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Efficacy and safety of IL-17 inhibitors for patients with psoriatic arthritis: a systematic review and meta-analysis

Q. GAO, Y.-X. ZHAO, X.-J. WANG, J. SHI, H.-M. WANG

Dermatology Department, Tianjin Academy of Traditional Chinese Medicine Affiliated Hospital, Tianjin, People's Republic of China

Abstract. – OBJECTIVE: The efficacy and safety of IL-17 inhibitors for patients with Psoriatic arthritis (PsA) is still a controversial issue.

MATERIALS AND METHODS: We systematically searched MEDLINE, EMBASE and Cochrane for randomized controlled trials that compared IL-17 inhibitors with placebo or TNF inhibitor adalimumab in patients with PsA.

RESULTS: Eleven studies with 5327 patients were included in the meta-analysis. IL-17 inhibitors were effective in achieving response rates of American College of Rheumatology (ACR) 20, ACR50 and ACR70 compared with the control group. The results of subgroup analyses showed that IL-17 inhibitors had significant advantages in increasing the response rates of ACR20, ACR50 and ACR70 over placebo. IL-17 inhibitors did not show advantages in the responses of ACR20 and ACR50, but they were associated with a higher rate of ACR70 when compared with adalimumab. The longer the follow-up time, the higher the response rates of ACR20, ACR50 and ACR70 in IL-17 inhibitors group. IL-17 inhibitors treatment also significantly increased the rates of PASI75 and PASI90 compared with controls. Additionally, IL-17 inhibitors were associated with higher risks of any Candida infections and injection site reactions and with a lower rate of allergic reactions or hypersensitivities compared with the control group.

CONCLUSIONS: This study provided a clear proof of beneficial effects of IL-17 inhibitors in improving joint disease activity in patients with PsA with an acceptable safety profile.

Key Words:
IL-17 inhibitors, Psoriatic arthritis, ACR, PASI, Meta-analysis.

Introduction

Psoriatic arthritis (PsA) is a chronic, immune-mediated, inflammatory arthropathy that presents with inflammation of the joints and entheses, including those of the axial skeleton[1]. It occurs in about 20%-30% of patients with psoriasis and has a prevalence of 2-4% in Western adults[2,3]. Traditional therapies of PsA consist of non-steroidal anti-inflammatory drugs (NSAID), glucocorticoid treatments and traditional systemic disease mitigating antirheumatic drugs (csDMARDs)[4,5]. Advances in understanding of pathogenesis have led to the discovery of the importance of biologics such as tumor necrosis factor (TNF) inhibitors and interleukin (IL)17 inhibitors in the treatment of PsA, especially for patients with PsA who have failed to disease-modifying antirheumatic drug (DMARD) and nonsteroidal anti-inflammatory therapies[1,6,7]. Before the advent of IL-17 inhibitors, TNF inhibitors were the only available biologics for this population. However, TNF inhibitors increased the risk of serious infections and exacerbated demyelination events[8], thus leading to the exploration of alternative strategies targeting the IL-23/IL-17 axis for the treatment of PsA[7]. IL-17 inhibitors, including monoclonal antibodies inhibiting IL-17A (secukinumab and ixekizumab), IL-17A receptor (brodalumab) and IL-17A/F (bimekizumab) have been studied in recent years. This type of biologics has been shown to provide the benefit in improving joint disease activity in patients with PsA in most trials[7,9]. Some studies[10,11] showed that the efficacy of these therapies was non-inferior to adalimumab, a TNF inhibitor, for the achievement of American College of Rheumatology (ACR20) or ACR50. To estimate the efficacy and safety of IL-17 inhibitors in the treatment of PsA, we conducted this systematic review and meta-analysis.

Materials and Methods

Search Strategy

Two authors independently performed an extensive search from the following data sources

Corresponding Author: Qin Gao, MD; e-mail: yuhongye@tmu.edu.cn

with language restricted to English: MEDLINE (from their earliest records to September 2020), EMBASE (from their earliest records to September 2020), and the Cochrane Library database (from their earliest records to September 2020). We used the text words of "Anti-Interleukin 17" OR "Interleukin 17" OR "Interleukin 17 inhibitor" OR "Secukinumab" OR "Ixekizumab" OR "Brodalumab" OR "Bimekizumab" AND"Psoriatic Arthritis" OR "PsA" OR "arthritis" AND"Randomized Controlled Trial (RCT)" OR "Randomly" OR "Randomized" OR "Controlled Clinical Trial" OR "Comparative Study" (Supplementary Material of protocol).

Data extraction, Outcomes, and Quality of Evidence

Two author extracted data using standard data extraction forms, which include participants, interventions, comparisons, outcomes, and adverse events. Primary outcomes included American College of Rheumatology 20 (ACR20, defined as at least 20% improvement in the American College of Rheumatology response criteria), ACR50 (defined as at least 50% improvement in the American College of Rheumatology response criteria), and/or ACR70 (defined as at least 70% improvement in the American College of Rheumatology response criteria). Secondary outcomes were defined as Psoriasis Area Severity Index (PASI) 70 and/or PASI 90. We used standard criteria (Cochrane risk of bias tool) to assess the inherent risk of bias of trials. Differences between these two authors were resolved by consultation with a third reviewer.

Study Selection and Inclusion Criteria

All RCTs that compared the efficacy or safety of IL-17 inhibitors with placebo or other active treatments were adopted. The inclusion criteria were defined as follows: (i) study population comprised participants aged 18 years old or older with PsA; (ii) the intervention were IL-17 inhibitors and comparison were placebo and/or other treatments; (iii) study outcomes included ACR20, ACR50, ACR70, PASI70, PASI 90 and/or drug-related adverse events (including serious adverse events, infection, respiratory tract infection, any candida infections, urinary tract infection, hepatic events, allergic reactions or hypersensitivities, injection site reactions, nasopharyngitis, headache, diarrhea, and inflammatory bowel disease); (iv) study design was RCT, in which sample size was larger than 50. We excluded phase 1 RCTs or studies without control group or lack of available data.

Statistical Analysis

We calculated relative risk (RR) and 95% confidence interval (CI) for outcomes using random-effects model. Weighted mean difference and standard deviation (SD) between groups was applied for continuous variables. Subgroup analysis was performed to determine the effect point of intervention measures. We analyzed heterogeneity by I^2 statistic to describe the percentage of variability. Begg Funnel plot was performed to assess potential publication bias. The result was considered significant with 2-sided $p < 0.05$. STATA, version 12.0 was used to perform the meta-analysis.

Results

General Description

The literature search yielded 645 articles, eventually, eleven studies[10-20] with 5327 patients were included in our meta-analysis according to the inclusion criteria (Figure 1). Of the contained eleven studies, eight studies (3491 patients) compared the efficacy of IL-17 inhibitors with placebo, two studies (1419 patients) compared the efficacy of IL-17 inhibitors with active control of adalimumab and one (417 patients) compared IL-17 inhibitors with active control of adalimumab and placebo. In total, eleven studies provided the rates of ACR20 and ACR50, seven provided the rate of ACR70. All studies reported the events of side effects. The characteristics of the included studies were summarized in Table I. These studies were performed from 2014 to 2020, with sample sizes ranging from 206 to 996. In the randomized control phase, the follow-up time during randomized control period of included studies were 12-52 weeks, as showed in Table I.

Primary Outcomes

Primary outcomes included the response rates of ACR20, ACR50 and ACR70 in our meta-analysis. Our results showed that IL-17 inhibitors were 1.29 times more likely to achieve an ACR20 response (RR 1.29, 95% CI 1.22 to 1.37, $p < 0.0001$; $I^2 = 93.5\%$, Figure 2A), 1.44 times for ACR50 response (RR 1.44, 95% CI 1.31 to 1.58, $p <$

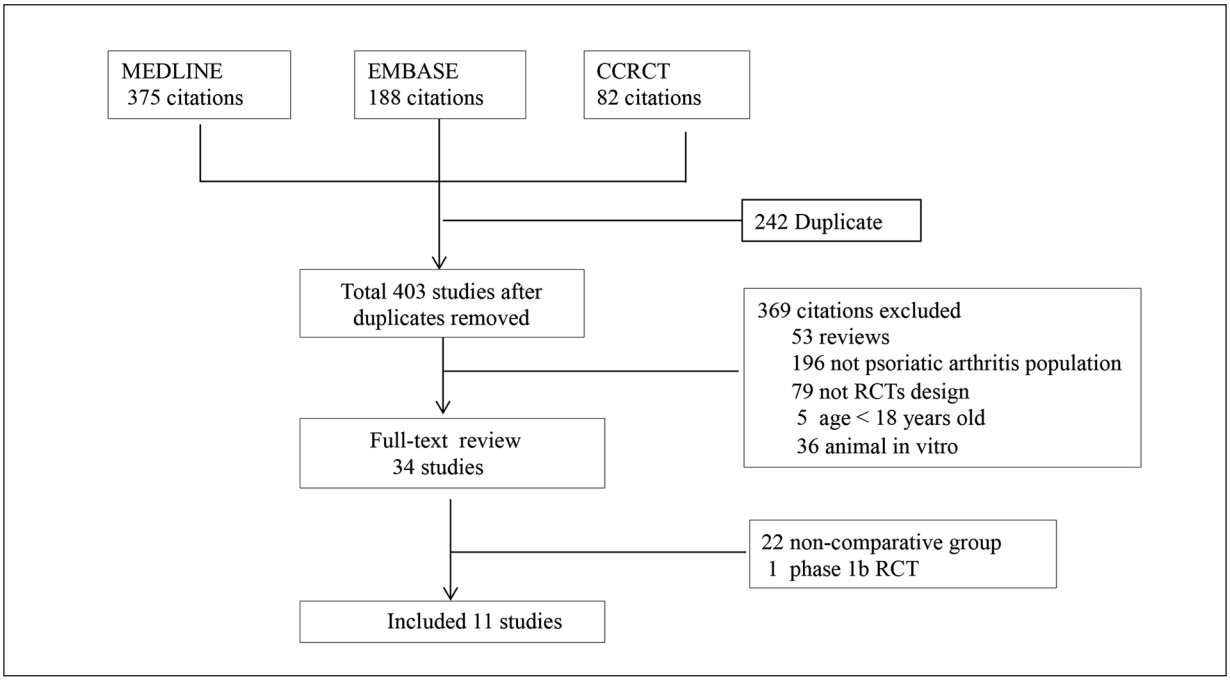

Figure 1. Process for identifying studies eligible for the meta-analysis.

0.0001; I^2 = 91.6%, Figure 2B) and 1.28 times for ACR70 response (RR 1.28, 95% CI 1.11 to 1.49, $p < 0.0001$; I^2 = 48.4%, Figure 2C) compared with the control group. Subgroup analyses stratified by drug type of control group and follow-up time during randomized control period were further undertook to determine the effect of IL-17 inhibitors therapy, which were showed in Figures 3-5. The results demonstrated that IL-17 inhibitors had significant advantages in increasing ACR20 (RR 2.38, 95% CI 2.12 to 2.66, $p < 0.0001$; I^2 = 0.0%, Figure 3), ACR50 (RR 3.91, 95% CI 3.20 to 4.78, $p < 0.0001$, Figure 4) and ACR70 (RR 3.19, 95% CI 1.88 to 5.42, $p < 0.0001$, Figure 5) responses compared with placebo. Compared with TNF inhibitor adalimumab, IL-17 inhibitors did not show the above advantages in ACR20 (RR 1.02, 95% CI 0.95 to 1.09, $p = 0.55$, Figure 3) and ACR50 (RR 1.09, 95% CI 0.99 to 1.21, $p = 0.09$, Figure 4) responses, but they were associated with a higher response rate of ACR70 (RR 1.20, 95% CI 1.03 to 1.39, $p = 0.02$, Figure 5). Furthermore, higher response rates of ACR20, ACR50 and ACR70 were observed within the first 24 weeks of the follow-up. However, there were no significant differences between IL-17 inhibitors group and the control group with the response rates at weeks 52.

Secondary Outcomes

Ten studies reported the response rate of PASI70, and nine studies reported the rate of PASI90. The results showed that IL-17 inhibitors significantly increased the response rates of PASI75 (RR 1.49, 95% CI 1.39 to 1.60, $p < 0.0001$, Figure 6A) and PASI90 (RR 1.73, 95% CI 1.55 to 1.93, $p < 0.0001$, Figure 6B). The results of subgroup analyses showed that IL-17 inhibitors significantly increased the response rates of PASI75 (RR 5.15, 95% CI 4.21 to 6.30, $p < 0.0001$; Figure 7A) and PASI90 (RR 4.34, 95% CI 3.42 to 5.50, $p < 0.0001$; Figure 7B) compared with placebo. When compared with adalimumab, IL-17 inhibitors also showed the above advantages in achieving PASI75 (RR 1.21, 95% CI 1.12 to 1.31, $p < 0.0001$; Figure 7A) and PASI90 responses (RR 1.33, 95% CI 1.18 to 1.49, $p < 0.0001$; Figure 7B).

Adverse Events

Data on adverse events reported in the included studies during randomized control period were provided in Table II. Results showed the risk of any candida infections in IL-17 inhibitors group was 1.99 times higher than that of the control group (95% CI 1.004 to 3.81; $p = 0.04$). Among other adverse effects of IL-17 inhibitors therapy, the risk of injection site reactions had a statistical-

Table I. Baseline characteristics of patients in meta-analysis.

	Phase	Age (years)	Male (%)	Weight (kg)	Interventions	Controls	No.of patients	MTX use, %	TNF-α naïve, %	Study Primary outcomes	Secondary outcomes
BE ACTIVE2020	IIb	49.3 ± 12.4	60.0	85.7 ± 18.5	Bimekizuma	Placebo	206	63.6	NA	ACR at week 12	PASI
EXCEED 2020	III	49.0 ± 12.4	51.2	83.8 ± 18.7	Secukinumab	Adalimumab	853	NA	NA	ACR at week 52	PASI
FUTURE 1 2015	III	49 ± 11.7	45.54	82.9 ± 20.5	Secukinumab	Placebo	606	60.7	70.6	ACR at week 24	PASI
FUTURE 2 2015	III	47.9 ± 12.1	46.6	87.1 ± 19.7	Secukinumab	Placebo	397	46.6	65.0	ACR at week 24	PASI
FUTURE 3 2018	III	49.8 ± 12.4	45.2	85.6 ± 19.4	Secukinumab	Placebo	414	47.6	68.1	ACR at week 24	PASI
FUTURE 4 2019	III	49 ± 12.1	41.9	85.1 ± 20.3	Secukinumab	Placebo	341	49.9	76.3	ACR at week 16	PASI
FUTURE 5 2018	III	48.6 ±12.4	50.2	83.4 ± 19.3	Secukinumab	Placebo	996	50.1	70.4	ACR at week 16	PASI
Mease et al.2014	II	52.7 ± 12.4	36.3	90.7 ± 21.3	Brodalumab	Placebo	168	50.0	NA	ACR at week 12	PASI
SPIRIT-P1 2017	III	49.5 ± 11.9	46.0	85.6 ± 20.9	Ixekizumab	Placebo; Adalimumab	417	14.6	54.2	ACR at week 24	PASI
SPIRIT-P2 2017	III	51.9 ± 12.1	46.6	88.6 ± 21.7	Ixekizumab	Placebo	363	NA	41.1	ACR at week 24	PASI
SPIRIT-H2H 2020	IIIb/IV	47.9 ± 12.1	55.1	83.6 ± 19.1	Ixekizumab	Adalimumab	566	NA	59.4	ACR at week 12	NA

TNF, tumor necrosis factor; MTX, Methotrexate; ACR, American College of Rheumatology; PASI, Psoriasis Area Severity Index; NA, not available.

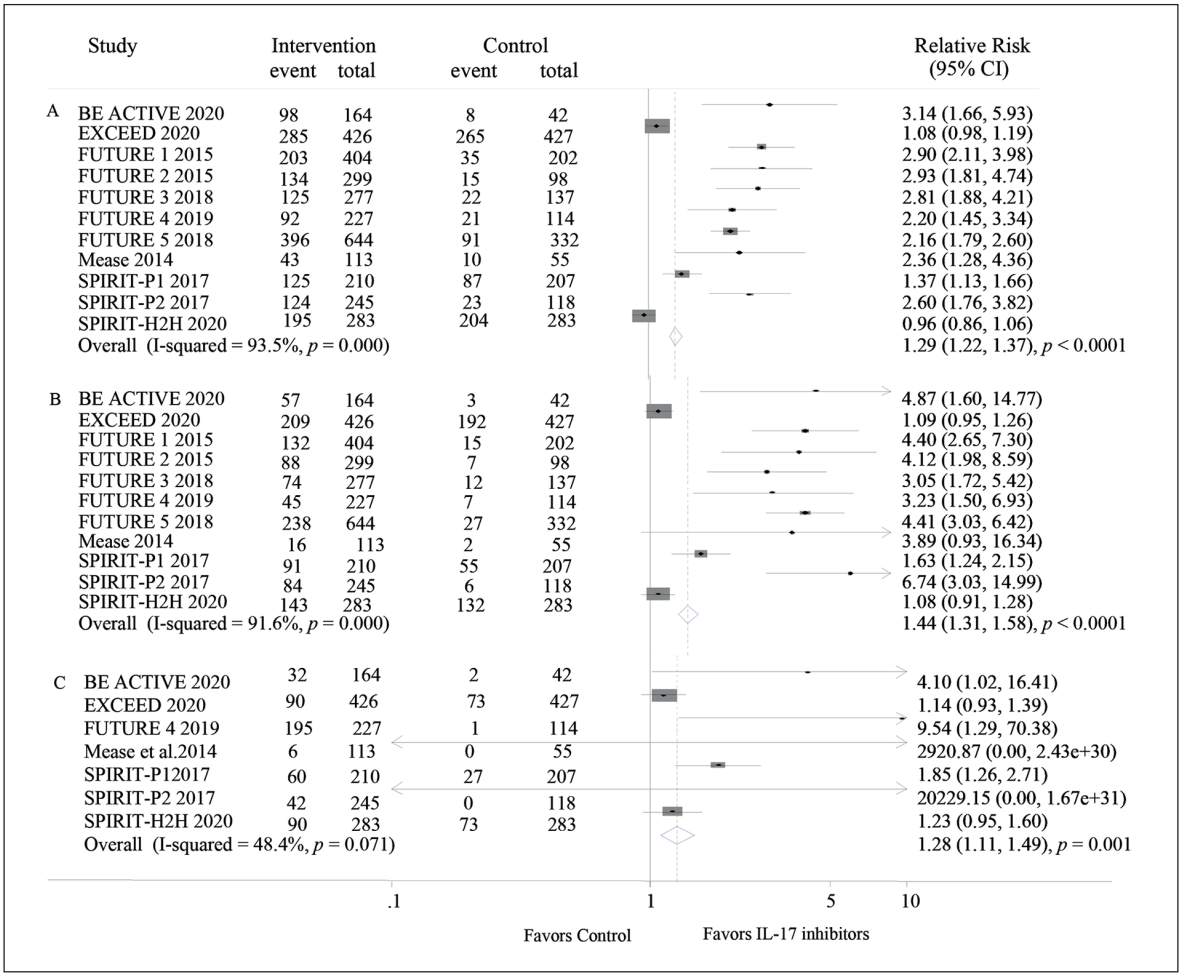

Figure 2. Effects of IL-17 inhibitors compared with placebo or other active control for the responses of ACR20 **(A)**, ACR50 **(B)** and ACR70 **(C)** in patients with psoriatic arthritis.

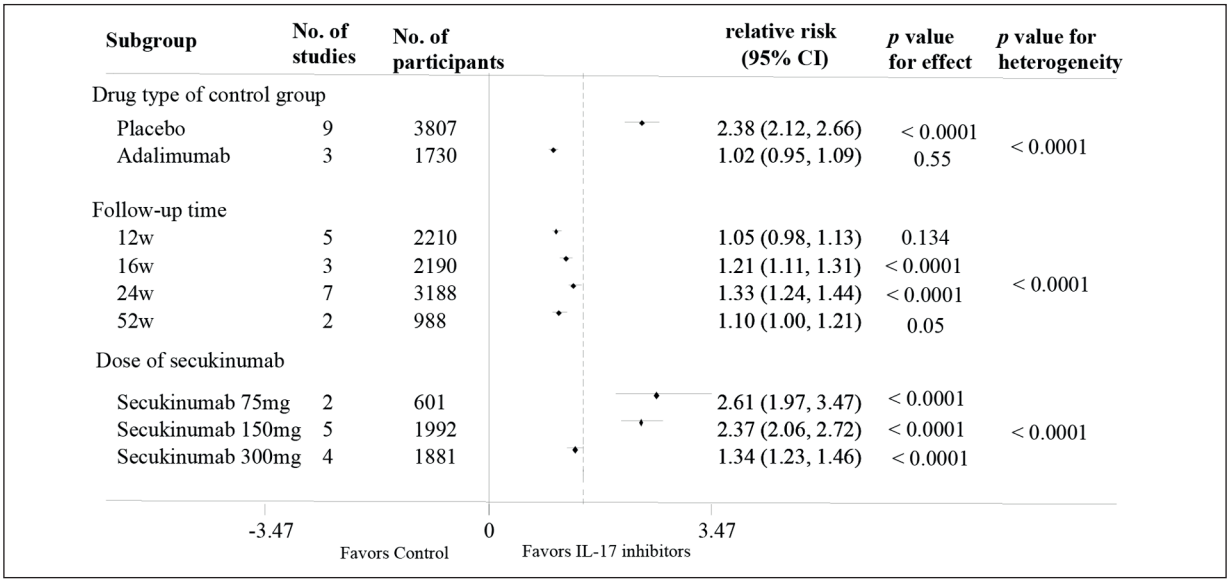

Figure 3. Summary of subgroup analysis for the response of ACR20 in patients with psoriatic arthritis.

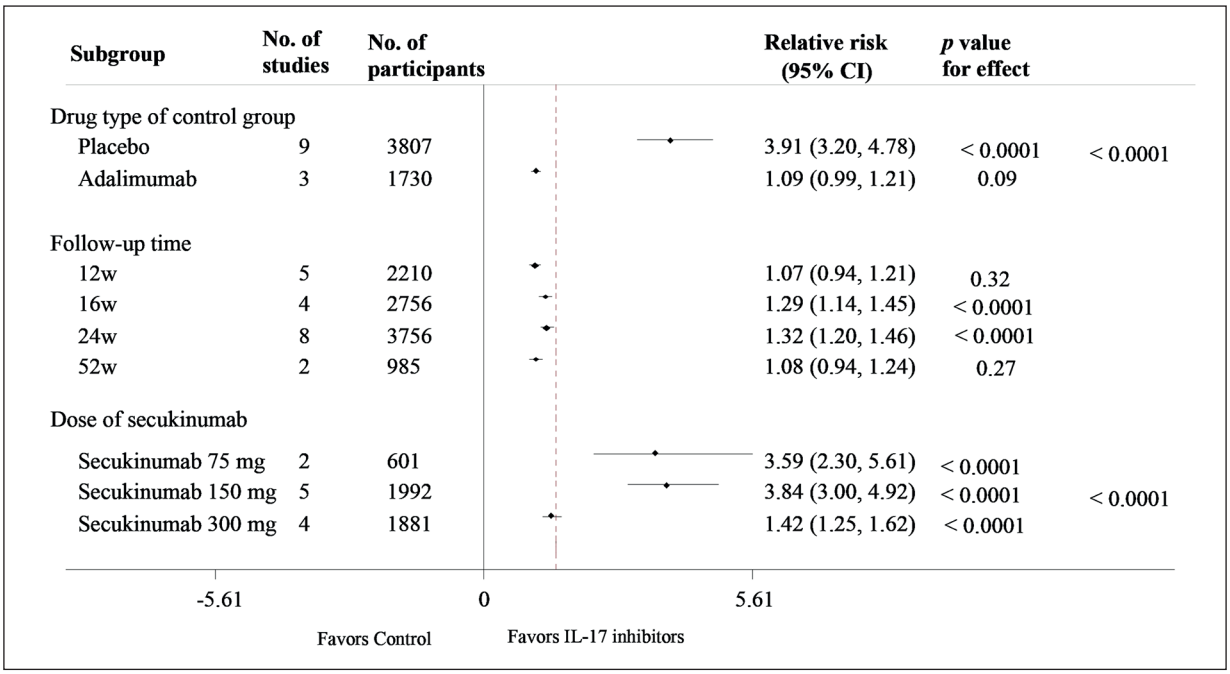

Figure 4. Summary of subgroup analysis for the response of ACR50 in patients with psoriatic arthritis.

ly increase (1.57, 95% CI 1.16 to 2.24; $p = 0.004$) compared with placebo or other active control. The results of subgroup analysis based on the type of IL-17 inhibitors showed that the injection site reaction rate was highest in the ixekizumab group (RR 3.97, 95% CI 2.61 to 6.04, $p < 0.0001$, **Supplementary Figure 1**), and lowest in the secukinumab group (RR 0.49, 95% CI 0.30 to 0.80, $p = 0.004$, **Supplementary Figure 1**). The rate was similar between the brodalumab group and the control group (RR 0.49, 95% CI 0.10 to 2.33, $p = 0.37$, **Supplementary Figure 1**). It was worth noting that IL-17 inhibitors therapy had a lower risk of allergic reactions or hypersensitivities (0.72, 95% CI 0.52 to 0.99; $p = 0.04$, Table II). No statistically significant differences in the risks of other adverse events, including any adverse events, serious adverse events, infection,

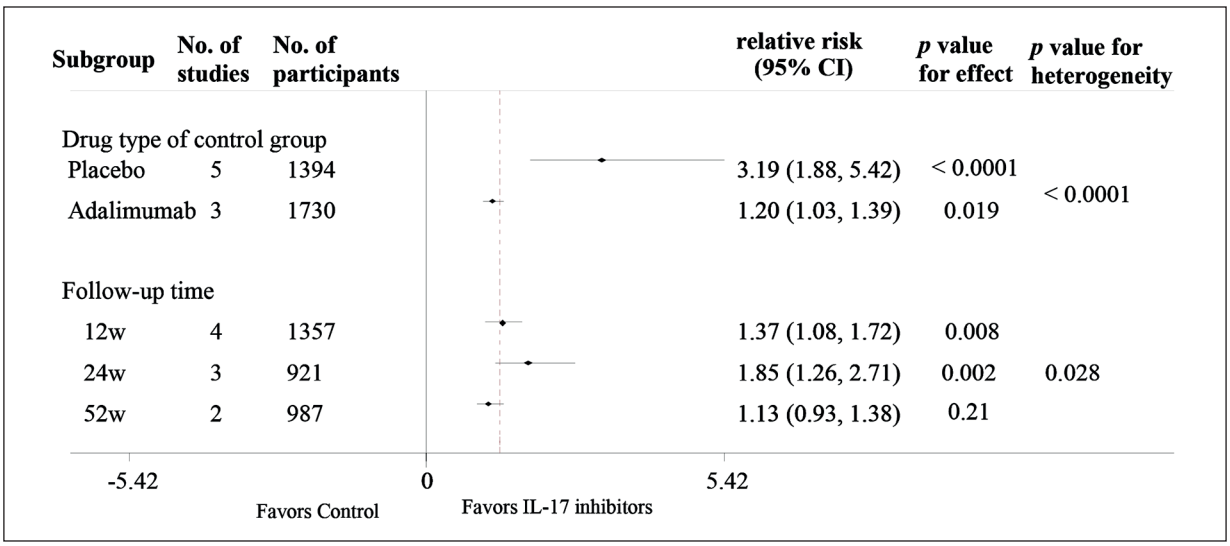

Figure 5. Summary of subgroup analysis for the response of ACR70 in patients with psoriatic arthritis.

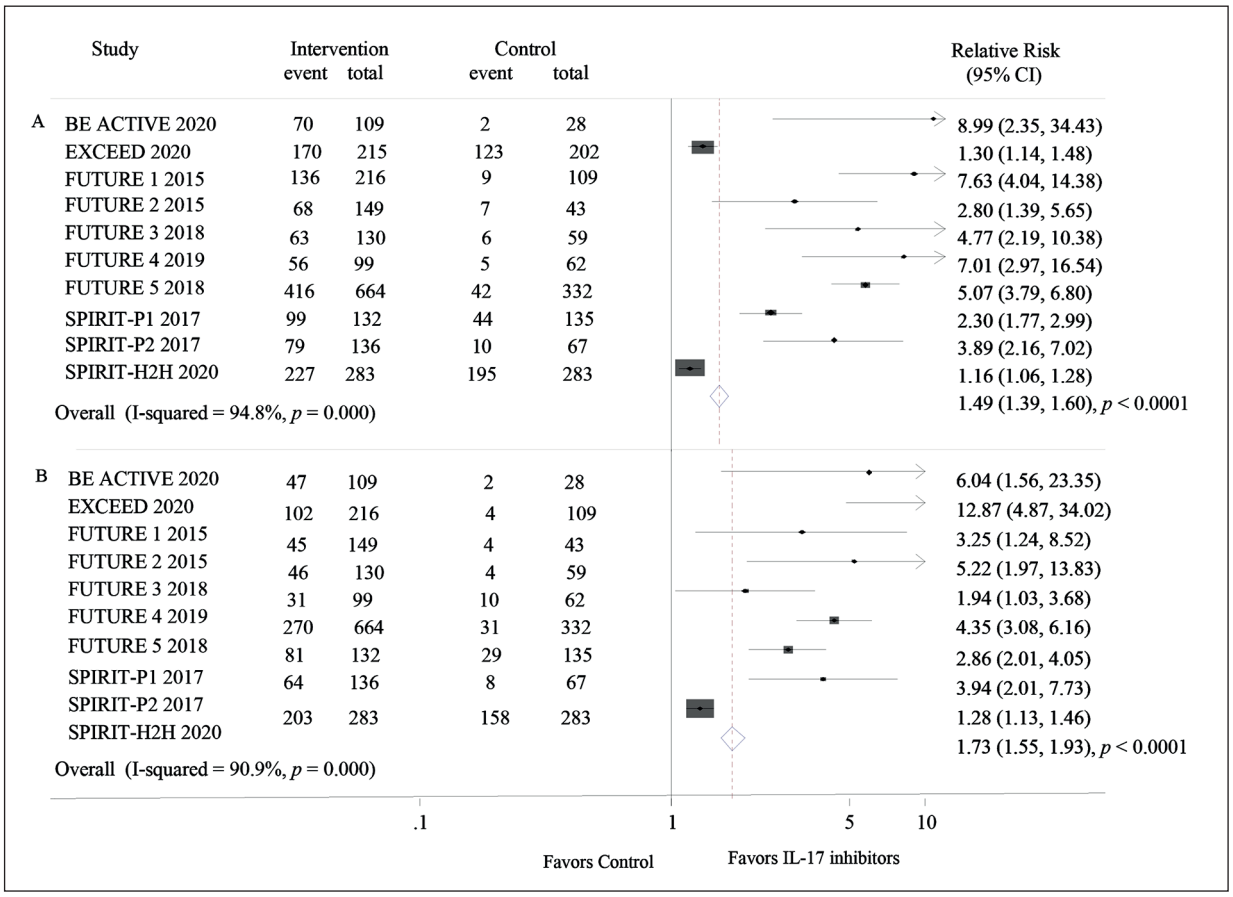

Figure 6. Effects of IL-17 inhibitors compared with placebo or other active control for the responses of PASI 75 **(A)** and PASI90 **(B)** in patients with psoriatic arthritis.

respiratory tract infection, urinary tract infection, hepatic events, nasopharyngitis, headache, diarrhea, and inflammatory bowel disease were found between IL-17 inhibitors and control therapy (Table II, all $p > 0.05$).

Quality Assessment and Publication Bias

The inherent risk of bias of trials was performed for all studies by Cochrane Collaboration tool. As listed in Table III, the inherent risks of bias of trials were generally low. Statistical testing showed no evidence of publication bias for ACR20 (Begg's test z = 1.58, $p = 0.12$), which was displayed in **Supplementary Figure 2**.

Discussion

This meta-analysis by pooling evidence from RCTs was conducted to estimate relative efficacy and safety of IL-17 inhibitors (secukinumab, ixekizumab, brodalumab and bimekizumab) in the treatment of PsA, and eventually, 11 RCTs with 5327 patients met our inclusion criteria. We found that IL-17 inhibitors provided clear beneficial effects in patients with PsA with an acceptable safety profile.

Several published meta-analyses[21-26] evaluated the effects of IL-17 inhibitors and other biologics on PsA. A meta-analysis conducted by Naik et al[26] revealed that in patients with active PsA, IL-17 inhibitors produced a clinically significant improvement in joint disease activity with acceptable safety and tolerability for short-term treatment compared to placebo. A network meta-analysis to investigate the comparative efficacy, safety and tolerability of IL-6, IL-12/23 and IL-17 inhibitors for patients with active PsA showed that IL-17 inhibitors of secukinumab and ixekizumab demonstrated superior efficacy over placebo in achieving a response rates of ACR20 and ACR50[25]. Lu et al[21] conducted a network meta-analysis, including 29 RCTs with 10,204 participants and 17 treatments to summarize and

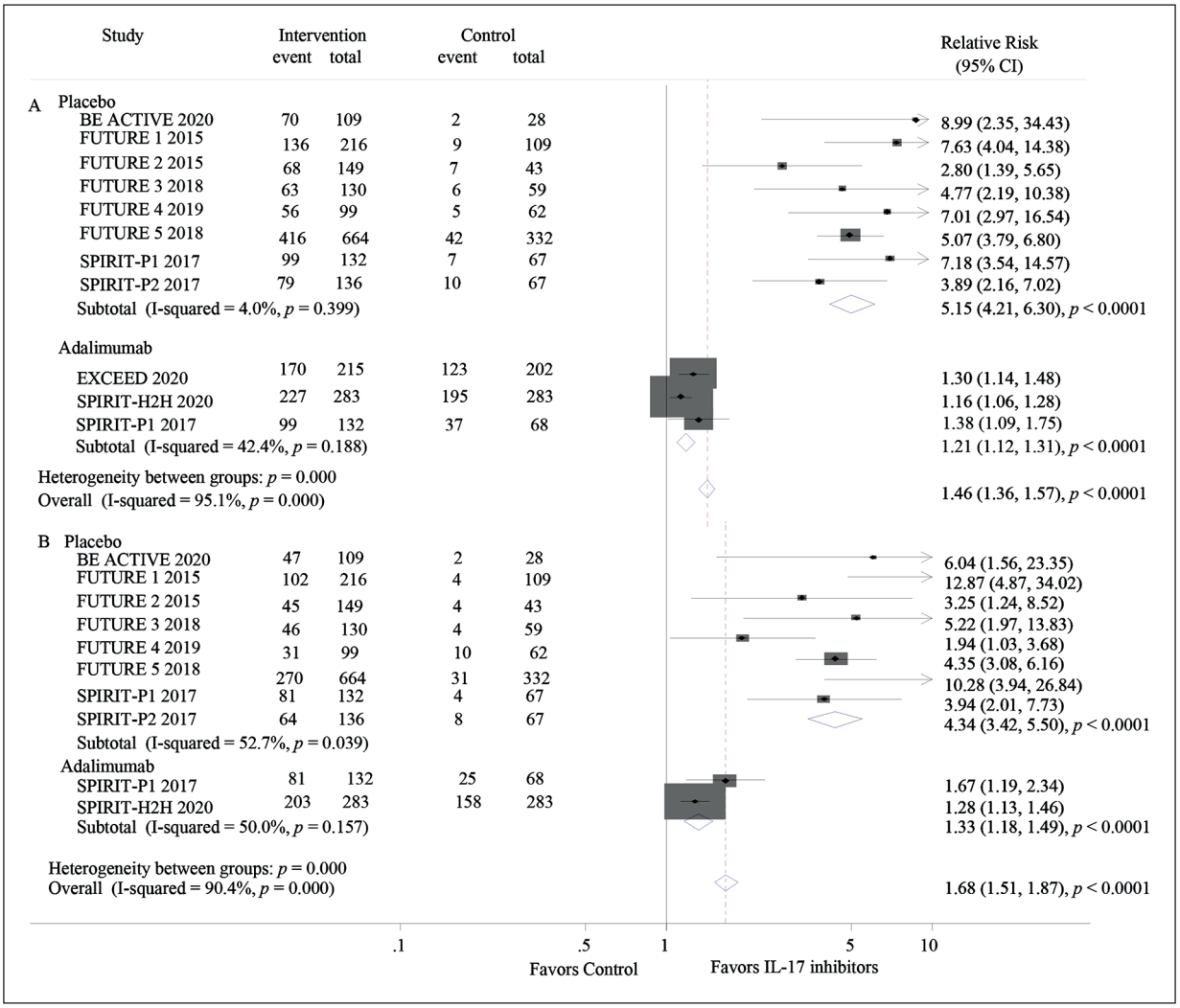

Figure 7. Summary of subgroup analyses for the responses of PASI75 **(A)** and PASI90 **(B)** in patients with psoriatic arthritis.

Table II. Adverse events reported in the included studies.

Adverse events	Studies reporting	Intervention (n/n)	Control (n/n)	RR (95% CI)	p value
Any adverse event	6	1043/1683	650/961	0.98 (0.93,1.04)	0.56
Serious adverse events	8	77/2205	58/1142	0.72 (0.50,1.03)	0.07
Infection	7	734/2241	486/1377	1.05 (0.96,1.15)	0.26
Respiratory tract infection	8	218/2525	131/1380	0.95 (0.77,1.17)	0.61
Any Candida infections	8	53/2883	13/1748	1.99 (1.004,3.81)	**0.04**
Urinary tract infection	4	46/1485	17/685	1.20 (0.69,2.09)	0.52
Hepatic events	3	43/829	23/367	0.80 (0.43,1.32)	0.38
Allergic reactions or hypersensitivities	4	77/1374	80/1035	0.72 (0.52,0.99)	**0.045**
Injection site reactions	6	210/2153	79/1422	1.57 (1.16,2.14)	**0.004**
Nasopharyngitis	7	186/2184	315/1244	1.02 (0.82,1.26)	0.87
Headache	8	136/2848	72/1576	1.13 (0.85,1.50)	0.41
Diarrhea	7	100/2444	73/1374	0.84 (0.62,1.14)	0.27
Inflammatory bowel disease	5	7/2024	0/1322	3.54 (0.62,20,09)	0.15

Table III. Inherent risk of bias of included trials.

Trial	Sequence generation	Allocation concealment	Blinding			Incomplete outcome data	Selective outcome reporting	Other source of bias
			Participants	Personnel	Outcome assessors			
BE ACTIVE2020	LOW	LOW	LOW	LOW	LOW	LOW	LOW	UNCLEAR
EXCEED 2020	LOW	LOW	LOW	LOW	LOW	HIHGH	LOW	UNCLEAR
FUTURE 1 2015	LOW	UNCLEAR	LOW	LOW	UNCLEAR	HIGH	UNCLEAR	UNCLEAR
FUTURE 2 2015	LOW	LOW	LOW	LOW	LOW	LOW	LOW	UNCLEAR
FUTURE 3 2018	LOW	UNCLEAR	LOW	LOW	LOW	LOW	LOW	UNCLEAR
FUTURE 4 2019	LOW	UNCLEAR	LOW	LOW	LOW	LOW	LOW	UNCLEAR
FUTURE 5 2018	LOW	LOW	LOW	LOW	LOW	LOW	LOW	UNCLEAR
Mease 2014	LOW	UNCLEAR	LOW	LOW	LOW	HIGH	LOW	UNCLEAR
SPIRIT-P1 2017	LOW	LOW	LOW	LOW	LOW	LOW	LOW	UNCLEAR
SPIRIT-P2 2017	LOW	LOW	LOW	LOW	LOW	LOW	LOW	UNCLEAR
SPIRIT-H2H 2020	LOW	LOW	HIGH	HIGH	LOW	LOW	LOW	UNCLEAR

Assessment of risk bias according to the Cochrane collaboration tool, low risk of bias was represented as “LOW” and high risk was “HIGH”.

investigate the comparative efficacy and safety of targeted disease-modifying antirheumatic drugs (DMARDs). The results showed that during induction therapy (first 12-16 weeks), the treatments of secukinumab and ixekizumab were more efficacious than placebo in achieving ACR20 and PASI75 responses. Consistent with above findings, our results revealed that IL-17 inhibitors had superior efficacy over placebo not only in achieving ACR20, ACR50 and ACR70 responses but also in response to PASI75 and PASI90. However, compared with adalimumab, IL-17 inhibitors were only associated with higher response rates of ACR70, PASI75 and PASI90, but they had no superior efficacy in ACR20 and ACR50 responses. Consistent with our present results, a network meta-analysis conducted by McInnes et al[27] showed secukinumab had no significant advantage over adalimumab in achieving the response rates of ACR20, ACR50 and ACR70, but had higher response rates of PASI75 and PASI90 at 12-16 weeks treatment. This disparity may be attributed to the differential expression of IL-17A gene, which is upregulated in skin than in joints for patients with PsA[6,28]. These findings suggested that in PsA patients, particularly in the presence of relevant skin involvement, IL-17 inhibitors would be preferred over TNF-α inhibitor-adalimumab for the elimination of skin problems. More trials that compared different IL-17 inhibitors with other TNF-α inhibitors are needed to build more evidence for recommending these agents as first-line biologic treatment of active PsA. Furthermore, we found that higher rates of ACR20, ACR50 and ACR70 were observed in studies as the follow-up time increased. However, RCTs have often been criticized because of enrolled patients with similar features who may not represent all patients with PsA in daily clinical practice. Therefore, there is the need of real-world data from a large number of patients with PsA around the world to assess the efficiency and safety of IL-17 inhibitors[29,30].

The safety of IL-17 inhibitors in PsA patients is the focus of concern. Serious adverse events, infection, hepatic events, nasopharyngitis, headache, diarrhea, candida infections, injection site reactions and inflammatory bowel disease were common side effects[10-20,31]. Among these side effects, SAE and infection were major concerns. Our results showed that the risks of any adverse events, infections and serious adverse events did not differ significantly between the IL-17 inhibitors and control groups. Naik et al[26] found that there were no significant differences in the risks of SAE and infections between IL-17 inhibitors and placebo groups. In this study, the risk of any candida infections in IL-17 inhibitors group was 1.99 times higher than that of the control group. The findings in several studies supported that the IL-17 inhibitors were associated with the occurrence of candidiasis[32-34]. IL-17 played an important role in the innate and adaptive response to infection, especially in mucocutaneous defense against candida, thus increased the risk of infections caused by candida[35]. Although the risk of Candida infection increased during anti-IL-17 therapies, the infection was mild or moderate in severity. There was no need to usually interrupt administration of IL-17 inhibitors if patients were monitored and treated properly[36]. Injection site reaction was a common side effect of IL-17 inhibitors[37,38]. Georgakopoulos[38] reported that of the 60 patients, 13.3% experienced injection site reaction/erythema/pain after 12 weeks of ixekizumab treatment. We also noted there were more local injection site reactions happened in the IL-17 inhibitors group. A previous meta-analysis[31] assessing adverse events with IL-17 and IL-23 inhibitors for psoriasis and psoriatic arthritis showed that injection site reaction was one of the most prevalent adverse events of ixekizumab compared with those with brodalumab, guselkumab and placebo after 52 weeks treatment. We undertook a subgroup analysis and found that injection site reaction was more frequent in the ixekizumab group than that in the secukinumab, brodalumab and the control groups. This disparity may be the result of different frequencies of administration of ixekizumab, brodalumab and secukinumab. Thus, large trials are needed to compare the side effects of different types of IL-17 inhibitors. There are also specific AEs that should be considered. The occurrences and exacerbations of inflammatory bowel disease have been reported in psoriatic patients receiving IL-17 inhibitors, though the prevalence of inflammatory bowel disease is known to be higher in patients with psoriasis than that in healthy individuals[32,36,39]. There was no significant difference in inflammatory bowel disease between IL-17 inhibitors and placebo or active control according to the results of this study, however, biological agents other than IL-17 inhibitors still should be considered when treating patients diagnosed with inflammatory bowel disease or with a history of inflammatory bowel disease. No significant differences were found in the risks of other adverse events including respiratory tract

infection, urinary tract infection, hepatic events, nasopharyngitis, headache, diarrhea between IL-17 inhibitors and control group in our study. In general, the IL-17 inhibitors were generally safe and well tolerated.

Including new RCTs, large volume of data and rigorous statistic methodology were major strengths of this meta-analysis. However, our study had some limitations. Firstly, limited number of studies and scant primary data prevented us from undertaking a subgroup analysis of the primary outcomes of treatments by patients with TNF-α naïve or not, leaving effects of IL-17 inhibitors in this population uncertain. Secondly, we were unable to assess the long-term safety of IL-17 inhibitors in active PsA due to the shorter follow-up period of the trials. Thirdly, we did not compare the efficacy of IL-17 inhibitors with other TNF-α inhibitors because of poorly available data. Fourthly, we did not register this analysis with PROSPERO.

Conclusions

This study provides a clear proof of beneficial effects of IL-17 inhibitors in improving joint disease activity in patients with PsA with an acceptable safety profile. In the presence of relevant skin involvement, IL-17 inhibitors would be preferred over a TNF-α inhibitor adalimumab. More trials that compared IL-17 inhibitors with TNF-α inhibitors are needed to build more evidence for recommending these agents as first-line biologic treatment of active PsA.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Ethical Privacy Statement

No approval was required for ethical privacy because the study does not involve direct contact with patients or their personal information.

Authors' Contribution

Qin Gao designed the study; Yanxia Zhao, Xiujuan Wang searched literature; Qin Gao, Jing Shi, and Hongmei Wang extracted and analyzed data; Qin Gao drafted the manuscript. All authors agree to be accountable for all aspects of the work.

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