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Efficacy and safety of upadacitinib, a selective JAK-1 inhibitor in treatment of ankylosing spondylitis: a meta-analysis

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Abstract

Objective To systemically assess efficacy and safety of upadacitinib (UPA), a selective inhibitor of Janus kinase 1 (JAK1) in treatment of ankylosing spondylitis (AS).

Methods Available databases were used to retrieve literatures of randomized controlled trials (RCTs) of UPA for AS treatment until February 2024. After that, the data were extracted and the Revman 5.4 software was used to conduct a meta-analysis.

Results A total of 6 articles and 1653 patients (920 in a UPA group (15 mg, q.d) and 733 in a placebo group) were selected in this study. Respectively, UPA treatment significantly increased numbers of the AS patients having 40%, 20%, or partial remission (PR) improvement in assessment of spondylo arthritis international society (ASAS) (ASAS 40: 95%CI: 2.41–4.3, $p < 0.00001$; ASAS 20: 95%CI: 2.12–3.62, $p < 0.00001$; ASAS PR: 95%CI: 2.81–7.48, $p < 0.00001$), Bath ankylosing spondylitis disease activity index (BASDAI50) (95%CI: 2.28 ~ 4.10, $p < 0.00001$), quality of life (95%CI: 2.06 ~ 3.17, $p < 0.00001$), AS disease activity score low disease activity (ASDAS LDA) (95%CI: 3.07~9.96, $p < 0.00001$), ASDAS inactive disease (ID) (95%CI: 2.03 ~ 17.22, $p = 0.001$), short-form 36 physical component summary (SF-36PCS) (95%CI: 1.53 ~2.81, $p < 0.00001$), and markedly reduced ASDAS C-reactive protein (CRP) (95%CI: -1.22 ~ -0.42, $p < 0.0001$), total back pain score (95%CI: -2.01 ~ -0.51, $p = 0.001$), nighttime back pain score (95%CI: -1.96 ~ -0.54, $p = 0.0006$), spondylo arthritis research consortium of Canada magnetic resonance imaging (SPARCC MRI) spine score (95%CI: -7.78–-3.50, $p < 0.00001$) and SPARCC MRI sacroiliac joint score (95%CI: -5.99 – -3.09, $p < 0.00001$), Bath ankylosing spondylitis function index (BASFI) score (95%CI: -1.45 ~ -0.81, $p < 0.00001$), Maastricht ankylosing spondylitis enthesitis score (MASES) (95%CI: -2.34~-0.35, $p = 0.008$). Except for neutropenia (95%CI: 1.25 ~ 15.60, $p = 0.02$), no other adverse effects (AEs) were significantly different between the UPA treatment and placebo.

Conclusions Through a literature analysis, it reveals that UPA offers significant therapeutic benefits to AS patients with a relatively high safety profile.

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Keywords Upadacitinib, Ankylosing spondylitis, Efficacy, Safety, Meta-analysis

Introduction

Axial spinal arthritis (axSpA) is a chronic inflammatory rheumatic disease mainly damaging spine and sacroiliac joint [1]. AxSpA is classified as non-imaging axial spondylitis (nr axSpA) and ankylosing spondylitis (AS) according to imaging manifestations and clinical symptoms [2, 3]. AS, also known as spinal arthritis or serum negative spinal arthropathy, is mainly characterized by inflammations of sacroiliac joints and spinal attachments. It belongs to the category of rheumatism with unclear etiology.

AS, which usually appears in early adulthood, normally has morbidities in different ethnic groups from 0.1 to 1.4% [4]. AS often progresses from the sacroiliac joints, gradually ascending to involve the cervical spine. In the early stage, inflammatory pain may occur in the joints, accompanied by spasms and stiffness in surrounding muscle, which is evident in the morning. In addition, it manifests as relieved nighttime pain through physical activity or taking painkillers. With the progress of this disease, spinal segments and joints gradually deform, limiting body movement function. In the late stage, the entire spine and lower limbs bend forward.

Due to its debilitating nature, long-term and irreversibly structural damage, and a negative impact on quality of life, the therapeutic goal of AS is to control its symptoms and elevate health-related quality of life (HRQL). Currently, it is recommended to apply long-term pharmacological and non-pharmacological treatments for AS [5].

According to recommendations of American society of rheumatology (ACR) and spondylitis association of America (SAA), the first-line drug is nonsteroidal anti-inflammatory drugs (NSAIDs). For those patients who have poor responses to the NSAIDs, biologically modified anti-rheumatic drugs (bDMARDs) such as tumor necrosis factor-α (TNF-α) antagonist or interleukin-17 (IL-17) receptor inhibitor will be taken into consideration [6]. Although bDMARDs in combination with NSAIDs can achieve a good therapeutic efficacy and delay the progression, the long-term use of these drugs will affect normal functions of liver, kidney, and gastrointestinal tract. Further, only 40%~50% of the patients achieve ASAS 40 [7, 8]. Thus, it is necessary to search for a more effective and safer strategy for AS treatment.

Currently, Janus kinase (JAK) inhibitors are becoming a new alternative for autoimmune diseases. Compared with the bDMARDs, the JAK inhibitors will prevent the spread and transfer of inflammation more thoroughly [9]. In addition, its oral administration has become a unique and convenient way compared to biological agents [9, 10]. The ASAS and the European league against rheumatism (EULAR) recommend to use the JAK inhibitors in patients with high disease activity after receiving routine treatments [11]. Nowadays, the updated recommendations suggest the JAK inhibitors as an alternative when the patients did not respond to bDMARDs.

UPA is a JAK inhibitor already has been applied in clinic to cure psoriatic arthritis, ulcerative colitis, Crohn's disease, and atopic dermatitis [12–15]. At present, it has been reported that UPA is effective and well tolerated in the active AS patients with poor responses to NSAIDs or bDMARDs [16]. Up to now, the current research data for efficacy and safety of UPA is relatively scarce due to limited clinical studies. In this study, we conducted a meta-analysis to assess the efficacy and safety of UPA for AS treatment.

Materials and methods

Search strategy

This meta-analysis was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement. Databases including PubMed, Embase, Elsevier, Springer, Google Scholar, Cochrane Library, and CNKI were used to select eligible references from inception to February 2024. Search terms were listed as follows.

(i) "upadacitinib" (title/abstract/keywords/Medical Subject Headings (MeSH));
(ii) "ankylosing spondylitis" or "Bechterew's disease" or "AS" or "HLA-B27 positive spondyloarthritis" or "Chronic inflammatory back pain" or "Sacroiliitis" (title/abstract/keywords/MeSH);
(iii) "randomized controlled trial (RCT)" (title/abstract/keywords/MeSH);
(iv) these search queries were combined using "AND". The references were retrieved regardless of language of publication, study design, and publication type.

Retrieved the databases to search for the RCT literatures on UPA for AS treatment using the keywords "upadacitinib" and "spondylitis ankylosing", "Bechterew's disease" or "AS" or "HLA-B27 positive spondyloarthritis" or "Chronic inflammatory back pain" or "Sacroiliitis". A total of 763 studies were screened and then the duplicates were removed. After that, read titles and abstracts of these articles to exclude non-RCT, reviews, comments, meta-analysis, and articles that didn't match this study.

Data extract

Two researchers independently reviewed the retrieved literatures. If consensus was reached, the literatures would be included; Once disagreements occurred, a third researcher would intervene and resolve through a panel discussion ultimately.

The extracted data included author, year of publication, number of cases, gender, grouping, treatment and duration, indicators, and adverse reactions.

Risk of bias assessment

Cochrane Risk of Bias Assessment Tool was used to evaluate risks of biases which included random sequences generation (selection bias) and allocation concealment (selection bias), blinding (implementation bias), blind evaluation (measurement bias), data integrity (follow-up bias), selective reporting (reporting bias), and other biases. The risk of biases (ROB) levels of the included literatures was classified as "low", "high", and "unclear". They were presented as green, red, and yellow, respectively.

Data presentation and statistical analysis

The meta-analysis was conducted by using the Revman 5.4 software available at https://training.cochrane.org/online-learning/core-software/revman. The data were analyzed by relative ratio (OR) represented as 95% confidence interval (95% CI). A p value of less than 0.05 is thought to be significant. The heterogeneity was analyzed by Q-test using the I^2 statistic suggested by the Cochrane Collaboration. When the heterogeneity was low ($I^2 < 50\%$, $p > 0.05$), a fixed effects model (FEM) is used for meta-analysis. Otherwise, a random effects model (REM) is used ($I^2 > 50\%$, $p < 0.05$) [17].

Results

General information of included studies

Initially, 209 relevant studies were retrieved. Imported them into the Note Express to exclude deduplicates. Read the titles and abstracts of the included studies carefully to exclude non-RCT, meta-analysis, review, comments, and cell or animal experiments. After that, read carefully to exclude those having no consistent outcome or no complete data. Finally, 6 studies [16, 18–22] were included, all of which met the quality standards. The screening process for the literatures was displayed in Fig. 1.

A total of 920 patients were included in this study. The patients in the treatment group (460) and control groups (460) received oral UPA (15 mg, q.d) and placebo (q.d) for the continuous 14 weeks, respectively. Three studies [16, 20, 21] reported ASAS 40, ASAS 20, ASAS PR, BASDAI50, ASDAS LDA, and ASDAS ID; Two studies [18, 19] reported SF-36PCS and quality of life; Two studies [16, 20] reported ASDAS CRP, total back pain, and nocturnal back pain; Two studies [16, 22] reported SPARCC MRI; Three studies [16, 20, 22] reported MASES and BASFI. The general information of the included studies was shown in Table 1, and detailed definitions of these indicators were shown in Table 2.

Risk of bias

One study [19] had high risk of bias, which was associated with random sequence generation (selection bias). Also, it [19] has an unclear risk of bias for incomplete outcome data (attrition bias). In addition, two studies [18, 20] had unclear risk of bias due to random sequence generation (selection bias). Briefly, the risk percentage of each bias of the included studies was shown in Fig. 2A, and the bias of single item of the included studies was summarized in Fig. 2B.

UPA exerts a significant therapeutic effect on AS

Three studies [16, 20, 21] reported ASAS40, ASAS20, and ASAS PR. A FEM was used to compare numbers of the patients with ASAS 40 and ASAS 20 between the placebo and UPA groups (ASAS 40: $p = 0.77$, $I^2 = 0\%$; ASAS 20: $p = 0.87$, $I^2 = 0\%$). Correspondingly, a REM was used to compare ASAS PR between the two groups ($p = 0.08$, $I^2 = 60\%$). It demonstrated that UPA significantly increased the numbers of the AS patients with ASAS 40, ASAS 20, and ASAS PR compared to the placebo (ASAS 40: OR = 3.22, 95%CI: 2.41–4.3, $p < 0.00001$; ASAS 20: OR = 2.77, 95%CI: 2.12–3.62, $p < 0.00001$; ASAS PR: OR = 4.58, 95%CI: 2.81–7.48, $p < 0.00001$), respectively. Further, no obvious risk of publication bias was found in the studies (Fig. 3A).

BASDAI50 was reported in the three studies [16, 20, 21]. The meta-analysis by a FEM ($I^2 = 0\%$, $p = 0.59$) showed that the number of the AS patients with BASDAI50 in the UPA group was more than that in the placebo group (OR = 3.05, 95%CI: 2.28–4.10, $p < 0.00001$) (Fig. 3B).

Three studies [16, 20, 21] reported low disease activity (LDA) score and inactive disease (ID) score after the UPA (15 mg, q.d) or placebo treatment for continuous 14 weeks. The meta-analysis by a REM ($I^2 = 66\%$, $p = 0.05$) revealed that the number of the AS patients with LDA or ID in the UPA group were more than that in the placebo group (LDA: OR = 5.53, 95%CI: 3.07–9.96, $p < 0.00001$; ID: OR = 5.91, 95%CI: 2.03–17.22, $p = 0.001$), respectively (Fig. 3C and D).

Two studies [16, 20] assessed ASDAS CRP between the two groups. The meta-analysis by a REM ($I^2 = 86\%$, $p = 0.008$) indicated that UPA treatment for continuous 14 weeks significantly reduced ASDAS CRP compared

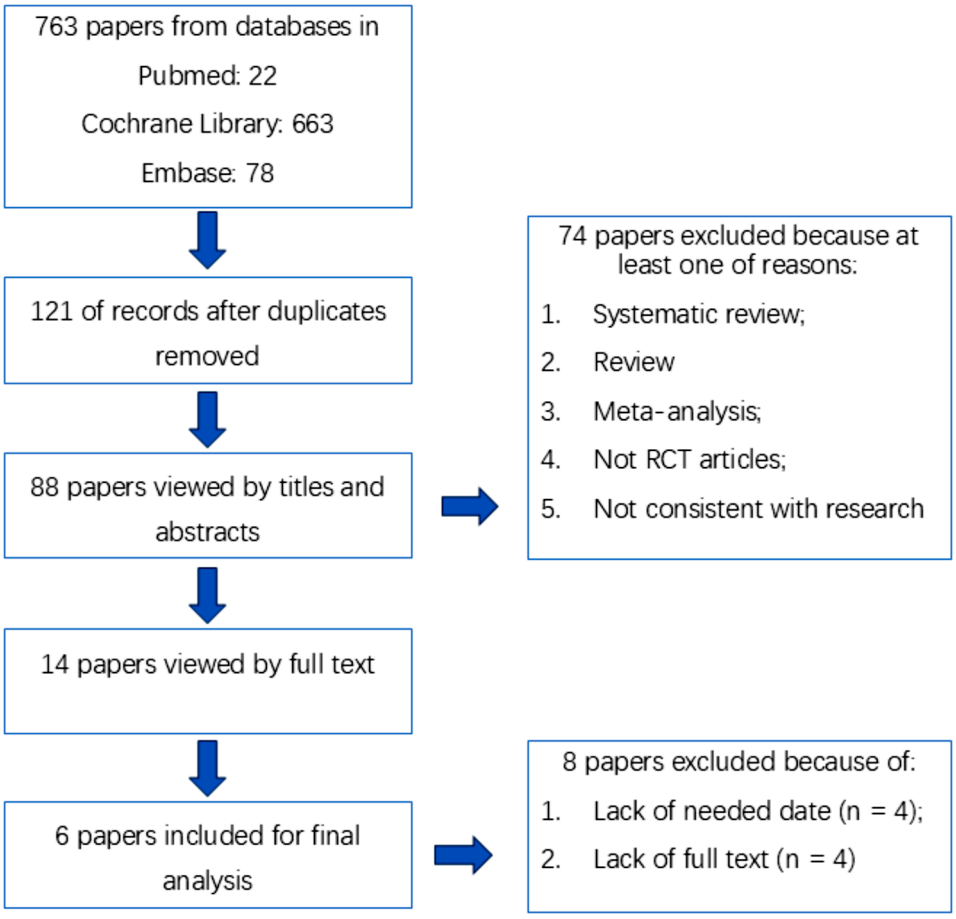

Fig. 1 Literature screening and disposition

Table 1 General information of included studies

Study	Language	Number		Number of gender (Male/Female)		Age (Years)	
		Placebo	UPA	Placebo	UPA	Placebo	UPA
Navarro-Compán, 2023 [18]	English	209	211	158/51	153/58	42.2 ± 11.8	42.6 ± 12.4
Kiltz, 2023 [19]	English	157	156	63/94	67/89	42.5 ± 12.4	41.6 ± 12.0
Deodhar, 2022a [20]	English	157	156	63/94	67/89	42.5 ± 12.4	41.6 ± 12.0
van der Heijde, 2022 [16]	English	209	211	158/51	153/58	42.2 ± 11.8	42.6 ± 12.4
Deodhar, 2022b [21]	English	94	93	69/25	63/30	43.7 ± 12.1	47.0 ± 11.8
van der Heijde, 2019 [22]	English	94	93	69/25	63/30	43.7 ± 12.1	47.0 ± 11.8

Table 2 Details of tested indicators

Indicator	Detail
ASAS	Assessment of spondylo arthritis international society improvement of 40% (ASAS 40): improvement of at least 3 in 4 indices ≥ 40% and improvement score ≥ 2 (total score 10) or ≥ 20 (total score 100) ASAS 20: improvement of at least 3 in 4 indices ≥ 20% and improvement score ≥ 1 (total score 10) or ≥ 10 (total score 100) ASAS PR: improvement of all 4 indices ≤ 20% and improvement score ≤ 2 (total score 10) or ≤ 20 (total score 100)
BASDAI50	Bath ankylosing spondylitis disease activity index improvement of 50%
ASDAS LDA	ASDAS low disease activity [C-reactive protein (CRP) < 2.1 mg/L]
ASDAS ID	ASDAS inactive disease (CRP < 1.32 mg/L)
BASFI	Bath ankylosing spondylitis function index
MASES	Maastricht ankylosing spondylitis enthesitis score
SPARCC MRI	Spondylo arthritis research consortium of Canada magnetic resonance imaging spine SPARCC MRI sacroiliac joint
ASDAS CRP	Ankylosing spondylitis disease activity score C-reactive protein
Improvement of quality of life	ASQOL: Ankylosing spondylitis quality of life inventory ASAS HI: ASAS health index
SF-36PCS	Physical component summary score of the short form 36

Note ASAS 40, ASAS 20, ASAS PR, BASDAI50, Improvement of quality of life, ASDAS LDA, ASDAS ID, and SF-36PCS refer to numbers of the AS patients in the placebo and UPA groups (15 mg, q.d, 14 w) whom reach criteria of these indices; ASDAS CRP, total back pain, nighttime back pain, SPARCC MRI, BASFI, and MASES refer to difference values of these indices' scores between the treatment (Placebo or UPA treatment at 14th week) and the baseline (Placebo or UPA treatment at 0 week)

to the placebo (Mean Difference = -0.82, 95% CI: -1.22 – -0.42, $p < 0.0001$) (Fig. 3E).

BASFI and MASES scores of the AS patients were reported in the three studies [16, 20, 22]. The meta-analysis by a FEM ($I^2 = 0\%$, $p = 0.67$) showed a significant difference in BASFI between the two groups (Mean Difference = -1.13, 95% CI: -1.45 – -0.81, $p < 0.00001$) (Fig. 3F). Similarly, the meta-analysis by a REM ($I^2 = 75\%$, $p = 0.02$) showed that UPA markedly reduced MASES score compared to the placebo (Mean Difference = -1.34, 95%CI: -2.34 – -0.35, $p = 0.008$) (Fig. 3G).

Two studies [16, 20] reported improvements of total back pain score and nighttime back pain score. The analyses by the REMs (Total back pain: $I^2 = 77\%$, $p = 0.04$; Nighttime back pain: $I^2 = 69\%$, $p = 0.07$) showed that UPA significantly improved the total back pain score (Mean Difference = -1.26, 95%CI: -2.01 – -0.51, $p = 0.001$) and nighttime back pain score (Mean Difference = -1.25, 95%CI: -1.96 – -0.54, $p = 0.0006$), respectively (Fig. 3H and I).

SPARCC MRI spine and joint scores were evaluated by the three studies [16, 20, 22]. The meta-analysis by a FEM ($I^2 = 0\%$, $p = 0.48$) demonstrated that UPA significantly improved SPARCC MRI spine score (Mean Difference = -5.64, 95%CI: -7.78 – -3.50, $p < 0.00001$) and SPARCC MRI sacroiliac joint score (Mean Difference = -4.54, 95%CI: -5.99 – -3.09, $p < 0.00001$) compared to the placebo, respectively (Fig. 3J). Meanwhile, no obvious risk of publication bias was in these studies.

Taken together, compared with the placebo, UPA (15 mg, q.d) for AS treatment for the continuous 14 weeks significantly improved joint functions, reduced joint inflammation and disease activity, and delayed disease progress, which offered significant therapeutic benefits to AS.

UPA improves quality of life and health status of AS patients

Two studies [18, 19] reported UPA improved the AS patients' quality of life and health status. The meta-analysis by a FEM ($I^2 = 0\%$, $p = 0.69$) showed that UPA significantly increased ASQOL (OR = 2.62, 95%CI: 1.95–3.54, $p < 0.00001$) and ASAS HI (OR = 2.48, 95%CI: 1.81–3.38, $p < 0.00001$), respectively (Fig. 4A). In addition, UPA markedly elevated SF-36PCS of the AS patients ($I^2 = 0\%$, $p = 0.69$, OR = 2.08, 95%CI: 1.53–2.81, $p < 0.00001$) (Fig. 4B). No obvious risk of publication bias was found in these included studies.

AEs of UPA in AS patients

Three studies [16, 20, 22] reported AEs after the UPA therapy. Except for neutropenia (OR = 4.42, 95%CI: 1.25–15.60, $p = 0.02$), there were no significant differences in other AEs such as serious AE (OR = 2.79, 95%CI: 0.88–8.84, $p = 0.08$), serious infection (OR = 5.06, 95%CI: 0.87–29.36, $p = 0.07$), anemia (OR = 3.01, 95%CI: 0.47–19.23, $p = 0.24$), lymphocytopenia (OR = 0.49, 95%CI: 0.04–5.48, $p = 0.56$), hepatic disorder (OR = 1.69, 95%CI: 0.73–3.91, $p = 0.22$), and uveitis (OR = 0.71, 95%CI: 0.14–3.61, $p = 0.68$) between the UPA group and placebo group (Fig. 5).

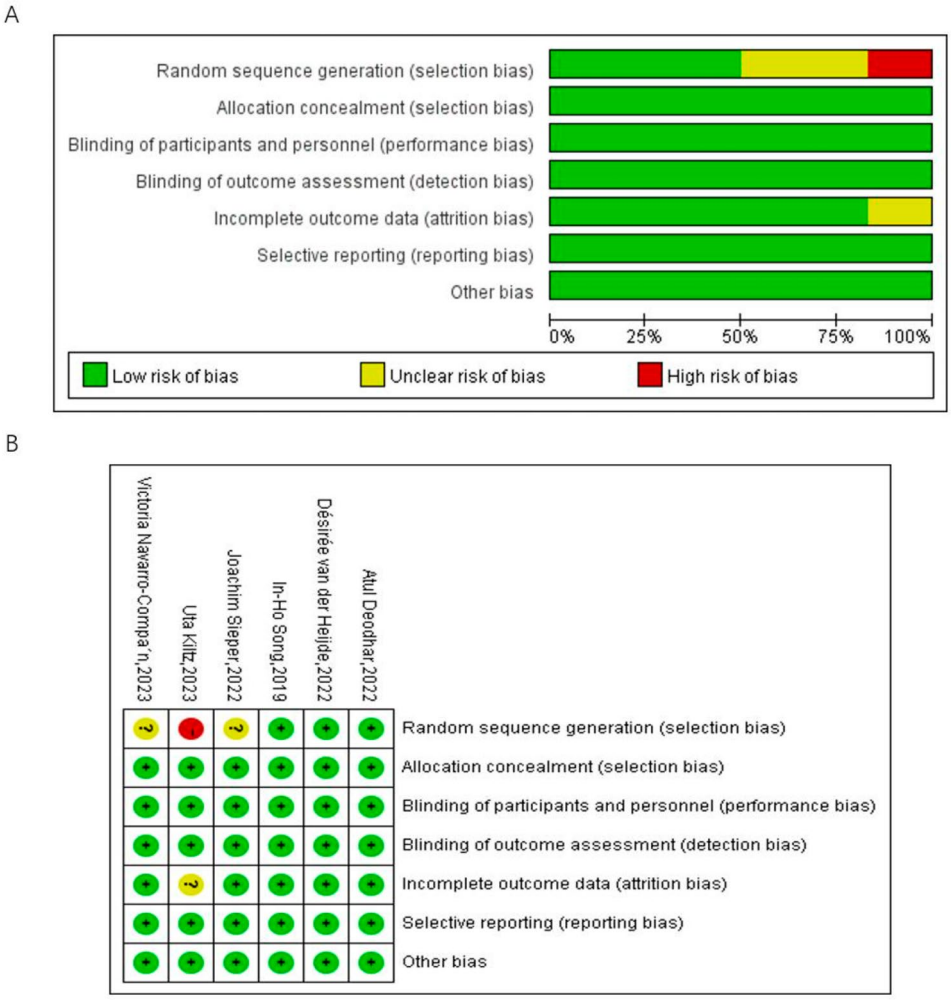

Fig. 2 Risks of biases of included studies. **A**, Risk percentage of each bias in the studies; **B**, Summary of risks' assessments of the studies

Discussion

AS is a chronic inflammatory rheumatic disease affecting axial skeleton. Further, it seriously threatens lives and quality of life of patients. Thus, it is necessary to control symptoms of this disease, including preventing structural damage, and maintaining normal functions of bones and joints. Currently, NSAIDs, TNF-α antagonist and IL-17 receptor inhibitor are commonly used to treat AS. However, some patients still respond poorly to these reagents. Recently, UPA, a specific JAK-1 inhibitor, has been selected as an alternative when the efficacy isn't satisfactory after receiving NSAIDs or TNF-α antagonist or IL-17 receptor inhibitor [23]. JAK is an intracellular enzyme transmitting membranous signals generated by cytokine interactions or growth factor receptors. In this case, the JAKs' phosphorylation activates signal transduction and signal transcription activator (STAT), which regulates intracellular gene expression and other activities. Correspondingly, UPA regulates this signaling pathway at the JAKs' sites by blocking the phosphorylation and activation of STAT.

JAKs transmit cytokine signals through their own pairing including JAK1/JAK2, JAK1/JAK3, JAK1/TYK2, JAK2/JAK2, and JAK2/TYK2. The inhibitory effects of UPA on JAK1 and JAK2 are stronger than JAK3 and TYK2. Furthermore, its inhibitory effects on JAK1 and JAK1/JAK3-mediated STAT phosphorylation are stronger than those mediated by JAK2/JAK2.

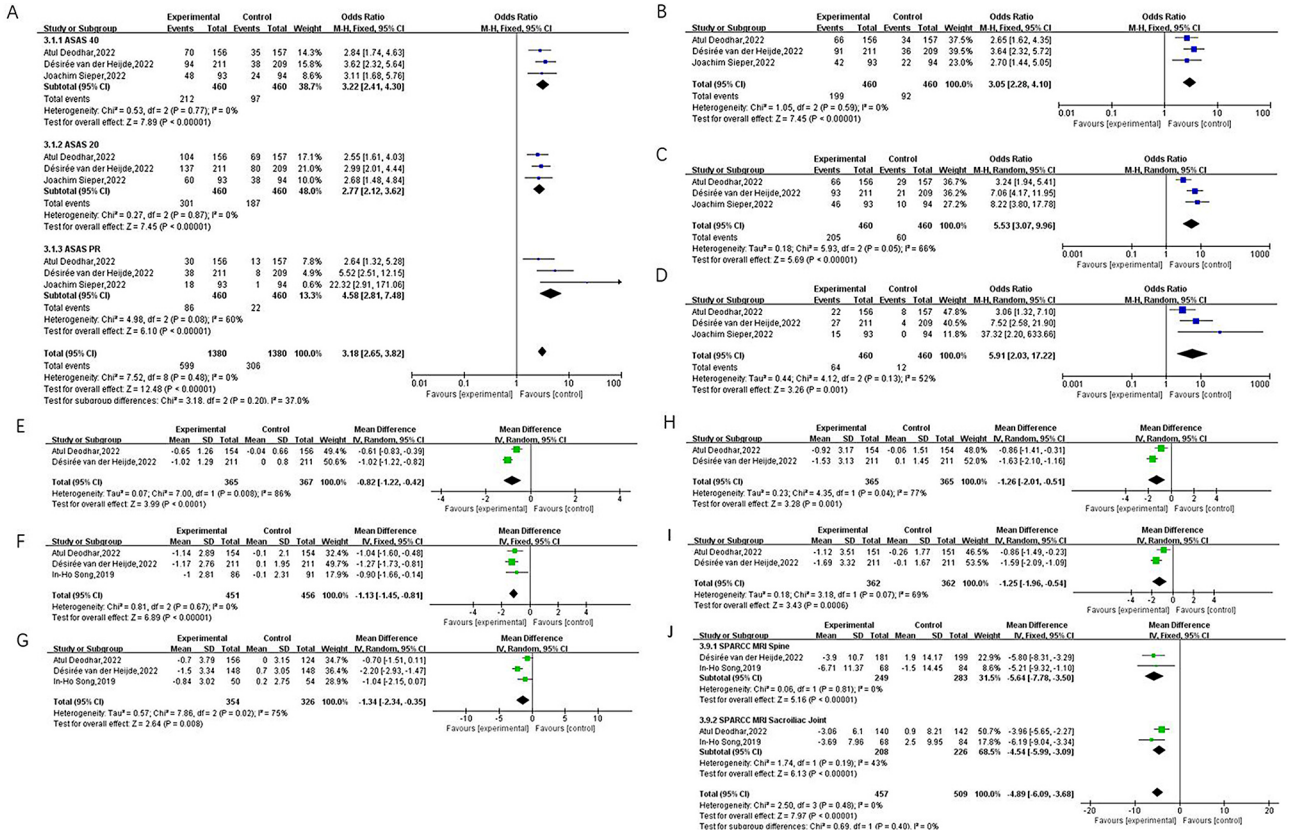

Fig. 3 Efficacy of UPA in AS patients. **A**, Number of AS patients with ASAS criteria in groups; **B**, Number of AS patients with BASDAI50 in groups; **C**, Number of AS patients with ASDAS LDA in groups; **D**, Number of AS patients with ASDAS ID in groups; **E**, ASDAS CRP of AS patients before and after UPA or placebo treatment; **F**, BASFI score of AS patients before and after UPA or placebo treatment; **G**, MASES score of AS patients before and after UPA or placebo treatment; **H**, Total back pain score of AS patients before and after UPA or placebo treatment; **I**, Nighttime back pain score of AS patients before and after UPA or placebo treatment; **J**, SPARCC MRI score of AS patients before and after UPA or placebo treatment

At present, a small number of studies systematically evaluate the efficacy and safety of UPA in treating AS. So, through this meta-analysis, we conducted a meta to assess the efficacy and safety of UPA for AS treatment.

A total of 6 articles and 1653 patients were included in accordance with the related inclusion and exclusion criteria. The meta-analysis showed that high heterogeneity occurred in some indices such as ASDAS CRP, ASDAS LDA, ASDAS ID, SF-36PCS, total back pain score, and nighttime back pain score in the included studies. So, a REM was used to assay these indices above. Also, positive comorbidity was observed in the presence of high I^2, which was usually thought to be significant heterogeneities across studies. However, some argued that high I^2 didn't always equate to high heterogeneity in meta-analysis of prevalence. It might be influenced by the number of included studies and point estimation which couldn't provide distribution information of overall parameters [24].

No significant heterogeneities were observed in ASAS, BASDAI50, quality of life, SPARCC MRI, BASFI, SF-36PCS, and adverse reactions (AEs). Further, the numbers of AS patients with ASAS 40 and BASDAI 50 respectively increased to 45% and 45% after the UPA treatment for the continuous 14 weeks. The BASFI score decreased by about 1.15 folds at 14th week. Compared with commonly anti-TNF-αfor AS treatment, the BASDAI50 reached 52% at 6th month, and the BASFI decreased by 2.6 folds [25]. In addition, both spinal MRI inflammation score and sacroiliac joint MRI inflammation score significantly decreased after the UPA therapy. Based on SF-36PCS and quality of life scores, UPA significantly improved quality of life of the AS patients compared to the placebo.

The meta-analysis of safety found that except for neutropenia, other AEs including severe AEs, severe infection, anemia, lymphopenia, hepatic disorder, uveitis were not statistically significant between the UPA group and the placebo group. Neutropenia was thought

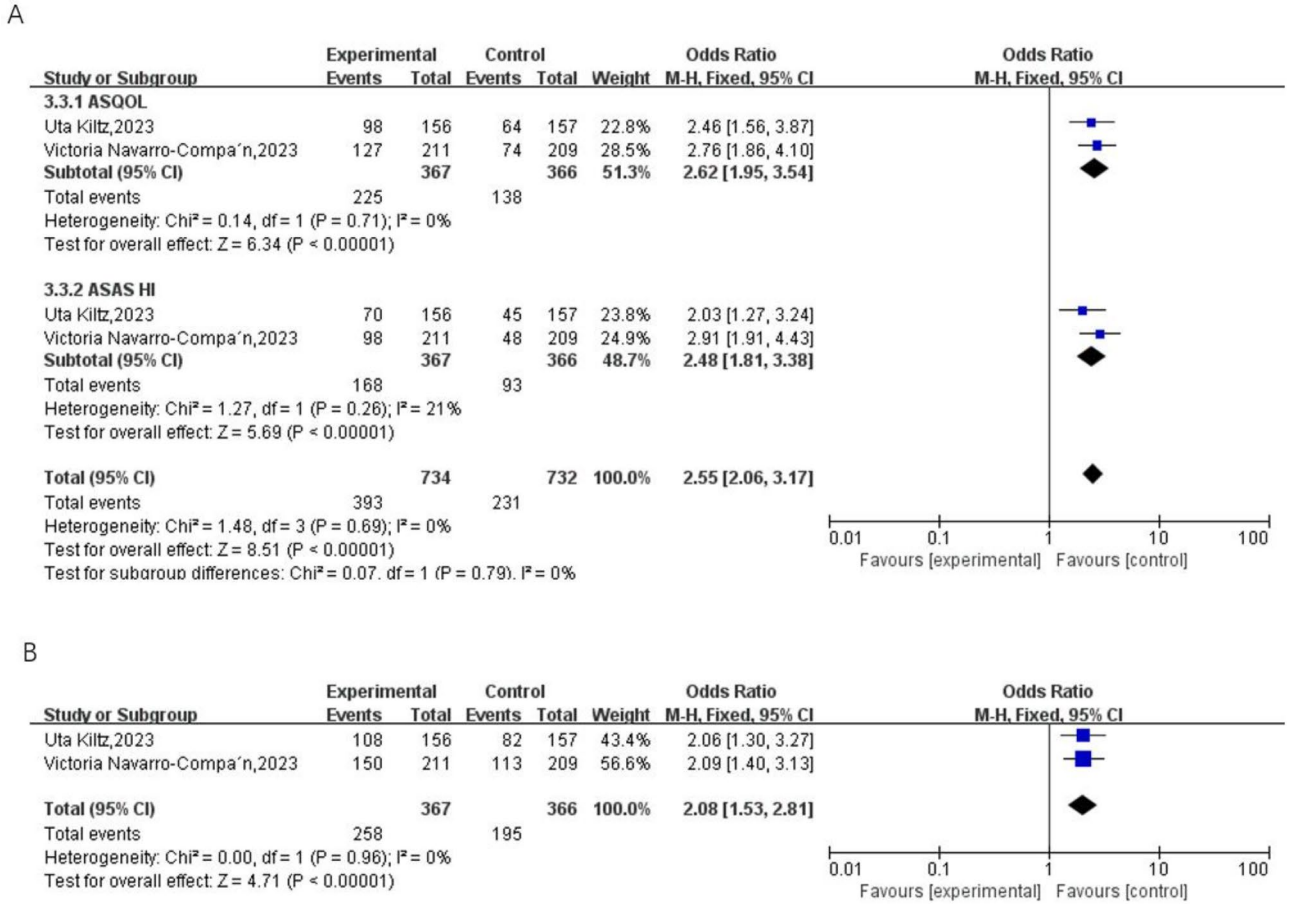

Fig. 4 Effects of UPA on quality of life and health status of AS patients. **A**, Effects of UPA on ASQOL and ASAS HI of AS patients; **B**, Effect of UPA on SF-36PCS of AS patients

to be one main AE of UPA, which was not reported in the previous meta-analyses. Similarly, a clinical trial of Crohn's disease also suggested that neutropenia was more frequent in 30-mg UPA group [26]. So, neutropenia should be monitored when 30-mg UPA is applied daily. In addition, the treatments for neutropenia include removing cause of disease, symptomatic treatment, increasing neutrophil count with hematopoietic growth factors, and others.

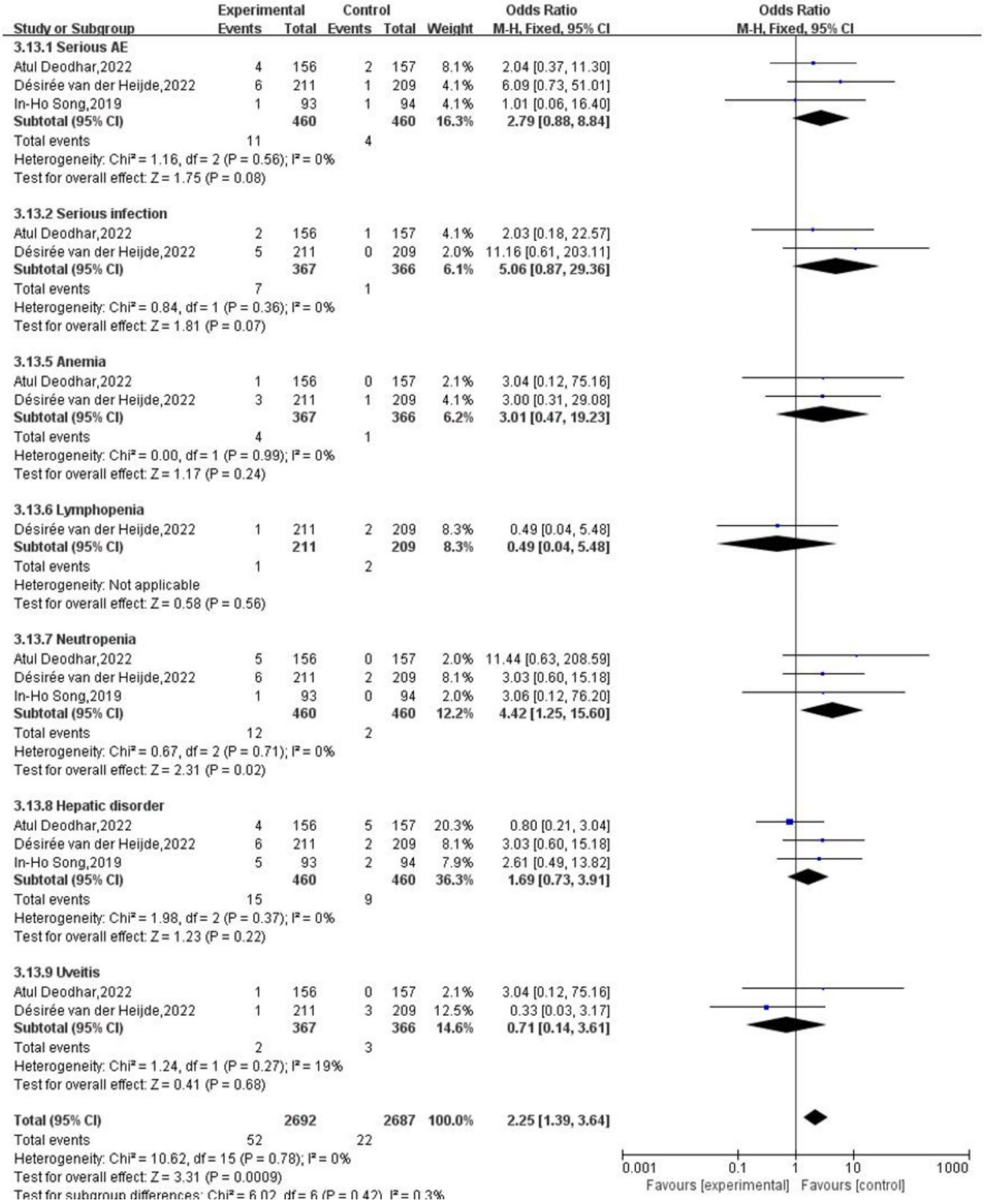

Fig. 5 AEs of UPA in AS patients

Conclusions

In summary, through the meta-analysis, UPA offers significant therapeutic benefits to AS with relatively high safety.

Abbreviations

ACR	American society of rheumatology
AEs	Adverse effects
AS	Ankylosing spondylitis
ASAS	Assessment of spondylo arthritis international society
ASDAS	Ankylosing spondylitis disease activity score
axSpA	Axial spinal arthritis
BASFI	Bath ankylosing spondylitis function index
bDMARDs	Biologically modified anti-rheumatic drugs
CNKI	China national knowledge infrastructure
CRP	C-reactive protein
EULAR	European league against rheumatism
FEM	Fixed effects model
HRQL	Health-related quality of life
ID	Inactive disease
IL-17	Interleukin-17
JAK	Janus kinase
LDA	Low disease activity
MASES	Maastricht ankylosing spondylitis enthesitis score
NSAIDs	Nonsteroidal anti-inflammatory drugs
OR	Relative ratio
PR	Partial remission
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
RCTs	Randomized controlled trials
REM	Random effects model
SF-36PCS	Short-form 36 physical component summary
SPARCC MRI	Spondylo arthritis research consortium of Canada magnetic resonance imaging
TYK	Tyrosine kinase
TNF-α	Tumor necrosis factor-α
UPA	Upadacitinib

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41927-025-00467-1.

Supplementary Material 1

Author contributions

Qi Yao analyzed the data, and wrote the English version of this manuscript. Yixuan Zhu collected the data, performed meta-analysis, and wrote the Chinese version of this manuscript. Yanling Ma and Yanfang Pu collected the data of this study. Zhiqing Zhang and Xueting Yang designed this study. All authors reviewed the manuscript.

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Data availability

Data is provided within supplementary information files.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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