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Comparative efficacy of biologics for patients with inadequately controlled asthma: A network meta-analysis

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ABSTRACT

Background: Few studies have evaluated the comparative efficacy of biologics for asthma. This network meta-analysis aimed to compare the efficacy of biologics.

Methods: This study included randomized controlled trials (RCTs) evaluating the efficacy of a biologic compared to a placebo or another biologic in patients with inadequately controlled asthma despite high-intensity treatment, published by January 6, 2022. Two researchers independently searched the PubMed, Embase, Web of Science, and Scopus and assessed the risk of bias using the Cochrane tool. The outcomes of interest were the annual asthma exacerbation rate (AER), forced expiratory volume per second before bronchodilator use (preBD FEV1), the asthma control questionnaire (ACQ), and asthma quality of life questionnaire (AQLQ) results. A frequentist network meta-analysis was conducted, and a random effects model was used to draw pooled incidence rate ratio or standardized mean differences.

Results: Twenty-three RCTs with 8376 participants were retrieved. All biologics included in this study were associated with significantly better effects than placebo in AER, preBD FEV1, and ACQ outcomes. Although there were no significant differences between the biologics in the overall study population, patients with eosinophil levels $\geq$300 cells/μL or eosinophilic asthma showed that dupilumab and tezepelumab were significantly better than anti-IL-5 biologics in improving preBD FEV1. Additionally, in patients with eosinophil levels $\geq$300 cells/μL, benralizumab, unlike reslizumab, performed significantly better than placebo in improving ACQ and AQLQ outcomes.

Conclusion: The comparative effects of biologics can be considered with phenotypes and biomarkers to help clinicians select an appropriate treatment for inadequately controlled asthma.

Keywords: Asthma, Biologics, Efficacy, Inadequately controlled, Network meta-analysis

INTRODUCTION

Asthma is a heterogeneous chronic inflammatory disease that necessitates constant treatment and care.[1] Several drugs, such as inhaled corticosteroids (ICS), long-acting beta-2 agonists (LABA), and short-acting beta-2 agonists (SABA),

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have been used to relieve asthma symptoms, reduce exacerbation incidences, and maintain lung function.[2] Generally, asthma treatment involves a stepwise approach with these medications. Stepping up the treatment intensity is considered when patients demonstrate poor symptom control despite good adherence to current medications and appropriate inhaler usage.[2] However, in some patients, particularly those with Type 2 asthma, symptoms remain uncontrolled even with high-intensity treatment (medium to high dose ICS plus LABA or oral corticosteroids).[2-5] These patients, though a small proportion of asthma cases, are notably more susceptible to frequent and life-threatening exacerbations, which reduce the quality of life and increase the cost burden.[6-8]

Biologics are used for treating these patients.[9,10] Biologics are designed to target specific effectors, providing the potential for more effective asthma management that is inadequately controlled with standard treatments, unlike conventional chemical drugs.[10] Biologics currently approved for treating severe asthma, such as omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab, target downstream effectors of Type 2 asthma signaling pathways, such as immunoglobulin E (IgE), interleukin (IL)-4, IL-5, and IL-13.[11] Additionally, biologics targeting upstream effectors, such as IL-25, IL-33, and thymic stromal lymphopoietin (TSLP), are recently studied, which can affect both subsets of Type 2 asthma (allergic and eosinophilic asthma) and non-Type 2 asthma.[11]

Currently, the Global Initiative for Asthma (GINA) guideline recommends the use of biologics based on asthma inflammatory phenotypes and biomarkers (eg, IgE, blood eosinophil count, FeNO) associated with the characteristics of allergic or eosinophilic asthma. However, some limitations were observed. In particular, some patients with overlapping allergic and eosinophilic asthma may exhibit increased IgE and eosinophils levels, thereby meeting more than 1 selection criterion.[12,13] Conversely, various biologics are sometimes recommended without prioritization under 1 criterion. For instance, anti-IL-5, anti-IL-4Rα, or anti-TSLP are all options in severe eosinophilic asthma cases characterized by high eosinophils and exacerbation episodes in the previous year.[2] Therefore, an unmet need about which biologics may be more effective than others in treating patients with inadequately controlled asthma was observed in clinical practice.

Comparing efficacy between biologics will provide evidence to support appropriate biologic selection. As there are few comparative trials directly comparing biologics, this study used a network meta-analysis (NMA) to compare biologics by connecting the common comparators of indirect trials and providing treatment modalities based on the calculated estimates. Although there were some previous NMAs, most of them excluded omalizumab or reslizumab, or reported only 1 outcome, which restricted comparative information on efficacy.[14-18] Thus, this study performed NMA on several important outcomes for asthma treatment to compare the efficacy of biologics targeting upstream or downstream effectors of Type 2 asthma in patients with inadequately controlled asthma.

MATERIALS AND METHODS

This study was an NMA that enables simultaneous comparison of multiple treatments by pooling direct and indirect evidence from clinical trials, following the process of: 1) study search, 2) study selection, 3) data extraction, 4) quality assessment, and 5) statistical analysis. This was done according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for the reporting of systematic reviews incorporating NMAs of Health Care Interventions.[19] The protocol of this study was registered at the International Prospective Register of Systematic Reviews (PROSPERO: CRD42022324908).

Search strategy and selection criteria

Relevant articles were searched for in the major electronic databases, such as PubMed, Embase, Web of Science, and Scopus. The cutoff publication date was January 6, 2022. The search strategies were organized using the population, intervention, comparison, outcome, and study design (PICOS) framework to reduce variations in the characteristics of the articles retrieved (Table 1). The search terms selected randomized controlled trials (RCTs) or clinical trials. The

detailed search strategy and PICOS framework are documented in the supporting information file (Supplemental Tables 1 and 2).

The inclusion criteria were as follows: 1) a study population with inadequately controlled asthma despite medium to high dose ICS with a second controller, including LABA or oral corticosteroids; 2) patients aged 12 years and older; 3) treatment with biologics targeting mediators of Type 2 asthma; 4) active controls or placebo as comparators; and 5) annualized asthma exacerbation rate (AER), forced expiratory volume per second before bronchodilator use (preBD FEV1), asthma control questionnaire (ACQ), or asthma quality of life questionnaire (AQLQ) for patient-reported outcome (PRO) assessment as outcomes. Studies were excluded if they were not original articles (eg, letters, conference abstracts, editorials, case reports, protocols, reviews) or had non-extractable data. For drugs under development, biologics that failed to achieve the primary endpoint in the latest clinical trial were excluded.

To sort eligible RCTs, 2 screening steps consisting of title/abstract and full-text filtering were performed according to the predetermined inclusion and exclusion criteria and PICOS framework. At each stage, 2 researchers independently reviewed the articles from the database. Any disagreements were resolved through discussion between the 2 researchers or moderated by a senior researcher. A flow diagram of the article selection process following the PRISMA guideline is presented in Fig. 1.

PICOS	Definition
Population	Patients with inadequately controlled asthma and ages of ≥12 years
Intervention	Biologics targeting Type 2 asthma mediators
Comparison	Other active controls or placebo
Outcomes	Reporting 1 or more of the following outcomes 1. Annualized asthma exacerbation rate (AER) 2. Forced expiratory volume per second before bronchodilator use (preBD FEV1) 3. Asthma control questionnaire (ACQ)-5, -6, or -7 4. Asthma quality of life questionnaire (AQLQ)
Study design	Randomized controlled study

Table 1. PICOS framework

Study outcomes

The outcomes of interest were AER, preBD FEV1, ACQ, and AQLQ, which are frequently reported endpoints in related RCTs. Asthma exacerbation in this NMA was defined as worsening of asthma that resulted in: 1) oral corticosteroid use, 2) visiting the emergency room or accessing urgent care, or 3) hospitalization because of asthma.[2] AER is a direct indicator of worsening asthma and a key contributor to increasing asthma-related healthcare costs.[20] PreBD FEV1 refers to the maximal amount of air a person can forcefully exhale in 1 s before the use of bronchodilators. A greater value indicates better pulmonary function. The minimal clinically important difference (MCID) for preBD FEV1 has not been established, but approximately 100 mL is regarded as MCID.[21] ACQ is a PRO to measure how well asthma was controlled during the preceding week. The selected articles used 1 of 3 versions of ACQ (ACQ-5, -6, or -7). ACQ-5 assesses the patient's asthma symptoms, while ACQ-6 asks the number of short-acting bronchodilators used in addition to ACQ-5. ACQ-7 asks for the value of preBD FEV1 (%) in addition to ACQ-6. All the ACQ versions employed a 7-point Likert scale for each item, ranging from 0 (no disability) to 6 (highest disability), with scores calculated as the average of these items. The AQLQ is a PRO that assesses the asthma-related quality of life. It comprises 32 items in 4 domains; symptoms, activity limitation, emotional function, and environmental stimuli. Each item is scored from 1 to 7 points and the overall score is the average of all responses. A higher total score indicates a better quality of life.

Data extraction and risk of bias assessment

Data extraction was performed using a prespecified Excel format. The 2 researchers independently extracted data including the study information (first author name, year of publication), the study population characteristics (number of patients and mean age per group, the intensity of

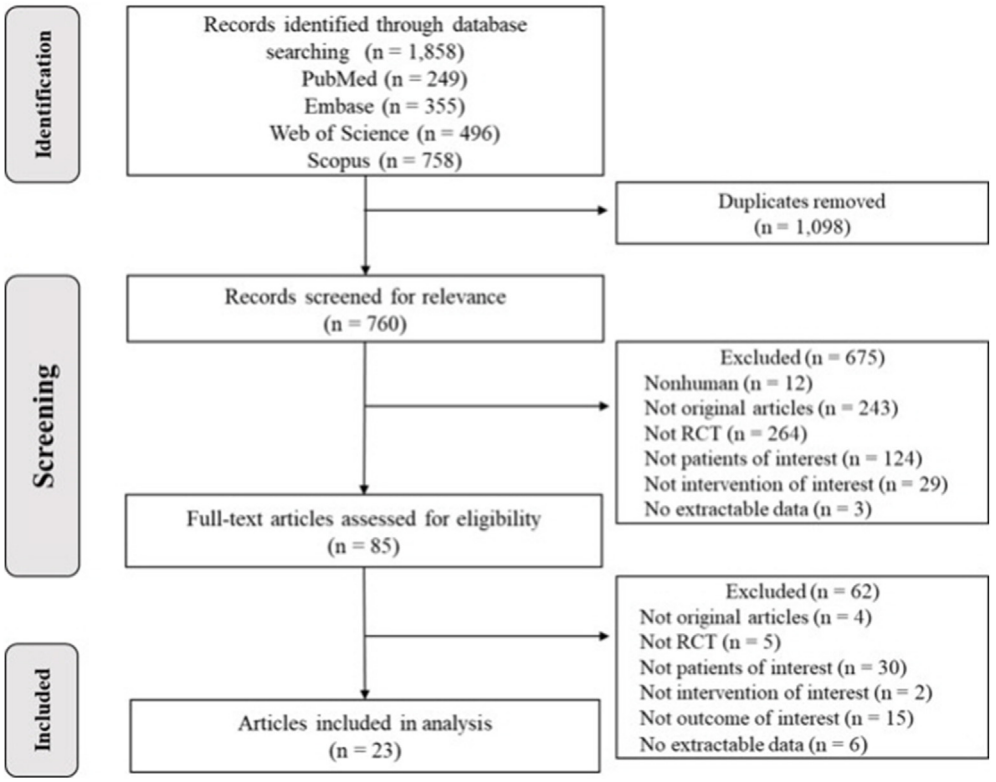

Fig. 1 Flow diagram of article selection. Abbreviation: RCT, randomized controlled study

ICS used, blood eosinophil level, number of exacerbations in the previous year), intervention(s) (type and dose of biologics, treatment duration), control(s), study outcome(s) (AER, preBD FEV1, ACQ, or AQLQ), and study results from selected articles. Because individual patient data were not usually reported in the articles, only summary estimates were used for the NMA. Mean and standard deviation (SD) were used directly for analysis. However, the mean with standard error and median with 95% confidence interval (CI) or range were used for analysis after conversion to mean with SD.

The risk of bias in the included articles was assessed according to the algorithm from the revised version of the Cochrane risk of bias tool for randomized trials (RoB 2.0).[22] The potential bias arising from each of 6 domains (randomization process, deviations from intended interventions, missing data, outcome measurement, and selective reporting) was judged as "high risk," "low risk," or "some concerns." Two researchers independently evaluated the risk of bias and cross-checked the assessment. Any discrepancies were resolved through discussion or mediation with the senior researcher.

Statistical analysis

To compare the treatment effects for asthma between biologics, this study conducted frequentist NMA using the "netmeta" package of R version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria). Continuous outcomes were expressed as standardized mean difference (SMD) with 95% CI. Meanwhile, AER was suggested as an incidence rate ratio (IRR) with 95% CI. It was calculated by the number of asthma exacerbations divided by person-years to minimize the effect of different study durations. Higgins I^2 and Cochran's Q test were used to confirm the homogeneity among studies and measure inconsistencies between direct and indirect comparisons. The I^2 index was interpreted as the percentage of the total variability in a set of effect sizes due to true heterogeneity, ie, between-studies variability. Higgins I^2 of $>75\%$ is generally regarded with considerable statistical heterogeneity among included studies.[23] Additionally, a random effects model, which allows for heterogeneous effects, was adopted to draw pooled comparative estimates and address the heterogeneous effects among the included articles, as suggested in the Cochrane Handbook, a guide for NMA, to incorporate the unexplained

heterogeneity.[23] Publication bias or small-study effects were assessed with a comparison-adjusted funnel plot. A P-score with a range of 0–1 was used to measure the mean degree of certainty that 1 treatment outperforms another, indicating the treatment ranking.[24] In accordance with the basic NMA assumptions, outcomes were computed as multiple treatment comparisons only if a head-to-head trial existed; otherwise, an indirect treatment comparison was utilized.[25] The pooled comparative estimates represent the pooled effect size between the intervention (a biologic) and the comparator (placebo or other biologic) by statistically integrating the effect sizes of the included trials.

Subgroup analyses stratified patients according to blood eosinophil levels (≥300 cells/μL or <300 cells/μL), by grouping patients as eosinophilic asthma patients, or by grouping interventions based on their target effectors. Eosinophilic asthma patients were defined as those with blood eosinophils >150 cells/μL, FeNO >20 ppb, or sputum eosinophil levels >1%.[26] Omalizumab was not included in the subgroup analysis of patients according to blood eosinophil level and eosinophilic asthma, as there were no blood eosinophil data in the articles of this drug. Subgroup analysis according to target effectors classified the biologics into 5 groups: anti-IgE, anti-IL-4/IL-13, anti-IL-5, anti-TSLP, and anti-IL-33. Sensitivity analysis to assess the reliability of this NMA was performed by excluding articles with a high risk of bias.

RESULTS

Study selection and characteristics

The initial searches retrieved 1858 articles. After screening, 23 relevant articles with 8376 participants were analyzed (Fig. 1). The detailed characteristics of the included articles are reported in Supplemental Table 3. Eight types of biologics targeting Type 2 asthma mediators were studied. Of the 23 analyzed articles, 1 directly compared the efficacy of itepekimab and dupilumab for asthma, and the others compared biologics and placebo: 5 studied omalizumab, 5 benralizumab, 3 dupilumab, 4 reslizumab, 2 mepolizumab, 3 tezepelumab, 1 itepekimab, and 1 astegolimab. The study durations ranged from 12 to 52 weeks. Owing to the limited number of head-to-head trials, the pooled effect size of the AER outcome was estimated based on indirect comparison. Meanwhile, for the preBD FEV1, ACQ, and AQLQ outcomes, biologics were compared directly, and indirectly via NMA. The netgraph of each outcome reflected the geometry of the treatment network (Fig. 2). Three of the articles were found to be at high risk of bias, originating from the randomization process and missing outcome data. The rest had a mild or moderate risk, mainly due to missing outcome data (Supplemental Fig. 1). Summary estimates of individual articles used to calculate the overall effect size for each outcome are presented in Supplemental Table 4.

Network meta-analysis with the overall study population

Table 2 shows, for each outcome, the number of articles included in the analysis, heterogeneity among studies, and inconsistency between direct and indirect comparisons. Additionally, it presents the pooled comparative estimates for each biologic compared to placebo. All biologics were significantly more effective than placebo in improving all study outcomes, except for the effects of reslizumab and omalizumab on AQLQ outcome. No heterogeneity or inconsistency was identified across the articles in the NMA for the overall study population except AER (I^2 = 55%, moderate) and ACQ outcome (I^2 = 41%, substantial).[23] Omalizumab had consistently high rankings in AER, preBD FEV1, and ACQ (Fig. 3). There were no significant differences in efficacy between the biologics in all outcomes (Supplemental Table 5). Publication bias was identified for AQLQ (p = 0.040), but not for other outcomes (Supplemental Fig. 2).

Subgroup analyses

All biologics included in the subgroup analysis of patients with eosinophil counts ≥300 cells/μL showed significantly more positive effects than placebo in improving AER and preBD FEV1 outcomes (Supplemental Table 6A). However, ACQ and AQLQ showed differing results. Only benralizumab was significantly superior to placebo on the ACQ. Further, dupilumab, tezepelumab, and benralizumab significantly

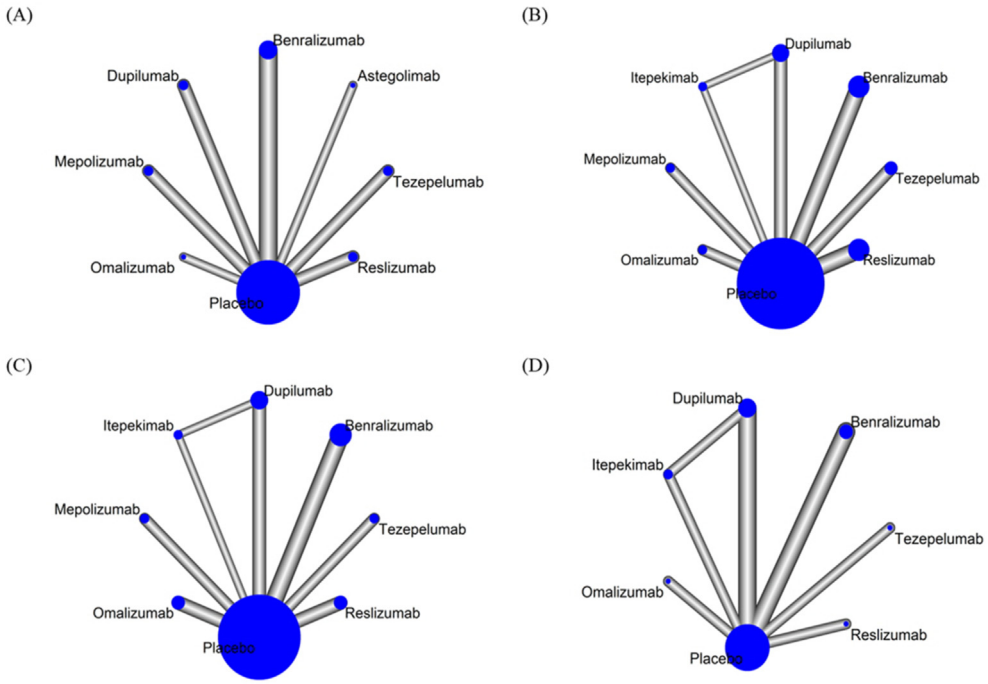

Fig. 2 Network graphs of each outcome. The network geometry of (a) AER, (b) preBD FEV1, (c) ACQ, and (d) AQLQ is presented to show the overall connection between the included trials. Each circle node represents the treatment used in the trial, and the size of the node is proportional to the number of participants in each treatment group. A line between 2 nodes indicates at least 1 direct trial whose width is proportional to the number of trials with the same comparison. Abbreviations: AER, annualized asthma exacerbation rate; preBD FEV1; forced expiratory volume per second before bronchodilator use; ACQ, asthma control questionnaire; AQLQ, asthma quality of life questionnaire

outperformed placebo on the AQLQ. When comparing biologics, only dupilumab, and tezepelumab showed significantly better effects than other biologics on improving preBD FEV1. Dupilumab was significantly superior to reslizumab and benralizumab (SMD 0.30, 95% CI 0.01–0.58; SMD 0.45, 95% CI 0.24–0.65, respectively) and tezepelumab was significantly superior to benralizumab (SMD 0.30, 95% CI 0.06–0.54) (Fig. 4A).

In patients with eosinophil levels <300 cells/μL, the pooled estimate of astegolimab was significantly superior to placebo in AER. For preBD FEV1 outcome, tezepelumab, and dupilumab were significantly better than placebo but with no significant differences between biologics (Fig. 4B). Benralizumab and tezepelumab had better treatment effects than placebo in ACQ outcomes (Supplemental Table 6B). The analysis for AQLQ outcome was not available because there were too few articles in the subgroup of patients with low eosinophil levels.

In eosinophilic asthma patients, all biologics analyzed were significantly better for AER, preBD FEV1, and ACQ than placebo. For AQLQ, dupilumab, tezepelumab, and benralizumab were significantly better than placebo (Supplemental Table 6C). Compared to benralizumab and mepolizumab, significantly greater efficacies with respect to preBD FEV1 were found in dupilumab (SMD 0.40, 95% CI 0.21–0.60; SMD 0.44, 95% CI 0.23–0.66) and tezepelumab (SMD 0.26, 95% CI 0.03–0.48; SMD 0.30, 95% CI 0.05–0.54) (Fig. 4C). The significant differences between biologics regarding pulmonary function in this study all satisfied the MCID of 100 mL.

In a subgroup analysis according to target effectors, the results showed that biologics targeting TSLP, IL-4/IL-13, IL-5 or IL-5 receptor, and IL-33 were significantly superior to placebo in all outcomes of interest (Supplemental Table 6D). However, biologics targeting IgE showed significantly better effects than placebo in AER, preBD FEV1, and ACQ, but not AQLQ. There

AER[a]		preBD FEV1		ACQ[a]		AQLQ	
Number of articles	14	Number of articles	22	Number of articles	20	Number of articles	11
Heterogeneity	55.0%	Heterogeneity	0%	Heterogeneity	41.4%	Heterogeneity	0%
Inconsistency	NA	Inconsistency	$p = 0.86$	Inconsistency	$p = 0.57$	Inconsistency	$p = 0.60$
Comparison	**Pooled comparative estimates (IRR, [95% CI])**	**Comparison**	**Pooled comparative estimates (SMD, [95% CI])**	**Comparison**	**Pooled comparative estimates (SMD, [95% CI])**	**Comparison**	**Pooled comparative estimates (SMD, [95% CI])**
Tezepelumab vs. placebo	0.39 [0.28; 0.55]	Omalizumab vs. placebo	0.62 [0.14; 1.10]	Mepolizumab vs. placebo	−0.42 [−0.61; −0.22]	Itepekimab vs. placebo	0.39 [0.16; 0.63]
Omalizumab vs. placebo	0.39 [0.25; 0.63]	Dupilumab vs. placebo	0.33 [0.21; 0.45]	Omalizumab vs. placebo	−0.35 [−0.55; −0.16]	Tezepelumab vs. placebo	0.31 [0.18; 0.44]
Mepolizumab vs. placebo	0.44 [0.32; 0.62]	Benralizumab vs. placebo	0.30 [0.21; 0.39]	Benralizumab vs. placebo	−0.35 [−0.48; −0.21]	Dupilumab vs. placebo	0.30 [0.20; 0.41]
Reslizumab vs. placebo	0.46 [0.32; 0.64]	Itepekimab vs. placebo	0.31 [0.07; 0.54]	Itepekimab vs. placebo	−0.35 [−0.63; −0.07]	Benralizumab vs. placebo	0.27 [0.13; 0.40]
Dupilumab vs. placebo	0.46 [0.32; 0.66]	Tezepelumab vs. placebo	0.30 [0.19; 0.41]	Tezepelumab vs. placebo	−0.35 [−0.56; −0.14]	Reslizumab vs. placebo	0.20 [−0.08; 0.47]
Benralizumab vs. placebo	0.52 [0.41; 0.66]	Mepolizumab vs. placebo	0.26 [0.13; 0.39]	Dupilumab vs. placebo	−0.31 [−0.48; −0.15]	Omalizumab vs. placebo	0.20 [−0.01; 0.40]
Astegolimab vs. placebo	0.57 [0.34; 0.96]	Reslizumab vs. placebo	0.26 [0.16; 0.36]	Reslizumab vs. placebo	−0.25 [−0.45; −0.05]		

Table 2. Pooled comparative estimates of network meta-analysis compared to placebo. *Table 2 shows the pooled comparative estimates of biologics compared to placebo in AER, preBD FEV1, ACQ, and AQLQ outcomes. The number of studies, magnitude of heterogeneity among studies, and inconsistency between direct and indirect comparisons in all study outcomes are presented. Abbreviations: AER, annualized asthma exacerbation rate; preBD FEV1, forced expiratory volume per second before bronchodilator use; ACQ, asthma control questionnaire; AQLQ, asthma quality of life questionnaire; NA, not addressed; IRR, incidence rate ratio; SMD, standardized mean difference. [a]AER and ACQ indicate that the lower the estimate, the better the effects of biologics compared to placebo*

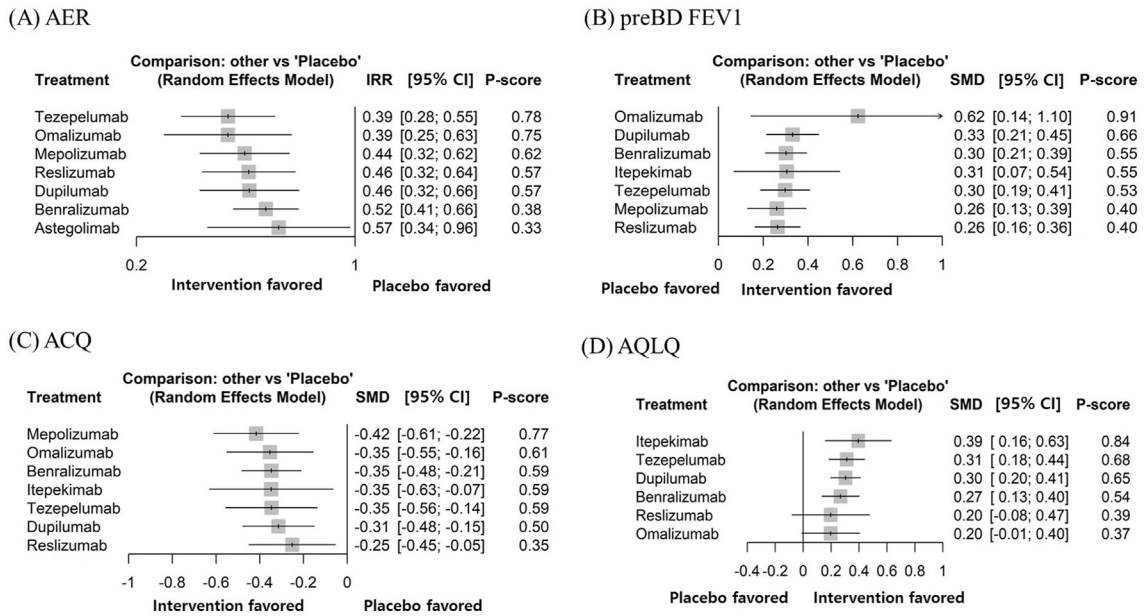

Fig. 3 Forest plot of network meta-analysis for the overall population in each outcome. The pooled comparative estimates and 95% CI of each biologic compared to placebo in (A) AER, (B) preBD FEV1, (C) ACQ, and (D) AQLQ are documented in each forest plot. Biologics are listed in order of descending treatment ranking based on P-score. Abbreviations: ACQ, Asthma control questionnaire; AER, annualized asthma exacerbation rate; AQLQ, asthma quality of life questionnaire; IRR, incidence rate ratio; preBD FEV1, forced expiratory volume per second before bronchodilator use; SMD, standardized mean difference

were no statistical differences between the biologic groups according to target.

Sensitivity analysis

Sensitivity analysis was conducted after excluding the 3 articles with a high risk of bias. The sensitivity analysis results aligned with the original results (Supplemental Table 7). All biologics included in the sensitivity analysis were significantly better than placebo in AER and preBD FEV1. Meanwhile, compared to placebo, reslizumab, and omalizumab did not show significant superiority regarding ACQ and AQLQ, respectively. Additionally, there were no significant differences between the biologics.

DISCUSSION

This study reported the comparative efficacy of biologics versus placebo or other biologics in patients with inadequately controlled asthma regarding exacerbation, pulmonary function, asthma control, and asthma quality of life. All biologics were significantly more effective than placebo for AER, preBD FEV1, and ACQ outcomes, but no significant differences were found between biologics. However, significant differences between biologics appeared in certain subgroups, particularly in improving preBD FEV1. In patients with eosinophil counts $\geq$300 cells/μL, dupilumab showed significantly better effects than reslizumab and benralizumab. Similarly, tezepelumab significantly outperformed benralizumab. Dupilumab, and tezepelumab showed significantly favorable effects in improving preBD FEV1 compared to benralizumab and mepolizumab in patients with eosinophilic asthma. Differences between dupilumab or tezepelumab and others in preBD FEV1 met the MCID.

This study used NMA to compare the effects of multiple biologics simultaneously. NMA enables comparisons between treatments despite no direct comparison trials.[27] It assesses comparative estimates between treatments, indicating the difference in their effect size. NMA improves the precision of these estimates by synthesizing data from direct and indirect trials, thereby indicating pooled comparative estimates. However, some key assumptions need to be satisfied before conducting an NMA: transitivity, similarity, and consistency. Several methodological and statistical approaches can be used to satisfy these assumptions. First, robust inclusion and

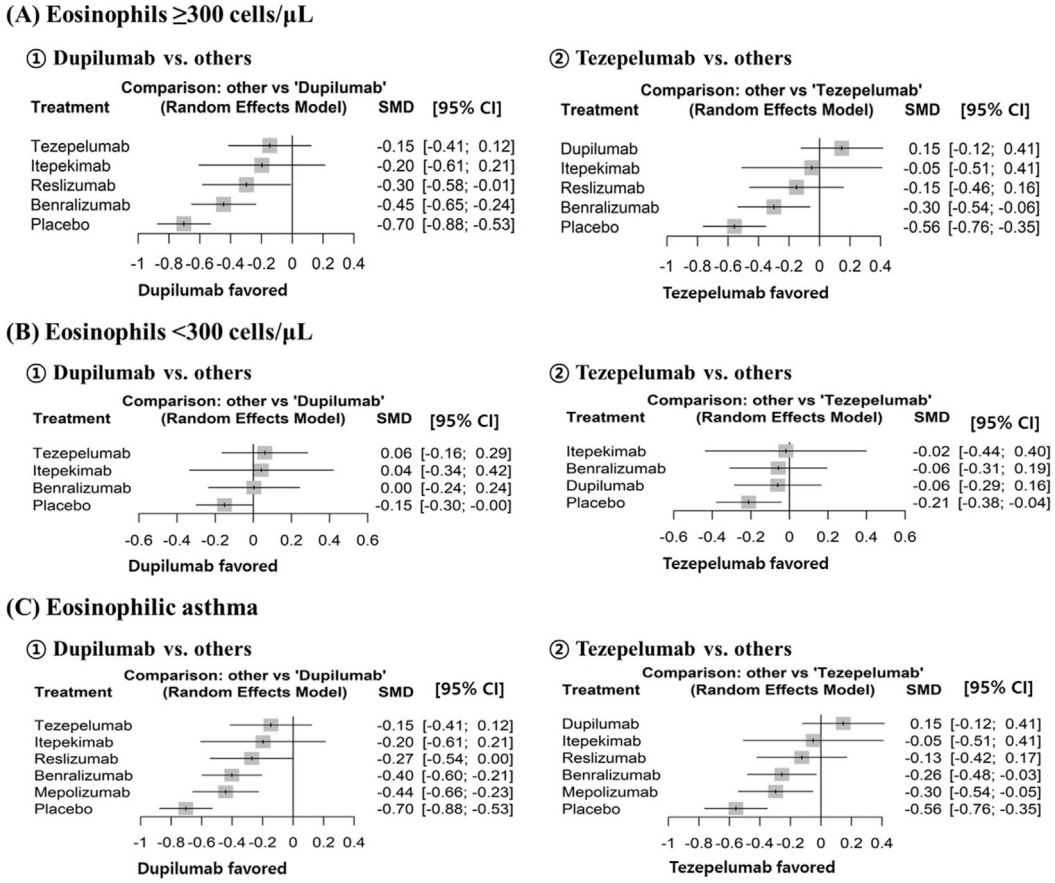

Fig. 4 Forest plot of network meta-analysis for subgroups in preBD FEV1. The pooled comparative estimates and 95% CI for patients with (A) eosinophil levels ≥300 cells/μL, (B) eosinophil levels <300 cells/μL, and (C) eosinophilic asthma are presented. Comparison of effects between dupilumab or tezepelumab and other biologics on preBD FEV1 outcomes are shown as forest plots. The lower estimates in these plots indicate better effects of dupilumab or tezepelumab compared to others in improving preBD FEV1. Abbreviations: preBD FEV1, forced expiratory volume per second before bronchodilator use; SMD, standardized mean difference

exclusion criteria are adopted in the article selection process. Second, a random effects model can be applied to address heterogeneity that is difficult to explain.[23] Accordingly, 2 independent researchers applied strict criteria to select articles and random effects model was applied in this study. Additionally, Higgins I^2 was calculated to confirm the absence of statistically considerable heterogeneity among the included studies (Table 2). Moreover, subgroup analyses were conducted based on the specified study population conditions, such as eosinophil levels, to rule out some differences that may not be fully detected by statistical analysis.

The potential favorable effects of dupilumab and tezepelumab in subgroup analyses of patients with elevated eosinophil counts or eosinophilic asthma may be partly explained by the biologics' mechanisms of action. Dupilumab, compared to anti-IL-5 biologics, demonstrated a broader mechanism of action and has also been approved for atopic dermatitis, chronic rhinosinusitis with nasal polyposis, and eosinophilic esophagitis, which often occur with asthma.[28-30] It can affect allergic and eosinophilic asthma, unlike anti-IL-5 biologics. It binds to the alpha subunit of IL-4, which hinders the binding of IL-4 and IL-13 to the receptor. Since IL-4 and IL-13 are key mediators of Type 2 inflammation, dupilumab can comprehensively suppress both allergic and eosinophilic subtypes of Type 2 inflammation. In a mouse model, blocking IL-5 only reduced eosinophil levels, whereas IL-4, and IL-13 impacted several features of Type 2 inflammations, such as IgE production, trafficking of eosinophils, activating immune cells and cytokines, and mucus secretion.[31] Furthermore,

dupilumab may exert better efficacy on pulmonary function than IL-5-related biologics because IL-4 and IL-13 induce airway hyperresponsiveness, airway remodeling through goblet cell hyperplasia and collagen deposition, and mucus production. Whereas, IL-5 mainly focuses on the maturation, migration, proliferation, and activation of eosinophils.[32–34] In isolated human small airways, IL-4 and IL-13 induced airway hyperresponsiveness, but IL-5 did not.[35] Additionally, given the bidirectional relationship between asthma and several concurrent diseases,[36–39] dupilumab may have a better effect on pulmonary function than other biologics by improving the symptoms of these comorbidities.

Several mechanisms explained the possibility of better efficacy of tezepelumab. First, tezepelumab exerts extensive effects not only on 2 subtypes of Type 2 asthma (allergic and eosinophilic) but also non-Type 2 asthma, while the effects of anti-IL-5 biologics may be limited to eosinophilic asthma. It is attributed to its target TSLP, the upstream effector of the Type 2 asthma inflammatory process.[40,41] TSLP initiates the inflammatory cascade affecting both allergic eosinophilic and non-allergic eosinophilic Type 2 asthma. Furthermore, tezepelumab can impact Type 2 and non-Type 2 inflammatory asthma, because TSLP promotes neutrophilic inflammation, a key characteristic of non-Type 2 asthma.[42,43] Second, there is growing evidence that TSLP induces airway smooth muscle cell migration and stimulates fibroblast cells to produce collagen, thereby causing airway structural changes (eg, thickening, hyperplasia, hypertrophy, and fibrosis).[44–46] This impact of tezepelumab on airway remodeling may explain its better efficacy in pulmonary function shown in these results.

Moreover, the results of this NMA provide additional clues toward addressing the unmet treatment needs of patients with inadequately controlled asthma. First, itepekimab and astegolimab were significantly better than placebo and demonstrated similar efficacy with other biologics. They target IL-33, which has a pivotal role in asthma pathogenesis. As an alarmin cytokine positioned at the top of the signaling pathway of asthma inflammation, IL-33 stimulates the TSLP-dendritic cells-OX40-ligand axis, causing initiation and maintenance of Th2 cell-mediated inflammation.[47] Further, IL-33 is involved in the production, activation, and survival of mast cells, eosinophils, and basophils.[48] Therefore, given that some patients still do not respond to currently approved biologics, anti-IL-33 biologics may provide another option. Further studies will be needed to establish their effects fully. Second, while benralizumab and reslizumab target the same cytokine (IL-5) or cell type (eosinophils), benralizumab showed significantly more favorable effects on PROs, such as ACQ, or AQLQ, than placebo, but reslizumab did not. Benralizumab hinders IL-5 receptor binding and thereby inhibits differentiation and maturation of eosinophil in the bone marrow via its Fab domain binding to the α subunit of the IL-5 receptor. Further, benralizumab strongly triggers apoptosis of circulating and tissue-resident eosinophils through antibody-dependent cell-mediated cytotoxicity via its Fc domain binding to FcγRIIIa expressed on natural killer cells, neutrophils, and macrophages.[49] This dual function significantly induces and maintains a larger eosinophil depletion than that caused by other biologics targeting IL-5.[50,51] Therefore, benralizumab's effects can translate into a fast and considerable improvement of PROs. Current asthma guidelines usually indicate that 1 of the anti-IL-5 biologics can be used in treating patients with severe eosinophilic asthma without a detailed explanation of differences in effectiveness between the anti-IL-5 biologics. Therefore, this study's findings may provide clues toward determining which anti-IL-5 biologics to use in a clinical setting. Although this NMA was unable to examine safety outcomes due to limited data from included studies, further research on safety outcomes would provide a deeper understanding of the safety and efficacy of anti-IL-5 biologics.

This study has some meaningful strengths. First, to the best of our knowledge, this study is a state-of-the-art NMA involving biologics that have been developed or are under development for asthma, such as anti-IL-33 biologics.[26] Second, it can help clinicians select a specific biologic considering each patient's treatment goals in addition to asthma phenotype by presenting comparative effects among biologics that are not documented

in current guidelines. Third, the results show the potential of anti-IL-33 (itepekimab and astegolimab) in terms of their treatment efficacy for patients with inadequately controlled asthma. However, further studies are needed to validate our results.

This study also has limitations to be considered when interpreting the results. First, there may have been some heterogeneity regarding the study population or study outcomes in the analyzed articles. The possibility of moderate and substantial heterogeneity was observed in AER and ACQ outcomes, respectively. Baseline asthma severity or asthma type (allergic or eosinophilic) varied based on the study population of the included articles. Additionally, the use of 3 ACQ versions (ACQ-5, -6, or -7) in this NMA may have caused heterogeneity in PROs. This NMA study used a random effects model and performed subgroup analyses to resolve potential heterogeneity issues. However, differences between articles that may not be fully detected by statistical analysis need to be considered when interpreting study results. Second, articles with omalizumab were not included in the subgroup analyses based on eosinophil levels because the original studies did not perform blood eosinophil counts. Therefore, the results of subgroup analysis according to eosinophil counts should be interpreted with this in mind. Third, the AER outcome was carried out by indirect analysis because of the limited head-to-head trials. More direct comparison studies between biologics are needed. Lastly, this study focused on the inflammatory phenotype of asthma and its relevant biomarkers, while some other factors can be associated with asthma control. In particular, an association between obesity and levels of Type 2 biomarkers, including eosinophils, has been reported.[52] Obesity is known to promote airway remodeling triggered by excess Type 2 cytokine-producing cell and eosinophil accumulation.[53] Unfortunately, the trials included in this analysis reported summary estimates rather than individual patient data and had limited information on obesity. Therefore, it was not possible to assess the effect of patient weight on the outcomes of the current study.

Although this NMA did not reveal a significant difference between biologics for exacerbation, pulmonary function, and PROs in patients with inadequately controlled asthma, subgroup analyses showed that some biologics had significant advantages on pulmonary function or some PROs. Therefore, the results of this study can be considered with phenotypes and biomarkers when selecting biologics for the treatment of inadequately controlled asthma. This may help clinicians in their decision-making and serve as the foundation for future studies identifying the effects of biologics targeting upstream effectors.

Abbreviations

ICS, inhaled corticosteroids; LABA, long-acting beta-2 agonists; IL, interleukin; TSLP, thymic stromal lymphopoietin; NMA, network meta-analysis; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PICOS, population, intervention, comparison, outcome, and study design; RCT, randomized controlled trial; AER, annualized asthma exacerbation rate; preBD FEV1, forced expiratory volume per second before bronchodilator use; ACQ, asthma control questionnaire; AQLQ, asthma quality of life questionnaire; PRO, patient-reported outcome; MCID, minimal clinically important difference; SD, standard deviation; CI, confidence interval; SMD, standardized mean difference; IRR, incidence rate ratio

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Availability of data and materials

All data relevant to the current study are included in this article and its Supplemental file.

Author contributions

Conception and design: HK, KK; Data acquisition: HK, KK; Data Analysis: HK, MGK, and KK; Interpretation: HK, MGK, SK, and KK; Original Draft: HK; Critical revision: HK, MGK, SK, JL, YB, JP, and KK. All authors read and approved the final version of the manuscript.

Ethics approval

This network meta-analysis is based on data from published literature and does not perform testing of human or animal subjects. Therefore, the ethics approval was not required.

Authors' consent for publication
The publication of the manuscript to this journal have been approved by all authors and institutes where the work was carried out.

Confirmation of unpublished work
The authors confirm that this manuscript is original, has not been published before, and is not currently being considered for publication elsewhere.

Declaration of competing interest
The authors report no competing interests.

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Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2024.100934.

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