REVIEW ARTICLE



Efficacy and safety of interleukin-17A inhibitors in patients with ankylosing spondylitis: a systematic review and meta-analysis of randomized controlled trials

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Received: 21 October 2020 / Revised: 1 December 2020 / Accepted: 10 December 2020 / Published online: 12 January 2021 (© The Author(s) 2021

Abstract

To assess the efficacy and safety of interleukin (IL)-17A inhibitors in patients with ankylosing spondylitis (AS). PubMed, EMBASE, and Web of Science were searched up to 5 February 2020 for randomized controlled trials (RCTs) that assessed the efficacy and safety of IL-17A inhibitors in patients with AS. We used a meta-analytic approach to perform a random effects analysis or fixed effects analysis according to heterogeneity. Subgroup analyses between studies included medication, time to primary endpoint, and data source. Odds ratios (ORs) or mean differences (MDs) were used to assess the efficacy and safety of IL-17A inhibitors in AS. A total of ten RCTs with 2613 patients were eligible for inclusion in the analysis (six for secukinumab, two for ixekizumab, one for netakimab, and one for bimekizumab). Compared to placebo, IL-17A inhibitors improved ASAS20 response rate (OR = 2.58; p < 0.01) and ASAS40 response rate (OR = 2.80; p < 0.01), and significantly increased the risk of AEs (OR = 1.23; p = 0.03) and nasopharyngitis (OR = 1.72; p < 0.01), but not SAEs (OR = 0.87; p = 0.60). IL-17A inhibitors demonstrated better efficacy in patients with AS in several evaluation indicators. However, the safety of IL-17A inhibitors remains to be further studied in studies with larger sample size and longer follow-up times.

Keywords Ankylosing spondylitis · IL-17A inhibitors · Meta-analysis · Randomized controlled trial

Introduction

Ankylosing spondylitis (AS), also termed radiographic spondyloarthritis, is a primary subtype of axial spondyloarthritis. AS is a chronic inflammatory rheumatic disease, which is featured with axial inflammation, and imaging-visible structural damages in the spine and sacroiliac joints [1-3]. With an incidence of 0.02–0.35% [4], AS not

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Weijian Liu m201775647@hust.edu.cn only decreases the work productivity, and life quality [5], but also results in heavy burdens of public health care all over the world [6]. The molecular and pathogenesis mechanisms that underlie AS still have many dark sides. Although the exact etiology and pathogenesis mechanisms are not clear, many studies have instructed that the occurrence of AS is closely related to the positive expression of human leukocyte antigen (HLA)-B27 [7, 8]. Immune system also promotes the

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development and progression of AS, which can be characterized by overexpression of inflammatory cytokines and abnormal activation of immune cells in AS patients.

During the past decades, researchers have kept exploring the therapies for AS. Physical therapy is proved to be efficacious for AS patients. However, its application is limited due to high expense and low accessibility [9]. For AS patients suffering from pain and stiffness, non-steroidal anti-inflammatory drugs (NSAIDs) are recommended as the first-line treatment [10]. Recently, biological disease-modifying antirheumatic drugs (bDMARDs) emerged as novel therapies for AS. For example, tumor necrosis factor (TNF) inhibitors are recommended to patients with AS who are in persistent disease activity period [10]. Nevertheless, NSAIDs and TNF inhibitors are not always effective and well-tolerated for all types of AS patients [10, 11]. Therefore, novel therapeutic alternatives for AS are highly required.

Mounting studies have demonstrated that interleukin (IL)-23/IL-17 axis was highly associated with immune dysfunction and activated autoimmune inflammation. Further studies demonstrated that IL-23/IL-17 axis was involved in the pathogenesis of multiple rheumatoid diseases, including spondyloarthritis, psoriasis, rheumatoid arthritis, and inflammatory bowel diseases [12-14]. IL-17, also named as cytotoxic T lymphocyte antigen 8 (CTLA8), was first cloned from activated T cells in 1993 [15]. IL-17 family includes six members from IL-17A to IL-17F, of which IL-17A and IL-17F are crucial proinflammatory cytokines [16]. Soon after the discovery of IL-17, the IL-17 receptor (IL-17R) family was identified consisting of five members ranging from IL-17RA to IL-17RE [17]. The IL-17 members may combine with the IL-17Rs [18], and then activate various inflammatory pathways, including the nuclear factor κB (NF- κB) pathway, the mitogen-activated protein kinases (MAPKs) pathway, and the CCAAT/enhancer-binding proteins (C/EBPs) pathway [19]. The activation of these signal transduction pathways leads to the overexpression of various proinflammatory cytokines, such as IL-6, IL-8, TNF- α , and IL-1 β [18]. Notably, in the individuals with AS, serum level of IL-17 [20] and IL-23 [21] as well as the number of T helper (Th) 17 cells [22–25] in peripheral blood and facet joints [26] were increased compared with healthy control subjects.

Based on a growing body of researches, IL-17A was recognized as a novel therapeutic target for AS. Biological IL-17A inhibitors, which are crucial members of bDMARDs, could directly combine with IL-17A and inhibit its function [27]. IL-17A inhibitors are well established and known as efficient and safe for the treatment of psoriasis [28], rheumatoid arthritis [29, 30], and inflammatory bowel diseases [31]. Recently, increasing randomized controlled trials (RCTs) [32–41] have investigated the efficacy and safety of IL-17A inhibitors in AS, but the clinical value of IL-17A inhibitors in AS is still an area of controversy due to different drug types and dosages. Previous meta-analysis on biological agents for AS treatment only included one or two studies about IL-17A inhibitors [42, 43], after that there were few newly established studies. As such, an updated quantification of the efficacy and safety of IL-17A inhibitors was warranted.

Herein, considering that a number of studies have demonstrated the impact of IL-17A inhibitors in AS, the present systematic review and meta-analysis were conducted to comprehensively understand the efficacy and safety profile of IL-17A inhibitors in AS.

Materials and methods

This meta-analysis was performed in accordance with the Cochrane Handbook for Systematic Review of Interventions [44].

Literature retrieval

A comprehensive literature retrieval was carried out in PubMed, EMBASE, and Web of Science up to February 5, 2020, by two reviewers independently. The search was performed using the terms "ixekizumab OR taltz OR LY2439821 OR secukinumab OR cosentyx OR AIN 457 OR bimekizumab OR UCB4940 OR netakimab OR Anti IL-17 OR Interleukin 17 OR IL-17 inhibitor OR Interleukin 17 inhibitor" AND "ankylosing spondylitis OR spondyloarthritis." In addition, reference lists of the relevant articles and reviews were examined carefully to identify additional eligible articles.

Selection criteria

Articles were included in this analysis if they met all the following criteria: (1) the study was a RCT; (2) patients were diagnosed as AS according to the modified New York criteria; (3) treatment groups received IL-17A inhibitors and control groups received placebo in the RCTs; (4) the efficacy or safety outcomes were reported in the RCTs; (5) the language of the articles was English. Additionally, we excluded animal studies, observational studies, reviews, commentaries, letters, and RCTs that examined other interventions. For the publications with repetitive trial numbers according to the ClinicalTrials. gov identifier, only the most recent one was included. Two authors independently screened all studies by title or abstract and then by a full text evaluation; any discrepancy was solved by discussion.

Data extraction and quality assessment

Data extraction was carried out independently by two authors using a predefined form. We extracted the following information from each included study as follows: first author, publication year, NCT number, region, time to primary endpoint, study duration, medication and dosage, number of cases, mean age, ratio of males, disease duration, HLA-B27positive rate, baseline data of the Bath AS disease activity index (BASDAI).

Quality assessment was performed using the Cochrane Collaboration's tool. We assessed risk of bias according to the following bias categories: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other bias. Each segment was assessed as high risk, low risk, or unclear risk of bias.

Efficacy and safety outcomes

Primary efficacy outcomes were as follows: 20% improvement according to the Assessment of SpondyloArthritis international Society (ASAS) criteria (ASAS20 response), and 40% improvement according to ASAS criteria (ASAS40 response). Other efficacy outcomes were 20% or more improvement in five of the six ASAS response domains (ASAS5/6 response), the change from baseline in total BASDAI, and a score of ≤ 2 units in each of the four core ASAS domains (ASAS partial remission). Safety outcomes included adverse events (AEs), serious adverse events (SAEs), nasopharyngitis, discontinuation due to any AEs (DDAAEs), infections, and serious infections.

Statistical analysis

Review Manager 5.3 was used to perform the data analysis. Odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were considered as the effect size for dichotomous variables, and mean differences (MDs) with 95% CIs were for continuous variables. We performed Cochran I-squared test to assess the heterogeneity among studies. It was supposed that no significant heterogeneity existed among studies if $I^2 <$ 50%, and thus a fixed-effects model was applied. Otherwise, a random-effects model was considered to be more appropriate if $I^2 > 50\%$. To explore the source of heterogeneity among studies and to test the robustness of the results, we further conducted subgroup analyses by the following factors: medication (secukinumab, ixekizumab, netakimab, or bimekizumab), time to primary endpoint (6 weeks, 12 weeks or 16 weeks), and data source (full-text article or conference abstract). If included studies held several treatment arms in terms of dosage, we combined relevant treatment groups into one treatment group, as the Cochrane Handbook for Systematic Review of Interventions recommended [44]. Sensitivity analysis was conducted by omitting any of the studies at a time to further evaluate the stability and credibility of the analytical results. Statistical significance was defined as P value < 0.05.

Results

Study selection and characteristics of included studies

The searching process was summarized in Fig. 1. According to the study searching strategy stated above, 370 records were identified through database searching and 10 records were obtained from the references of the identified articles. After removing 118 duplicated records, we screened the remaining 262 records and excluded 194 records according to the title and the abstract. Then, full texts of the remaining 68 articles were viewed carefully, and 58 of them were excluded. Finally, ten RCTs with 2613 patients were included in our meta-analysis in total, of which seven were published in articles and three were reported in conference abstracts.

Among ten eligible studies in this meta-analysis, there were six studies for secukinumab, two studies for ixekizumab, one study for netakimab, and one study for bimekizumab. Characteristics of included studies were summarized in Table 1. In summary, (1) the year of publication ranged from 2013 to 2019; (2) the sample size ranged from 30 to 458; (3) the time to primary endpoint was 6 weeks for Baeten (2013) [32], 12 weeks for van der Heijde (2018) (2) [41], and 16 weeks for other eight studies; (4) mean age of patients ranged from 40.1 to 47.4 years; (5) the ratio of males ranged from 52.6 to 84.5%; (6) mean disease duration ranged from 5.2 to 13 years; (7) eight studies [33–35, 37–41] had different treatment arms based on dosage; (8) nine studies [32-34, 36–41] declared that they were sponsored. After the time of primary endpoint, all patients in both the treatment groups and the placebo groups entered an extended treatment period and received IL-17A inhibitors treatment. It should be noted that one patient in the treatment group of Baeten (2013) [32] was excluded from the efficacy analysis but included in the safety analysis due to a dosing error. The quality and the risks of bias of included studies were presented in Fig. 2. Notably, there were three RCTs being reported in conference abstracts respectively, and comprehensive information and data were not available.

Efficacy of IL-17A inhibitors

ASAS20 response

ASAS20 response was defined as an outcome that patients achieved 20% improvement according to ASAS criteria. As a primary efficacy outcome indicator for AS, ASAS20 response was reported in nine studies consisting of 2309 patients. No significant heterogeneity among the RCTs was detected ($I^2 = 18\%$), and thus a fixed-effects model was performed. Compared with placebo, IL-17A inhibitors significantly improved the rate of ASAS20 response (OR = 2.58; 95% CI, 2.16 to 3.09; p < 0.01) (Fig. 3A). Subgroup analyses





were performed according to three factors: medication (secukinumab, ixekizumab, or netakimab), time to primary endpoint (6 weeks or 16 weeks), and data source (full text or conference abstract) (Table 2). The results indicated that the efficacy of IL-17A inhibitors on ASAS20 response kept significant in the subgroup analyses. Furthermore, we performed sensitivity analysis and the result showed that the statistical significance was not altered after omitting any of the studies, further confirming the stability and credibility of the eventual results.

ASAS40 response

ASAS40 response was also a crucial outcome indicator which represented patients achieved 40% improvement according to ASAS criteria. Seven studies with 1762 patients were included in the analysis of ASAS40 response. A fixed-effects model was more appropriate due to non-significant heterogeneity $(I^2 = 41\%)$. IL-17A inhibitors made a significant improvement on ASAS40 response rate in AS (OR = 2.80; 95% CI, 2.19 to 3.58; p < 0.01) (Fig. 3B). We further conducted subgroup analyses and we found that the efficacy of IL-17A inhibitors on ASAS40 response remained significant and the outcomes were presented in Table 2. Additionally, sensitivity analysis was performed and the result remained significant after omitting single study one by one.

Other efficacy outcomes

There were five studies reporting data for ASAS5/6 response, four studies for the change from baseline in total BASDAI,

and three studies for ASAS partial remission. Random effect model was suitable for the analyses of ASAS5/6 response $(I^2 = 75\%)$ and the change from baseline in total BASDAI $(I^2 = 100\%)$ owing to obvious heterogeneity. However, in the analysis of ASAS partial remission $(I^2 = 0\%)$, no heterogeneity between the RCTs was detected and thus the fixed-effects model was performed. The results indicated that IL-17A inhibitors could significantly improve ASAS5/6 response rate (OR = 4.01; 95% CI, 2.00 to 8.02; p < 0.01) (Fig. 3C) and ASAS partial remission rate (OR = 5.93; 95% CI, 2.83 to 12.45; p < 0.01) (Fig. 3D), and reduce BASDAI score (MD = -1.13; 95% CI, -1.72 to -0.55; p < 0.01) (Fig. 3E), indicating the favorable curative effects of IL-17A inhibitors in AS. Sensitivity analyses showed that removing any of the studies did not influence the results significantly.

Safety of IL-17A inhibitors

AEs

Eight studies with 2066 patients were included in the analysis of AEs. No heterogeneity between the RCTs was detected $(I^2 = 0\%)$ and a fixed-effects model was performed. Comparing to placebo, IL-17A inhibitors increased risk of AEs (OR = 1.23; 95% CI, 1.02 to 1.49; p = 0.03) (Fig. 4A). We performed subgroup analyses and found that ixekizumab (OR = 1.44; 95% CI, 1.01 to 2.05; p = 0.04) rather than secukinumab (OR = 1.20; 95% CI, 0.94 to 1.53; p = 0.15) increased the risk of AEs (Table 2). When we removed Deodhar (2016) [33] or Deodhar (2019) [34], the results were altered to

Table 1 Charae	steristics of inclue	led studies in the meta-analys	IS.								
Author (year)	ClinicalTrials. gov identifier	Region	Time to primary endpoint (weeks)	Study duration (weeks)	Medication	Number of cases	Age (years) ^a	Males ratios (%)	Disease duration (years) ^a	HLA-B27 positive rate (%)	Baseline BASDAI ^a
Baeten (2013) [32]	NCT00809159	8 centers in Europe	6	28	SEC 2× 10 mg/kg	24	41.1 (10.1)	58	10.1 (12.2)	70	7.1 (1.40)
Doodhor (2016)	MCT01250175	106 contour	16	63	placebo SEC 150 mg	6 175	45.0 (10.0) 40 1 (11 6)	83	10.2 (12.0) 6 5 (6 0)	83	7.2 (1.76)
Decuman (2010) [33]	CI TOCCIDI ONI		10	70	SEC 75 mg	124	42.3 (13.2)	71	(7.9) C.0 (7.9) Q.7	80 80	6.1(1.4)
					placebo	122	43.1 (12.4)	70	8.3 (8.9)	74	6.5 (1.5)
Deodhar (2019)	NCT02696798	106 centers in	16	52	IXE 80 mg	98	44.2 (10.8)	76.5	11.7 (8.8)	NA	7.5 (1.3)
[34]		15 countries			Q2W IXE 80 mg	114	47.4 (13.4)	79.8	10.1 (7.8)	NA	7.5 (1.3)
					Q4W	101					
- -					placebo	104	46.6 (12.7)	83.7	(0.01) 0.51	NA	(1.3)
Erdes (2019)	NA	NA	16	NA	NTK 40 mg	22	NA	NA	NA	NA	NA
[cc]					NTK 80 mg	22	NA	NA	NA	NA	NA
					NTK 120 mg	22	NA	NA	NA	NA	NA
					placebo	23	NA	NA	NA	NA	NA
Huang (2019)	NCT02896127	China, Czech Republic,	16	52	SEC 150 mg	305	NA	NA	NA	NA	NA
[36]		South Korea and the UK			placebo	153	NA	NA	NA	NA	NA
Kivitz (2018)	NCT02159053	85 centers in 19 countries	16	104	SEC 150 mg	116	44.5 (11.6)	69.8	8.4 (10.8)	86.2	7.0 (1.2)
[37]					SEC 150 mg	117	41.2 (11.1)	0.07	65(76)	84.6	6 05 (1 3)
					without						
					load		i : : :		:		:
					placebo	117	43.4 (12.5)	65	7.1 (9.2)	79.5	7.1 (1.2)
Pavelka (2017)	NCT02008916	54 centers across the	16	52	SEC 300 mg	76	42.1 (11.8)	65.8	5.3 (7.3)	73.7	7.0 (1.4)
[38]		America and Europe			SEC 150 mg	74	42.9 (11.1)	62.2	6.0 (7.2)	70.3	7.0 (1.4)
					placebo	76	42.7 (11.4)	52.6	5.2 (6.4)	69.7	6.9 (1.3)
Sieper (2016)	NCT01649375	106 centers	16	52	SEC 150 mg	72	41.9 (12.5)	64	7.0 (8.2)	79	6.6 (1.5)
[39]					SEC 75 mg	73	44.4 (13.1)	70	5.3 (7.4)	73	6.6 (1.3)
					placebo	74	43.6 (13.2)	76	6.4 (8.9)	78	6.8 (1.3)
van der Heijde	NCT02696785	84 centers in	16	52	IXE 80 mg	83	41.3 (11.2)	77	8.2 (9.0)	06	6.7 (1.6)
(2018) (1)		12 countries			Q2W	č		č			5
[40]					LXE 80 mg O4W	81	41.0 (12.1)	84	8.3 (9.6)	93	6.8 (1.3)
					placebo	87	42.7 (12.0)	83	6.8 (7.6)	89	6.8 (1.2)
van der Heijde	NCT02963506	NA	12	48	BIM 16 mg	243	42.2 (11.8)	84.5	NA	NA	NA
(2018) (2)					BIM 64 mg				NA	NA	NA
[41]					BIM 160 mg				NA	NA	NA

Author (year)	ClinicalTrials. gov identifier	Region	Time to primary endpoint (weeks)	Study duration (weeks)	Medication	Number of cases	Age (years) ^a	Males ratios (%)	Disease duration (years) ^a	HLA-B27 positive rate (%)	Baseline BASDAI ^a
					BIM 320 mg placebo	60			NA NA	NA NA	NA NA
SEC, secukinum	ab; IXE, ixekizun	nab; NTK, netakimab; BIM, bi	imekizumab; BASDA	I, Bath AS Dis	sease Activity Inc	dex; Q2W, 6	svery 2 weeks; Q	4W, every 4	· weeks		

SD

Data were shown by mean and

Table 1 (continued)

be insignificant (p = 0.21 or 0.18, respectively), indicating that increased risk of AEs might be derived from these two studies.

SAEs

Eight studies with 2221 patients were included in the analysis of SAEs. A fixed-effects model was performed in the analysis of SAEs ($I^2 = 0\%$). Meta-analysis of SAEs demonstrated that IL-17A inhibitors did not increase the risk of SAEs (OR = 0.87; 95% CI, 0.51 to 1.48; p = 0.60) (Fig. 4B). We further conducted subgroup analyses. The result did not indicate statistically significant differences between secukinumab and placebo (OR = 0.87; 95% CI, 0.47 to 1.61; p = 0.66), as well as ixekizumab and placebo (OR = 0.86; 95% CI, 0.30 to 2.49; p = 0.41) (Table 2). Removing any of the studies did not influence the result significantly.

Nasopharyngitis

Nasopharyngitis was the most commonly reported adverse event among these studies. Seven studies with 1763 patients were included in the analysis of nasopharyngitis. No heterogeneity among the RCTs was detected ($I^2 = 0\%$) and a fixed-effects model was performed. Comparing to placebo, IL-17A inhibitors increased the risk of nasopharyngitis (OR = 1.72; 95% CI, 1.15 to 2.57; p < 0.01) (Fig. 4C). The result of subgroup analyses indicated that secukinumab (OR = 1.84; 95% CI, 1.16 to 2.94; p = 0.01) rather than ixekizumab (OR = 1.39; 95% CI, 0.63 to 3.06; p = 0.41) increased the risk of nasopharyngitis (Table 2). Removing any of the studies did not influence the result significantly.

DDAAEs and deaths

There were five studies reporting data for DDAAEs. No heterogeneity was detected in the analysis of DDAAEs ($I^2 = 37\%$) and a fixed-effects model was performed. IL-17A inhibitors showed no impact on DDAAEs (OR = 1.19; 95% CI, 0.61 to 2.32; p = 0.62) (Fig. 4D). As for deaths, one death occurred in the placebo group in Deodhar (2016) [33] due to depression and suicide, one death occurred in the treatment group of secukinumab 75 mg in Sieper (2016) [39], and one death occurred in the treatment group of ixekizumab 80 mg every 2 weeks (Q2W) in Deodhar (2019) as a result of depression and suicide [34]. The impact of IL-17A inhibitors on the risk of death was not analyzed owing to limited data.

Infections and serious infections

Four studies were included for the analysis of infections. Significant heterogeneity was detected in the analysis of infections ($l^2 = 58\%$) and the random-effects model was performed. IL-17A inhibitors increased the risk of infections



Fig. 2 The quality of included studies evaluated by the Cochrane Collaboration's tool

(OR = 2.08; 95% CI, 1.25 to 3.47; p < 0.01) (Fig. 4E). In addition, there were totally 5 serious infections among the included patients: 1 patient in the treatment group of secukinumab 150 mg with a loading regimen (secukinumab 150 mg with load) in Kivitz (2018) [37], 2 patients in treatment group of ixekizumab 80 mg every 4 weeks (Q4W) in Deodhar (2019) [34], and 2 patient in the treatment groups in van der Heijde (2018) (1) [40]. Meta-analysis of serious infections did not indicate statistically significant differences between treatment and control groups (OR = 2.23; 95% CI, 0.38 to 13.21; p = 0.38) (Fig. 4F).

Discussion

AS, a part of a larger class of spondyloarthropathies, is a relatively common, chronic, and serious autoimmune disease

mainly affecting the axial skeleton and spinal joints, eventually reducing the quality of life, also extorting heavy economic burdens and pressure on individuals and the society. As the disease progresses, ankylosis is a major characteristic of AS in advanced cases, leading to the fusion of vertebrae, decreased mobility, and increased long-term disability. Notably, although there are many available treatments to effectively relieve the symptoms of AS, there is no cure method currently. The treatment options for patients with AS were really limited. In recent years, the potential application of bDMARDs has gradually attracted extensive attention of researchers, and the clinical management of AS has been significantly changed as a result of the introduction of bDMARDs.

IL-17, mainly produced by Th17 cells, plays a crucial role in protecting hosts from bacterial and fungal infections under physiological condition. In addition, IL-17 could improve the expression of various proinflammatory cytokines and further lead to inflammatory activation. Recently, IL-17A inhibitors were proved to be novel bDMARDs for several autoimmune diseases, including psoriasis [28], rheumatoid arthritis [29, 30], and inflammatory bowel disease [31]. Overexpressed IL-17 was also highly involved in the autoimmune dysfunction and the disease progression in AS patients. However, the clinical value of IL-17A inhibitors is still controversial. To our best knowledge, the current meta-analysis is the first to comprehensively evaluate the efficacy and safety of IL-17A inhibitors in patients with AS.

Through pooling the data of 10 independent RCTs and comprehensively analyzing the ASAS20 response, ASAS40 response, ASAS5/6 response, and ASAS partial remission, we found that IL-17A inhibitors significantly alleviated the clinical signs and symptoms of AS. In addition, disease activity was controlled by IL-17A inhibitors as measured by decreased BASDAI. Significant heterogeneity was detected in the analysis of ASAS5/6 response and BASDAI, which may reduce the credibility of the data to some extent. Furthermore, after the time of primary endpoint, all patients in both the treatment groups and the placebo groups entered an extended treatment period and received IL-17A inhibitors. There are 7 extension studies reporting that secukinumab possesses sustained efficacy in AS through 1 to 5 years [45–51]. Similarly, the extension studies of ixekizumab demonstrated that the efficacy through 52 weeks was consistent with 16 weeks [52]. Therefore, IL-17A inhibitors demonstrated favorable curative effects in patients with AS and were expected to be promising drugs for AS.

AEs, nasopharyngitis, and infections were found to be more frequently in treatment groups compared with placebo. However, there was no evidence that IL-17A inhibitors increased the risk of SAEs, serious infections, and DDAAEs. As for the death risk, OR was not obtained owing to limited data. To be specific, there were totally three deaths in the included trials, two of which happened in the treatment

 Table 2
 The results of subgroup analyses by factors of medication, time to primary endpoint, and data source

Outcome	Subgroup	No. of studies	No. of patients	OR (95% CI)	P value
Medication					
ASAS20	SEC	6	1653	2.54 (2.05, 3.14)	< 0.01
	IXE	2	567	2.47 (1.72, 3.57)	< 0.01
	NET	1	89	5.85 (2.08, 16.47)	< 0.01
ASAS40	SEC	5	1195	2.54 (1.90, 3.41)	< 0.01
	IXE	2	567	3.49 (2.22, 5.48)	< 0.01
AEs	SEC	5	1196	1.20 (0.94, 1.53)	0.15
	IXE	2	567	1.44 (1.01, 2.05)	0.04
	BIM	1	303	0.93 (0.52, 1.66)	0.81
Nasopharyngitis	SEC	5	1196	1.84 (1.16, 2.94)	0.01
	IXE	2	567	1.39 (0.63, 3.06)	0.41
SAEs	SEC	6	1654	0.87 (0.47, 1.61)	0.66
	IXE	2	567	0.86 (0.30, 2.49)	0.78
Time to endpoint					
ASAS20	6 weeks	1	29	7.78 (0.78, 77.93)	0.08
	16 weeks	8	2280	2.56 (2.14, 3.07)	< 0.01
ASAS40	6 weeks	1	29	2.19 (0.21, 22.34)	0.51
	16 weeks	6	1733	2.81 (2.19, 3.59)	< 0.01
AEs	6 weeks	1	30	1.21 (0.04, 33.21)	0.91
	12 weeks	1	303	0.93 (0.52, 1.66)	0.81
	16 weeks	6	1733	1.27 (1.04, 1.56)	0.02
Nasopharyngitis	6 weeks	1	30	5.57 (0.28, 112.01)	0.26
	16 weeks	6	1733	1.66 (1.11, 2.50)	0.01
SAEs	6 weeks	1	30	0.83 (0.03, 22.87)	0.91
	16 weeks	7	2191	0.87 (0.51, 1.49)	0.61
Data source					
ASAS20	Full text	7	1762	2.55 (2.07, 3.13)	< 0.01
	Conference abstract	2	547	2.70 (1.86, 3.92)	< 0.01
AEs	Full text	7	1763	1.27 (1.04, 1.56)	0.02
	Conference abstract	1	303	0.93 (0.52, 1.66)	0.81
SAEs	Full text	7	1763	0.74 (0.41, 1.33)	0.32
	Conference abstract	1	458	1.69 (0.46, 6.25)	0.43

SEC, secukinumab; IXE, ixekizumab; NTK, netakimab; BIM, bimekizumab

groups. Furthermore, IL-17A inhibitors may increase the risk of neutropenia owing to the immunosuppressive properties of these biologics [33, 34]. Therefore, attention should be paid to this problem when applying IL-17A inhibitors in the treatment of AS. Since this finding was based on a relatively small number of studies, the results should be interpreted prudently. Likewise, the safety of IL-17A inhibitors was controversial in other autoimmune diseases. A meta-analysis of twenty-seven RCTs showed that IL-17A inhibitors increased the risk of AEs in moderate-to-severe plaque psoriasis [53]. In addition, the risk of AEs but not SAEs was increased by IL-17A inhibitors in patients with psoriasis and psoriatic arthritis [54]. However, Kunwar et al. performed a meta-analysis of seven RCTs about rheumatoid arthritis and reported that IL-17A inhibitors did not significantly increase the risk of AEs or SAEs in rheumatoid arthritis [55]. Therefore, the safety of IL-17A inhibitors remains to be further studied.

As a consequence of the introduction of bDMARDs, TNF inhibitors were considered as usual first-line bDMARDs treatment. However, due to intolerance and inefficacy of TNF inhibitors, IL-17A inhibitors as a novel bDMARDs were recommended for AS patients who do not respond to TNF inhibitors according to 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis [10]. Moreover, a cost-effectiveness analysis in Finland indicated that secukinumab was less costly and more effective compared to adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab in AS treatment [56]. Also,

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Fig. 3 The efficacy evaluation of IL-17A inhibitors in AS. Forest plots of ORs for ASAS20 response (A), ASAS40 response (B), ASAS5/6 response (C), and ASAS partial remission (D) in patients with AS. Forest plots of MD for BASDAI (E) in patients with AS

а		Experim	ental	Contr	ol		Odds Ratio	Odds Ratio
	Study or Subaroup	Events	Total	Events	Total	Weight	M-H. Fixed, 95% C	M-H, Fixed, 95% Cl
_	Baeten (2013)	1/	23	1	6	0.4%	7 78 [0 78 77 93]	· · ·
	Doodbor (2016)	150	240	25	122	12.6%	3 77 12 36 6 011	
	Deodhar (2010)	100	249	33	122	12.0 /0	0.44 [4.00, 0.01]	
	Deodnar (2019)	101	212	31	104	14.7%	2.14 [1.30, 3.53]	
	Erdes (2019)	54	66	10	23	1.8%	5.85 [2.08, 16.47]	
	Huang (2019)	178	305	56	153	21.0%	2.43 [1.63, 3.62]	
	Kivitz (2018)	141	233	55	117	19.6%	1.73 [1.10, 2.70]	
	Pavelka (2017)	89	150	28	76	10.2%	2.50 [1.42, 4.42]	
	Sieper (2017)	74	145	21	74	9.2%	2.63 [1.44, 4.80]	
	van der Heijde (2018) (1)	109	164	35	87	10.4%	2.94 [1.72, 5.04]	
	Total (95% CI)		1547		762	100.0%	2.58 [2.16, 3.09]	•
	Total events	910		272				
	Heterogeneity: Chi ² = 9.75,	, df = 8 (P =	= 0.28); I	² = 18%				
	Test for overall effect: Z = 2	10.28 (P <	0.00001)				0.01 0.1 I 10 100
								Favours placebo Favours IE-17A Inhibitor
b		Evenerin	ontol	Contr	-		Odda Batia	Odda Batia
	01 J	Experim	Tental	Contr	01	141-1-1-4	Odds Ratio	Odds Ratio
-	Study or Subgroup	Events	Total	Events	Total	weight	WI-H, FIXed, 95% C	M-H, Fixed, 95% Cl
	Baeten (2013)	7	23	1	6	1.3%	2.19 [0.21, 22.34]	
	Deodhar (2016)	93	249	16	122	15.8%	3.95 [2.20, 7.09]	
	Deodhar (2019)	59	212	13	104	14.8%	2.70 [1.40, 5.19]	
	Kivitz (2018)	87	233	33	117	32.4%	1.52 [0.94, 2.46]	
	Pavelka (2017)	62	150	16	76	14.7%	2.64 [1.39, 5.01]	_ _
	Sieper (2017)	45	145	8	74	8.6%	3.71 [1.65, 8.38]	
	van der Heijde (2018) (1)	82	164	16	87	12.3%	4.44 [2.38, 8.27]	_
	Total (95% CI)		1176		586	100.0%	2.80 [2.19, 3.58]	◆
	Total events	435		103				
	Heterogeneity: Chi ² = 10.18	8. df = 6 (P	= 0.12):	$ ^2 = 41\%$				
	Test for overall effect: Z = 8	8.24 (P < 0	.00001)					0.01 0.1 1 10 100
			,					Favours placebo Favours IL-17A inhibitor
C	5			2 4 1			Odda Datia	Odda Datia
v	er i e i e i	xperiment		Sontrol			Udds Ratio	Odds Ratio
-	Study or Subgroup EV	vents I	otal Ev	ents lo		eight M	-H, Random, 95% C	M-H, Random, 95% Cl
	Baeten (2013)	8	23	0	6 4	4.6%	7.13 [0.36, 142.56]	
	Deodhar (2016)	117	249	16 1	22 2	5.2%	5.87 [3.28, 10.50]	
	Kivitz (2018)	93	233	34 1	17 20	6.8%	1.62 [1.01, 2.61]	
	Pavelka (2017)	61	150	11	76 23	3.1%	4.05 [1.98, 8.30]	
	Sieper (2017)	56	145	6	74 20	0.3%	7.13 [2.90, 17.52]	
	Total (95% CI)	;	B00	3	95 10	0.0%	4.01 [2.00, 8.02]	\bullet
	Total events	335		67				
	Heterogeneity: Tau ² = 0.41	1; Chi² = 1	5.80, df =	= 4 (P = 0	.003); I	² = 75%		
	Test for overall effect: Z =	3.92 (P < 0	0.0001)					U.U1 U.1 1 10 100
								Favours placebo Favours IE-17A IIIIIbitor
-								
d	F	vneriment	al	Control			Odds Ratio	Odds Ratio
•	Study or Subgroup	vonte T	otal Ev	onte To	tal M	oight I	ULL Eived 05% Cl	M-H Eixed 95% Cl
-	Deadbar (2016)	20	240	4 4	20 6	0.00/	E 40 [4 04 45 74]	
	Deodriar (2016)	39	249	4	22 0	0.0%	5.46 [1.91, 15.71]	
	Pavelka (2017)	23	150	1	76 1	2.4% 1	3.58 [1.80, 102.63]	
	Sieper (2017)	21	145	3	74 3	87.5%	4.01 [1.15, 13.91]	•
	Total (95% CI)		544	2	72 10	0.0%	5.93 [2.83, 12.45]	
	Total events	83		8				
	Heterogeneity: Chi ² = 1.05	5, df = 2 (P	= 0.59);	$I^2 = 0\%$			F	
	Test for overall effect: Z =	4.71 (P <	0.00001)			,	Eavours placebo Eavours II -17A inhibitor
е		vnorimert	al	Contra			Moon Difference	Moon Difference
	Einer Subaroup Mor	speriment	ai Totol M	contro	N Toto	l Woight	Wear Difference	Wear Difference
-	Deadbar (2016)	<u>an 30</u>	240 4		<u>10(a</u>		1 74 [4 70 4 7	
	-2.3 Kivita (2016) -2.3	00 U.17	249 -(J.09 U.18	122	25.0%	-1.74 [-1.78, -1.70	
	NIVIZ (2018) -2	2.0 0.23	233 -	1.00 0.2	. 117	25.0%	-0.04 [-0.69, -0.59	-
	Favelka (2017) -2	2.0 0.35	100	-1.5 0.3	. 76	24.9%	-1.00 [-1.09, -0.91	
	Sieper (2017)	-2 0.28	145 -0	0.05 0.25	0 74	25.0%	-1.15 [-1.22, -1.08	
	Total (95% CI)		777		200	100.0%	-1 13 [.4 72 .0 55	
		Chi2 - 400	111	- 2 /	389	100.0%	o -1.13 [-1.72, -0.55	
	Test for evers" -ff -th 7 = 0.36;	Cni ⁺ = 132	:1.59, df :	= 3 (P < 0	.00001); I^ = 100'	70	-1 -0.5 0 0.5 1
	rest for overall effect: Z = 3		000Z)					Favours IL-17A inhibitor Favours placebo

secukinumab was proved to be the most cost-effective treatment option versus other biologics in AS by numerous researches conducted in Canada [57], Argentina [58], the UK [59], and Russia [60].

Besides the 10 included RCTs, more trials are planned or conducted to further evaluate the efficacy and safety of IL-17A inhibitors in AS. In detail, there are three ongoing or planned studies for secukinumab (identifier: NCT03259074, NCT02763046, NCT03350815), two for bimekizumab (identifier: NCT03215277 and NCT03355573), and one for netakimab (identifier: NCT03447704). Because these studies are not completed, we have had no access to the relevant data so far. Therefore, we will pay close attention to the progress of these studies in the future.

Some potential limitations in our study should be acknowledged. First, we could not obtain the comprehensive information and data of three included RCTs reported in three conference abstracts respectively [35, 36, 41]. Second, the number of RCTs included in this study was still relatively small, especially for a certain type of medication, there were only two

Fig. 4 The safety evaluation of IL-17A inhibitors in AS. Forest plots of ORs for AEs (A), SAEs (B), nasopharyngitis (C), DDAAEs (D), infections (E), and serious infections

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а		Experim	ental	Contr	ol		Odds Ratio	Odds Ratio
-	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
	Baeten (2013)	23	24	6	6	0.3%	1.21 [0.04, 33.21]	
	Deodhar (2016)	170	249	68	122	15.3%	1.71 [1.09, 2.67]	
	Deodhar (2019)	132	212	51	104	13.6%	1.71 [1.07, 2.76]	
	Kivitz (2018)	131	233	64	117	19.7%	1.06 [0.68, 1.66]	
	Pavelka (2017) Siener (2017)	68	150	33	76	12.6%	1.08 [0.62, 1.88]	
	Sieper (2017)	89	145	47	74	12.7%	0.91 [0.51, 1.63]	
	van der Heijde (2018) (1)	89	243	23	60	12.3%	0.93 [0.52, 1.66]	
		03	240	20	00	12.570	0.35 [0.52, 1.00]	
	Total (95% CI)		1420		646	100.0%	1.23 [1.02, 1.49]	•
	Total events	772		326				
	Heterogeneity: Chi ² = 6.54,	df = 7 (P =	= 0.48); I	² = 0%				
	Test for overall effect: Z = 2	2.13 (P = 0	.03)					Favours placebo Favours IL-17A inhibitor
h								
D		Experim	ental	Contr	ol		Odds Ratio	Odds Ratio
-	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
	Baeten (2013)	1	24	0	6	2.6%	0.83 [0.03, 22.87]	
	Deodhar (2016)	5	249	5	122	23.0%	0.48 [0.14, 1.69]	
	Deodnar (2019)	10	212	5	104	12 50/	0.68 [0.21, 2.18]	
	Huang (2019)	10	305	3	100	18.3%	1.69 [0.46, 6.25]	
	Pavelka (2017)	1	150	1	76	4.6%	0.50 [0.03, 8, 16]	
	Sieper (2017)	8	145	3	74	13.1%	1.38 [0.36, 5.37]	
	van der Heijde (2018) (1)	2	164	õ	87	2.2%	2.69 [0.13, 56.71]	
	Total (95% CI)		1482		739	100.0%	0.87 [0.51, 1.48]	
	Total events	38		21				
	Heterogeneity: Chi ² = 3.79,	df = 7 (P =	= 0.80); I	² = 0%				
	Test for overall effect: Z = 0	0.52 (P = 0	.60)					Favours placebo Favours IL-17A inhibitor
C								
v		Experim	ental	Contr	ol		Odds Ratio	Odds Ratio
-	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
	Baeten (2013)	20	24	0	100	1.4%	5.57 [0.28, 112.01]	, , , , , , , , , , , , , , , , , , ,
	Deodhar (2016) Deodhar (2019)	30	249	9	122	20.5%	1.72 [0.79, 3.75]	
	Kivitz (2018)	28	212	10	117	9.4% 29.2%	1 46 [0.68, 3 12]	-+
	Pavelka (2017)	20	150	2	76	6.2%	2.36 [0.50, 11.21]	
	Sieper (2017)	14	145	3	74	9.0%	2.53 [0.70, 9.10]	
	van der Heijde (2018) (1)	11	164	6	87	18.3%	0.97 [0.35, 2.72]	
	, , , , , , ,							
	Total (95% CI)		1177		586	100.0%	1.72 [1.15, 2.57]	•
	Total events	112		33				
	Heterogeneity: Chi ² = 2.60,	df = 6 (P =	= 0.86); I	² = 0%				0.01 0.1 1 10 100
	Test for overall effect: Z = 2	2.64 (P = 0	.008)					Favours placebo Favours IL-17A inhibitor
_								
A								
u		Exporim	ontal	Contr	al		Odde Patio	Odde Patio
u	Study or Subaroup	Experim Events	ental Total	Contr Events	ol Total	Weight	Odds Ratio M-H. Fixed, 95% Cl	Odds Ratio M-H. Fixed, 95% Cl
u	Study or Subgroup Deodhar (2016)	Experim Events 3	ental <u>Total</u> 249	Contr Events 5	ol <u>Total</u> 122	Weight 41.1%	Odds Ratio <u>M-H, Fixed, 95% Cl</u> 0.29 [0.07, 1,21]	Odds Ratio M-H, Fixed, 95% Cl
u -	<u>Study or Subgroup</u> Deodhar (2016) Deodhar (2019)	Experim Events 3 13	ental Total 249 212	Contr Events 5 2	ol <u>Total</u> 122 104	<u>Weight</u> 41.1% 15.6%	Odds Ratio <u>M-H, Fixed, 95% C</u> 0.29 [0.07, 1.21] 3.33 [0.74, 15.05]	Odds Ratio M-H. Fixed. 95% Cl
u -	Study or Subgroup Deodhar (2016) Deodhar (2019) Kivitz (2018)	Experim Events 3 13 3	ental <u>Total</u> 249 212 233	Contr Events 5 2 1	ol <u>Total</u> 122 104 117	Weight 41.1% 15.6% 8.1%	Odds Ratio <u>M-H. Fixed, 95% Cl</u> 0.29 [0.07, 1.21] 3.33 [0.74, 15.05] 1.51 [0.16, 14.71]	Odds Ratio M-H. Fixed. 95% Cl
u -	Study or Subgroup Deodhar (2016) Deodhar (2019) Kivitz (2018) Sieper (2017)	Experim Events 3 13 3 7	ental Total 249 212 233 145	Contr Events 5 2 1 4	ol <u>Total</u> 122 104 117 74	Weight 41.1% 15.6% 8.1% 31.2%	Odds Ratio <u>M-H. Fixed, 95% Cl</u> 0.29 [0.07, 1.21] 3.33 [0.74, 15.05] 1.51 [0.16, 14.71] 0.89 [0.25, 3.13]	Odds Ratio M-H, Fixed, 95% Cl
u	Study or Subgroup Deodhar (2016) Deodhar (2019) Kivitz (2018) Sieper (2017) van der Heijde (2018) (1)	Experim Events 3 13 3 7 3	ental <u>Total</u> 249 212 233 145 164	Contr Events 5 2 1 4 0	ol <u>Total</u> 122 104 117 74 87	Weight 41.1% 15.6% 8.1% 31.2% 4.0%	Odds Ratio M-H. Fixed. 95% Cl 0.29 [0.07, 1.21] 3.33 [0.74, 15.05] 1.51 [0.16, 14.71] 0.89 [0.25, 3.13] 3.79 [0.19, 74.26]	Odds Ratio M-H, Fixed. 95% Cl
u -	Study or Subgroup Deodhar (2016) Deodhar (2019) Kivitz (2018) Sieper (2017) van der Heijde (2018) (1)	Experim Events 3 13 3 7 3	Total 249 212 233 145 164	Contr Events 5 2 1 4 0	ol <u>Total</u> 122 104 117 74 87	Weight 41.1% 15.6% 8.1% 31.2% 4.0%	Odds Ratio M-H. Fixed. 95% Cl 0.29 [0.07, 1.21] 3.33 [0.74, 15.05] 1.51 [0.16, 14.71] 0.89 [0.25, 3.13] 3.79 [0.19, 74.26]	Odds Ratio M-H, Fixed, 95% Cl
u -	Study or Subgroup Deodhar (2016) Deodhar (2019) Kivitz (2018) Sieper (2017) van der Heijde (2018) (1) Total (95% CI)	Experim Events 3 13 3 7 3	rental 249 212 233 145 164 1003	Contr Events 5 2 1 4 0	ol <u>Total</u> 122 104 117 74 87 504	Weight 41.1% 15.6% 8.1% 31.2% 4.0% 100.0%	Odds Ratio M-H, Fixed, 95% CI 0.29 [0.07, 1.21] 3.33 [0.74, 15.05] 1.51 [0.16, 14.71] 0.89 [0.25, 3.13] 3.79 [0.19, 74.26] 1.19 [0.61, 2.32]	Odds Ratio M-H. Fixed. 95% Cl
u	Study or Subgroup Deodhar (2016) Deodhar (2019) Kivitz (2018) Sieper (2017) van der Heijde (2018) (1) Total (95% CI) Total events Hetergreenstier, Chi ² = 6.36	Experim Events 3 13 3 7 3 29 df = 4 (Pa	ental Total 249 212 233 145 164 1003	Contr Events 5 2 1 4 0 12 2 = 37%	ol <u>Total</u> 122 104 117 74 87 504	Weight 41.1% 15.6% 8.1% 31.2% 4.0% 100.0%	Odds Ratio <u>M-H, Fixed, 95% CI</u> 0.29 [0.07, 1.21] 3.33 [0.74, 15.05] 1.51 [0.16, 14.71] 0.89 [0.25, 3.13] 3.79 [0.19, 74.26] 1.19 [0.61, 2.32]	Odds Ratio M-H. Fixed. 95% CI
u .	Study or Subgroup Deodhar (2016) Deodhar (2019) Kivitz (2018) Sieper (2017) van der Heijde (2018) (1) Total (95% CI) Total events Heterogeneity: Chi ² = 6.36, Test for overall effect: Z = 6	Experim Events 3 13 3 7 3 29 off = 4 (P = 0 0.50 (P = 0	ental <u>Total</u> 249 212 233 145 164 1003 = 0.17); I	Contr <u>Events</u> 5 2 1 4 0 2 2 = 37%	ol <u>Total</u> 122 104 117 74 87 504	Weight 41.1% 15.6% 8.1% 31.2% 4.0% 100.0%	Odds Ratio <u>M-H. Fixed, 95% CI</u> 0.29 [0.07, 1.21] 3.33 [0.74, 15.05] 1.51 [0.16, 14, 71] 0.89 [0.25, 3.13] 3.79 [0.19, 74.26] 1.19 [0.61, 2.32]	Odds Ratio M-H, Fixed. 95% Cl
u	Study or Subgroup Deodhar (2016) Deodhar (2019) Kivitz (2018) Sieper (2017) van der Heijde (2018) (1) Total (95% CI) Total events Heterogeneity: Chi ² = 6.36, Test for overall effect: Z = 0	Experim Events 3 13 3 7 3 29 df = 4 (P = 0.50 (P = 0	ental <u>Total</u> 249 212 233 145 164 1003 = 0.17); I .62)	Contr Events 5 2 1 4 0 2 2 = 37%	ol <u>Total</u> 122 104 117 74 87 504	Weight 41.1% 15.6% 8.1% 31.2% 4.0% 100.0%	Odds Ratio M-H. Fixed, 95% CI 0.29 [0:07, 1.21] 3.33 [0.74, 15.05] 1.51 [0.16, 14, 71] 0.89 [0.25, 3.13] 3.79 [0.19, 74.26] 1.19 [0.61, 2.32]	Odds Ratio M-H, Fixed, 95% CI
u _	Study or Subgroup Deodhar (2016) Deodhar (2019) Kivitz (2018) Sieper (2017) van der Heijde (2018) (1) Total (95% CI) Total events Heterogeneity: Chi ² = 6.36, Test for overall effect: Z = (Experim Events 3 13 3 7 3 29 df = 4 (P = 0 0.50 (P = 0	ental <u>Total</u> 249 212 233 145 164 1003 = 0.17); I .62)	Contr <u>Events</u> 5 2 1 4 0 12 ² = 37%	ol <u>Total</u> 122 104 117 74 87 504	Weight 41.1% 15.6% 8.1% 31.2% 4.0% 100.0%	Odds Ratio M-H, Fixed, 95% CI 0.29 [0.07, 1.21] 3.33 [0.74, 15.05] 1.51 [0.16, 14, 71] 0.89 [0.25, 3.13] 3.79 [0.19, 74.26] 1.19 [0.61, 2.32]	Odds Ratio M-H, Fixed, 95% CI
e	Study or Subgroup Deodhar (2016) Deodhar (2019) Kivitz (2018) Sieper (2017) van der Heijde (2018) (1) Total (95% CI) Total events Heterogeneity: Chi ² = 6.36, Test for overall effect: Z = 0	Experim Events 3 13 3 7 3 29 df = 4 (P = 0 0.50 (P = 0 Experime	Total 249 212 233 145 164 1003 = 0.17); I .62)	Contr <u>Events</u> 5 2 1 4 0 12 ² = 37% Contro	ol <u>Total</u> 122 104 117 74 87 504	Weight 41.1% 15.6% 8.1% 31.2% 4.0% 100.0%	Odds Ratio M-H. Fixed. 95% CI 0.29 [0.07, 1.21] 3.33 [0.74, 15.05] 1.51 [0.16, 14.71] 0.89 [0.25, 3.13] 3.79 [0.19, 74.26] 1.19 [0.61, 2.32] Odds Ratio	Odds Ratio M-H. Fixed. 95% C1 0.01 0.1 10 100 Favours placebo Favours IL-17A inhibitor Odds Ratio
e	Study or Subgroup Deodhar (2018) Deodhar (2019) Kivitz (2018) Sieper (2017) van der Heijde (2018) (1) Total (95% CI) Total events Heterogeneity: Chi ² = 6.36, Test for overall effect: Z = (Study or Subgroup	Experim Events 3 3 7 3 29 df = 4 (P = 0 0.50 (P = 0 Experime Events	Total 249 212 233 145 164 1003 = 0.17); I .62)	Contro <u>Events</u> 5 2 1 4 0 12 ² = 37% Contro <u>Events</u>	ol <u>Total</u> 122 104 117 74 87 504 I Fotal	Weight 41.1% 15.6% 8.1% 31.2% 4.0% 100.0% Weight	Odds Ratio <u>M-H. Fixed, 95% CI</u> 0.29 [0.07, 1.21] 3.33 [0.74, 15.05] 1.51 [0.16, 14, 71] 0.89 [0.25, 3.13] 3.79 [0.19, 74.26] 1.19 [0.61, 2.32] Odds Ratio <u>M-H. Random, 95% C</u>	Odds Ratio M-H, Fixed, 95% Cl 0.01 0.1 1 10 100 Favours placebo Favours IL-17A inhibitor Odds Ratio Cl M-H, Random, 95% Cl
e	Study or Subgroup Deodhar (2016) Deodhar (2019) Kivitz (2018) Sieper (2017) van der Heijde (2018) (1) Total (95% CI) Total events Heterogeneity: Chi² = 6.36, Test for overall effect: Z = 0 Study or Subgroup Deodhar (2016)	Experim <u>Events</u> 3 13 3 7 3 29 df = 4 (P = 0 .50 (P = 0 <u>Experime</u> <u>Events</u> 75	ental Total 249 212 233 145 164 1003 = 0.17); I .62) ental Total 249	Contro 5 2 1 4 0 2 2 = 37% Contro Events 15	ol <u>Total</u> 122 104 117 74 87 504	Weight 41.1% 15.6% 8.1% 31.2% 4.0% 100.0% Weight 26.8%	Odds Ratio <u>M-H. Fixed, 95% CI</u> 0.29 [0.07, 1.21] 3.33 [0.74, 15.05] 1.51 [0.16, 14, 71] 0.89 [0.25, 3.13] 3.79 [0.19, 74.26] 1.19 [0.61, 2.32] Odds Ratio <u>M-H. Random, 95% C</u> 3.07 [1.68, 5.63]	Odds Ratio M-H, Fixed. 95% Cl 0.01 0.1 1 10 100 Favours placebo Favours IL-17A inhibitor Odds Ratio Cl M-H, Random. 95% Cl
e	Study or Subgroup Deodhar (2016) Deodhar (2019) Kivitz (2018) Sieper (2017) van der Heijde (2018) (1) Total (95% CI) Total events Heterogeneity: Chi ² = 6.36, Test for overall effect: Z = 0 Study or Subgroup Deodhar (2016) Deodhar (2019)	Experim Events 3 13 3 7 3 29 df = 4 (P = 0 0.50 (P = 0 Experime Events 75 57	ental Total 249 212 233 145 164 1003 = 0.17); I .62) ental Total 249 212 233 145 164 249 212 233 145 164 249 212 233 145 249 212 233 145 164 249 212 233 145 264 212 233 145 264 264 212 233 145 264 203 212 233 145 264 203 203 203 203 203 203 203 203	Contr <u>Events</u> 5 2 1 4 0 12 ² = 37% Contro <u>Events</u> 15 10	ol <u>Total</u> 122 104 117 74 87 504 I <u>Fotal</u> 122 104	Weight 41.1% 15.6% 8.1% 31.2% 4.0% 100.0% Weight 26.8% 23.2%	Odds Ratio M-H, Fixed, 95% CI 0.29 [0.07, 1.21] 3.33 [0.74, 15.05] 1.51 [0.16, 14, 71] 0.89 [0.25, 3.13] 3.79 [0.19, 74.26] 1.19 [0.61, 2.32] Odds Ratio M-H, Random, 95% C 3.07 [1.68, 5.63] 3.46 [1.68, 7.10]	Odds Ratio M-H, Fixed, 95% Cl
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e	Study or Subgroup Deodhar (2016) Deodhar (2019) Kivitz (2018) Sieper (2017) van der Heijde (2018) (1) Total (95% CI) Total events Heterogeneity: Chi² = 6.36, Test for overall effect: Z = (0) Study or Subgroup Deodhar (2016) Deodhar (2016) Sieper (2017) van der Heijde (2018) (1) Total (95% CI)	Experim <u>Events</u> 3 3 3 7 3 29 df = 4 (P = 0 0.50 (P = 0 Experime <u>Events</u> 75 57 46 33	ental Total 249 212 233 145 164 1003 = 0.17); I .62) ental Total 249 212 249 212 145 164 770	Contro 5 2 1 4 0 12 2 = 37% Contro Events 15 10 20 13	ol Total 122 104 117 74 87 504	Weight 41.1% 15.6% 8.1% 31.2% 4.0% 100.0% Weight 26.8% 23.2% 26.3% 23.7% 100.0%	Odds Ratio <u>M-H. Fixed, 95% CI</u> 0.29 [0.07, 1.21] 3.33 [0.74, 15.05] 1.51 [0.16, 14, 71] 0.89 [0.25, 3.13] 3.79 [0.19, 74.26] 1.19 [0.61, 2.32] Odds Ratio <u>M-H. Random, 95% C</u> 3.07 [1.68, 5.63] 3.46 [1.68, 7.10] 1.25 [0.67, 2.33] 1.43 [0.71, 2.89] 2.08 [1.25, 3.47]	Odds Ratio M-H, Fixed. 95% Cl
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e	Study or Subgroup Deodhar (2016) Deodhar (2019) Kivitz (2018) Sieper (2017) van der Heijde (2018) (1) Total (95% CI) Total events Heterogeneity: Chi ² = 6.36, Test for overall effect: Z = (Study or Subgroup Deodhar (2016) Deodhar (2019) Sieper (2017) van der Heijde (2018) (1) Total (95% CI) Total events Heterogeneity: Tau ² = 0.16;	Experim Events 3 3 7 3 29 df = 4 (P = 0 20 50 (P = 0 Experime Experime 5 57 46 33 211 Chi ² = 7.1 ²	Image: constraint of the system 249 242 233 145 164 1003 ental Total Total 212 249 212 145 164 70 9, df = 3	Contro 5 2 1 4 0 2 2 = 37% Contro Events 15 10 20 13 58 (P = 0.07)	ol <u>Total</u> 122 104 117 74 87 504 I <u>Fotal</u> 122 104 74 87 387 ;; ² = 5	Weight 41.1% 15.6% 8.1% 31.2% 4.0% 100.0% Weight 26.8% 23.2% 26.3% 23.7% 100.0% 8%	Odds Ratio M-H, Fixed, 95% CI 0.29 [0.07, 1.21] 3.33 [0.74, 15.05] 1.51 [0.16, 14, 71] 0.89 [0.25, 3.13] 3.79 [0.19, 74.26] 1.19 [0.61, 2.32] Odds Ratio M-H, Random, 95% C 3.07 [1.68, 5.63] 3.46 [1.68, 7.10] 1.25 [0.67, 2.33] 1.43 [0.71, 2.89] 2.08 [1.25, 3.47]	Odds Ratio M-H, Fixed, 95% Cl 0.01 0.1 1 10 100 Favours placebo Favours IL-17A inhibitor Odds Ratio Ddds Ratio
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e	Study or Subgroup Deodhar (2016) Deodhar (2019) Kivitz (2018) Sieper (2017) van der Heijde (2018) (1) Total (95% CI) Total events Heterogeneity: Chi ² = 6.36, Test for overall effect: Z = 0 Study or Subgroup Deodhar (2016) Deodhar (2019) Sieper (2017) van der Heijde (2018) (1) Total (95% CI) Total events Heterogeneity: Tau ² = 0.16; Test for overall effect: Z = 2	Experim 3 3 3 3 29 df = 4 (P = 0 0.50 (P = 0 Experime Events 75 57 46 33 211 Chi ² = 7.1' .82 (P = 0.0	Total 249 212 233 145 164 1003 e 0.17); I 6.62) ental Total 249 249 9.164 770 9. df = 3 9.005)	Contr Events 5 2 1 4 0 12 ² = 37% Contro Events 10 20 13 58 (P = 0.07)	ol Total 122 104 117 74 87 504 122 104 74 87 387 ; ² = 5	Weight 15.6% 8.1% 31.2% 4.0% 100.0% 26.8% 23.2% 26.3% 23.7% 100.0%	Odds Ratio M-H. Fixed, 95% CI 0.29 [0:07, 1.21] 3.33 [0.74, 15.05] 1.51 [0.16, 14, 71] 0.89 [0.25, 3.13] 3.79 [0.19, 74.26] 1.19 [0.61, 2.32] Odds Ratio M-H. Random, 95% C 3.07 [1.68, 5.63] 3.46 [1.68, 7.10] 1.25 [0.67, 2.33] 1.43 [0.71, 2.89] 2.08 [1.25, 3.47]	Odds Ratio M-H, Fixed, 95% Cl
e f	Study or Subgroup Deodhar (2016) Deodhar (2019) Kivitz (2018) Sieper (2017) van der Heijde (2018) (1) Total (95% CI) Total events Heterogeneity: Chi ² = 6.36, Test for overall effect: Z = (Study or Subgroup Deodhar (2016) Deodhar (2019) Sieper (2017) van der Heijde (2018) (1) Total (95% CI) Total events Heterogeneity: Tau ² = 0.16; Test for overall effect: Z = 2	Experim Events 3 3 3 7 3 29 df = 4 (P = 0. 50 (P = 0) Experime 75 57 46 33 211 Chi ² = 7.1: .82 (P = 0.)	Total 249 212 233 145 164 1003 e0.17); I 6.62) ental Total 249 212 249 212 164 770 9, df = 3 9005)	Contro 5 2 1 4 0 2 2 = 37% Contro Events 15 10 20 13 58 (P = 0.07) Contro	ol <u>Total</u> 122 104 117 74 87 504 122 104 124 104 74 87 387 ; ² = 5	Weight 41.1% 15.6% 8.1% 31.2% 4.0% 100.0% Weight 26.3% 23.2% 26.3% 23.7% 100.0% 8%	Odds Ratio <u>M-H. Fixed, 95% CI</u> 0.29 [0.07, 1.21] 3.33 [0.74, 15.05] 1.51 [0.16, 14, 71] 0.89 [0.25, 3.13] 3.79 [0.19, 74.26] 1.19 [0.61, 2.32] 0dds Ratio <u>M-H. Random, 95% C</u> 3.07 [1.68, 563] 3.46 [1.68, 7.10] 1.25 [0.67, 2.33] 1.43 [0.71, 2.89] 2.08 [1.25, 3.47] Odds Ratio	Odds Ratio M-H, Fixed, 95% Cl 0.01 0.1 1 10 100 Favours placebo Favours IL-17A inhibitor Odds Ratio 0.01 0.1 1 10 100 Favours placebo Favours IL-17A inhibitor Favours placebo Favours IL-17A inhibitor Odds Ratio
e f	Study or Subgroup Deodhar (2018) Deodhar (2019) Kivitz (2018) Sieper (2017) van der Heijde (2018) (1) Total (95% Cl) Total events Heterogeneity: Chi ² = 6.36, Test for overall effect: Z = 0 Study or Subgroup Deodhar (2019) Sieper (2017) van der Heijde (2018) (1) Total (95% Cl) Study or Subgroup	Experim Events 3 3 3 7 3 29 df = 4 (P = 0) 57 46 33 211 Chi ² = 7.1: .82 (P = 0.) Experime Experime	Total 7 249 212 233 1455 164 1003 ental 7 99, df = 3 99, df = 3 0005)	Contro 2 2 1 4 0 12 2 = 37% Contro Events 58 (P = 0.07) Contro 28 Contro 13 58	ol <u>Total</u> 122 104 117 74 87 504 I <u>Fotal</u> 122 104 74 87 387 ; ² = 5 ol <u>Total</u>	Weight 41.1% 15.6% 8.1% 31.2% 4.0% 100.0% Weight 26.8% 23.2% 26.3% 23.7% 100.0% 8%	Odds Ratio <u>M-H. Fixed, 95% CI</u> 0.29 [0.07, 1.21] 3.33 [0.74, 15.05] 1.51 [0.16, 14, 71] 0.89 [0.25, 3.13] 3.79 [0.19, 74.26] 1.19 [0.61, 2.32] 0dds Ratio <u>M-H. Random, 95% C</u> 3.07 [1.68, 5.63] 3.46 [1.68, 7.10] 1.25 [0.67, 2.33] 1.43 [0.71, 2.89] 2.08 [1.25, 3.47] Odds Ratio <u>M-H. Fixed, 95% C</u>	Odds Ratio M-H, Fixed, 95% Cl 0.01 0.1 1 10 100 Favours placebo Favours IL-17A inhibitor Odds Ratio 0.01 0.1 1 10 100 Favours placebo Favours IL-17A inhibitor Odds Ratio 0.01 0.1 1 10 100 Favours placebo Favours IL-17A inhibitor
e f	Study or Subgroup Deodhar (2016) Deodhar (2019) Kivitz (2018) Sieper (2017) van der Heijde (2018) (1) Total (95% CI) Total events Heterogeneity: Chi² = 6.36, Test for overall effect: Z = 0 Study or Subgroup Deodhar (2016) Deodhar (2019) Sieper (2017) van der Heijde (2018) (1) Total (95% CI) Total events Heterogeneity: Tau² = 0.16; Test for overall effect: Z = 2 Study or Subgroup Deodhar (2019)	Experim Events 3 3 3 3 29 df = 4 (P = 0. 50 (P = 0) Experime 211 Chi ² = 7.1' .82 (P = 0. Expering Experime 2	Total 7 249 212 233 145 164 1003 e0.17); 1 antal Total 249 249 201 212 145 770 9, df = 3 0005) mental Total 212 145	Contro 2 1 4 0 12 2 = 37% Contro Events 58 (P = 0.07) 58 (P = 0.07) Contro 13 0 13 0 13 0 13 0 13 0 10 10 10 10 10 10 10 10 10	ol <u>Total</u> 122 104 117 74 87 504 1 <u>Total</u> 104 74 87 387 ; ² = 5 ol <u>Total</u> 104 74 122 104 74 122 104 74 87 387 122 104 74 125 126 127 117 74 127 504 127 127 117 74 127 504 127 127 127 127 127 127 127 127	Weight 41.1% 15.6% 8.1% 31.2% 26.8% 23.2% 26.3% 23.7% 100.0%	Odds Ratio <u>M-H. Fixed, 95% CI</u> 0.29 [0.07, 1.21] 3.33 [0.74, 15.05] 1.51 [0.16, 14, 71] 0.89 [0.25, 3.13] 3.79 [0.19, 74.26] 1.19 [0.61, 2.32] Odds Ratio <u>M-H. Random, 95% C</u> 3.07 [1.68, 5.63] 3.46 [1.68, 7.10] 1.25 [0.67, 2.33] 1.43 [0.71, 2.89] 2.08 [1.25, 3.47] Odds Ratio <u>M-H. Fixed, 95% C</u> 2.48 [0.12, 52.17]	Odds Ratio M-H, Fixed, 95% Cl 0.01 0.1 1 0 100 Favours placebo Favours IL-17A inhibitor Odds Ratio 0.01 0.1 1 10 100 Favours placebo Favours IL-17A inhibitor Odds Ratio 0.01 0.1 1 10 100 Favours placebo Favours IL-17A inhibitor Odds Ratio 0.01 0.1 1 10 100 Favours placebo Favours IL-17A inhibitor
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studies available for ixekizumab, one study for netakimab and one study for bimekizumab. More trials are warranted in the future to further assess the efficacy and safety of IL-17A inhibitors in AS. Third, dose-effect relationship of IL-17A inhibitors was not analyzed due to various kinds of medications and limited trials for each. In addition, different treatment arms in eight included studies were combined into one treatment group respectively.

In conclusion, the results from this meta-analysis showed that IL-17A inhibitors significantly improved clinical signs and symptoms of AS, which supported the application of IL-17A inhibitors in the treatment of AS. However, studies with larger sample size and longer follow-up times are firmly warranted to evaluate the safety of IL-17A inhibitors in AS.

Authors' contributions Zengwu Shao designed the outline of the metaanalysis and edited the work. Peng Wang and Binwu Hu performed literature retrieval and screened the studies. Peng Wang and Shuo Zhang extracted data and performed statistical analysis. Peng Wang and Binwu Hu drafted the manuscript. Zengwu Shao and Shuo Zhang revised the manuscript. Weijian Liu, Xiao Lv, and Songfeng Chen created the tables and figures. All authors approved the manuscript.

Funding This work was supported by The National Key Research and Development Program of China [grant numbers 2016YFC1100100]; the Major Research Plan of National Natural Science Foundation of China [grant numbers 91649204].

Data availability Not applicable.

Compliance with ethical standards

Disclosures None.

Code availability Not applicable.

Abbreviations IL, interleukin; AS, ankylosing spondylitis; RCT, randomized controlled trial; ASAS, the Assessment of SpondyloArthritis International Society; ASAS20, 20% improvement according to ASAS criteria; ASAS40, 40% improvement according to ASAS criteria; BASDAI, Bath AS disease activity index; OR, odds ratio; MD, mean difference; AE, adverse event; SAE, serious adverse event; CI, confidence interval; DDAAEs, discontinuation due to any AEs; HLA, human leukocyte antigen; NSAID, non-steroidal anti-inflammatory drug; bDMARD, biological disease-modifying antirheumatic drugs; TNF, tumor necrosis factor; CTLA8, cytotoxic T lymphocyte antigen 8; IL-17R, IL-17 receptor; NF-κB, nuclear factor κB; MAPK, mitogen-activated protein kinase; C/EBP, CCAAT/enhancer-binding protein; Th, T helper; SEC, secukinumab; IXE, ixekizumab; NTK, netakimab; BIM: bimekizumab

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