

Original

**Effectiveness of Therapeutic Monoclonal Antibodies for
Asthma Control in Uncontrolled Eosinophilic Asthma
—A Meta-analysis of Randomized Controlled Trials—**

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Abstract: The overall efficacy of therapeutic monoclonal antibodies (mAbs) for asthma control in patients with uncontrolled eosinophilic asthma remains to be fully characterized. We conducted a meta-analysis of randomized controlled trials (RCTs) to analyze the efficacies of new therapeutic mAbs, such as anti-interleukin (IL)-13 therapies, anti-IL4/13 therapies, and anti-IL-5 therapies, compared with that of a placebo in patients with uncontrolled asthma. This meta-analysis complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The primary efficacy outcome was asthma control as assessed by Asthma Control Questionnaire (ACQ) scores. Pooled estimates are presented as standardized mean differences (Std MDs) with 95% confidence intervals (CIs). Seven RCTs of therapeutic mAbs, including anti-IL-13, anti-IL-4/13, and anti-IL-5, met the criteria for study inclusion. The overall Std MD of changes in the ACQ score was -0.31 (95% CI, -0.45 to -0.17 ; $P < 0.0001$). These results strongly indicate that therapeutic mAbs are effective in controlling asthma in patients with uncontrolled eosinophilic asthma.

Key words: asthma, therapeutic monoclonal antibodies, interleukin-13, interleukin-4/13, interleukin-5

Introduction

The increased global use of inhaled corticosteroids (ICS) has helped to significantly reduce the frequency of hospitalizations for patients with acute exacerbations of bronchial asthma^{1,2)}. However, many patients do not achieve optimal asthma control despite using a combination of ICS and other anti-asthma medications, including systemic glucocorticoids³⁾. Therefore, there is currently an unmet medical need for further treatment options for patients with uncontrolled asthma¹⁻³⁾.

Recently, humanized therapeutic monoclonal antibodies (mAbs) targeting inflammatory signaling and downstream pathways, such as anti-IgE mAbs or anti-interleukin (IL)-5 mAbs, have

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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 or IL-4/13. These mAbs mediate many features of allergic inflammation associated with pulmonary diseases that cause airway obstruction, such as goblet cell metaplasia, airway hyper-responsiveness, and mucus hypersecretion^{4,7}.

Several phase 2 or 3 studies have revealed that these new therapeutic mAbs, including anti-IL-13, anti-IL4/13, and anti-IL-5 therapies, significantly improve pulmonary function and the incidence of asthma exacerbation compared with a placebo in uncontrolled eosinophilic asthma^{5,8}. Moreover, the frequencies of drug-related adverse events were similar between these therapeutic agents and the placebo. Based on these results, these emerging and potential therapeutic mAbs are now expected to be effective and well-tolerated treatment options for patients with uncontrolled eosinophilic asthma⁵. However, randomized controlled trials (RCTs) of these therapeutic mAbs have reported mixed results regarding their efficacy in asthma control; this is partly due to differences in asthma severity or inclusion criteria among the studies. Therefore, the overall efficacy of these therapeutic agents in asthma control has not been fully evaluated and data remain limited.

In our opinion, a meta-analysis of RCTs targeting patients with inadequately controlled severe or moderate-to-severe eosinophilic asthma is essential for evaluating the efficacy of these therapeutic mAbs in asthma control, as these therapeutic options are required primarily for patients with poor asthma control. Therefore, the aim of the present meta-analysis of RCTs was to compare the overall efficacy of therapeutic mAbs with that of a placebo in patients with uncontrolled eosinophilic asthma.

Materials and methods

Literature search

A meta-analysis of RCTs was conducted to investigate the efficacy of therapeutic mAbs compared with that of a placebo for asthma control in patients with uncontrolled eosinophilic asthma. This meta-analysis complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines^{9,10}. A literature search was conducted in MEDLINE (PubMed), Scopus, and the Cochrane Library database in September 2017. PubMed was used primarily 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. In addition, the Cochrane Library database was searched for additional references. No restrictions were imposed on the search language. Additional relevant articles were identified in the reference lists of the retrieved articles. The electronic databases were searched independently by two investigators (KA and AT). If there were 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) they were RCTs assessing the clinical efficacy of anti-IL-13, anti-IL-4/13, or anti-IL-5 therapies in adolescents or adults aged ≥ 12 years with a diagnosis of uncontrolled or inadequately controlled severe or moderate-to-severe eosinophilic asthma; and 2) the study outcomes included asthma control. Observational, case-control, cohort, and non-blinded clinical trials were excluded. Further exclusion criteria included a history of current or former smoking, treatment with maintenance oral corticosteroids, pregnancy, and recent parasitic infection. 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 from articles based on predefined criteria. The predefined primary outcome was a change in patients' reported asthma control, which was assessed by an asthma control questionnaire (ACQ) score. If the efficacy outcomes in a study were compared between patients divided into groups with high and low levels of biomarkers, only the patients in the high-biomarker group were included in the present meta-analysis. If efficacy outcomes were compared between patients treated with high and low doses of these therapeutic mAbs, only the patients in the high-dose groups were included in the present meta-analysis.

Risk of bias assessments

A Cochrane-recommended methodology¹¹⁾ was used to examine each study included in the present meta-analysis for the following parameters: random sequence generation; allocation concealment; blinding of participants or personnel, or outcome assessment; incomplete outcome data; selective reporting; and other forms of potential bias. The methodological quality of the eligible trials was also evaluated using the Jadad score, which grades studies based on their randomization, blinding, and dropout results¹²⁾.

Statistical analysis

Statistical heterogeneity among the trials was assessed using the I^2 statistic^{13,14)}, which measures the degree of heterogeneity in outcome measures by calculating the percentage of the total variation among the eligible studies. Values of 50% or higher indicated significant heterogeneity. The significance of heterogeneity was tested using χ^2 statistics. Random-effects models^{15,16)} were planned regardless of the presence of statistically significant heterogeneity.

We speculated that different versions of the ACQ may have been used to assess asthma control in the studies included in the present meta-analysis. For example, the ACQ-5, ACQ-6, or ACQ-7 may have been used. Although these questionnaires share a common purpose of assessing asthma control, we cannot statistically integrate the results from different questionnaires. To resolve this problem, we converted the mean differences in the ACQ scores between the therapeutic mAbs groups and placebo groups in the eligible studies to standardized mean differ-

ences (Std MDs). Pooled estimates were presented as Std MDs with 95% confidence intervals (CIs)¹⁷⁾. Subgroup analysis for each individual mAb was also performed. Publication bias was evaluated with a funnel plot, and statistical analysis was performed using Egger's test¹⁸⁾. 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 Figure 1. In all, 468 articles were identified during the literature search: 143 were retrieved from PubMed, 285 were retrieved from Scopus, and 40 were retrieved from the Cochrane Library database. Of these, 33 records remained after duplicates were removed. Based on screening of the title/abstract and full text, six reports with a total of 2,277 randomized patients were ultimately included in the present meta-analysis. Of these, one report included the results of two independent RCTs; therefore, seven RCTs in total were included in this meta-analysis¹⁹⁻²⁴⁾. Three studies compared outcomes between a high-biomarker group, a low-biomarker group, and a placebo group^{19,21,24)}. According to the predefined inclusion criteria for the present study, only the high-biomarker and placebo groups were included in this meta-analysis. Five studies were assigned a Jadad score of 5, and one was assigned a score of 3, establishing the high quality of these studies. The study characteristics are listed in Tables 1 and 2.

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 or personnel (performance bias), 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 one study and performance bias in one study²⁴⁾. Our determinations of these assessments are shown in Figure 2.

Primary efficacy outcome

Asthma control was assessed by an ACQ score in seven RCTs. In two studies, efficacy outcomes were compared between patients with high and low biomarker levels; in these cases, only the patients in the high-biomarker groups were included in the present meta-analysis. There was significant inter-study heterogeneity, as measured by the *I*² statistic, and the analysis in the present study was performed using a random-effects model. Based on the ACQ scores, the results of the present meta-analysis revealed a significant improvement in asthma control following treatment with therapeutic mAbs, with no improvement in the placebo group (Std MD, -0.31; 95% CI, -0.45 to -0.17; *P* < 0.0001). Subgroup analysis of anti-IL-13 therapies, anti-IL-4/13 therapies, and anti-IL-5 therapies based on ACQ scores also revealed significant improvements in asthma

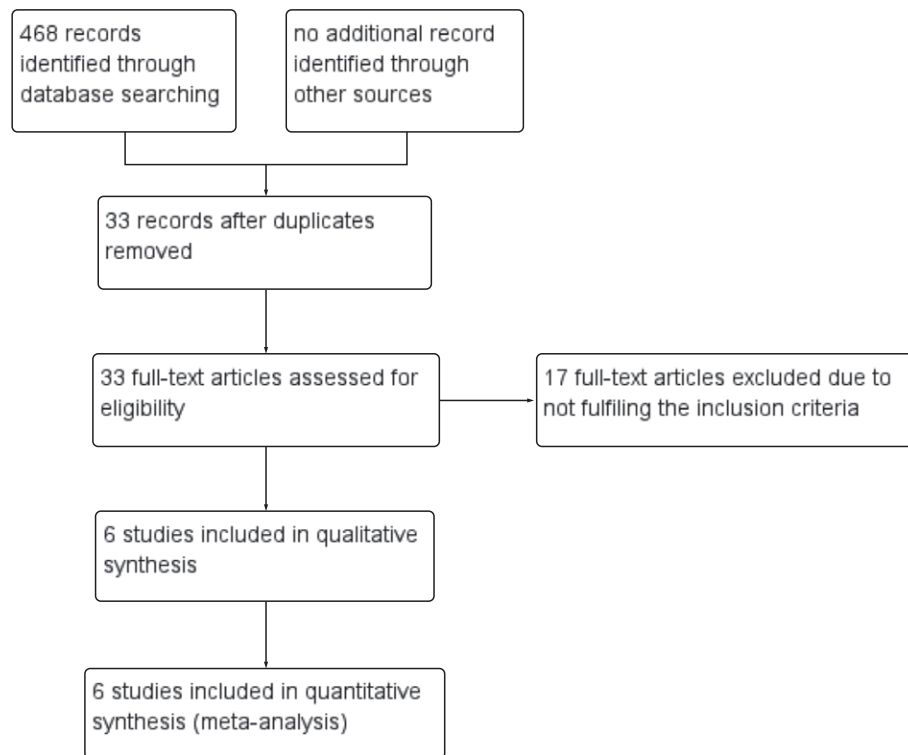


Fig. 1. Study selection process

control compared with the placebo, with Std MDs of -0.13 (95% CI, -0.26 to -0.01 ; $P < 0.003$), -0.57 (95% CI, -0.83 to -0.31 ; $P < 0.0001$), and -0.35 (95% CI, -0.51 to -0.19 ; $P < 0.0001$), respectively (Fig. 3).

Publication bias

Four studies evaluated the differences in the ACQ scores between patients receiving therapeutic mAbs and those receiving a placebo. An Egger's funnel plot suggested that there was no publication bias ($P = 0.173$; Fig. 4); therefore, we consider the results of this meta-analysis to be valid.

Discussion

In the present meta-analysis, we assessed the overall efficacy of therapeutic mAbs compared with that of a placebo in facilitating asthma control in patients with uncontrolled eosinophilic asthma. Our results indicated that asthma control improved significantly following treatment with therapeutic mAbs compared with a placebo treatment. Subgroup analysis also demonstrated that asthma control improved significantly following anti-IL-13, anti-IL-4/13, and anti-IL-5 therapies.

Previous RCTs and meta-analyses of anti-IL-13 therapies have shown mixed results regarding efficacy outcomes. These apparent discrepancies result from inter-study differences in asthma severity and definitions of complications, as well as differences in mAb dosage and frequency of

Table 1. Characteristics of the studies included in the present meta-analysis (continued in Table 2)

Reference (#)	Study design	Groups	Dosage and administration	No. subjects enrolled (M/F)	Mean age (years)	Severity of asthma	Treatment period (weeks)	Outcomes	Jadad Score**
Wenzel <i>et al</i> , 2013 ²⁰	RCT (2 arms)	DPL-300 mg* Placebo*	300 mg DPL, SC, weekly Placebo, SC, e2w	52 (26/26) 52 (26/26)	37.8 41.6	Moderate to severe	12	AE (PE) FEV _{1.0} PEF ACQ-5 NA SABA use	5
Ortega <i>et al</i> , 2014 ²³	RCT (3 arms)	MPZ-75 mg MPZ-100 mg Placebo	75 mg MPZ, IV, e4w 100 mg MPZ, SC, e4w Placebo, e4w	191 (85/106) 194 (78/116) 191 (84/107)	50 51 49	Severe	32	AE (PE) ACQ-5 SGRQ	5
Hanania <i>et al</i> , 2016 (LAVOLTA 1) ²¹	RCT (6 arms)	LBZ-125 mg-BH* LBZ-375 mg-BH Placebo-BH* LBZ-125 mg-BL LBZ-375 mg-BL Placebo-BL	125 mg LRK, SC, e4w 375 mg LRK, SC, e4w Placebo, SC, e4w 125 mg LRK, SC, e4w 375 mg LRK, SC, e4w Placebo, SC, e4w	255 (NR/NR) 251 (NR/NR) 256 (NR/NR) 104 (NR/NR) 109 (NR/NR) 106 (NR/NR)	NR NR NR NR NR NR	Uncontrolled	52	AE (PE) FEV _{1.0} AQLQ ACQ-5	5
Hanania <i>et al</i> , 2016 (LAVOLTA 2) ²¹	RCT (6 arms)	LBZ-125 mg-BH* LBZ-375 mg-BH Placebo-BH* LBZ-125 mg-BL LBZ-375 mg-BL Placebo-BL	125 mg LRK, SC, e4w 375 mg LRK, SC, e4w Placebo, SC, e4w 125 mg LRK, SC, e4w 375 mg LRK, SC, e4w Placebo, SC, e4w	251 (NR/NR) 257 (NR/NR) 247 (NR/NR) 106 (NR/NR) 99 (NR/NR) 107 (NR/NR)	NR NR NR NR NR NR	Uncontrolled	52	AE (PE) FEV _{1.0} AQLQ ACQ-5	5
Corren <i>et al</i> , 2016	RCT (4 arms)	RSZ-3.0 mg/kg-EH* Placebo-EH* RSZ 3.0 mg/kg-EL Placebo-EL	3.0 mg RSZ, IV, e4w Placebo, IV, e4w 3.0 mg RSZ, IV, e4w Placebo, IV, e4w	77 (NR/NR) 19 (NR/NR) 316 (NR/NR) 76 (NR/NR)	NR NR NR NR	Inadequately controlled	16	FEV _{1.0} (PE) ACQ-7 SABA use FVC ACQ-6	3

F, female; M, male; RCT, randomized controlled trial; DPL, dupilumab; SC, administered subcutaneously; e2w, every two weeks; e4w, every four weeks; LBZ, lebrikizumab; NR, not reported; BH, biomarker high; BL, biomarker low; RSZ, reslizumab; IV, administered intravenously; * patient groups included in the present meta-analysis; ** Jadad Score (12); AE, asthma exacerbation; PE, primary endpoint; FEV_{1.0}, forced expiratory volume at 1 second; PEF, peak flow; AQLQ, Asthma Quality of Life Questionnaire; ACQ, Asthma Quality of Life; SABA, short acting beta-2 agonist; FVC, forced vital capacity.

Table 2. Characteristics of the studies included in the present meta-analysis (continued from Table 1)

Reference (#)	Study design	Groups	Dosage and administration	No. subjects enrolled (M/F)	Mean age (years)	Severity of asthma	Treatment period (weeks)	Outcomes	Jadad Score
Wenzel <i>et al</i> , 2016 ⁽¹⁹⁾	RCT (10 arms)	DPL-200 mg-EH	200 mg DPL, SC, e4w	154 (NR/NR)	NR	Moderate to severe	24	FEV _{1.0} (PE)	5
		DPL-300 mg-EH	300 mg DPL, SC, e4w	157 (NR/NR)	NR			AE	
		DPL-200 mg-EH	200 mg DPL, SC, e2w	150 (NR/NR)	NR			ACO-5	
		DPL-300 mg-EH*	300 mg DPL, SC, e2w	157 (NR/NR)	NR			AQLQ	
		Placebo-EH*	Placebo, SC	158 (NR/NR)	NR			FeNO	
		DPL-200 mg-EL	200 mg DPL, SC, e4w	62 (NR/NR)	NR				
		DPL-300 mg-EL	300 mg DPL, SC, e4w	66 (NR/NR)	NR				
		DPL-200 mg-EL	200 mg DPL, SC, e2w	65 (NR/NR)	NR				
		DPL-300 mg-EL	300 mg DPL, SC, e2w	64 (NR/NR)	NR				
		Placebo-EL	Placebo, SC	68 (NR/NR)	NR				
Chupp <i>et al</i> , 2017 ⁽²²⁾	RCT (2 arms)	MPZ 100 mg*	100 mg MPZ, SC, e4w	274 (149/125)	52.1	Severe	24	SGRO (PE)	5
		Placebo*	Placebo, SC	277 (176/101)	49.8			FEV _{1.0} ACO-5 PEF FVC AE	

F, female; M, male; RCT, randomized controlled trial; DPL, dupilumab; SC, administered subcutaneously; e2w, every two weeks; e4w, every four weeks; LBZ, lebrikizumab; NR, not reported; BH, biomarker high; BL, biomarker low; RSZ, reslizumab; IV, administered intravenously; *patient groups included in the present meta-analysis; AE, asthma exacerbation; PE, primary endpoint; FEV_{1.0}, forced expiratory volume at 1 second; PEF, peak flow; AQLQ, Asthma Quality of Life Questionnaire; ACO, Asthma Quality of Life; SABA; short acting beta-2 agonist; FVC, forced vital capacity.

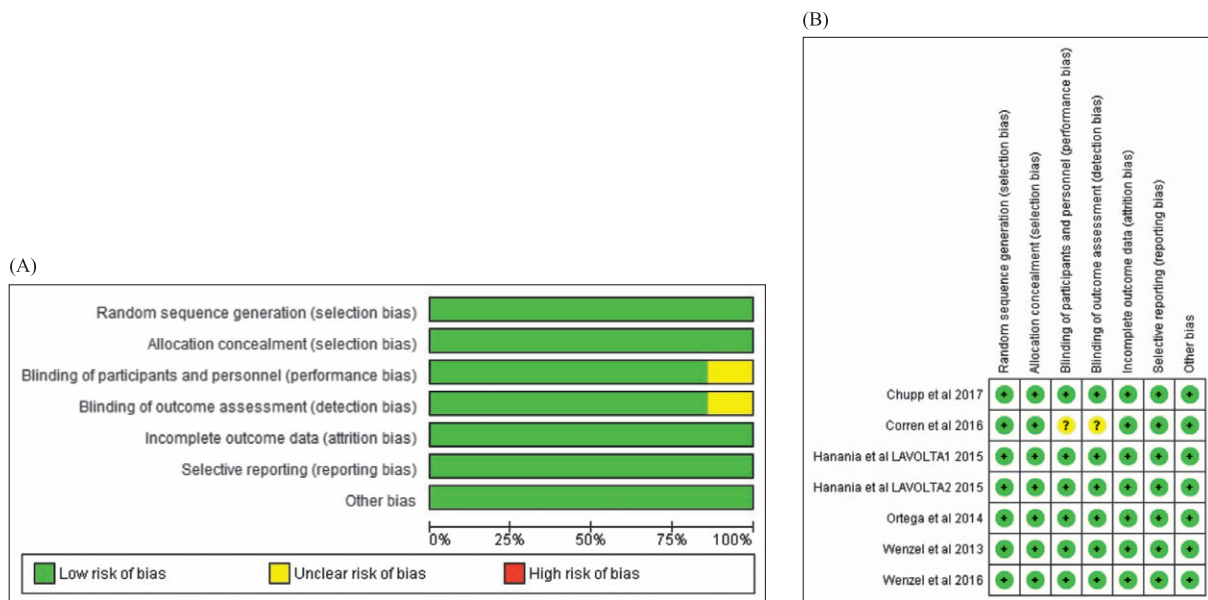


Fig. 2. Bias assessment summary. (A) The risk-of-bias graph presenting the items at risk of bias for each study as percentages, as judged by the authors. (B) The risk-of-bias summary presenting the items at risk of bias for each study, as judged by the authors.

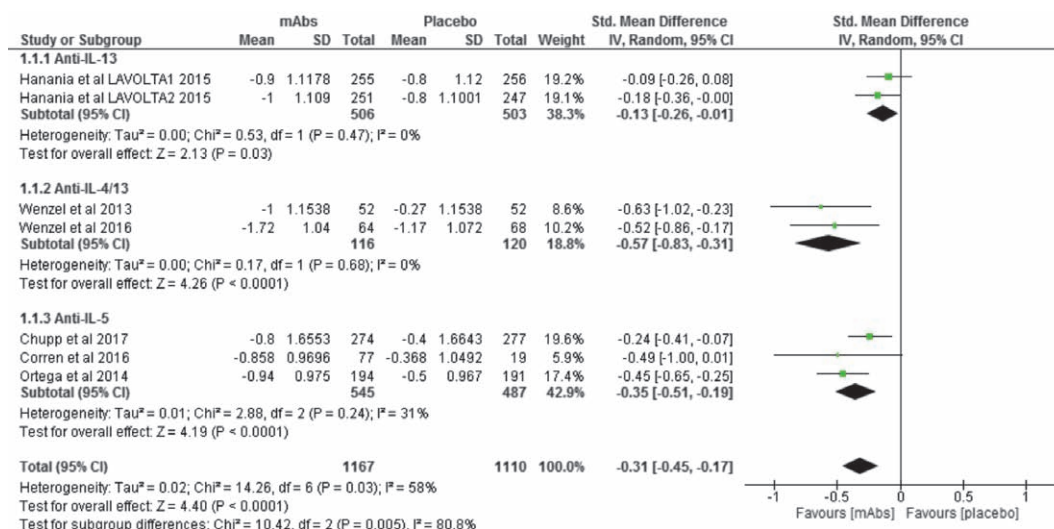


Fig. 3. Forest plots of asthma control, showing the differences in asthma control questionnaire (ACQ) scores assessed as standardized mean differences (Std MD) for patients treated with anti-interleukin (IL)-13, anti-IL-4/13, and anti-IL-5 therapies and a placebo. mAbs, monoclonal antibodies; SE, standard error; CI, confidence interval.

administration. The results of our meta-analysis indicate that anti-IL-13 therapies have an overall positive effect for asthma control. Although the difference in ACQ scores in patients treated with anti-IL-13 therapy in our meta-analysis was statistically but not clinically significant (-0.13 ; $P < 0.003$), this result still indicated that anti-IL-13 therapies are efficacious for asthma control. This is supported by the results of our previous meta-analysis, which revealed that efficacy

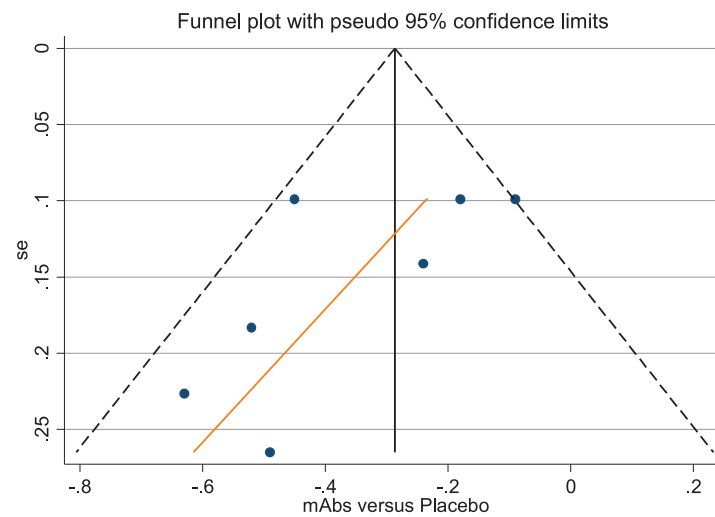


Fig. 4. The funnel plot of Egger *et al*¹⁸⁾ of the seven studies evaluated in the present meta-analysis investigating the effects of therapeutic monoclonal antibodies and a placebo on changes in asthma control questionnaire (ACQ) scores. mAbs, monoclonal antibodies ; SE, standard error.

outcomes, such as pulmonary function, significantly improved in patients treated with anti-IL-13 therapies compared with patients treated with a placebo even though there was no clinically significant difference in ACQ scores between these groups²⁵⁾. The findings of the present study strongly support the use of therapeutic mAbs as an effective treatment option for patients with uncontrolled eosinophilic asthma.

To the best of our knowledge the present study is the first meta-analysis to compare the overall efficacies of therapeutic mAbs against a placebo for asthma control in patients with uncontrolled eosinophilic asthma. We found that treatment with these therapeutic agents was effective in terms of asthma control. However, the present study has several limitations that should be considered. First, only published studies were considered, and it is possible that publication bias may be present, although this was not apparent from the funnel plot results. Second, a meta-analysis is a form of retrospective research that is subject to the same methodological limitations as retrospective studies. For example, all six studies included in the present meta-analysis were supported by a pharmaceutical company, and the authors reported receiving grant support or uncompensated support. Therefore, these sources of funding may have influenced study outcomes. Moreover, outcome selection bias may have occurred. Third, in addition to differences in the therapeutic mAbs used, the drug dosages and frequency of administration varied among the studies included in the present meta-analysis. Furthermore, the total dosages of these therapeutic agents varied, partly due to different study durations, and this may have affected the final conclusions. Fourth, the definition of uncontrolled eosinophilic asthma varied among the studies included in the present meta-analysis. Finally, we only included a small number of

studies (seven) in our meta-analysis. Although meta-analyses involving small numbers of studies are not uncommon in orphan disease research, they may be confounded by the presence of heterogeneity.

In conclusion, we assessed the efficacy of therapeutic mAbs compared with that of a placebo for asthma control. The results indicated that asthma control improved significantly in patients treated with anti-IL-13 compared with those in the placebo group. These results suggest that monoclonal therapies are effective in patients with uncontrolled eosinophilic asthma. Further studies are required to confirm the efficacy profiles of new therapeutic mAbs in patients with uncontrolled eosinophilic asthma.

Funding

None.

Conflicts of interest disclosure

The authors have no conflicts of interest to disclose.

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[Received October 28, 2017 : Accepted January 30, 2018]