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GUIDELINE

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Efficacy and safety of treatment with dupilumab for severe asthma: A systematic review of the EAACI guidelines—Recommendations on the use of biologicals in severe asthma

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Abbreviations: ACQ, Asthma Control Questionnaire; AE, adverse event; AQLQ, Asthma-related Quality of Life Questionnaire; CHEC, Consensus on Health Economic Criteria; CI, confidence interval; EAACI, European Academy of Allergy and Clinical Immunology; EMA, European Medicines Agency; EURONHEED, European Network of Health Economic Evaluation Databases; FDA, Food and Drug Administration; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 s; 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; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QALY, quality-adjusted life-year; QoL, quality of life; RCT, randomized controlled trial; ROB, risk of bias; RR, rate ratio; SC, subcutaneous; SOC, standard of care; SR, systematic review; T2, type 2; TASS, Total Asthma Symptoms Scores.

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Abstract

Dupilumab, a fully human monoclonal antibody against interleukin-4 receptor α, is approved as add-on maintenance treatment for inadequately controlled type 2 severe asthma. This systematic review evaluated the efficacy, safety and economic impact of dupilumab compared to standard of care for uncontrolled severe asthma. PubMed, EMBASE and Cochrane Library were searched for RCTs and health economic evaluations. Critical and important asthma-related outcomes were evaluated. The risk of bias and the certainty of the evidence were assessed using GRADE. Three RCTs including 2735 subjects >12 years old and 24-52 weeks of follow-up were included. Dupilumab reduced with high certainty severe asthma exacerbations (Incidence rate ratio 0.51; 95% CI 0.45-0.59) and the percentage use of oral corticosteroid use (mean difference (MD) −28.2 mg/d; 95% CI −40.7 to −15.7). Asthma control (ACQ-5), quality of life (AQLQ) and rescue medication use [puffs/d] improved, without reaching the minimal important clinical difference: ACQ-5 MD −0.28 (95% CI −0.39 to −0.17); AQLQ MD +0.28 (95% CI 0.20-0.37); and rescue medication MD −0.35 (95% CI −0.73 to +0.02). FEV_1 increased (MD +0.15; 95% CI +0.11 to +0.18) (moderate certainty). There was an increased rate of dupilumab-related adverse events (AEs) (moderate certainty) and of drug-related serious AEs (low certainty). The incremental cost-effectiveness ratio of dupilumab versus standard therapy was 464 000$/QALY (moderate certainty). More data on long-term safety are needed both for children and for adults, together with more efficacy data in the paediatric population.

KEYWORDS
cost-effectiveness, dupilumab, exacerbations, oral corticosteroids, severe asthma

1 | INTRODUCTION

The main goal in the management of patients with severe asthma is achieving disease control and reducing risk of attacks while avoiding harm from controller therapies.[1,2] Despite extensive efforts, there is still a small proportion of patients with severe asthma insufficiently controlled with the current medications, with a significant burden due to high morbidity and costs.[3-8] Current guidelines support the targeted approach in uncontrolled severe asthma, and several biologicals are approved for use in these patients.[1,2]

IL-4 and IL-13 are key cytokines in driving the initiation and chronicity of type 2 (T2) inflammation, an important inflammatory pathway in severe asthma.[9-11] Dupilumab is a fully human anti-IL-4 receptor α (IL-4Rα) monoclonal antibody that blocks both IL-4- and IL-13-mediated signalling pathways. It has been recently approved for adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma. According to the European Medicines Agency (EMA), dupilumab is recommended for severe asthma with T2 inflammation characterized by raised blood eosinophils and/or fractional exhaled nitric oxide (FeNO), inadequately controlled with high-dose inhaled corticosteroids (ICS) plus another maintenance treatment.[12] The US Food and Drug Administration (FDA) recommends dupilumab for an eosinophilic phenotype or for oral corticosteroid (OCS)–dependent asthma.[13]

The European Academy of Allergy and Clinical Immunology (EAACI) is developing clinical practice guidelines for the use of biologicals in patients with severe asthma. To inform key clinical recommendations, a systematic review (SR) evaluated the effectiveness and safety of dupilumab for patients with uncontrolled severe asthma.

2 | METHODS

2.1 | Guideline Development Group

The EAACI Asthma Voting Panel and Steering Committee included clinicians and researchers with different backgrounds (the complete list of experts is available from the EAACI website) who voluntarily participate in the EAACI biologics guideline. 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 the treatment with dupilumab efficacious and safe for patients with severe asthma?" The population was defined as subjects with confirmed diagnosis of asthma inadequately controlled on ICS and additional controllers. The outcomes were prioritized by the GDG using a 1-to-9 scale (7-9: critical; 4-6: important; 1-3: of limited importance), as suggested by the GRADE approach. The critical outcomes were exacerbations, asthma control, quality of life (QoL) and safety (drug-related adverse events (AEs) and drug-related serious AE (SAEs)), and the important outcomes were lung function (forced expiratory volume in 1 s [FEV_1]), OCS and ICS use and rescue medication use (Table 1).

The GDG also framed a cost-effectiveness question to assess the economic impact of dupilumab versus standard of care. The selected outcomes of interest were costs, resource use and the incremental cost-effectiveness ratios (ICERs) per quality-adjusted life-years (QALYs).

2.3 | Search methodology

Electronic algorithms in combination with controlled vocabulary and search terms were used to identify relevant randomized controlled trials (RCTs) and economic evaluations in (a) MEDLINE (via PubMed, January 2019), (b) Cochrane Controlled Trials Register (via The Cochrane Library, January 2019) and (c) EMBASE (via Ovid, January 2019). Search algorithms were adapted to the requirements of each database, and validated filters were used to retrieve appropriate designs (Table S1). Additional studies provided by the GDG and previous SR were also evaluated.

2.4 | Eligibility criteria and selection of studies

The SR included RCTs comparing dupilumab versus placebo added to usual care/standard of care in patient with severe asthma, and reporting one of the outcomes of interest as formulated by the GDG. The SR excluded studies with dose or route not approved by the EMA or FDA, papers published as abstract or conference communications or those not published in English. After initial calibration, two

TABLE 1 Structured clinical question

Population	Intervention	Comparison	Outcomes
Adults and adolescents (≥12 y old) with confirmed diagnosis of severe asthma not adequately controlled on ICS and additional controllers	• An initial dose of 400 mg (two 200 mg injections) followed by 200 mg given every other week, or • An initial dose of 600 mg (two 300 mg injections) followed by 300 mg given every other week	Placebo or usual care/ standard of care	Critical • Exacerbation rate. Measured by annualized rate of severe exacerbation (number of exacerbations per person year), defined as a deterioration of asthma requiring: (a) the use of systemic corticosteroids for ≥3 d or (b) hospitalization/emergency room visit because of asthma, requiring systemic corticosteroids • Asthma control: assessed by Asthma Control Questionnaire (ACQ-5) • Quality of life: assessed by asthma quality of life questionnaire (AQLQ) • Safety (drug-related adverse events; drug-related serious adverse events) Important • Reduction in inhaled corticosteroid (ICS) and oral corticosteroid (OCS) doses • Reduction in rescue medication • Improvement in Prebronchodilator forced expiratory volume in 1 s (FEV_1, L) • Reduction in Fraction of exhaled nitric oxide (FeNO)

reviewers independently screened the search results based on the title and abstract, followed by independent assessment of the eligibility based on the full text. In case of disagreement, a third reviewer was consulted. References were managed with Endnote version X7 software (Thomson Reuters).

2.5 | Data extraction and risk of bias assessment

One reviewer independently extracted the main characteristics of eligible studies (study design, patient population, mean age of population, follow-up and outcomes of interest), and a second reviewer double-checked and confirmed. If needed, authors of included studies were contacted to provide additional data. The Cochrane Risk of Bias tool for randomized trials was used to assess the risk of bias (ROB) of the included studies.[14] The ROB was judged as low, high or unclear 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 economic 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 analysis results), sources of funding and conflict of interest. Methodological limitations of the complete economic evaluation were evaluated by 2 reviewers using the Consensus on Health Economic Criteria (CHEC) checklist.[15] Transferability to the European context was assessed using the European Network of Health Economic Evaluation Databases (EURONHEED) checklist.[16,17]

2.6 | Data synthesis and analysis

The main results of the SR are described narratively and tabulated as summary of findings. Data were pooled and meta-analysed using Review Manager (Review Manager V.5.3; Cochrane Collaboration) using the random-effects model approach. For dichotomous variables, data were pooled as incidence rate ratios (IRR) or risk ratios (RRs). For continuous outcomes, mean differences (MDs) with 95% confidence intervals (CI) were used. If mean or standard deviations (SD), or changes of mean and SDs from baseline, were not reported, standard errors (SE), CI or the correlation coefficient was used. Where multiple arms were compared to a common placebo arm, SE were adjusted to avoid the unit of analysis error.[18]

The magnitude of heterogeneity between the included studies was calculated using the Higgins I^2 statistic interpreted according to the Cochrane Handbook guidelines.[19] To account for clinical heterogeneity, subgroup analysis was predefined if possible by different doses of dupilumab (200 mg or 300 mg), baseline eosinophil counts, biomarkers (FeNO) and ROB. The median estimate reported in the control arms was used as baseline risk to estimate absolute effects. For the economic evidence, results are summarized narratively and tabulated, including the incremental ratios and the degree of uncertainty.

2.7 | Certainty of the evidence

The certainty (quality) of the evidence of efficacy, safety and economic impact was rated for each outcome as high, moderate, low or very low, following the GRADE approach and the standard GRADE domains (risk of bias, imprecision, inconsistency, indirectness and publication bias).[20,21] For the evaluation of imprecision for each outcome, the following thresholds for the minimal important difference (MID) were considered when available: 0.5 for ACQ and AQLQ (with disclaimer as calculated pre-/post-treatment), 0.81 puff/d for use of rescue medication and 20% for exhaled NO.[22-25] For FEV1, the applied MID was 0.2 L, as agreed by consensus by the GDG.

3 | RESULTS

3.1 | Studies included and excluded from the systematic review

As per the Cochrane Handbook for Systematic Reviews of Interventions, the eligibility process of the original studies is summarized using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart (Figure 1A,B).

The current search identified in total 3441 citations. After excluding duplicates and screening the title and abstract, 12 full-text papers were evaluated for the efficacy and safety; 9 were excluded due to different population of interest, nonrandomized double-blind study design or dose not approved by the regulatory authorities, and three RCTs were included.[26-28]For the economic evidence, 35 full papers were evaluated and only one cost-effectiveness analysis was considered suitable for inclusion (Figure 1B).[29]

3.2 | Characteristic of included studies

The key characteristics of studies included are detailed in Table 2 and the ones excluded are described in Table S2. The RCTs evaluated included 2735 patients with severe asthma uncontrolled under treatment with ICS,[26,27] or with OCS,[28] plus up to two additional controllers. All studies included subjects aged 12 or older, mean age (SD) 47.9 years (15.3-51.3). The follow-up under dupilumab treatment ranged from 24 weeks[26,28] to 1 year.[27]

3.3 | Evidence of efficacy and safety

The summary of the results and certainty of evidence per outcome is included in Tables 3 and 4.

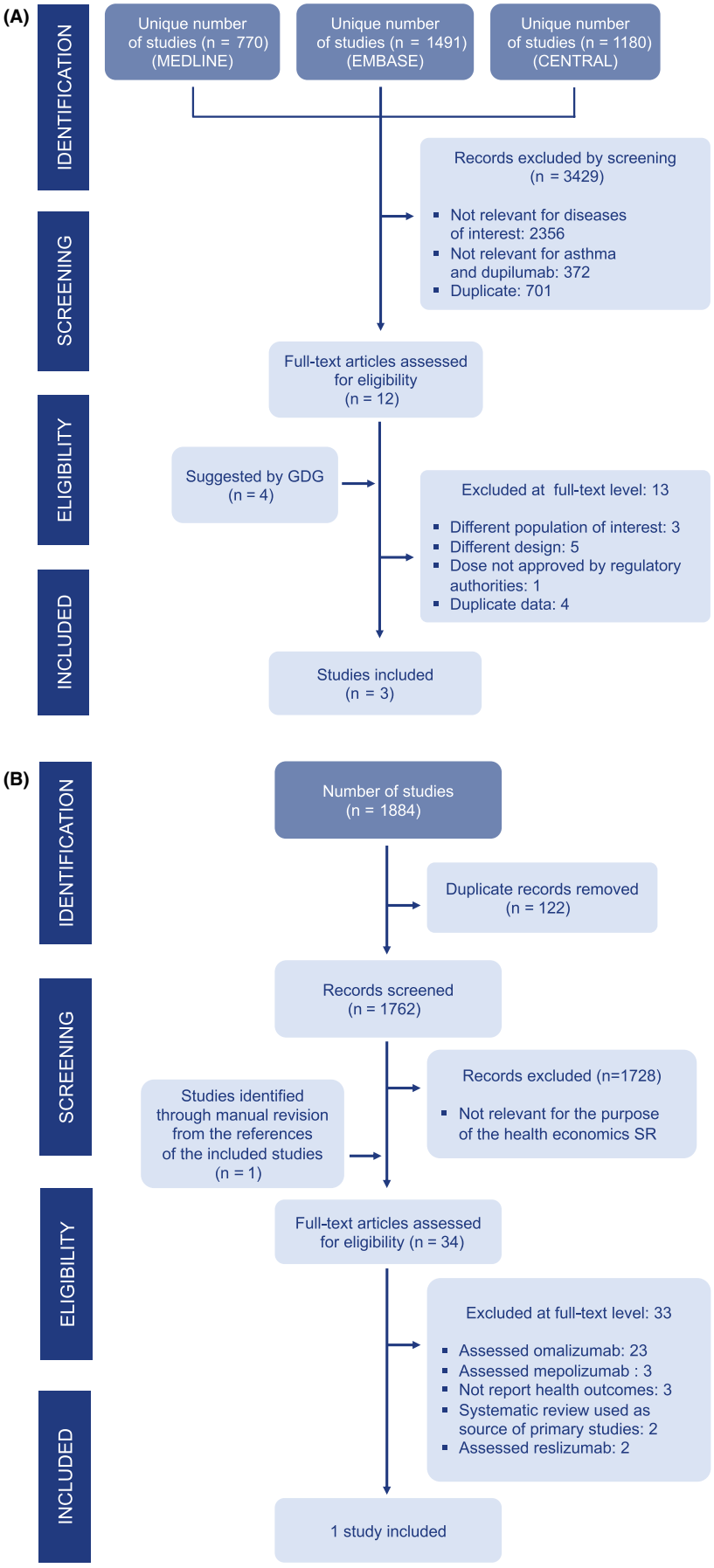

FIGURE 1 Study flow chart. A, Studies evaluating the clinical efficacy. B, Studies evaluating the economic impact of dupilumab

TABLE 2 Characteristics and summary of results of the studies included for the evaluation of dupilumab efficacy, safety and economic impact

Author, year, trial number and name	Study design (number of subjects included)	Age (y) Mean (SD)	Population	Intervention	Control	Follow-up
Studies evaluating clinical efficacy						
Castro 2018 [27] NCT02414854 Liberty Asthma Quest	Multicentre RCT (N = 1902)	47.9 (15.3)	Patients with asthma uncontrolled under medium- to high-dose ICS plus up to two additional controllers	Dupilumab 200 mg s.c. every 2 wk (loading dose, 400 mg). or Dupilumab 300 mg s.c. every 2 wk (loading dose, 600 mg)	Matching placebo	52 wk
Rabe 2018[28] NCT02528214 Liberty Asthma Venture	Multicentre RCT (N = 210)	51.3 (12.6)	Patients with severe asthma on maintenance oral corticosteroids (OCS) and high-dose ICS in combination with a second controller	Dupilumab 300 mg s.c. every 2 wk (loading dose, 600 mg)	Matching placebo	24 wk
Wenzel 2016[26] NCT01854047 DRI12544	Multicentre RCT (N = 776)	48.0 (12.8)	Patients with moderate-to-severe asthma uncontrolled on high-dose ICS/long-acting beta-2 agonist	Dupilumab 200 mg s.c. every 2 wk (loading dose, 400 mg). or Dupilumab 300 mg s.c. every 2 wk (loading dose, 600 mg)	Matching placebo	24 wk

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
Studies evaluating the economic evidence for dupilumab										
ICER 2019	Cost-utility Markov model, USA	Lifetime dupilumab in addition to standard treatment	Lifetime standard treatment	Lifetime, US healthcare perspective. Societal in the sensitivity analysis	704 000$ (2018 US dollars)	1.51 QALYs	464 000$/ QALY	17.5/20	13.5/16	Government grants and nonprofit foundations

3.3.1 | Severe asthma exacerbations

Each of the three RCTs reported the annualized severe exacerbation rate assessed at different time points: week 24[26,28] and week 52.[27] Overall, dupilumab reduced with high certainty of evidence the rate of severe exacerbations compared to placebo (IRR 0.51; 95% CI 0.45-0.59). There were no differences between the dupilumab dose subgroups (200 mg vs. 300 mg) (P = .91). The decrease in asthma exacerbations rate was significantly higher in the subgroup of patients with ≥300 eosinophils/μL at baseline (P = .001): IRR 0.35 (95% CI 0.28-0.44) versus 0.63 (95% CI 0.48-0.83) in the subgroup with <300 eosinophils/μL. Similarly, patients with high levels of FeNO responded better to dupilumab with a significantly higher decrease in exacerbations rate (P < .0001): IRR 0.76 (95% CI 0.61-0.95 in the low FeNO subgroup (<25 ppb), 0.38 (95% CI 0.28-0.53) in the subgroup with intermediate increase in FeNO (25 ppb ≤ FeNO <50 ppb) and 0.33 (95% CI 0.24-0.46) in the high FeNO subgroup (≥50 ppb) (Figure S1).

3.3.2 | Asthma control

All three RCTs measured asthma control using the ACQ-5 scores. The pooled results showed that dupilumab improved asthma control (MD −0.28; 95% CI −0.39 to −0.17; high certainty of evidence), but did not reach the MID threshold of 0.5.[22]

3.3.3 | Quality of life

Two RCTs reported on the QoL outcome measured by AQLQ.[26,27] The pooled analysis showed improvement in the QoL (MD +0.28; 95% CI

TABLE 3 Summary of available evidence for the outcomes of interest (listed by outcome)

Dupilumab compared to standard of care for asthma					
Population: patients with severe asthma uncontrolled under ICS/OSC and 1-2 additional controllers					
Intervention: dupilumab					
Comparison: standard of care					
Outcomes	**No. of participants evaluated for a particular outcome (no. of studies pooled for the SR) Follow-up range**	**Certainty of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects*** **Risk with placebo**	**Risk difference with dupilumab**
Exacerbation Rate Ratio Assessed with annualized asthma exacerbations rate	2735 (3 RCTs)[26-28] 24-52 wk	⨁⨁⨁⨁ High[4,a]	IRR 0.51 (0.45-0.59)[b]	90 per 1000	757 fewer per 1000 (from 836 fewer to 655 fewer)
Lung Function Assessed with FEV1 in L	2577 (3 RCTs)[26-28] 24-52 wk	⨁⨁⨁◯ Moderate[4,a,c,d]	-	-	MD +0.15 (+0.11 to +0.18)[b]
Asthma Control Assessed with Asthma Control Questionnaire-5 (ACQ-5) Scale from 1 to 5	2516 (3 RCTs)[26-28] 24-52 wk	⨁⨁⨁⨁ High[4,a,e]	-	-	MD -0.28 (-0.39 to -0.17)[b]
Quality of life Assessed with Asthma Quality of Life Questionnaire (AQLQ) Scale from 1 to 7	2046 (2 RCTs) [26,27] 24-52 wk	⨁⨁⨁⨁ High[4,a,f]	-	-	MD +0.28 (+0.2 to +0.37)[b]
Safety Treatment-related adverse events (AEs)	356 (1 RCT)[26] Mean 24 wk	⨁⨁⨁◯ Moderate[4,a,j]	RR 1.12 (0.98-1.28)[k]	711 per 1000	85 more per 1000 (14 fewer to 199 more)
Safety Treatment-related serious adverse events (SAEs)	356 (1 RCT)[26] Mean 24 wk	⨁⨁◯◯ Low[4,a,k]	RR 1.23 (0.54-2.77)	56 per 1000	13 more per 1000 (26 fewer to 98 more)
Reduction in rescue medication use Assessed with puffs/d	568 (1 RCT)[26] 24-52 wk	⨁⨁⨁⨁ High[4,a]	-	-	MD -0.35 (-0.73 to +0.02)
Reduction of oral corticosteroid use Assessed with percentage of reduction decrease	210 (1 RCT)[28] Mean 24 wk	⨁⨁⨁⨁ High[4,a]	-	-	MD -28.2 (-40.7 to -15.7)
Fraction of exhaled nitric oxide (FeNO) Assessed with mean % change (ppb)	2375 (2 RCTs)[26,27] Mean 24 wk	⨁⨁⨁◯ Moderate[4-6,a,h]	-	-	MD -38.57 (-48.83 to -28.31)[g]

Note: GRADE Working Group grades of evidence.

High certainty: High confidence: 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 limited 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.

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).

[a]All three trials in our meta-analysis were industry-funded, all by the same company (Sanofi-Regeneron Pharmaceuticals), and all showed positive results. No observational or industry-independent randomized trials were identified to compare with the results derived from the included RCTs.

[b]There was no relevant subgroup effect by dupilumab dose.

[c]Downgraded because FEV1 is considered a surrogate outcome of asthma control of symptoms, with a variable correlation with asthma symptoms.[35]

(Continues)

TABLE 3 (Continued)

[d]Minimal important difference (MID) of 0.23 L.[22]

[e]The MID of ACQ-5 is 0.5 points.[24]

[f]The MID of AQLQ is 0.5 points.[24]

[g]The MID decrease of the FENO value is defined as a difference larger than 20% for values over 50 ppb or more than 10 ppb for values lower than 50 ppb from one visit to the next.[25]

[h]Downgraded because FeNO is not consistently considered a good surrogate of inflammation.[36,37]

[i]For rescue medication use, the MID is a reduction by 0.81 puffs/d.[22]

[j]The effect may be both harmful and beneficial.

[k]Few events were reported in both intervention and control arms, and the effect may be both harmful and beneficial.

+0.2 to +0.37; high certainty of evidence), but without reaching the MID of 0.5.[24]

3.3.4 | Safety

Dupilumab probably increases (moderate certainty) drug-related AEs at 24 weeks: RR 1.12; 95% CI 0.98-1.28; 85 more per 1000 patients; from 14 fewer to 199 more. Dupilumab may slightly increase (low certainty) drug-related SAEs (RR 1.23; 95% CI 0.54-2.77; 13 more AEs per 1000 patients from 26 fewer to 98 more) (Figure S2).

3.3.5 | Oral corticosteroids use

Rabe et al[28] reported a decrease in OCS use following dupilumab. The pooled analysis of the two doses included showed that dupilumab reduces with high certainty the percentage use of OCS compared to the placebo (MD −28.2 mg/d; 95% CI −40.7 to −15.7).

3.3.6 | Use of rescue medication

Dupilumab reduces the use of rescue medication (MD −0.35 puffs/d; 95% CI −0.73 to +0.02; high certainty of evidence), without reaching the MID of 0.81 puffs/d.[22]

3.3.7 | Lung function

All three RCTs included reported an increase in FEV_1 from baseline at 12 weeks[27] and 24 weeks.[26,28] The pooled analysis showed that dupilumab increases FEV_1 (MD + 0.15 L; 95% CI +0.11 to +0.18; moderate certainty), without reaching the MID of 0.2 L. There was no difference between dose (200 mg vs. 300 mg) subgroups (P = .79). There was better efficacy for patients with ≥300 eosinophils/μL (P < .0001): 0.23 (95% CI 0.18-0.29) increase in FEV_1 in the subgroup ≥300 eosinophils/μL at baseline versus 0.08 (95% CI 0.04-0.13) increase in patients with <300 eosinophils/μL. Similarly, FEV_1 increased significantly higher (P < .0001) in the subgroup with high level of FeNO: FEV_1 increase 0.07 (95% CI −0.01 to 0.15) in the FeNO < 25 ppb subgroup, 0.16 (95% CI 0.09-0.22) in the 25 ppb ≤ FeNO <50 ppb subgroup and 0.34 (95% CI 0.25-0.43) in the FeNO ≥ 50 ppb subgroup.

3.4 | FeNO

Two RCTs reported the mean percentage change of FeNO at 24 weeks compared to baseline.[26,27] The pooled analysis showed that dupilumab probably reduces (moderate certainty) FeNO levels (MD −38.57%; 95% CI −48.83 to −28.31 lower), above the MID of 20% (File S1).[25]

3.5 | Paediatric subgroup analysis

The data from the paediatric subgroup (12-18 years old) were not different from those of the adult group.

3.6 | Evidence of cost-effectiveness

The Markov model assessing dupilumab versus standard therapy was tested for the United States.[29] The cost of dupilumab 300 mg by subcutaneous injection once every 2 weeks was 2774.65$ (2018 US dollars). The base case analysis reported an ICER of 464 000$/QALY. The deterministic sensitivity analysis showed large variations in the ICER value from 300 000$ to 1 000 000$ (0.85-0.81 utilities gained). At a threshold for willingness to pay of 50 000$, dupilumab is not cost-effective. The same holds true for the ICER of 269 000$ in the "responder to treatment" scenario (moderate certainty) (Table 4). The moderate certainty derives from limitations in utility estimates for the biological and the standard therapy for the nonexacerbation health state, in the annual exacerbation rates for standard therapy, and in the costs of chronic OCS use. There was also significant indirectness since these results may not be applicable outside high-income countries.

4 | DISCUSSION

4.1 | Main findings

The current systematic review shows that dupilumab as an add-on treatment for severe asthma uncontrolled under ICS plus a second

TABLE 4 Summary of available evidence on economic impact. Comparison: Dupilumab in addition to standard therapy vs. standard therapy

Quality assessment							Summary of resources and costs			
No. of studies	Study design	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Incremental cost per patient[a]	Incremental effect per patient[a]	ICER	Quality
ICER per QALY (high-quality study—not funded by Industry)										
1	Cost-utility, Markov model	Not serious[b]	Not serious	Serious[c]	Serious[d]	Not serious	704 000$ (lifetime horizon)	1.51 QALYs (lifetime horizon)	464 000$/ QALY	⊕⊕⊕◯ Moderate

Abbreviations: $, US dollar;ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

[a]Incremental cost and effect due to the addition of dupilumab.

[b]Markov model study with low risk of bias (CHEC score 13 or higher).

[c]One single study performed in the United States. The results may not be applicable to other countries.

[d]The deterministic sensitivity analysis showed large variations in the ICER value from 300 000$ to 1 000 000$ (0.85-0.81 utilities gained, respectively). Furthermore, at a threshold of 50 000, the probability for dupilumab to be cost-effective was 0%.

controller reduces with high certainty the rate of asthma exacerbations and the use of OCS. Although asthma control, quality of life and FEV_1 are improved and use of rescue medication is reduced, dupilumab does not reach above the MID threshold. However, in the subgroup with high blood eosinophils and high FeNO the improvement in FEV1 is above the MID threshold. Dupilumab probably increases short-term drug-related AEs and may increase drug-related SAEs. With an ICER as add-on therapy of 464 000 (above the 50 000$ threshold for willingness to pay), it may not be cost-effective (moderate certainty). However, this threshold has been recently contested and the value of individual thresholds was suggested to be referred to instead.[30,31]

Overall, the risk of bias across the included studies was of no important concerns for the quality of the evidence. All the studies included in the SR were funded by the same company and reported positive results raising a concern of publication bias. Moderate certainty of evidence for the economic impact was available from one single study with low risk of bias but with important indirectness (single study performed in the United States that may not be applicable to other countries).

4.2 | Results in the context of previous published SR

The current SR shows a similar effect of dupilumab for reducing asthma exacerbation rate, improving quality of life, asthma control and FEV_1 as compared to previous SRs.[32,33] These two previous SRs showed little to no difference for the AE rate,[32,33] while this systematic review found that dupilumab probably increases the risk of AEs. The difference can be explained by the fact that in the current analysis, only drug-related AEs were included, excluding AEs related to uncontrolled asthma (ie the asthma worsening).

There are some differences between these previous reviews and ours. Previous systematic reviews[32,33] did not assess the use of rescue medication. Only one systematic review examined oral corticosteroid use as an outcome.[34] This SR reported fewer patient-reported outcomes[33] and included also non–FDA/EMA-approved doses.[32,34] The current systematic review considered patient-related important outcomes (ie quality of life) as critical and only included the regulatory approved doses. Different from the systematic review published by Zayed et al, the current SR did not include exclusively studies on patients with blood eosinophil counts more than 300/μL. Another systematic review published recently only described the results of included trials.[34]

Another important difference is that previous systematic reviews only assessed the risk of bias and heterogeneity without further interpretation. We assessed the certainty of evidence using the GRADE approach, considering the heterogeneity of the results, imprecision and indirectness. As examples for surrogate outcomes (ie FEV_1, FeNO), the evidence was rated down for indirectness and MID was considered when evaluating for imprecision.

4.3 | Limitations and strengths

The current review has several strengths. An exhaustive search from three main databases was conducted for both desirable and undesirable effects as well as the cost-effectiveness. Rigorous methods following the Cochrane Handbook for Systematic Reviews of Interventions were used, including the GRADE approach to rate the certainty of the evidence. Only regulatory approved doses were included, together with the most updated results available from RCTs. Patient-related important outcomes were prioritized. Results are provided in friendly tabulated summaries using optimal presentation formats for patients, clinicians and policymakers.

There are limitations as well to the current SR. Only studies published in English were included. However, we screened studies included in previous SR and obtained additional studies through the GDG, which made it unlikely that key studies were missed. Observational studies that could inform outcomes with low quality of evidence (ie serious adverse events) were not included. We did not conduct a "the novo" economic analysis for the cost-effectiveness

outcomes. Instead, a rigorous and explicit critical appraisal of the economic evidence was done, which might be useful for the decision of using dupilumab in different countries.

4.4 | Implications for practice and research

While dupilumab shows an improvement for all the important outcomes for patients with uncontrolled severe asthma, there is a dissociated effect with significant improvement in exacerbation rate and OCS use and modest improvement in asthma control, quality of life and rescue medication use. The subgroup analysis showed a better efficacy for patients with strong T2 inflammation signature (blood eosinophils > 300/μL and/or FeNO > 50 ppb). There are limited data on the economic impact. In this context, panels are likely to formulate conditional rather than strong recommendations for dupilumab use.

Although short-term safety data are reassuring, more accurate AE reporting is warranted, in combination with long-term safety evaluation, including observational studies and registries. There are limited data available to support the efficacy and safety in the paediatric population, highlighting the urgent unmet need for rigorous trials with biologicals in children with uncontrolled severe asthma.

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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