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GUIDELINE

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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; AE, adverse events; AQLQ, asthma quality of life questionnaire; 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 Medicines 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 1 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; ICER, incremental cost-effectiveness ratio (ICERs); ICS, inhaled corticosteroids; Ig, immunoglobulin; IL, interleukin; IRR, incidence rate ratios; LABA, long-acting beta-2 agonist; LTRA, leukotriene receptor antagonist; MD, mean difference; MID, minimal important difference; OCS, oral corticosteroids; QALY, quality-adjusted life-years; QoL, quality of life; RCT, randomized controlled trial; ROB, risk of bias; RR, risk ratio; SARP, Severe Asthma Research Program; SGRQ, St George's Respiratory Questionnaire; SR, systematic review; T2, type 2; TASS, total asthma symptoms scores; U-BIOPRED, The Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes.

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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) vs 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 annualized 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); and 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 annualized 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)].

KEYWORDS
benralizumab, dupilumab, exacerbations, omalizumabsevere allergic asthma

1 | BACKGROUND

Allergic asthma is a frequent asthma phenotype. It is usually defined by the presence of sensitization to environmental allergens, with a clinical correlation between exposure and symptoms supporting the diagnosis.[1-3] The immunopathological distinction between allergic and "nonallergic" asthma or between eosinophilic and allergic asthma is not so clear. Total immunoglobulin (Ig) E levels, usually higher compared with "nonallergic" asthma, may overlap between the allergic and "nonallergic" asthma. The atopic background is associated with increased type 2 (T2) cytokines (interleukin (IL)-4, IL-13 and IL-5) and IL-33, IL-25 and TSLP potentiate T2 inflammation.[4-8] 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 nonsmokers, smokers and ex-smokers.[15] Allergic asthma was reported to be associated with greater healthcare utilization 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.

2 | METHODS

2.1 | 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).

2.2 | Structured question and outcome prioritization

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 prioritized by the GDG using a 1-9 scale (7-9 critical; 4-6 important; and 1-3 of limited importance), as suggested by the GRADE approach. The critical outcomes were as follows: 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 as follows: lung function measured by the force expiratory volume at first second (FEV_1), decrease in inhaled corticosteroids (ICS) and oral corticosteroids (OCS) dose, and rescue medication use (Table S1).

The GDG also framed a cost-effectiveness question to assess the economic impact of these biologicals vs 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.

2.3 | 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 predefined 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.

2.4 | Study selection

The SR included only randomized controlled trials (RCTs) of patients with uncontrolled severe allergic asthma that compared benralizumab, dupilumab and omalizumab as add-on to the standard of care vs placebo. Separate searches were performed for each of the three 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 US Food and Drug Administration Agency (FDA) and/or the European Medicines 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.

2.5 | 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 (eg type of economic evaluation, perspective, time horizon, discount, sources of information and model type), relevant outcomes and costs (eg 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]

2.6 | 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 vs 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 and 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.

2.7 | 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.[30-33] For FEV_1 the GDG panel recommended a MID of 0.20 litres (L).

3 | RESULTS

3.1 | Search process

The selection process is summarized in the PRISMA flow chart (Figure 1). From 3441 unique citations, from database searches we selected 91 to be appraised as full text. Thirty-seven publications from 28 RCTs were included: three RCTs (from three publications) for benralizumab,[34-36] one RCT (from two publications) for dupilumab,[37,38] 21 RCTs (from 27 publications) for omalizumab for the population ≥ 12 years old[39-64] and 3 RCTs (from five 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.

3.2 | 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 vs 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 3208 patients (1602 on treatment vs 1606 on placebo), dupilumab trials, 1083 patients (721 on treatment arm vs 362 on placebo), and omalizumab, 6847 patients (3754 on treatment vs 3,093 on placebo). The characteristics of studies included for the economical impact are presented in Table S4.

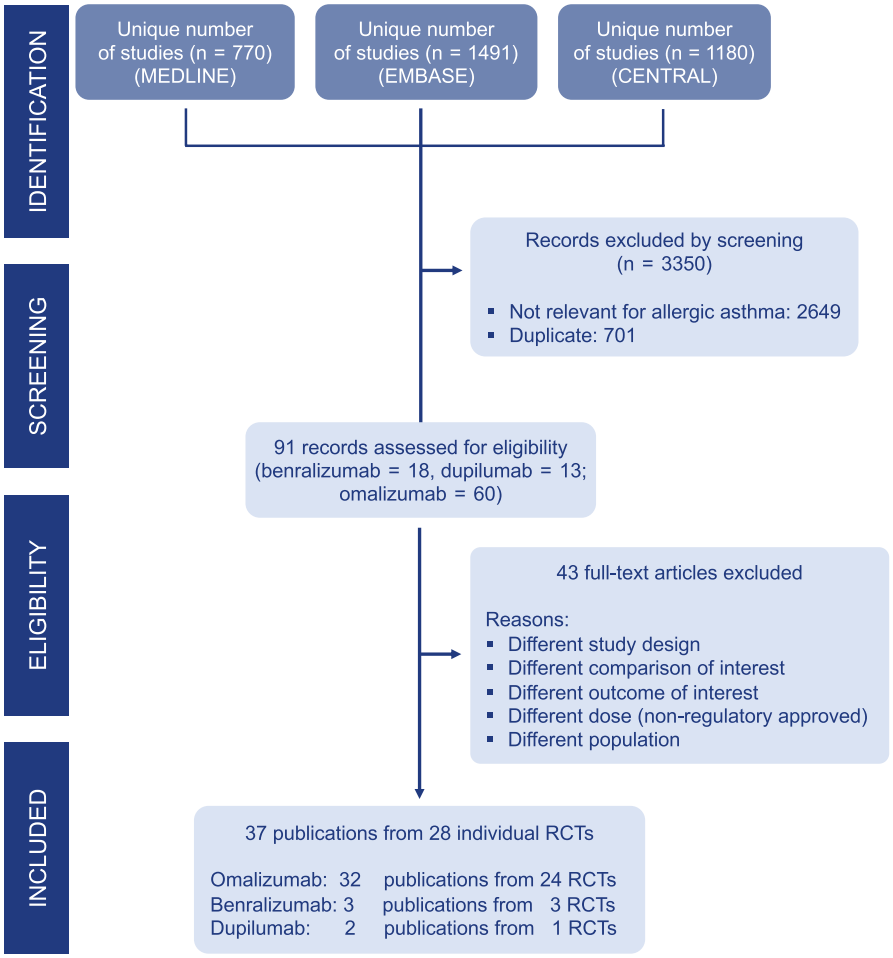

FIGURE 1 Study flow chart for the evaluation of evidence of efficacy and safety

3.3 | Evidence of efficacy

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

3.3.1 | 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; and 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 = .88).

3.3.2 | 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.

3.3.3 | Global evaluation of treatment effectiveness

Global evaluation of treatment effectiveness (GETE) was evaluated for omalizumab vs standard of care. Ten RCTs reported GETE assessed by physicians/investigators[40,43,47,48,54,59,62,63,66,68] and eight 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 = .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 = .001).

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

Outcomes	No 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] 48-56 wk	⨁⨁⨁⨁ HIGH[2,a]	Incidence rate ratio 0.63 (0.50-0.81)	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] 48-56 wk	⨁⨁⨁⨁ 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 y and older [AQLQ(S)+12], between-group difference at the end of treatment	404 (2 RCTs)[34] 48-56 wk	⨁⨁⨁⨁ HIGH[2,5,a,c]	-	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 wk	⨁⨁◯◯ LOW[2,a,d,e]	Risk ratio 1.41 (0.87-2.27)	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 wk	⨁⨁◯◯ LOW[2,a,d,e]	Risk ratio 0.56 (0.22-1.44)	147 per 1.000	65 fewer per 1.000 (114 fewer-65 more)
Lung function assessed with prebronchodilator FEV1 (mL) between-group difference at the end of treatment)	490 (2 RCTs)[34] 48-56 wk	⨁⨁⨁◯ MODERATE[2-4,a,f,g]	-	The mean lung function was **0** L	MD + **0.055 L** (−0.025 to +0.136)

Note: 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.
Abbreviations: CI, confidence interval; MD, mean difference; and RR, risk ratio.

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]For AQLQ(S) + 12, the minimal important difference is 0.5.[32]

[d]Downgraded one level due to indirectness (data from severe asthma patients that may have or may have not allergic asthma)

[e]The effect may both be harmful or beneficial. Estimations are based on less than 300 events; thus, there is probably important imprecision.

[f]Downgraded because FEV1 is considered a surrogate outcome of asthma control of symptoms, with a variable correlation with asthma symptoms.[103]

[g]The effect may both be harmful or beneficial. The minimal important difference (MID) for FEV1 is 0.20 L (Guidelines Development Group consensus).

*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).

3.3.4 | Quality of life (QoL)

Asthma quality of life questionnaire (AQLQ) score was reported for benralizumab in two RCTs[34] and for omalizumab in nine RCTs.[40,47,51,52,54,55,62,63,67] Benralizumab improved QoL> 0.5 points from baseline 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 1.16-1.51. There was no difference between adolescent/adults (RR 1.31; 95%CI 1.14-1.51) and children 6-11 years old (RR 1.43; 95%CI 1.12 to 1.83) (P = .37).

3.4 | Evidence for safety

3.4.1 | Drug-related adverse events

Drug-related AE were reported for benralizumab in one RCT[35] and in seven 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

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

Outcomes	No 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 wk	⨁⨁⨁⨁ HIGH[2,a]	Incidence rate ratio 0.58 (0.47-0.73)	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 1-5	1013 (1 RCT)[38] 24 wk	⨁⨁⨁⨁ HIGH[2,7,a,b]	-	The mean asthma control was **0**	MD - **0.27** (−0.4 to −0.14)
Lung function assessed with forced expiratory volume in 1 second (FEV1 in L) change from baseline	1055 (1 RCT)[38] 12 wk	⨁⨁◯◯ LOW[2-5,a,c,d]	-	The mean lung function change from baseline was **0** L	MD + **0.15 L** (+0.09 to +0.2)

Note: 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.

*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).

Abbreviations: CI, confidence interval; MD, mean difference.

Explanations:

[a]The study included was funded by Sanofi and Regeneron Pharmaceuticals. No industry-independent observational or randomized trials were identified to compare the results. The GDG members considered that there were no major concerns about potential publication/sponsorship bias

[b]The effect of dupilumab is below the MID (0.5 points). [32]

[c]Downgraded because FEV1 is considered a surrogate outcome of asthma control of symptoms, with a uncertain correlation with asthma symptoms.[103]

[d]The minimal important difference (MID) for FEV1 is 0.20 L (GDG consensus).

0.92 to 1.57) and children 6-11 years old (RR of 6.78; 95% CI 0.90 to 50.91) (P = .10).

3.4.2 | Drug-related serious adverse events

Drug-related SAE were reported for benralizumab in one RCT[36] and for omalizumab in two RCTs.[51,60] Benralizumab may reduce the incidence of SAE (RR 0.56; 95%CI 0.22-1.44) 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 1000 patients, from four fewer to 43 more) with low certainty of evidence. No drug-related SAE were reported for children 6-11 years old.

3.5 | Corticosteroid and rescue medication

3.5.1 | Inhaled corticosteroid dose

Inhaled corticosteroid dose dose reduction was evaluated only for omalizumab vs 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 = .16).

3.5.2 | 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 in prednisolone equivalent milligrams per day at 32 weeks (MD −6.7; 95%CI −12.93 to −0.47).

3.5.3 | 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

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

Outcomes	No 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 annualized rate	2772 (6 RCTs)[42,44,51,54,55,68] 24-52 wk [a]	⨁⨁⨁⨁ HIGH[b,c,d]	Incidence rate ratio 0.56 (0.45-0.69)[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] 26-52 wk	⨁⨁⨁◯ 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)[40,43,47,48,54,59,62,63,66,68] 16-52 wk	⨁⨁⨁⨁ HIGH[b,d,j]	Risk ratio 1.50 (1.32-1.70)[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 wk-52 wk	⨁⨁⨁⨁ HIGH[b,d,l]	Risk ratio 1.32 (1.16-1.51)[m]	563 per 1.000	180 more per 1.000 (90 more to 287 more)[m]
Any drug-related AE	2341 (7 RCTs)[43,50,54,63,66-68] 16-52 wk	⨁⨁⨁◯ MODERATE [ab,b,d]	Risk ratio 1.27 (0.93-1.74)	127 per 1.000	34 more per 1.000 (9 fewer to 94 more)
Any drug-related SAE)	1163 (2 RCTs)[51,60] 16 wk-48 wk	⨁⨁⨁◯ MODERATE [ab,b,d]	Risk ratio 1.62 (0.76-3.45)	18 per 1.000	11 more per 1.000 (4 fewer to 43 more)
Lung function (FEV1) assessed with absolute FEV1 (L) change vs baseline	1209 (6 RCTs)[42,43,55,60-62] range 12-52 wk [n,o]	⨁⨁◯◯ LOW[21-23b,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) vs baseline	1735 (7 RCTs)[41,48,49,52,58-60] 12-36 wk[t]	⨁⨁⨁◯ MODERATE[21-23,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 vs baseline	1861 (5 RCTs)[41,42,46,52,65] 24-52 wk	⨁⨁⨁⨁ 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)[41,42,52,54,59,66,68] 16-52 wk [22, w]	⨁⨁⨁⨁ HIGH[b,d,x]	-	The mean 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)[41,51,65]	⨁⨁⨁◯ MODERATE[32,33,b,d,z]	-	The mean FeNO level change from baseline was 0 ppb	MD 4.65 ppb lower (7.39 lower to 1.92 lower)[aa]

Note: GRADE Working Group grades of evidenceHigh 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

Abbreviations: CI, confidence interval; MD, mean difference; RR, risk ratio; and SMD, standardized mean difference

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 y 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]Nine studies included reported exacerbations as "patients who had ≥1 exacerbation," the pooled risk ratio was 0.59(95% CI 0.52-0.67). Three 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 wk[44,54,63,68] and at 48-52 wk.[42,51,55,68] Lanier 2009 included patients aged 6-12 y 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,[43,56,65] the pooled mean different was 0.57(95% CI 0.17-0.97). We also included the ACQ scores assessed by five studies,[46,51,52,59,68] the pooled standard mean difference was −0.20 (95% CI −0.26 to −0.14)

[i]The pooled effect of ACQ-6 evaluated at 16 wk,[44] 24-32 wk[44,59] and at 52 wk.[56]

[j]Although there were a high I^2 (67%.), this was influenced by only one study with low number of events.

[k]The pooled data were assessed at 16 and 20 wk,[48,62] and 52 wk[68]; Other studies evaluated at 24-28 wk. 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 (I^2 = 83%), but probably unimportant heterogeneity.

[m]The mean change of AQLQ scores was assessed by seven studies, the pooled standard mean difference was 0,34 (95% IC 0.18-0.49)

[n]Milgrom reported FEV1 in children (6-12 y old) for 28 wk 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 = .28) and 52 mL (P = .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 y old) for 28 wk 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 prebronchodilator 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 y old) with 28 wk 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 18.8 L/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 = .004]) but probably unimportant heterogeneity.

[y]The MID of FeNO change from baseline is more than 10 ppb.[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 YY.[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.

[ab]The effect may both be harmful or beneficial.

*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).

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 = .55).

3.5.4 | Lung function

Forced exhalation volume in 1 second variation in litres was reported in two RCT for benralizumab,[34] one for dupilumab[38] and six RCTs for omalizumab.[42,43,55,60-62] Both dupilumab (MD 0.15; 95%CI 0.09-0.20) and omalizumab (MD 0.17; 95%CI 0.02-0.32) 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 −0.025-0.136; moderate certainty of evidence). None of the biologicals showed an increase in FEV1 above the MID.

3.6 | 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 hospitalization, 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 nonexacerbation 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).

4 | DISCUSSION

4.1 | 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 (ie ACQ, AQLQ) and indirectness (ie 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 €.

4.2 | 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.[96-98] 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 (ie 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

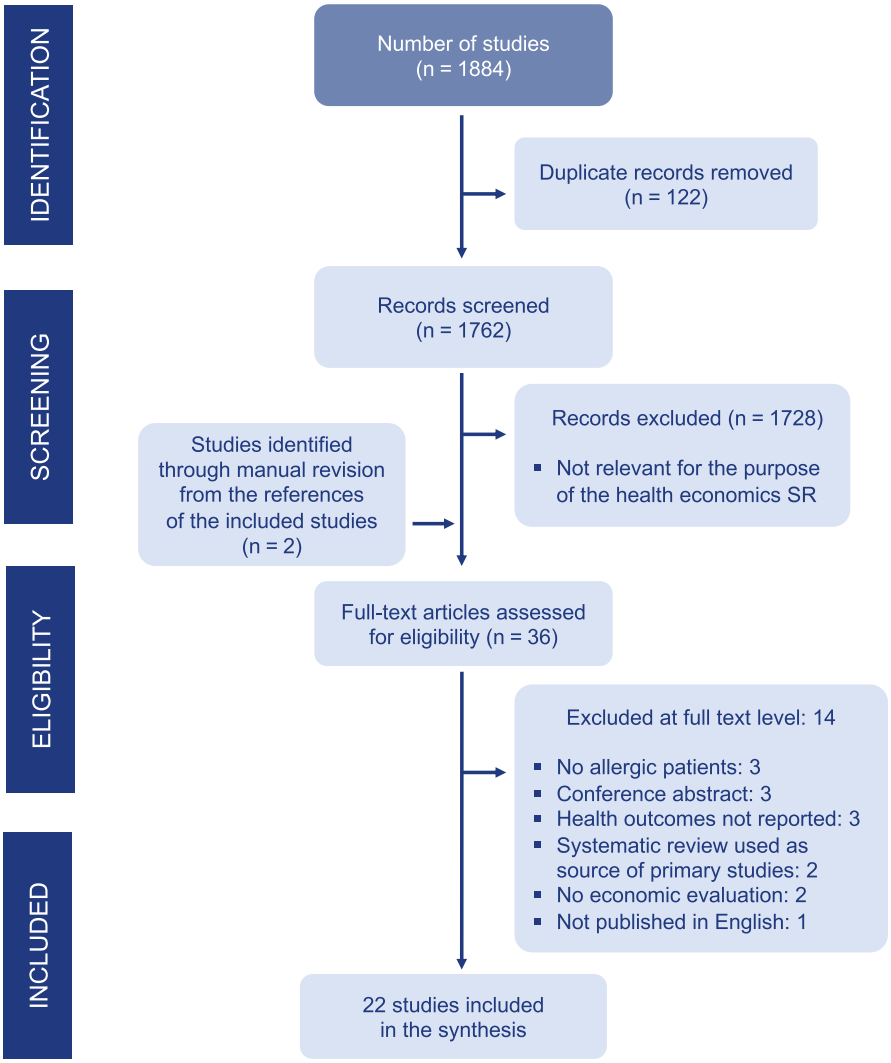

FIGURE 2 Study flow chart for the economic evidence

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]

4.3 | 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 policymakers, 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 (eg 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 chosen. This approach could be useful for the decisions of using biologicals across different countries.

4.4 | 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 (eg 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 are reassuring, more accurate reporting is warranted, in combination with long-term safety evaluation, including observational studies and registries.[104] For omalizumab, there are good data available to support its efficacy and safety in the paediatric population;[104] however, for benralizumab and dupilumab the data are limited highlighting the urgent unmet need for rigorous trials with biologicals in severe asthma in the paediatric population.

CONFLICT OF INTEREST

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REFERENCES

1. https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf. Accessed December 23, 2019.
2. Agache I, Lau S, Akdis CA, et al. EAACI guidelines on allergen immunotherapy: house dust mite-driven allergic asthma al. *Allergy*. 2019;74(5):855-873.
3. Ring J, Jutel M, Papadopoulos N, Pfaar O, Akdis C. Provocative proposal for a revised nomenclature for allergy and other hypersensitivity diseases. *Allergy*. 2018;73(10):1939-1940.

4. Boonpiyathad T, Sözener ZC, Satitsuksanoa P, Akdis CA. Immunologic mechanisms in asthma. *Semin Immunol*. 2019;46:101333.
5. Matucci A, Vultaggio A, Maggi E, Kasujee I. Is IgE or eosinophils the key player in allergic asthma pathogenesis? Are we asking the right question? *Respir Res*. 2018;19(1):113.
6. Agache I, Cojanu C, Laculiceanu A, Rogozea L. Critical points on the use of biologicals in allergic diseases and asthma. *Allergy Asthma Immunol Res*. 2020;12(1):24-41.
7. Palomares Ó, Sánchez-Ramón S, Dávila I, et al. dIvergEnt: how IgE axis contributes to the continuum of allergic asthma and anti-IgE therapies. *Int J Mol Sci*. 2017;18(6):E1328.
8. Huang YC, Weng CM, Lee MJ, Lin SM, Wang CH, Kuo HP. Endotypes of severe allergic asthma patients who clinically benefit from anti-IgE therapy. *Clin Exp Allergy*. 2019;49(1):44-53.
9. Khumalo J, Kirstein F, Scibiorek M, Hadebe S, Brombacher F. Therapeutic and prophylactic deletion of IL-4Rα-signaling ameliorates established ovalbumin induced allergic asthma. *Allergy*. 2019. [Epub ahead of print]. https://doi.org/10.1111/all.14137
10. Djukanović R, Wilson SJ, Kraft M, et al. Effects of treatment with anti-immunoglobulin E antibody omalizumab on airway inflammation in allergic asthma. *Am J Respir Crit Care Med*. 2004;170(6):583-593.
11. Mukherjee M, Kjarsgaard M, Radford K, et al. Omalizumab in patients with severe asthma and persistent sputum eosinophilia. *Allergy Asthma Clin Immunol*. 2019;15:21.
12. Haselkorn T, Szefler SJ, Simons FE, et al. Allergy, total serum immunoglobulin E, and airflow in children and adolescents in TENOR. *Pediatr Allergy Immunol*. 2010;21(8):1157-1165.
13. Moore WC, Meyers DA, Wenzel SE, et al. Identification of asthma phenotypes using cluster analysis in the severe asthma research program. *Am J Respir Crit Care Med*. 2010;181(4):315-323.
14. European Network for Understanding Mechanisms of Severe Asthma. The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. European Network for Understanding Mechanisms of Severe Asthma. *Eur Respir J*. 2003;22:470-477.
15. Shaw D, Sousa AR, Fowler SJ, et al. Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort. *Eur Respir J*. 2015;46(5):1308-1321.
16. Lafeuille MH, Gravel J, Figliomeni M, Zhang J, Lefebvre P. Burden of illness of patients with allergic asthma versus non-allergic asthma. *J Asthma*. 2013;50(8):900-907.
17. https://www.ema.europa.eu/en/medicines/human/EPAR/xolair. Accessed December 23, 2019.
18. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/103976s5225lbl.pdf. Accessed December 23, 2019.
19. https://www.ema.europa.eu/en/medicines/human/EPAR/fasenra. Accessed December 23, 2019.
20. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761070Orig1s000Approv.pdf. Accessed December 23, 2019.
21. https://www.ema.europa.eu/en/medicines/human/summaries-opinion/dupixent-0. Accessed December 23, 2019.
22. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761055s007lbl.pdf. Accessed December 23, 2019.
23. Higgins JP, Altman DG, Gøtzsche P, et al. The cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
24. Evers S, Goossens M, de Vet H, van Tulder M, Ament A. Criteria list for assessment of methodological quality of economic evaluations: consensus on health economic criteria. *Int J Technol Assess Health Care*. 2005;21(2):240-245.
25. Hutter F, Antoñanzas F. Economic evaluations in the EURONHEED: a comparative analysis. *Pharmacoeconomics*. 2009;27(7):561-570.
26. Nixon J, Rice S, Drummond M, Boulenger S, Ulmann P, de Pouvourville G. Guidelines for completing the EURONHEED transferability information checklists. *Eur J Health Econ*. 2009;10(2):157-165.
27. Rücker G, Cates CJ, Schwarzer G. Methods for including information from multi-arm trials in pairwise meta-analysis. *Res Synth Methods*. 2017;8(4):392-403.
28. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926.
29. Guyatt GH, Oxman AD, Sultan S, et al. GRADE guidelines. rating up the quality of evidence. *J Clin Epidemiol*. 2011;64(12):1311-1316.
30. Santanello NC, Zhang J, Seidenberg B, Reiss TF, Barber BL. What are minimal important changes for asthma measures in a clinical trial? *Eur Respir J*. 1999;14(1):23-27.
31. Jones PW. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. *Eur Respir J*. 2002;19(3):398-404.
32. Juniper EF, Svensson K, Mörk AC, Ståhl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med*. 2005;99(5):553-558.
33. Dweik RA, Boggs PB, Erzurum SC, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *Am J Respir Crit Care Med*. 2011;184(5):602-615.
34. Chipps BE, Newbold P, Hirsch I, Trudo F, Goldman M. Benralizumab efficacy by atopy status and serum immunoglobulin E for patients with severe, uncontrolled asthma. *Ann Allergy Asthma Immunol*. 2018;120(5):504-511.
35. FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor alpha monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2016;388(10056):2128-2141.
36. Nair P, Wenzel S, Rabe KF, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. *N Engl J Med*. 2017;376(25):2448-2458.
37. Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med*. 2018;378(26):2486-2496.
38. Corren J, Castro M, O'Riordan T, et al. Dupilumab efficacy in patients with uncontrolled, moderate-to-severe allergic asthma. *J Allergy Clin Immunol Pract*. 2019;8(2):516-526.
39. Busse W, Corren J, Lanier BQ, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol*. 2001;108(2):184-190.
40. Finn A, Gross G, van Bavel J, et al. Omalizumab improves asthma-related quality of life in patients with severe allergic asthma. *J Allergy Clin Immunol*. 2003;111(2):278-284.
41. Lanier BQ, Corren J, Lumry W, Liu J, Fowler-Taylor A, Gupta N. Omalizumab is effective in the long-term control of severe allergic asthma. *Ann Allergy Asthma Immunol*. 2003;91(2):154-159.
42. Ayres J, Higgins B, Chilvers ER, Ayre G, Blogg M, Fox H. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with poorly controlled (moderate-to-severe) allergic asthma. *Allergy*. 2004;59(7):701-708.
43. Bardelas J, Figliomeni M, Kianifard F, Meng X. A 26-week, randomized, double-blind, placebo-controlled, multicenter study to evaluate the effect of omalizumab on asthma control in patients with persistent allergic asthma. *J Asthma* 2012;49(2):144-152.
44. Bousquet J, Siergiejko Z, Swiebocka E, et al. Persistency of response to omalizumab therapy in severe allergic (IgE-mediated) asthma. *Allergy*. 2011;66(5):671-678.
45. Siergiejko Z, Świebocka E, Smith N, et al. Oral corticosteroid sparing with omalizumab in severe allergic (IgE-mediated) asthma patients. *Curr Med Res Opin*. 2011;27(11):2223-2228.

46. Solèr M, Matz J, Townley R, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J*. 2001;18(2):254-261.
47. Buhl R, Hanf G, Soler M, et al. The anti-IgE antibody omalizumab improves asthma-related quality of life in patients with allergic asthma. *Eur Respir J*. 2002;20(5):1088-1094.
48. Chanez P, Contin-Bordes C, Garcia G, et al. Omalizumab-induced decrease of FcξRI expression in patients with severe allergic asthma. *Respir Med*. 2010;104(11):1608-1617.
49. Corren J, Wood RA, Patel D, et al. Effects of omalizumab on changes in pulmonary function induced by controlled cat room challenge. *J Allergy Clin Immunol*. 2011;127(2):398-405.
50. Cruz AA, Lima F, Sarinho E, et al. Safety of anti-immunoglobulin E therapy with omalizumab in allergic patients at risk of geohelminth infection. *Clin Exp Allergy*. 2007;37(2):197-207.
51. Hanania NA, Alpan O, Hamilos DL, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. *Ann Intern Med*. 2011;154(9):573-582.
52. Holgate ST, Chuchalin A, Hebert J, et al. Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. *Clin Exp Allergy*. 2004;34(4):632-638.
53. Hoshino M, Ohtawa J. Effects of adding omalizumab, an anti-immunoglobulin E antibody, on airway wall thickening in asthma. *Respiration*. 2012;83(6):520-528.
54. Humbert M, Beasley R, Ayres J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy*. 2005;60(3):309-316.
55. Niven R, Chung KF, Panahloo Z, Blogg M, Ayre G. Effectiveness of omalizumab in patients with inadequately controlled severe persistent allergic asthma: an open-label study. *Respir Med*. 2008;102(10):1371-1378.
56. Ledford D, Busse W, Trzaskoma B, et al. A randomized multicenter study evaluating Xolair persistence of response after long-term therapy. *J Allergy Clin Immunol*. 2017;140(1):162-169.
57. van Rensen EL, Evertse CE, van Schadewijk WA, et al. Eosinophils in bronchial mucosa of asthmatics after allergen challenge: effect of anti-IgE treatment. *Allergy*. 2009;64(1):72-80.
58. Pasha MA, Jourd'heuil D, Jourd'heuil F, et al. The effect of omalizumab on small airway inflammation as measured by exhaled nitric oxide in moderate-to-severe asthmatic patients. *Allergy Asthma Proc*. 2014;35(3):241-249.
59. Li J, Kang J, Wang C, Yang J, et al. Omalizumab improves quality of life and asthma control in Chinese patients with moderate to severe asthma: a randomized phase III study. *Allergy Asthma Immunol Res*. 2016;8(4):319-328.
60. Ohta K, Miyamoto T, Amagasaki T, Yamamoto M, 1304 Study Group. Efficacy and safety of omalizumab in an Asian population with moderate-to-severe persistent asthma. *Respirology*. 2009;14(8):1156-1165.
61. Prieto L, Gutiérrez V, Colás C, et al. Effect of omalizumab on adenosine 5'-monophosphate responsiveness in subjects with allergic asthma. *Int Arch Allergy Immunol*. 2006;139(2):122-131.
62. Rubin AS, Souza-Machado A, Andradre-Lima M, Ferreira F, Honda A. Effect of omalizumab as add-on therapy on asthma-related quality of life in severe allergic asthma: a Brazilian study (QUALITX). *J Asthma*. 2012;49(3):288-293.
63. Vignola AM, Humbert M, Bousquet J, et al. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR. *Allergy*. 2004;59(7):709-717.
64. Zielen S, Lieb A, De La Motte S, et al. Omalizumab protects against allergen- induced bronchoconstriction in allergic (immunoglobulin E-mediated) asthma. *Int Arch Allergy Immunol*. 2013;160(1):102-110.
65. Busse WW, Morgan WJ, Gergen PJ, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *N Engl J Med*. 2011;364(11):1005-1015.
66. Milgrom H, Berger W, Nayak A, et al. Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). *Pediatrics*. 2001;108(2):E36.
67. Lemanske RF Jr, Nayak A, McAlary M, Everhard F, Fowler-Taylor A, Gupta N. Omalizumab improves asthma-related quality of life in children with allergic asthma. *Pediatrics*. 2002;110(5):e55.
68. Lanier B, Bridges T, Kulus M, Taylor AF, Berhane I, Vidaurre CF. Omalizumab for the treatment of exacerbations in children with inadequately controlled allergic (IgE-mediated) asthma. *J Allergy Clin Immunol*. 2009;124(6):1210-1216.
69. Kulus M, Hébert J, Garcia E, Fowler Taylor A, Fernandez Vidaurre C, Blogg M. Omalizumab in children with inadequately controlled severe allergic (IgE-mediated) asthma. *Curr Med Res Opin*. 2010;26(6):1285-1293.
70. ICER. Institute for Clinical and Economic Review. Biologic Therapies for Treatment of Asthma Associated with Type 2 Inflammation: Effectiveness, Value, and Value-Based Price Benchmarks. https://icer-review.org/material/asthma-final-evidence-report/.Accessed September 2019.
71. Tikhonova I, Long L, Ocean N. Benralizumab for treating severe asthma: A Single Technology Appraisal. Peninsula Technology Assessment Group (PenTAG).2018.
72. Brown R, Turk F, Dale P, Bousquet J. Cost-effectiveness of omalizumab in patients with severe persistent allergic asthma. *Allergy*. 2007;62(2):149-153.
73. Campbell JD, Spackman DE, Sullivan SD. The costs and consequences of omalizumab in uncontrolled asthma from a USA payer perspective. *Allergy*. 2010;65(9):1141-1148.
74. Negro D, Pradelli L, Tognella S, Micheletto C, Iannazzo S. Cost-utility of add-on omalizumab in difficult-to-treat allergic asthma in Italy. *Eur Ann Allergy Clin Immunol*. 2011;43(2):45-53.
75. Negro D, Tognella S, Pradelli L. A 36-month study on the cost/utility of add-on omalizumab in persistent difficult-to-treat atopic asthma in Italy. *J Asthma*. 2012;49(8):843-848.
76. Dewilde S, Turk F, Tambour M, Sandström T. The economic value of anti-IgE in severe persistent, IgE-mediated (allergic) asthma patients: adaptation of INNOVATE to Sweden. *Curr Med Res Opin*. 2006;22(9):1765-1776.
77. Entrenas Costa MF, Soto Campos JG, Padilla-Galo A, et al. Economic impact and clinical outcomes of omalizumab add-on therapy for patients with severe persistent asthma: a real-world study. *Pharmacoecon Open*. 2019;3(3):333-342.
78. Faria R, McKenna C, Palmer S. Optimizing the position and use of omalizumab for severe persistent allergic asthma using cost-effectiveness analysis. *Value Health*. 2014;17(8):772-782.
79. Jahnz-Rozyk K, Lis J, Warchoł M, Kucharczyk A. Clinical and economic impact of a one-year treatment with omalizumab in patients with severe allergic asthma within a drug programme in Poland. *BMC Pulm Med*. 2018;18(1):48.
80. Levy AN, García a Ruiz AJ, García-Agua Soler N, Sanjuan MV. Cost-effectiveness of omalizumab in severe persistent asthma in Spain: a real-life perspective. *J Asthma*. 2015;52(2):205-210.
81. Menzella F, Facciolongo N, Piro R, et al. Clinical and pharmacoeconomic aspects of omalizumab: a 4-year follow-up. *Ther Adv Respir Dis*. 2012;6(2):87-95.
82. Morishima T, Kai H, Imanaka Y. Cost-effectiveness analysis of omalizumab for the treatment of severe asthma in japan and the value of responder prediction methods based on a multinational trial. *Value Health Reg Issues*. 2013;2(1):29-36.
83. Norman G, Faria R, Paton F, et al. Omalizumab for the treatment of severe persistent allergic asthma: a systematic review and economic evaluation. *Health Technol Assess*. 2013;17(52):1-342.

84. Oba Y, Salzman GA. Cost-effectiveness analysis of omalizumab in adults and adolescents with moderate-to-severe allergic asthma. *J Allergy Clin Immunol*. 2004;114(2):265-269.
85. Suzuki C, Lopes da Silva N, Kumar P, Pathak P, Ong SH. Cost-effectiveness of omalizumab add-on to standard-of-care therapy in patients with uncontrolled severe allergic asthma in a Brazilian healthcare setting. *J Med Econ*. 2017;20(8):832-839.
86. van Nooten F, Stern S, Braunstahl GJ, Thompson C, Groot M, Brown RE. Cost-effectiveness of omalizumab for uncontrolled allergic asthma in the Netherlands. *J Med Econ*. 2013;16(3):342-348.
87. Vennera M, Valero A, Uría E, Forné C, Picado C. Cost-effectiveness analysis of omalizumab for the treatment of severe persistent asthma in real clinical practice in Spain. *Clin Drug Investig*. 2016;36(7):567-578.
88. Wu AC, Paltiel AD, Kuntz KM, Weiss ST, Fuhlbrigge AL. Cost-effectiveness of omalizumab in adults with severe asthma: results from the asthma policy model. *J Allergy Clin Immunol*. 2007;120(5):1146-1152.
89. Zafari Z, Sadatsafavi M, Mark FitzGerald J, Canadian Respiratory Research Network. Cost-effectiveness of tiotropium versus omalizumab for uncontrolled allergic asthma in US. *Cost Eff Resour Alloc*. 2018;16:3.
90. Zafari Z, Sadatsafavi M, Marra CA, Chen W, FitzGerald JM. Cost-effectiveness of bronchial thermoplasty, omalizumab, and standard therapy for moderate-to-severe allergic asthma. *PLoS ONE*. 2016;11(1):e0146003.
91. Zhou H, Lu Y, Wu B, Che D. Cost-effectiveness of omalizumab for the treatment of inadequately controlled severe allergic asthma in Chinese children. *J Asthma*. 2020;57(1):87–94.
92. Lloyd A, Turk F, Leighton T, Canonica GW. Psychometric evaluation of global evaluation of treatment effectiveness: a tool to assess patients with moderate-to-severe allergic asthma. *J Med Econ*. 2007;10(3):285-296.
93. Tian BP, Zhang GS, Lou J, Zhou HB, Cui W. Efficacy and safety of benralizumab for eosinophilic asthma: a systematic review and meta-analysis of randomized controlled trials. *J Asthma*. 2018;55(9):956-965.
94. Liu W, Ma X, Zhou W. Adverse events of benralizumab in moderate to severe eosinophilic asthma: a meta-analysis. *Medicine (Baltimore)*. 2019;98(22):e15868.
95. Zayed Y, Kheiri B, Banifadel M, et al. Dupilumab safety and efficacy in uncontrolled asthma: a systematic review and meta-analysis of randomized clinical trials. *J Asthma*. 2018;1-10. Epub ahead of print. https://doi.org/10.1080/02770903.2018.1520865
96. Normansell R, Walker S, Milan SJ, Walters EH, Nair P. Omalizumab for asthma in adults and children. *Cochrane Database Syst Rev*. 2014;1:CD003559.
97. Rodrigo GJ, Neffen H. Systematic review on the use of omalizumab for the treatment of asthmatic children and adolescents. *Pediatr Allergy Immunol*. 2015;26(6):551-556.
98. Corren J, Kavati A, Ortiz B, et al. Efficacy and safety of omalizumab in children and adolescents with moderate-to-severe asthma: a systematic literature review. *Allergy Asthma Proc*. 2017;38(4):250-263.
99. McQueen RB, Sheehan DN, Whittington MD, van Boven JFM, Campbell JD. Cost-effectiveness of biological asthma treatments: a systematic review and recommendations for future economic evaluations. *Pharmacoeconomics*. 2018;36(8):957-971.
100. Rodriguez-Martinez CE, Sossa-Briceño MP, Castro-Rodriguez JA. Cost effectiveness of pharmacological treatments for asthma: a systematic review. *Pharmacoeconomics*. 2018;36(10):1165-1200.
101. Einarson TR, Bereza BG, Nielsen TA, Van Laer J, Hemels ME. Systematic review of models used in economic analyses in moderate-to-severe asthma and COPD. *J Med Econ*. 2016;19(4):319-355.
102. Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome. *Cochrane Database Syst Rev*. 2017;2:MR000033.
103. Aburuz S, McElnay J, Gamble J, Millership J, Heaney L. Relationship between lung function and asthma symptoms in patients with difficult to control asthma. *J Asthma*. 2005;42(10):859-864.
104. MacDonald KM, Kavati A, Ortiz B, Alhossan A, Lee CS, Abraham I. Short- and long-term real-world effectiveness of omalizumab in severe allergic asthma: systematic review of 42 studies published 2008–2018. *Expert Rev Clin Immunol*. 2019;15(5):553-569.
105. Hastie AT, Moore WC, Li H, et al. Biomarker surrogates do not accurately predict sputum eosinophil and neutrophil percentages in asthmatic subjects. *J Allergy Clin Immunol*. 2013;132(1):72-80.
106. Wagener AH, de Nijs SB, Lutter R, et al. External validation of blood eosinophils, FE(NO) and serum periostin as surrogates for sputum eosinophils in asthma. *Thorax*. 2015;70(2):115-120.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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