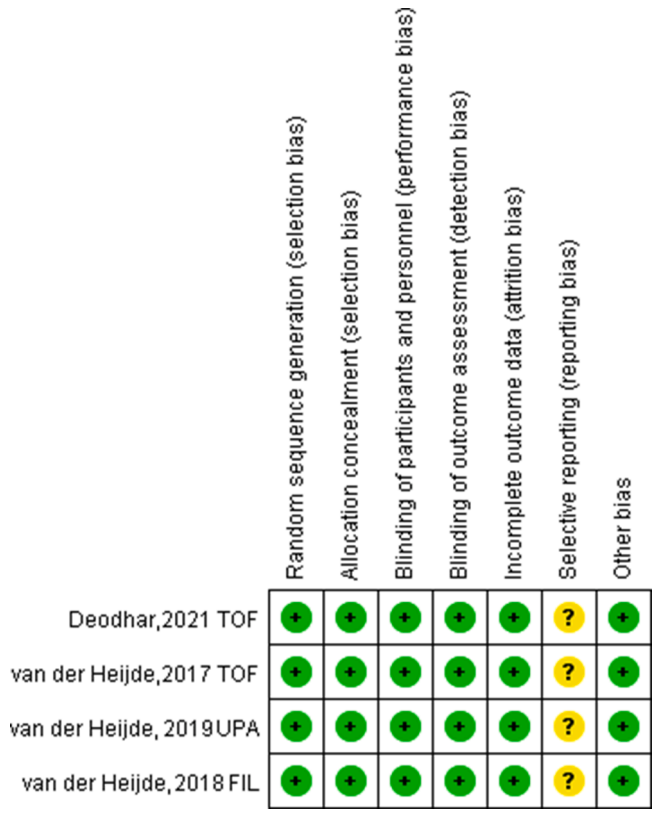

Fig. 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

through reading the full texts for further eligibility; and 20 articles were excluded with the following reasons: not meeting the inclusion criteria, duplicate data reporting, or not RCT study. At last 4 RCTs were included in the meta-analysis [9–12].

3.2. Characteristics of the included studies

Characteristics of the included RCT studies were shown in Table 1. The inclusion criteria included an established diagnosis of adult AS based on the 1984 Modified New York Criteria and active disease despite NSAIDs therapy or intolerant to NSAIDs. Stable dose of cDMARD therapy for at least 4 weeks prior to baseline was allowed. The outcome measures included percentage of participants achieving responses of ASAS 20, ASAS 40, ASAS 5/6, Bath AS disease activity index (BASDAI) 50, ASAS Partial Remission, ASDAS Clinically Important Improvement, ASDAS Major Improvement, ASDAS inactive disease, and changes from baseline in AS disease activity score using C-reactive protein (ASDAS-CRP), Bath AS functional index (BASFI), Bath AS metrology index (BASMI), Maastricht AS enthesitis score (MASES), AS Quality of Life (ASQoL) Score, Short-Form-36 health survey (SF-36) including physical and mental component summary (SF-36 PCS and MCS) scores, Functional Assessment of Chronic Illness Therapy-fatigue (FACIT-F) score and Work Productivity and Activity Impairment (WPAI) Overall Work Impairment score.

3.3. Quality assessment results

Risk of bias summary for each included study was presented in Fig. 2. All of the studies were RCT trials. The patients were randomized to receive either placebo or JAK inhibitor. All trials performed quadruple blinding (participant, care provider, investigator, outcomes assessor).

4. Results of the meta-analysis

4.1. Efficacy of JAK inhibitor versus placebo in treating AS

All of the four RCTs with 779 participants reported the significantly better response rates of ASAS 20, ASAS 40, BASDAI 50, ASDAS Clinically Important Improvement, ASDAS Major Improvement, and ASDAS inactive disease in JAK inhibitor group, and the estimated RRs and 95% CIs were listed in Table 2 and Fig. 3. The response rates of ASAS 5/6 and ASAS Partial Remission were also significantly higher in the JAK inhibitor group than in the placebo group (Table 2, Fig. 3). Except for ΔSF-36 MCS, other efficacy outcomes, including ΔASDAS-CRP, ΔMASES, ΔASQoL, ΔSF-36 PCS, ΔBASDAI, ΔBASFI, ΔBASMI, ΔFACIT-F total score, ΔSPARCC SI joint score, ΔSPARCC Spine score and ΔWPAI Overall Work Impairment, demonstrated significant differences between the two groups, indicating better efficacy in JAK inhibitor group (Table 2).

4.2. Safety of JAK inhibitor versus placebo in treating AS

The incidence of AEs and SAEs showed no significant differences between the JAK inhibitor and placebo groups (Fig. 4).

Table 2
Meta-analysis of effects of JAK inhibitor versus placebo in treating AS.

Outcome	Studies	Participants	RR or MD (95%CI)	P value	Heterogeneity (I^2)	P value
ASAS 20	4	779	1.73 [1.47, 2.03]	<0.01	0%	0.67
ASAS 40	4	779	2.31 [1.80, 2.97]	<0.01	0%	0.46
ASAS 5/6	3	592	3.38 [1.94, 5.87]	<0.01	59%	0.09
BASDAI 50	4	779	2.06 [1.61, 2.63]	<0.01	0%	0.80
ASAS Partial Remission	3	572	5.64 [2.56, 12.47]	<0.01	0%	0.39
ASDAS Clinically Important Improvement	4	779	2.72 [2.18, 3.39]	<0.01	0%	0.52
ASDAS Major Improvement	4	779	5.10 [2.24, 11.62]	<0.01	63%	0.05
ASDAS inactive disease	4	779	6.80 [1.25, 36.93]	0.03	55%	0.08
ΔASDAS-CRP	4	747	-0.88 [-1.01, -0.74]	<0.01	10%	0.34
ΔMASES	4	547	-0.67 [-1.06, -0.28]	<0.01	0%	0.87
ΔASQoL	3	551	-1.99 [-2.73, -1.25]	<0.01	0%	0.58
ΔSF-36 MCS	3	582	1.66 [0.02, 3.30]	0.05	0%	0.60
ΔSF-36 PCS	3	582	3.85 [2.68, 5.03]	<0.01	0%	0.81
ΔBASDAI	3	589	-1.20 [-1.54, -0.86]	<0.01	0%	0.37
ΔBASFI	4	761	-1.06 [-1.35, -0.77]	<0.01	0%	0.63
ΔBASMI	4	764	-0.37 [-0.52, -0.21]	<0.01	44%	0.15
ΔFACIT- F total score	3	588	3.44 [1.90, 4.97]	<0.01	0%	0.99
ΔSPARCC SI joint score	3	400	-3.09 [-4.18, -2.00]	<0.01	4%	0.35
ΔSPARCC Spine score	3	400	-5.96 [-7.50, -4.42]	<0.01	0%	0.61
ΔWPAI Overall Work Impairment	2	255	-10.18 [-18.30, -2.07]	0.01	51%	0.15

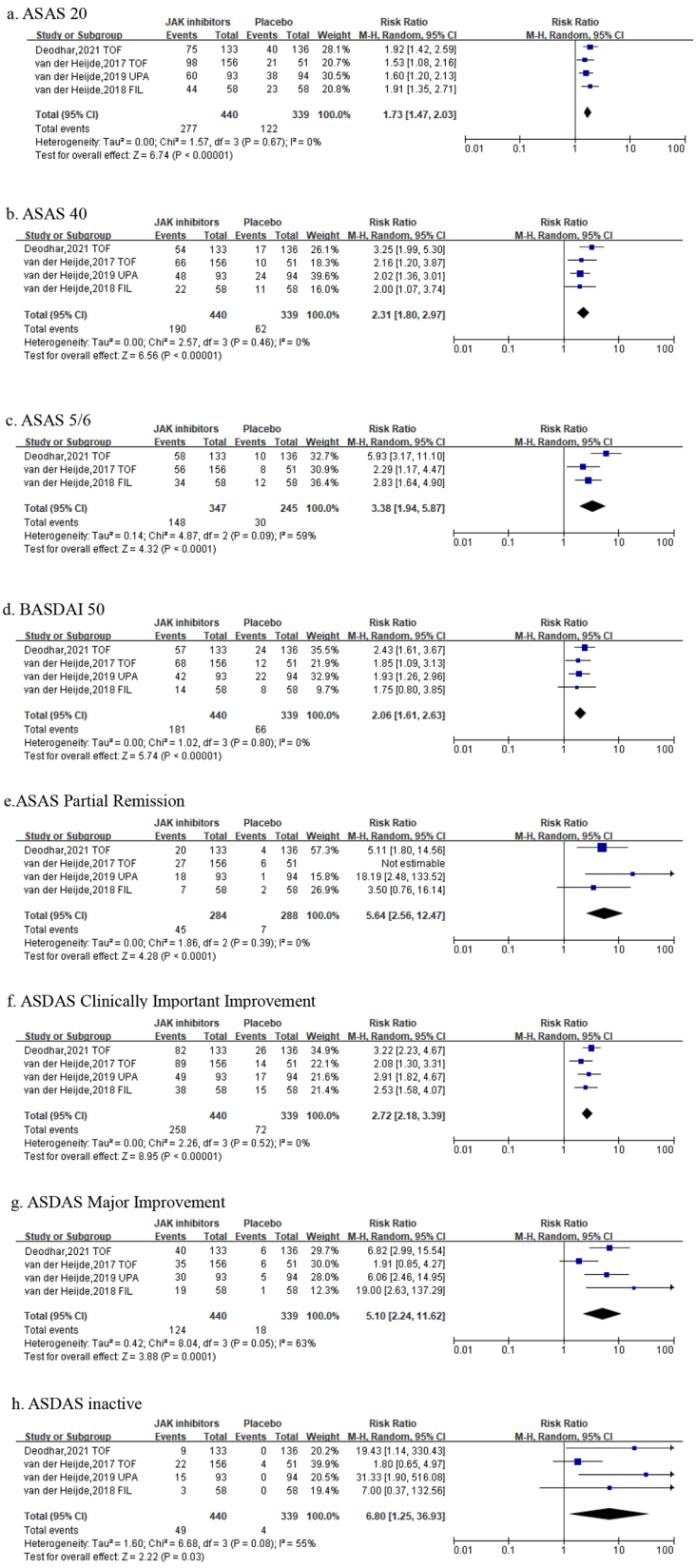

Fig. 3. Meta-analysis of efficacy of JAK inhibitor versus placebo in treating AS.

4.3. Heterogeneity and sensitivity analysis

Significant heterogeneity (I^2>50%) was found in the meta-analysis of efficacy outcomes including ASAS 5/6 (59%), ASDAS Major Improvement(63%), ASDAS inactive disease(55%), and ΔWPAI Overall Work Impairment(51%). Sensitivity analysis was conducted by removing one single trial each time, and the results showed the source of heterogeneity attributed to the study of Deodhar 2021 in assessing

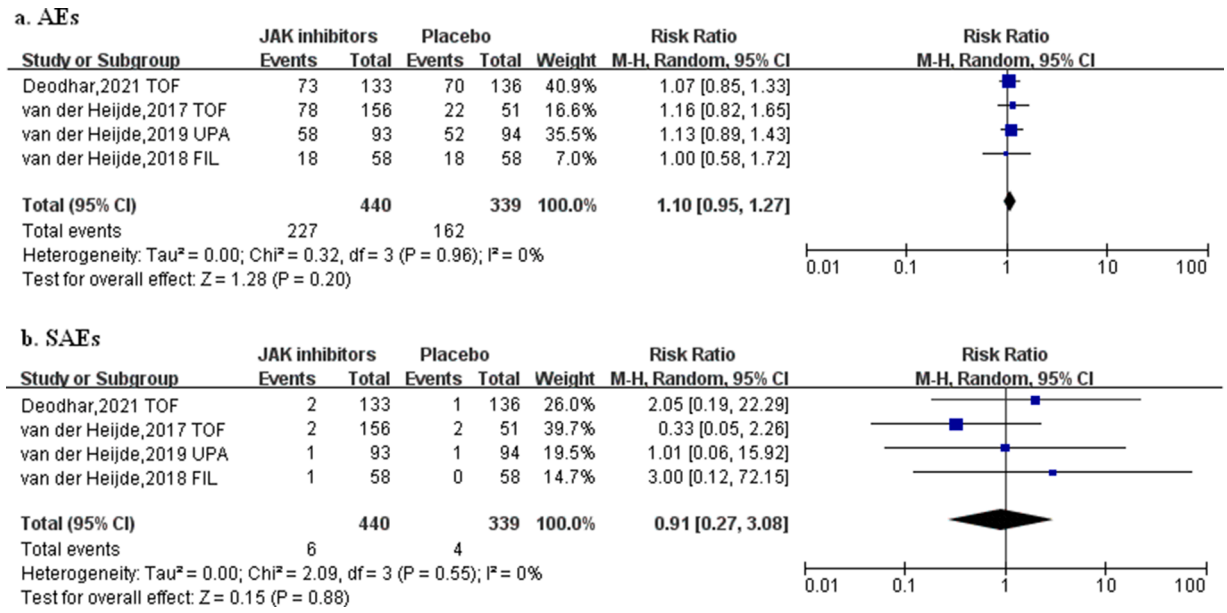

Fig. 4. Meta-analysis of safety of JAK inhibitor versus placebo in treating AS.

ASAS5/6[9], and the study of van der Heijde 2017 in ASDAS Major Improvement and ASDAS inactive disease [10]. Only two RCTs were included in the meta-analysis of ΔWPAI Overall Work Impairment [9, 11], the cause of heterogeneity presumably came from the difference between the magnitude of the effect size.

5. Discussion

This is the most up-to-date meta-analysis which assessed the efficacy and safety of JAK inhibitor treatment in patients with active AS. Our meta-analysis has a different strength as compared with the previous meta-analysis of the similar topic [13]. Firstly, we included the most recent and up-to-date literature in our meta-analysis. We collected data from four eligible RCTs that provided outcomes of JAK inhibitor treatment in active AS compared with placebo. And also, we were trying to do a perfect and precise data collection by checking the results posted on ClinicalTrials.gov or EU Clinical Trials Register. Among four RCTs, three kinds of JAK inhibitors were evaluated; a phaseIII and a phase II study assessed tofacitinib [9,10], one phase II/III study assessed upadacitinib [11], and one phase II study assessed filgotinib [12]. The selectivity of JAK inhibitor can be influenced by multiple factors and is dose-dependent. Among the JAK inhibitors currently under study for inflammatory diseases, it was generally accepted that clinically used doses of tofacitinib is preferentially a JAK 1, 3 inhibitor over JAK2, upadacitinib is a selective JAK1 inhibitor with effects on JAK2, and filgotinib is a highly selective JAK1 inhibitor [14,15]. Secondly, in a dose-ranging phase II study of tofacitinib in adults with active AS [10], we combined the effect indicators of different dosage groups according to the Cochrane Handbook recommendations, which were trying to minimize the selection bias and information bias. Thirdly, we included as much outcome measures as possible. In this meta-analysis, most of the comparisons showed satisfactory and significant improvements in JAK inhibitor group, including percentage of participants achieving response of ASAS20, ASAS40, ASAS 5/6, BASDAI50, and changes from baseline in ASDAS-CRP, MASES, ASQoL, SF-36 PCS, BASDAI, BASFI, BASMI, FACIT-F total score, SPARCC joint score and WPAI Overall Work Impairment, which indicated a promising efficacy of JAK inhibitor in the treatment of active AS not only in mitigating disease activity, but also substantially improving patient's physical function, emotional well-being and social participation. And also, we do not find significant differences regarding the number of participants with AEs or SAEs between JAK inhibitors and placebo.

However, there were some disadvantages in the current study. Firstly, the number of studies included in this meta-analysis was relatively small, which led to inevitable publication bias and selection bias, although no evidence of publication bias was detected in the present meta-analysis. Secondly, due to limited studies we could not do detailed subgroup analysis according to the kind of JAK inhibitor, dosage or JAK selectivity. And therefore, whether one JAK inhibitor is more effective or safer than another remains to be further investigated. Similarly, we could not rule out the bias caused by sex, age, ethnicity, disease duration, heterogenous spectrum of clinical manifestations and the time frame of studies.

Despite these disadvantages and that further researches are needed to assess the long-term efficacy and safety of JAK inhibitors, the evidences reported in our meta-analysis are currently the most updated and high-grade in this field, which provides solid evidence for JAK inhibitor as a new direction and novel therapeutic strategy for the patients with active AS.

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Data sharing

All data will be available upon request for academic researchers.

CRediT authorship contribution statement

Shu Li: Conceptualization, Investigation, Data curation, Formal analysis, Writing – original draft. **Fen Li:** Investigation, Data curation. **Ni Mao:** Investigation, Data curation. **Jia Wang:** Supervision. **Xi Xie:** Conceptualization, Investigation, Methodology, Supervision, Writing – original draft.

Declaration of Competing Interest

None.

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