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GUIDELINE

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Efficacy and safety of treatment with biologicals (benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab) for severe eosinophilic 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-related quality of life questionnaire; CHEC, consensus health economic criteria; CI, confidence interval; EAACI, European Academy of Allergy and Clinical Immunology; EMA, European Medicine Agency; EURONHEED, European Network of Health Economic Evaluation Databases; FDA, Food and Drug administration; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in one second; GDG, guideline development group; GINA, Global Initiative for Asthma; GRADE, Grading of Recommendations Assessment, Development and Evaluation; ICER, Incremental cost-effectiveness ratio; ICS, inhaled corticosteroids; Ig, immunoglobulin; IL, interleukin; IRR, incidence rate ratio; IV, intravenous; 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; SC, subcutaneous; SGRQ, St George's Respiratory Questionnaire; SOC, standard of care; SR, systematic review; T2, type 2; TASS, Total Asthma Symptoms Scores.

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Abstract

Five biologicals have been approved for severe eosinophilic asthma, a well-recognized phenotype. Systematic reviews (SR) evaluated the efficacy and safety of benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab (alphabetical order) compared to standard of care for severe eosinophilic 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 for each of the biologicals. The risk of bias and the certainty of the evidence were assessed using GRADE. 19 RCTs (three RCTs for benralizumab, three RCTs for dupilumab, three RCTs for mepolizumab, five RCTs for omalizumab and five RCTs for reslizumab), including subjects 12 to 75 years old (except for omalizumab including also subjects 6-11 years old), ranging from 12 to 56 weeks were evaluated. All biologicals reduce exacerbation rates with high certainty of evidence: benralizumab incidence rate ratio (IRR) 0.53 (95% CI 0.39 to 0.72), dupilumab (IRR) 0.43 (95% CI 0.32 to 0.59), mepolizumab IRR 0.49 (95% CI 0.38 to 0.66), omalizumab (IRR) 0.56 (95% CI 0.40 to 0.77) and reslizumab (IRR) 0.46 (95% CI 0.37 to 0.58). Benralizumab, dupilumab and mepolizumab reduce the daily dose of oral corticosteroids (OCS) with high certainty of evidence. All evaluated biologicals probably improve asthma control, QoL and FEV_1, without reaching the minimal important difference (moderate certainty). Benralizumab, mepolizumab and reslizumab slightly increase drug-related adverse events (AE) and drug-related serious AE (low to very low certainty of evidence). The incremental cost-effectiveness ratio per quality-adjusted life year value is above the willingness to pay threshold for all biologicals (moderate certainty). Potential savings are driven by decrease in hospitalizations, emergency and primary care visits. There is high certainty that all approved biologicals reduce the rate of severe asthma exacerbations and for benralizumab, dupilumab and mepolizumab for reducing OCS. There is moderate certainty for improving asthma control, QoL, FEV_1. More data on long-term safety are needed together with more efficacy data in the paediatric population.

KEYWORDS

biologicals, cost-effectiveness, efficacy, severe-eosinophilic-asthma, safety

1 | INTRODUCTION

There are still a significant proportion of patients with severe asthma having uncontrolled or partially controlled asthma despite correct management. These patients represent a special challenge related to extensive diagnostic evaluation and high consumption of healthcare resources.[1-4] Severe asthma is defined as inadequate control of asthma under high-intensity treatment with inhaled corticosteroids (ICS) and additional controllers (including oral corticosteroid [OCS]) for at least six months per year, or by loss of asthma control on the attempt to reduce the high-intensity treatment.[5] Before any further treatments are evaluated, differential diagnoses of asthma should be ruled out, comorbidities should be treated, persistent triggers should be eliminated, and patient adherence should be optimized.[2,5,6] Considering the availability of specific targeted therapies for type 2 (T2) asthma, the management approach to severe asthma currently includes a phenotyping step for the identification of allergic, eosinophilic and non-T2 phenotypes.[7,8]

Eosinophils are prominent pathogenic cells involved in asthma. Increased blood or sputum eosinophils were related to frequent asthma exacerbations and disease severity and are used to guide treatment decisions.[9-11] Most human diseases accompanied by elevated blood eosinophils are associated with increased interleukin (IL)-5 production. Although IL-5 plays a central role in eosinophil biology, it is neither necessary nor sufficient for fully inducing an eosinophil-mediated disease. In humans, IL-5 is often co-expressed with other T2 cytokines including IL-4 and IL-13 and associated in atopic individuals with increased immunoglobulin (Ig)-E production.[12-16] This overlap between the key pathogenetic pathways (IL-5–, IL-4/IL-13– and IgE-driven eosinophilic inflammation) toughens the choice of a biological for the eosinophilic asthma phenotype. Therefore, future novel approaches to better identify predominant pathways at the molecular level (endotypes) are demanded.

In the last decades, new add-on therapies for severe asthma have been developed and may be applied depending on asthma phenotype and endotype.[7,8,13] Anti–IL-5 monoclonal antibodies (mepolizumab and reslizumab) are approved for severe asthma and peripheral eosinophilia.[17-20] Benralizumab, a monoclonal antibody that binds to the α subunit of IL-5 receptor (IL-5Rα), was also recently approved for eosinophilic asthma.[21,22] Dupilumab, a monoclonal antibody directed against the α subunit of the IL-4 receptor (IL-4Rα) acting as a dual inhibitor of both IL-4– and IL-13–mediated signalling pathways, was approved for T2 asthma.[23,24] Omalizumab, a humanized monoclonal anti-IgE antibody, was the first biological approved for IgE-mediated persistent allergic asthma.[25,26]

The European Academy of Allergy and Clinical Immunology (EAACI) is developing clinical practice guidelines for the use of biologicals in patients with severe asthma. Three interlinked systematic reviews (SR) were performed to inform the formulation of key clinical recommendations. The current SR is focusing on eosinophilic asthma assessing the current evidence regarding efficacy, safety and economic impact of the biologicals with current regulatory approval for patients with uncontrolled severe asthma (ie benralizumab, dupilumab, omalizumab, mepolizumab and reslizumab, in alphabetical order).

2 | METHODS

2.1 | Guideline Development Group

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

2.2 | Structured question and outcomes prioritization

The GDG framed the clinical question as follows: "Is the treatment with biologicals (ie benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab) efficacious and safe for patients with uncontrolled severe eosinophilic asthma?" For the purpose of this SR, the population of interest was defined as subjects with any of the following: a sputum eosinophil count of ≥1% or an asthma-related peripheral blood eosinophil count of ≥150 cells/μL, or a fractional exhaled nitric oxide (FeNO) of ≥20 ppb.[27] The outcomes were prioritized 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, QoL and safety and the important outcomes included lung function (forced expiratory volume in one second—FEV_1), OCS and ICS use and rescue medication use (Table S1). Safety was assessed evaluating the rate of drug-related adverse events (AE) or drug-related serious AEs.

The GDG also framed a cost-effectiveness question to assess the economic impact of these biologicals versus standard of care for patients with uncontrolled severe eosinophilic asthma. The outcomes of interest were costs and resource use, as well as the incremental

cost-effectiveness ratios (ICERs) per both quality-adjusted life years (QALY) and per asthma-specific outcomes.

2.3 | Data sources and search methodology

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 individual studies for evidence of effects and economic evaluations, including systematic reviews as source of individual studies. Search terms were adapted to each database, and validated filters were used to retrieve appropriate designs (table S2). Members of the GDG were requested to provide additional studies for evaluation.

2.4 | Study selection

Randomized controlled trials (RCTs) of patients with uncontrolled severe eosinophilic asthma that compared benralizumab, dupilumab, mepolizumab, omalizumab or reslizumab versus standard of care were included in the SR. Separate searches for each of the five biologicals evaluated were performed. The SR excluded studies in which the dose or the route of the biological was not approved by the European Medical Agency (EMA) or by Unites States Food and Drug administration (FDA). Abstracts or conference communications not published as full articles in peer-reviewed journals were also excluded. Only studies published in English were considered. 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. Discrepancies were solved either by consensus or with the help of a third reviewer. All citations retrieved were imported into the 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, requested 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.[28] The ROB was judged as low, high or unclear risk for each domain: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective reporting.

For the health economics analysis, two reviewers extracted the main characteristics of included studies (eg type of economic evaluation, perspective, time horizon, discounting, sources of information, model type), relevant outcomes and costs (eg ICERs, sensitivity analyses results), sources of funding and conflict of interest. Two reviewers assessed the methodological limitations using the consensus on health economics criteria (CHEC) checklist.[29] Transferability to the European context was assessed using the European Network of Health Economic Evaluation Databases (EURONHEED) checklist.[30,31]

2.6 | Data synthesis and analysis

The main results of the SR are described narratively and tabulated as summary of findings. For dichotomous variables, data were pooled as incidence rate ratio (IRR) and risk ratios (RR). For continuous data, mean differences (MD), with 95% confidence intervals, were used. Change in the observed asthma-related outcomes was assessed between biologicals and placebo from baseline to the end of the treatment. A random-effects model was used to pool data (Review Manager V5.3). Where multiple arms were compared to a common placebo arm, standard errors were adjusted to avoid the unit of analysis error.[32]

Statistical heterogeneity between studies was assessed using the Cochrane chi-square test and the magnitude of heterogeneity with the I^2 statistic. To account for clinical heterogeneity, the analyses were stratified whenever possible by different doses of the biological, age, relevant biomarkers (blood eosinophils, FeNO) and ROB. Additionally, post hoc subgroup analysis by baseline use of OCS was performed. To estimate the absolute effects for each comparison, the median estimate reported in the control arms was used as baseline risk. 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 for each outcome was rated as high, moderate, low or very low considering the standard GRADE domains: ROB, imprecision, inconsistency, indirectness and publication bias.[33,34] For the evaluation of imprecision for each asthma-related outcome evaluated, where available, the minimal important difference (MID) thresholds were considered.[35-38] For $FEV_{1,}$ a MID of 0.20 L was considered as recommended by consensus by the GDG.

3 | RESULTS

3.1 | Search results

The eligibility process is summarized in a PRISMA flow chart (Figure 1). A total of 3441 unique citations were retrieved from database searches, and 145 were appraised as full text. 135 publications were excluded due to differences in population, outcomes of interest, design or regulatory unapproved dose and/or route (Table S3). Twenty-eight publications from 19 RCTs were evaluated. These included three RCTs for benralizumab[39-41]; three for dupilumab[42-44]; three for mepolizumab[45-47]; five for omalizumab[48-51]; and five for reslizumab.[52-55]

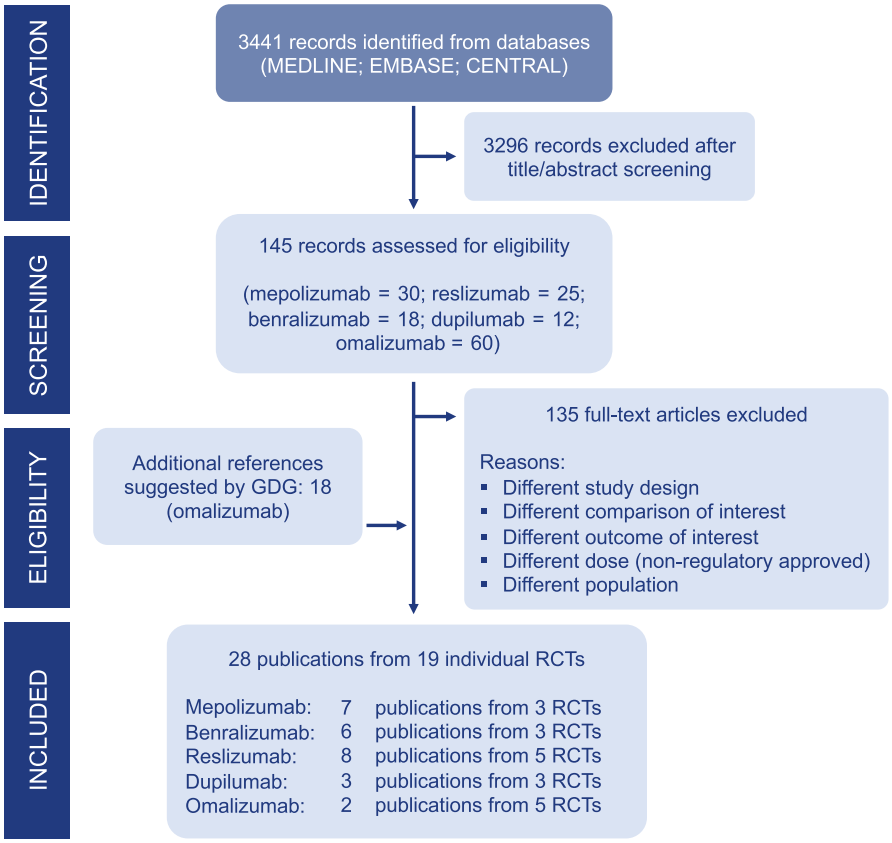

FIGURE 1 Study flow chart for the selecting evidence for efficacy and safety of the biologicals in severe eosinophilic asthma

3.2 | Characteristic of included studies

The characteristics of studies evaluated for evidence of efficacy and safety are detailed in Table 1. All studies randomized to either an intervention arm or a standard of care/placebo arm. All were RCTs, conducted during the previous eight years (2011-2019). The follow-up under study medication ranged from 12 to 56 weeks. All studies included subjects aged 12-75 years old, and studies of omalizumab also included children from 6 years old. The characteristics of the health economics studies included are available in Table 2.

3.3 | Evidence of efficacy and safety

Tables 3-7 present the summary of the results and certainty of evidence for asthma-related outcomes evaluated. The meta-analysis plots can be found in the supplementary file.

3.3.1 | Severe asthma exacerbation rate

The annualized exacerbation rates were reported in three benralizumab trials,[39-41] three dupilumab trials,[42-44] three mepolizumab trials,[45-47] three omalizumab trials[48,50,51] and five reslizumab trials.[52-55] All biologicals reduced asthma exacerbations rate compared to standard of care with high certainty of evidence: benralizumab IRR 0.53; 95% CI 0.39 to 0.72; dupilumab IRR 0.44; 95% CI 0.32 to 0.59; mepolizumab IRR 0.49 95% CI 0.38 to 0.66; omalizumab IRR 0.56; 95% CI 0.40 to 0.77; and reslizumab IRR 0.46; 95% CI 0.37 to 0.58.

A separate analysis of the studies[41,44,46] designed to assess as primary outcome the OCS sparing effect of the biological compared to standard of care was performed. All three studies significantly reduced the rate of exacerbations in the OCS sparing protocol with high certainty of evidence: benralizumab IRR 0.30; 95% CI 0.17 to 0.53; dupilumab IRR 0.42; 95%CI 0.25 to 0.69; and mepolizumab IRR 0.68; 95%CI 0.47 to 0.98.

3.3.2 | Asthma control

The change in asthma control following biologicals addition was evaluated using Asthma Control Questionnaires (ACQ) scores and the Total Asthma Symptoms Scores (TASS). Dupilumab, omalizumab and mepolizumab probably improve asthma control with moderate certainty of evidence: dupilumab (ACQ-5) MD −0.48; 95% −0.88 to −0.09 [42-44]; omalizumab (TASS) MD −0.16; 95% −0.51 to 0.19 [48-51] and mepolizumab (ACQ-5) MD −0.43; 95% CI −0.56 to −0.31.[45-47] Nevertheless, none of the biologicals showed an improvement above the MID threshold of 0.5.

3.3.3 | Quality of life

QoL was reported in three benralizumab trials[39-41]; two dupilumab trials[42,43]; three mepolizumab trials[45-47]; one omalizumab trial[48]

TABLE 1 Summary of the characteristics of the included studies evaluating clinical efficacy of benralizumab, mepolizumab, omalizumab and reslizumab as add-on for uncontrolled severe asthma

Author, year (Trial Name)	Outcomes assessment	Age (y) Mean ± SD Range	Population (N)	Intervention Type Number of patients exposed (N)	Control
Benralizumab					
Bleecker 2016[39] (SIROCCO)	48	47.6 ± 14.5 12-75	Severe, uncontrolled asthma (N = 1205)	Benralizumab: 30 mg SC Q8W (N = 398) Benralizumab: 30 mg SC Q4W (N = 400)	Standard of care (SOC)
FitzGerald 2016[40] (CALIMA)	56	49.0 ± 14.3 12-75	Severe, uncontrolled asthma (N = 1306)	Benralizumab: 30 mg SC Q8W (N = 441) Benralizumab 30mg SC Q4W (N = 425)	SOC
Nair 2017[41] (ZONDA)	24	52.9 ± 10.1 18-75	Severe, uncontrolled asthma receiving daily OCS (N = 220)	Benralizumab 30mg SC Q8W (N = 73) Benralizumab 30mg SC Q4W (N = 72)	SOC
Dupilumab					
Castro 2018[43] (Liberty Asthma QUEST)	52	47.9 ± 15.3 >12	Uncontrolled asthma (N = 1902)	Dupilumab 200 mg SC Q2W (loading dose, 400mg) (N = 631) Dupilumab 300 mg SC Q2W (loading dose, 600mg) (N = 633)	SOC
Rabe 2018[44]	24	51.3 ± 12.6 >18	Oral glucocorticoid-treated asthma (N = 210)	Dupilumab 300 mg SC Q2W (N = 103)	SOC
Wenzel 2016[42]	24	48.0 ± 12,8 >18	Moderate to severe, uncontrolled asthma (N = 776)	Dupilumab 200 mg SC Q2W Dupilumab 300 mg SC Q2W Dupilumab 200 mg SC Q4W Dupilumab 300 mg SC Q4W	SOC
Mepolizumab					
Bel 2014[46] (SIRIUS)	24	50 16-74	Severe, eosinophilic asthma receiving daily OCS (N = 135)	100 mg SC Q4W (N = 69)	SOC
Ortega 2014[47] (MENSA)	32	51 12-81	Severe, eosinophilic asthma (N = 576)	75-mg IV Q4W (N-191) 100-mg SC Q4W (N = 194)	SOC
Chupp 2017[45] (MUSCA)	24	49.8 >12	Severe, eosinophilic asthma (N = 551)	100 mg SC Q4W (N = 274)	SOC

(Continues)

TABLE 1 (Continued)

Author, year (Trial Name)	Outcomes assessment	Age (y) Mean ± SD Range	Population (N)	Intervention Type Number of patients exposed (N)	Control
Omalizumab					
Casale 2018[51]	16	39.7 ± 13.8 12-75	Eosinophilic asthma (N = 1071)	SC Q2W or Q4W at a dose calculated based on body weight and baseline serum IgE levels (150 mg or 300 mg Q4W or 225 mg, 300 mg, or 375 mg Q2W) (N = 542)	SOC
Hanania 2013[48]	48	44 ± 15 12-75	Uncontrolled severe persistent allergic asthma (N = 850) Subgroup high blood eosinophils (N = 414) or high FeNO (N = 101)	Dose determined by the European omalizumab dosing table, ensuring a minimum omalizumab dose of 0.008 mg/kg/IgE (IU/mL) Q2W or a minimum of 0.016 mg/kg/IgE (IU/mL) Q4W.	SOC
Sorkness 2013[49]	48	10.7 ± 3.6 6-20	Moderate to severe persistent allergic asthma Subgroup with high FeNO (N = 155)	Dose determined the expanded FDA dosage table, ensuring a minimum dose of 0.016 mg/kg/IgE (IU/mL) every month	SOC
Busse 2013[50]	28	12-75	Patients with atopic asthma Subgroup with eosinophilic asthma (N = 51)	Dose determined by the European omalizumab dosing table, ensuring a minimum omalizumab dose of 0.008 mg/kg/IgE (IU/mL) Q2W or a minimum of 0.016 mg/kg/IgE (IU/mL) Q4W	SOC
Reslizumab					
Bjermer 2016[55]	16	43 12-75	Inadequately controlled eosinophilic asthma (N = 311)	Reslizumab 3.0 mg/kg IV Q4W (N = 106)	SOC
Castro 2011[52]	12	44.9 ± 13.94 (18-75)	Inadequately controlled eosinophilic asthma (N = 106)	Reslizumab 3.0 mg/kg IV Q4W (N = 53)	SOC
Castro 2015[53]	52	49 (12-75)	Inadequately controlled eosinophilic asthma (N = 953)	Reslizumab 3 mg/kg IV Q4W (N = 477)	SOC
Corren 2016[54]	16	44.9 (18-65)	Inadequately controlled asthma Subgroup with baseline eosinophils ≥ 400 cells/μL (n = 96)	Reslizumab 3 mg/kg IV Q4W (N = 77)	SOC

TABLE 2 Summary of the characteristics of the included studies evaluating the economical impact of biologicals as add-on for uncontrolled severe asthma

Author, year	Design, Country	Intervention	Control	Time horizon, perspective	Difference in cost (year value)	Difference in outcome	ICER	Risk of bias (CHEC score)	Transferability score	Source of funding
Benralizumab										
ICER 2019[56]	Cost-utility Markov model, US	Lifetime Benralizumab in addition to SOC	Lifetime SOC	Lifetime, US healthcare perspective. Societal in the sensitivity analysis.	581 000 $ (2018 US Dollars)	1.41 QALY	412 000 $/ QALY	17.5/20	13.5/16	Government grants and nonprofit foundations
Tikhonova 2018[57]	Cost-utility Markov model, UK	Lifetime Benralizumab in addition to SOC	Lifetime SOC	Lifetime, UK NHS perspective. Societal in the sensitivity analysis.	Not Reported	QALY not reported	39 135 £/ QALY	15.5/20	12.5/16	AstraZeneca financed the original model critiqued by the University of Exeter
Dupilumab										
ICER 2019[56]	Cost-utility Markov model, US	Lifetime Dupilumab in addition to SOC	Lifetime SOC	Lifetime, US healthcare perspective. Societal in the sensitivity analysis.	704 000 $ (2018 US Dollars)	1.51 QALY	464 000 $/ QALY	17.5/20	13.5/16	Government grants and nonprofit foundations
Mepolizumab										
Whittington 2017[58]	Cost-utility Markov model, US	Lifetime Mepolizumab in addition to SOC	Lifetime SOC	Lifetime, health system	589 941 $ (2014 US Dollar)	1.53 QALY	385 546 $/ QALY	16/20	14/16	Institute for Clinical and Economic Review
Reslizumab										
Han 2019[59]	Cost-utility Markov model, South Korea	Lifetime Reslizumab in addition to SOC	Lifetime SOC	Lifetime, societal	119 394 $ (2018 US Dollars)	5.17 QALY	23 081 $/ QALY	16.5/20	13/16	Teva-Handok Pharma
Lam 2018[60]	Cost-utility Markov model, US	5-year Reslizumab in addition to SOC	5-year SOC	5-year, societal	24 404 $ (2017 US Dollar)	0.035 QALY	697 403 $/ QALY	16/20	12.5/16	University of Southern California, US

TABLE 3 Summary of findings for Benralizumab compared to standard of care for eosinophilic 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 benralizumab
Exacerbations Assessed with annualized asthma exacerbation rate	1373 (3 RCTs)[39-41] 28 to 56 weeks	⨁⨁⨁⨁ HIGH[3,a,b]	**Incidence rate ratio 0.53** (0.39 to 0.72)[c,d]	1500 exacerbations per 1000 patients per year	**705 fewer exacerbations per 1.000 patients per year** (915 fewer to 420 fewer)
Asthma Control Assessed with ACQ-6 score between-group difference at the end of the study	1373 (3 RCTs)[39-41] 28 to 56 weeks	⨁⨁⨁⨁ HIGH[3,4,b,e,f]	—		mean difference—**0.26** (−0.46 to − 0.07 fewer)[c,g]
Quality of life Assessed with Asthma Quality of Life Questionnaire for 12 years and older	1333 (3 RCTs)[39-41] 28 to 52 weeks	⨁⨁⨁⨁ HIGH[3,6,b,j,k]	—		mean difference + **0.23** (+0.11 to + 0.36)[c]
Any drug-related adverse event (AE) Assessed with number of events	478 (1 RCT)[40] 56 wk	⨁⨁⨁◯ MODERATE[3,b,l]	**Risk ratio 1.41** (0.87 to 2.27)	105 per 1.000	**43 more per 1.000** (14 fewer to 133 more)
Any serious adverse event (SAE) unrelated to asthma exacerbation Assessed with number of events	148 (1 RCT)[41] 28 wk	⨁⨁◯◯ LOW[3,b,l]	**Risk ratio 0.56** (0.22 to 1.44)	147 per 1.000	**65 fewer per 1.000** (114 fewer to 65 more)
Decrease in OCS use Assessed with reduction in daily OCS dose of ≥50%	148 (1 RCT)[41] 28 wk	⨁⨁⨁⨁ HIGH[3,b]	**Risk ratio 1.76** (1.26 to 2.47)	373 per 1.000	**284 more per 1.000** (97 more to 549 more)
Lung function Assessed with prebronchodilator FEV1 (mL) between-group difference at the end of the study	1370 (3 RCTs)[39-41] 28 to 56 wk	⨁⨁⨁◯ MODERATE[3-5,b,h,i]	—		mean difference + **140 mL** (+90 to + 190)[c]
Rescue medication use Assessed with puffs/day	0 studies	—	Not estimable		

*__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).

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: Little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Statistically significant (I^2 = 65%) but probably unimportant heterogeneity.

b. All included studies were funded by industry, and all showed positive results. No industry-independent observational or randomized studies were identified to contrast results. Therefore, the quality of the evidence was downgraded for potential publication bias.[70]

c. The pooled data were assessed at 28 wk [41] and at 48-52 wk.[71] Goldman 2017 included patients aged 12-17 y old.

d. In the current systematic review, 2 studies reporting the effect on exacerbation leading to emergency room visits or hospitalizations were also included. The pooled risk ratio was 0.24 (95% CI 0.03-1.72; see full-text report).

e. Statistically significant (I^2 = 61%) but probably unimportant heterogeneity.

f. The minimal important difference (MID) for ACQ-6 is 0.5 points.[35]

g. In the current systematic review 3, studies reporting the effect on total asthma control score change were also included. The pooled mean difference was −0.19 (95CI% −0.31 to −0.08), see full-text report.

h. Quality of the evidence was downgraded because FEV1 is considered a surrogate outcome for asthma control, with a variable correlation with asthma symptoms.[72]

i. The panel agreed that minimal important difference for FEV1 is 0.20 L.

j. Statistically significant (I^2 = 55%) but probably unimportant heterogeneity.

k. For AQLQ(S)+12 the MID is 0.5.[37]

l. The effect may both be harmful or beneficial. Small sample size and number of events.

TABLE 4 Summary of findings of Dupilumab compared to standard of care for eosinophilic 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 dupilumab
Exacerbations Assessed with annualized asthma exacerbation rate	1712 (3 RCTs)[42-44] 24 to 52 wk	⨁⨁⨁⨁ HIGH[4,a,b]	**Incidence rate ratio 0.44** (0.32 to 0.59)	1570 exacerbations per 1000 patients per year	**894 fewer exacerbations per 1000 patients per year** (1086 fewer to 655 fewer)[c]
Asthma control assessed with: Asthma Control Questionnaire −5 Scale from: 1 to 5	507 (1 RCT)[42] 24 wk	⨁⨁⨁◯ MODERATE[4,8,a,b,g]	—		mean difference—**0.48** (−0.88 lower to −0.09)
Quality of life Assessed with asthma Quality of Life Questionnaire Scale from: 1 to 7	958 (2 RCTs)[43,44] 24 to 52 wk	⨁⨁⨁◯ MODERATE[4,9,a,b,h]	—		mean difference + **0.42** (+0.25 to +0.59)
Treatment-related adverse events (AE) Assessed with number of events	264 (1 RCT)[42] 24 wk	⨁⨁⨁◯ MODERATE[4,a,b,m]	**Risk ratio 1.00** (0.88 to 1.13)	794 per 1.000	**0 fewer per 1.000** (95 fewer to 103 more)
Treatment-related serious adverse events (SAE) Assessed with number of events	264 (1 RCT)[42] 24 wk	⨁⨁◯◯ LOW[4,a,b,m]	**Risk ratio 1.46** (0.60 to 3.54)	59 per 1.000	**27 more per 1.000** (24 fewer to 149 more)
Decrease in OCS dose Assessed with percentage of reduction compared to baseline	150 (1 RCT)[42] 24 wk	⨁⨁⨁⨁ HIGH[4,a,b]	—		mean difference—**29.4%** (−43.23 to −15.57)
Lung function Assessed with FEV1 in mL	1030 (3 RCTs)[42-44] 24 to 52 wk	⨁⨁◯◯ LOW[4-7,a,b,d,e,f]	—		mean difference + **180 mL** (+110 to +250)
Fraction of exhaled nitric oxide Assessed with mean % change (ppb) from baseline	150 (1 RCT)[42] 24 wk	⨁⨁◯◯ LOW[4,10-12,a,b,i,j]	—		mean difference—**40.11%** (−78.68 to −1.55)
Rescue medication use Assessed with puffs/day	143 (1 RCT)[42] 24 to 52 wk	⨁⨁⨁◯ MODERATE[4,7,a,b,k,l]	—		mean difference—**0.56 puff/day** (−2.28 to +1.16)

*__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).

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: Little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Explanations

a. All included studies had a high risk of selective reporting bias.[42-44] However, the evidence quality was not downgraded because most of the outcomes of interest for our analysis were reported.

b. All included studies were founded by industry and the same company (Sanofi and Regeneron Pharmaceuticals), and all showed positive results. No industry-independent observational or randomized trials were identified to contrast the results. Therefore, the quality of the evidence was downgraded for potential publication bias.[70]

c. Two studies (Rabe 2018, Wenzel 2016) assessed exacerbations at 24 wk and Castro 2018 at 52 wk.

d. The quality of the evidence was downgraded because FEV1 is considered a surrogate outcome of asthma control, with a variable correlation with asthma symptoms.[72]

e. The panel agreed that minimal important difference (MID) for FEV1 is 0.20 L and considered the effect as imprecise.

f. The panel agreed that minimal important difference (MID) for FEV1 is 0.20 L and thus the effect was considered as imprecise.

g. Downgraded because the effect of dupilumab is beneficial but the lower side of the CI is less than the MID(0.5 points).[37]

h. Downgraded because the effect of dupilumab is beneficial but the lower side of the CI is less than the MID(0.5 points).[37]

(Continues)

TABLE 4 (Continued)

i. Downgraded because FeNO is not consistently considered a good surrogate of eosinophilic inflammation.[73,74]

j. From one visit to the next, a change greater than 20% for basal values over 50 ppb or more than 10 ppb for basal values lower than 50 ppb may indicate significant response.[38]

k. Downgraded because the effect may both be beneficial and harmful.

l. The MID for rescue medication use is a reduction by 0.81 puffs/d.[35]

m. The effect may both be harmful or beneficial. Small number of events.

TABLE 5 Summary of findings of mepolizumab compared to standard of care for eosinophilic 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 mepolizumab
Exacerbations Exacerbation rate ratio Assessed with the annualized rates of asthma exacerbations	1071 (3 RCTs)[45-47] 24 to 32 wk	⨁⨁⨁⨁ HIGH[4,5,a,b,c]	**Incidence rate ratio 0.49** (0.38 to 0.66)	1700 exacerbations per 1000 patients per year	**870 fewer exacerbations per 1000 patients per year** (592 fewer to 1079 fewer)
Exacerbations leading to hospitalization Assessed with the annualized rate of asthma exacerbations leading to hospitalization	(2 RCTs)[45,47] 24 to 32 wk	⨁⨁⨁⨁ HIGH[4,5]	**Incidence rate ratio 0.30** (0.13 to 0.71)	100 exacerbations per 1000 patients per year	**70 fewer exacerbations per 1000 patients per year** (29 fewer to 87 fewer)
Asthma control Assessed with: ACQ-5 score between-group difference at the end of the study Scale from: 0 to 6[9,j]	912 (3 RCTs)[45,47]	⨁⨁⨁◯ MODERATE[4,5,a,c,i]	—		mean difference—**0.43** (−0.56 to −0.31)
Quality of life Assessed with St. George's Respiratory Questionnaire between-group difference at the end of the study	1045 (3 RCTs)[45-47] 24 to 32 wk[10,k]	⨁⨁⨁◯ MODERATE[4,5,a,c,l]	—		mean difference—**7.14** (−9.07 to −5.21)
Treatment-related adverse events (AE) Assessed with number of events	1071 (3 RCTs)[45-47]	⨁⨁⨁⨁ HIGH[4,5,c]	**Risk ratio 1.35** (1.01 to 1.80)	796 per 1.000	**279 more per 1.000** (8 more to 637 more)
Treatment-related serious adverse events (SAE) Assessed with number of events	385 (1 RCT)[47]	⨁◯◯◯ VERY LOW[4,5,c,m,n]	**Risk ratio 0.98** (0.06 to 15.63)	5 per 1.000	**0 fewer per 1.000** (−5 fewer to 77 more)
Lung function assessed with prebronchodilator FEV1 (mL) between-group difference at the end of the study	1043 (3 RCTs)[45-47] 24 to 32 wk[6,e]	⨁⨁⨁◯ MODERATE[4,5,7,a,c,f]	—		mean difference + **110.9 mL** (+58.91 to +162.89)
Lung function assessed with AM peak expiratory flow (PEF)	936 (2 RCTs)[77] 24 wk[66,g]	⨁⨁◯◯ LOW[4,5,c,h,i]	—		mean difference + **22.46** (+13.98 to +30.94)
Rescue medication use assessed with puffs/day	(1 RCT)[45] 21 to 24 wks[o]	⨁⨁⨁⨁ HIGH[4,5,c]	—		mean difference **−0.1 puff/d** (−0.35 to +0.15)

*__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).

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: Little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

(Continues)

TABLE 5 (Continued)

Explanations

a. Two of three studies had a high risk of attrition bias.[45,47] Modified intention-to-treat analysis was conducted (ie patients were analysed as treated, not as randomized).

b. Probable unimportant heterogeneity

c. Included studies were all funded by industry, and all showed positive results. We identified two industry-independent observational trials that showed similar effects with our meta-analysis.[76,77]

d. Mean rates of exacerbation requiring hospitalization across studies were very low (ie from 0.02 to 0.10 exacerbations requiring hospitalization per person-year), both in the placebo and intervention arms

e. The panel agreed that minimal important difference (MID) for FEV1 is 0.20 L.

f. Downgraded because FEV1 is considered a surrogate outcome of asthma control of symptoms, with a variable correlation with asthma symptoms.[72]

g. The MID of PEF is 18.8 L/min.[35]

h. Potential attrition bias because PEF baseline values reported in the primary publication[47] differed from values reported in post hoc analysis publication.[77]

i. Downgraded because the lower CI boundary crosses the MID threshold

j. 0.5 points is the minimal important difference for the Asthma Control Questionnaire (ACQ-5 score).[37]

k.>−4.0 was considered the threshold for the MID for quality of life measured with the St. George's Respiratory Questionnaire.[36]

l. The St. George's Respiratory Questionnaire SGRQ is not a disease-specific questionnaire for asthma.

m. Findings from only 1 RCT available. Downgraded due to publication bias

n. Very few numbers of events per arm

o. The minimal important difference for rescue medication use is −0.81 puffs/d.[35]

and three reslizumab trials.[53-55] Changes in QoL were evaluated using the Asthma Quality of Life Questionnaire (AQLQ) for all biologicals, except for mepolizumab that used the St. George's Respiratory Questionnaire (SGRQ) score. All the addition of all biologicals improved QoL with moderate to high certainty, although below the MID: benralizumab MD + 0.23 (95% CI 0.11 to 0.36); dupilumab MD + 0.42 (95% CI + 0.25 to + 0.59); mepolizumab (SGRQ) MD −7.14 (95% CI −9.07 to −5.21); omalizumab MD + 0.13 (95% CI +0.11 to +0.37); and reslizumab MD + 0.17 (95% CI +0.08 to +0.25).

3.3.4 | Safety

Drug-related AE were assessed in two trials for benralizumab,[40,41] one trial for dupilumab,[42] three mepolizumab trials,[45-47] one trial for omalizumab [48] and three trials for reslizumab.[52,53,55] For mepolizumab, there is an increased likelihood of drug-related AE (RR 1.35; 95% CI 1.01 to 1.80; high certainty of evidence). Benralizumab and reslizumab probably increases drug-related AE (moderate certainty of evidence): benralizumab RR 1.41, 95% CI 0.87 to 2.27; reslizumab RR 1.18, 95% CI 0.89 to 1.56. For dupilumab and omalizumab, the RR is rather small: dupilumab RR of 1.00, 95% CI 0.88 to 1.13; and omalizumab RR 1.01, 95% CI 0.91 to 1.1.

There is low to very low certainty of evidence that drug-related serious AE may increase with the use of dupilumab RR 1.46 (95% 0.60 to 3.54) and reslizumab RR 4.71 (95% 0.54 to 41.31). For benralizumab and mepolizumab, results are inconclusive: benralizumab RR 0.56 (95% CI 0.22 to 1.44) and mepolizumab RR 0.98 (95% CI 0.06 to 15.63). Data were not fully reported in all trials; thus, the certainty of evidence was downgraded due to the low number of events.

3.3.5 | Reduction in oral corticosteroids use

Benralizumab, dupilumab and mepolizumab showed with high certainty of evidence, a reduction in daily OCS: benralizumab >50% (RR 1.76, 95%CI 1.26 to 2.47); dupilumab 29.4% (95% CI 43.2 lower to 15.57 lower); and mepolizumab >50% (RR 1.61; 95%CI 1.07-2.41).[41,44,46] Mepolizumab showed a reduction in OCS to 5mg/day or less (crude RR 1.71; 95%CI 1.11 to 2.55, P = .01) and a reduction of 100% in daily OCS (crude RR 1.91; 95% CI 0.69 to 5.30, P = .2) compared to placebo.

3.3.6 | Reduction of rescue medication use

This end point was assessed only for mepolizumab and showed no clinically significant reduction in the daily use of rescue medication after 24 weeks (MD—0.1 puffs/day; CI 95% −0.35 to 0.15).[45]

3.3.7 | Lung function - FEV_1

The change from baseline of FEV_1 was assessed for benralizumab,[39-41] mepolizumab,[45-47] omalizumab [48] and reslizumab.[52-55] Compared to standard of care, there was an increase in FEV_1, but below the MID agreed by the GDG (moderate certainty of evidence): benralizumab MD + 140mL (95% CI +90 to +190); mepolizumab MD + 110.9 mL (95% CI +58.91 to +162.89), reslizumab MD + 141.82 mL (95% CI +89.23 to +194.41); and omalizumab mean percentage change + 3.7% (95% CI 2.1% to 9.5%). There is low certainty of evidence that for patients with baseline eosinophils ≥300 cells/μL dupilumab may increase FEV_1 compared to standard of care [MD + 180 mL (95% CI 110 to 250)].

TABLE 6 Summary of findings of Omalizumab compared to standard of care for eosinophilic 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
Exacerbations Assessed with annual asthma exacerbations rate	779 (3 RCTs)[48,50,51] 16 to 48 wk	⨁⨁⨁⨁ HIGH[4,a,b]	**Incidence rate ratio 0.56** (0.40 to 0.77)	660 exacerbations per 1000 patients per year	**290 fewer exacerbations per 1.000 patients per year** (396 fewer to 152 fewer)
Asthma Control Assessed with Total Asthma Symptoms Score	414 (1 RCT)[48] 48 wk	⨁⨁◯◯ LOW[4,a,b,c,d]	—		mean difference—**0.16** (−0.51 to +0.19)[e,f]
Quality of Life Assessed with Asthma Quality of Life Questionnaire	414 (1 RCT)[48] 48 wk	⨁⨁⨁◯ MODERATE[4,a,b,d]	—		mean difference + 0.13 (−0.11 to +0.37)[l]
Any adverse event Assessed with number of events	414 (1 RCT)[48] 48 wk	⨁⨁⨁◯ MODERATE[4,a,b,d]	**Risk ratio 1.01** (0.91 to 1.11)	794 per 1.000	**8 more per 1.000** (71 fewer to 87 more)
Lung Function Assessed with % prebronchodilator FEV1 between-group difference at the end of the study	(2 RCTs)[48,50] 24 to 48 wk	⨁⨁⨁◯ MODERATE[4,5,a,b,g,h,i]	—		Mean difference + **3.7%** (−2.1 lower to +9.5)[j,k]
Rescue medication use Assessed with puffs/day change from baseline	414 (1 RCT)[48] 48 wk	⨁⨁⨁◯ MODERATE[4,a,b,d]	—		Mean difference—**0.34** (−0.83 to +0.15)[6,m,n]

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: Little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Information of included studies from nonpredefined subgroup analysis.

b. Included studies were all funded by industry, and all showed positive results. We identified one industry-independent observational trial that showed similar effects with our meta-analysis.[78]

c. The total asthma symptoms score is an unvalidated scale.

d. The effect may both be harmful or beneficial.

e. Data from subgroup of patients with blood eosinophil count ≥260/μL. This study also reported total asthma symptoms score for the subgroup of FeNO ≥24ppb, the mean difference is −0.25 (CI 95% −0.77 to 0.27).

f. In the current systematic review, we also included one study[49] reporting the effect on the symptom days over the previous 2 wk at 48 wk follow-up, the mean difference is −0.45 (P = .05; see full-text report).

g. Statistically significant (I^2 = 70%), but probably unimportant heterogeneity.

h. Downgraded because FEV1 is considered a surrogate outcome of asthma control of symptoms, with a variable correlation with asthma symptoms.[72]

i. The panel agreed that minimal important difference (MID) for FEV1 is 0.20 L.

j. Population with different threshold of eosinophil counts across the studies: ≥200 cells/μL,[51] ≥300 cells/μL [50] and ≥260 cells/μL.[48]

k. One of the included studies [48] also reported the effect on FEV1% change for a population with FeNO ≥24 ppb, the LS mean difference is 3.20 (CI 95% −0.74 to 0.27). The pooled effect evaluated at 48 wk[48] and 24 wk.[50]

l. Data from subgroup of patients with blood eosinophil count ≥260/μL. This study also reported AQLQ for the subgroup of FeNO ≥24 ppb, the mean difference is 0.37 (CI 95% 0.01 to 0.73).

m. This study also reported the effect on rescue medication use for the subgroup of FeNO ≥24 ppb, the mean difference is −0.49 (CI 95% −0.88 to −0.11).

n. The MID for rescue medication use is 0.81 puffs/d.[35]

3.4 | Evidence of resource use and cost-effectiveness

After screening 1884 hits and reviewing 36 full-text articles, five economic evaluations were included (Figure 2). Two studies evaluated benralizumab,[56,57] one dupilumab,[57] one mepolizumab[58] and two reslizumab[59,60] (Table 2). Most of the excluded studies evaluated allergic patients (Table S4). Overall, the resources needed for adding the biological to standard asthma therapy are

TABLE 7 Summary of findings of Reslizumab compared to standard of care for eosinophilic asthma

Outcomes	No. of participants (studies) Follow-up (mean or range)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard of care	Risk difference with reslizumab
Exacerbations Assessed with annualized rate of asthma exacerbations[a]	1059 (3 RCTs)[1,2] 52 wk	⨁⨁⨁⨁ HIGH[3,b]	**Rate ratio 0.46** (0.37 to 0.58)[c]	1800 exacerbations per 1000 patients per year	**972 fewer exacerbations per 1000 patients per year** (1134 fewer to 756 fewer)
Exacerbations leading to ER visit or hospitalization Assessed with annualized rate of asthma exacerbations	953 (2 RCTs)[1] 52 wk	⨁⨁⨁◯ MODERATE[3,b,d]	**Rate ratio 0.67** (0.39 to 1.17)	120 exacerbations per 1000 patients per year	**40 fewer exacerbations per 1000 patients per year** (73 fewer to 20 more)
Asthma control Assessed with Asthma Control Questionnaire-7 Scale from: 0 to 6	1359 (5 RCTs)[1,2,4,5] 15 to 16 wk	⨁⨁⨁⨁ HIGH[3,8,b,h]	–		mean difference—**0.25** (−0.34 to −0.16)
Quality of life assessed with Asthma Quality of Life Questionnaire Scale from: 1 to 7	1153 (3 RCTs)[1,4] 15 to 16 wk	⨁⨁⨁⨁ HIGH[3,10,b,k]	–		mean difference + **0.17** (+0.08 to + 0.25)[l]
Treatment-related adverse events Assessed with number of events	1269 (4 RCTs)[1,2,4] 15 to 52 wk	⨁⨁⨁◯ MODERATE[3,b,o]	**Rate ratio 1.18** (0.89 to 1.56)[p]	125 per 1.000	**22 more per 1.000** (14 fewer to 70 more)[p]
Treatment-related serious adverse events Assessed with number of events	1269 (4 RCTs)[1,2,4] 15 to 52 weeks[p]	⨁⨁◯◯ LOW[3,b,q]	**Rate ratio 4.71** (0.54 to 41.31)	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)
Decrease in inhaled corticosteroid (ICS) and oral corticosteroid (OCS) dose	0 studies	–	–	–	–
Lung function Assessed with: FEV_1 in mL	1360 (5 RCTs)[1,2,4,5] 15 to 16 wk	⨁⨁⨁◯ MODERATE[3,6,7,b,e,f]	–		mean difference + **141.82 mL** (+89.23 to 194.41)[g+]
Rescue medication use Assessed with puffs/day	1251 (4 RCTs)[1,4,5] 16 wk	⨁⨁⨁⨁ HIGH[3,7,b,n]	–		mean difference—**0.24** (−0.46 to −0.02)
Asthma symptoms Assessed with: Asthma Symptom Utility Index Scale from: 0 to 1	1157 (3 RCTs)[1,4] 16 to 16 wk	⨁⨁⨁⨁ HIGH[3,9,b,j]	–		mean difference + **0.05** (+0.03 to +0.07 higher)
Changes in blood eosinophil counts Assessed with: cells/μL	1264 (4 RCTs)[1,2,4] 15 to 16 wk	⨁⨁⨁◯ MODERATE [3,11,b,m]	–		mean difference—**468.58** (−494.92 to −442.24)

*__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).

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: Little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

(Continues)

TABLE 7 (Continued)

Explanations

a. Clinically significant asthma exacerbations: episodes of asthma worsening with systemic corticosteroids for 3 or more days, a two-times increase in the dose of either inhaled corticosteroids or the need for asthma-related emergency treatment.

b. All included studies were funded by industry, and all showed positive results. No industry-independent observational or randomized studies were identified to contrast the results. Therefore, the quality of the evidence was downgraded for potential publication bias.[70]

c. The pooled effect of risk ratio was assessed at 15 wk,[52] and the rate ratio was evaluated at 52 wk.[53]

d. Downgraded because the absolute effect includes both potential clinically meaningful benefits and harms.

e. Downgraded because FEV1 is considered a surrogate outcome of asthma control of symptoms, with a variable correlation with asthma symptoms.[72]

f. The panel agreed that minimal important difference (MID) for FEV1 is 0.20 L.

g. Castro 2015 also assessed FEV1 at 52 wk, and the mean difference from baseline was 122.28 mL (45.54, 199.02). We also included 3 studies [52,54,55] reporting FVC (mL), and the pooled mean difference was 205.94 (88.69, 323.19); see full-text report.

h. MID for ACQ-7 is 0.5 points (Juniper 2005).

i. Castro 2015 also assessed ACQ-7 at 52 wk, and the mean difference from baseline of ACQ-7 was −0.25 (−0.34, −0.16), see full-text report.

j. MID for the Asthma symptoms utility index is an increase of 0.09 points.[79]

k. MID of AQLQ is 0.5 points.[37]

l. Castro 2015 also assessed AQLQ at 52 wk, the mean difference from baseline was 0.29 (0.18, 0.41), see full-text report.

m. Reduction in blood eosinophil counts is a surrogate end point and not validated as a valuable outcome for monitoring asthma therapy.[80]

n. MID for rescue medication use is a reduction by 0.81 puffs/d.[35]

o. The effect may both be harmful or beneficial.

p. Data regarding this outcome was extracted from www.clinicaltrials.gov for ref. [52] and ref. [53]

q. Very few events in both arms, thus it is not possible to estimate precisely the effect size between arms.

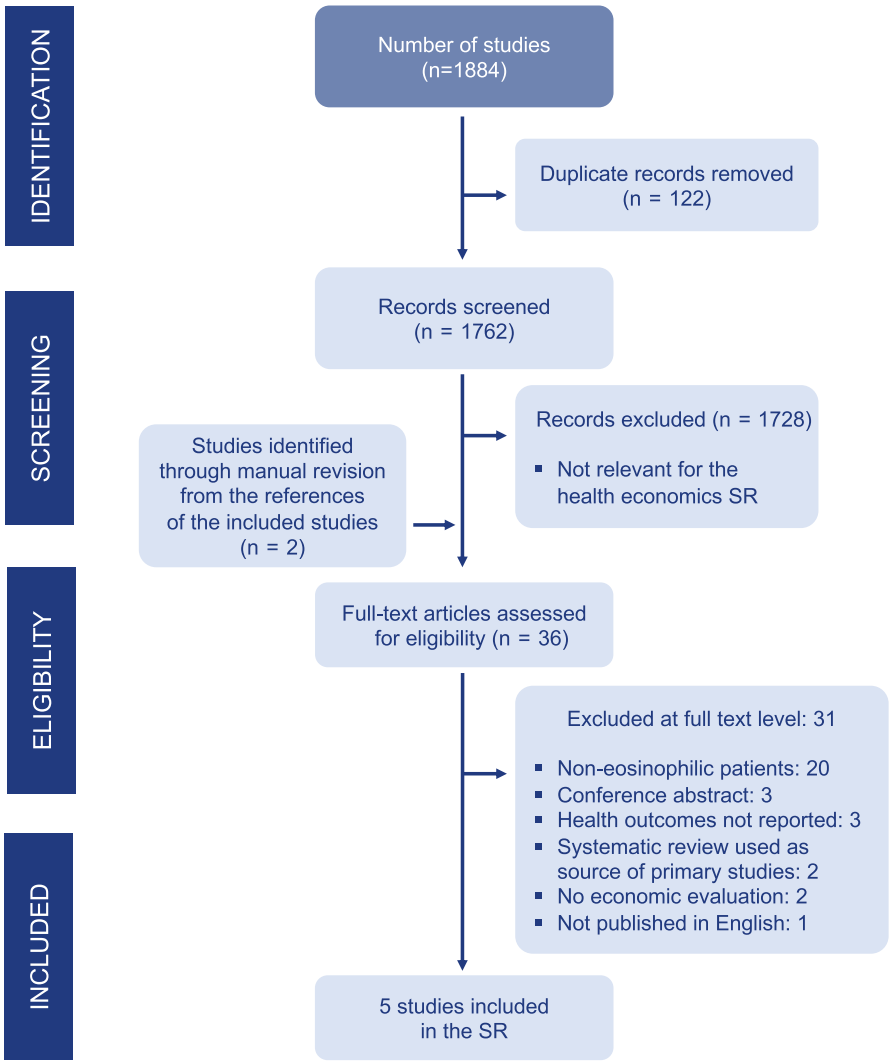

FIGURE 2 Study flow chart for selecting the economic evidence for biologicals in severe eosinophilic asthma

mainly the cost of the drug and its administration. The potential savings are related to decreased rate of hospitalization, emergency department care and primary care visits (Table S5). The evaluation of the cost-effectiveness of benralizumab shows important variation in ICER from 39 135 £/QALY (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 Tikhonova et al report (Table S6). For dupilumab, the reported ICER is 401 000 $/QALY in patients with ≥300 eosinophils/μL (moderate certainty of the evidence). The results are uncertain for the utility estimates for the nonexacerbation health state for both the biological and standard of care asthma therapy, for the annual exacerbation rates for standard therapy and for the costs of chronic OCS use (Table S6). For mepolizumab, the cost-utility Markov model with low risk of bias (high-quality study) reported an ICER/QALY value of 385 546 $ (low certainty of the evidence). There is also variation across patients. The most favourable ICER towards mepolizumab was 160 000 $ in the responder group of patients (Table S6). The reslizumab base-case analyses demonstrate important variation across studies in terms of the cost-effectiveness results. The ICER/QALY varied from 23 081 $/ QALY (low certainty of the evidence) to 697 403 $/ QALY (moderate certainty of the evidence). The key driver for this difference was the cost of reslizumab. The study not funded by industry[60] reported a higher cost of reslizumab (approximately 4000 $ per month) compared to the study funded by industry (991 $ per month).[59] It has to be noted that there is a lack of proper studies to drive firm conclusions due to the heterogeneity of published studies. Furthermore, modelling cost-effectiveness studies considering direct and indirect costs applicable to each context is needed (Table S6).

4 | DISCUSSION

4.1 | Main findings

Our systematic review of efficacy shows high certainty for reducing the rate of severe asthma exacerbations for all the biologicals evaluated (benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab) as add-on treatment for patients with severe uncontrolled eosinophilic asthma. The certainty is moderate for improving asthma control, QoL and lung function (FEV_1) improvement, not reaching the MID. Only benralizumab, dupilumab and mepolizumab provided data about the use of OCS, showing a reduction in the daily dose of OCS compared to standard of care (high certainty of evidence).

The main reasons to downgrade the certainty of evidence were ROB, imprecision and indirectness. Overall, the included studies for the evidence of efficacy were of low ROB. Of note, all included studies were funded by industry and all showed positive results, which might raise concerns of on a potential sponsorship bias. Although short-term safety data are reassuring, the rate of drug-related AE was not comprehensibly reported; thus, there is low to very low certainty for drug-related serious AE. With the exception of omalizumab, there is scarce data on the efficacy of the evaluated biologicals for eosinophilic asthma in the paediatric population. With the exception of omalizumab and mepolizumab, no data are available for long-term safety, both in children and in adults.

The resources needed for adding the biological treatment to asthma standard therapy are mainly driven by the cost of the drug and its administration. With the approval of autoinjectors for most of these agents, the costs for administration should decline. The potential savings are explained by the decreased rate of hospitalization, emergency department care and primary care visits. However, we cannot accurately assess the reductions in indirect costs such as improvements leading to improved work and school productivity and decreased absenteeism. The current SR of cost-effectiveness showed, for all the biologicals, an ICER per QALY value significantly above the willingness to pay threshold in most European countries (30 000 €/QALY). The certainty of the economic evidence is moderately derived from studies with low ROB but with important imprecision (large variations in the ICER values) and indirectness (differences in healthcare systems and year of conduction of the study), impeding both the transferability and generalization of the results. Additional publication bias might be envisaged.

4.2 | Current results in the context of previous results

Aligned with our results, previous SR of benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab in severe asthma reported a reduction to approximately half of exacerbations, and an improvement in health-related QoL scores, asthma control and FEV_1.[61-68] However, there are some important differences that need to be mentioned. Previous mepolizumab SR allowed the inclusion of nonapproved doses,[64,65] while the current SR included only licensed doses and routes of administration making the results more applicable to the daily practice. Another important difference is that the certainty of the evidence was assessed using the GRADE approach. In contrast with the previous reviews assessing only the ROB of the trials, the current SR evaluated the heterogeneity, imprecision and indirectness of the included evidence. As an example, using the MID to assess for the imprecision, one can appreciate the clinical relevance of the change (ie asthma control, QoL and FEV_1): although the change was statistically significant it did not reach the MID. Last but not least, the current review assessed the effect of all the biologicals across a comprehensive compilation of asthma-related outcomes giving the clinicians a better perspective of the drug profile.

In contrast with our results, a SR of eight benralizumab trials showed a lower risk of both AE (RR 0.94; 95% CI 0.90-0.98) and serious AE (RR 0.82; 95% CI 0.68-0.98).[61] The possible explanation for this difference is that we limited our assessment to drug-related AE and excluded asthma worsening events, assessed solely as efficacy measures.

Another review assessing the cost-effectiveness of mepolizumab for eosinophilic asthma showed that mepolizumab is cost-effective

only when targeting specific subgroups with very severe asthma or by considerable price discounts. The key drivers of cost-effectiveness included day-to-day health-related QoL, asthma-related mortality, acquisition price of the biological therapy and time horizon. These results are similar to our evaluation for mepolizumab.[69]

4.3 | Strengths and limitations

The current systematic review has several strengths. An exhaustive evaluation of both desirable and undesirable effects of the use of biologicals, as well as their economic impact was performed. The compilation of critical and important asthma-related outcomes provides a more comprehensive perspective of the drug profile. The current SR used rigorous methods including the GRADE approach to rate the certainty of the evidence, with transparent judgements about the quality of evidence. We included the most updated results available from the included RCTs and only considered licensed doses and routes of administration. We provided friendly tabulated summaries of findings using optimal presentation format for patients, clinicians and policymakers supporting all the stakeholders in their endeavour to formulate recommendations for the use of biologicals in severe uncontrolled eosinophilic asthma.

There are 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 that variable (basal exacerbation rate), as it was not predefined or requested in the protocol or during the systematic review. The systematic review included only English language articles; however, the risk of selection bias is probably small because we screened previous systematic reviews and the GDG included several international experts in the field; thus, the possibility of missing results from non-English articles is unlikely. We did not include observational studies that could have been informative for some of the outcomes with low or very low-quality evidence from RCTs (eg serious AE). We did not conduct a de novo economic analysis for the cost-effectiveness outcomes. However, we followed the global perspective on the use of biological treatment in different health systems, which may be useful for the decision of using the biologicals in different countries. Finally, this review is limited to patients with eosinophilic asthma which restricted the number and scope of studies analysed, especially for omalizumab and dupilumab.

4.4 | Implications for practice and research

All evaluated biologicals (benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab) showed a significant improvement in critical and important related asthma outcomes such as exacerbation rate and for benralizumab, dupilumab and mepolizumab also an OCS dose reduction. However, the systematic review confirms the dissociated effect as these drugs have a modest effect on asthma control, quality of life and lung function. The health economics and ICER analyses demonstrate above the willingness to pay threshold. Given the high cost of these drugs, their use will probably be limited to specific circumstances such as patients with severe uncontrolled asthma where the desired outcome is to decrease the exacerbation rate or the OCS use. In this context, panels are more likely to formulate conditional recommendations as opposed to strong.

Although short-term safety data are reassuring, more accurate reporting from clinical trials is warranted in combination with long-term safety and cost-effectiveness evaluations, including real-world studies, registries and big data analysis. There is limited data available to support the efficacy and safety in the paediatric population (with the exception of omalizumab), highlighting the urgent unmet need for rigorous trials with biologicals in severe eosinophilic asthma in this population. Finally, the better understanding of predominant and personalized asthma endotypes and well-controlled head-to-head, industry-independent comparisons would provide useful data to better inform clinicians about choosing the right biologic for the right patient.

CONFLICT OF INTEREST

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SUPPORTING INFORMATION

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

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