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ORIGINAL ARTICLE

Meta-analysis of IL-17 inhibitors in two populations of rheumatoid arthritis patients: biologic-naïve or tumor necrosis factor inhibitor inadequate responders

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Abstract

Objectives To evaluate the efficacy and safety of interleukin 17 (IL-17) inhibitors in two rheumatoid arthritis (RA) populations: biologic-naïve or tumor necrosis factor inhibitor inadequate responders (TNF-IR).

Method A systematic search was performed in major electronic databases to identify relevant randomized controlled trials (RCTs) reporting the American College of Rheumatology 20% (ACR20), ACR50, ACR70 responses and adverse events (AEs) of IL-17 inhibitors versus placebo in patients with RA. We divided these patients into two subgroups: biologic-naïve or TNF-IR. The meta-analysis was performed using Review Manager 5.3 software. Results were expressed as risk ratio (RR) with pertinent 95% confidence interval (95% CI).

Results Ten studies with a total of 2499 patients were included. For biologic-naïve patients, ACR50 and ACR70 responses were significantly better with IL-17 inhibitors than placebo (RR = 1.71, 95% CI 1.23–2.38, $P = 0.001$ and RR = 2.63, 95% CI 1.10–6.25, $P = 0.03$, respectively), but ACR20 responses for IL-17 inhibitors were not statistically superior to placebo (RR = 1.34, 95% CI 0.94–1.91, $P = 0.11$). For TNF-IR, IL-17 inhibitors were effective in achieving ACR20 (RR = 1.67, 95% CI 1.40–2.00, $P < 0.00001$), ACR50 (RR = 1.94, 95% CI 1.43–2.63, $P < 0.0001$), and ACR70 (RR = 2.11, 95% CI 1.26–3.55, $P = 0.005$) compared to placebo. In the safety analysis, IL-17 inhibitors did not show increased risk of any AEs by comparing to placebo in both biologic-naïve patients and TNF-IR.

Conclusion IL-17 inhibitors were effective in the treatment of RA without increased risk of AEs, whether for biologic-naïve patients or TNF-IR.

Key Points
- *In this meta-analysis comparing IL-17 inhibitors with placebo in 2499 rheumatoid arthritis patients, IL-17 inhibitors improved ACR50 and ACR70, but not ACR20, responses in biologic-naïve patients.*
- *IL-17 inhibitors improved ACR20, ACR50, and ACR70 responses in tumor necrosis factor inhibitor inadequate responders.*

Keywords Biologic-naïve · IL-17 inhibitors · Meta-analysis · Rheumatoid arthritis · TNF-IR

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Introduction

Rheumatoid arthritis (RA) is an inflammatory and systemic autoimmune disease affecting approximately 1% of the adults worldwide [1]. It is characterized by chronic, symmetrical, multiple joints, and invasive synovitis that mainly involves the peripheral joints [2]. It is usually a progressive disease with cartilage damage, joint destruction, and complications of numerous extra-articular manifestations, which is associated with deformed joint, decline in functional status, decreased quality of life, and premature mortality [3, 4].

Conventional disease-modifying anti-rheumatic drugs (DMARDs) are used as a first-line therapy for the patients newly diagnosed with RA [5]. However, these DMARDs only work for a small percentage of patients. Novel biological agents have increasingly become the focus in RA therapeutic regimens.

Tumor necrosis factor (TNF)-α inhibitors gradually replace conventional medicine and are initial choices for RA patients who fail to respond to DMARDs and/or could not tolerate their toxicities [6]. However, in clinical practice, a proportion of patients treated with anti-TNF-α agents presented with inadequate treatment response [7] or intolerable side effects [8]. Hence, novel biological agents represent a promising therapeutic avenue for these patients.

Current scientific evidence shows that interleukin 17 (IL-17) and IL-17-producing-T helper cells (Th17) play an important role in the progression of RA [9, 10]. IL-17 induces negative feedback regulation through the induction of prostaglandin E2 (PGE2) while it stimulates proinflammatory pathways such as inflammatory cytokine production, pannus growth, and synovial neoangiogenesis, resulting in structural destruction of rheumatoid joints [11–13]. Current research shows that there is a significantly elevated level of IL-17 in synovium, serum, and synovial fluid from treatment-naïve early RA patients [14]. Therefore, it is indicated that blockade of IL-17 may reduce inflammation and bone erosions [15]. Moreover, it could be a most concerned therapeutic method for patients with RA.

In recent years, randomized controlled trials (RCTs) of IL-17 inhibitors for the treatment of RA have been reported and the conclusions are different. In addition, it is not known whether IL-17 inhibitors would be effective in patients who have an inadequate response to TNF inhibitors (TNF-IR) or biologic-naïve. Some researches [16, 17] showed other biologic treatments can produce significant benefits in patients who had TNF-IR, but an independent study [18] got an opposite conclusion. The aim of our meta-analysis was to review systematically available evidence on efficacy and safety of IL-17 inhibitors in the two RA populations.

Methods

Eligibility criteria

All eligible studies in this meta-analysis met the following criteria: (i) they were RCTs that enrolled patients with rheumatoid arthritis; (ii) duration of treatment as the main limitation was ≥ 10 weeks; (iii) they used a parallel design or crossover design of IL-17 inhibitors versus placebo; (iv) the reported data on American College of Rheumatology 20% (ACR20), ACR50, ACR70 response and adverse events (AEs) were investigated; and (v) eligible patients are biologic-naïve or TNF-IR.

Search strategy

A systematic review of the literature was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement protocol [19]. We searched electronic database of Pubmed, Embase, and Cochrane Library for publications from inception through April 2018 using the keywords "rheumatoid arthritis," "secukinumab," "brodalumab," "ixekizumab," "AIN457," "AMG827," "LY2439821" "anti-IL-17," "IL-17 inhibitor" or "IL-17 antagonists."

Data extraction

Articles screening was performed by two independent researchers. Firstly, they evaluated titles and abstracts of cited articles to determine their relevance. Then, they reviewed full papers to confirm all trials meeting the eligibility criteria. Discrepancies were further resolved through discussion or agreement of a third researcher. When there were multiple studies from the same trial, the most completely or recently reported data were eligible.

Methodological quality

Methodological quality of included trials was further assessed using modified Jadad score [20]. Scores ranged from 0 to 8 (a high score indicating high quality) with a score of ≥ 4 indicating high quality.

Meta-analysis

The analysis of efficacy was dependent on the increasing number of patients achieving ACR20, ACR50, and ACR70 responses from baseline. We assess safety by reviewing AEs, including any AEs, serious adverse events (SAEs), infection, hypertension, and neutropenia. Subgroup analyses for two different RA populations were performed.

The statistical analysis was assessed by using Review Manager 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark) from the Cochrane Collaboration. The dichotomous variables were assessed using risk ratio (RR), and continuous variables were assessed using mean differences (MD). $P < 0.05$ was considered statistically significant, and 95% confidence interval (CI) were reported.

Homogeneity was tested by using the Q statistic the I^2 statistic [21]. When I^2 was higher than 50%, random-effects model was used and which indicates a statistical heterogeneity. Otherwise, when I^2 was lower than 50%, a fixed-effects model was used. We performed a subgroup analysis to assess the potential confounding effect of heterogeneity and comparing the efficacy and safety of different subgroups.

All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

Results

Literature search and study characteristics

A total of 293 potential relevant articles were retrieved initially from various electronic databases. We retrieved 247 studies after removing duplicates. After reviewing the titles and abstracts, 38 articles were assessed for eligibility. However, 28 articles were excluded due to various reasons (not RCT, no required data or mixed biologic-naïve, and TNF-IR). Finally, ten studies [22–31] including eleven RCTs met eligibility criteria in the final analysis (Fig. 1). Seven articles [22–28] compared the efficacy and safety of IL-17 inhibitor with placebo in biologics-naïve patients. Four articles [24, 29–31] evaluated the efficacy and safety of IL-17 inhibitor in TNF-IR. The article published by Genovese MC et al. in 2014 [24] contains an analysis of IL-17 inhibitor versus placebo in both two RA populations. Although the article published by Genovese MC et al. in 2013 [32] reported the efficacy and

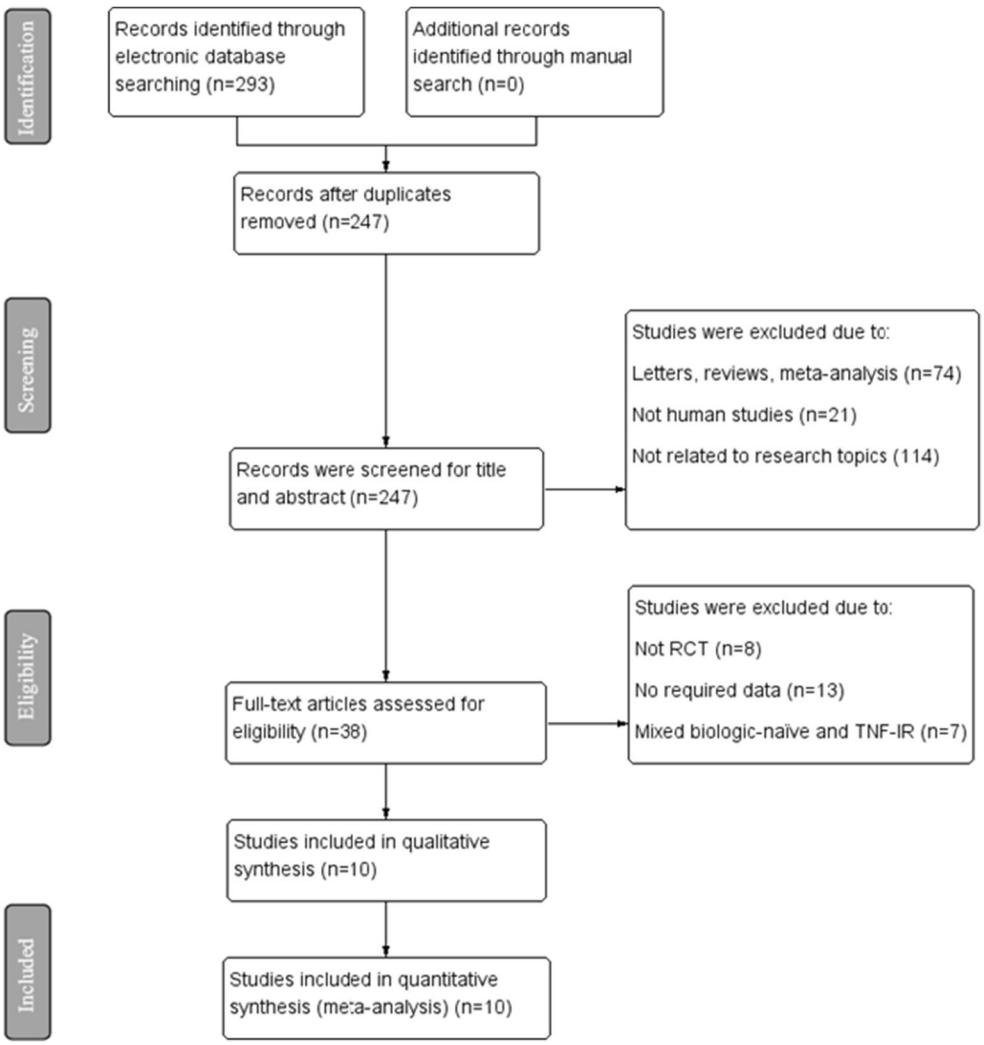

Fig. 1 Study flow diagram

Table 1 Basic characteristics of included studies

Study	Dose and dosing schedule	No. of patients	Female patients *n* (%)	Age (years)	Disease duration (years)	Study duration	Treatment history of included patient	Modified Jadad score	Phase
Tlustochowicz W 2016 SEC [20]	SEC 10 mg/kg IV at weeks 0, 2, and 4, then 150 mg SC every 4 weeks	88	67 (76.1)	53.8 ± 11.81	7.7 ± 7.91	16 weeks	No biologic agent; MTX, corticosteroids or NSAIDs at a stable dose for ≥ 4 weeks.	6	Phase II
	SEC 150 mg SC every 4 weeks	89	72 (80.9)	54.5 ± 12.26	7.6 ± 7.14				
	placebo	44	37 (84.1)	53.5 ± 9.33	7.5 ± 7.72				
Burmester GR 2015 SEC [21]	SEC 10 mg/kg IV every 2 weeks	68	48 (70.6)	49.5 ± 11.4	6.0 ± 7.1	12 weeks	No biologic agent; DMARD-naive or had failed at DMARD ≥ 3 months.	8	Phase II
	Placebo	32	25 (78.1)	54.5 ± 10.3	6.5 ± 7.4				
Genovese MC 2014 IXE [22] part 1 biologic-naive	IXE 3 mg IV at weeks 0, 1, 2, 4, 6, 8, and10	40	33 (83)	52 ± 10	8 ± 8	12 weeks	No biologic agent; MTX for ≥ 12 weeks and at a stable dose (7.5 to 25 mg/week) for ≥ 8 weeks; HCQ or SSZ at a stable dose for ≥ 8 weeks; PDN ≤ 10 mg/day for ≥ 4 weeks.	6	Phase II
	IXE 10 mg IV at weeks 0, 1, 2, 4, 6, 8, and10	35	27 (77)	54 ± 11	7 ± 8				
	IXE 30 mg IV at weeks 0, 1, 2, 4, 6, 8, and10	37	31 (84)	53 ± 12	7 ± 7				
	IXE 80 mg IV at weeks 0, 1, 2, 4, 6, 8, and10	57	52 (91)	53 ± 11	7 ± 8				
	IXE 180 mg IV at weeks 0, 1, 2, 4, 6, 8, and10	37	30 (81)	52 ± 11	6 ± 5				
	Placebo	54	47 (87)	53 ± 10	6 ± 6				
Genovese MC 2014 IXE [22] part2 TNF-IR	IXE 80 mg IV at weeks 0, 1, 2, 4, 6, 8, and10	65	57 (88)	55 ± 11	13 ± 9	12 weeks	TNF-IR ≥ 3 months before randomization; regularly treated with ≥ 1 conventional DMARD in a stable dose that could include any combination of 1 or more of MTX, HCQ, and SZZ; all other conventional DMARDs were allowed as single-agent use only.	6	Phase II
	IXE 180 mg IV at weeks 0, 1, 2, 4, 6, 8, and10	59	51 (86)	52 ± 10	11 ± 7				
	Placebo	64	55 (86)	53 ± 10	10 ± 6				
Genovese MC 2010 IXE [23] part B	IXE 0.2 mg/kg IV every 2 weeks	19	16 (84.2)	59.6 ± 8.4	10.5 ± 13.02	10 weeks	No biologic agent; stable use of ≥ 1 DMARDs for ≥ 4 weeks. (MTX 7.5–25 mg/week, HCQ ≥ 400 mg/day, SSZ 1000–3000 mg/day, LEF 5–20 mg/day, or AZA ≥ 150 mg/day or 2 mg/kg/day). Combinations of MTX, HCQ, and/or SSZ were allowed.	7	Phase I
	IXE 0.6 mg/kg IV every 2 weeks	20	19 (95)	57.7 ± 11.5	10.9 ± 10.21				
	IXE 2.0 mg/kg IV every 2 weeks	20	15 (75)	55.6 ± 8.2	6.1 ± 5.48				
	Placebo	18	18 (100)	54.4 ± 9.7	6.5 ± 5.67				
Pavelka K 2015 BRO [24]	BRO 70 mg SC every 2 weeks	63	50 (79)	53 ± 11	7.2 ± 6.8	12 weeks	No biologic agent; MTX for ≥ 12 weeks and at a stable dose (15 to 25 mg/week) for ≥ 4 weeks; stable doses of NSAIDs or corticosteroids ≥ 4 weeks; PDN ≤ 10 mg/day.	6	Phase II
	BRO 140 mg SC every 2 weeks	63	49 (78)	55 ± 10	7.6 ± 7.3				
	BRO 210 mg SC every 2 weeks	63	50 (79)	52 ± 10	7.6 ± 6.9				
	Placebo	63	51 (81)	51 ± 12	8.1 ± 7.9				
Martin DA 2013 BRO [25]	BRO 50 mg SC every 2 weeks	6	6 (100)	46 ± 12	NR	12 weeks	No biologic agent; MTX for ≥ 12 weeks and at a stable dose (15 to 25 mg/week) for ≥ 4 weeks; stable doses of NSAIDs or corticosteroids ≥ 4 weeks; PDN ≤ 10 mg/day.	7	Phase IB
	BRO 140 mg SC every 2 weeks	6	6 (100)	57 ± 9	NR				
	BRO 210 mg SC every 2 weeks	6	5 (83)	46 ± 10	NR				
	Placebo SC	6	5 (83)	52 ± 10	NR				
	BRO 420 mg IV every 2 weeks	6	5 (83)	56 ± 7	NR				
	BRO 700 mg IV every 2 weeks	6	3 (50)	50 ± 6	NR				
	Placebo IV	4	4 (100)	56 ± 12	NR				
Hueber W 2010 SEC [26]	SEC 10 mg/kg IV at weeks 0 and 3	26	19 (73)	49.9 ± 8.53	3.9 (1–20)	16 weeks	No biologic agent; MTX at a stable dose (≤ 25 mg/week) for ≥ 3 months	6	NR
	Placebo	26	20 (77)	49.8 ± 15.19	2.9 (1–37)				
Blanco FJ 2017 SEC [27]	SEC 10 mg/kg IV at weeks 0, 2 and 4 followed by					16 weeks	TNF-IR ≥ 3 months before randomization; MTX (7.5–25 mg/week) or any other	6	Phase III
	SEC 75 mg SC every 4 weeks	138	119 (86.2)	54.9 ± 11.3	10.2 ± 8.7				
	SEC 150 mg SC every 4 weeks	137	109 (79.6)	55.9 ± 12.3	9.5 ± 8.0				

Table 1 (continued)

Study	Dose and dosing schedule	No. of patients	Female patients *n* (%)	Age (years)	Disease duration (years)	Study duration	Treatment history of included patient	Modified Jadad score	Phase
	Placebo	138	115 (83.3)	55.5 ± 12.1	10.3 ± 7.7		DMARD ≥ 3 months and in a stable dose for at least 4 weeks		
Dokoupilová E 2018 SEC [28]	SEC 75 mg SC at weeks 0, 1, 2, 3, and 4, and then every 4 weeks	80	70 (87.5)	53.2 ± 10.2	10.8 ± 7.3	24 weeks	TNF-IR ≥ 3 months before randomization; ≤ 1 DMARDs on a stable dose ≥ 4 weeks before randomization; NSAIDs on a stable dose within 4 weeks preceding randomization.	6	Phase III
	SEC 150 mg SC at weeks 0, 1, 2, 3, and 4, and then every 4 weeks	81	67 (82.7)	55.1 ± 12.7	10.7 ± 7.4				
	Placebo	81	65 (80.2)	54.2 ± 11.0	10.5 ± 8.1				
Tahir H 2017 SEC [29]	SEC 75 mg SC at weeks 0, 2, and 4, and then every 4 weeks	210	186 (88.6)	53.3 ± 12.3	8.4 ± 8.0	24 weeks	TNF-IR ≥3 months before randomization; MTX ≥ 3 months and in a stable dose for at least 4 weeks; stable doses of NSAIDs or corticosteroids ≥ 4 weeks.	6	Phase III
	SEC 150 mg SC at weeks 0, 2, and 4, and then every 4 weeks	213	188 (88.3)	53.2 ± 11.6	9.0 ± 8.0				
	Placebo	214	182 (85.0)	52.2 ± 11.6	7.8 ± 8.0				

SEC, secukinumab; *IXE*, ixekizumab; *BRO*, brodalumab; *IV*, intravenous; *SC*, subcutaneous; *MTX*, methotrexate; *NSAIDs*, non-steroidal anti-inflammatory drugs; *DMARD*, disease-modifying anti-rheumatic drug; *HCQ*, hydroxychloroquine; *SSZ*, sulfasalazine; *LEF*, leflunomide; *AZA*, azathioprine; *PDN*, prednisone; *TNF-IR*, inadequate response to at least one anti-TNF-α agent

safety of different doses of secukinumab in patients with active RA, they mixed the biologic-naïve patients and TNF-IR, so we excluded this article. The pooled analysis included 2499 patients with RA (1022 patients in biologics-naïve subgroup and 1477 patients in TNF-IR subgroup). The majority of studies included were allocated high-quality scores (all of the eleven RCTs had a score ≥ 6). Included studies, basic characteristics of enrolled patients, details about drug therapy, study duration, and modified Jadad scores are briefly presented in Table 1.

Efficacy

ACR20 response Nine studies including ten RCTs with 2481 patients reported the proportion of patients meeting ACR20 improvement criteria. Compared to placebo, IL-17 inhibitors showed a trend toward efficacy but did not have statistical significance in achieving ACR20 response [53.4% vs. 43.9%; RR = 1.34, 95% CI 0.94–1.91, $P = 0.11$, $I^2 = 77\%$; Fig. 2] for biologics-naïve patients. The proportion of ACR20 responders was statistically higher with IL-17 inhibitors compared to placebo in TNF-IR [37.6% vs. 22.5%; RR = 1.67, 95% CI 1.40–2.00, $P < 0.00001$, $I^2 = 0\%$; Fig. 2].

ACR50 response Eight studies including nine RCTs with 2403 patients reported the proportion of patients meeting ACR50 improvement criteria. Compared to placebo, IL-17 inhibitors were more effective in achieving ACR50 response for both biologics-naïve (25.1% vs. 16.5%; RR = 1.71, 95% CI 1.23–2.38, $P = 0.001$, $I^2 = 60\%$; Fig. 3) and TNF-IR (17.9% vs. 9.3%; RR = 1.94, 95% CI 1.43–2.63, $P < 0.0001$, $I^2 = 11\%$; Fig. 3).

ACR70 response Eight studies including nine RCTs with 2329 patients reported the proportion of patients meeting ACR70 improvement criteria. Compared to placebo, IL-17 inhibitors were more effective in achieving ACR70 response for both biologics-naïve (7.7% vs. 2.7%; RR = 2.63, 95% CI 1.10–6.25, $P = 0.03$, $I^2 = 6\%$; Fig. 4) and TNF-IR (7.2% vs. 3.4%; RR = 2.11, 95% CI 1.26–3.55, $P = 0.005$, $I^2 = 0\%$; Fig. 4).

Safety

The focus in safety that accompanies IL-17 inhibitor therapy for patients with RA was on infection, hypertension, and neutropenia. The most commonly reported infection events were upper respiratory tract infections, urinary tract infections, and diarrhea.

For biologics-naïve patients, results for safety indicated that the IL-17 inhibitor did not increase the risks of any AEs (53.0% vs. 47.6%; RR = 1.14, 95% CI 0.98–1.32, $P = 0.09$, $I^2 = 0\%$) or SAEs (18.3% vs. 13.0%; RR = 1.16, 95% CI 0.86–1.55, $P = 0.33$, $I^2 = 0\%$). In the analysis of individual

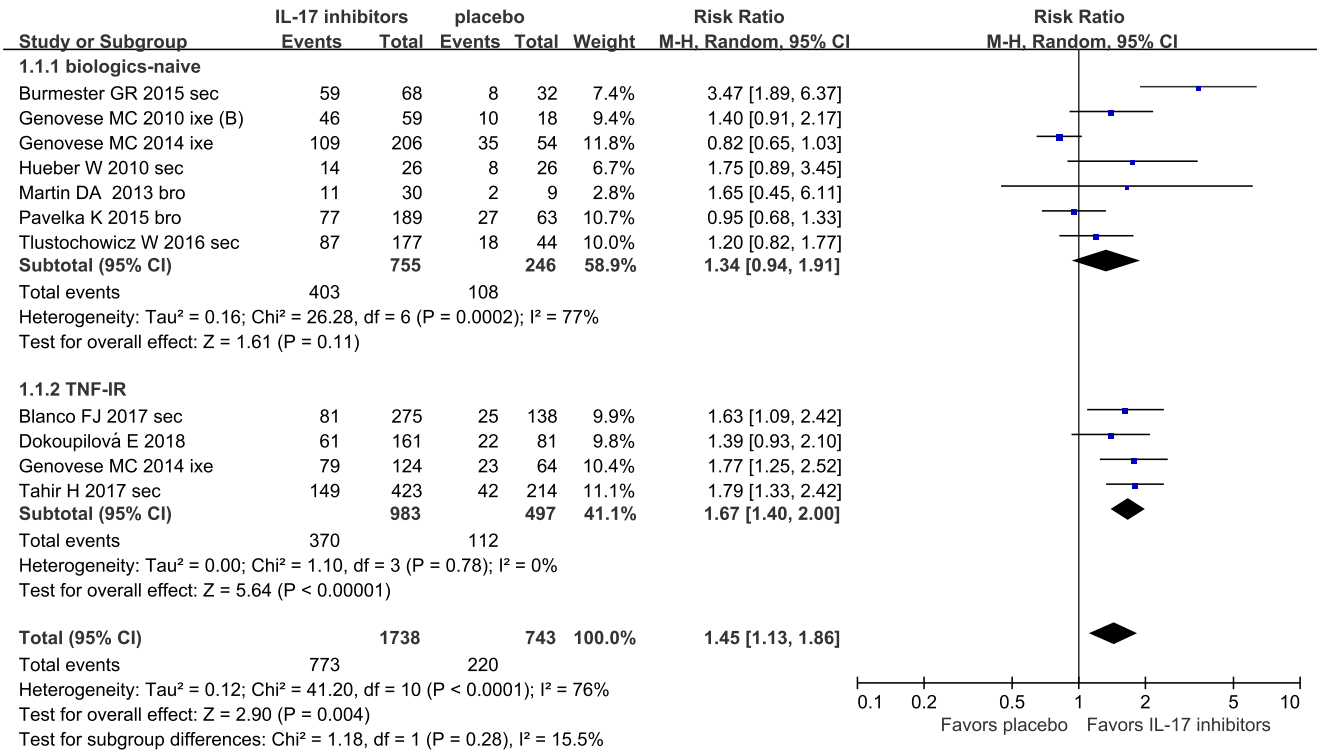

Fig. 2 Forest plot of the proportion of patients with ACR20 response between IL-17 inhibitors and placebo for rheumatoid arthritis

adverse events, IL-17 inhibitors also had not significant increase in the risk of upper respiratory tract infections (4.2% vs. 1.0%; RR = 2.72, 95% CI 0.91–8.13, $P = 0.07$, $I^2 = 0\%$), urinary tract infection (5.3% vs. 4.4%; RR = 1.18, 95% CI 0.50–2.80, $P = 0.71$, $I^2 = 13\%$), diarrhea (8.8% vs. 2.2%; RR = 1.98, 95% CI 0.45–8.68, $P = 0.37$, $I^2 = 0\%$), hypertension (4.2% vs. 4.5%; RR = 0.92, 95% CI 0.33–2.58, $P = 0.88$, $I^2 = 44\%$), or neutropenia (2.3% vs. 0%; RR = 2.00, 95% CI 0.25–16.02, $P = 0.52$, $I^2 = 0\%$). Nineteen of 771 biologics-naïve patients in IL-17 inhibitors group and 6 of 251 patients

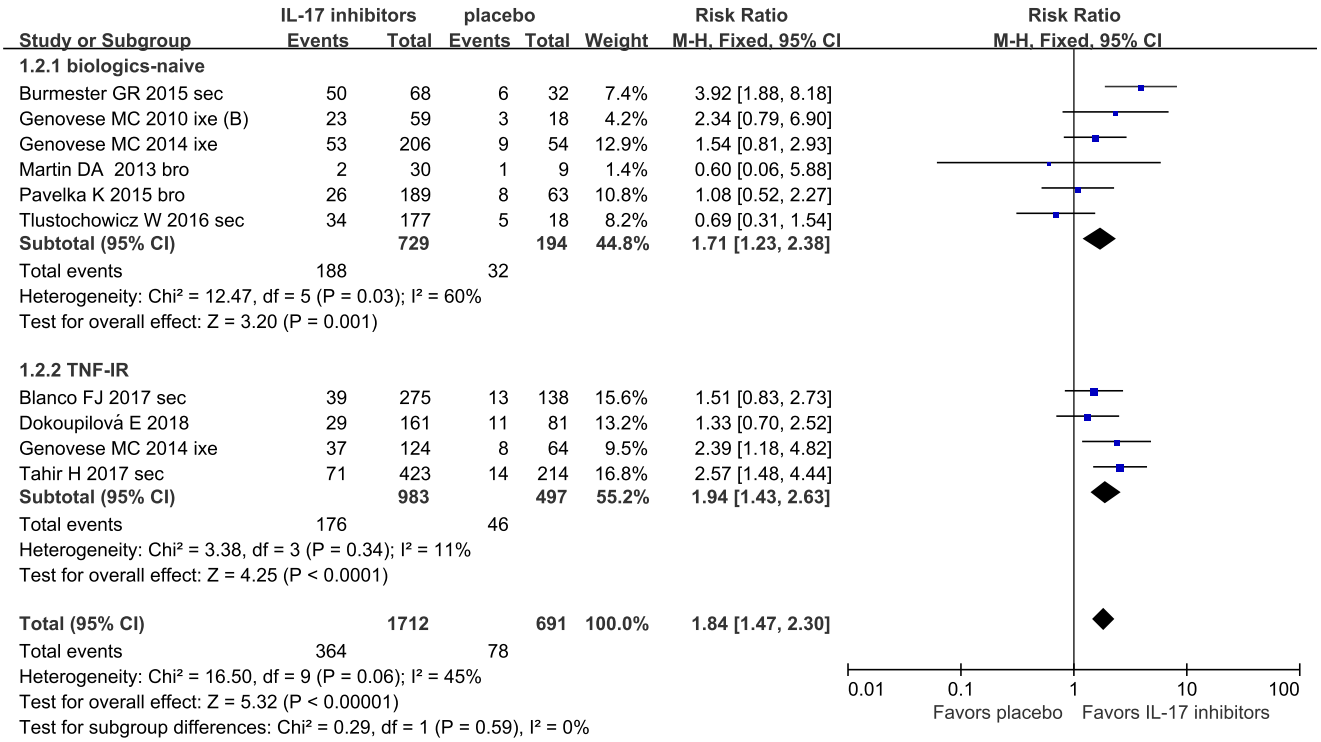

Fig. 3 Forest plot of the proportion of patients with ACR50 response between IL-17 inhibitors and placebo for rheumatoid arthritis

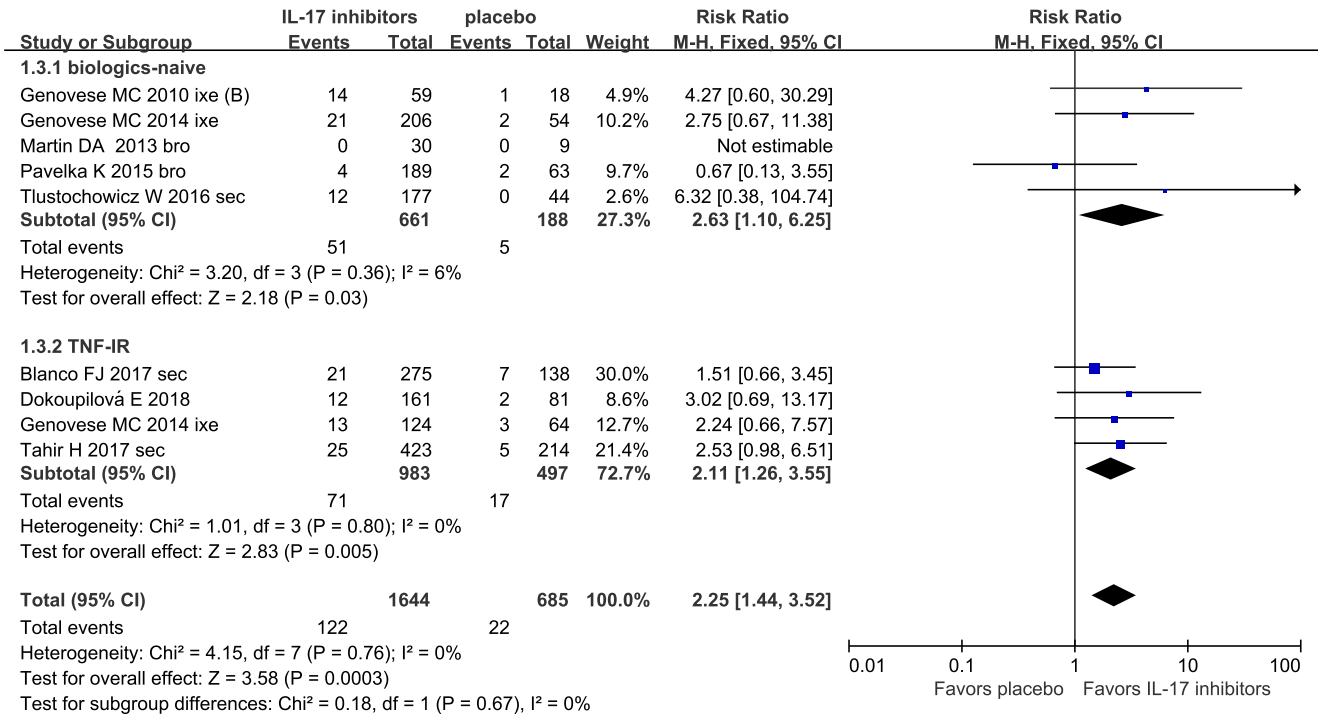

Fig. 4 Forest plot of the proportion of patients with ACR70 response between IL-17 inhibitors and placebo for rheumatoid arthritis

in placebo group leaded to discontinuations due to adverse events; however, no significant difference between the two groups (2.5% vs. 2.4%; RR = 0.88, 95% CI 0.39–1.96, P = 0.75, I^2 = 8%).

For TNF-IR, we found that the IL-17 inhibitor also did not increase the risks of any AEs (58.4% vs. 53.4%; RR = 1.09, 95% CI 0.99–1.21, P = 0.07, I^2 = 44%) or SAEs (4.6% vs. 2.8%; RR = 1.59, 95% CI 0.89–2.85, P = 0.12, I^2 = 34%). In the analysis of individual AEs, IL-17 inhibitors had not significant increase in the risk of upper respiratory tract infections (3.7% vs. 4.8%; RR = 0.76, 95% CI 0.44–1.33, P = 0.34, I^2 = 0%), urinary tract infection (3.1% vs. 3.2%; RR = 0.96, 95% CI 0.44–2.13, P = 0.93, I^2 = 37%), diarrhea (3.0% vs. 1.4%; RR = 1.99, 95% CI 0.78–5.03, P = 0.15, I^2 = 73%), hypertension (3.0% vs. 2.1%; RR = 1.41, 95% CI 0.68–2.93, P = 0.36, I^2 = 0%), or neutropenia (1.3% vs. 0.8%; RR = 1.52, 95% CI 0.52–4.38, P = 0.44, I^2 = 0%). Twenty-four of 981 TNF-IR in IL-17 inhibitors group and 14 of 496 patients in placebo group leaded to discontinuations due to adverse events, also no significant difference between two groups (2.4% vs. 2.8%; RR = 0.87, 95% CI 0.45–1.66, P = 0.67, I^2 = 38%). The results of safety outcomes for two rheumatoid arthritis populations were shown in Table 2 respectively.

Table 2 The results for safety outcomes analyzed separately for two rheumatoid arthritis populations: biologic-naïve and tumor necrosis factor inhibitor inadequate responders

Outcomes	Bologic-naïve	TNF-IR
	RR (95% CI), P value, I2 (P value), number of studies	RR (95% CI), P value, I^2 (P value), number of studies
Any adverse events	1.14 (0.98 to 1.32), P = 0.09, I^2 = 0% (P = 0.92), 6 studies	1.09 (0.99 to 1.21), P = 0.07, I^2 = 44% (P = 0.15), 4 studies
Serious adverse events	1.16 (0.86 to 1.55), P = 0.33, I^2 = 0% (P = 0.79), 7 studies	1.59 (0.89 to 2.85), P = 0.12, I^2 = 34% (P = 0.21), 4 studies
Upper respiratory tract infection	2.72 (0.91 to 8.13), P = 0.07, I^2 = 0% (P = 0.85), 5 studies	0.76 (0.44 to 1.33), P = 0.34, I^2 = 0% (P = 0.95), 3 studies
Urinary tract infection	1.18 (0.50 to 2.80), P = 0.71, I^2 = 13% (P = 0.31), 3 studies	0.96 (0.44 to 2.13), P = 0.93, I^2 = 37% (P = 0.21), 2 studies
Diarrhea	1.98 (0.45 to 8.68), P = 0.37, I^2 = 0% (P = 0.77), 3 studies	1.99 (0.78 to 5.03), P = 0.15, I^2 = 73% (P = 0.06), 2 studies
Hypertension	0.92 (0.33 to 2.58), P = 0.88, I^2 = 44% (P = 0.18), 2 studies	1.41 (0.68 to 2.93), P = 0.36, I^2 = 0% (P = 0.48), 3 studies
Neutropenia	2.00 (0.25 to 16.02), P = 0.52, I^2 = 0% (P = 0.85), 2 studies	1.52 (0.52 to 4.38), P = 0.44, I^2 = 0% (P = 0.56), 4 studies
Discontinuations due to adverse events	0.88 (0.39 to 1.96), P = 0.75, I^2 = 8% (P = 0.37), 8 studies	0.87 (0.45 to 1.66), P = 0.67, I^2 = 38% (P = 0.19), 4 studies

TNF-IR, tumor necrosis factor inhibitor inadequate responders; *RR*, risk ratios; *95% CI*, 95% confidence intervals; $I^2 > 50\%$, heterogeneity; $I^2 < 50\%$, homogeneity

In addition, brodalumab should be more concerned. Some of the patients receiving brodalumab have serious adverse events, including suicide. An article reported that four patients died of suicide after receiving brodalumab [33]. One of the included articles [26] reported a suicide attempter in the 210-mg brodalumab group, although there was no clear evidence in the current study that suicidal tendencies were related to the use of brodalumab.

Discussion

The meta-analysis results show that IL-17 inhibitors are effective in achieving target of ACR20, ACR50, and ACR70 without increasing risks of any AEs, serious AEs, or individual AEs in both biologic-naïve and TNF-IR patients with RA. In Kunwar' s meta-analysis [34] of seven RCTs with 1226 patients, IL-17 inhibitors were effective in the treatment of RA without increased risk of any or serious AEs, consistent with our observations in this study with higher number of RCTs ($n = 11$) and patients ($n = 2499$).

Many previous RCTs showed that some other biological agents such as abatacept [17], rituximab [18], tocilizumab [35], and golimumab [36] could improve therapeutic outcomes in TNF-IR patients with RA. Similar results appeared on IL-17 inhibitors in our meta-analysis. Alzabin S's study showed that patients with lack of response to anti-TNF-α agents had a relatively high baseline Th17 cell level [37], which may be a possible mechanism for this result.

Safety analysis showed IL-17 inhibitors did not increase in the incidence of any AEs, SAEs, infections, hypertension, neutropenia, or treatment discontinuations compared with placebo. The infections mentioned in this article mainly referred to upper respiratory tract infection, urinary tract infection, and diarrhea. IL-17A plays an important role in host defense against microorganisms and in the development of chronic inflammation [38, 39]. Therefore, IL-17 inhibitors can increase the incidence of infection. However, our study showed that IL-17 inhibitors were relatively safe for patients with upper respiratory tract infections, urinary tract infections, and diarrhea.

The risk of hypertension in RA patients is increased compared with normal people, which may be related to inflammatory activity [40]. While some DMARDs [41] for the treatment of RA can also lead to elevated blood pressure, IL-17 inhibitors do not increase the incidence of hypertension, showing its safety in cardiovascular events.

Some patients included in this article were taking concomitant methotrexate, which has also been associated with neutropenia [42]. However, the use of Il-17 inhibitors did not increase the risk of neutropenia in either biologics-naïve or TNF-IR subgroup. Therefore, IL-17 inhibitors are more suitable for patients who have had adverse reactions to previous drug us.

A 64-week study [43] of safety and efficacy of subcutaneous ixekizumab treatment in biologic-naïve and TNF-IR patients with RA showed that most AEs were mild to moderate in severity and did not lead to research discontinuation. Clinical responses observed at week 16 (improving RA signs and symptoms) were maintained or improved through the whole 64 weeks.

There are several limitations to our meta-analysis: relatively small number of included studies, variable forms and doses of IL-17 inhibitors, and short study duration. We combined data on three IL-17 inhibitors: secukinumab, ixekizumab, and brodalumab, respectively. Some of the patients were injected subcutaneously and some were injected intravenously; besides, the dosage of the same drug is different in these studies. For example, patients were all given secukinumab; some were assigned to receive intravenous at a dose of 10 mg/kg, while others were assigned to receive subcutaneous 75 mg or 150 mg. The durations of included studies are ranging from 10 to 24 weeks. The short time of follow-up of the studies is the biggest limitation. In order to acquire more accurate results, more high-quality, large-scale, long following-up clinical trials are needed.

In summary, IL-17 inhibitors are clearly effective and well tolerated in patients with RA who are either naive to biologic agents or have a TNF-IR.

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Compliance with ethical standards

Disclosures None.

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