Efficacy and safety of monoclonal antibodies targeting interleukin-17 pathway for inflammatory arthritis: a meta-analysis of randomized controlled clinical trials

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Abstract: T-helper 17 (Th17) pathway plays an important and distinct role in autoimmunity and inflammation. A growing body of evidence demonstrates that interleukin-17 (IL-17) is also synthesized in inflammatory arthritis tissues and exerts potent proinflammatory and joint-destructive activities. Clinical studies have been performed to evaluate the therapeutic efficacy of antibodies blocking the IL-17 signaling pathway in patients with rheumatoid arthritis (RA). In this study, we performed a meta-analysis to systematically evaluate the clinical effects of IL-17 antibodies in RA patients. By searching PubMed, five randomized, placebo-controlled randomized controlled clinical trials that tested three antibodies against IL-17A (LY2439821 and secukinumab/AIN457) and the IL-17A receptor (brodalumab) were identified. The primary outcomes that were analyzed include American College of Rheumatology (ACR) Improvement Criteria and Disease Activity Score in 28 joints (DAS28). Meanwhile, the safety and adverse effects were also systematically analyzed. The results of the meta-analysis demonstrated that IL-17 antibody is effective in ameliorating the RA symptoms. Specifically, IL-17-blocking antibody significantly reduced ACR20 and ACR50. It also dramatically reduced DAS28, an index that measures tenderness and swelling severity of joints. The side effects of and intolerance to the antibody treatment were higher than those in the placebo control. The analysis result provides evidence-based information for clinical use of these agents in the treatment of inflammatory arthritis.

Keywords: interleukin-17A, arthritis, meta-analysis, rheumatoid arthritis, clinical trials

Introduction

Rheumatoid arthritis (RA) is a chronic, inflammatory, and systemic autoimmune disease that affects ~1% of the population all over the world.[1] In RA patients, the affected joints contain autoreactive T- and B-cells that produce proinflammatory cytokines, resulting in cartilage and bone damage.[1] Targeting these cytokines provides a strategy for treatment, including disease-modifying antirheumatic drugs (DMARDs).[2,3] such as methotrexate (MTX). However, these DMARDs only work for a small proportion of patients. New medicines are urgently in demand.

In 1995, Yao et al[4] discovered that human T-cells could produce a proinflammatory cytokine, interleukin (IL)-17. These IL-17-producing cells are mainly a subset of cluster of differentiation 4 (CD4+) T-cells, a type of CD4+ "helper" lymphocytes named Th17 cells.[5,6] IL-17 levels are extremely low or undetectable in normal human peripheral blood, while the levels are elevated in peripheral blood or synovial fluid in RA patients.[7–10]

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Immunohistochemistry techniques led to the identification of a subset of IL-17-expressing T-cells in the synovium of RA patients.[11,12] Moreover, the number of IL-17A-positive cells was also increased in children with juvenile inflammatory arthritis joints.[13] Blocking IL-17A can reduce IL-6 expression and formation of collagen breakdown products.[14]

Th17 cells mediate the inflammation process by stimulating production of cytokines, chemokines, and matrix metalloproteinases.[15] Many human autoimmune diseases, including RA and psoriatic arthritis, are associated with abnormal Th17 activity.[16,17] Inhibition of IL-17 signaling through a ligand or its receptor could reduce inflammation and bone erosion in animal arthritis models.[18] Meanwhile, clinical investigations have also been carried out to target IL-17A signaling for alleviating the symptoms of RA. This meta-analysis was undertaken to evaluate the results of clinical trials and to provide evidence-based information for using these agents in clinical treatment of inflammatory arthritis.

Methods
Database search, selection criteria, and quality assessment

Database search was performed in PubMed using the keywords "interleukin-17A" and "rheumatoid arthritis". Eligible studies were selected based on the following criteria: 1) study design: randomized, double-blinded, placebo-controlled clinical trials (RCTs); 2) subjects: patients with RA; 3) intervention: administration of antibodies for blocking IL-17A signaling, including LY2439821 used by Genovese et al,[19] a humanized anti-IL-17 monoclonal antibody; secukinumab (AIN457), a fully human monoclonal anti-IL-17A antibody used by Genovese et al,[20] Hueber et al,[21] and Patel et al;[22] brodalumab, a human anti-IL-17 receptor monoclonal antibody used by Martin et al.[23] The quality of included trials was assessed using the Jadad scale score (zero to five), with a score of ≥3 indicating high quality.[24]

Outcomes, data extraction, and statistical analysis

Effects of treatment were measured by the improvement in the percentage of patients achieving American College of Rheumatology (ACR) scores ACR20, ACR50, and ACR70 according to Felson's method.[25] Another measurement, Disease Activity Score in 28 joints (DAS28), was also used in the studies based on standard guidelines.[26]

All analyses were performed using the Review Manager, version 5.1.0 (Cochrane Collaboration, Oxford, UK). The χ^2 Cochran Q-test was performed to detect heterogeneity.

Random- or fixed-effects inverse variance-weighted method was used to test the difference in significance levels.[27] Mean difference and the associated 95% confidence interval (CI) for ACR20/50/70 were used to assess the significance of difference.

Results
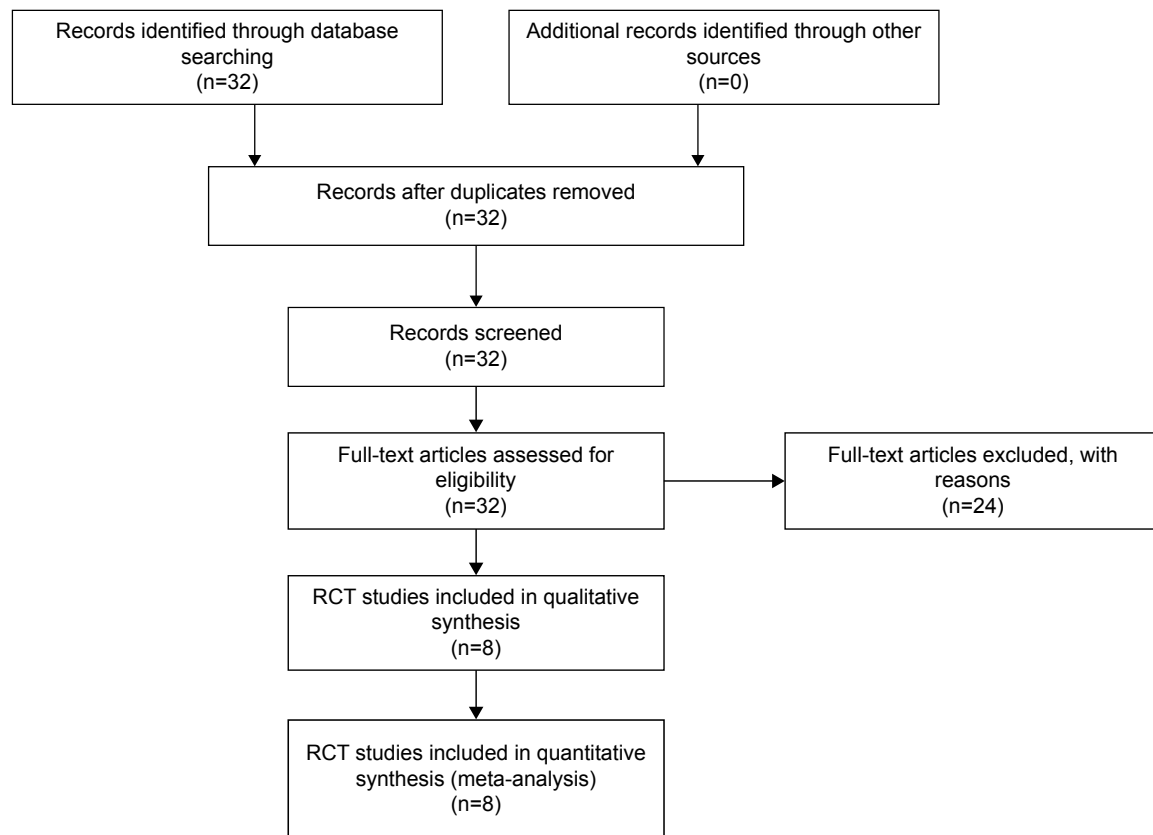### Identification of eligible studies from database search

In order to obtain eligible clinical studies, we first carried out a database search. The terms "interleukin-17A" and "rheumatoid arthritis" were used as the keywords to search the PubMed database, which resulted in a total of 32 articles being retrieved. Further stringent selections were performed by using filtering criteria with the clinical trials and RCTs. We identified five eligible studies, namely, Genevese et al,[19,20] Hueber et al,[21] Martin et al,[23] and Patel et al[22] (Figure 1). These randomized, double-blind, and placebo-controlled studies are summarized briefly in Table 1.

Three different antibodies were tested by three different research groups; the antibodies include LY2439821, a human anti-IL-17 monoclonal antibody used in Genovese et al,[19] secukinumab (AIN457), a human anti-IL-17A antibody tested in Genovese et al,[20] Hueber et al,[21] and Patel et al;[22] brodalumab (AMG827), a human anti-IL-17 receptor A monoclonal antibody tested in Martin et al.[23]

Meta-analysis of the outcomes tested

A major end point used in these studies was the ACR score, a widely used standard to measure the improvement in symptom reduction in RA patients. We collected the ACR20, ACR50, and ACR70 values from the eligible studies identified from the search, including Genovese et al,[19,20] Hueber et al,[21] Martin et al,[23] and Patel et al.[22] A meta-analysis was performed and results are presented in Figure 2, showing that treatment with the IL-17-signaling blockers had a dramatic effect on ACR20 (Figure 2A, $P=0.0005$) and ACR50 (Figure 2B, $P=0.007$). ACR70 tends to change, but the effect is not significant enough (Figure 2C, $P=0.1$). Of note, brodalumab, the IL-17A receptor antibody, resulted in a lesser effect than the other three IL-17A antibodies,[23] suggesting that neutralizing of IL-17A ligand provides a more efficient approach for RA treatment.

Another readout, DAS28, was derived from tender 28-joint and swollen 28-joint counts.[26] All three studies using IL-17-neutralizing antibodies found marked reduction in the joint swollen points relative to the placebo control treatment, supporting the efficacy of these antibodies in alleviating the RA symptoms. In Genovese et al,[19] greater decrease in DAS28

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Figure 1 Flow diagram for study selection.
Abbreviation: RCT, randomized controlled trial.

was observed after treatment with the antibody LY2439821 ($P<0.05$): −2.3, −2.4, and −2.3 in 0.2 mg/kg, 2.0 mg/kg, and all-combined groups, respectively, compared to that in the placebo control group (−1.7). Similar findings were achieved by antibody treatment using secukinumab (AIN457) in Genovese et al,[20] Hueber et al,[21] and Patel et al.[22]
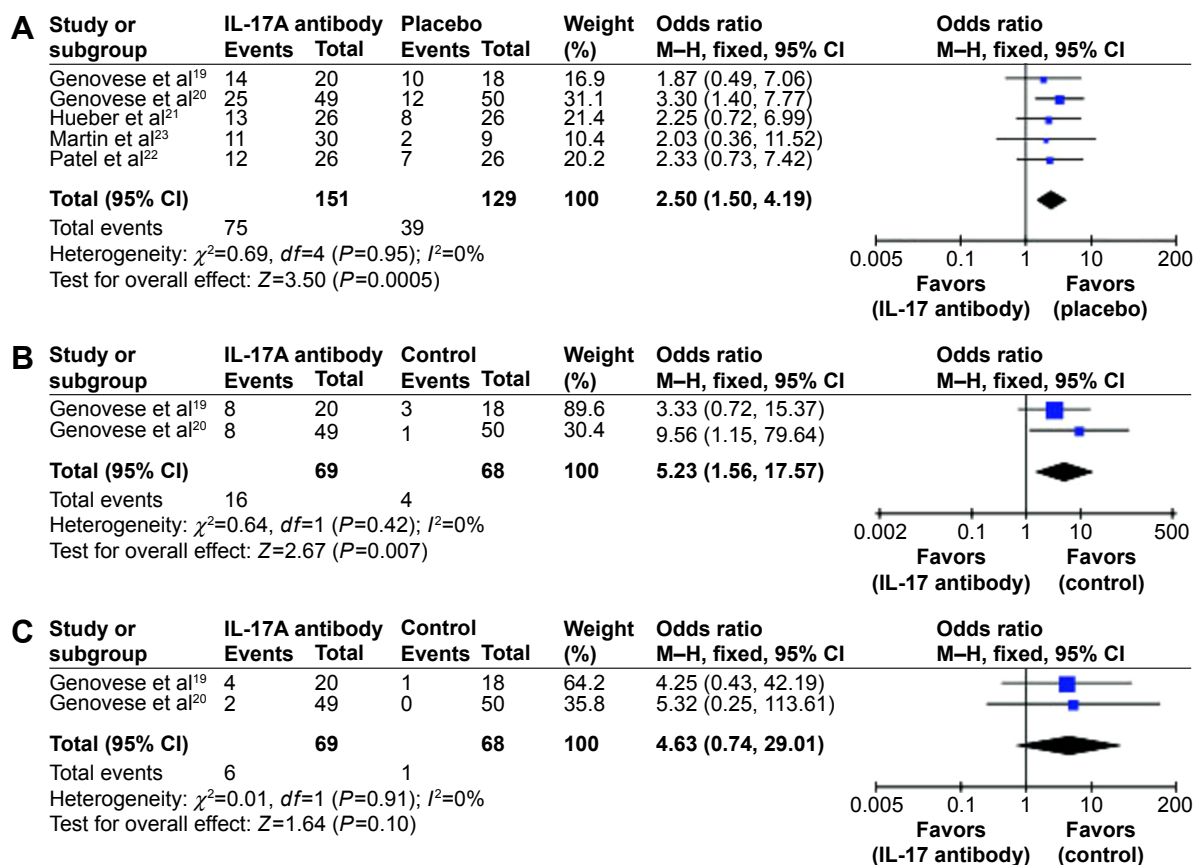
Safety and adverse effects

Adverse effects were investigated in these studies, and we performed a meta-analysis for the same. The median doses of IL-17A antibodies were chosen for analysis: 75 mg secukinumab in Genovese et al[20] (doses tested ranged from 25 mg to 300 mg) and 0.6 mg/kg LY249821

Table 1 Summary of studies using IL-17A antibodies as a treatment for the rheumatoid arthritis

Study (year)	Design	Number of patients	IL-17A antibody administered	Outcomes or end point	Jadad score
Genovese et al, 2010[19]	RCT	20 RA patients in part A and 77 patients in part B	LY2439821 (ixekizumab), from 0.06 mg/kg to 2.0 mg/kg intravenously one dose (part A) or five doses in total, one dose every 2 weeks	ACR and DAS28	4
Genovese et al, 2013[20]	RCT	237 patients with inadequate response to methotrexate	Secukinumab, 25 mg, 75 mg, 150 mg, 300 mg, and placebo	ACR20 and DAS28	5
Hueber et al, 2010[21]	RCT	52 RA patients	AIN457 at doses of 3–10 mg/kg, intravenously	ACR20	3
Martin et al, 2013[23]	RCT	52 RA patients	Brodalumab, 50 mg, 140 mg, or 210 mg subcutaneously, every 2 weeks for six doses per group, or 420 mg or 700 mg intravenously every 4 weeks for two doses per group	ACR20, ACR50, and ACR70	4
Patel et al, 2013[22]	RCT	52 RA patients for short time and 237 RA patients for long time	10 mg/kg secukinumab short time (4 weeks); 25–300 mg for longer time (16 weeks)	ACR20	5

Abbreviations: ACR, American College of Rheumatology; DAS, Disease Activity Score; IL, interleukin; RA, rheumatoid arthritis; RCT, randomized controlled trial.
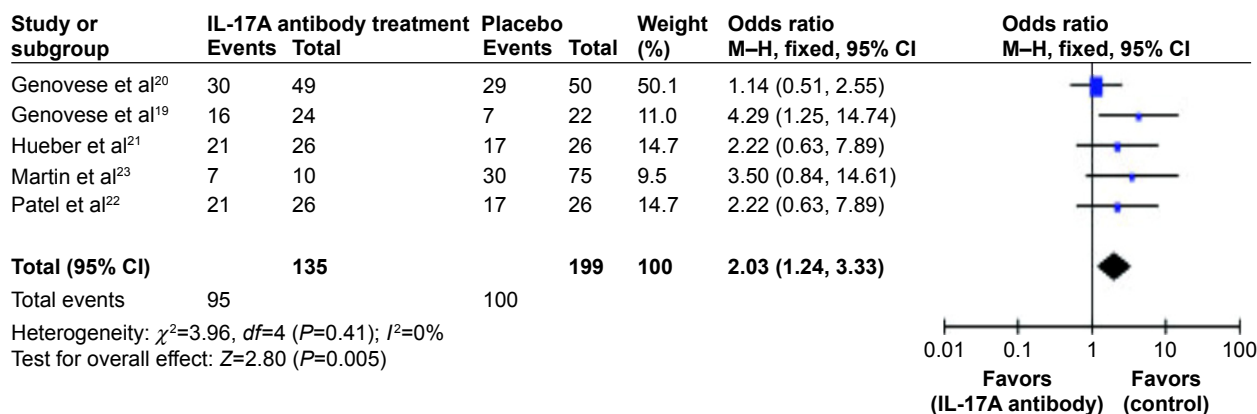
A

Study or subgroup	IL-17A antibody Events	Total	Placebo Events	Total	Weight (%)	Odds ratio M–H, fixed, 95% CI	Odds ratio M–H, fixed, 95% CI
Genovese et al[19]	14	20	10	18	16.9	1.87 (0.49, 7.06)	
Genovese et al[20]	25	49	12	50	31.1	3.30 (1.40, 7.77)	
Hueber et al[21]	13	26	8	26	21.4	2.25 (0.72, 6.99)	
Martin et al[23]	11	30	2	9	10.4	2.03 (0.36, 11.52)	
Patel et al[22]	12	26	7	26	20.2	2.33 (0.73, 7.42)	
Total (95% CI)		**151**		**129**	**100**	**2.50 (1.50, 4.19)**	
Total events	75		39				

Heterogeneity: χ^2=0.69, df=4 (P=0.95); I^2=0%
Test for overall effect: Z=3.50 (P=0.0005)

0.005 0.1 1 10 200
Favors (IL-17 antibody)   Favors (placebo)

B

Study or subgroup	IL-17A antibody Events	Total	Control Events	Total	Weight (%)	Odds ratio M–H, fixed, 95% CI	Odds ratio M–H, fixed, 95% CI
Genovese et al[19]	8	20	3	18	89.6	3.33 (0.72, 15.37)	
Genovese et al[20]	8	49	1	50	30.4	9.56 (1.15, 79.64)	
Total (95% CI)		**69**		**68**	**100**	**5.23 (1.56, 17.57)**	
Total events	16		4				

Heterogeneity: χ^2=0.64, df=1 (P=0.42); I^2=0%
Test for overall effect: Z=2.67 (P=0.007)

0.002 0.1 1 10 500
Favors (IL-17 antibody)   Favors (control)

C

Study or subgroup	IL-17A antibody Events	Total	Control Events	Total	Weight (%)	Odds ratio M–H, fixed, 95% CI	Odds ratio M–H, fixed, 95% CI
Genovese et al[19]	4	20	1	18	64.2	4.25 (0.43, 42.19)	
Genovese et al[20]	2	49	0	50	35.8	5.32 (0.25, 113.61)	
Total (95% CI)		**69**		**68**	**100**	**4.63 (0.74, 29.01)**	
Total events	6		1				

Heterogeneity: χ^2=0.01, df=1 (P=0.91); I^2=0%
Test for overall effect: Z=1.64 (P=0.10)

0.005 0.1 1 10 200
Favors (IL-17 antibody)   Favors (control)

Figure 2 Forest plot of meta-analysis.
Notes: Figure demonstrates the improved scores of ACR20 after antibody treatment, as described in Genovese et al,[19,20] Hueber et al,[21] Martin et al,[23] and Patel et al[22] (**A**), and the increased levels of ACR50 (**B**) and ACR70 (**C**) in Genovese et al.[19,20] Meta-analysis was performed using a fixed model.
Abbreviations: ACR, American College of Rheumatology; CI, confidence interval; IL, interleukin; M–H, Mantel–Haenszel method.

in Genovese et al[19] (doses tested ranged from 0.6 mg/kg to 2.0 mg/kg). Meta-analysis results demonstrated the total events of adverse effects were significantly higher in IL-17A-treated patients than in placebo control-treated patients (odds ratio [OR] =2.03; 95% CI: 1.24–3.33; P=0.005; Figure 3). Hueber et al[21] reported one severe adverse effect (SAE) (laryngeal abscess due to RA of the cricoarytenoid joint) in AIN457-treated patients. Two SAEs (interstitial lung disease and brachial plexopathy) were recorded in the placebo-treated group. AIN457 treatment slightly increased

Study or subgroup	IL-17A antibody treatment Events	Total	Placebo Events	Total	Weight (%)	Odds ratio M–H, fixed, 95% CI	Odds ratio M–H, fixed, 95% CI
Genovese et al[20]	30	49	29	50	50.1	1.14 (0.51, 2.55)	
Genovese et al[19]	16	24	7	22	11.0	4.29 (1.25, 14.74)	
Hueber et al[21]	21	26	17	26	14.7	2.22 (0.63, 7.89)	
Martin et al[23]	7	10	30	75	9.5	3.50 (0.84, 14.61)	
Patel et al[22]	21	26	17	26	14.7	2.22 (0.63, 7.89)	
Total (95% CI)		**135**		**199**	**100**	**2.03 (1.24, 3.33)**	
Total events	95		100				

Heterogeneity: χ^2=3.96, df=4 (P=0.41); I^2=0%
Test for overall effect: Z=2.80 (P=0.005)

0.01 0.1 1 10 100
Favors (IL-17A antibody)   Favors (control)

Figure 3 Forest plot of studies selected for meta-analysis of adverse effects.
Note: Meta-analysis was performed in fixed model.
Abbreviations: CI, confidence interval; IL, interleukin; M–H, Mantel–Haenszel method.
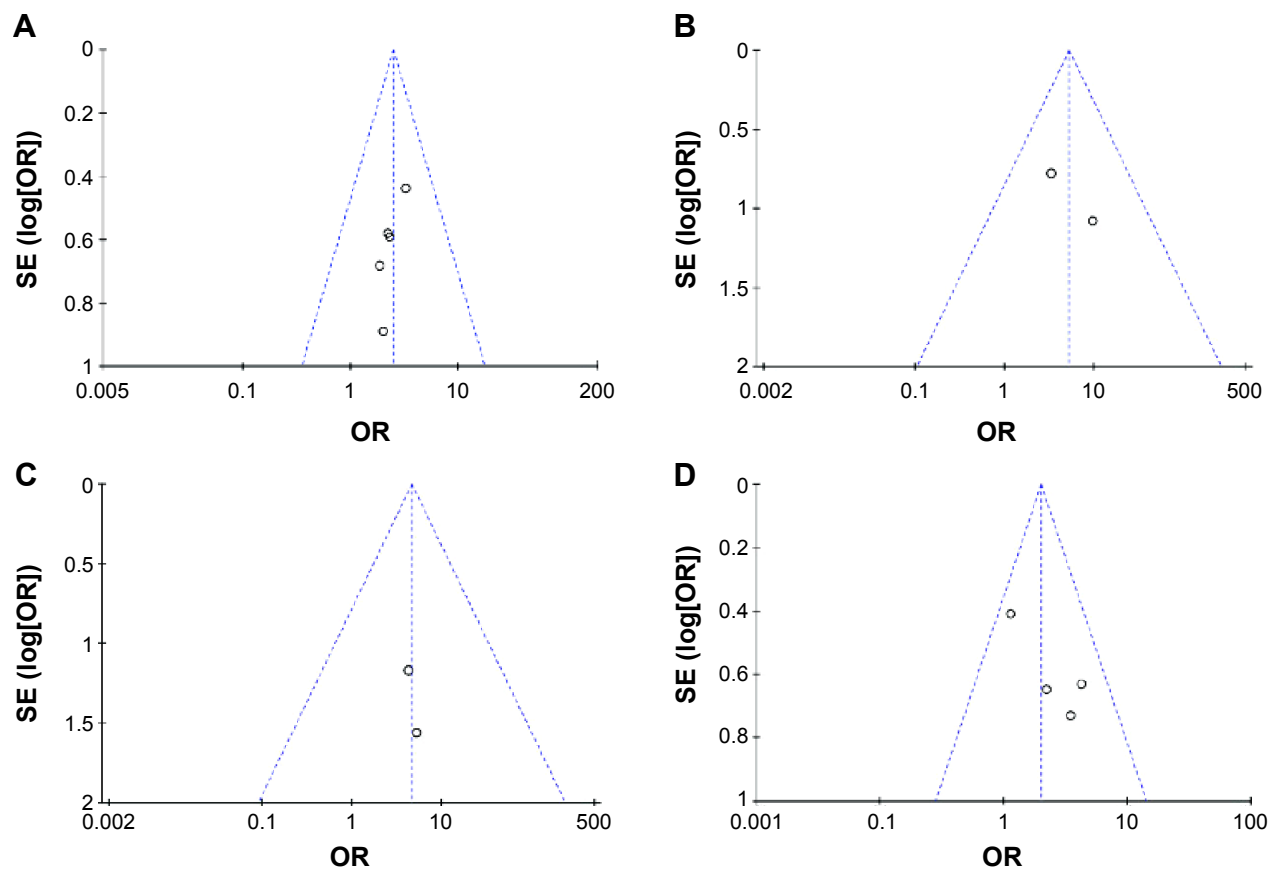
Figure 4 Funnel plot of studies selected for meta-analysis of ACR20 (**A**), ACR50 (**B**), ACR70 (**C**), and adverse effects (**D**).
Abbreviations: ACR, American College of Rheumatology; OR, odds ratio; SE, standard error.

the overall AE incidence. Headache, diarrhea, leukemia, and vertigo were reported in patients treated with LY2439821. However, these side effects occurred equally in placebo-treated patients.

Assessment for publication bias

In order to assess the publication bias, Begg's funnel plots test[28] was performed. As shown in Figure 4, the symmetrical patterns of these plots indicate that there is no publication bias in the studies selected for meta-analysis of ACR20 (Figure 4A), ACR50 (Figure 4B), and ACR70 (Figure 4C), There is also no publication bias in the studies selected for meta-analysis of AEs (Figure 4D).

Discussion

In this study, we performed a meta-analysis on five clinical trials investigating therapeutic antibodies blocking the IL-17A signaling pathway of RA. The results demonstrated the beneficial role of IL-17A antibody in the alleviation of RA symptoms, as measured by ACR20/50/70 and DAS28, two widely used outcomes for assessment of recovery from

this disease. The reduced tender joint count, swollen joint count, and pain after the antibody treatment might have resulted from the blockage of some step in the immune response pathway, such as production of cytokines or chemokines and neutrophil recruitment.[7]

IL-17A signaling plays a key role in this inflammatory disease.[29–33] In the mouse model, IL-17 overexpression gave rise to joint inflammation, as well as bone and cartilage damage.[34] By contrast, disruption of IL-17 signaling in the mouse can protect the bone cartilage from arthritis induction.[35–37] Murine Th17 cells play critical roles in chronic, erosive diseases,[38,39] with Toll-like receptor 4 having been proven to be critical in Th17-mediated inflammatory arthritis.[40,41]

Moreover, IL-17A antibody has also beneficial effects on other immune-mediated diseases, such as psoriasis, a skin autoimmune disease. Psoriatic arthritis also affects many people in the world. The IL-17A antibody secukinumab has also been shown to have beneficial effects on patients with this disease. IL-17A expression is increased in patients with psoriatic arthritis,[42–44] along with increased IL-17A receptor levels,[42] in these patients.

One of these antibodies, brodalumab, has little effect on RA. It is a human immunoglobulin G2 monoclonal antibody against IL-17 receptor A and blocks the biological activity of IL-17A and IL-17F, as well as A/F heterodimer signaling. This antibody was tested and found to be capable of suppressing the inflammatory process in psoriasis.[16] This might be due to the multiple ligands involved in RA.

Tumor necrosis factor (TNF) can regulate IL-17A signaling; an anti-TNF antibody, infliximab, was tested in terms of its ability to reduce the number of IL-17-producing cells and decrease the disease activity.[45] Other TNF-blocking treatments had a similar effect in RA patients.[46,47] Yue et al demonstrated a decrease in peripheral Th17 cells in RA patients treated with adalimumab/MTX.[48] Therefore, targeting Th17 cells provides a tool to treat inflammatory diseases such as RA.

However, antibodies targeting Th17 may have potential side effects that would adversely affect their clinical application. It has been reported that neutralization of IL-17 in mice exacerbated *Candida*-induced dermatitis in skin.[49] Moreover, it is suspected that neutralization of IL-17RA might be linked to suicidal thoughts.[50] However, increased plasma concentration of proinflammatory cytokines, especially IL-17a, after myocardial infarction plays an important role in the stress reaction that predisposes to depression during the next 6 months.[51] A recent study also demonstrated a higher rate of injection site reaction and allergy.[52] The exact roles of IL-17a and IL-17-neutralizing antibodies in this process remain to be elucidated, and comprehensive evaluation of these agents for clinical application will be needed.

Acknowledgment

Disclosure

The authors report no conflicts of interest in this work.

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