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Article type : Guidelines

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Efficacy and safety of treatment with biologicals (benralizumab, dupilumab and omalizumab) for severe allergic asthma

A systematic review for the EAACI Guidelines - recommendations on the use of biologicals in severe asthma

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Abbreviations

ACQ = asthma control questionnaire

AQLQ = asthma related quality of life questionnaire
AE = adverse events
BDP = beclomethasone dipropionate
CHEC = health economics criteria checklist
CI = confidence interval
DPP4 = Dipeptidyl peptidase-4
EAACI = European Academy of Allergy and Clinical Immunology
EMA = European Medicine Agency
ENFUMOSA = European Network for Understanding Mechanisms of Severe Asthma
EURONHEED = European Network of Health Economic Evaluation Databases
FDA = Food and Drug administration
FeNO = fractional exhaled nitric oxide
FEV1 = forced exhalation volume in one second
FP = fluticasone propionate
GDG = Guideline Development Group
GETE = global evaluation of treatment effectiveness
GINA = Global Initiative for Asthma
GRADE = Grading of Recommendations Assessment, Development and Evaluation
ICS = inhaled corticosteroids
ICER = Incremental cost-effectiveness ratio (ICERs)
Ig = immunoglobulin
IL = interleukin
IRR = incidence rate ratios
LABA = long acting beta 2 agonist
LTRA = leukotriene receptor antagonist
MID = minimal important difference
MD = mean difference
OCS = oral corticosteroids
QALY = Quality adjusted life-years
QoL = quality of life
RCT = randomised controlled trial
ROB = risk of bias
RR = risk ratio
SARP = Severe Asthma Research Program
SGRQ = St George's Respiratory Questionnaire

SR = systematic review
TASS = Total Asthma Symptoms Scores
T2 = type 2
U-BIOPRED = The Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes

Key words

benralizumab; cost-effectiveness; dupilumab; allergic asthma; exacerbations; omalizumab; severe asthma;

Abstract

Allergic asthma is a frequent asthma phenotype. Both IgE and type 2 cytokines are increased, with some degree of overlap with other phenotypes.

Systematic reviews assessed the efficacy and safety of benralizumab, dupilumab and omalizumab (alphabetical order) versus standard of care for patients with uncontrolled severe allergic asthma. Pubmed, EMBASE and Cochrane Library were searched to identify RCTs and health economic evaluations, published in English. Critical and important asthma-related outcomes were evaluated. The risk of bias and the certainty of the evidence were assessed using GRADE.

All three biologicals reduced with high certainty the annualised asthma exacerbation rate: benralizumab incidence rate ratios (IRR) 0.63 (95% CI 0.50–0.81); dupilumab IRR 0.58 (95%CI 0.47–0.73); omalizumab IRR 0.56 (95%CI 0.42–0.73). Benralizumab and dupilumab improved asthma control with high certainty and omalizumab with moderate certainty, however none reached the minimal important difference (MID). Both benralizumab and omalizumab improved QoL with high certainty, but only omalizumab reached the MID. Omalizumab enabled ICS dose reduction with high certainty. Benralizumab and omalizumab showed an increase in drug-related adverse events (AEs) with low to moderate certainty. All three biologicals had moderate certainty for an ICER/QALY value above the willingness to pay threshold. There was high certainty that in children 6-12 years old omalizumab decreased the annualised exacerbation rate [IRR 0.57 (95%CI 0.45-0.72)], improved QoL [relative risk 1.43 (95%CI 1.12 -1.83)], reduced ICS [mean difference (MD) -0.45 (95% CI -0.58 to -0.32)] and rescue medication use [MD -0.41 (95%CI -0.66 to -0.15)].

BACKGROUND

Allergic asthma is a frequent asthma phenotype. It is usually defined by the presence of sensitisation to environmental allergens, with a clinical correlation between exposure and symptoms supporting the diagnosis (1,2,3). The immunopathological distinction between allergic and “non-allergic” asthma or between eosinophilic and allergic asthma is not so clear. Total immunoglobulin (Ig) E levels, usually higher compared to “non-allergic” asthma, may overlap between the allergic and “non-allergic” asthma. The atopic background is associated with increased type 2 (T2) cytokines (interleukin (IL)-4, IL-13, IL-5) and IL-33, IL-25 and TSLP potentiate T2 inflammation (4,5,6,7,8). Abrogation of IL-4Rα signalling after established allergic airway disease prevents the development of ovalbumin-induced airway hyperreactivity, eosinophilia and goblet cell metaplasia (9). Targeting the IgE pathway with omalizumab might reduce sputum and tissue eosinophils, CD3+, CD4+, and CD8+ T lymphocytes, B lymphocytes and cells staining for interleukin-4, although this was not replicated in all studies (10,11).

Allergic asthma clinical spectrum ranges from mild to severe. Atopy has been reported to be inversely associated with persistent airflow obstruction and airway remodelling (12). The true prevalence of severe allergic asthma is difficult to estimate. The proportion of asthmatics with severe disease and a negative skin prick test varies from 17 to 34% in the Severe Asthma Research Program (SARP) study to 50% in the European Network for Understanding Mechanisms of Severe Asthma (ENFUMOSA) study (13,14). The Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes (U-BIOPRED) cohort reported a 76.6% incidence of atopy in severe asthma, including non-smokers, smokers, and ex-smokers (15). Allergic asthma was reported to be associated with greater healthcare utilisation and costs (16).

From its availability for clinical use nearly two decades ago for severe asthma, omalizumab, the first biological acknowledged by Global Initiative on Asthma (GINA) as add-on therapy against severe uncontrolled asthma, has gained strong evidence of efficacy and safety in the treatment of severe asthma not controlled by standard-of-care therapy. It is licensed for severe (and moderate in USA) IgE-mediated allergic asthma (17,18). Benralizumab, a monoclonal antibody that binds to the α subunit of IL-5 receptor (IL-5Rα) was recently approved for severe eosinophilic asthma (19,20). Dupilumab, a monoclonal antibody directed against the α subunit of the IL-4 receptor (IL-4Rα) acting as a dual antagonist of both IL-4 and IL-13 was approved for severe type 2 asthma (21,22).

The European Academy of Allergy and Clinical Immunology (EAACI) is developing clinical practice guidelines for the use of biologicals in patients with severe asthma. This systematic review (SR) assessed the current evidence for the efficacy, safety and the economic impact for

benralizumab, dupilumab and omalizumab (alphabetical order) as add-on treatment for patients with uncontrolled severe allergic asthma.

METHODS

Guideline Development Group

The EAACI Asthma Voting Panel and Guidelines Steering Committee include clinicians and researchers with different backgrounds (the complete list of experts is available from the EAACI website) whom voluntarily participate in the development of EAACI clinical practice guidelines for the use biologicals in severe asthma. They are referred to as the Guideline Development Group (GDG).

Structured question and outcome prioritisation

The GDG framed the clinical question as "Is treatment with benralizumab, dupilumab and omalizumab efficacious and safe for patients with allergic asthma?". For the purpose of this systematic review the population was defined as subjects diagnosed with moderate to severe allergic asthma with asthma symptoms due to exposure to a perennial aeroallergen and serum Ig E levels of 30-1300 IU/mL not be adequately controlled on inhaled steroids (ICS) and/or other background controllers. The asthma related outcomes were prioritised by the GDG using a 1 to 9 scale (7 to 9 critical; 4 to 6 important; 1 to 3 of limited importance), as suggested by the GRADE approach. The critical outcomes were: exacerbations, asthma control measured by the asthma control questionnaire (ACQ) and asthma control test (ACT), quality of life (QoL) measured by asthma quality of life questionnaire (AQLQ) and safety. The important outcomes were: lung function measured by the force expiratory volume at first second (FEV_1), decrease in inhaled corticosteroids (ICS) and oral corticosteroids (OCS) dose, healthcare resource utilisation and rescue medication use (Table S1).

The GDG also framed a cost-effectiveness question to assess the economic impact of these biologicals versus standard of care. The outcomes of interest were costs and resources use, the incremental cost-effectiveness ratios (ICERs) per both quality adjusted life-years (QALY), and asthma-related outcomes.

Data sources and searches

MEDLINE (via PubMed, January 2019), EMBASE (via Ovid, January 2019) and CENTRAL (via The Cochrane Library, January 2019) databases were searched using pre-defined algorithms for

both SR and individual studies for the evidence of efficacy, safety and economic evaluations. Search terms were adapted to each database, and validated filters were used to retrieve appropriate designs. The references of included studies were revised as well. Members of the GDG were requested to provide additional studies.

Study selection

The SR included only randomised controlled trials (RCTs) of patients with uncontrolled severe allergic asthma that compared benralizumab, dupilumab and omalizumab as add on to the standard of care versus placebo. Separate searches were performed for each of the 3 biologicals evaluated. Only studies published in English were included. Abstracts or conference communications not published as full articles in peer reviewed journals and RCTs using doses or routes not approved by U.S. Food and Drug Administration Agency (FDA) and/or the European Medicaments Agency (EMA) were excluded. Two reviewers independently assessed the references based on title and abstract. Then, two reviewers independently assessed the eligibility of the studies according to inclusion criteria based on full text. Discrepancies were solved by consensus or with the help of a third reviewer. All citations retrieved were imported into bibliographic reference software (EndNote X5; Thomson Reuters) to discard duplicates and record screening decisions.

Data extraction and risk of bias assessment

Details of the study design, patient population, setting, follow-up and results were extracted by one reviewer, and confirmed by a second reviewer. If needed, additional data from the authors of the included studies were requested. The risk of bias (ROB) was assessed using the Cochrane Risk of Bias Assessment tool. Each domain (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting) was evaluated as low, high or unclear ROB (23).

For the health economics analysis, two reviewers extracted the main characteristics of included studies (e.g. type of economic evaluation, perspective, time horizon, discount, sources of information, model type), relevant outcomes and costs (e.g. ICERs, sensitivity analyses results), sources of funding, and conflict of interest. Two reviewers assessed the methodological limitations of the complete economic evaluations with the consensus on health economics criteria checklist (CHEC) (24). Transferability to the European context was assessed using the European Network of Health Economic Evaluation Databases (EURONHEED) checklist (25, 26).

Data synthesis and analysis

Main results are described narratively and tabulated as summary of findings. For dichotomous data results are pooled as incidence rate ratios (IRR) and risks ratios (RR). For continuous data results are reported as mean differences (MD), with 95% confidence intervals (CI). For each outcome the change from baseline to the end of the treatment versus placebo was assessed. A random-effects model was used to pool data (Review Manager v 5.3). Where multiple arms were compared to a common placebo arm standard errors were adjusted to avoid unit of analysis error (27). Statistical heterogeneity between studies was assessed with the Cochrane chi-square test, and the magnitude of heterogeneity with the I^2 statistic. To account for clinical heterogeneity, whenever possible subgroup analyses were performed for different doses, age groups, total IgE serum levels and biomarkers (FeNO, DPP4, periostin). A post hoc subgroup analysis for the rate of severe asthma exacerbation following the reduction in the OCS dose was added. The median estimate reported in the control arms of the included RCTs was used as baseline risk to estimate absolute effects for each comparison.

For the economic evidence, results are summarized narratively and tabulated, including the ICERs and the degree of uncertainty.

Certainty of evidence

The certainty (quality) of the evidence of efficacy, safety and economic impact was rated as high, moderate, low or very low, for each outcome in line with the standard GRADE domains (ROB, imprecision, inconsistency, indirectness and publication bias) (28,29). To evaluate the imprecision for each outcome the minimal important difference (MID) thresholds were considered where available (30,31,32,33). For FEV_1 the GDG panel recommended a MID of 0.20 litres (L).

RESULTS

Search results

The selection process is summarised in the PRISMA flowchart (Figure 1). From 3,441 unique citations from data base searches we selected 91 to be appraised as full text. 37 publications from 28 RCTs were included: 3 RCTs (from 3 publications) for benralizumab (34,35,36), 1 RCT (from 2 publications) for dupilumab (37,38), 21 RCTs (from 27 publications) for omalizumab for the population ≥12 years old (39-64) and 3 RCTs (from 5 publications) for omalizumab for 6-20 years old (65-69) (table S2). Publications excluded due to population or outcomes of interest not relevant, different comparisons, or regulatory unapproved dose or route are included in table S3.

Characteristic of included studies

The description of studies included for the evidence of efficacy and safety are detailed in table S1. All were randomized control trials, conducted between 2011 and 2018, including patients with uncontrolled severe allergic asthma receiving the biological in addition to standard of care versus placebo. The follow-up under study medication ranged from 12 to 56 weeks. The age of the patients included ranged from 12 to 75 years old, except for omalizumab that included children 6-11 years old as well. Benralizumab trials evaluated 3,208 patients (1,602 on treatment versus 1,606 on placebo), dupilumab trials 1,083 patients (721 on treatment arm versus 362 on placebo) and omalizumab, 6,847 patients (3,754 on treatment versus 3,093 on placebo) . The characteristics of studies included for the economical impact are presented in table S4 (supplement).

Evidence of efficacy

The summary of the results and certainty of evidence per outcome are summarized in Tables 1,2,3, S8, figures S1 and S2.

Severe asthma exacerbation rate

Two RCTs for benralizumab (34), one RCT for dupilumab (38) and six RCTs for omalizumab (42, 44, 51, 54, 55, 68), reported annualized exacerbations rates. All three biologicals reduced asthma exacerbation rate compared to standard of care with high certainty of the evidence: benralizumab IRR 0.63; 95%CI 0.50 to 0.81; dupilumab IRR 0.58; 95%CI 0.47 to 0.73; omalizumab IRR 0.56; 95%CI 0.45 to 0.69;. No differences were found for omalizumab between children 6-11 years old and adolescent/adults (p=0.88).

Asthma control

Two RCTs for benralizumab (34), one RCT for dupilumab (38) and three RCTs for omalizumab (44, 56, 59) reported ACQ-6 scores. Benralizumab (MD -0.17; 95%CI -0.34 to 0.00) and dupilumab (MD -0.27; 95%CI -0.40 to -0.14) improve asthma control compare to standard of care (high certainty of evidence). Omalizumab probably improves asthma control compared to standard of care in adolescent/adults (MD -0.38; 95%CI -0.68 to -0.09; moderate certainty). ACQ was not evaluated for children 6-11 years old. None of the biologicals showed a reduction above the MID.

Global evaluation of treatment effectiveness

Global evaluation of treatment effectiveness (GETE) was evaluated for omalizumab versus standard of care. Ten RCTs reported GETE assessed by physicians/investigators (40, 43, 47,48,

54, 59, 62, 63, 66, 68,) and 8 RCTs GETE assessed by patients (40, 44, 47, 54, 59, 62,63,68). The overall effect for GETE evaluated by physicians/investigators showed an increase with high certainty of evidence in the proportion of treatment effectiveness evaluations rated as excellent or good (RR 1.50; 95%CI 1.32 to 1.70). There were no differences between children 6-11 years old (RR 1.41; 95%CI 1.25 to 1.58) and adolescent/adults (RR 1.55; 95%CI 1.31 to 1.83) (p=0.34). The overall effect for GETE evaluated by patients showed a similar significant improvement (RR 1.49; 95%CI 1.26 to 1.77). A significantly larger increase in GETE was observed in adolescent/adults (RR 1.57; 95%CI 1.3 to 1.89) compared to the 6-11 years old population (RR 1.11; 95%CI 1.01 to 1.23) (p=0.001).

Quality of life (QoL)

Asthma quality of life questionnaire (AQLQ) score were reported for benralizumab in two RCTs (34) and for omalizumab in 9 RCTs (40, 47, 51, 52, 54, 55, 62,63,67). Benralizumab improved QoL in the population who met atopy and IgE criteria (MD 0.1; 95%CI -0.08 to 0.28; high certainty), however the improvement was below the MID. Omalizumab increases with high certainty of evidence the QoL in adults and children: RR 1.32; 95%CI 1.16 to 1.51.There was no difference between adolescent/adults (RR 1.31; 95%CI 1.14 to 1.51) and children 6-11 years old (RR 1.43; 95%CI 1.12 to 1.83) (p=0.37).

Evidence for safety

Drug-related adverse events

Drug-related AE were reported for benralizumab in 1 RCT (35) and in 7 RCTs for omalizumab (41, 43, 50, 54,60,63,66). Both biologicals showed an increase in drug-related AE compared to standard of care: benralizumab RR 1.41 (95%CI 0.87 to 2.27; low certainty); omalizumab (children 6-11 years old and adolescents/adults) RR 1.27 (95% CI 0.93 to 1.72; moderate certainty of evidence). No differences were observed between adolescent/adults (RR 1.2; 95%CI 0.92 to 1.57) and children 6-11 years old (RR of 6.78; 95% CI 0.90 to 50.91) (p=0.10).

Drug-related serious adverse events

Drug-related SAE were reported for benralizumab in one RCT (36) and for omalizumab in 2 RCTs (51, 60). Benralizumab may reduce the incidence of SAE (RR 0.56; 95%CI 0.22 to 1.44) but there is low certainty of evidence. Omalizumab may increase SAE in adolescent/adults (RR 1.62; 95%CI 0.76 to 3.45; 11 more per 1,000 patients, from 4 fewer to 43 more) with low certainty of evidence. No drug-related SAE were reported for children 6-11 years old.

Corticosteroid and rescue medication

Inhaled corticosteroid dose

ICS dose reduction was evaluated only for omalizumab versus placebo in five RCTs (41, 42, 46, 52, 65). The addition of omalizumab reduced ICS dose both in children 6-11 years old and in adolescent/adults with high certainty of the evidence (overall effect MD -0.38; 95%CI -0.48 to -0.29). There were no differences between children 6-11 years old (MD -0.31; 95%CI -0.45 to -0.18) and adolescent/adults (MD -0.45; 95%CI -0.58 to -0.32) (p=0.16).

Oral corticosteroids dose

The reduction in OCS use from baseline was reported for omalizumab in a subpopulation of patients with severe asthma requiring OCS maintenance throughout the run-in phase (8 weeks prior to randomization) (45). Compared to standard of care omalizumab showed a significant reduction of prednisolone equivalent milligrams per day at 32 weeks (MD -6.7; 95%CI -12.93 to -0.47).

Rescue medication use (puffs/day)

The variation in rescue medication use was evaluated only for omalizumab, both in adolescent/adults (42, 46, 51, 52, 59) and in children 6-11 years old (66, 68). Omalizumab reduced with high certainty the rescue medication use in the overall population (MD -0.47; 95%CI -0.68 to -0.27). There were no differences between children 6-11 years old (MD -0.41; 95%CI -0.66 to -0.15]) and adolescent/adults (MD -0.52; 95%CI -0.80 to -0.24) (p=0.55).

Lung function

FEV_1 variation in litres was reported in two RCT for benralizumab (34), one for dupilumab (38) and six RCTs for omalizumab (42, 43, 55, 60, 61, 62). Both dupilumab (MD 0.15; 95%CI 0.09 to 0.20) and omalizumab (MD 0.17; 95%CI 0.02 to 0.32) improve FEV_1 with low certainty of evidence. Benralizumab probably does not increase FEV_1 in the population that met atopy and IgE criteria (MD 0.055; 95%CI -0.025 to 0.136; moderate certainty of evidence).

Evidence of cost-effectiveness

After screening 1884 hits and reviewing 36 full text articles, 22 economic evaluations were included (figure 2, table S3). Two studies evaluated benralizumab (70,71), one dupilumab (70) and twenty studies omalizumab (72-91) (table S3). Most of the studies excluded did not evaluate

patients with allergic asthma (3/14), did not report health outcomes (3/14) or were conference abstracts (3/14) (table S4).

For benralizumab there was an important variation of ICER from 39,135 £ (low certainty of the evidence) to 412,000 $ / QALY (moderate certainty of the evidence). The key driver for this difference is unclear since there is missing information in the report (71). However, in both studies the ICER/ QALY was higher than the 30,000 € threshold for the willingness to pay (tables S5 and S6). Overall, the resources needed for adding the biologic treatment to standard therapy are mainly the cost of the drug and its administration (table S7). The potential savings are related to decreased rate of hospitalisation, emergency department care, primary care visits, and the management of a clinically significant severe exacerbation (tables S5 and S6).

For dupilumab the reported ICER was 269,000 $ for the 'responder to treatment' scenario. The uncertainty resides in the potential ROB in the utility estimates for the biological and standard therapy for the non-exacerbation health state, for standard therapy and annual exacerbation, and costs of chronic OCS use (moderate certainty of the evidence) (table S6 and S7).

For omalizumab there is important variation across studies in terms of the cost-effectiveness results. Cost-utility Markov model studies with low ROB (high quality studies) consistently show ICER / QALY values higher than the willingness to pay threshold in most European countries with moderate certainty of the evidence. Low quality studies reported ICER values lower than 30,000 €, with very low certainty of the evidence. The difference can be explained by the fact that the low quality studies assumed a higher asthma-related mortality risk and a higher QoL improvement with omalizumab. Furthermore, these studies were limited in their time horizon to up to 1 year (table S6 and S7).

DISCUSSION

Main findings

Overall the included studies were of low concern of ROB for most of the reported asthma related outcomes. All included studies were funded by the industry and all showed positive results, which raised concerns of potential sponsorship bias. The main reasons to downgrade the certainty of evidence were ROB due to the use of not validated tools for some outcomes, imprecision (i.e. ACQ, AQLQ) and indirectness (i.e. FEV_1, FeNO as surrogate outcomes).

The current systematic review of efficacy showed with high certainty that benralizumab, dupilumab and omalizumab as add-on to standard of care reduce the exacerbation rates for

patients with allergic asthma older than 12 years (adolescent/adults). Similarly, for children 6-11 years old with allergic asthma, omalizumab as add-on treatment significantly reduces the exacerbations rates.

The improvement in asthma control with benralizumab and dupilumab did not reach the MID. Omalizumab improves asthma control if GETE is considered, however the results are inconsistent with the ACQ score analysis. There is no evidence to support a MID for GETE. However, the first three response levels of both the physician and patient versions of the GETE ("complete control of asthma," "marked improvement of asthma," and "discernible, but limited improvement of asthma") are clearly differentiated from each other and this clear differentiation is associated with clinically important differences in terms of clinical indices and some AQLQ subscales (92).

Omalizumab also improves quality of life for children and adolescents/adults. Benralizumab did not show a clinically relevant improvement.

Rescue medication use (puffs/day), inhaled and oral corticosteroid use were evaluated only for omalizumab. The current SR showed with high certainty a reduction, both for children and adolescent/adults.

Although short term safety data are reassuring there is low to very low certainty for serious adverse effects. The very low certainty derives from the fact that drug related AEs were reported combined with worsening of asthma symptoms or were not reported in detail in the main publication or in the supplementary documents.

All three biologicals evaluated had with moderate certainty of the evidence an ICER/QALY value above the willingness to pay threshold of 30,000 €.

Current results in the context of previous results

Similar to results reported by this SR, all previous systematic reviews evaluating benralizumab, dupilumab and omalizumab efficacy and safety in adolescent/adults with allergic severe asthma reported a reduction of approximately half of annualized exacerbations in the population (93-97). The reduction in the exacerbation rates reported by the previous systematic reviews that evaluated omalizumab in children 6-11 years old was also very similar (96, 97, 98). Aligned with the current results the systematic review that evaluated asthma control and quality of life (96) in adolescent/adults population for omalizumab reported an improvement on these outcomes. The

current SR highlighted with high certainty that the improvement in QoL following the addition of omalizumab is clinically relevant.

An important difference between the current SR and the previous SRs is the assessment of the certainty of evidence using the GRADE approach. With the exception of Normansell all previous SRs limited their evaluation to the risk of bias of the included trials. The current SR evaluated the heterogeneity, imprecision and the indirectness of the evidence. As an example, MID used for the assessment of imprecision, enabled us to determine the clinical relevance of the variation for each outcome.

A previous SR of 20 economic evaluations included 19 studies that assessed the cost-effectiveness of omalizumab. Ten studies concluded that omalizumab was cost-effective for base-case scenarios, four studies showed that omalizumab was not cost-effective, and the remaining studies reported that omalizumab was cost-effective only when targeted to specific severe subgroups or when given considerable price discounts. The key drivers of cost-effectiveness included day-to-day health-related QoL, asthma-related mortality, acquisition price of biological therapy, and time horizon. The SR concluded that in order to improve the value for biologicals in asthma they should target specific populations (i.e. responders) or discounted acquisition price should be granted (99). Another review of 72 studies assessing the cost-effectiveness of asthma treatment, reported that among patients with uncontrolled severe persistent allergic asthma, omalizumab could be cost-effective in patients with more severe disease. The quality among studies was uneven and the main cost-effectiveness drivers were the cost or rate of asthma exacerbations, the cost or rate of use of asthma medication, asthma mortality risk and the rate of utilization of health services for asthma (100). A third review of 53 economic evaluations, evaluating patients with asthma and COPD included nine assessments of omalizumab use. This review concluded that few economic evaluations used validated models and identified controversies among results (101).

Strengths and limitations

The current SR has several strengths. A comprehensive evaluation of both desirable and undesirable effects of the use of benralizumab, dupilumab and omalizumab for allergic asthma was conducted, including the assessment of their economic impact. This compilation of outcomes provided an improved perspective of the biologicals profile. Rigorous methods including the GRADE approach to rate the certainty of the evidence were used, leading to transparent and precise judgement of the quality of evidence. The most updated results available from the included RCTs were included and only licensed doses and/or routes of the biologicals were

considered. Results are provided in friendly tabulated summaries using optimal presentation format for patients, clinicians and policy makers, thus offering a consistent support for the decision of use biologicals for patients with uncontrolled severe allergic asthma.

There are however several limitations. The basal exacerbation rate was used to estimate the absolute benefit for each drug/analysis. However, we did not perform a subgroup or sensitivity analysis based on the basal exacerbation rate. To ensure the robustness of the results based on high quality data observational studies that could have been informative for some of the outcomes with low or very low quality evidence from RCTs (e.g. serious adverse events) were not included in the SR. Only English language articles were included, however, the risk of selection bias is probably small because previous systematic reviews were carefully screened, and the GDG included several international experts in the field, thus the possibility of missing results from non-English articles is unlikely. A 'the novo' economic analysis for the cost-effectiveness outcomes was not conducted. Instead, a global perspective on the use of biologicals in different health systems, with a rigorous and explicit critical appraisal of the available evidence was choosen, that could be useful for the decisions of using biologicals across different countries.

Implications for practice and research

Despite biologicals showing an improvement in asthma related critical and important outcomes, the observed overall effect is relatively modest (reducing exacerbations but only probably improving asthma control, quality of life or lung function). Given the high cost of these drugs their use will probably be limited to very specific circumstances (e.g. patients with severe asthma uncontrolled under standard treatment). In this context panels are likely to formulate conditional recommendations on the use of biologicals.

Although short term safety data is reassuring more accurate reporting is warranted, in combination with long-term safety evaluation, including observational studies and registries. For omalizumab there is good data available to support its efficacy and safety in the pediatric population however for benralizumab and dupilumab the data are limited highlighting the urgent unmet need for rigorous trials with biologicals in severe asthma in the pediatric population.

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COI statement

IA serves as associate editor of Allergy. **CR**, **JB, YS, MP, IS,** and **PA-C** have received funding from EAACI. **CA** and **MA** report grants from Allergopharma, Idorsia, Swiss National Science Foundation, Christine Kühne-Center for Allergy Research and Education, European Commission Horizon 2020 Framework Programme, Cure, Novartis Research Institutes, Astra Zeneca, Scibase, and CA is also on the Sanofi/Regeneron advisory board. **T Casale** reports grants and/or personal fees from Genentech, Novartis, Sanofi Regeneron, GSK, and Amgen. JC declares

grants or personal fees from AZ, Genentech/Roche, Novartis, Optinose, Sanofi, Stallergenes, and TEVA. **SG** reports personal fees from AstraZeneca, GSK and Novartis. **TE** has received grants or other from DBV, Innovation Fund Denmark, Regeneron, the Allergy and Anaphylaxis Program SickKids; serves as associate editor for Allergy and in the local advisory board of ALK. **JG** reports personal fees from Regeneron, Ena Theraputics, MedImmune/AstraZeneca, and stock options from Meissa Vaccines Inc. In addition, JG has a pending patents on Methods of Propagating Rhinovirus C in Previously Unsusceptible Cell Lines, and on Adapted Rhinovirus C. **NH** reports funding, honoraria or personal fees from GSK, AstraZeneca, Boehringer Ingelheim, Novartis and Sanofi Genzyme, Regeneron, Genentech, Sunovion, and Mylan. **PN** reports grants and/or personal fees from AZ, Novartis, Teva, Sanofi, Roche, Novartis, Merck, and Equillium. **LOM** reports grants from GSK and personal fees from AHL. **NGP** reports personal fees from Novartis, Nutricia, HAL, Menarini/Faes Farma, Sanofi, Mylan/Meda, Biomay, AstraZeneca, GSK, MSD, Asit Biotech, Boehringer Ingelheim, and grants from Gerolymatos International SA and Capricare. **AP** has received grants, personal fees, non-financial support or other from GlaxoSmithKline, AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, TEVA, Mundipharma, Zambon, Novartis, Menarini, Sanofi/Regeneron, Roche, Fondazione Maugeri, Fondazione Chiesi, Edmond Pharma. **LP** reports grants, personal fees or non-financial support from Novartis, AstraZeneca, GSK, TEVA, Boehringer-Ingelheim, Chiesi, Sanofi, Menarini, Mundipharma, Esteve, and ROVI. **SQ** reports personal fees and non-financial support from GSK, AZ, Sanofi, Novartis, Mundipharma, Teva, and Allergy Therapeutics. **JSastre** declares personal fees and non-financial support from Novartis, GSK, AstraZeneca, Sanofi, and Mundipharma. **MS** reports personal fees or research funding from ASIT Biotech.sa, Allergy Therapeutics, ALK, Regeneron, Merck, Immune Tolerance Network, Leti Laboratorios, and Allergopharma. **CC-A** reports funding from EAACI. **OP** received research grants from Inmunotek S.L. and Novartis; received fees for giving scientific lectures from: Allergy Therapeutics, Amgen, AstraZeneca, Diater, GSK, Inmunotek S.L, Novartis, Sanofi-Genzyme and Stallergenes; participated in advisory boards from Novartis and Sanofi-Genzyme. **MJ** reports personal fees from ALK-Abello, Allergopharma , Stallergenes, Anergis, Allergy Therapeutics, Circassia, Leti, Biomay, HAL, Astra-Zeneca, GSK, Novartis, Teva, Vectura, UCB, Takeda, Roche, Janssen, MedImmune, and Chiesi. All other authors have no conflict of interest within the scope of the submitted work.

Figure 1: Study flowchart for the evaluation of evidence of efficacy and safety

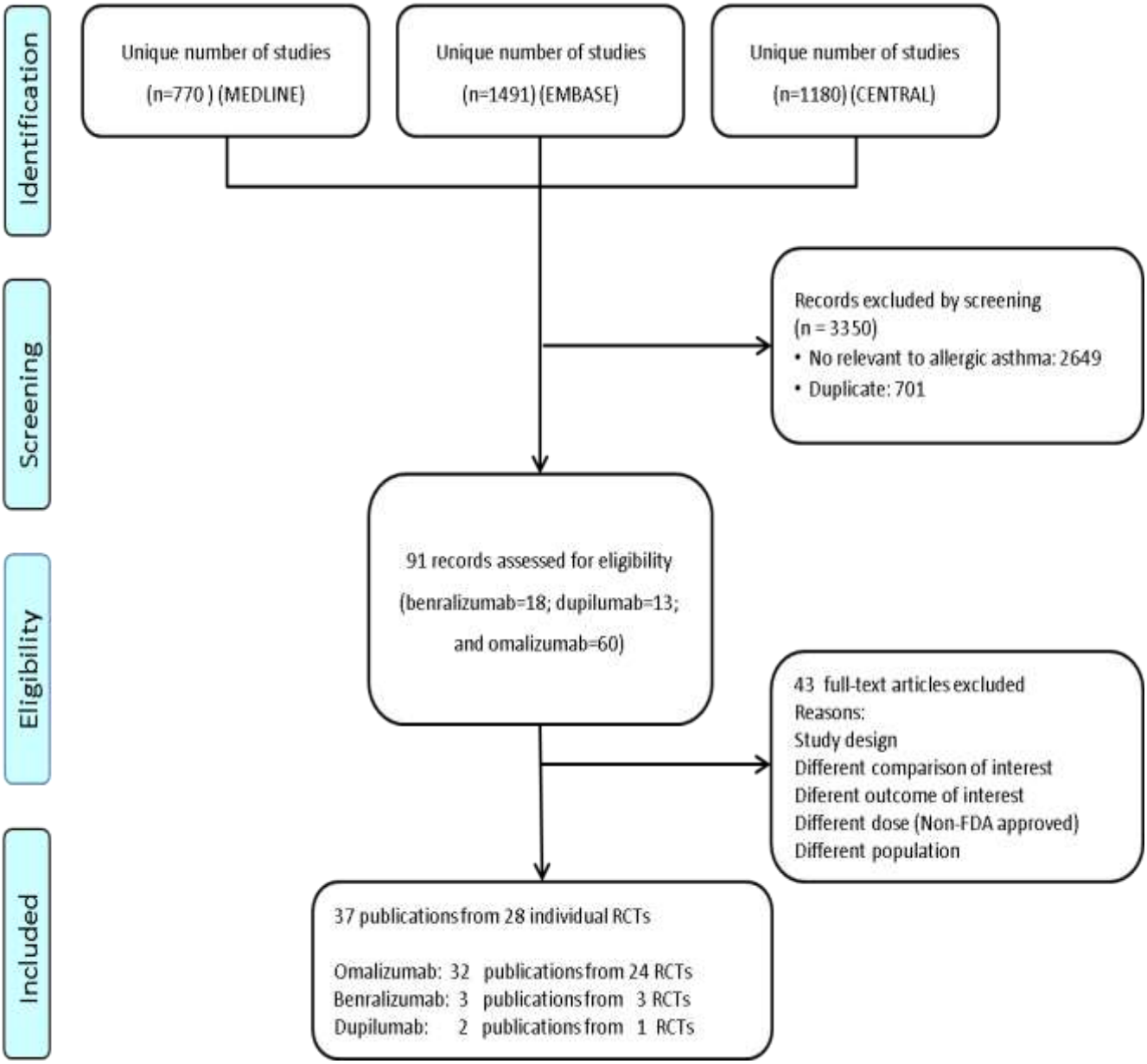

Figure 2. Study flowchart for the economic evidence

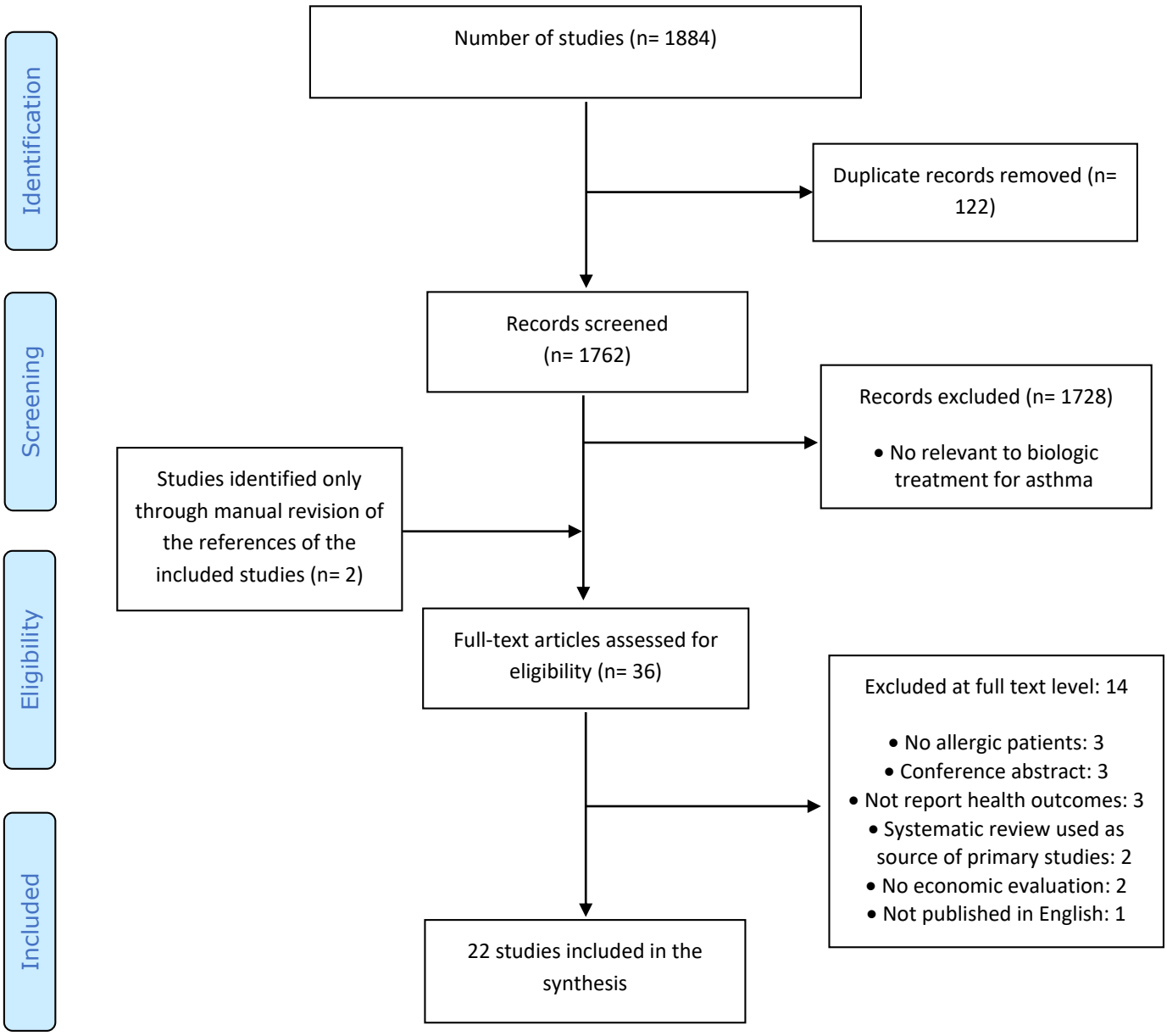

Table 1: Summary of findings for benralizumab efficacy and safety compared to standard of care for allergic asthma

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard of care	Risk difference with Benralizumab
Exacerbations assessed with annual asthma exacerbation rate	297 (2 RCTs) [34] 48 weeks to 56 weeks	⊕⊕⊕⊕ HIGH [2,a]	**Rate ratio** **0.63** (0.50 to 0.81)	13 per 1.000	**5 fewer per 1.000** (6 fewer to 2 fewer)
Asthma Control assessed with: ACQ-6 score between-group-difference at the end of treatment	414 (2 RCTs) [34] 48 weeks to 56 weeks	⊕⊕⊕⊕ HIGH [2,3,a,b]	-	The mean asthma Control was **0** Mean change	MD - **0.17** (-0.34 to 0)
Quality of Life assessed with: Quality of Life Questionnaire for 12 years and older [AQLQ(S)+12], between-group-difference at the end of treatment	404 (2 RCTs) [34] 48 weeks to 56 weeks	⊕⊕⊕⊕ HIGH [2,5,a,e]	-	The mean quality of Life was **0** Mean change	MD +**0.1** (-0.08 to +0.28)
Any drug related adverse event assessed with: Number of events- Urgent care visit, or admission to hospital	478 (1 RCT) [35] 56 weeks	⊕⊕◯◯ LOW [2,a,f,g]	**Rate ratio 1.41** (0.87 to 2.27)	105 per 1.000	**43 more per 1.000** (14 fewer to 133 more)
Any drug related serious adverse event assessed with: Number of SAE unrelated to asthma exacerbation	148 (1 RCT) [36] 28 weeks	⊕⊕◯◯ LOW [2,a,f,g]	**Rate ratio 0.56** (0.22 to 1.44)	147 per 1.000	**65 fewer per 1.000** (114 fewer to 65 more)
Lung function assessed with: Pre-bronchodilator FEV1 (mL) between-group-difference at the end of treatment)	490 (2 RCTs) [34] 48 weeks to 56 weeks	⊕⊕⊕◯ MODERATE [2,3,4,a,c,d]	-	The mean lung function was **0** L	MD + **0.055 L** (-0.025 to + 0.136)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard of care	Risk difference with Benralizumab

GRADE Working Group grades of evidence
High certainty: High confidence that the true effect lies close to that of the estimate of the effect
Moderate certainty: Moderate confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect
Very low certainty: Very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

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Explanations

a. Included studies were all funded by industry, and all showed positive results. No industry-independent observational or randomized studies were identified to contrast the results. Therefore, evidence was downgraded for potential publication bias (102).
b. For ACQ-6 the minimal important difference is 0.5 points (30)
c. Downgraded because FEV1 is considered a surrogate outcome of asthma control of symptoms, with a variable correlation with asthma symptoms (103).
d. The effect may both be harmful or beneficial. The minimal important difference (MID) for FEV1 is 0.20 L (Guidelines development group consensus).
e. For AQLQ(S) + 12 the minimal important difference is 0.5 (32)
f. Downgraded one level due to indirectness (data from severe asthma patients that may have or may have not allergic asthma)
g. The effect may both be harmful or beneficial. Estimations are based on less than 300 events, thus there is probably important imprecision.

Table 2: Summary of findings of dupilumab compared to standard of care for allergic asthma

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard of care	Risk difference with Dupilumab
Clinically significant exacerbations rate ratio assessed with: annual asthma exacerbations	1083 (1 RCT) [38] 52 weeks	⊕⊕⊕⊕ HIGH [2,a]	**Rate ratio 0.58** (0.47 to 0.73)	**Moderate**	
				10 per 1.000	**4 fewer per 1.000** (5 fewer to 3 fewer)
Asthma control assessed with: Asthma Control Questionnaire (ACQ-5) Scale from: 1 to 5	1013 (1 RCT) [38] 24 weeks	⊕⊕⊕⊕ HIGH [2,7,a,d]	-	The mean asthma control was **0**	MD - **0.27** (-0.4 to -0.14)
Lung function assessed with: Forced expiratory volume in one second (FEV1 in L) change from baseline	1055 (1 RCT) [38] 12 weeks	⊕⊕◯◯ LOW [2,3,4,5,a,b,c]	-	The mean lung funtion change from baseline was **0** L	MD + **0.15 L** (+0.09 to + 0.2)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: High confidence that the true effect lies close to that of the estimate of the effect
Moderate certainty: Moderately confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect
Very low certainty: Very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Explanations

a. The study included was funded by Sanofi and Regeneron Pharmaceuticals. No industry-independent observational or randomised trials were identified to compare the results. The GDG members considered that there were no major concerns about potential publication/sponsorship bias
b. Downgraded because FEV1 is considered a surrogate outcome of asthma control of symptoms, with a uncertain correlation with asthma symptoms (103).
c. The minimal important difference (MID) for FEV1 is 0.20 L (GDG consensus).
d. The effect of dupilumab is below the MID (0.5 points). (32)

Table 3: Summary of findings of omalizumab efficacy and safety compared to standard of care for allergic asthma

Outcomes	№ of participants (studies) Follow-up range	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard of care	Risk difference with Omalizumab
Annual rate of clinically significant asthma exacerbations assessed with annualised rate	2772 (6 RCTs) [42,44,51,54,55,68] 24 weeks to 52 weeks [a]	⊕⊕⊕⊕ HIGH [b,c,d]	**Rate ratio 0.56** (0.45 to 0.69) [e,f]	**Low**	
				14 per 1.000	**616 fewer per 1.000** (770 fewer to 378 fewer)
Asthma control assessed with ACQ-6 score;	939 (3 RCTs) [44,56,59] 26 weeks to 52 weeks	⊕⊕⊕◯ MODERATE [9,b,d,g]	-	The mean asthma Control was **0** point	MD **0.38 point lower** (0.68 lower to 0.09 lower) [h,i]
Global evaluation of treatment effectiveness assessed with: physicians/investigators' assessment	3783 (10 RCTs) [68, 54,59,62,66,40,48,47,43,63] 16 weeks to 52 weeks	⊕⊕⊕⊕ HIGH [b,d,j]	**Rate ratio 1.50** (1.32 to 1.70) [k]	418 per 1.000	**209 more per 1.000** (134 more to 292 more) [k]
Clinically significant improvement of Asthma Quality of Life (≥0.5 from baseline) assessed with: AQLQ Questionnaire (S)	3540 (9 RCTs) [40,47,51,52,54,55,62,63,67] 12 weeks to 52 weeks	⊕⊕⊕⊕ HIGH [b,d,l]	**Rate ratio 1.32** (1.16 to 1.51) [m]	563 per 1.000	**180 more per 1.000** (90 more to 287 more) [m]
Any drug-related AE	2341 (7 RCTs) [68,54,66, 43, 63, 67, 50] 16 weeks to 52 weeks	⊕⊕⊕◯ MODERATE [ab,b,d]	**Rate ratio 1.27** (0.93 to 1.74)	127 per 1.000	**34 more per 1.000** (9 fewer to 94 more)
Any drug-related SAE)	1163 (2 RCTs) [51, 60] 16 weeks to 48 weeks	⊕⊕⊕◯ MODERATE [ab,b,d]	**Rate ratio 1.62** (0.76 to 3.45)	18 per 1.000	**11 more per 1.000** (4 fewer to 43 more)

Outcomes	№ of participants (studies) Follow-up range	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard of care	Risk difference with Omalizumab
Lung function (FEV1) assessed with absolute FEV1 (L) change versus baseline	1209 (6 RCTs) [55, 42,62, 43, 60, 61] range 12 weeks to 52 weeks [n,o]	⊕⊕◯◯ LOW [21,22,23,b,p,q,r]	-	The mean lung function was **0** L	MD **0.17 L higher** (0.02 higher to 0.32 higher) [s]
Lung function (PEF) assessed with morning PEF rate change (L/m) versus baseline	1735 (7 RCTs) [59, 48, 52,60, 41,58,49] 12 weeks to 36 weeks [t]	⊕⊕⊕◯ MODERATE [21,22,23,b,p,r,u]	-	The mean lung function was **0**	MD **10.04 higher** (7.49 higher to 12.6 higher)
Decrease in inhaled corticosteroid assessed as µg/day variation versus baseline	1861 (5 RCTs) [41, 42, 46, 52, 65] 24 weeks to 52 weeks	⊕⊕⊕⊕ HIGH [23,b,r,v]	-	-	SMD **0.38 SD lower** (0.48 lower to 0.29 lower)
Rescue medication use (puffs/day) assessed with change from baseline	3367 (7 RCTs) [68, 54, 42, 59, 66, 52, 41] 16 weeks to 52 weeks [22,w]	⊕⊕⊕⊕ HIGH [b,d,x]	-	The mean the change from baseline of Rescue medication use (puffs/day) was **0** puff/day	MD **0.47 puff/day fewer** (0.68 fewer to 0.27 fewer)
FeNO level change from baseline [29,y]	495 (3 RCTs) [51, 65,41]	⊕⊕⊕◯ MODERATE [32,33,b,d,z]	-	The mean feNO leval change from baseline was **0** ppb	MD **4.65 ppb lower** (7.39 lower to 1.92 lower) [aa]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio; **SMD:** Standardised mean difference

GRADE Working Group grades of evidence
High certainty: High confidence that the true effect lies close to that of the estimate of the effect
Moderate certainty: Moderate confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect
Very low certainty: Very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Explanations

a. Clinical significant asthma exacerbation: episodes of asthma worsening requiring treatment with systemic corticosteroids.
b. Despite some studies being at high risk of bias for some of the domains, the effect observed in all of them is similar.
c. Lanier included patients aged 6-12 years old, all had allergic asthma (68).
d. Included studies were all funded by industry, and all showed positive results. No industry-independent observational or randomized studies were identified to compare the results. Therefore, evidence was downgraded for potential publication bias (102).
e. 9 studies included reported exacerbations as "patients who had ≥1 exacerbation", the pooled risk ratio was 0.59(95% CI 0.52-0.67). 3 studies included reported clinically significant severe asthma exacerbation, the pooled rate ration was 0.51 (95% CI 0.39-0.67)
f. The pooled effect of risk ratio evaluated at 24-28 weeks (44, 54, 68, 63) and at 48-52 weeks (42, 51, 68, 55). Lanier 2009 included patients aged 6-12 years old.
g. Downgraded because the effect of omalizumab is beneficial but the upper side of the CI is less than the minimal important difference (MID=0.5) (32).
h. Asthma control using asthma control test (ACT) was assessed by three studies (65, 43, 56), the pooled mean different was 0.57(95% CI 0.17-0.97). We also included the ACQ scores assessed by 5 studies (68, 51, 52, 59, 46), the pooled standard mean difference was -0.20 (95% CI -0.26 - -0.14)
i. The pooled effect of ACQ-6 evaluated at 16 weeks (44), 24-32 weeks (44, 59), and at 52 weeks (56).
j. Although there were a high I2 (67%.), this was influenced by only one study with low number of events.
k. The pooled data were assessed at 16 and 20 weeks (48, 62), and 52 weeks (68); Other studies evaluated at 24-28 weeks. GETE evaluated by patients show that omalizumab is more effective than placebo, the risk ratio was 1.49 (1.26-1.77), see full text report.
l. Statistically significant (I2=83%), but probably unimportant heterogeneity.
m. The mean change of AQLQ scores was assessed by 7 studies, the pooled standard mean difference was 0,34 (95% IC 0.18-0.49)
n. Milgrom reported FEV1 in children (6-12 years old) for 28 weeks follow up (64). The Mean change from baseline was 93.9 mL in the omalizumab group and 28.3 mL in the placebo group. Lanier reported between group differences in FEV1 at week 48 and 52 in 40 ml (p=0.28) and 52 ml (p=0.16) (41).
o. Lung function was also reported as ratio FEV1/FVCx100. Busse reported the ratio in 77.5±0.38 in the intervention group and 77.3±0.36 in the placebo group (63). Milgrom also reported mean FVC in children (6-12 years old) for 28 weeks follow up. Mean FVC change from baseline was 132.7 in the omalizumab group and 132.7 mL in the placebo group at week 28 (64). See full text report.
p. Downgraded because FEV1 and PEF are considered surrogate outcomes for asthma control, with an inconsistent correlation with asthma symptoms (101).
q. The minimal important difference (MID) for FEV1 is 0.20 L (Guidelines Development Group consensus).
r. Included studies were all funded by industry, and all showed positive results. One observational study showed similar results (102), therefore, we did not downgrade for potential publication bias.
s. The predicted value for pre-bronchodilator FEV1 was assessed by 6 studies, the pooled standard mean difference was 1.05 (95% CI 0.35-1.75), see full text report.
t. Milgrom 2001 reported PEFR in children (6-12 years old) with 28 weeks of follow up. Mean morning PEFR change from baseline was 8.5 L/min in the omalizumab group, and 1 L/min in the placebo group at week 28)
u. Average MID is 18.8L/min (30)
v. High heterogeneity (91%); Not downgraded as all effects favour intervention.
w. For rescue medication use MID is the reduction by 0.81 puffs/day (30)
x. Statistically significant (68% (p=0.004)) but probably unimportant heterogeneity.
y. The MID of FeNO change from baseline is more than 10ppb (33).
z. Downgraded because FeNO is not consistently considered a good surrogate of asthmatic inflammation (105, 106)
aa. FeNO change was reported according to IgE level by one study (64). The median percentage change was -7.2 (for IgE 30-300 IU/ml) and -16 (for IgE 700–2,000 IU/ml) in the Omalizumab group and 64 in the placebo group.
bb. ab. The effect may both be harmful or beneficial.