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Th17 Inhibitors in Active Psoriatic Arthritis: A Systematic Review and Meta-Analysis of Randomized Controlled Clinical Trials

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Keywords
Meta-analysis · Biological therapy · Active psoriatic arthritis · Systematic review · Th17 pathway inhibitors

Abstract
Background: Several biologics targeting the Th17 pathway have been developed for the treatment of psoriatic arthritis (PsA), a disabling disease with moderate response and an increased incidence of serious infections to first-line biologics (TNF-α antagonists). Th17 inhibitors could replace TNF-α antagonists as first-line biologic agents. We determined the overall treatment effect of Th17 pathway inhibitors compared to placebo or active control on American College of Rheumatology (ACR) 20 response at week 12 (primary objective), risk of infections, discontinuation of treatment due to adverse events, and serious adverse events during the placebo-controlled period (12–24 weeks) in adults with active PsA in published randomized controlled trials. ***Methods:*** The SCOPUS database was searched. The Cochrane risk of bias tool was used for assessing quality. The pooled relative risk (RR) was derived from random effects models. ***Results:*** Seven randomized controlled trials were included which randomized 1,718 patients to Th17 inhibitors and 840 to placebo. Patients treated with Th17 inhibitors had an RR of 2.04 (95% CI: 1.79–2.33; $p < 0.001$) for achieving an ACR20 response at week 12 ($I^2 = 0\%$; $p = 0.89$) compared to placebo-treated patients. There was no evidence of publication bias. The result was consistent for study phase and outcome (ACR50/70), mechanism of action and TNF-α naivety. RR of infections was 1.06 (0.91–1.23), that of candida infections was 3.35 (0.75–14.95), that of serious adverse events was 0.82 (0.42–1.59) and that of discontinuation of treatment was 0.54 (0.31–0.93) among treated versus placebo subjects. No incident cases of tuberculosis were reported. ***Conclusion:*** In patients with active PsA, biologics targeting the Th17 axis produce a clinically significant improvement in joint disease activity with acceptable safety and tolerability for short-term treatment compared to placebo.

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Introduction

Psoriasis affects up to 3% of the world's population. Up to 30% of psoriasis patients are affected by psoriatic arthritis (PsA) [1]. PsA is a chronic, debilitating, immune-mediated inflammatory disease (T cell mediated) and is associated with significant disability (joint damage), poor quality of life, and reduced life expectancy [1, 2].

Elucidation of the role of Th17 (type-17 helper T cells) pathway in the pathogenesis of psoriasis and PsA has revolutionized the drug development and treatment approach for chronic plaque psoriasis and PsA [3]. IL-17A has been shown to drive the development of skin lesions in psoriasis and enthesitis in PsA while IL-23 induces differentiation of naive T cells to Th17 producing more IL-17A [4–7]. Prior to the availability of agents that targeted this pathway, TNF antagonists were the only biologics available for treatment following failure to disease-modifying antirheumatic drug (DMARD) therapy and symptomatic pain relief using nonsteroidal anti-inflammatory drugs (NSAIDs) and steroids. TNF blockers increase the risk of serious infections including tuberculosis and opportunistic infections and have also produced exacerbation of or incident cases of demyelination [8]. The lack of a durable response after discontinuation and the increased risk of serious infections during continued treatment have led to the exploration of alternative strategies including Th17 pathway inhibitors to treat psoriasis and PsA [3].

Multiple new biologics inhibiting the Th17 pathway including IL-17A (secukinumab and ixekizumab), IL-17A receptor (brodalumab), IL-12/23p40 (ustekinumab) and IL-23p19 inhibitors (tildrakizumab and guselkumab) have been studied in the recent past, and this is ongoing. Ustekinumab, secukinumab and ixekizumab have been FDA approved for psoriasis, and ustekinumab and secukinumab have been approved by the FDA for use in active PsA. The other agents are under clinical development for the PsA indication [3].

This emerging class of biologics has shown treatment benefit for PsA in separate trials to a varying extent [3], but the overall treatment effect on key disease activity measures has to be quantified systematically. The safety and tolerability profile of agents which target this pathway as a class is not clear and would be important to study as safety issues and treatment discontinuation due to intolerance or safety reasons results in disease relapse amongst those who show response and/or achieve remission.

Hence, we performed a systematic review and meta-analysis of randomized controlled clinical trials (excluding phase 1 studies) to quantify the overall combined short-term treatment effect (intention to treat) of Th17 pathway-targeting biologics indicated by patients achieving a composite end point, namely an ACR (American College of Rheumatology) 20 response at week 12, an end point used in arthritis trials accepted internationally by regulatory agencies as a clinically meaningful improvement in arthritis disease activity (20% improvement from baseline for core ACR components) [9]. In addition, the combined treatment effect for ACR50 and 70 (50 and 70% improvement from baseline in ACR components) in weeks 12 and 24 were also quantified in this meta-analysis.

The combined overall risk of adverse events of interest, namely infection, candida infections, tuberculosis, serious adverse events, and tolerability profile assessed by discontinuation of Th17 pathway inhibitors due to drug-related adverse events or intolerance, were also quantified for the placebo-controlled period (12–24 weeks) (see online suppl. Table 1 and suppl. protocol 1; see www.karger.com/doi/10.1159/000484520 for all online suppl. material). We hypothesized that in adult patients with active PsA who failed DMARD and/or TNF-α antagonists, Th17 pathway inhibitors would overall be superior when compared to placebo in producing a higher proportion of ACR20 responders at 12 weeks of treatment.

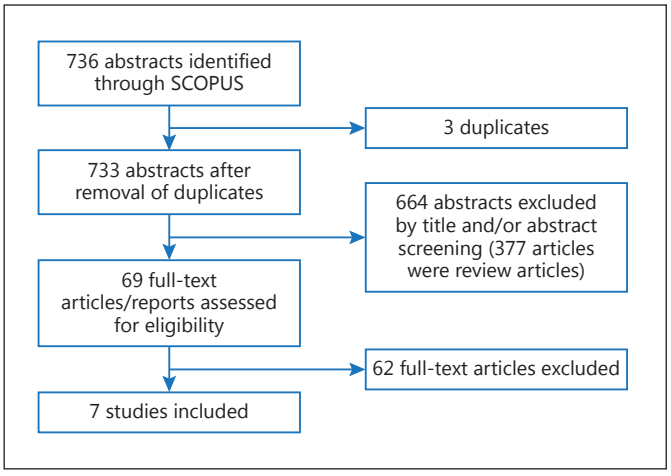

Fig. 1. PRISMA flowchart for overall search results.

Materials and Methods

For further details, see the online supplementary material [10–14] (Fig. 1).

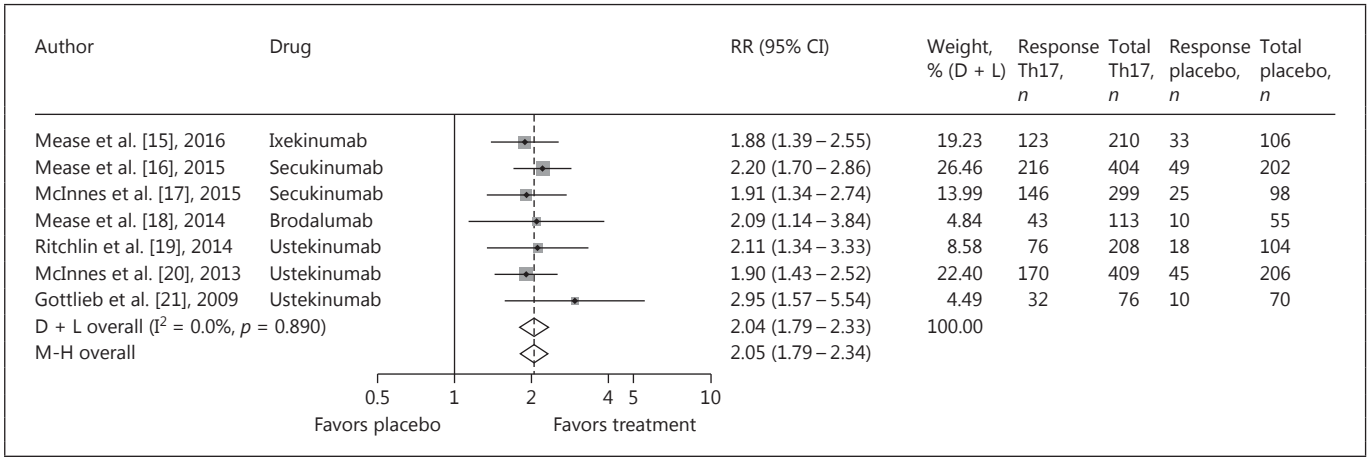

Fig. 2. Forest plot for primary end point – ACR20 at week 12 (Th17 inhibitors vs. placebo). D + L, DerSimonian and Laird random effects method; M-H, Mantel-Haenszel fixed effects method.

Table 1. Characteristics of included studies

Author	Drug	Phase	ACR20, week 12	ACR20, week 24	ACR50, week 12	ACR50, week 24	ACR70, week 12	ACR70, week 24		
Mease et al. [15], 2016	Ixekinumab	3	Secondary	Primary	Secondary	Secondary	Secondary	Secondary		
Mease et al. [16], 2015	Secukinumab	3	Secondary	Primary	Secondary	Secondary	Secondary	Secondary		
McInnes et al. [17], 2015	Secukinumab	3	Secondary	Primary	Secondary	Secondary	Secondary	Secondary		
Mease et al. [18], 2014	Brodalumab	2	Primary	NA	Secondary	NA	Secondary	NA		
Ritchlin et al. [19], 2014	Ustekinumab	3	Secondary	Primary	NA	Secondary	NA	Secondary		
McInnes et al. [20], 2013	Ustekinumab	3	Secondary	Primary	NA	Secondary	NA	Secondary		
Gottlieb et al. [21], 2009	Ustekinumab	2	Primary	NE	Secondary	NE	Secondary	NE		
Author	Mean age, years	Male, %	White, %	Mean BMI	Mean weight, kg	TNF-α naive	MTX use, %	DAS28-CRP	PASI	SF-36
Mease et al. [15], 2016	50.6	45.3	93.4	29.2	83.8	Yes	55.7	4.9	6.2	34
Mease et al. [16], 2015	48.5	47.5	76.2	NA	80	No	61.9	4.9	15.1	36.8
McInnes et al. [17], 2015	49.9	40	96	NA	86.2	No	51	4.7	11.6	37.4
Mease et al. [18], 2014	53	45	93	31	90	No	42	5.5	NA	NA
Ritchlin et al. [19], 2014	48	49	NA	30.5	NA	No	47.1	5.2	NA	NA
McInnes et al. [20], 2013	48	52.4	NA	29.7	NA	Yes	46.6	5.2	8.8	NA
Gottlieb et al. [21], 2009	47.5	53	NA	NA	NA	No	21	NA	9.75	NA

Age, male, white, BMI (body mass index), weight, TNF-α (tumor necrosis factor-α), methotrexate (MTX), DAS28-CRP (Disease Activity Score in 28 joints/C-reactive protein), PASI (Psoriasis Area Severity Index), and SF-36 (36-item Short-Form Health Survey) were reported at baseline in the placebo group. NA, not available; NE, not eligible.

Results

We included 7 randomized controlled trials in the meta-analysis with 1,718 patients in the treatment arm and 840 patients in the placebo arm (Table 1) [15–21]. The flowchart of study selection is presented in Figure 1. Of the 7 included studies, 1 investigated ixekizumab, 2 secukinumab, 1 brodalumab, and 3 ustekinumab (Table 1 and online suppl. Table 1).

Risk of Bias across Studies and in Individual Studies

The Cochrane risk of bias assessment across studies was found to be low risk for selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias (see online suppl. Fig. 1) across studies. The risk of bias assessment for individual studies is presented in Figure 2.

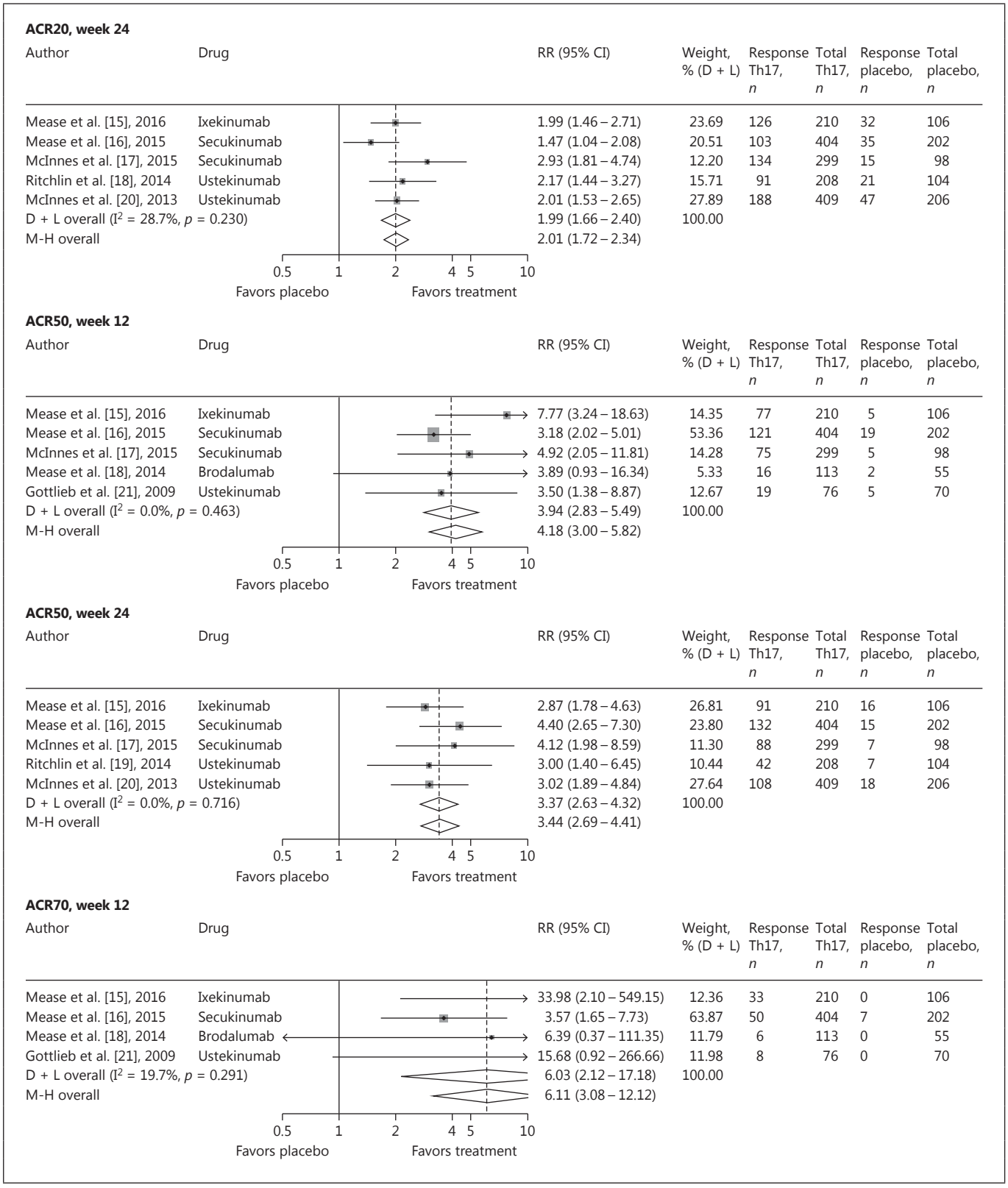

Fig. 3. Forest plots for secondary efficacy objectives (Th17 inhibitors vs. placebo) at weeks 12 and 24. D + L, DerSimonian and Laird random effects method; M-H, Mantel-Haenszel fixed effects method.

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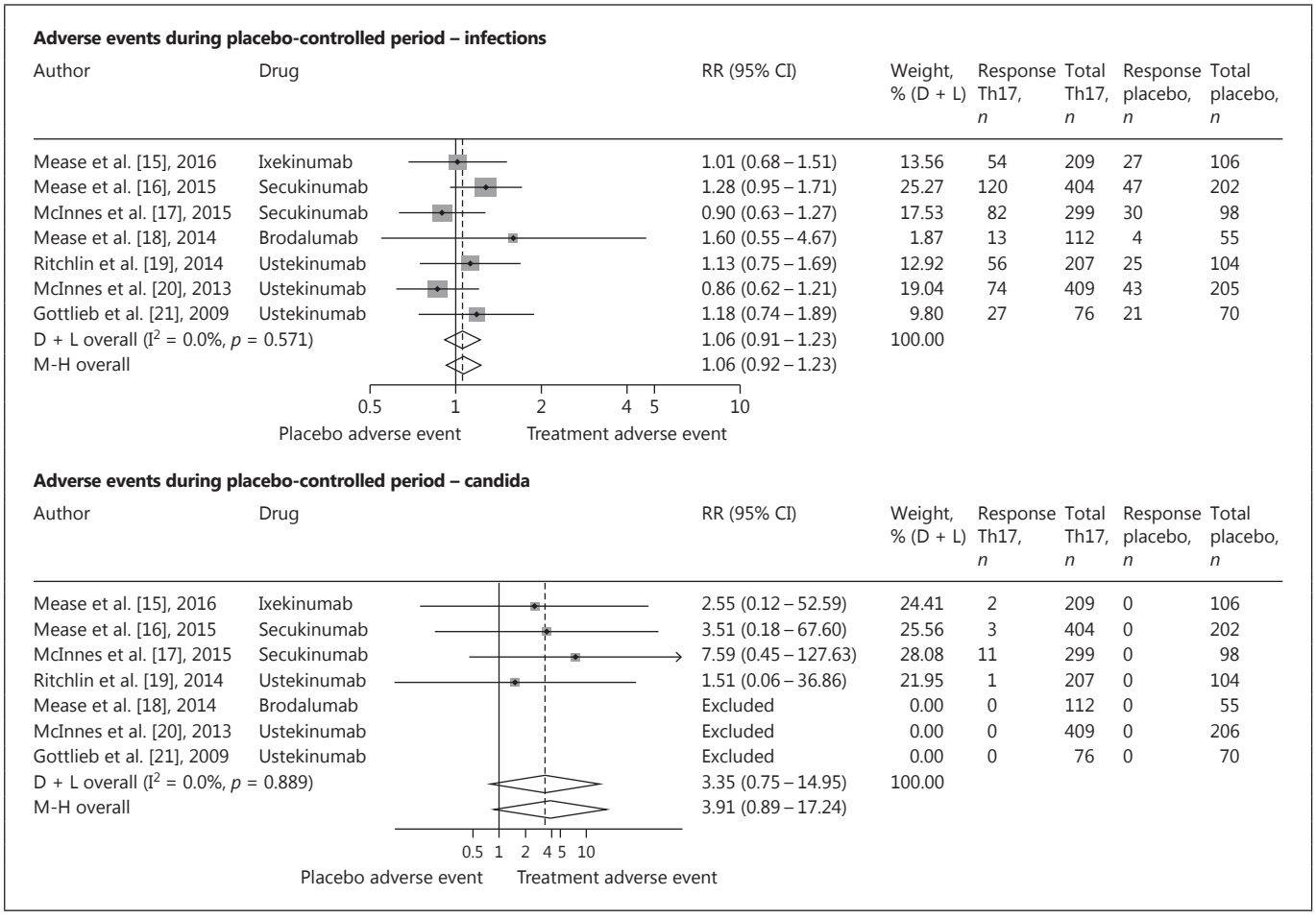

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Efficacy

In random effects models, patients treated with Th17 inhibitors were 2.04 times more likely to achieve an ACR20 response (relative risk, RR: 2.04, 95% confidence interval, CI: 1.79–2.33; $p < 0.001$; heterogeneity $p = 0.89$ and $I^2 = 0\%$) at week 12 (Fig. 2). Corresponding likelihoods for patients to achieve treatment response were 2.01 times (RR: 2.01, 95% CI: 1.72–2.34; $p < 0.001$) for ACR20 at week 24, 3.94 times for ACR50 at week 12 (RR: 3.94, 95% CI: 2.83–5.49; $p < 0.001$), 3.37 times for ACR50 at week 24 (RR: 3.37, 95% CI: 2.83–4.32; $p < 0.001$), 6.03 times for ACR70 at week 12 (RR: 6.03, 95% CI: 2.12–17.18; $p = 0.0007$) and 5.65 times for ACR70 at week 24 (RR: 5.65, 95% CI: 3.57–8.95; $p < 0.001$), respectively (Fig. 3 for ACR20/week 24, ACR50/weeks 12 and 24 and ACR70/week 12; see online suppl. Fig. 2 for ACR70/week 24). However, only 5 studies reported ACR20 at week 24, ACR50 at weeks 12 and 24 and ACR70 at week 24 with only 4 studies reporting ACR70 at week 12. There was no significant heterogeneity noted across efficacy end points.

Safety

The incidences of infections (RR: 1.06, 95% CI: 0.91–1.23; $p = 0.448$) and serious adverse events (RR: 0.82, 95% CI: 0.42–1.59; $p = 0.553$) were not significantly different among those treated with Th17 pathway inhibitors compared to placebo during the placebo-controlled period (Fig. 4). Incident cases of candida infection were reported in 4 studies while there were no infections seen in the 3 remaining studies. There was a trend towards a higher risk for developing candida infections but the CIs were wide with a nonsignificant p value (RR: 3.35, 95% CI: 0.75–14.95; $p = 0.113$) (Fig. 4). No cases of tuberculosis were reported in either active or placebo treatment arms for included studies, and hence this was not amenable to meta-analysis. Discontinuation of study treatment was lower in the treated group compared to placebo (RR: 0.54, 95% CI:

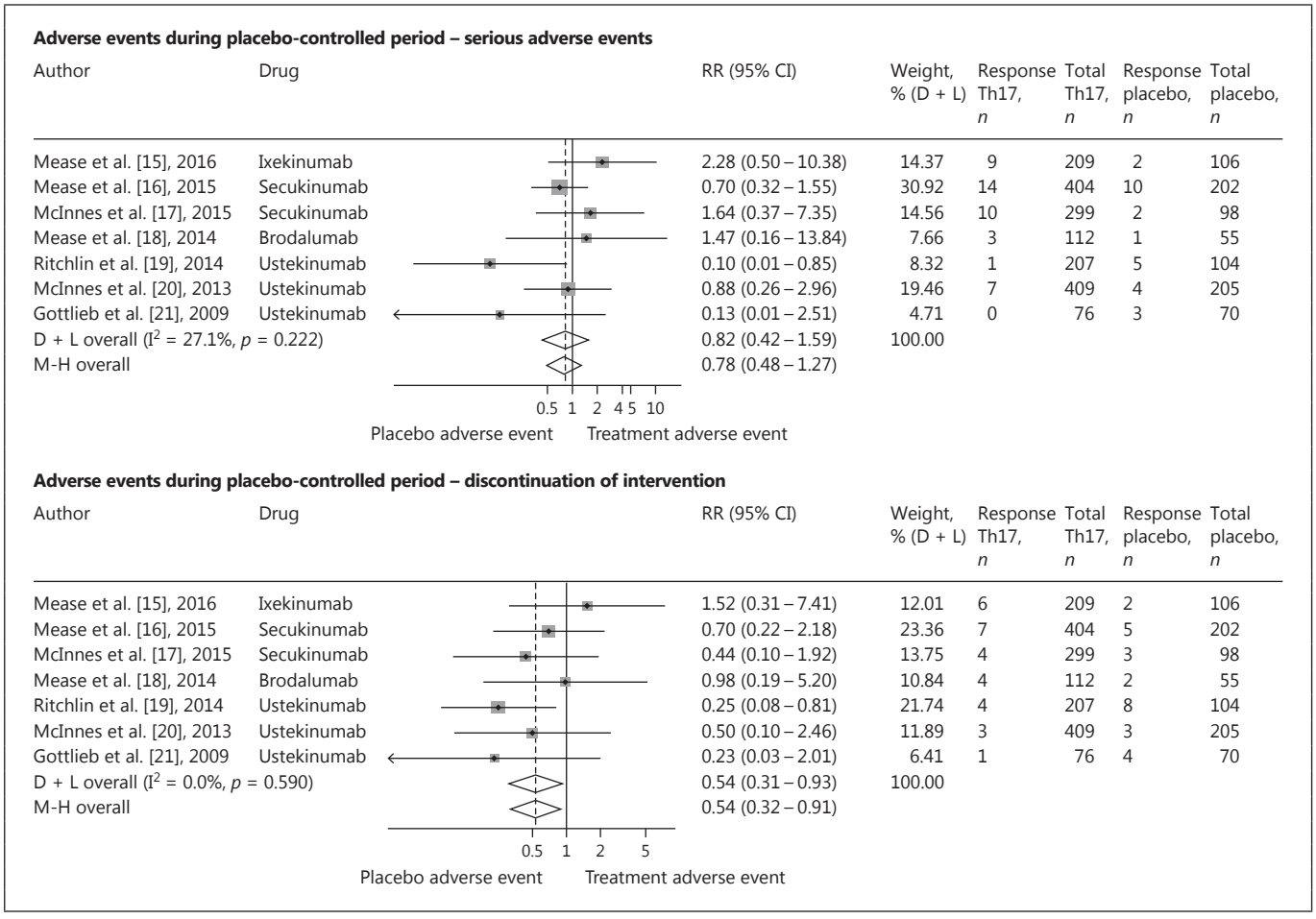


Fig. 4. Forest plots for secondary safety objectives (Th17 inhibitors vs. placebo) for the placebo-controlled period. D + L, DerSimonian and Laird random effects method; M-H, Mantel-Haenszel fixed effects method.

0.31–0.93; p = 0.025) as shown in Figure 4. There was no significant heterogeneity noted across safety end points.

Sensitivity Analysis

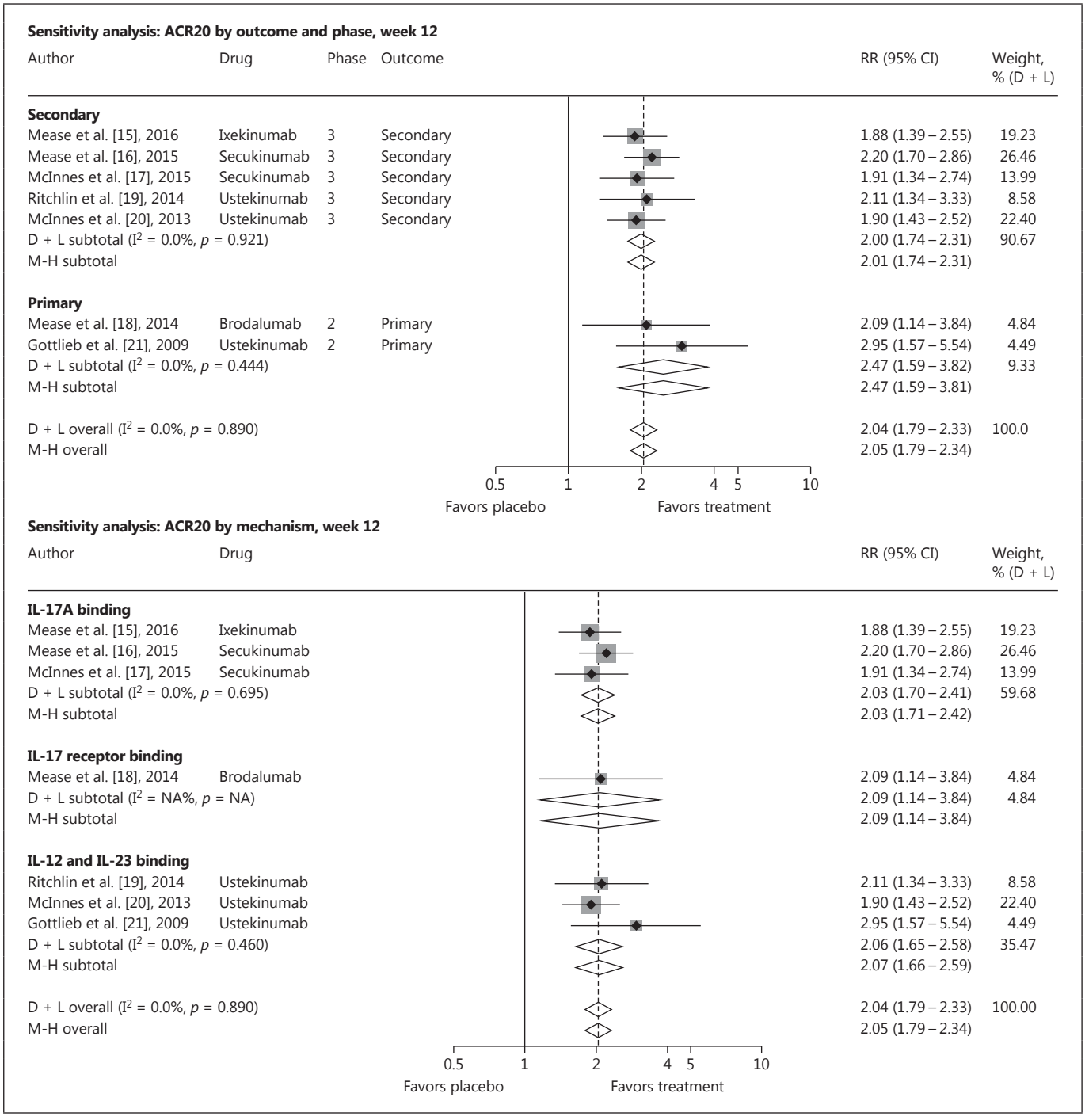
Removing 1 study at a time for the primary end point of ACR20 at week 12 showed that not any single study altered the interpretation of the meta-analysis and resulted in pooled estimates very close to the overall pooled risk ratio using all 7 studies (see online suppl. Fig. 3). This confirms the robustness of the findings for the primary outcome. Analysis by outcome and phase, mechanism of action (IL-17A binding vs. IL-17 receptor binding vs. IL-12/23p40 binding), and TNF-α naivety did not alter the interpretation or the direction of the effect and demonstrates consistent treatment benefit irrespective of these subgroup analyses (Fig. 5). Random and fixed models showed similar results.

Meta-Regression

Meta-regression analysis did not show any significant baseline study characteristic predictors for the log RR of ACR20 response at week 12. The covariates included in meta-regression were baseline age, gender, baseline DAS28-CRP (Disease Activity Score in 28 joints/C-reactive protein) score, history of methotrexate use and baseline PASI score (Fig. 6). The following variables were reported in less than 5 studies and were not included in the meta-regression: percentage of whites, mean body weight, mean body mass index.

Publication Bias

The funnel plot for ACR20 (week 12) showed slight asymmetry, but Egger's test of the intercept (bias p = 0.287) and Begg's rank correlation test (Kendall's τ, p = 0.368) showed no evidence of publication bias. This was



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confirmed by Duval and Tweedie's trim and fill method which showed zero imputed studies added to the funnel plot (Fig. 5) and thus an unchanged random effects model point estimate and 95% CI.

Discussion

Since the discovery of the Th17 cells and understanding of their biological function, the focus of drug development for inflammatory disorders has shifted from targeting Th1 pathway cytokines to the Th17 axis in which IL-

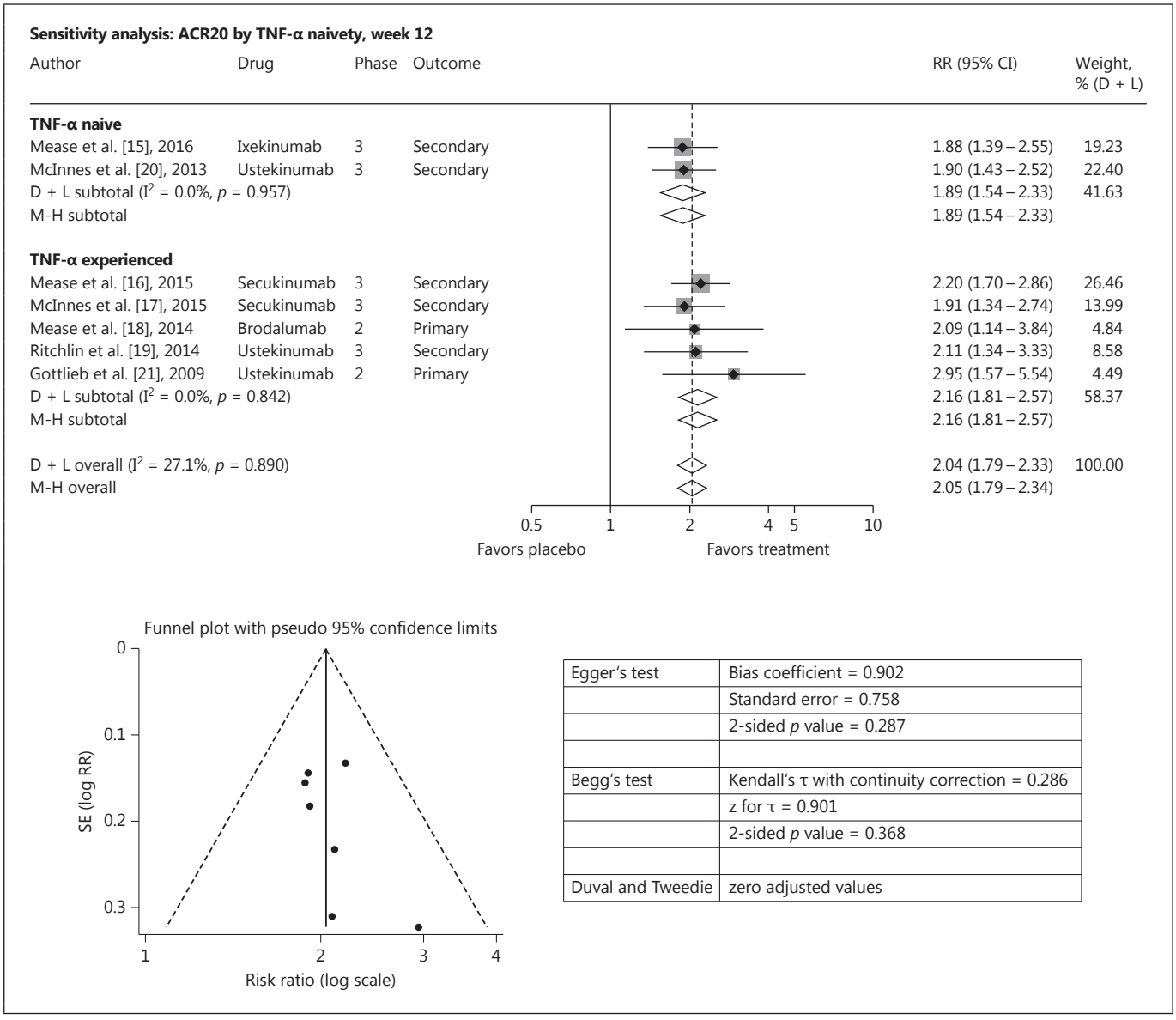
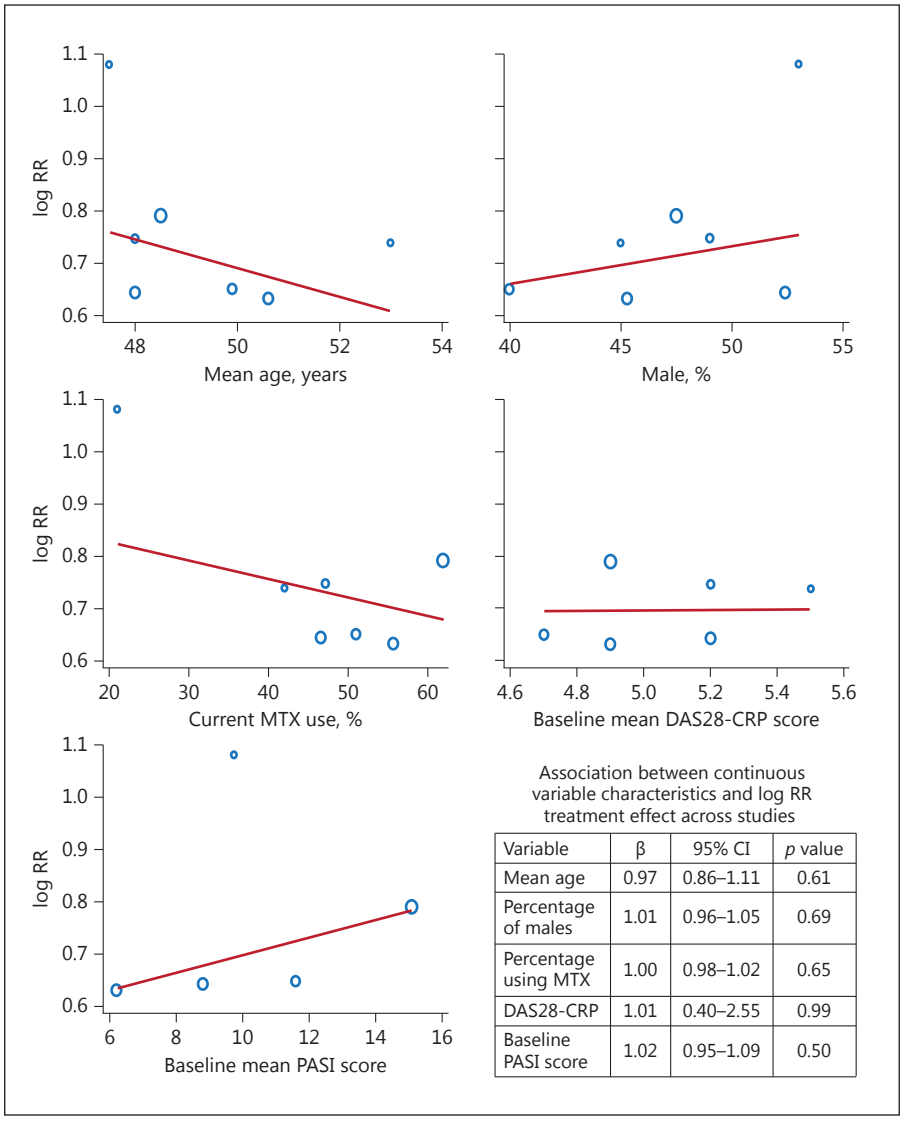


Fig. 5. Sensitivity analysis and publication bias (funnel plot and statistical tests; Th17 inhibitors vs. placebo) for ACR20 response at week 12. D + L, DerSimonian and Laird random effects method; M-H, Mantel-Haenszel fixed effects method.

17A is the dominant cytokine involved in inflammatory manifestations seen in psoriasis and PsA [3]. The Th17 pathway is important as an antimicrobial defense mechanism for extracellular infections including fungal infections while the Th1 pathway is involved in combating intracellular infections such as tuberculosis [22]. In the quiescent state, it is important for the function of epithelium of the small intestine [23, 24]. In inflammatory states, Th17 cells produce high amounts of IL-17A and IL-22 with the inflammatory response largely driven by IL-17A resulting in characteristic inflammation of synovium (enthesitis) and bone erosion seen in PsA and skin lesions seen in psoriasis [23, 24]. IL-23 is involved in the differentiation of Th17 lineage in turn producing potent IL-17A driving the inflammation of the synovium and skin. IL-23 is induced by a variety of factors including microbial antigens, gut microbiome alteration, and HLA-B27 [25]. There has been a steady increase in the development of the number of biologics targeting the Th17 pathway to treat psoriasis and PsA [3].



Association between continuous variable characteristics and log RR treatment effect across studies

Variable	β	95% CI	*p* value
Mean age	0.97	0.86–1.11	0.61
Percentage of males	1.01	0.96–1.05	0.69
Percentage using MTX	1.00	0.98–1.02	0.65
DAS28-CRP	1.01	0.40–2.55	0.99
Baseline PASI score	1.02	0.95–1.09	0.50

Fig. 6. Meta-regression analysis investigating the association of continuous baseline characteristics and the log relative risk (RR) treatment effect across studies (ACR20 response at week 12). MTX, methotrexate; DAS28-CRP, Disease Activity Score in 28 joints/C-reactive protein; PASI, Psoriasis Area Severity Score.

The European League against Rheumatism recommendations for clinical management of active PsA [26] for mild disease without features of axial involvement is symptomatic treatment with NSAIDs only, whereas oral methotrexate 15–25 mg/week remains the choice for first-line nonbiologic DMARDs for those who fail NSAID treatment with or without local corticosteroid injections. Inadequate response after at least 12 weeks of DMARD treatment for moderate to severe disease warrants first-line biologic treatment, usually a TNF-α antagonist such as adalimumab or infliximab. Failure to respond to 1 TNF-α antagonist is usually approached by changing to an alternative TNF-α antagonist such as etanercept. Failure to both or intolerance or contraindication to TNF-α antagonist is now recommended to be treated with secukinumab, an IL-17A inhibitor, or ustekinumab (IL-12/23p40 inhibitor) which are the 2 FDA-approved biologics targeting the Th17 pathway for PsA till date [26].

Summary of Evidence

This systematic review incorporates evidence from the most recent study published for ixekizumab (IL-17A inhibitor) in PsA in addition to other biologics targeting this pathway such as secukinumab, ustekinumab and brodalumab, 2 of which are FDA approved for active PsA (secukinumab and ustekinumab). Guselkumab study results for the phase 3 trial in active PsA are expected in early 2017, and hence this trial was not included as the

results were unavailable at the time of the review. No PsA studies were registered specifically for tildrakizumab per searches in clinical trial registries.

We found that patients treated with Th17 inhibitors were 2.04 times more likely to achieve an ACR20 response at week 12 (Fig. 2). The result was consistent across studies for outcomes (ACR50 and ACR70), length of study (weeks 12 and 24), study phase (2 and 3), primary and secondary outcome, mechanism of action (IL-17A binding vs. IL-17 receptor binding vs. IL-12/23p40 subunit targeting), TNF-α naivety, and baseline differences (Fig. 4, 5). Heterogeneity was low demonstrated by I^2 and Q statistic. There was no evidence of publication bias and no studies missing under the Duval and Tweedie trim and fill procedure (Fig. 4). Random and fixed models point estimates and 95% CIs for the combined studies were similar. A detailed Cochrane risk of bias assessment across studies was found to be low risk for selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias (see online suppl. Fig. 1). These were FDA- or EMA-regulated trials following stringent guidelines proposed by the regulatory agencies in line with International Conference on Harmonization - Good Clinical Practice (ICH-GCP) guidelines, and it is therefore expected that the risk of bias was uniformly low across all domains in all 7 studies although there is an inherent bias on account of all studies being industry sponsored that must be considered which were conducted to support registration with regulatory bodies worldwide.

Discontinuation was more frequent in the placebo than in the active group, which may be due to lack of effect and demand for therapy in the placebo group.

The estimates for adverse events of interest, namely infections and serious adverse events, did not differ significantly between the active and the placebo groups (Fig. 4). However, since side effects are less common compared with treatment effects, even our meta-analysis is underpowered to detect a significant risk. The data, however, do not point at a very high rate of side effects for infections and serious adverse effects from the active treatments. The pooled estimates for candida infections were however higher compared to placebo but the CIs were wide and included the null value. It must be noted that given the function of the cytokines involved in this pathway combating microbial agents including parasites and fungi, the risk of infection, especially candida infection, still exists and is also more relevant for a longer-term treatment and can pose a theoretical risk similar to those of the TNF-α antagonists [27]. This meta-analysis could not evaluate the long-term safety in active PsA because of the shorter placebo-controlled duration of the trials. These results are generalizable to patients with active PsA of moderate to severe disease who have an inadequate response to DMARD and/or an anti-TNFα antagonist and represented patient populations from across the world with a variety of ethnic groups (Table 1 and online suppl. Table 1).

Strengths

The meta-analysis has been timely summarizing evidence from an evolving class of drugs which has the potential to replace TNF-α antagonists as first-line biologic treatment given excellent treatment responses with an acceptable safety and tolerability profile although evidence is for short-term treatment at present. As more data become available from ongoing studies and longer-term studies, a better evaluation can be made about the scope of clinical application for Th17-inhibiting biologic agents.

Our study has considered key prognostic factors including prior exposure to TNF-α antagonists and demonstrated in subgroup analysis that the overall direction of treatment effect was unchanged irrespective of prior exposure to TNF-α antagonists which is important given the interest to evaluate these agents earlier in the course of the disease.

While meta-analysis has been performed for this class of drugs for psoriasis based on current evidence, a comprehensive meta-analysis addressing the role of this evolving class of biologics was lacking for active PsA. Existing meta-analyses looked at biologics in general rather than Th17-targeting drugs as a distinct class although there are reviews published [3, 28].

We showed in the meta-analyses that despite underlying differences which could potentially impact the treatment effect in patient, design, and outcome characteristics, the effect sizes were similar in both random and fixed effect models but not identical across studies. This was especially relevant in the setting of combining different doses and regimens for each Th17 inhibitor, and similar effect estimates between the random and fixed effects models with low heterogeneity demonstrated that combining different doses and regimens was not a source of significant heterogeneity.

Limitations

Most of the studies included placebo as the comparator, and head-to-head comparisons were limited. Hence, direct evidence of relative efficacy of Th17-targeting biologics to first-line biologics targeting TNF-α was not investigated which could have provided a more valuable

evidence for evaluating these agents as first-line biologic treatment for active PsA. Also, insufficient outcome data on other aspects of PsA, such as enthesitis, dactylitis, or axial involvement, hamper the comparison of the different modalities on these manifestations, which are also a relevant part of the disease. Moreover, long-term treatment effect, durability of response, radiological improvement, and long-term safety profile could not be assessed due to the limited placebo-controlled duration of trials and crossover to active treatment. Given the low number of studies in the meta-analysis, the power to detect publication bias by Egger's and Begg's tests may be low.

While a network meta-analysis would have been ideal to assess relative efficacy through indirect comparisons amongst Th17 inhibitors and/or anti-TNF biologics, it was not feasible as most studies were designed to evaluate the efficacy of Th17 agents compared to placebo and the assumptions underlying a network meta-analysis were untestable. There were also not enough trials to warrant a network analysis.

Conclusions

Biologics targeting the Th17 axis produce a clinically significant improvement in joint disease activity for patients with moderate to severe active PsA with an acceptable safety and tolerability profile for short-term treatment (12–24 weeks) compared to placebo. Trials designed to compare head to head different Th17 agents with TNF-α antagonists are necessary to build more evidence for recommending these agents as first-line biologic treatment of active PsA.

Key Message

In active psoriatic arthritis, Th17 inhibitors produce a clinically significant improvement in joint disease activity.

Acknowledgments

The authors thank Dr. Miguel Hernan, Dr. Brian Healy, and Barbara Dickerman for their support and statistical guidance during the conception and conduct of the systematic review and meta-analysis.

Statement of Ethics

Formal ethical clearance is not warranted as the review uses secondary nonconfidential data from published/unpublished studies. Further, as a review, it does not directly involve any direct intervention with patients.

Disclosure Statement

G.S.N. was previously employed with Biocon. L.E.K. has received fees for speaking and consultancy from Pfizer, AbbVie, Amgen, UCB, Celgene, BMS, MSD, Biogen, Novartis, Eli Lilly, and Janssen Pharmaceuticals.

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