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The Clinical Efficacy of Type 2 Inflammation-Specific Agents Targeting Interleukins in Reducing Exacerbations in Severe Asthma: A Meta-Analysis

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Purpose: Monoclonal antibodies against type 2 inflammatory pathways are currently promising therapeutics for severe asthma. The aim of this study was to determine how well type 2 (T2) inflammation-specific agents targeting interleukins reduce the rate of asthma exacerbations (AE) in patients with severe asthma.

Materials and Methods: We performed a systematic review and meta-analysis in accordance with PRISMA guidelines. A systematic literature search was conducted in PubMed, Embase, and the Cochrane Central Register. The primary outcome was the reduction rate of annualized AEs.

Results: We analyzed 17 studies comprising 11800 subjects. A total of 6197 patients received T2-specific agents (benralizumab, dupilumab, lebrikizumab, mepolizumab, reslizumab, and tralokinumab). Overall, T2-specific agents were significantly associated with a lower risk of AE, compared with placebo [rate ratio (RR) 0.58, 95% confidence interval (CI) 0.51 to 0.66]. Among all studied agents, only tralokinumab did not demonstrate a reduction in AE. The efficacy of T2-specific agents in reducing AE was maintained regardless of the pathway used. A subgroup analysis indicated that T2-specific agents further reduced the risk of AE in patients with eosinophil counts of ≥300 cells/μL (RR 0.41, 95% CI 0.32 to 0.53).

Conclusion: Our findings suggest that T2-specific agents are significantly associated with a reduced rate of AE, compared with placebo. Their efficacy appears to be enhanced in patients with eosinophil counts of ≥300 cells/μL.

Key Words: Asthma, biological therapy, antibodies, monoclonal, meta-analysis

INTRODUCTION

Asthma is a heterogeneous disease usually characterized by chronic airway inflammation.[1] Approximately 20% of asthma patients have severe asthma, which is defined as asthma that can only be managed with high-dose inhaled corticosteroids plus a second controller therapy or systemic corticosteroids.[2,3] Most patients with severe asthma frequently receive systemic corticosteroids to control symptoms and to reduce asthma exacerbations (AE),[4] and they experience more frequent AEs than those with mild to moderate disease.[4]

Type 2 (T2) inflammation is driven by eosinophils, mast cells, basophils, T helper-2 lymphocytes [which secrete interleukin (IL)-4, IL-5, and IL-13], group 2 innate lymphoid cells, and the production of epithelial cell–derived alarmins, such as thymic stromal lymphopoietin (TSLP).[5,6] Approximately 50 percent of patients with severe asthma have persistent elevated markers for T2 inflammation. In severe asthma patients,

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T2 inflammation is associated with asthma severity, increased frequency of AE, and reduced lung function.[7,8]

Although corticosteroids reduce the number of inflammatory cells, they cause substantial health problems. Therefore, patients with severe asthma need alternative treatments that target the airway eosinophilic inflammatory pathway. Currently, several monoclonal antibodies have been developed against specific inflammatory pathways as novel add-on therapies for severe asthma, and several studies have well established the favorable outcomes of those agents, such as their oral glucocorticoid sparing effect, improved lung function, and control of AEs.[9]

Because AEs are the most significant complication of asthma and are associated with morbidity and mortality, we used them as the primary outcome measure in this review.[3] The aim of this study was to perform a systematic review and meta-analysis to investigate the efficacy of T2 inflammation-specific (T2-specific) agents targeting ILs in reducing the rate of AEs in patients with severe asthma.

MATERIALS AND METHODS

Data sources and search strategy

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[10] We used the following terms: "asthma" AND (["benralizumab" OR "dupilumab" OR "lebrikizumab" OR "mepolizumab" OR "reslizumab" OR "tralokinumab"] OR ["antibodies, monoclonal"] OR ["anti-IL*" OR "anti-interleukin*"]). We searched three electronic databases (PubMed, Embase, and the Cochrane Central Register) for relevant articles published before August 29, 2021. The reference lists of every article were retrieved, and relevant reviews were investigated manually to find more potentially relevant research. Because this study is a systematic review of published articles, neither informed consent nor ethics approval was required.

Study selection and data extraction

This meta-analysis included all studies that met the following criteria: 1) the design was a randomized controlled trial (RCT); 2) the study examined the efficacy of T2-specific agents targeting ILs in patients with severe asthma; 3) the outcomes included AE; 4) relative rate ratio (RR) and 95% confidence intervals (CIs) were reported (or the information to calculate them was available); and 5) the study was published in a peer-reviewed English language journal. Review articles, case reports, commentaries, and extension or post-hoc studies were excluded.

The outcome of interest in this meta-analysis was the reduced rate of annual AEs at the study endpoint in patients receiving T2-specific agents targeting ILs, compared with placebo. AE was defined as treatment with a course of systemic corticosteroids for at least 3 days irrespective of hospitalization, and severe asthma was regarded as worsening asthma despite treatment with a medium-to-high-dose inhaled corticosteroid in combination with up to two controllers. When multiple treatment arms were presented in a single trial, we selected only the arms likely to be performed clinically. The dosing for each agent is described in Supplementary Table 1 (only online).

Two authors independently retrieved potentially relevant studies, reviewed each study according to the predefined criteria for eligibility, and extracted data. Any disagreements that arose during the process of study selection and data extraction were resolved through discussion. A predefined form was used to extract the following data from each study: author, year of publication, study sites, number of patients, age, sex, baseline eosinophil count, baseline forced expiratory volume in 1 second (FEV_1), number of AEs in the past 12 months, percentage of former smokers, baseline asthma control score, nasal polyposis, primary and secondary endpoints, and distinct features in the study population.

Risk of bias assessment

The quality of RCTs was evaluated using the Cochrane Handbook for Systemic Reviews of Interventions Risk of Bias Tool.[11] This scale evaluates the following criteria: sequence generation/allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other sources of bias. The risk of bias is labeled as high, low, or unclear. If any item of randomization or blinding was judged to be high risk, the trial was deemed to have a high risk of bias. Discrepancies were resolved by consensus among the authors. Publication bias was assessed using a funnel plot, and statistical significance was evaluated using Egger's regression tests.[12]

Data synthesis and statistical analysis

We extracted the RRs and associated 95% CIs for T2-specific agents to assess reductions in the annual rate of AEs, compared with placebo. Between-study statistical heterogeneity was assessed using I^2 and the Cochrane Q test.[13] Heterogeneity was assessed using I^2 statistics on a scale of 0%–100%. A fixed-effects model was used unless I^2 was >50%, indicating a substantial level of between-study heterogeneity, in which case a random-effects model was used. We additionally performed subgroup analyses according to the T2 inflammation pathway (IL-5 and other than IL-5) and eosinophil count (<300 cells/μL vs. ≥300 cells/μL). A p-value<0.05 was considered statistically significant. Statistical analyses were performed with Stata statistical software (Version 14.2, Stata Corp LP, College Station, TX, USA) and Review Manager (Version 5.3, Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

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RESULTS

Fig. 1 presents the literature search process. A total of 9642 published articles were initially identified (1564 articles from PubMed, 6879 articles from Embase, and 1199 articles from the Cochrane Central Register). After removing duplicate articles, we screened 7555 potentially eligible articles. During the review of titles and abstracts, 7495 search records were removed, and the remaining 60 articles were evaluated by reading the full text. Forty-three articles were excluded for the reasons shown in Fig. 1. In the end, 17 studies were included in our final analysis.[14-30]

The accompanying Supplementary Table 1 (only online) summarizes the features of the included studies. The total number of patients in our systematic review and meta-analysis was 11800, of whom 6197 were treated with T2-specific agents and 5603 received placebo. All studies were published between 2009 and 2019. Our quality assessment of the included RCTs is reported in the Supplementary Fig. 1 (only online). Overall, the risk of bias assessed by the Cochrane Risk of Bias Tool was judged to be low.

The pooled estimates of treatment efficacy, in terms of a reduced AE rate with the use of T2-specific agents, were weighted and combined using a generic inverse-variance and random effect model. The annualized RRs for AE were analyzable for three benralizumab,[14-16] three dupilumab,[17-19] two lebrikizumab,[20,21] five mepolizumab,[22-26] one reslizumab,[27] and three tralokinumab studies.[28-30] Overall, the RR for the number of annual AEs showed that T2-specific agents had a favorable effect, compared with placebo (RR 0.58, 95% CI 0.51 to 0.66) (Fig. 2), with a 42% absolute risk reduction. The heterogeneity was high (I^2=72%, p<0.01). The results of Egger's regression test for asymmetry in the included studies indicated no significant publication bias (p=0.156), and a visual inspection of the plot also showed no evidence of bias (Fig. 3).

When we analyzed the effect of each T2-specific agent, most of them were associated with significant reductions in annual AE rates: benralizumab (RR 0.58, 95% CI 0.44 to 0.77, I^2=69%, p=0.01), dupilumab (RR 0.46, 95% CI 0.37 to 0.56, I^2=39%, p=0.16), lebrikizumab (RR 0.67, 95% CI 0.52 to 0.86, I^2=61%, p=0.01), mepolizumab (RR 0.51, 95% CI 0.45 to 0.58, I^2=0%, p=0.46), and reslizumab (RR 0.46, 95% CI 0.37 to 0.58). Only

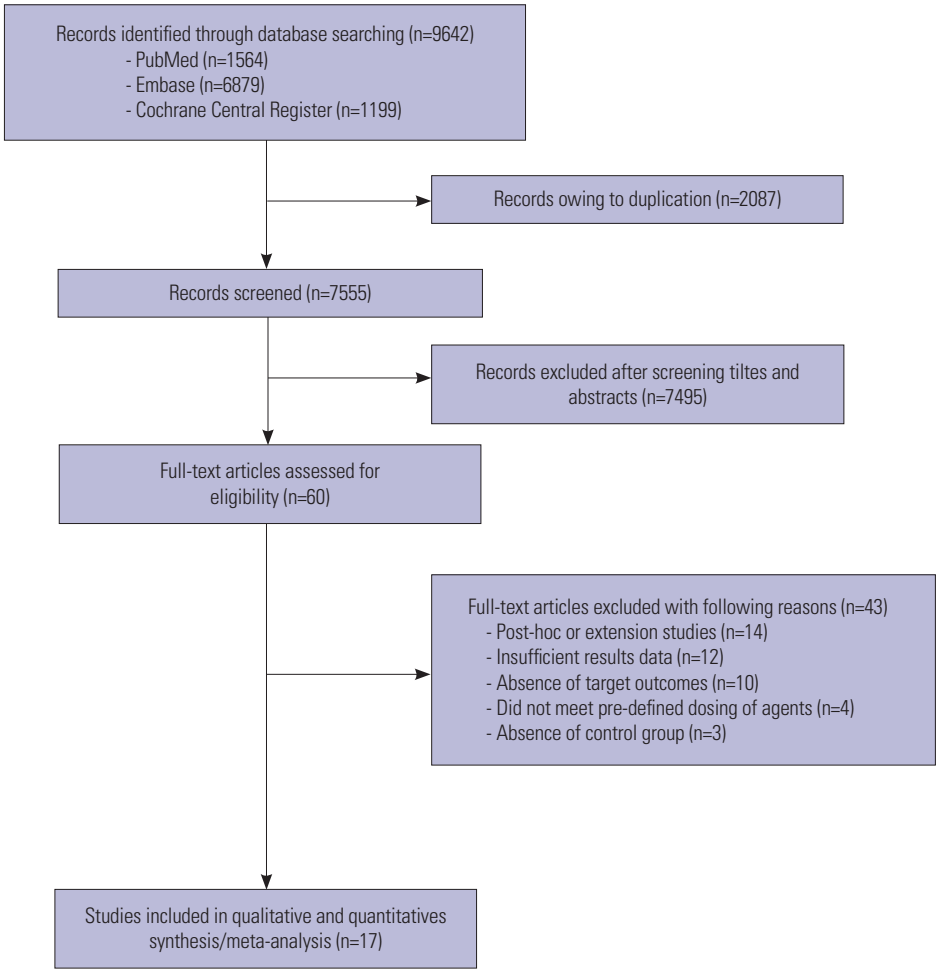

Fig. 1. Flow diagram for identifying eligible studies.

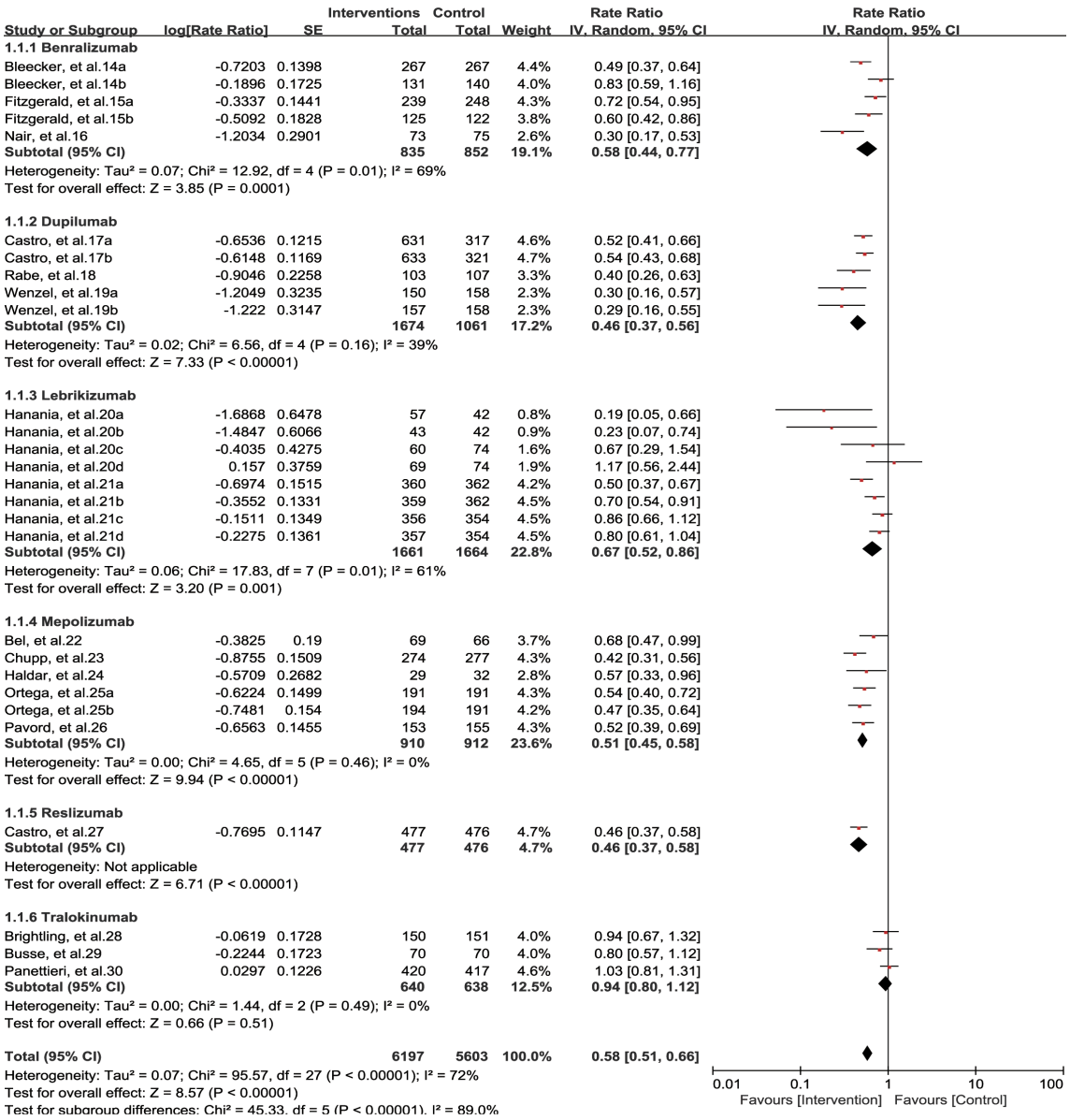

Fig. 2. Forest plots for the rate of annual asthma exacerbations in severe asthma patients receiving type 2 inflammation-specific agents, compared with placebo. SE, standard error; CI, confidence interval; IV, inverse variance; df, degrees of freedom.

tralokinumab was not statistically associated with reductions in AEs, compared with placebo (RR 0.94, 95% CI 0.80 to 1.12, I^2=0%, p=0.49) (Fig. 2). When we performed a sensitivity analysis by selectively excluding studies for tralokinumab from the overall analysis, the AE rate decreased further (RR 0.53, 95% CI 0.47 to 0.59, I^2=66%, p<0.01).

Because a substantial degree of heterogeneity existed among the trials, we performed subgroup analyses to explore heterogeneity according to the T2 inflammatory pathway targeted by each agent and blood eosinophil counts. The reduction in the risk of AE caused by the targeting agents was found for both pathways: IL-5 (RR 0.54, 95% CI 0.47 to 0.61, I^2=50%, p=0.02) and other IL than IL-5 (RR 0.62, 95% CI 0.51 to 0.75, I^2=75%, p<0.01) (Fig. 4).

When the analysis was restricted to patients with an eosinophil count of ≥ 300 cells/μL, the risk of AE was decreased (RR 0.41, 95% CI 0.32 to 0.53, I^2=68%, p<0.01) (Fig. 5A). Meanwhile, patients with eosinophil counts of <300 cells/μL showed a higher risk of AE while taking T2-specific therapy than those whose eosinophil count was ≥300 cells/μL (RR 0.67, 95% CI 0.54 to 0.84, I^2=48%, p=0.05) (Fig. 5B).

DISCUSSION

In this systematic review and meta-analysis, we investigated reduction rates in annual AEs caused by the use of T2-specific agents in patients with severe asthma. The RR for the number

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of annual AEs showed that the T2-specific agents had a favorable effect compared with placebo (RR 0.58, 95% CI 0.51 to 0.66), which can be translated into an absolute risk reduction of 42%. These findings support the clinical efficacy of T2-specific agents in the treatment of severe asthma.

Individually, benralizumab, dupilumab, lebrikizumab, mepolizumab, and reslizumab exhibited considerable effectiveness in reducing the annual AE rate, compared with placebo, in the pooled estimates. Dupilumab and reslizumab showed the highest risk reduction rate (54%) among the T2-specific agents. However, we could not conclusively rank the superiority of the agents from the pooled estimates for the following reasons. First, we found no RCTs directly comparing T2-specific agents with each other. We found only one retrospective multicenter study comparing the treatment efficacy of mepolizumab and benralizumab, which both target the IL-5 pathway, over 12 months in patients with severe eosinophilic asthma.[31] Both groups showed similar improvements in clinical parameters, including FEV_1, AE rate, oral corticosteroid use and dose, and asthma control test score.[31] Second, the between-study heterogeneity was considerable in our meta-analysis. The studies included in our pooled estimates had different study protocols, which could cause substantial heterogeneity in their results. The study population in our study was also heterogeneous and relatively inconsistent across the included studies, differing in variables such as baseline lung function, the number of AE, whether oral glucocorticoids were allowed, and eosinophil count.

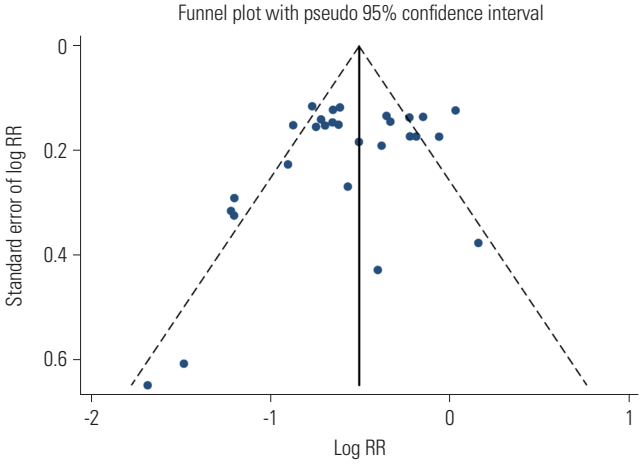


Fig. 3. Funnel plot assessing publication bias. RR, rate ratio.

To investigate potential sources of heterogeneity, we performed additional subgroup analyses. The positive effective-

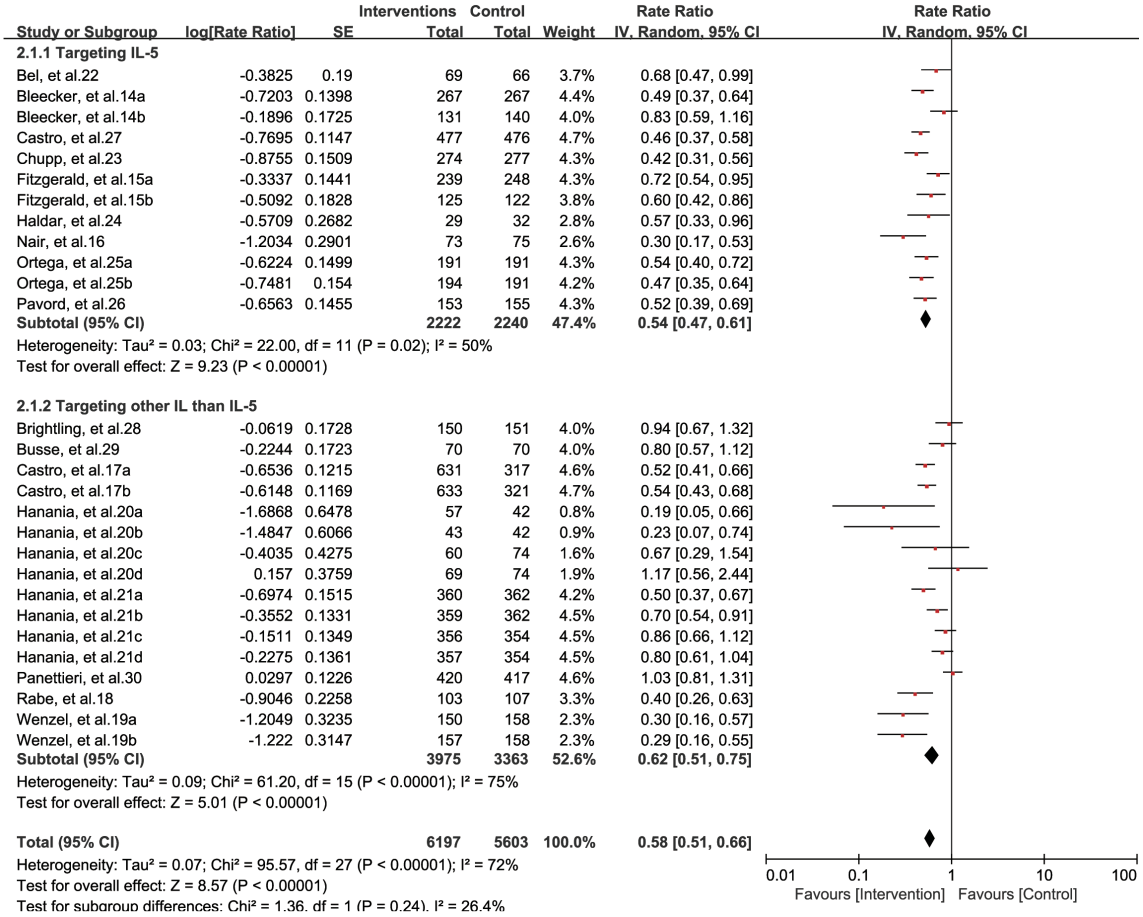
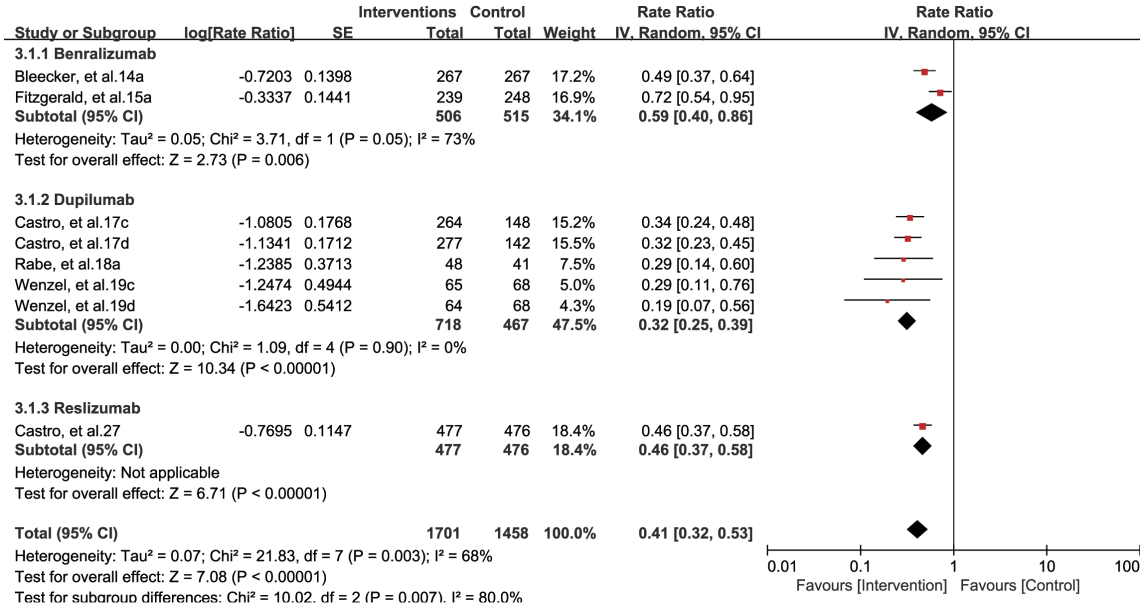


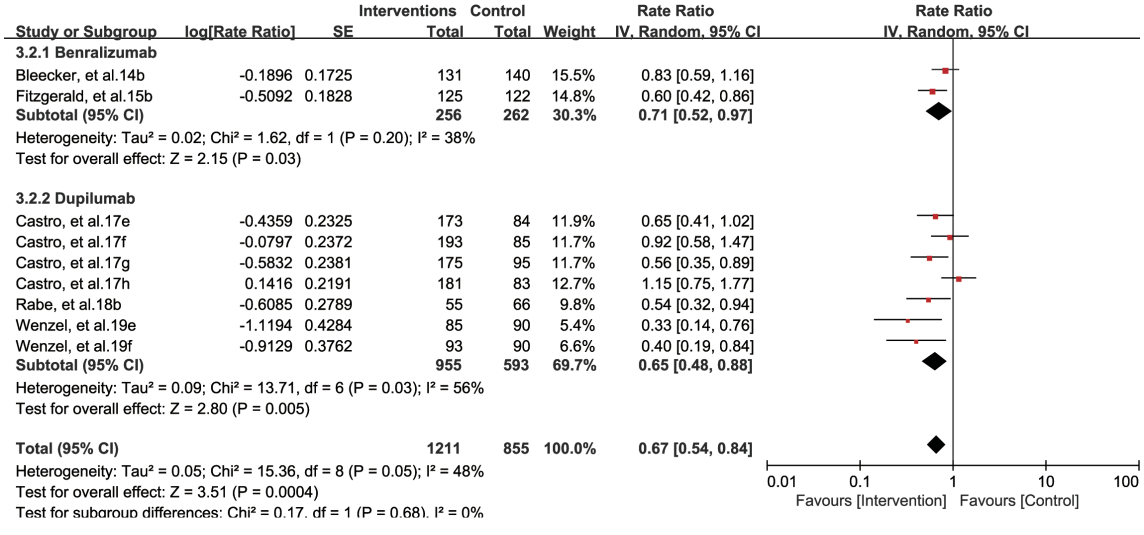
Fig. 4. Forest plots for the rate of annual asthma exacerbations in severe asthma patients receiving type 2 inflammation-specific agents, compared with placebo, according to the target pathway. SE, standard error; CI, confidence interval; IV, inverse variance; df, degrees of freedom.

ness of T2-specific agents for reducing annual AE was maintained regardless of the targeted T2-pathway. In addition, eosinophil count was considered as a potential source of heterogeneity. In line with findings from previous studies, T2-specific agents were found to be more effective in patients with high T2 inflammation than in patients with low T2 inflammation.[32] In the pooled estimates, the T2-specific agents reduced the annual AE rate by approximately 61% in patients with uncontrolled asthma whose blood eosinophil counts were ≥300 cells/μL. On the other hand, in severe asthma patients whose eosinophil counts were <300 cells/μL, the efficacy of the T2-specific agents decreased to an AE reduction of approximately 34%. Although high eosinophil counts in peripheral blood have been shown to be associated with T2 inflammation in asthma, the use of inhaled corticosteroids can profoundly affect blood eosinophil concentrations.[33] Therefore, eosinophilia in peripheral blood as a T2 inflammation marker should be interpreted carefully in light of the patient's current inhaled corticosteroid dose.[33]

Only tralokinumab, a human IL-13 neutralizing monoclonal antibody, failed to lower the annual risk of AE. Serum periostin and dipeptidyl peptidase-4 have been reported as blood bio-



A



B

Fig. 5. Forest plots for the rate of annual asthma exacerbations in severe asthma patients receiving type 2 inflammation–specific agents, compared with placebo, according to (A) eosinophil count ≥300 and (B) <300 cells/μL. SE, standard error; CI, confidence interval; IV, inverse variance; df, degrees of freedom.

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markers that represent IL-13 activation in the airway epithelium.[28] Those markers might be considered to predict a response to anti-IL-13 monoclonal antibodies.[28] Another IL-13 monoclonal antibody, lebrikizumab, showed favorable outcomes in patients with increased serum periostin levels.[34] IL-13 induces airway smooth muscle contractility and bronchial hyperresponsiveness.[28] Based on those mechanisms, tralokinumab produced significant improvement in lung function, as shown by FEV_1, compared with placebo, in severe asthma patients.[28]

TSLP, a cytokine derived from airway epithelial cells, is implicated in both T2 inflammation and various interactions between airway structural cells and immune cells.[6] TSLP levels are associated with airway narrowing, asthma severity, and glucocorticoid resistance.[35] Recently, the clinical efficacy of tezepelumab, a human monoclonal antibody that blocks TSLP, has been reported.[36,37] Because the human monoclonal antibody that blocks TSLP did not meet our inclusion criteria, we did not include tezepelumab in this study. Instead, we performed a separate analysis. In the pooled estimates from two RCTs, the reduction in annual acute AE was greater with tezepelumab than with placebo (RR 0.38, 95% CI 0.25 to 0.57, I^2=65%, p=0.09).[36,37] Therefore, an anti-TSLP blocker could play a role in managing severe asthma beyond T2 inflammation.[36]

Prior to our research, several meta-analyses for biologic agents in severe asthma have been reported.[38-44] However, some of these studies are limited to studies of biologic agents related to specific pathways or particular monoclonal antibodies.[38-41] Another study primarily investigated changes in lung function, asthma control, and asthma quality of life rather than reduced rates of AE as a primary outcome.[42] Although one study and it's updated analysis assessed the reduced AE ratio as the primary outcome like our analysis, the study data were limited to pooled estimates for individual agents.[43,44]

The major strength of this study is that we conducted additional subgroup analysis in addition to assessing overall and individual T2-specific agents targeting ILs to reduce the rate of AE in patients with severe asthma. By assessing these values according to individual agents, specific pathway, and eosinophil counts, our study found evidence that it may be plausible to use any existing agents in this population. Additionally, we only included high-quality RCT studies for rigorous evaluation, differing from other meta-analysis research.[40] Although observational studies also play an important role in evaluating the effectiveness and safety of biologic agents, they are significantly affected by several unmanageable confounding factors, which can cause substantial heterogeneity.

Our study has some limitations. First, there was statistically significant heterogeneity among the selected studies, as previously mentioned. Therefore, our results should be interpreted carefully. Second, the outcome of interest in this study was all clinically significant AEs. However, the definition of AE in the selected studies varied, which might have introduced bias. Third, most of the research included in the pooled analysis lasted from 24 to 52 weeks. Because asthma is a chronic disease, another limitation of our study is that we are unable to explain how long the treatment efficacy is maintained. Additional data on the long-term use of T2-specific agents are needed.

In this systematic review and meta-analysis, we demonstrated that overall, T2-specific agents are significantly associated with a reduced rate of annual AE, compared with placebo, though there was between-study heterogeneity. In subgroup analysis, we found significantly greater reductions in AE in patients with raised eosinophils (≥300 cells/μL). Our findings are consistent with the statements of current guidelines, and T2-specific agents can be considered as add-on therapy for severe asthma patients.

AVAILABILITY OF DATA AND MATERIAL

All data generated or analyzed during this study are included in the published article.

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AUTHOR CONTRIBUTIONS

Conceptualization: Jonghoo Lee. Data curation: Jonghoo Lee and Jae-Uk Song. Formal analysis: Jonghoo Lee and Jae-Uk Song. Funding acquisition: Jonghoo Lee. Investigation: Jonghoo Lee and Jae-Uk Song. Methodology: Jonghoo Lee and Jae-Uk Song. Project administration: Jonghoo Lee. Resources: Jonghoo Lee and Jae-Uk Song. Software: Jonghoo Lee. Supervision: Jonghoo Lee. Validation: Jonghoo Lee and Jae-Uk Song. Visualization: Jonghoo Lee. Writing—original draft: Jonghoo Lee and Jae-Uk Song. Writing—review & editing: all authors. Approval of final manuscript: all authors.

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