Efficacy and safety of dupilumab for moderate-to-severe atopic dermatitis: a systematic review for the EAACI Biologicals Guidelines

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Abstract

This systematic review evaluates the efficacy, safety and economic impact of dupilumabcompared to standard of care for

uncontrolled moderate-to-severe atopic dermatitis (AD). Pubmed, EMBASE and Cochrane Library were searched for RCTs and health economic evaluations. Critical and important AD-related outcomes were considered. The risk of bias and the certainty of the evidence were assessed using GRADE. Seven RCTs including 1845 subjects > 12 years treated with dupilumab16 to 52 weeks were evaluated. For adultsthere is high certainty that dupilumabdecreasesSCORAD (MD -30,72; 95%CI -34,65% to -26,79%) and EASI-75 (RR 3.09; 95%CI 2.45 to 3.89), pruritus (RR 2.96; 95%CI 2.37 to 3.70), rescue medication (RR 3.46; 95%CI 2.79 to 4.30), sleep disturbance (MD -7.29; 95%CI -8.23 to -6.35), anxiety/depression (MD -3.08; 95% CI -4.41 to -1.75) and improves quality of life (MD -4.80; 95% CI -5.55 to -4.06). The efficacy for adolescents is similar. Dupilumab-related adverse events (AEs) slightly increase (low certainty). The evidence for dupilumab-related serious AE is uncertain. The incremental cost-effectiveness ratio ranged from 28,500 £ (low certainty) to 124,541 US$ (moderate certainty).More data on long term safety are needed both for children and adults, together with more efficacy data in the paediatric population.

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Abstract (200 words)

This systematic review evaluates the efficacy, safety and economic impact of dupilumab compared to standard of care for uncontrolled moderate-to-severe atopic dermatitis (AD).

Pubmed, EMBASE and Cochrane Library were searched for RCTs and health economic evaluations. Critical and important AD-related outcomes were considered. The risk of bias and the certainty of the evidence were assessed using GRADE.

Seven RCTs including 1845 subjects > 12 years treated with dupilumab 16 to 52 weeks were evaluated. For adults there is high certainty that dupilumab decreases SCORAD (MD -30,72; 95%CI -34,65% to -26,79%) and EASI-75 (RR 3.09; 95%CI 2.45 to 3.89), pruritus (RR 2.96; 95%CI 2.37 to 3.70), rescue medication (RR 3.46; 95%CI 2.79 to 4.30), sleep disturbance (MD -7.29; 95%CI -8.23 to -6.35), anxiety/depression (MD -3.08; 95% CI -4.41 to -1.75) and improves quality of life (MD -4.80; 95% CI -5.55 to -4.06). The efficacy for adolescents is similar. Dupilumab-related adverse events (AEs) slightly increase (low certainty). The evidence for dupilumab-related serious AE is uncertain. The incremental cost-effectiveness ratio ranged from 28,500 £ (low certainty) to 124,541 US$ (moderate certainty). More data on long term safety are needed both for children and adults, together with more efficacy data in the paediatric population.

Registration : PROSPERO (CRD42020153645).

Abbreviations

AD = atopic dermatitis

AE = adverse events

CDLQI = Children's Dermatology Life Quality Index

CHEC = Consensus health economic criteria

CI = confidence interval

DLQI = Dermatology Life Quality Index

EAACI = European Academy of Allergy and Clinical Immunology

EASI = Eczema Area and Severity Index

EMA = European Medicine Agency

FDA = Food and Drug administration

GDG = Guideline Development Group

GISS = Global Individual Sign Score

GRADE = Grading of Recommendations Assessment, Development and Evaluation

HAD-A = Hospital Anxiety and Depression Scale of anxiety

HADS-D = = Hospital Anxiety and Depression Scale of anxiety or depression

ICER = Incremental cost-effectiveness ratio

Ig = immunoglobulin

IGA = Investigator´s Global Assessment

IL = interleukin

IRR = incidence rate ratio

MD = mean difference

MID = minimal important difference

NRS = numerical rating scale

OCS = oral corticosteroids

POEM = Patient-Oriented Eczema Measure

PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analysis

QALY = Quality adjusted life-years

QoL = quality of life

RCT = randomised controlled trial

ROB = risk of bias

SOC = standard of care

RR= rate ratio

SC= subcutaneous

SR = systematic review

T2 = type 2

Key words

Atopic dermatitis; cost-effectiveness; dupilumab; EASI; SCORAD

Introduction

Atopic dermatitis (AD) is a chronic inflammatory and relapsing disease characterised by dry and scale skin, eczematous lesions and intense itching that might turn chronic. AD displays a highly complex pathophysiology and heterogeneous phenotypes, which are illustrated by different features such as age of disease onset, variable response to triggers, spectrum of severity, barrier defect, potential of IgE autoreactivity and comorbidities (asthma, rhinitis, food allergy and infections) (1,2,3,4,5,6). Similar to asthma, AD research is developing and shaping precision medicine approaches aiming towards a biomarker based molecular taxonomy (7,8,9,10).

IL-4 and IL-13 are key cytokines in driving the initiation and chronicity of type 2 (T2) inflammation, a dominant inflammatory pathway in AD (11,12). 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 (13,14). The European Medical Agency (EMA) recommends dupilumab for moderate-to-severe AD in adult and adolescents (12 years and older) patients who are candidates for systemic therapy (15). The United States Food and Drug Administration (FDA) recommends dupilumab for patients aged 6 years and older with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable (16).

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

Methods

Guidelines Development Group

The EAACI Atopic dermatitis 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 development of the EAACI biologicals guideline. They are referred to as the Guidelines Development Group (GDG).

Structured question and outcome prioritisation

The GDG framed the clinical question as "Is the treatment with dupilumab efficacious and safe for adult and adolescent patients with uncontrolled moderate-to-severe AD?" (table 1). Population was defined as patients ([?]12 years or older) with confirmed diagnosis of moderate-to-severe AD. Moderate-to-severe disease was defined as an Investigator´s Global Assessment (IGA) score of three or higher at baseline or an Eczema Area and Severity Index (EASI) score of 12 or higher at baseline. AD related outcomes were prioritised by the GDG group 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 (table 2). The critical outcomes were SCORAD 75; EASI 50 or 75; pruritus and safety (drug-related adverse events (AE) and drug-related serious AE (SAE)). The important outcomes were IGA, resource utilisation, rescue medication use, pain, sleep disturbance, symptoms of anxiety and depression, and Quality of life (QoL) (tables 1 and 2). The GDG also framed a cost-effectiveness question to assess the economic impact of dupilumab versus standard of care or the best standard of care. The selected outcomes of interest were costs, resource use, and the incremental cost-effectiveness ratios (ICERs) per quality adjusted life-years (QALY).

Data source and searches

Electronic algorithms in combination with controlled vocabulary and search terms were used to identify relevant randomised controlled trials (RCTs) and economic evaluations in: i) MEDLINE (via PubMed, February 2020); ii) Cochrane Controlled Trials Register (via The Cochrane Library, February 2020), and; iii) EMBASE (via Ovid, February 2020). Search algorithms were adapted to the requirements of each database, and validated filters were used to retrieve appropriate designs (tables S1 and S2). Additional studies provided by the GDG and previous SR were also evaluated (figure 1A and 1B).

Eligibility criteria and selection of studies

The SR included RCTs comparing dupilumab versus placebo added to usual care/standard of care in patient with moderate-to-severe AD, and reporting one of the outcomes of interest as formulated by the GDG (figure 1 A and B). The SR excluded studies with dose or route not approved by the EMA or FDA, papers published as abstract or conference communications or not published in English. After initial calibration two 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 X9 software (Thomson Reuters, New York, USA).

Data extraction and risk of bias assessment

One reviewer independently extracted the main characteristics of eligible studies (study design, patient population, mean age, follow up, and outcomes of interest), and a second reviewer checked for accuracy. If needed, authors of included studies were contacted to provide additional data. The Cochrane Risk of Bias tool for randomised trials was used to assess the risk of bias (ROB) of the included studies (15). The ROB was judged as low, high or unclear for each domain: random sequence generation, allocation concealment, blinding of participants and personnel, blinding for outcome assessment, incomplete outcome data, and selective reporting (figure S1) (16,17,18).

For the health economics analysis, two reviewers extracted the main characteristics of included studies (type of economic evaluation, perspective, time horizon, discounting, sources of information, model type), relevant outcomes (costs, ICERs, sensitivity analyses results), sources of funding, and conflict of interest. Methodological limitations of the economic evaluations were evaluated by two reviewers using the consensus on health economics criteria checklist (CHEC) (19). Transferability to the European context was assessed using the European Network of Health Economic Evaluation Databases (EURONHEED) checklist (20,21).

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, Oxford, UK) using the random effects model approach. For binary outcomes pooled relative risk ratios and rate ratios (RRs) were calculated. 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 were used. Where multiple arms were compared to a common placebo arm, SE were adjusted to avoid the unit of analysis error (22).

The magnitude of heterogeneity between the included studies was calculated using the Higgings' I2 statistic interpreted according to the Cochrane Handbook guidelines (23). To account for clinical heterogeneity, subgroup analysis was predefined if possible by different doses of dupilumab, age 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 cost, incremental effectiveness, ICERs and the degree of uncertainty.

Certainty of 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) (24,25). For the evaluation of imprecision

for each outcome the following thresholds for the minimal important difference (MID) were considered when available: 8.7 points for Scoring Atopic Dermatitis (SCORAD) (26,27); 6.6 points for Eczema Area and Severity Index (EASI) (27,28); 4 points for Patient-Oriented Eczema Measure (POEM) (27,29); 4 points for the Dermatology Life Quality Index (DLQI) (30); 6 points for Children's DLQI (CDLQI) (31); 3 points for numerical rating scale (NRS) for adults (32,33) and 4 points for adolescents (31); 8 points or less for the Hospital Anxiety and Depression Scale of anxiety (HAD-A) or depression (HADS-D) (34).

Results

Results are presented following the GRADE informative statements (35).

The systematic search retrieved 4377 citations. After excluding duplicates and screening the title and abstract, 29 full text papers were retrieved for the evaluation of dupilumab's efficacy and safety (figure 1A). Twenty-two studies were excluded due to lack of abstract, dose not approved by the regulatory authorities, and duplicate data. Nine additional articles were suggested by the GDG group but excluded due to dose not approved by the regulatory authorities, non-randomised double-blind study design, not reporting outcomes of interests, or duplicate data (Table S3). The SR for the efficacy and safety included seven RCTs (36, 37, 38, 39, 40, 41) (figure 1A). For the economic evidence, after screening 1552 hits, five studies were considered suitable for inclusion (51,52, 53, 54,55) (figure 1B).

Characteristic of included studies

The main characteristics of the studies included are detailed in Tables S4 and S5. The RCTs included in the SR evaluated 1678 adults and 167 adolescents with moderate-to-severe AD inadequately controlled by topical treatment. Follow-up under treatment ranged from 16 weeks (36,37,39, 40) to one year (38). One RCT recruited responders from SOLO trials and continued the intervention for another 36 weeks (41). In all trials evaluated only regulatory-approved doses were considered.

Evidence of efficacy and safety

The summary of findings and certainty of evidence per outcome are reported in Tables 3, 4, 5A and 5B.

SCORAD index

Six RCTs included in the SR reported the percentage change from baseline in SCORAD index assessed at 16 weeks (36,37,39,40). Dupilumab reduced with high certainty of evidence the SCORAD value compared to standard of care in adults (MD -30,72%; 95% CI -34,65% to -26,79%) and in adolescents (MD -34%; 95% CI -43.74% to -24.26%). One study reported on SCORAD reduction at 52 weeks (MD -32.1%; 95%CI, -39.27% to -24.93%) (38). Another RCT reported a small to no effect in the 36 weeks follow-up of SOLO trials (MD + 0.97%; 95%CI +0.69% to +1.25%) (41).

Eczema Area and Severity Index (EASI)

Six RCTs reported the proportion of patients achieving 75% improvement (EASI-75) at 16 weeks (36,37,38,39,40). Dupilumab treatment in adult patients with standard of care versus placebo resulted with high certainty in a significant increase in the number of patients who achieved EASI-75 (RR 3.09; 95%CI 2.45 to 3.89; absolute increase +383 per 1000 patients, 95%CI from +266 to +530). Similar results were reported for adolescents (RR 5.03; 95%CI 2.37 to 10.71; absolute increase +332 per 1000 patients, 95%CI from +113 to +800). All six RCTs also reported the proportion of patients with 50% improvement (EASI-50) at 16 weeks. Their results showed a significant increase in EASI-50 responders compared to standard of care in adults (RR 2.43; 95%CI 2.04 to 2.89) and adolescents (RR 4.71; 95%CI 2.64 to 8.40). A comparable increase

was reported at 52 weeks for EASI-75 (RR 3.02; 95%CI 2.29 to 3.98) and EASI-50 (RR 2.63; 95% CI 2.12 to 3.26) in one RCT (38). The impact on EASI was maintained during the 36 weeks of follow-up in the SOLO trials (EASI-75 RR 2.36, 95%CI 1.66 to 3.34; EASI-50 RR 1.85, 95%CI 1.39 to 2.44) (41).

Pruritus

Six RCTs measured the effect of dupilumab treatment on pruritus through the proportion of patients with an improvement of [?] 4 points in the numerical rating scale (NRS) at 16 weeks (36,37,38,39,40). Dupilumab significantly reduced pruritus with high certainty of evidence, both for adults (RR 2.96; 95% CI; 2.37 to 3.70; absolute effect + 311 per 1.000 patients, 95%CI from +217 to +429) and for adolescents (RR 7.68; 95% CI; 2.83 to 20.84; absolute effect +318 per 1.000 patients, 95%CI from + 87 to +945). One study (38) reported a significant reduction of pruritus at 24 weeks (RR 3.98; 95%CI 2.71 to 5.84) and at 52 weeks (RR 3.36; 95% CI 2.45 to 4.60), and the effect was maintained during the 36 weeks follow-up (SOLO trials; RR 3.83, 95%CI 2.10 to 6.97) (41). The effect on pruritus was also quantified by percent change from baseline of peak pruritus NRS score (36,37,38,39,40,41). The pooled analysis illustrated a significant dupilumab-induced NRS score improvement at 16 weeks for adults (MD -28.04%; 95% CI -32.65% to -23.43%) and for adolescents (MD -28.90%; 95% CI -39.34% to -18.46%). In the 36 weeks follow-up period of SOLO trials no improvement in the NRS score was reported (MD -0.53%, 95%CI -0.79 to -0.26) (41).

Safety

Dupilumab may increase (low certainty of evidence) treatment-related AE at 16 weeks (RR 1.29; 95%CI 0.62 to 2.72; absolute increase +118 per 1000 patients; 95% CI from -155 to +702) (36,39). Most of the treatment-related AEs were eye inflammation (conjunctivitis). Dupilumab was safe in adolescents: the analysis of the potential increase in dupilumab-related AE showed little to no difference with moderate certainty (RR 1.04; 95%CI 0.85 to 1.26; absolute increase +28 per 1000 patients; 95%CI from - 104 to + 180) (40). Dupilumab-related severe AE were reduced for adults (RR 0.50; 95%CI 0.09 to 2.70; absolute increase -12 per 1.000 patients; 95%CI from -22 to +40) and for adolescents (RR 0.35; 95%CI 0.01 to 8.36, absolute increase -8 per 1000 patients; 95%CI from -12 to +87). The evidence is very uncertain both for adults and adolescents. The SOLO trials reported decreased treatment-related AE (RR 0.86, 95%CI 0.75 to 1.00) and increase treatment-related severe AE (RR 2.95, 95%CI 0.36 to 24.07) (41).

Investigator's Global Assessment (IGA) score

Four RCTs defined the primary outcome as the proportion of patients who achieved both a score of 0/1 (0=clear or 1=almost clear) on the investigator's global assessment and a reduction of [?] 2 points from baseline at 16 weeks (37,38,39). Dupilumab significantly increased the proportion of patients' achieving both end-points with high certainty of evidence (RR 3.46; 95% CI 2.79 to 4.3; absolute effect + 270 per 1.000 patients, 95%CI from + 197 to +363). Two other RCTs (36,40) defined the primary outcome as the proportion of patients with an IGA response 0/1 at 16 weeks, showing a significant effect both for adults (RR 18.11; 95%CI 2.50 to 131.17) and for adolescents (RR 10.37; 95%CI 2.50 to 42.95). The effect was maintained in the 36 weeks follow-up of SOLO trials (RR 2.47, 95%CI 1.65 to 3.71) (41).

Use of rescue medication

Five RCTs reported on this outcome at 16 weeks (37,38,39,40). The pooled analysis showed that dupilumab significantly reduces with high certainty of evidence the proportion of the patients who use any rescue medication, both for adults (RR 0.36; 95%CI 0.28 to 0.46, absolute effect - 270 per 1.000 patients, 95%CI from - 304 to - 228 fewer) and for adolescents (RR 0.35; 95%CI 0.22 to 0.56, absolute effect - 382 per 1.000 patients, 95%CI from -45 to -259). The effect was maintained in the 36 weeks follow-up of SOLO trials (MD 0.69, 95%CI 0.43 to 0.96) (41).

Pain

One RCT included in the SR measured the effect of dupilumab on pain trough the proportion of patients with no complains in the item 4 (pain/discomfort) of the EQ-5D questionnaire. For the adult population, dupilumab significantly reduced the number of patients with pain and discomfort, with high certainty of evidence (RR 1.89; 95%CI 1.44 to 2.49; absolute effect + 330 more per 1,000 patients; 95%CI +163 to +552) (39).

Sleep disturbance

Six RCTs measured the impact on sleep disturbance with the change in the POEM score at 16 weeks. Dupilumab significantly reduced the severity of sleep disturbance (MID=4) with high certainty of evidence in adults (MD -7.29; 95%CI -8.23 to -6.35) (36,37,38,39) and with moderate certainty of evidence in adolescents (MD -6.30; 95%CI -8.81 to -3.79) (40). One RCT evaluated POEM at 52 weeks and showed a similar effect (MD is -8.4; 95%CI -10.12 to -6.68) (38). In the 36 weeks follow-up of SOLO trials, an opposite effect was reported (MD 0.96, 95%CI 0.68 to 1.23) (41).

Anxiety and depression

Six RCTs reported this outcome considering the change from baseline of HADS at 16 weeks. The pooled analysis showed that dupilumab reduces symptoms of anxiety and depression with high certainty of evidence in adults (MD -3.08; 95%CI -4.41 to -1.75) and with moderate certainty in adolescents (MD -1.30; 95%CI -3.38 to +0.78). In the 36 weeks follow-up of SOLO trials an opposite effect was reported (MD 0.31, 95%CI 0.04 to 0.57) (41). Two RCTs (38,39)) evaluated this outcome as the proportion of the patients with no clinically relevant symptoms of anxiety and depression at 16 weeks (RR 1.78; 95% CI 1.35 to 2.33) and one of the two RCTs reported a better effect at 52 weeks (RR 2.40; 95%CI 1.5 to 3.87) (38).

Quality of life

QoL outcome was measured by DLQI for adults (36,37,38,39) and by CDLQI for adolescents (40). The pooled analysis showed a significant improvement (above the MID of 4 and 6, respectively) in the QoL with high certainty of evidence both for adults (MD -4.80; 95%CI -5.55 to -4.06) and for adolescents (MD -13.60; 95%CI -15.13 to -12.07). Four RCTs reported on the QoL in adults with AD measured by Global Individual Sign Score (GISS) (37, 38, 39) and showed that dupilumab improves QoL (MD -26.39%; 95% CI -30.62% to -22.15%). Dupilumab improves QoL at 52 weeks: DLQI (MD -4.40; 95%CI -5.7 to -3.05) and GISS (MD -29.10%; 95%CI from -36.67% to -21.53%) (38). In the 36 weeks follow-up of SOLO trials, deterioration of QoL was reported (MD 0.74, 95%CI 0.47 to 1.01) (41).

Cost-effectiveness

Four Markov model-based evaluations assessing dupilumab versus standard of care (42, 43, 44, 45), and one comparing dupilumab with best supportive care (education, psychological support, emollients, topical corticosteroids, bandages, and hospitalisation) (46) were included into the analysis. Three evaluations were conducted from the perspective of the United States' healthcare system (42,43,44), one was performed in Canada (45), and one in the UK (46). The annual dupilumab related cost per patient was highest in the US studies (up to 37,000 US$) followed by the Canadian study (25,918 C$) and by the UK study (16,500 PS). The costs of medication were lower in the UK (632.45 PS) compared with Canada (959.94 C$) and the US (up to 1,300.00 US$). The ICER per QALY of dupilumab added to the standard of care was 100,000 US$ or higher (42,43,44,45). The sensitivity analyses showed variations in the ICER from 78,300 US$ in

patients with severe AD to 159,988 US$ in those with moderate AD. The Canadian Agency for Drugs and Technologies in Health (CADTH) undertook an analysis for patients, refractory to, or ineligible for systemic immunosuppressant therapies obtaining an ICER of 133,877 C$, which is within the range of ICERs found by the US studies (Table 5A). The National Institute for Clinical Excellence undertook an analysis of dupilumab as fifth-line treatment, after topical therapies and systemic immunosuppressant have failed. In this scenario the ICER value was 28,495.00 PS, which is lower than the previous ones (Table 5B).

There was moderate certainty of the evidence for the studies assessing the economic impact of dupilumab versus standard of care due to concerns for indirectness, as unitary costs were provided by studies performed in the US (42,43,44) and Canada (45). These results may not apply outside high-income countries. There was low certainty for the study that compared dupilumab with the best supportive care due to serious concerns for indirectness in the comparator (including therapies beyond topical treatment) and the population (patients receiving dupilumab as fifth-line treatment, after systemic immunosuppressant therapies).

Discussion

Main findings

The current systematic review showed that dupilumab as add-on treatment for moderate-to-severe AD in adults and adolescents significantly reduces short-term (16 weeks) AD symptoms, severity, use of rescue medication, and improves quality of life. For adults there is good evidence for long-term efficacy (52 weeks). Dupilumab may increase short-term drug-related AE. The evidence for severe drug-related AE is very uncertain. All RCTs were mainly powered for efficacy and less powered to show rare adverse events which are now frequently reported in the post-marketing literature.

The ICER per QALY of dupilumab versus standard of care was above 100,000 US$, considered as threshold for the willingness to pay in several high-income countries (47). Drug-related costs were the key driver of this ICER in all studies. The CADTH analysis recommended a price reduction of at least 54% to obtain an ICER value below the threshold of 50,000 C$. Another important factor impacting the ICER was the profile of patients included in the analysis. In the NICE analysis, dupilumab plus topical corticosteroids was found to be cost-effective for treating atopic dermatitis not responding to other systemic therapies, such as ciclosporin, methotrexate, azathioprine and mycophenolate mofetil, or when these options were contraindicated or not tolerate. Dupilumab improved their quality of life compared to best supportive care and it was key for generating an acceptable ICER value of 28,500 PS, which is in line with previous authors suggesting that the high cost of dupilumab for severe AD is offset by the quality of life improvement (48).

The main reason to downgrade the certainty of the evidence for the efficacy and safety outcomes was imprecision and inconsistency, and the indirectness for economic data. All the studies were funded by the same company and reported positive effects, which might raise concerns for a potential sponsorship bias. Moderate certainty of evidence for economic impact was available from three studies with low risk of bias but with important indirectness. All economic analyses were performed in high-income countries in line with their health system perspectives, thus their results may not be applicable to other countries.

Current report in the context of previous research

This SR is the most up to date review on the effectiveness, safety and economic impact on dupilumab in AD. Similar to previous SRs the current analysis reinforces the short-term (16 weeks) efficacy of dupilumab in improving SCORAD, EASI, IGA, pruritus, and quality of life (49,50,51). In addition, the current SR provides evidence for long-term (52 weeks) benefit in adults.

According to the current SR in adults with AD dupilumab may increase treatment-related AE (conjunctivitis/ injection side reactions/ eosinophilia), although there is low certainty of evidence. The evidence for treatment-related severe AE is very uncertain both for adults and for adolescents. The pooled analysis from laboratory findings from three randomized, double-blinded, placebo-controlled phase 3 trials showed no clinically important changes in routine laboratory parameters that could be attributed to dupilumab, thus supporting the use of dupilumab as a systemic treatment for moderate-to-severe AD that does not require laboratory monitoring (52).

The use of variable outcomes limited the conclusions of previous SRs (50). For the current SR the GDG predefined and prioritised AD-related outcomes.

Previous SRs included all dupilumab doses for AD, while the current SR only included FDA/EMA approved doses, which are more informative for issuing recommendations for clinical practice.

Although a recent SR included the efficacy of dupilumab for adolescent AD population (51), they did not report separately for this population.

Furthermore, the current SR followed the GRADE approach for rating of the certainty of evidence. In contrast to previous SRs (49,50) that assessed only the risk of bias, the current SR considered all relevant aspects related with the certainty of evidence like heterogeneity, indirectness or imprecision of the results.

Finally, an evaluation of cost-effectiveness was included, thus providing additional support for the GDG in formulating recommendations.

Limitations and strengths

The current SR has several strengths. First, a comprehensive systematic search was conducted on three databases, checking for efficacy, safety and cost-effectiveness. Second, rigorous evaluation methods were employed, including the use of the GRADE approach to rate the certainty of the evidence. The outcomes included were prioritised beforehand and the minimal important difference was considered when available for all AD-related outcomes.

Optimal presentation of results into tabulated format (summary of findings) is provided aiming to improve communication to patients, clinicians, and other stakeholders.

There are some limitations as well. Only studies published in English were included. However, the studies included in previous systematic reviews were thoroughly evaluated and additional studies were suggested by the GDG, which decreases the possibility of missing studies. No observational studies were included, which could inform better on outcomes with low quality of evidence (i.e, serious adverse events). However, they will be considered when formulating recommendations. A '*de novo* ' economic analysis was not conducted; however, a rigorous and explicit critical appraisal and transferability assessment of cost-effectiveness data is provided.

Conclusion

Dupilumab demonstrated a significant short-term benefit for the adults and adolescents with uncontrolled moderate-to-severe atopic dermatitis, by improving symptoms and disease severity, reducing the use of rescue medications and improving the quality of life. For adults there is evidence for long-term benefit. Thresholds for cost-effectiveness are probably acceptable for some high-income countries, however dupilumab might not be equally cost-effective in countries with limited resources.

Although short term safety data showed no visible increase of AE, more accurate AE reporting is warranted in RCTs for both adult and adolescent population, combined with long-term safety evaluation using obser-

vational and effectiveness studies and registries. There are several ongoing open-label studies (53,54) and registries (55) evaluating the long-term safety and efficacy of dupilumab in atopic dermatitis that are likely to be informative in formulating recommendations.

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