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Review

Anti-interleukin-13, a Monoclonal Antibody, in Uncontrolled Asthma : Systematic Review and Meta-analysis

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Abstract : The overall efficacy and safety of anti-interleukin (IL)-13 therapies remain to be fully characterized. We conducted a meta-analysis of randomized controlled trials (RCTs) on the efficacy and safety of anti-IL-13 therapies compared with placebo in patients with uncontrolled asthma. This meta-analysis complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The primary efficacy outcome was pulmonary function, and the primary safety outcome was the incidence rate of all adverse events (AAEs). Secondary outcomes included asthma exacerbation, asthma control, and asthma-related quality of life (QoL). Pooled estimates are presented as mean differences (MDs), hazard ratios (HRs) or risk ratios (RRs) with 95% confidence intervals (CIs). Five RCTs of anti-IL-13 therapies, including tralokinumab, GSK679586, or lebrikizumab, met the criteria for study inclusion. The overall MD for change in forced expiratory volume in 1 second was 0.08 (95% CI 0.02, 0.15). The RR for the incidence of AAEs compared with placebo was 1.03 (95% CI 0.86, 1.25). The time to first exacerbation improved significantly in the anti-IL-13 compared with placebo group (HR 0.69 ; 95% CI 0.55, 0.87). Analysis of asthma control and asthma-related QoL revealed significant improvements in the Asthma Control Questionnaire-6 and Asthma Quality of Life Questionnaire scores among anti-IL-13-compared with placebo-treated patients, with MDs of −0.17 (95% CI −0.29, −0.04) and 0.19 (95% CI 0.08, 0.31), respectively. These results strongly indicate that anti-IL-13 therapies are effective and generally well tolerated in patients with uncontrolled asthma.

Key words : asthma, GSK679586, interleukin-13, tralokinumab, lebrikizumab

Introduction

Increased global use of inhaled corticosteroids (ICS) has contributed to a significant reduction in the frequency of hospitalization for acute exacerbations in patients with bronchial asthma[1,2]. However, many patients do not achieve optimal asthma control despite a combination of ICS and other anti-asthma medications, including systemic glucocorticoids[3]. There is currently an unmet

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medical need for further treatment options for these patients with uncontrolled asthma[1–3].

Recently, humanized monoclonal antibodies (mAb) targeting inflammatory signaling and downstream pathways, such as anti-IgE mAb or anti-interleukin (IL)-5 mAb, have become available[4,5]. These agents are now considered to be the cornerstone of therapeutic options in asthma treatment[2,6].

Emerging and potential therapeutic targets include IL-13, which mediates many features of allergic inflammation associated with pulmonary diseases, such as goblet cell metaplasia, airway hyper-responsiveness, and mucus hypersecretion, which cause airway obstruction[4,7].

Phase 3 studies have revealed that lebrikizumab, an IgG4 humanized mAb that binds IL-13 with high affinity, significantly improves pulmonary function and asthma-related quality of life (QoL) compared with placebo in uncontrolled asthma[8]. Moreover, in that study, the frequency of drug-related adverse events was similar between lebrikizumab and placebo[8]. Based on these results, lebrikizumab is now expected to be an effective and well-tolerated treatment option for patients with uncontrolled asthma. However, randomized controlled trials (RCTs) of anti-IL-13 therapies, such as lebrikizumab, tralokinumab (an IL-13-specific human mAb that binds to and neutralizes IL-13), and GSK679586 (a humanized mAb that inhibits IL-13 binding to both IL-13 receptor $\alpha 1$ and $\alpha 2$), have reported mixed results regarding safety and efficacy outcomes; this is due, in part, to differences in asthma severity or inclusion criteria among the studies[8–10]. Therefore, the overall efficacy and safety of anti-IL-13 therapeutic agents have not been fully evaluated and data remain limited.

A recent meta-analysis assessed the overall efficacy and safety of anti-IL-13 therapeutic agents, including lebrikizumab and other agents, such as GSK679586 and tralokinumab[11]. That study highlighted the overall efficacy and safety of anti-IL-13 therapies in asthma patients; however, the severity of asthma varied among the RCTs included in that meta-analysis[11]. In our view, a meta-analysis of RCTs targeting patients with uncontrolled or moderate to severe asthma is essential to evaluate the efficacy and safety profiles of anti-IL-13 therapies because these therapeutic options are required primarily for patients with refractory asthma.

The aim of the present meta-analysis of RCTs was to compare the efficacy and safety profiles of anti-IL-13 therapies with those of placebo in patients with uncontrolled asthma.

Methods

Literature search

A meta-analysis of RCTs was conducted to investigate the efficacy and safety of anti-IL-13 therapies compared with placebo in patients with uncontrolled asthma. The meta-analysis complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[12,13]. A literature search was conducted in MEDLINE (PubMed), Scopus, and the Cochrane Library database (up to July 2017) using the terms "tralokinumab", "lebrikizumab", "GSK679586", and "asthma". PubMed was primarily used for the publication search because it is an open access database suitable for comprehensive literature searches. Scopus was used to ensure that all eligible articles were detected in PubMed. The Cochrane Library database was

also searched for additional references. No restrictions were imposed on the search language. Additional relevant articles in the reference lists of the articles retrieved were also identified. The electronic databases were independently searched by two investigators (KA and AT). In the case of discrepancies between the two investigators, a third investigator (HS) performed an additional evaluation, or the discrepancies were resolved by discussion with the research team.

Inclusion and exclusion criteria

Studies were considered eligible for inclusion in the present meta-analysis if they met the following criteria: 1) RCTs assessing the clinical efficacy and safety of tralokinumab, lebrikizumab, or GSK679586 in adolescents or adults aged ≥ 12 years with a diagnosis of uncontrolled, severe, or moderate to severe asthma; and 2) studies with outcomes including pulmonary function, any adverse event, asthma exacerbations, asthma control, or asthma-related QoL. Observational, case-control, cohort, and non-blinded clinical trials were excluded. All references were independently screened by KA and AT, in accordance with the inclusion and exclusion criteria.

Data extraction

Data from eligible studies were extracted on the basis of the predefined criteria from articles included in the present meta-analysis. The predefined primary efficacy outcome was pulmonary function, assessed by changes in forced expiratory volume in 1 second ($FEV_{1.0}$). The predefined primary safety outcome was the incidence rate of all adverse events. The predefined secondary outcomes included asthma exacerbations, asthma control, and asthma-related QoL assessed by time to first exacerbation, change in Asthma Control Questionnaire-6 (ACQ-6) score[14], and change in Asthma Quality of Life Questionnaire (AQLQ) score[15], respectively. If efficacy outcomes in studies were compared among patients divided into groups with high and low levels of biomarkers, only patients in the high biomarker groups were included in the present meta-analysis. If efficacy outcomes were compared among patients treated with high and low doses of anti-IL-13 therapies, only patients in the high-dose groups were included in the present meta-analysis.

Risk of bias assessments

Cochrane-recommended methodology[16] was used to examine each study included in the present meta-analysis for the following: random sequence generation; allocation concealment; blinding of participants, personnel, or outcome assessment; incomplete outcome data; selective reporting; and other forms of potential bias. The methodological quality of the included trials was also evaluated using the Jadad score, which grades studies based on their randomization, blinding, and dropout results[17].

Statistical analysis

Statistical heterogeneity among the trials was assessed using the I^2 statistic[18], which measures the degree of heterogeneity in outcome measures by calculating the percentage of the

total variation among the studies included, with values of 50% or higher indicating significant heterogeneity. The significance of heterogeneity was tested using χ^2 statistics. Random effects models[19] were planned regardless of the presence of statistically significant heterogeneity.

Differences in the efficacy and safety outcomes between the anti-IL-13 therapy and placebo groups were assessed, and pooled estimates are presented as the mean difference (MD; change in $FEV_{1.0}$, change in ACQ-6, and chance in AQLQ), risk ratios (RRs; incidence of any adverse events), and hazard ratios (HRs; time to first asthma exacerbation) with 95% confidence intervals (CIs). Subgroup analysis by anti-IL-13 agent for primary efficacy outcome (change in $FEV_{1.0}$) was also performed. Publication bias was evaluated by a funnel plot and statistical analysis was performed using Egger's test[20]. All *p*-values are two-sided and $p < 0.05$ was considered significant. All analyses were performed using RevMan (version 5.3; Cochrane Corporation, Oxford, UK) and STATA (version 14.0; Stata Corp., College Station, TX, USA).

Results

Study selection, Jadad scores, and study characteristics

The study selection process is shown in Fig. 1. In all, 109 articles were identified during the literature search: 52 were retrieved from PubMed, 46 were retrieved from Scopus, and 11 were retrieved from the Cochrane Library database. Of these, seven records remained after duplicates were removed. Based on screening of the title/abstract and full text, four reports with a total of

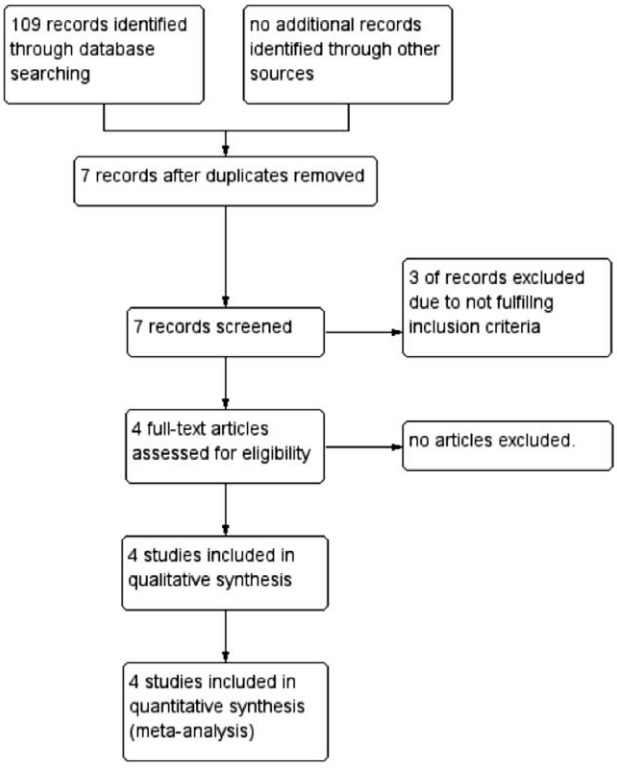

Fig. 1. Study selection process

1,702 randomized patients (intention to treat population) were ultimately included in the present meta-analysis. Of these, one reported the results of two independent RCTs; therefore, five RCTs were finally included in this meta-analysis[8-10, 21]. One study compared outcomes between a high biomarker group (serum periostin ≥ 50 ng/ml or blood eosinophil count ≥ 300 cells/μl), a low biomarker group (serum periostin < 50 ng/ml and blood eosinophil count < 300 cells/μl), and a placebo group[8]. According to the predefined inclusion criteria for the present study, only the high biomarker group and placebo group were included in the meta-analysis.

For all studies in the present meta-analysis, the exclusion criteria included a history of current or former smoking, treatment with maintenance oral corticosteroids, pregnancy, and recent parasitic infection. Two studies were assigned a Jadad score of 5[8, 10], one was assigned a score of 4[21], and one was assigned a score of 3[9], establishing the high quality of these studies. The study characteristics are listed in Table 1.

Risk of bias

The risk of study bias was evaluated on the basis of random sequence generation (selection bias); allocation concealment (selection bias); blinding of participants (performance bias), personnel, and outcome assessment (detection bias); incomplete outcome data (attrition bias); selective reporting (reporting bias); and other forms of potential bias. Each study was considered to have a low risk of bias for all factors, except for detection bias in two studies[9, 21] and performance bias in one study[9]. The authors' determinations of these assessments are shown in Fig. 2.

Primary efficacy outcome

Pulmonary function assessed by change in $FEV_{1.0}$

Pulmonary function was assessed by changes in $FEV_{1.0}$ in five RCTs[8-10, 21]. In one study, efficacy outcomes were compared between patients with high and low biomarker levels[8]; in this case, only patients in the high biomarker group were included in the present meta-analysis. A further study assessed efficacy outcomes of tralokinumab, comparing administration of the drug every 2 and 4 weeks[10]; patients treated with tralokinumab every 2 weeks were included in the present meta-analysis. There was significant inter-study heterogeneity, measured by the I^2 statistic, and all analyses in the present study were performed using the random-effect model. The results of the present meta-analysis of anti-IL-13 therapies revealed a significant improvement in pulmonary function, as assessed by changes in $FEV_{1.0}$, compared with placebo (MD 0.08; 95% CI 0.02, 0.15). Subgroup analysis of tralokinumab and lebrikizumab also revealed a significant improvement in pulmonary function, as assessed by changes in $FEV_{1.0}$, compared with placebo (MD 0.13 [95% CI 0.06, 0.13] and 0.10 [95% CI 0.05, 0.15], respectively; Fig. 3). However, subgroup analysis of GSK679586 revealed that there was no significant improvement in pulmonary function, as assessed by changes in $FEV_{1.0}$, compared with placebo (MD −0.04; 95% CI −0.12, 0.04; Fig. 3).

Table 1. Characteristics of the studies included in the present meta-analysis

Reference	Study design	Groups	Dosage and administration	No. subjects enrolled (M/F)	Mean age (years)	Severity of asthma	Study duration (weeks)	Jadad score
Piper *et al*[21]	RCT (4 arms)	TLK-600 mg	600 mg TLK, s.c., e2w	48 (20/28)	49.8	Moderate to severe uncontrolled	13	4
		TLK-300 mg	300 mg TLK, s.c., e2w	51 (15/36)	48.7			
		TLK-150 mg	150 mg TLK, s.c., e2w	47 (28/19)	43.4			
		TLK-combined*	—	146 (63/83)	47.4			
		Placebo*	Placebo, s.c., e2w	48 (15/33)	47.2			
De Boever *et al*[9]	RCT (2 arms)	GSK679586*	10 mg/kg GSK, i.v. 3om	99 (48/51)	51	Severe	24	3
		Placebo*	Placebo, i.v. 3om	99 (50/49)	51			
Brightling *et al*[10]	RCT (3 arms)	TLK-E2W*	300 mg TLK, s.c., e2w	150 (50/100)	49.7	Severe uncontrolled	48 or 50	5
		TLK-E4W	300 mg TLK, s.c., e4w	151 (51/100)	50.5			
		Placebo*	Placebo, s.c., e2w or e4w	151 (54/97)	50.3			
Hanania *et al* (LAVOLTA 1)[8]	RCT (6 arms)	LRK-125 mg-BH*	125 mg LRK, s.c., e4w	255 (NR/NR)	NR	Uncontrolled	52	5
		LRK-37.5 mg-BH	37.5 mg LRK, s.c., e4w	251 (NR/NR)	NR			
		Placebo-BH*	Placebo, s.c., e4w	256 (NR/NR)	NR			
		LRK-125 mg-BL	125 mg LRK, s.c., e4w	104 (NR/NR)	NR			
		LRK-37.5 mg-BL	37.5 mg LRK, s.c., e4w	109 (NR/NR)	NR			
		Placebo-BL	Placebo, s.c., e4w	106 (NR/NR)	NR			
Hanania *et al* (LAVOLTA 2)[8]	RCT (6 arms)	LRK-125 mg-BH*	125 mg LRK, s.c., e4w	251 (NR/NR)	NR	Uncontrolled	52	5
		LRK-37.5 mg-BH	37.5 mg LRK, s.c., e4w	257 (NR/NR)	NR			
		Placebo-BH*	Placebo, s.c., e4w	247 (NR/NR)	NR			
		LRK-125 mg-BL	125 mg LRK, s.c., e4w	106 (NR/NR)	NR			
		LRK-37.5 mg-BL	37.5 mg LRK, s.c., e4w	99 (NR/NR)	NR			
		Placebo-BL	Placebo, s.c., e4w	107 (NR/NR)	NR			

F, female; M, male; RCT, randomized controlled trial; TLK, tralokinumab; e2w, every 2 weeks; e4w, every 4 weeks; GSK, GSK679586; i.v. 3om, three once-monthly intravenous infusions; LRK, lebrikizumab; NR, not reported; BH, biomarker high; BL, biomarker low; *, groups included in the present meta-analysis.

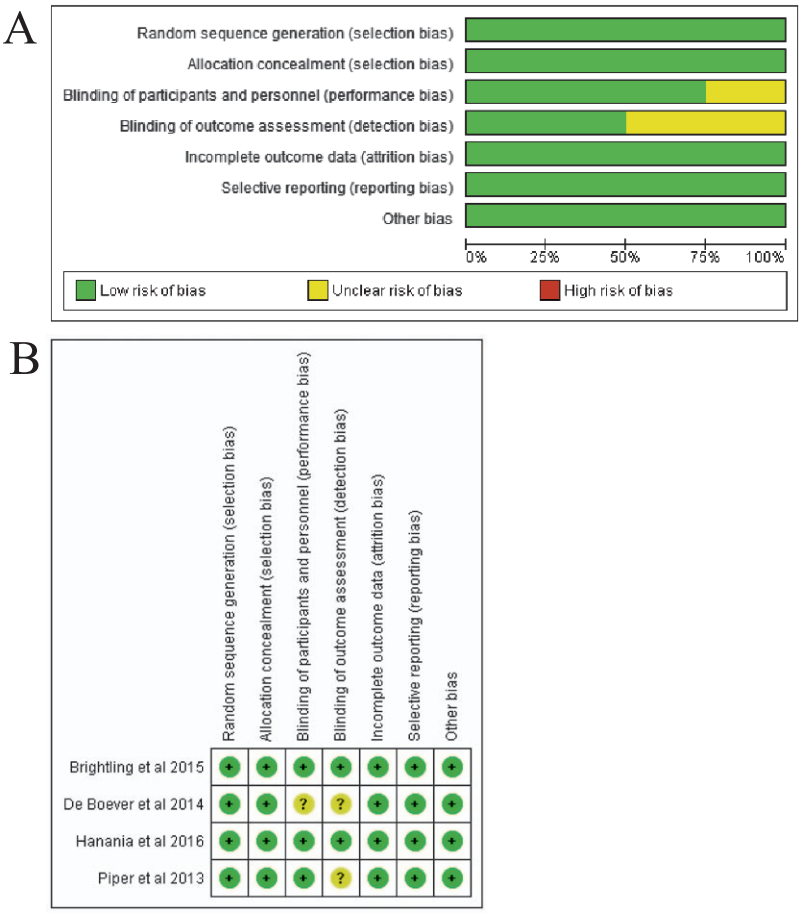

Fig. 2. Bias assessment summary. (A) Risk of bias graph showing author judgments of risk of bias items, presented as percentages in each study included. (B) Risk of bias summary showing author judgment of risk of bias items for each study included.

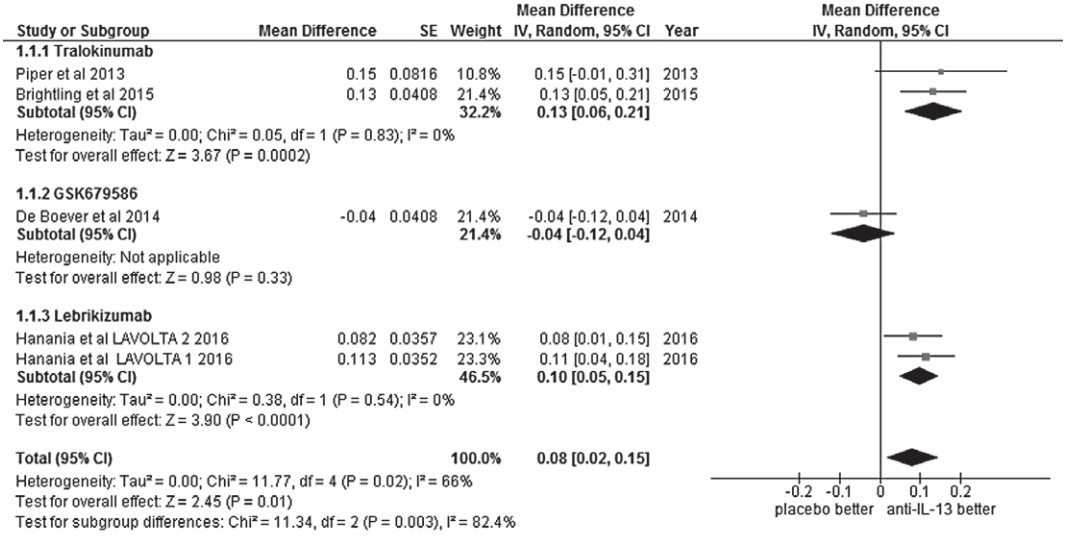

Fig. 3. Forest plots of pulmonary function, assessed as mean differences in the change in forced expiratory volume in 1 second ($FEV_{1.0}$), in patients treated with anti-interleukin (IL)-13 therapies and placebo. SE, standard error ; CI, confidence interval.

Primary safety outcome

All adverse events

The incidence of all adverse events was assessed in three RCTs[8–10]. There was no significant inter-study heterogeneity, as measured using the I^2 statistic, and all analyses in the present study were performed using the random-effect model. There were no significant differences between anti-IL-13 therapies and placebo in terms of the incidence rate of all adverse events (RR 1.03; 95% CI 0.86, 1.25; Fig. 4).

Secondary outcomes

Asthma exacerbation

Two RCTs assessed efficacy in terms of the prevention of asthma exacerbations, measured as time to the first exacerbation[8]. The two studies compared outcomes between patients with high and low levels of biomarkers[8], but only the high biomarker groups were included in the present meta-analysis. Furthermore, high and low doses of lebrikizumab were compared in those studies[8], but only patients treated with high-dose tralokinumab were included in the present meta-analysis. There was no significant inter-study heterogeneity, as measured using the I^2 statistic, and all analyses in the present study were performed using the random-effect model. The results of the present meta-analysis of anti-IL-13 therapies revealed a significant reduction in asthma exacerbations, as assessed by time to first exacerbation, compared with placebo (HR 0.69; 95% CI 0.55, 0.87; Fig. 5).

Asthma control (changes in ACQ-6 scores)

Asthma control was assessed by changes in ACQ-6 scores in three RCTs[9, 10, 21]. There was no significant inter-study heterogeneity, measured using the I^2 statistic, and all analyses in the present study were performed using the random-effect model. The results of the present meta-

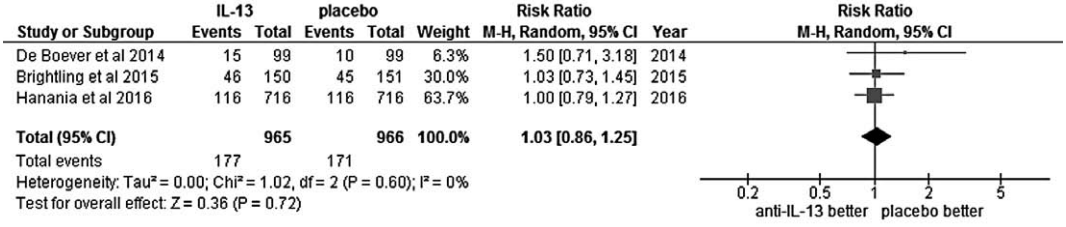

Fig. 4. Forest plots of the risk ratio of all adverse events between patients treated with anti-interleukin (IL)-13 therapies and placebo. CI, confidence interval.

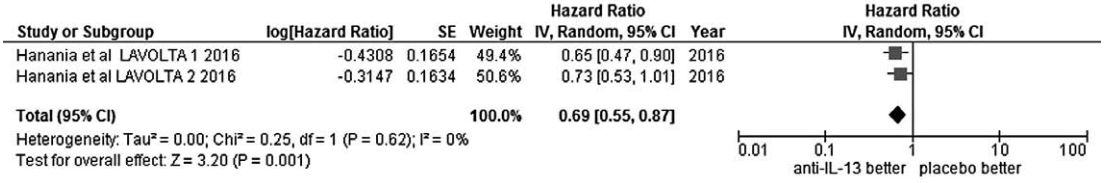

Fig. 5. Forest plots of hazard ratios of time to first asthma exacerbation in patients treated with anti-interleukin (IL)-13 therapies and placebo. CI, confidence interval.

analysis of anti-IL-13 therapies revealed a significant improvement in asthma control, as assessed by changes in ACQ-6 scores, compared with placebo (MD −0.17; 95% CI −0.29, −0.04; Fig. 6).

Asthma-related QoL (changes in AQLQ scores)

Asthma-related QoL was assessed by changes in AQLQ scores in three RCTs[9,10,21]. There was no significant inter-study heterogeneity, measured using the I^2 statistic, and all analyses in the present study were performed using the random-effect model. The results of the present meta-analysis of anti-IL-13 therapies revealed a significant improvement in asthma-related QoL, as assessed by changes in AQLQ scores, compared with placebo (MD 0.19; 95% CI 0.08, 0.31; Fig. 7).

Publication bias

Four studies evaluated differences in changes in $FEV_{1.0}$ between patients receiving anti-IL-13 therapies and those receiving placebo[8–10,21], with Egger's funnel plot suggesting no publication bias ($p = 0.816$; Fig. 8). Similarly, Egger's funnel plot indicated no publication bias for any of the other outcomes (all $p > 0.05$; data not shown); therefore, the results of the meta-analysis are considered valid.

Discussion

In the present meta-analysis, the efficacy of anti-IL-13 therapies (in terms of pulmonary function) and their safety from all adverse events were compared with placebo. The aim of this meta-analysis was to assess the overall efficacy and safety of anti-IL-13 therapies.

The results of the analysis indicate that pulmonary function improved significantly following

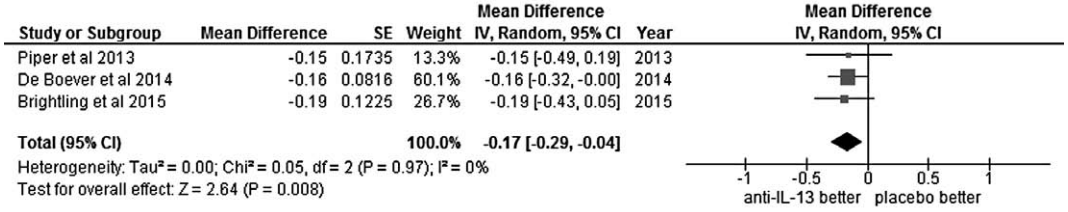

Fig. 6. Forest plots of asthma control, as assessed by the Asthma Control Questionnaire-6 (ACQ-6) score in patients treated with anti-interleukin (IL)-13 therapies and placebo. CI, confidence interval.

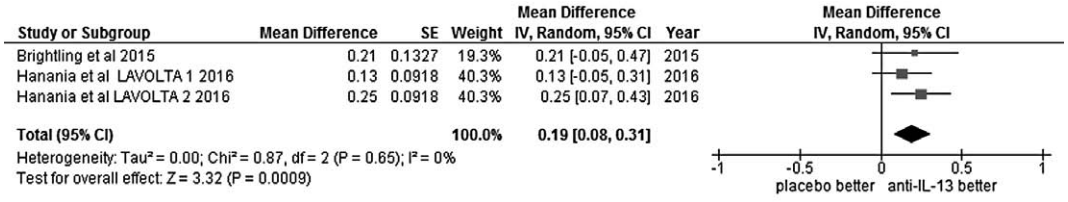

Fig. 7. Forest plots of asthma-related quality of life, as assessed by the Asthma Quality of Life Questionnaire (AQLQ) in patients treated with anti-interleukin (IL)-13 therapies and placebo. CI, confidence interval.

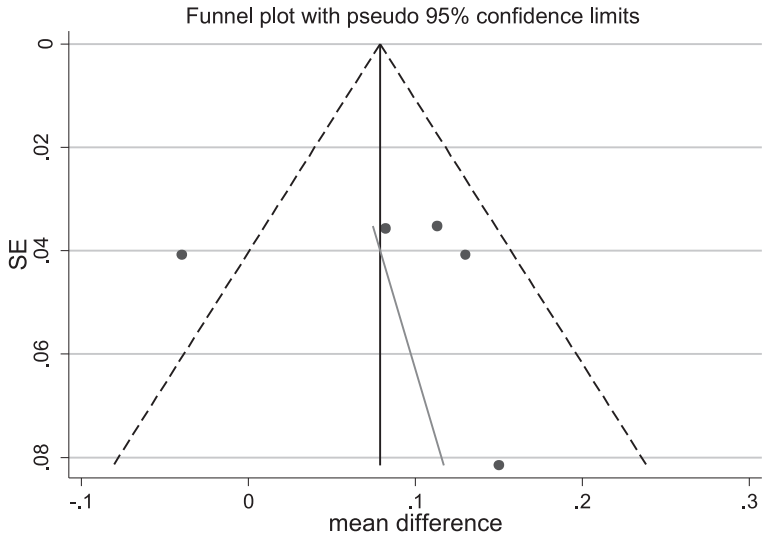

Fig. 8. Egger's funnel plot of the five studies evaluated in the present meta-analysis investigating the effects of anti-interleukin (IL)-13 therapies and placebo on changes in forced expiratory volume in 1 second ($FEV_{1.0}$). SE, standard error.

treatment with anti-IL-13 therapies compared with placebo. Subgroup analysis also demonstrated that the risk of deteriorating pulmonary function was significantly reduced and that pulmonary function improved significantly with tralokinumab and lebrikizumab, whereas there were no significant differences in pulmonary function between patients treated with GSK679586 and those receiving placebo.

There was no significant difference in the incidence of all adverse events between the anti-IL-13- and placebo-treated groups.

Secondary outcome analyses revealed that, compared with patients receiving placebo, asthma exacerbations were significantly reduced and asthma control and asthma-related QoL improved significantly among patients treated with anti-IL-13 therapies.

Previous RCTs and meta-analyses of anti-IL-13 therapies have shown mixed results regarding efficacy outcomes; these apparent discrepancies are the result of differences among studies in asthma severity and definitions of complications, as well as differences in the dosage and frequency of administration[8–10, 21]. Although only high biomarker or high-dose groups were included in the present meta-analysis, the results of the present study indicate the overall efficacy of these therapies in terms of pulmonary function, prevention of asthma exacerbations, and asthma-related QoL. The difference in ACQ-6 scores detected in the present meta-analysis (−0.17) was statistically, but not clinically, significant. This finding also indicates the efficacy of anti-IL-13 therapies for asthma control. The findings of the present study strongly support the use of anti-IL-13 therapies as an effective option for patients with uncontrolled asthma.

Regarding safety outcomes, the results of the present meta-analysis showed no significant differences in the incidence of all adverse events between the anti-IL-13 and placebo groups. This supports the overall safety of anti-IL-13 therapies.

To the best of our knowledge, the present study is the first meta-analysis to compare the efficacy and safety profiles of anti-IL-13 therapies and placebo in patients with uncontrolled asthma. We found that anti-IL-13 therapy was effective and generally well tolerated. In addition, the present analysis reports a novel finding, namely that pulmonary function, as assessed by $FEV_{1.0}$, improved significantly in the tralokinumab- and lebrikizumab-treated groups compared with placebo, but not in patients treated with GSK679586.

The present study has several limitations that should be taken into consideration. First, only published studies were considered, and it is possible that publication bias may be present, although this was not apparent in the funnel plot. Second, a meta-analysis is a form of retrospective research that is subject to the same methodological limitations as retrospective studies. For example, all five studies included in the present meta-analysis were supported by a pharmaceutical company, and the authors reported receiving grant support or uncompensated support. Therefore, the source of funding may have influenced outcomes. Moreover, outcome selection bias may have occurred. Third, drug dosage and frequency of administration varied among the studies included in the present meta-analysis. Moreover, the total dosage of anti-IL-13 agents varied, due, in part, to different study durations, and this may have affected the final conclusions. Finally, we only included a small sample of studies (five) in our meta-analysis. Although meta-analyses involving a small sample of studies are not uncommon in orphan diseases, they may be confounded by the presence of heterogeneity.

In conclusion, we assessed the efficacy and safety profiles of anti-IL-13 therapies compared with placebo. The results indicated that pulmonary function improved significantly in the anti-IL-13-treated group compared with placebo, and that there was no significant difference in the incidence of all adverse events between the two groups. These results suggest that anti-IL-13 therapies are effective and generally well tolerated in patients with uncontrolled asthma. Further studies are required to confirm the efficacy and safety profiles of anti-IL-13 therapies in patients with uncontrolled asthma.

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Conflicts of interest disclosure

The authors have no conflict of interest to disclose.

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