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Comparison of the Efficacy and Safety of Different Biologics in the Treatment of Moderate-to-Severe Eosinophilic Asthma in Children: A Network Meta-analysis

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ADMINISTRATIVE INFORMATION

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INTRODUCTION

Review question / Objective The objective of this network meta-analysis is to systematically evaluate and compare the efficacy and safety of four biologic agents—omalizumab, mepolizumab, benralizumab, and dupilumab—in the treatment of moderate-to-severe eosinophilic asthma in children and adolescents, in order to provide evidence-based guidance for clinical decision-making. The review question is defined using the PICOS framework as follows:

Population (P): Children and adolescents aged ≤ 18 years with a diagnosis of moderate-to-severe eosinophilic asthma (EA), defined by elevated peripheral blood eosinophil counts (typically ≥ 150 – 300 cells/mm³) and/or evidence of type 2-high inflammation.

Intervention (I): Biologic therapies, including omalizumab (anti-IgE), mepolizumab (anti-IL-5), benralizumab (anti-IL-5R α), and dupilumab (anti-

IL-4R α), administered as add-on therapy to standard asthma treatment.

Comparator (C): Placebo or standard asthma therapy (e.g., inhaled corticosteroids with or without long-acting beta-agonists).

Outcomes (O): Primary outcome—annual rate of acute asthma exacerbations. Secondary outcomes—changes in forced expiratory volume in one second (FEV₁), incidence of adverse events (AEs), incidence of serious adverse events (SAEs), asthma control, and quality of life.

Study design (S): Randomised controlled trials (RCTs) published in English or Chinese.

Through this comprehensive synthesis, we aim to determine the comparative ranking of these biologics and identify the optimal treatment strategy for different clinical scenarios in paediatric eosinophilic asthma management.

Condition being studied Eosinophilic asthma (EA) is a distinct phenotypic subtype of asthma characterized by elevated levels of eosinophils in

the peripheral blood and/or airways, driven predominantly by type 2 (T2) airway inflammation. In children, EA represents one of the most common and clinically challenging forms of asthma, accounting for a substantial proportion of moderate-to-severe paediatric asthma cases. The underlying pathophysiology involves the overproduction of T2 cytokines—particularly interleukin (IL)-4, IL-5, and IL-13—which promote eosinophil maturation, recruitment, and survival in the airway mucosa. This eosinophilic infiltration leads to chronic airway inflammation, epithelial damage, airway hyperresponsiveness, mucus hypersecretion, and ultimately, airway remodelling.

Clinically, children with moderate-to-severe EA typically present with frequent and severe acute exacerbations, persistent airflow limitation, poor response to conventional therapies (including high-dose inhaled corticosteroids and long-acting beta-agonists), and significantly impaired quality of life. Epidemiological data indicate that 50%–90% of patients with severe asthma exhibit eosinophilic inflammation, and the prevalence of EA is particularly high among the paediatric population. Despite the availability of standard stepwise pharmacological approaches, a considerable number of children with moderate-to-severe EA remain inadequately controlled, highlighting an urgent need for more targeted therapeutic strategies. The recognition of EA as a distinct pathophysiological entity has paved the way for the development of biologic agents that specifically target key components of the T2 inflammatory cascade—including anti-IgE (omalizumab), anti-IL-5 (mepolizumab), anti-IL-5R α (benralizumab), and anti-IL-4R α (dupilumab)—offering new hope for personalised management in this vulnerable population. This network meta-analysis aims to systematically compare the efficacy and safety of these biologics to guide evidence-based clinical decision-making for children with moderate-to-severe EA.

METHODS

Participant or population Children and adolescents aged ≤ 18 years with a clinical diagnosis of moderate-to-severe eosinophilic asthma (EA). Diagnosis is defined by elevated peripheral blood eosinophil counts (typically ≥ 150 – 300 cells/mm³, varying according to study criteria) and/or evidence of airway eosinophilic inflammation, or classified as type 2-high phenotype according to trial definitions. Studies focusing on adults (aged > 18 years) or mixed populations without separately reported paediatric data will be excluded.

Intervention The interventions of interest are biologic therapies targeting type 2 inflammatory pathways, specifically:

Omalizumab (anti-IgE monoclonal antibody)

Mepolizumab (anti-IL-5 monoclonal antibody)

Benralizumab (anti-IL-5R α monoclonal antibody)

Dupilumab (anti-IL-4R α monoclonal antibody)

These biologics are administered as add-on therapy to standard asthma treatment (e.g., inhaled corticosteroids with or without long-acting beta-agonists). The comparators include placebo or standard asthma therapy alone. Studies evaluating other biologics (e.g., lebrikizumab, tezepelumab) will be included only if they meet the eligibility criteria, but they are not the primary focus of this review.

Comparator The comparators of interest in this review are:

Placebo (matching placebo administered as add-on to standard asthma therapy)

Standard asthma therapy alone (e.g., inhaled corticosteroids with or without long-acting beta-agonists, with or without other controller medications), without biologic add-on treatment

Direct head-to-head comparisons between different biologics will also be included if available.

Study designs to be included Only randomised controlled trials (RCTs) will be included in this review. Eligible studies must compare at least one of the specified biologics (omalizumab, mepolizumab, benralizumab, or dupilumab) with placebo or standard asthma therapy in children with moderate-to-severe eosinophilic asthma. The following study types will be excluded: non-randomised studies, observational studies, case reports, case series, editorials, letters, reviews, systematic reviews, meta-analyses, and animal or in vitro studies. Cluster-randomised trials and crossover trials will be considered for inclusion if they.

Eligibility criteria In addition to the PICOS-defined criteria, the following eligibility requirements will apply:

Inclusion criteria:

Studies with a minimum follow-up duration of at least 12 weeks to ensure adequate assessment of efficacy and safety outcomes.

Studies reporting at least one of the outcomes of interest: annual rate of acute asthma exacerbations, changes in lung function (FEV₁),

adverse events (AEs), or serious adverse events (SAEs).

Studies with available full text or sufficient data in conference abstracts to allow data extraction. For studies with mixed adult and paediatric populations, inclusion requires that paediatric-specific subgroup data are separately reported and extractable.

Exclusion criteria:

Studies in which the biologic agent is used for conditions other than asthma (e.g., atopic dermatitis, chronic urticaria) without separate reporting of asthma outcomes.

Studies with <10 participants per treatment arm, as such small studies are unlikely to provide reliable effect estimates.

Studies published as abstracts only, without full-text publication and without sufficient data for analysis.

Duplicate publications: when multiple reports of the same trial are identified, the most complete or most recent publication will be included.

Studies with unclear or insufficient outcome data that cannot be obtained after contacting the authors.

Information sources The following electronic databases will be searched for relevant studies:

PubMed

Embase

Cochrane Library

Web of Science

China National Knowledge Infrastructure (CNKI)

Wanfang Data Knowledge Service Platform (WANFANG)

VIP (Chongqing VIP Chinese Science and Technology Periodical Database)

In addition to electronic database searches, the following supplementary sources will be explored:

Reference lists of included studies, previous systematic reviews, and meta-analyses on related topics will be manually screened to identify additional eligible studies.

Grey literature, including conference abstracts and proceedings from major respiratory and allergy societies (e.g., ERS, ATS, EAACI), will be searched to identify unpublished or ongoing studies.

Clinical trial registries (e.g., ClinicalTrials.gov, WHO ICTRP) will be consulted to identify completed but unpublished trials and to verify trial protocols.

No restrictions will be applied based on publication status (published, unpublished, or in-press), but only studies published in English or Chinese will be included.

The search will cover studies published up to March 31, 2026.

Main outcome(s) The primary outcome of this review is:

Annual rate of acute asthma exacerbations: defined as the number of asthma exacerbations requiring systemic corticosteroids (oral or parenteral) and/or emergency department visits or hospitalisations per patient per year. Effect measure: risk ratio (RR).

Secondary outcomes include:

Changes in forced expiratory volume in one second (FEV₁): measured as absolute change or percent change from baseline to end of treatment. Effect measure: standardised mean difference (SMD).

Incidence of adverse events (AEs): including any treatment-emergent adverse events. Effect measure: risk ratio (RR).

Incidence of serious adverse events (SAEs): including events that are life-threatening, require hospitalisation, or result in death. Effect measure: risk ratio (RR).

Asthma control: assessed using validated instruments such as the Asthma Control Questionnaire (ACQ) or Asthma Control Test (ACT). Effect measure: standardised mean difference (SMD).

Quality of life: assessed using validated instruments such as the Paediatric Asthma Quality of Life Questionnaire (PAQLQ). Effect measure: standardised mean difference (SMD).

Timing of outcome assessment: outcomes will be extracted at the time points reported in the original studies, with preference given to the end of the treatment period (ranging from 12 to 52 weeks). Where multiple time points are reported, the longest available follow-up data will be used. Effect measures will be summarised with 95% confidence intervals. Statistical significance will be set at $P < 0.05$.

Quality assessment / Risk of bias analysis The methodological quality and risk of bias of the included randomised controlled trials will be assessed independently by two reviewers using

the Cochrane Risk of Bias Tool (RoB 1.0) . Any disagreements will be resolved through discussion with a third reviewer.

The following seven domains will be evaluated for each included study:

Random sequence generation (selection bias): whether the allocation sequence was adequately generated (e.g., computer-generated random numbers, random number tables).

Allocation concealment (selection bias): whether the allocation sequence was adequately concealed from participants and investigators prior to assignment (e.g., central randomisation, sequentially numbered sealed envelopes).

Blinding of participants and personnel (performance bias): whether blinding of participants and study personnel was implemented to prevent knowledge of the assigned intervention.

Blinding of outcome assessment (detection bias): whether blinding of outcome assessors was implemented to prevent knowledge of the assigned intervention during outcome measurement.

Incomplete outcome data (attrition bias): whether incomplete outcome data were adequately addressed, including reporting of withdrawals, dropouts, and intention-to-treat analysis.

Selective reporting (reporting bias): whether the study reported all pre-specified outcomes as described in the trial protocol or methods section.

Other sources of bias: including baseline imbalance between groups, early termination of the trial, or other potential sources of bias not covered above.

Each domain will be rated as "low risk" , "high risk" , or "unclear risk" based on the criteria provided in the Cochrane Handbook. Studies will not be excluded based on the risk of bias assessment; however, the potential influence of bias on the overall findings will be considered in the discussion.

The risk of bias assessment will be performed using Review Manager 5.3 software, and the results will be presented as both a "risk of bias graph" (displaying the proportion of studies with each risk level across all domains) and a "risk of bias summary" (displaying the risk level for each domain for each individual study). This information will be used to inform the interpretation of the

meta-analysis results and to conduct sensitivity analyses excluding studies at high risk of bias if deemed appropriate.

Strategy of data synthesis Software: All statistical analyses will be performed using Stata 16.0 software with the network package, and Review Manager 5.3 will be used for risk of bias assessment.

Effect measures: For dichotomous outcomes (annual rate of acute asthma exacerbations, incidence of adverse events, incidence of serious adverse events), effect sizes will be expressed as risk ratios (RR) with 95% confidence intervals (95% CI). For continuous outcomes (FEV₁ changes, asthma control scores, quality of life scores), effect sizes will be expressed as standardised mean differences (SMD) with 95% CI, as different measurement instruments may be used across studies. Statistical significance will be set at $P < 0.05$.

Network meta-analysis: A frequentist network meta-analysis (NMA) will be conducted using a consistency model. Network evidence maps will be constructed to illustrate the direct comparisons among interventions, where nodes represent treatments (with node size proportional to sample size) and edges represent direct comparisons (with edge thickness proportional to the number of studies). The results will be presented as league tables, showing pairwise comparisons between all interventions. Heterogeneity tests will be performed to assess the consistency between direct and indirect evidence if closed loops are present in the evidence network.

Ranking of interventions: The relative ranking of each intervention for each outcome will be assessed using the cumulative ranked area under the curve (SUCRA) . A higher SUCRA value (closer to 100%) indicates a higher probability of being the best treatment, whereas a lower SUCRA value (closer to 0%) indicates a lower probability of being the best treatment.

Sensitivity analysis: To test the robustness of the results, a leave-one-out method will be employed, in which each study is sequentially excluded and the NMA is re-run to observe whether the pooled effect sizes and SUCRA rankings change substantially.

Specificity analysis: To assess the stability of the conclusions under different study restriction conditions, specificity analyses will be performed by excluding Chinese-language studies and by

excluding small-sample studies ($n < 200$ per arm or total sample size < 200), followed by re-running the NMA to observe changes in effect estimates and SUCRA rankings.

Publication bias: Publication bias and small-study effects will be assessed by visual inspection of funnel plots for the outcomes with the largest number of included studies. If asymmetry is detected, possible causes (e.g., publication bias, small-study effects, true heterogeneity) will be explored.

Subgroup analyses: Planned subgroup analyses include: (1) by baseline blood eosinophil count (≥ 300 vs. 150–300 cells/ μL), (2) by age group (6–11 years vs. 12–17 years), and (3) by treatment duration (≤ 24 weeks vs. > 24 weeks). These will be performed only if sufficient data are available.

Handling of missing data: Where necessary data are missing, attempts will be made to contact the corresponding authors of the original studies. If data remain unavailable, the study will be excluded from the relevant analysis, and this will be acknowledged as a limitation.

Subgroup analysis Subgroup analyses will be conducted to explore potential sources of heterogeneity and to assess whether treatment effects vary according to specific patient or study characteristics. The following subgroup analyses are planned, provided that sufficient data are available:

1. By baseline blood eosinophil count (BEC):

High threshold group: $\text{BEC} \geq 300$ cells/ μL

Low threshold group: BEC 150–300 cells/ μL

This analysis aims to determine whether the efficacy of biologics differs by the degree of eosinophilic inflammation at baseline, as previous studies have suggested that patients with higher eosinophil levels may derive greater benefit from anti-IL-5/anti-IL-5Ra and anti-IL-4Ra therapies.

2. By age group:

School-age children: 6–11 years

Adolescents: 12–17 years

This analysis will assess whether age-related differences in asthma pathophysiology, pharmacokinetics, or treatment response exist, given that children and adolescents may have

different disease trajectories and therapeutic needs.

3. By treatment duration:

Short-term treatment: ≤ 24 weeks

Long-term treatment: > 24 weeks

This analysis aims to determine whether treatment duration modifies the observed efficacy and safety profiles, as some biologics may require longer exposure to achieve maximal clinical benefit.

4. By prior exacerbation history (if data available):

Frequent exacerbators: ≥ 2 exacerbations in the previous year

Infrequent exacerbators: < 2 exacerbations in the previous year

5. By concomitant atopic conditions (if data available):

With allergic rhinitis or atopic dermatitis

Without allergic rhinitis or atopic dermatitis

Methodological approach: Subgroup analyses will be performed using meta-regression or by splitting the network into subgroups and comparing the treatment rankings and effect sizes between subgroups. Interaction tests will be used to assess whether the differences between subgroups are statistically significant.

Interpretation: Subgroup analyses will be considered exploratory rather than confirmatory. Results will be interpreted with caution, and findings will be presented descriptively. If data are insufficient for quantitative synthesis, a narrative summary will be provided. The limitations of subgroup analyses, including the risk of multiple testing and insufficient statistical power, will be acknowledged in the Discussion.

Sensitivity analysis Sensitivity analyses will be conducted to assess the robustness and reliability of the network meta-analysis findings by testing whether the results are influenced by specific methodological decisions, study characteristics, or individual studies.

1. **Leave-one-out analysis:** To evaluate whether the overall findings are driven by any single study, we will sequentially exclude each included study and re-perform the network meta-analysis. The pooled

effect estimates and SUCRA rankings will be compared with those from the primary analysis. If the exclusion of a particular study leads to a substantial change in the results, the influence of that study will be discussed, and the study characteristics will be examined to identify possible reasons for its impact.

2. Exclusion of high risk-of-bias studies: Studies assessed as having a high risk of bias in one or more key domains (e.g., lack of allocation concealment, absence of blinding, or high attrition) will be excluded from a separate sensitivity analysis. The results will be compared with the primary analysis to determine whether the inclusion of methodologically weak studies affects the overall conclusions. This analysis will help ensure that the review's findings are not unduly influenced by studies with important methodological limitations.

3. Fixed-effect vs. random-effects model: Although the primary analyses will be performed using a random-effects model to account for anticipated heterogeneity across studies, a sensitivity analysis using a fixed-effect model will also be conducted. If the results differ substantially between the two models, this will indicate that the choice of statistical model may influence the interpretation of the findings, and potential sources of heterogeneity will be explored further.

4. Exclusion of small-sample studies: Studies with small sample sizes (e.g., < 200 total participants) will be excluded in a sensitivity analysis to evaluate whether the results are influenced by studies with limited statistical precision. This is particularly relevant given that small studies may be more susceptible to publication bias and random error.

5. Exclusion of specific intervention groups: If direct head-to-head comparisons between specific biologics are limited, the exclusion of studies involving less commonly used agents (e.g., lebrikizumab) will be considered to determine whether the inclusion of these treatments affects the overall ranking of the primary biologics of interest.

Interpretation: The results of all sensitivity analyses will be reported and compared with the main findings. If the conclusions remain consistent across different analytical approaches, the robustness of the evidence will be strengthened. If substantial differences are observed, the possible reasons for these discrepancies will be discussed, and the findings will be interpreted with appropriate caution. All sensitivity analyses will be

conducted for the primary outcome (annual rate of acute asthma exacerbations) and, where feasible, for key secondary outcomes (adverse events and serious adverse events).

Country(ies) involved China, United States, France, Italy, Spain, Netherlands.

Keywords eosinophilic asthma; children; biologics; network meta-analysis; efficacy; safety.

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