Efficacy and safety of monoclonal antibodies in patients with uncontrolled asthma: a protocol for a systematic review and network meta-analysis

Review question

In patients with uncontrolled asthma, what is the efficacy and safety of monoclonal antibodies compared to one another when added to standard of care, and when compared to standard of care alone?

Searches

We will perform systematic literature searches of MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), FDA database, and EMA database from inception to December 2021 and then monitor subsequently for any new randomized trials. We will search randomized controlled trials in human subjects published in any language. Forward and backward citation searches will also be included

Types of study to be included

Published or unpublished randomized controlled trials of any size and in any language that compare monoclonal antibodies against placebo, standard of care, or another monoclonal antibody for treatment of asthma.

We will exclude review articles, commentaries, pharmacokinetic, pharmacodynamic and mechanistic studies, methodological articles; cross-sectional studies; cohort studies; reports only presented as conference abstracts unless they are conference abstracts from 2021 or 2022 of RCTs anticipated to be published in full publication form within the subsequent 12 months; studies exclusively evaluating pediatric patients less than 6 years old, pregnant patients; and studies with no comparison group.

Condition or domain being studied

Asthma

Participants/population

Studies including patients 6 years of age or older, with confirmed diagnosis of asthma (mild, moderate and severe).

Intervention(s), exposure(s)

Any monoclonal antibodies used for treatment of asthma. This includes but is not limited to:

Anti-IL-5 mAb (reslizumab, mepolizumab)
Anti-IL5Rα receptor mAb (benralizumab)
Anti-IL-4 mAb (pascolizumab)
Anti-IL-4Ralpha mAB (dupilumab, IMA-638)
Anti-IL-13 (lebrikizumab, tralokinumab, dectrekumab, anrukinzumab, cendakimab, IMA-026)
Anti-IL-13/IL-4
Anti-IL-13/IL-17
Anti-IgE mAb (omalizumab, ligelizumab, quilizumab)
Anti-Siglec-8 mAb (Antolimab)
Anti-IL-17 (Secukinumab)
Anti-IL-17 receptors (Brodalumab)
Anti-TSLP (Tezepelumab, CSJ117)
Anti-TSLPR
Anti-CCR4 (Mogamulizumab)
Anti-CCL11
Anti-TNF (Adalimumab, Certolizumab, Golimumab, Infliximab)
Anti-P40 subunit of IL-12/IL-23 (Ustekinumab)
Anti-Bc
Anti-IL-1 (Canakinumab)
Anti-IL-1R
Anti-IL-22 (Fezakinumab)
Anti-IL-31 (Nemolizumab)
Anti-IL-9 (Medi-528/Enokizumab)
Anti-IL-8
Anti-IL 33 (REGN3500/SAR440340/itepekimab, ANB020/etokimab)
Anti-ST2 (RG6149/AMG282/Astegolimab, GSK3772847/melrilimab)
Anti-IL 23 (risankizumab)
Anti-OX40L (Oxelumab)
Any doses, schedule of administration and route of administration will be included.

Concurrent treatments:
Use of other pharmacological treatments that are part of the standard care of asthma treatment. This includes ICS, LAMA, SAMA, LABA, SABA, systemic corticosteroids, theophylline and antileukotriene agents.

Comparator(s)/control

Placebo, standard of care, or another monoclonal antibody. Should sufficient time and resources allow, and if populations sufficiently similar, we may also look into comparison of biologics with other competing interventions (eg. bronchial thermoplasty and macrolides [azithromycin]).

Comparison pairs:
Our main comparison pairs will include the following:
Any individual monoclonal antibody versus placebo, versus standard of care, or versus a different monoclonal antibody.

Main outcome(s)

1. Moderate/severe asthma exacerbations, defined by any of the criteria below: (one or more exacerbation, and number of events (annualized exacerbation rates).
    - Systemic corticosteroid use for asthma exacerbation
    - Emergency department visit for asthma exacerbation
    - Hospitalization for asthma exacerbation
    - Intensive care visit or intubation for asthma exacerbation
    - If reported only as a composite outcome, then this will also be accepted. We will attempt to obtain all individual components from study authors.
2. Asthma control eg. Asthma control questionnaire, with preference from highest to lowest being ACQ5, AC6, then tools such as ACT or AC7).
3. Any asthma health-related quality of life measure, eg. Asthma Quality of Life Questionnaire (AQLQ)
4. Adverse outcomes (each will be analyzed separately.):
    a. Serious adverse events (includes mortality).
    b. Discontinuation due to adverse event.

Measures of effect

Absolute and relative risks with 95% confidence intervals will be used for the outcomes outlined above, displayed using forest plots and calculated using random effects models. Continuous outcomes will summarized as between group mean differences.

Data extraction (selection and coding)

We will translate non-English records. Two trained reviewers will, independently and in duplicate, screen identified abstracts and full-texts in Covidence using a pilot-tested standardized data form. Two trained reviewers will extract data independently and in duplicate. Reviewers will resolve discrepancies leading to consensus. If disagreements remain, a third researcher will adjudicate the conflict. All analyses will be by intention to treat (i.e., include all randomized patients to any treatment arm). Baseline characteristics to be captured include age, sex, obesity (eg. BMI, height, weight), smoking history, comorbidities (e.g: CRSwNP), number of severe asthma exacerbations in 52 weeks prior to enrolment, baseline dose of systemic corticosteroids, background therapy (eg. ICS, ICS-LABA, prednisone), baseline blood eosinophils (cells/μL), baseline IgE levels (IU/l).

Risk of bias assessment

We will perform risk of bias assessments of studies independently and in duplicate using the Cochrane collaboration Risk of Bias tool (version 2.0 modified). We will use a modified version that encourages reviewers to rate risk of bias as present, probably present, absent, or probably absent, rather than ‘unclear’ (J Clin Epidemiol 2012; 65(3): 262-7). We will consider a study at high risk of bias if any domain is rated as high or probably high risk of bias. We will evaluate the impact of risk of bias on estimation of

treatment effects by comparing studies with high versus low risk of bias in pairwise comparisons and evaluate for credible effect modification using tests for interaction and the ICEMAN tool (described below in the analysis of subgroups section). We hypothesize that the relative effect of biologics will be greater in studies with high versus low risk of bias.

Strategy for data synthesis

We will summarize dichotomous outcomes as relative risks, and continuous outcomes using mean differences. The preferred value to pool for continuous outcomes will be changes from baseline, with those estimated using ANCOVA adjusting for at least baseline values preferred over unadjusted estimates. If any combination of baseline, final value, and/or change from baseline mean or standard deviation values are not reported, then we will impute the data according to Furukawa et al. (J Clin Epidemiol. 2006 Jan;59(1):7-10) and Cochrane guidance (Handbook version 6, chapter 6.5.2) with preference for imputing SD correlation coefficients in the following hierarchy: (1) Using the median correlation coefficient reported (or able to be calculated from) among the most similar trials included, (2) using 0.7 in the main analysis and doing a sensitivity analysis using the more conservative coefficient of 0.5, (3) imputing median SD among the most similar trials included. If there are different measures for the continuous outcomes, we will use linear transformation of scales to convert them, according to GRADE guidance (Guyatt et al. J Clin Epidemiol. 2013 Feb;66(2):173-83), to the scale most familiar to clinicians. If measures of central tendency and variability are not reported as mean and standard deviation, we will assess for skew, and if not present, convert them to the according statistic according to Cochrane guidance and methods of Shi et al (Research Synthesis Methods, 11: 641-654). In the presence of skewed values, we will then estimate the SD using quantile-estimation, box-cox transformation, or approximate Bayesian computation (Statistical Methods in Medical Research, 29(9), 2520–2537; Res Syn Meth. 2021; 12(6): 842– 848), preferring the estimate that produces closest consistency from other values within the trial (eg. at baseline or change from baseline if the missing value is from the final assessment) and across included trials. If mean differences produce counterintuitive or extremely heterogenous results we will evaluate alternate summary measures including ratio of means, standardized mean differences, or after transformation (eg. geometric means). Of these 3 methods, the summary measure producing the least heterogeneity and most plausible estimates will be used. These pooled alternative measures will then be converted to mean differences using the most familiar instrument to clinicians. To facilitate interpretability, pooled continuous variable outcome estimates will be dichotomized according to GRADE guidance to the relative risk to improve from baseline by a minimally important difference (eg. 0.5 in the case of ACQ or AQLQ, and 0.2 L or 12% change for FEV1). We will synthesize the risk of more than one event per patient using incidence rates (multiple events per patient). If the number of events but neither the duration of patient-years or the incidence rate are reported, then we will estimate the incidence rate using the median study duration multiplied by the number of patients as the denominator. For time-to-event outcomes, we will perform shared frailty cox proportional hazards models, with prior validation of the assumption of proportional

hazards and individual study estimates. This may require digitization of Kaplan-Meier curves from published studies. All summary measures will be reported with 95%CIs.

We will perform conventional meta-analysis using random-effects models in Review Manager (v5.4) and STATA (version 14 or above). In the case when random effects models lead to counterintuitive results, we will switch to a fixed effects model. In cases of rare events we will follow rare event synthesis guidance (J Clin Epidemiol. 2021; 135:70-78), such as performing analysis by risk difference. All analyses will be by intention to treat (i.e., include all randomized patients to any treatment arm). The risk of missing outcome data will be assessed using the GRADE approach including evaluating the complete case scenario, the plausible scenario, and possibly extreme assumptions, for missing participant outcome data (J Clin Epidemiol. 2017 Jul;87:14-22). In studies in which authors used mixed methods or multiple imputation to address missing data, we will use the imputed data from the original studies. Heterogeneity among studies will be evaluated using the GRADE approach (Guyatt et al. J Clin Epidemiol. 2011 Dec;64(12):1294-302) which includes inspection of consistency point estimates and CIs, followed by consideration of statistical measures such as I^2, though they can be misleading for multiple reasons including when there are a large number of studies, the presence of large sample sizes or high event rates, or for continuous outcomes. Summary measures will include absolute and relative risks for the outcomes outlined above, displayed using forest plots. Publication bias will be assessed using the GRADE approach which can include inspecting funnel plots for strong evidence of possible small study effects. In case of missing, unpublished, or unclear data, we will contact study authors for clarification. We will calculate absolute event rates using credible large observational studies, and in their absence, the median event rate across the included trials.

We will perform a frequentist random-effects network meta-analysis to assess the relative effect of all interventions simultaneously. We will use the *netmeta* package of R version 3.4.3 (R Core Team, Vienna, Austria) to perform the network meta-analysis. We will draw the network plots using *networkplot* command of Stata/IC 15.1 for Windows (StataCorp, College Station, Texas, USA). We assume a common heterogeneity parameter for all treatment comparisons. We will generate the league table for network estimates, direct estimates will be informed by conventional meta-analysis, and indirect estimates will be informed by node-splitting analysis. We will calculate the statistical ranking of treatment as P-score (Frequentist analogue of the surface under the cumulative ranking curve (SUCRA)) for each treatment and categorize them according to the GRADE approach using a minimally contextualized framework with target of certainty of a non-zero effect.

To assess incoherence among direct and indirect network estimates, we will assess the consistency of point estimates and overlap in confidence intervals between the two estimates using the node-splitting model. To avoid implausibly wide CIs due to network sparsity, we will exclude nodes from the analysis that are comprised of less than 80 patients and/or do the analysis using a fixed effect model.

In cases where interventions may have a similar mechanism of action (eg. different doses or routes of administration of the same intervention, or interventions that act of similar biologic pathways) we will assess for differences in treatment effects using pairwise comparisons to assess for effect modification using tests for interaction and ICEMAN as per the analysis of subgroups or subsets section below. If there is no credible effect modification, we will then consider all treatments with similar mechanism of action as a single node. If there is credible effect modification, then we will analyze the interventions as separate nodes. If the network estimates using the interventions combined into a single node strongly disagree with the analysis run as separate nodes, then we will prefer the separate node analysis. If there is uncertainty in the (dis)agreement of the combined versus separated node approach, then we will present both networks, qualifying which we believe to be most trustworthy. If there is similarity in the combined versus separated node approaches, then we will present the combined node approach.

We will address publication bias using a comprehensive search, relationship of funding to study findings, and examining for strong evidence of small-study effects in comparison-adjusted funnel plot of treatment estimates. If there is strong evidence of small-study effects we will examine the list of studies excluded due to not meeting inclusion criteria such as reports of trials only as conference abstracts and inspect if their inclusion instead of initial exclusion leads to resolution of small-study effects.

We will assess intransitivity by comparing the distribution of known or credible effect modifiers within the overall study characteristics of trials (eg. median and range of mean age) comprising the comparisons included in the NMA. If there is strong suspicion for imbalance among comparisons then we will rate down for intransitivity. For our NMA, the current most credible effect modifier identified is baseline eosinophil count. If there is a high degree of effect modification, then we will rate down for intransitivity. Our current hypothesis is higher eosinophil count will bias towards higher drug response. If the assessment of harms using the asthma data alone is sufficiently imprecise to draw meaningful inferences, we will use outcome data from published systematic reviews addressing the same intervention used similarly in related conditions (eg. patients with chronic sinusitis with nasal polyposis, allergic rhinitis, atopic dermatitis). In these situations we will assess for credible effect modification by condition as per the ICEMAN tool and tests for interaction described below and present the most trustworthy estimate and may use Bayesian approaches in sensitivity analyses examining incorporation of this evidence.

Analysis of subgroups or subsets

We will explore prespecified hypotheses to examine heterogeneity using subgroup or (network) meta-regression analyses in a random-effects mode with preference, where applicable, for participant-level subgroup data over trial-level comparisons (ie. within rather between trial analyses). We will infer a credible subgroup effect using the instrument to assess the credibility of effect modification analyses (ICEMAN) tool

(CMAJ 2020 10;192:E901-6) and address subgroup analysis primarily in pairwise comparisons unless the same subgroup is present across all comparisons. If subgroup differences exist, but they are primarily small and quantitative differences, we will accept the overall analysis to be used in the NMA. If the variable determining subgroups is a continuous or ordered value, we will assess using regression techniques. Otherwise, we provide a preferred categorization of subgroup variables and will accept alternative categorizations per below.

- Age with preferred categories of pediatric (less than 18 years old) vs adult (18 years old or greater)
    - *We hypothesize that the relative effect of biologics will be greater in older patients compared to younger patients.*

- Blood eosinophils (and sputum eosinophils if data available, which would be looked at separately); i.e.T2- vs. non T2-asthma:
    - blood eosinophils preferred categories (<150, 151-300, >301 and < 450, >450), though we will accept <300, >300 as subgroups,
        - *We hypothesize that the relative effect of biologics is greater in patients with higher blood eosinophil counts compared to patients with lower blood sputum eosinophil counts.*

- High versus low risk of bias, as already described above in the Risk of bias section.

- Study design (study designs include parallel vs. cross-over studies and withdrawal vs. add on therapy).
    - Parallel studies are studies in which each patient is assigned the same treatment, for example either biologic or standard of care, throughout the entire study period vs. cross-over studies include studies in which each patient starts with a treatment during the initial part of the study and then is switched to the comparator treatment during the subsequent period of the study.
    - Treatment withdrawal (eg. studies where the treatment is added to standard care, then elements of standard care, such as daily oral corticosteroids, are withdrawn over time) vs. add-on therapy to standard care, without withdrawal of standard care medications over time.
    - We will run subgroup analysis of different study designs, and if we don't find credible differences in subgroup effect, then we will group studies together, irrespective of design.
        - *We hypothesize that the relative effect of biologics is similar irrespective of whether a trial was a cross over or a parallel group design but that the cross over studies may lead to counterintuitively narrow CIs.*
        - *We hypothesize that the relative effect of biologics may be greater in withdrawal vs. add on therapy studies.*

- Drug dosing (different dosing including weight-based dosing) and formulation (intravenous vs. subcutaneous)
    - We will run subgroup analysis of different drug doses and formulations, and if we don't find credible differences in subgroup effect, then we will group dosing or formulations together.
        - *We hypothesize that the relative effect of biologics is greater with higher doses compared to lower doses.*
        - *We hypothesize that the relative effect of biologics is greater with intravenous versus subcutaneous formulation.*

Certainty of evidence

We will assess the certainty of evidence using the grading of recommendations assessment, development, and evaluation (GRADE) approach for network meta-analysis (J Clin Epidemiol 2018 1;93:36-44, BMJ 2014 24;349). Two reviewers with experience in using GRADE will independently rate each domain for each comparison and resolve disagreements leading to consensus. We will rate the certainty for each comparison and outcome as high, moderate, low, or very low, based on considerations of risk of bias, inconsistency, indirectness, publication bias, intransitivity, incoherence, and imprecision (J Clin Epidemiol 2019 1;108:77-85; Journal Clin Epidemiol 2021 139:49–56). We will judge imprecision using a minimally contextualized approach, with a null effect as the threshold of importance.

Presentation of Results

The summary of findings will follow a similar format used previously to address drug treatments for COVID-19 (*BMJ* 2020;370:m2980) and monoclonal antibodies for chronic sinusitis with nasal polyposis (J Allergy Clin Immunol. 2021 Sep 17;S0091-6749(21)01393-2) emphasizing the comparisons of interventions available in clinical practice.

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None.

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English

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Review Ongoing

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Subject indexing assigned by CRD

Subject index terms

MeSH headings have not been applied to this record

Date of registration in PROSPERO

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Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No