

Review

Comparative Efficacy and Safety of Anti-Interleukin-5 Therapies and Placebo in Patients with Uncontrolled Eosinophilic Asthma : A Systematic Review and Meta-analysis of Phase 3 Trials

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Abstract : The overall efficacy and safety of anti-interleukin (IL)-5 therapies at currently recommended dosages and administration remain to be fully characterized. The present study was a meta-analysis of Phase 3 trials of the efficacy and safety of anti-IL-5 therapies at the currently recommended dosages and administration compared with placebo in patients with uncontrolled eosinophilic asthma. This meta-analysis complied with the PRISMA guidelines. The primary efficacy outcome was asthma exacerbation rate, and the primary safety outcomes included the incidence rates of all adverse events, asthma worsening, and injection site reactions. A subgroup analysis was also performed according to the type of anti-IL-5 agent. Pooled estimates are presented as rate ratios or relative risks (RRs) with 95% confidence intervals (CIs). Analyses included intention-to-treat cases. Six randomized controlled trials of anti-IL-5 therapies met the inclusion criteria. The overall rate ratio for asthma exacerbation was 0.54 (95% CI 0.47-0.61). The RRs (95% CIs) for the incidence of all adverse events, asthma worsening, and injection site reactions compared with placebo were 0.93 (0.89-0.96), 0.63 (0.56-0.72), and 1.59 (0.95-2.65), respectively. The subgroup analysis revealed that the incidence of injection site reactions was significantly higher among mepolizumab- than placebo-treated patients, with an RR of 2.56 (95% CI 1.15-5.68). These results suggest that anti-IL-5 therapies at the currently recommended dosages and administration are effective and generally well tolerated in patients with uncontrolled eosinophilic asthma. However, the occurrence of injection site reactions warrants specific attention, especially concerning mepolizumab administration.

Key words : asthma, benralizumab, interleukin-5, mepolizumab, reslizumab

Introduction

Increased global use of inhaled corticosteroids (ICS) has contributed to a significant reduction in the frequency of hospitalization for acute exacerbation in patients with bronchial asthma^{1, 2)}.

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However, there are still many patients whose asthma is not optimally controlled by a combination of ICS and systemic glucocorticoids³⁾. Therefore, there is an unmet medical need for additional treatment options for those patients with uncontrolled asthma¹⁻³⁾.

Previous Phase 3 studies revealed that mepolizumab, an anti-interleukin (IL)-5 monoclonal antibody (mAb), significantly reduced the incidence of asthma exacerbation and improved pulmonary function and patient-reported outcomes compared with placebo in uncontrolled eosinophilic asthma⁴⁻⁶⁾. Moreover, the frequencies of drug-related adverse events with mepolizumab were almost the same as those with placebo. Based on these results, mepolizumab is now considered to be an effective and well-tolerated treatment option for patients with uncontrolled eosinophilic asthma^{7,8)}. Several Phase 3 trials of benralizumab, an anti-IL-5 receptor mAb, and reslizumab, an anti-IL-5 mAb, have been completed, with the results showing that both anti-IL-5 agents are effective and well tolerated in patients with uncontrolled eosinophilic asthma, similar to mepolizumab⁹⁻¹¹⁾. However, the overall efficacy and safety of anti-IL-5 therapeutic agents at recommended dosages and administration has not been completely evaluated and data are lacking.

Several recent meta-analyses assessed the overall efficacy and safety of anti-IL-5 therapeutic agents, including mepolizumab and other agents, such as benralizumab and reslizumab. These studies have highlighted the overall efficacy and safety of anti-IL-5 therapies; however, the dosage and administration of anti-IL-5 therapeutic agents varied among the randomized controlled trials (RCTs) included in these meta-analyses^{12, 13)}. Therefore, we believe that an evaluation of the overall efficacy and safety profiles of anti-IL-5 therapies, at the currently recommended dosages and administration, via a meta-analysis of RCTs is essential to confirm the efficacy and safety of these treatments.

The aim of the present study was to compare the efficacy and safety profiles between anti-IL-5 therapies, at recommended dosages and administration, and placebo in patients with uncontrolled eosinophilic asthma by performing a meta-analysis of Phase 3 RCTs.

Methods

Literature search

The present meta-analysis of Phase 3 trials of the efficacy and safety of anti-IL-5 therapies at currently recommended dosages and administration compared with placebo in patients with uncontrolled eosinophilic asthma complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The MEDLINE (PubMed), Scopus, and Cochrane library databases were searched (up to December 2016) using the terms “mepolizumab”, “reslizumab”, “benralizumab”, and “asthma”. PubMed was primarily used in the search for publications 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 searched for additional references. EMBASE was not searched because it is not available in our institute. No restrictions were imposed on the search language. The reference lists of retrieved articles were also searched to identify any additional relevant publications. The electronic databases were independently searched by two investigators (KA and AT).

When discrepancies occurred between the two investigators, a third investigator (HS) conducted an additional evaluation of the articles in question, or the discrepancies were resolved by discussion within 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) Phase 3 studies that assessed the clinical efficacy and safety of currently recommended dosages and administration of mepolizumab, reslizumab, or benralizumab in adolescents or adults aged ≥ 12 years with a diagnosis of uncontrolled eosinophilic asthma; and 2) studies in which the outcomes included asthma exacerbation, pulmonary function, any adverse event, asthma worsening, injection site reaction, headache, nasopharyngitis, or bronchitis. Observational, case-control, cohort, and non-blinded clinical trials were excluded from the analysis. All references were independently screened by KA and AT in accordance with the inclusion and exclusion criteria. Discrepancies were resolved by a third investigator (HS) or discussion within the research team.

Data extraction

Data from eligible studies were extracted on the basis of the predefined criteria. The predefined primary efficacy outcome was the asthma exacerbation rate. The predefined primary safety outcomes were the incidence rates of all adverse events, asthma worsening, and injection site reaction, because these adverse events have frequently been reported in previous studies of anti-IL-5 therapies. The predefined secondary efficacy outcome was change in forced expiratory volume in 1 s ($FEV_{1.0}$). The predefined secondary safety outcomes were headache, nasopharyngitis, bronchitis, and death, because these adverse events have also been frequently reported in previous studies of anti-IL-5 therapies.

Risk of bias assessments

Cochrane-recommended methodology was used to examine each study included in the present meta-analysis for: random sequence generation; allocation concealment; blinding of the participants, personnel, or outcome assessment; incomplete outcome data; selective reporting; and other forms of potential bias⁷⁾. The methodological quality of the trials included in this analysis was also evaluated using the Jadad score, which grades studies based on their randomization, blinding, and dropout results⁸⁾.

Currently recommended dosages and administration of each anti-IL-5 agent

The currently recommended dosage and administration (referring both of routes of administration and the treatment regimens) of mepolizumab is 100 mg administered subcutaneously every 4 weeks^{4,5)}. For benralizumab and reslizumab, based on previous studies⁹⁻¹¹⁾, the currently recommended dosages and administration are 30 mg administered subcutaneously every 8 weeks and 3 mg/kg, i.v., every 4 weeks, respectively.

Statistical analysis

Statistical heterogeneity among trials was assessed using the I^2 statistic, which measures the degree of heterogeneity in outcome measures by calculating the percentage of the total variation among the included studies⁹⁾. I^2 values of 50% or higher indicate significant heterogeneity, and the significance of heterogeneity was tested with χ^2 statistics. Random¹⁰⁾ and fixed effects¹¹⁾ models were planned for cases with and without statistically significant heterogeneity, respectively.

Differences in the efficacy and safety outcomes between anti-IL-5 therapy and placebo groups were assessed, and pooled estimates are presented as the rate ratio (asthma exacerbation rate), the standardized mean difference (SMD; change in FEV_{1.0}), or risk ratio (RR; any adverse events, asthma worsening, injection site reactions, headache, nasopharyngitis, bronchitis, and death) with 95% confidence intervals (CIs). Subgroup analysis by anti-IL-5 agent was also performed. Publication bias was evaluated with a funnel plot and analyzed statistically using Begg's and Egger's tests. 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 (StataCorp, College Station, TX, USA).

Results

Study selection, Jadad scores, and study characteristics

The study selection process is shown in Fig. 1. In all, 662 potentially relevant citations were retrieved from the databases; 596 studies were excluded because they did not fulfill the inclusion criteria. Of the remaining studies, 49 were excluded because they were not RCTs, 13 were excluded because they were not Phase 3 studies, and one was excluded because outcome measures included the glucocorticoid-sparing effect. Thus, five studies were included in the present meta-analysis, of which one reported the results of two independent RCTs; therefore, six studies were finally included in the meta-analysis^{4, 5, 9-11)}. Four studies had a Jadad score of 5, whereas one had a score of 4, which confirmed their high quality. 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; allocation concealment; blinding of the participants, personnel, and outcome assessment; incomplete outcome data; selective reporting; and other forms of potential bias. Each study was considered to have a low risk of bias for all factors, except for performance bias in three studies and detection bias in two studies. The authors' determinations of these assessments are shown in Fig. 2.

Asthma exacerbation and change in FEV_{1.0}

Asthma exacerbation was assessed in all six of the RCTs and change in FEV_{1.0} was assessed in five. There was no inter-study heterogeneity, as measured using the I^2 statistic, and all analyses in the present study were performed using the fixed-effect model.

The results of the present meta-analysis of anti-IL-5 therapies revealed a significant reduction

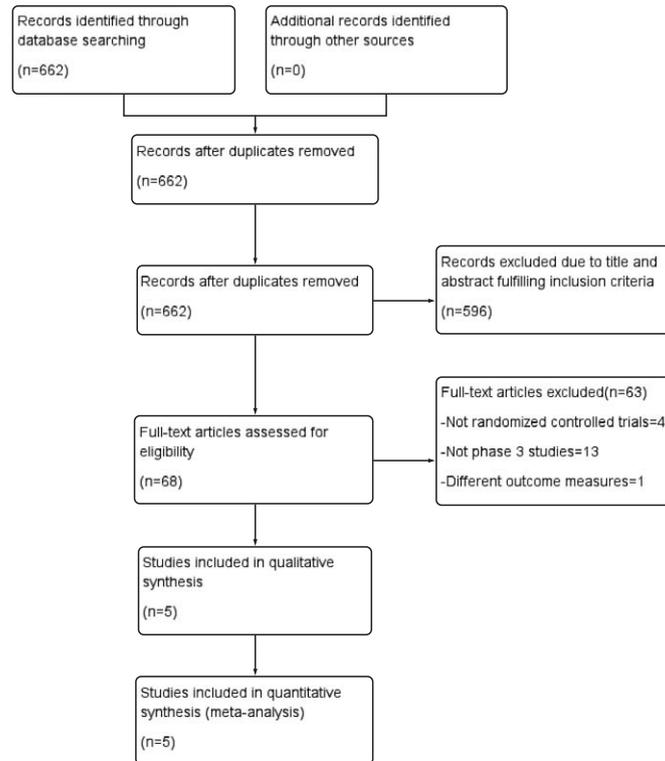


Fig. 1. Study selection process

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

Reference	Study name	Study design	Phase	Groups	Enrolled, n (M/F)	Average age, y	Severity of asthma	Study duration	Jadad score
Bel <i>et al.</i> 2014 ⁴⁾	SIRIUS	RCT (two arms)	III	100-MPZ Placebo	66 (36/ 30) 69 (25/ 44)	50 50	Severe	24 weeks	5
Ortega <i>et al.</i> 2014 ⁵⁾	MENSA	RCT (three arms)	III	100-MPZ 75-MPZ Placebo	194 (116/ 78) 191 (106/ 85) 191 (107/ 84)	49 50 51	Severe	32 weeks	5
Castro <i>et al.</i> 2015 ¹¹⁾	Study 1	RCT (two arms)	III	3-RSZ Placebo	245 (103/142) 244 (83/161)	48 49	Moderate to severe	52 weeks	4
Castro <i>et al.</i> 2015 ¹¹⁾	Study 2	RCT (two arms)	III	3-RSZ Placebo	232 (88/144) 232 (82/150)	48 48	Moderate to severe	52 weeks	4
Bleecker <i>et al.</i> 2016 ⁹⁾	SIROCCO	RCT (three arms)	III	*30-BRZ **30-BRZ Placebo	399 (124/275) 398 (146/252) 407 (138/269)	50.1 47.6 48.7	Severe	48 weeks	5
FitzGerald <i>et al.</i> 2016 ¹⁰⁾	CALIMA	RCT (three arms)	III	*30-BRZ **30-BRZ Placebo	425 (155/270) 441 (168/273) 440 (176/264)	50.0 49.0 48.8	Severe	56 weeks	5

F, female ; M, male ; RCT, randomized controlled trial ; 100-MPZ, 100 mg mepolizumab administrated subcutaneously every 4 weeks ; 75-MPZ, 75 mg benralizumab administrated intravenously every 4 weeks ; 3-RSZ, 3 mg/kg reslizumab administrated intravenously every 4 weeks ; *30-BRZ, 30 mg benralizumab administered subcutaneously every 4 weeks ; **30-BRZ, 30 mg benralizumab administered subcutaneously every 8 weeks

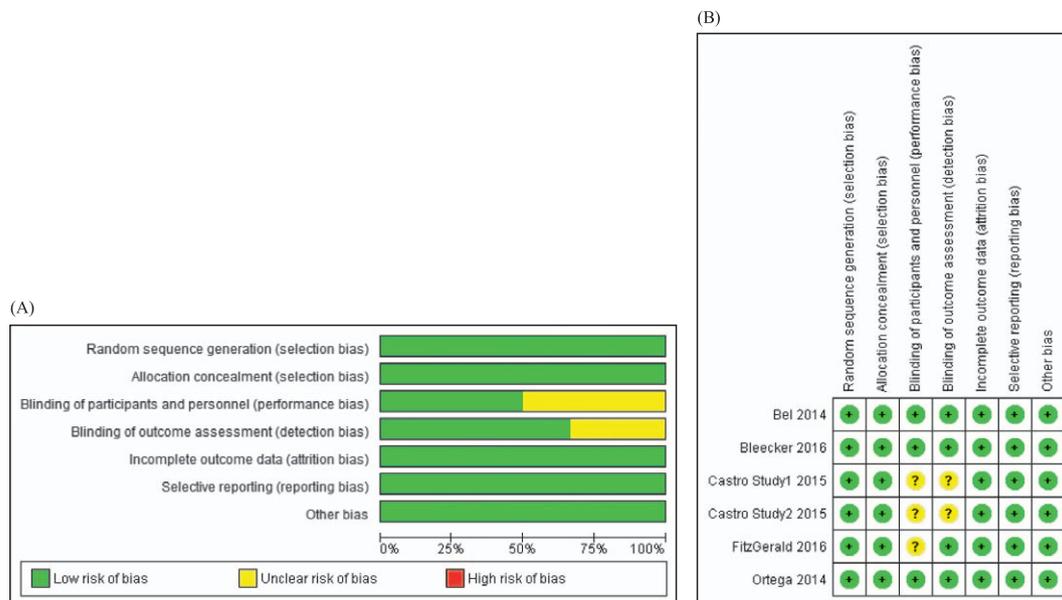


Fig. 2. Bias assessment summary. (A) Risk of bias graph showing author judgments of risk of bias items, presented as percentages in each study included. (B) Risk of bias summary showing author judgment of risk of bias items for each study included.

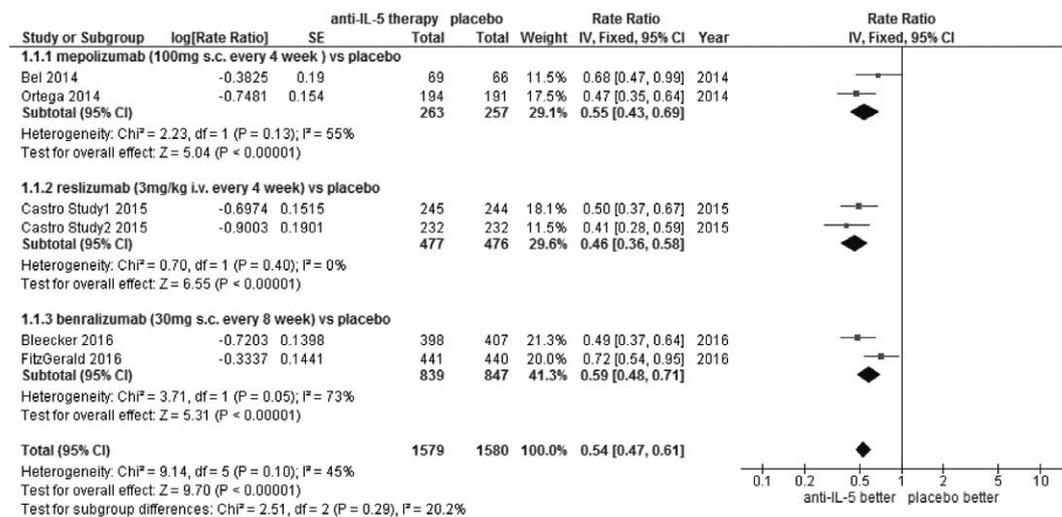


Fig. 3. Forest plots of the rate ratio of asthma exacerbation showing comparisons between anti-interleukin (IL)-5 therapies and placebo. SE, standard error; CI, confidence interval.

in asthma exacerbation rates compared with placebo, with a rate ratio of 0.54 (95% CI 0.47–0.61). The subgroup analysis of mepolizumab, reslizumab, and benralizumab also revealed a significant reduction in the incidence of asthma exacerbation compared with placebo, with rate ratios (95% CIs) of 0.55 (0.43–0.69), 0.46 (0.36–0.58), and 0.59 (0.47–0.71), respectively (Fig. 3).

The results of the present meta-analysis of anti-IL-5 therapies also revealed a significant

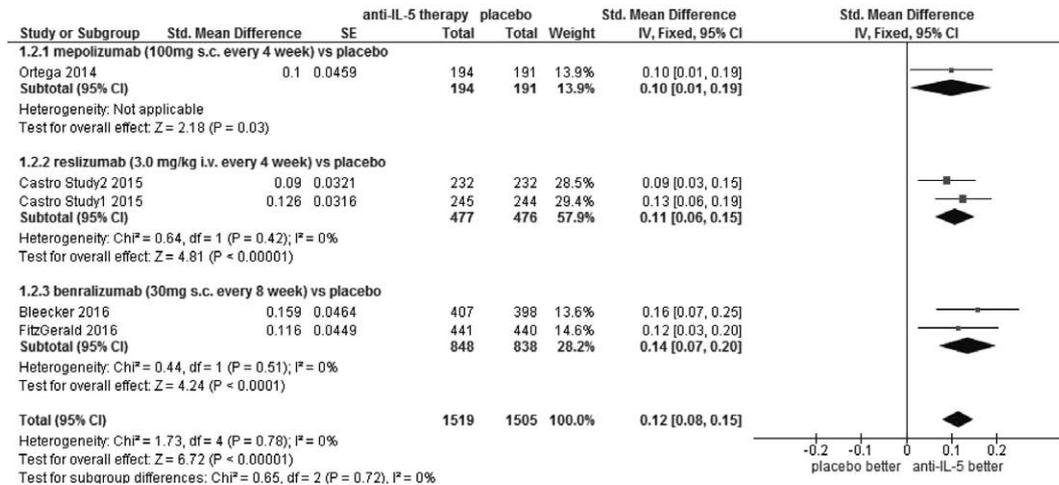


Fig. 4. Forest plots of changes in forced expiratory volume in 1 s ($FEV_{1.0}$) showing comparisons between anti-interleukin (IL)-5 therapies and placebo. SMD, standard mean difference; SE, standard error; CI, confidence interval.

improvement in $FEV_{1.0}$ compared with placebo, with an SMD of 0.12 (95% CI 0.08–0.15). The subgroup analysis of mepolizumab, reslizumab, and benralizumab also revealed a significant improvement in change in $FEV_{1.0}$ compared with placebo, with SMD (95% CIs) of 0.10 (0.01–0.19), 0.11 (0.06–0.15), and 0.14 (0.07–0.20), respectively (Fig. 4).

All adverse events, asthma worsening, injection site reaction, headache, nasopharyngitis, bronchitis, and death

There was a significant reduction in the incidence rate of all adverse events with anti-IL-5 therapies compared with placebo, with an RR of 0.93 (95% CI 0.89–0.96). The subgroup analysis of reslizumab and benralizumab also revealed a significant reduction in the incidence rate of all adverse events compared with placebo, with RRs (95% CIs) of 0.92 (0.86–0.97) and 0.93 (0.88–0.98), respectively. However, there were no significant differences in the incidence of all adverse events between mepolizumab and placebo, with an RR of 0.93 (95% CI 0.86–1.01; Fig. 5).

The results of the present meta-analysis of anti-IL-5 therapies revealed a significant reduction in asthma worsening compared with placebo, with an RR of 0.63 (95% CI 0.56–0.72). The subgroup analysis of mepolizumab, reslizumab, and benralizumab also revealed a significant reduction in the incidence rate of asthma worsening compared with placebo, with RRs (95% CIs) of 0.40 (0.22–0.70), 0.67 (0.57–0.77), and 0.64 (0.50–0.81), respectively (Fig. 6).

There were no significant differences in the incidence rates of injection site reaction, headache, and death between anti-IL-5 therapies and placebo, with RRs (95% CIs) of 1.59 (0.95–2.65), 1.18 (0.86–1.62), and 1.01 (0.33–3.12), respectively. However, the subgroup analysis revealed that the incidence of injection site reaction was significantly increased in the mepolizumab compared with placebo group, with an RR of 2.56 (95% CI 1.15–5.68; Figs. 7, 8).

There was a significant reduction in the incidence rate of nasopharyngitis with anti-IL-5 therapies compared with placebo, with an RR of 0.85 (95% CI 0.73–0.99), although there were no

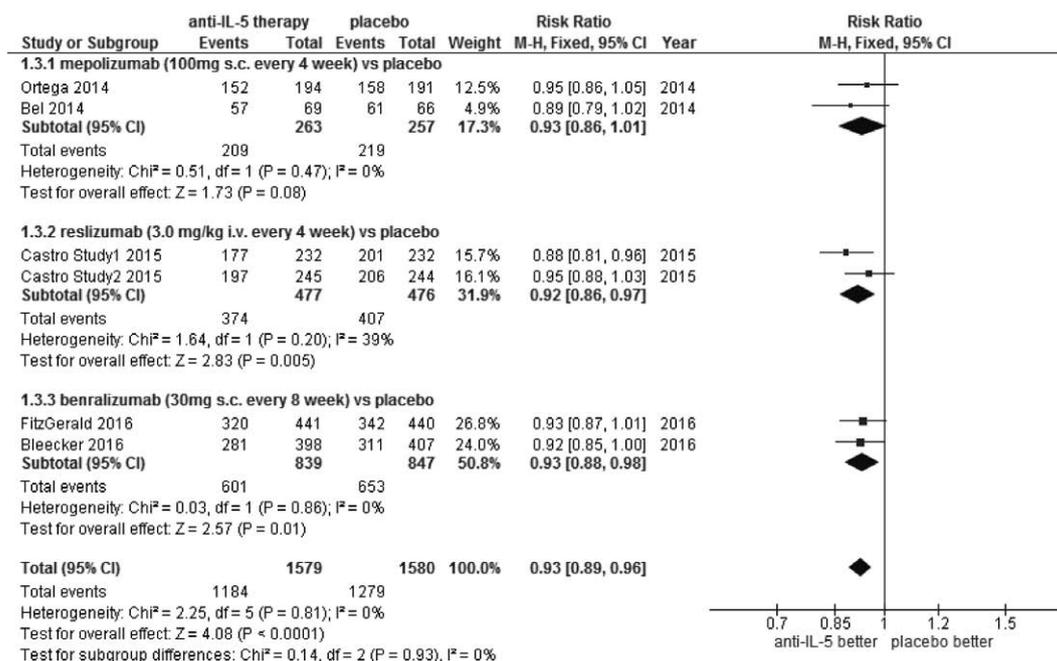


Fig. 5. Forest plots of all adverse events showing comparisons between anti-interleukin (IL)-5 therapies and placebo. CI, confidence interval.

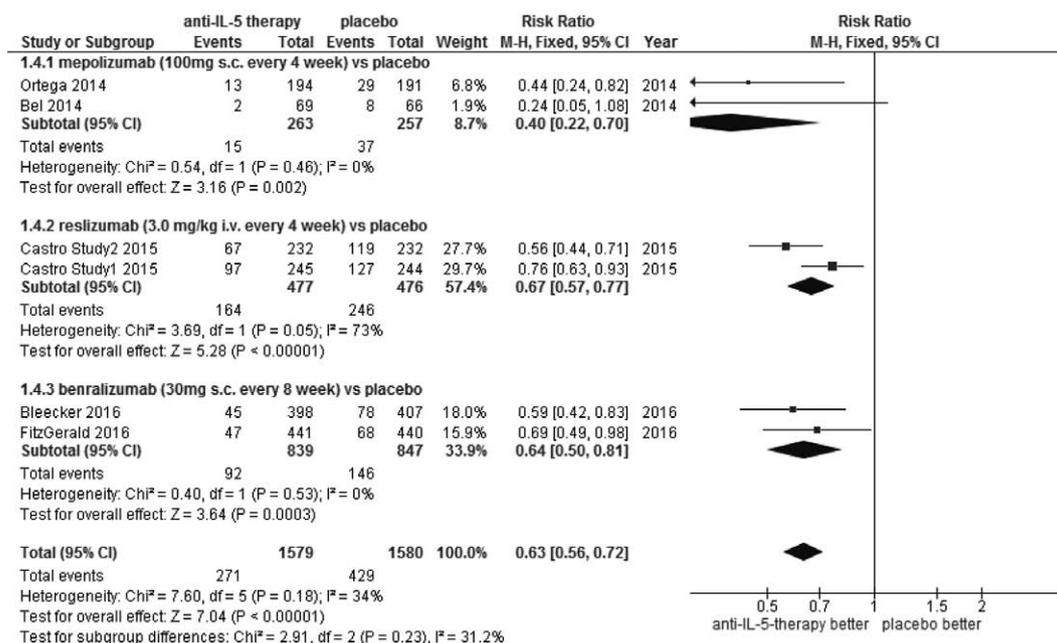


Fig. 6. Forest plots of asthma worsening showing comparisons between anti-interleukin (IL)-5 therapies and placebo. CI, confidence interval.

significant differences for mepolizumab, reslizumab, and benralizumab compared with placebo, with RRs (95% CIs) of 0.75 (0.53–1.07), 0.82 (0.62–1.08), and 0.91 (0.73–1.13), respectively (Fig. 9).

There was also a significant reduction in the incidence rate of bronchitis with anti-IL-5 therapies compared with placebo, with an RR of 0.64 (95% CI 0.45–0.90), although there were no

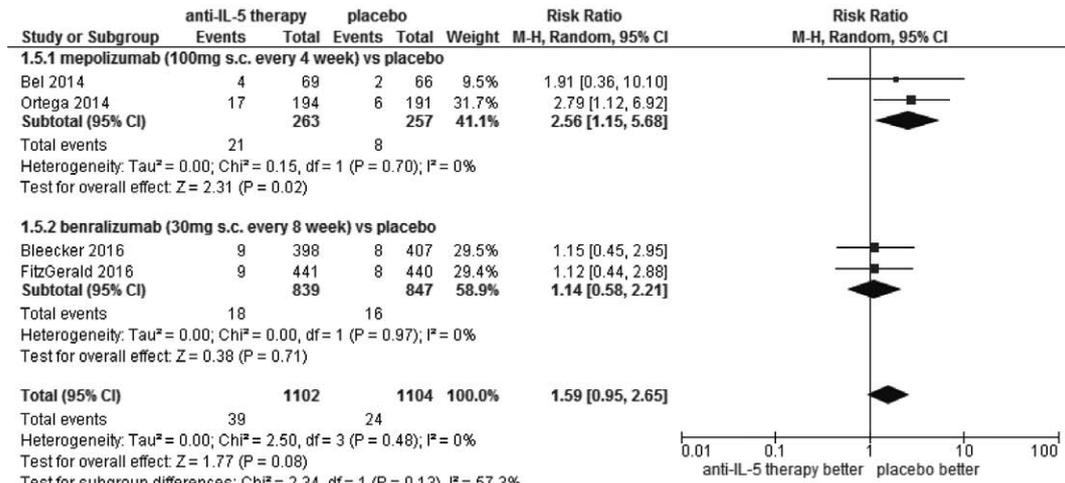


Fig. 7. Forest plots of injection site reaction showing comparisons between anti-interleukin (IL)-5 therapies and placebo. CI, confidence interval.

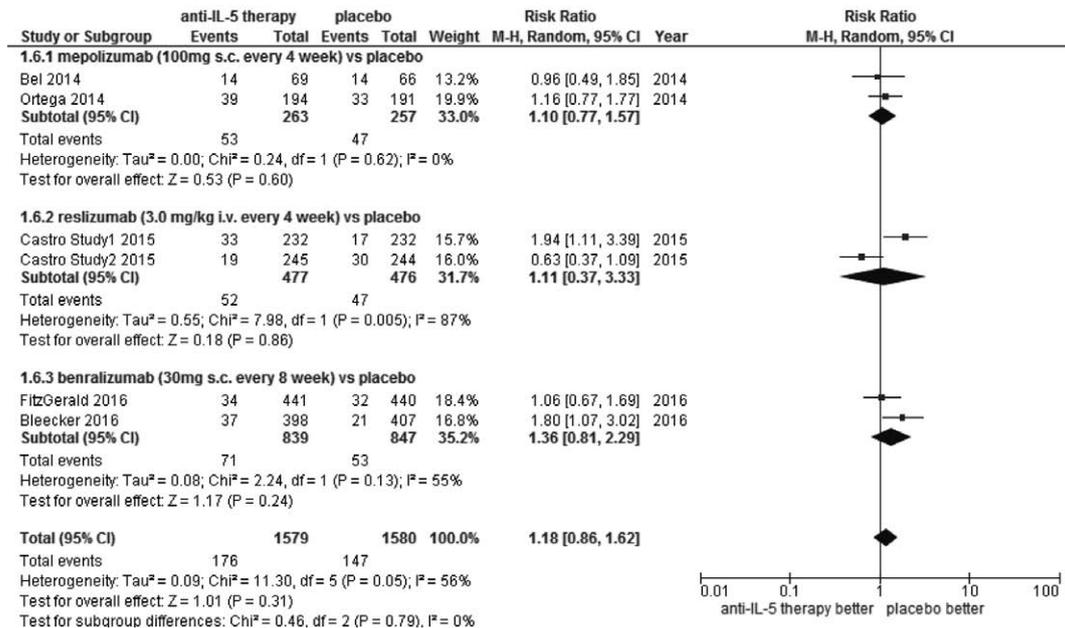


Fig. 8. Forest plots of headache showing comparisons between anti-interleukin (IL)-5 therapies and placebo. CI, confidence interval.

significant differences for mepolizumab, reslizumab, and benralizumab compared with placebo on the subgroup analysis, with RRs (95% CIs) of 0.69 (0.31–1.51), 0.33 (0.09–1.18), and 0.78 (0.57–1.06), respectively (Fig. 10).

There was no significant difference in the incidence rate of death between anti-IL-5 therapies and placebo, with an RR of 1.01 (95% CI 0.33–3.12; data not shown).

Publication bias

Differences in incidence of all adverse events between patients receiving anti-IL-5 therapies and those receiving placebo were evaluated with an Egger’s funnel plot in six studies, suggesting

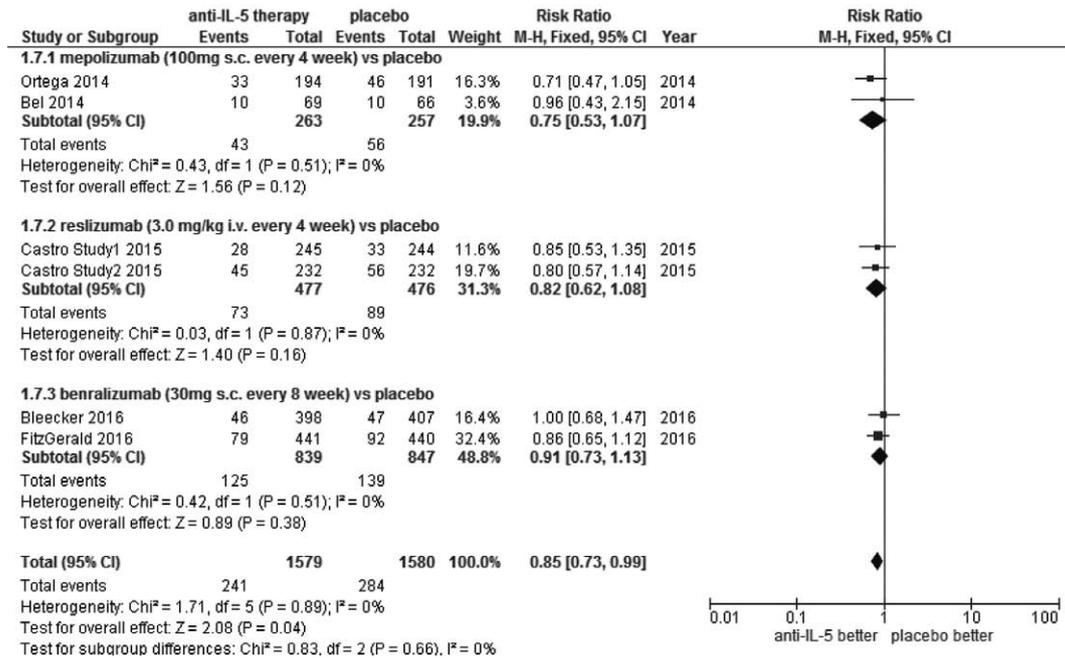


Fig. 9. Forest plots of nasopharyngitis showing comparisons between anti-interleukin (IL)-5 therapies and placebo. CI, confidence interval.

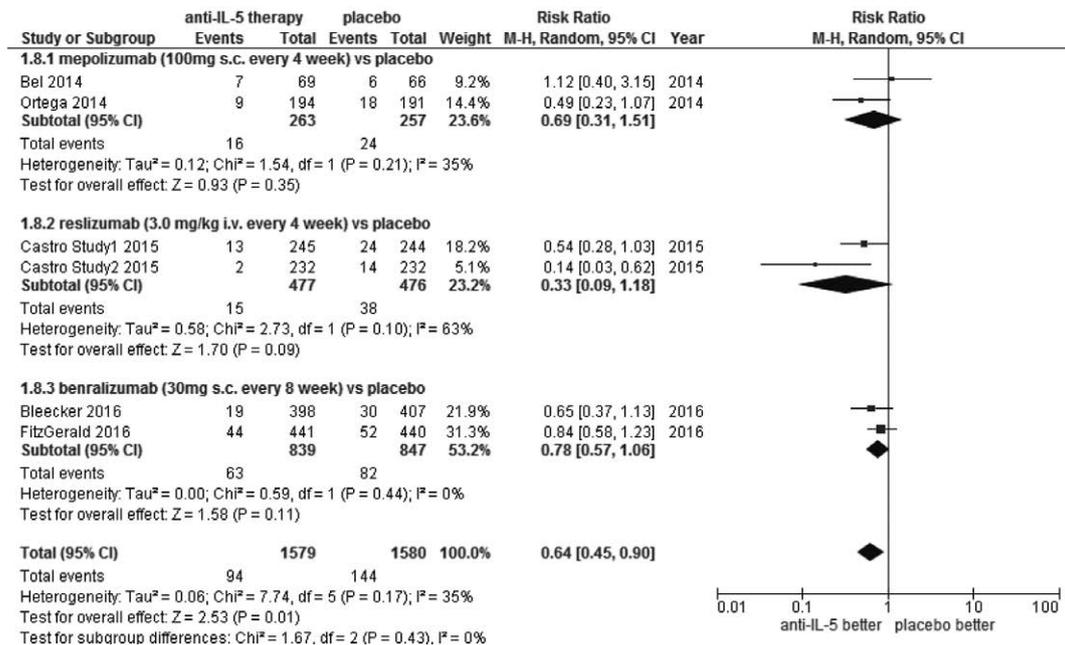


Fig. 10. Forest plots of bronchitis showing comparisons between anti-interleukin (IL)-5 therapies and placebo. CI, confidence interval.

no publication bias ($p = 0.142$; Fig. 11). Similarly, no publication bias was observed for any of the other outcomes as determined by Begg's and Egger's tests (all $p > 0.05$; data not shown). These results suggest that publication bias did not substantially affect the conclusions. Therefore, the results of the meta-analysis are considered valid.

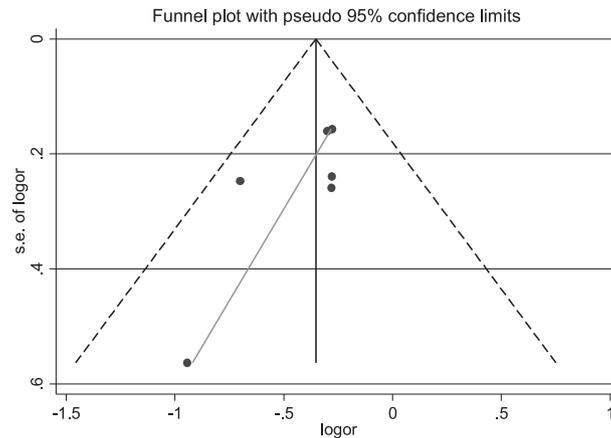


Fig. 11. Egger's funnel plot of the six studies evaluated in the present meta-analysis: effects of anti-interleukin (IL)-5 therapies and placebo on all adverse events. OR, odds ratio; SE, standard error.

Discussion

In the present meta-analysis we compared the efficacy (asthma exacerbations, pulmonary function) and safety (all adverse events, asthma worsening, injection site reactions, headache, nasopharyngitis, bronchitis, and death) of recommended dosages and administration of anti-IL-5 therapies compared with placebo. The aim of the present study was to assess the overall efficacy and safety of anti-IL-5 therapies.

The results indicate that the risk of asthma exacerbation was significantly reduced in the anti-IL-5 group compared with placebo, and that pulmonary function was significantly improved following treatment with the anti-IL-5 agents compared with placebo. The subgroup analysis also demonstrated that risk of asthma exacerbation was significantly reduced and that pulmonary function was significantly improved in the mepolizumab, reslizumab, and benralizumab groups compared with placebo.

The incidence of all adverse events, asthma worsening, nasopharyngitis, and bronchitis was significantly lower in the anti-IL-5 than placebo group. Although not significant, the incidence rates of injection site reactions and headache were more likely to be higher in the anti-IL-5 group than in the placebo group. There were no significant differences in the incidence of death between the two groups. The subgroup analysis demonstrated that the incidence rate of all adverse events in the reslizumab group was significantly reduced compared with placebo, whereas there were no significant differences compared with placebo in the mepolizumab and benralizumab groups. The incidence of asthma worsening was significantly lower in the mepolizumab, reslizumab, and benralizumab groups than in the placebo group. The incidence rate of injection site reactions was significantly higher in the mepolizumab than placebo group, whereas there were no significant differences between the benralizumab or reslizumab groups and the placebo group. Although there were no significant differences in the incidence of headache between the mepolizumab, reslizumab, or benralizumab groups and the placebo group, there was a trend for

a higher incidence of headache in the benralizumab compared with placebo group. There were no significant differences in the incidence of nasopharyngitis, bronchitis, and death between the mepolizumab, reslizumab, or benralizumab groups, and placebo.

Although previous RCTs and meta-analyses of anti-IL-5 therapies have shown similar results regarding efficacy and safety outcomes, there was variability in the degree of the efficacy and safety (e.g. risk of asthma exacerbation or incidence of all adverse events) among these studies, not only due to differences in asthma severity and definitions of complications, but also due to differences in dosage and administration^{4, 6, 9-13}.

As expected, the present meta-analysis assessing the efficacy of the currently recommended dosages and administration of anti-IL-5 therapies in patients with uncontrolled eosinophilic asthma showed results similar to those of previous Phase 3 studies. The results of the present study strongly support the theory that anti-IL-5 therapies are an effective treatment option for patients with uncontrolled eosinophilic asthma.

Regarding safety outcomes, the results of the present meta-analysis indicate that the incidence rate of all adverse events was significantly lower in the anti-IL-5 than placebo group. Although the difference in incidence rate of 0.07 was statistically but not clinically significant, this result indicates the safety of anti-IL-5 therapies.

The results of the present meta-analysis also indicate that the incidence rates of nasopharyngitis and bronchitis are significantly lower in the anti-IL-5 than placebo group, although the subgroup analysis of mepolizumab, reslizumab, and benralizumab did not reveal any significant differences between the individual anti-IL-5 agents and placebo. This may also suggest that anti-IL-5 therapies for nasopharyngitis and bronchitis are safe. Furthermore, this could indicate the efficacy of anti-IL-5 therapies for nasopharyngitis and bronchitis due to a therapeutic effect against eosinophilic airway inflammation.

In addition, the incidence rate of asthma worsening was significantly lower in the anti-IL-5 than placebo group. Subgroup analysis also revealed that the incidence rate of asthma worsening was significantly lower in the mepolizumab, benralizumab, and reslizumab groups compared with placebo. These results suggest that anti-IL-5 therapies are not only safe for the treatment of asthma worsening, but are also effective in preventing exacerbation of asthma.

In contrast, the results of the present study also demonstrated that, although not significant, there was tendency for the incidence rates of injection site reactions and headache to be higher in the anti-IL-5 therapy group than in the placebo group. Moreover, subgroup analysis revealed that the incidence rate of injection site reactions was significantly higher in the mepolizumab group than in the placebo group. This may be biologically plausible because enhanced levels of IL-5 are observed not only in the airway, but also in subcutaneous tissue after elevation of serum IL-5²⁰, whereas enhanced levels of eosinophils are observed primarily in the airways rather than in subcutaneous tissue in patients with eosinophilic asthma^{21, 22}. These results suggest that special attention is warranted regarding the occurrence of injection site reactions, especially with the administration of mepolizumab.

To the best of our knowledge, the present study is the first meta-analysis to compare the

efficacy and safety profiles between anti-IL-5 therapies, at the recommended dosages and administration, and placebo in patients with uncontrolled eosinophilic asthma. As expected, we found that anti-IL-5 therapy was effective and generally well tolerated. We also report a novel finding in that the incidence of injection site reactions was significantly increased at the recommended dosage and administration of mepolizumab compared with placebo.

The present study has several limitations. First, we only considered published studies 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 six studies included in the present meta-analysis were supported by a pharmaceutical company, and the authors of those studies reported receiving grant support or uncompensated support. Therefore, the source of funding may have influenced the outcomes. Moreover, outcome selection bias may have occurred. Third, the criteria for asthma worsening, injection site reactions, and headache were not detailed in the studies included in the present analysis, and may vary among studies, although consensus criteria for these outcomes have been established. Fourth, the total dosage of anti-IL-5 agents varied among studies included in the present meta-analysis due, in part, to different study durations, although dosages and administration were standardized to those currently recommended. The treatment duration of anti-IL-5 therapy remains to be standardized, and this may affect the final conclusions. Finally, we only included a small sample of studies (six) in the present meta-analysis. Although meta-analyses involving a small sample of studies are not uncommon in orphan disease, they may be confounded by the presence of heterogeneity²³⁾, although heterogeneity was not observed in the present meta-analysis.

In conclusion, we assessed the efficacy and safety profiles of anti-IL-5 therapies, at the currently recommended dosages and administration, compared with placebo. The results indicated that the risk of asthma exacerbation was significantly reduced and that pulmonary function was significantly improved in the anti-IL-5 compared with placebo group, and that the incidence of all adverse events, asthma worsening, nasopharyngitis, and bronchitis was significantly lower in the anti-IL-5 than placebo group. However, the subgroup analysis results originally demonstrated that the incidence of injection site reactions was significantly higher in the mepolizumab group than in the placebo group. These results suggest that anti-IL-5 therapies, at currently recommended dosages and administration, are effective and generally well tolerated in patients with uncontrolled eosinophilic asthma, but there is a need for special attention regarding the occurrence of injection site reactions, in particular regarding the administration of mepolizumab. The identification of some limitations in this meta-analysis indicates that further studies are necessary to confirm the efficacy and safety profiles of anti-IL-5 therapies, at recommended dosages and administration, in patients with uncontrolled eosinophilic asthma.

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Conflict of interest disclosure

None of the authors have any conflicts of interest to disclose.

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