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Adverse events of Dupilumab in adults with moderate-to-severe atopic dermatitis: A meta-analysis☆

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ABSTRACT

Background: Dupilumab, a fully human monoclonal antibody against interleukin-4 receptor alpha, inhibits the signals of interleukin-4 and interleukin-13, and has also shown significant efficacy in patients with moderate-to-severe atopic dermatitis (AD), while the effect of it on adverse events remains controversial.
Objective: To assess the influence of dupilumab on adverse events in adults with moderate-to-severe AD.
Method: Randomised controlled trials (RCTs) that compared dupilumab with a placebo for patients with moderate-to-severe AD were searched in the MEDLINE, EMBASE, Web of Science and Cochrane databases. The outcome of the study was the incidence of adverse events during the observation period.
Results: Eight RCTs were analysed in this study. Meta-analysis showed that patients treated with dupilumab had a lower risk of skin infection (risk ratio [RR] 0.54; 95% confidence interval [CI] 0.42–0.69) and exacerbation of AD (RR 0.44, 95% CI 0.34–0.59), but had a higher risk of injection-site reaction (RR 2.24, 95% CI 1.68–2.99), headache (RR 1.47, 95% CI 1.05–2.06), and conjunctivitis (RR 2.64, 95% CI 1.79–3.89) than did patients treated with a placebo. Nasopharyngitis, urinary tract infection, upper respiratory tract infection, and herpes virus infection were found balanced in dupilumab groups and placebo groups.
Conclusion: Dupilumab moderately reduced the risk of skin infection and the exacerbation of AD, slightly increased the risk of headache, and moderately increased the risk of injection-site reaction and conjunctivitis, but had little effect on other infections in adults with moderate-to-severe AD.

1. Introduction

Atopic dermatitis (AD) is a chronic, incurable disease characterised by robust type 2 helper T cell (Th2)-mediated immune responses to many environmental antigens, refractory pruritus and susceptibility to skin infection [1]. The prevalence of this disease is about 3% to 10% in adults and up to 20% in children [2–5]; 20% of the patients have moderate-to-severe AD [1], for which previous therapies, such as cyclosporine, have limited efficacy, numerous side effects and also increase the risk of infection [6–9]. Thus, it is necessary to find new therapies for patients with moderate-to-severe cases [10,11,9].

Dupilumab, a monoclonal antibody aimed at interleukin (IL)-4 receptor alpha, inhibits the signals of IL-4 and IL-13, which are type 2 cytokines that may be important drivers of atopic or allergic diseases such as AD and allergic asthma [12–17]. Several clinical studies on dupilumab have shown significant efficacy in adults with moderate-to-severe AD and it has also recently been approved by the US Food and Drug Administration as a new systemic therapy for this disease. However, the effect of it on adverse events in adults with this disease remains controversial [6,13,14,18,16]. The purpose of this study was to estimate the influence of dupilumab on adverse events in adult patients with moderate-to-severe AD.

2. Methods and materials

This work was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [19].

2.1. Search strategy

Two researchers (Z.Z.O. and C.C.) performed independent and comprehensive searches of the MEDLINE, EMBASE, Web of Science and the Cochrane Library from inception to December 2017. A combination

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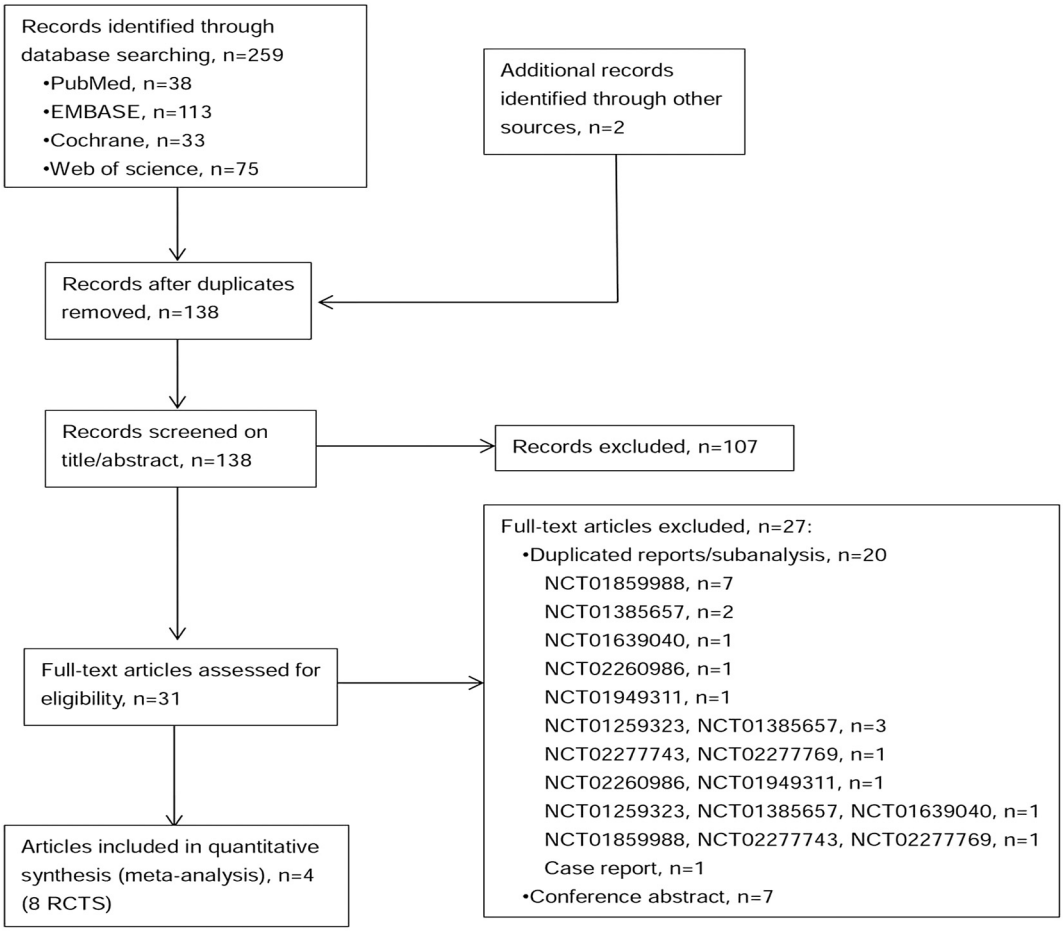

Fig. 1. Flow diagram of study selection. NCT, national clinical trial.

of MESH terms such as “dermatitis, atopic” and “SAR231893” and words like “atopic dermatitides” and “dupilumab” were used to search, the language was limited to English and there was no limit to study design.

2.2. Study selection

Studies meeting the following criteria were included: (1) the studies must have been randomised controlled trials; (2) patients enrolled in the studies must have been diagnosed with AD; (3) Investigator's Global Assessment score of patients must have been 3 or higher at screening and baseline; (4) intervention of these studies must have contained dupilumab; (5) Outcomes of these studies must contain adverse events. Appropriate literature was assessed independently by two reviewers (Z.Z.O. and C.C.) according to the criteria stated previously, and discrepancies resolved through discussion.

2.3. Data extraction

The two researchers independently and carefully read the full text and supplementary appendix of the studies included (protocols were read if necessary). Study type, character of participants, method and duration of interventions, adverse events, as well as the assessment time-points were extracted from these studies separately, and discrepancies resolved through discussion. We also sent e-mails to the authors for detailed data if key data were absent.

2.4. Assessment of risk of bias

The two researchers assessed the risk of bias of each trial by using the Cochrane Collaboration's Risk of Bias tool independently. We assessed the risk of bias using random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias methods. All these judgments were reported as “low risk of bias,” “unclear” or “high risk of bias.”

2.5. Data synthesis

Study M4A and study M4B were pooled as study M4A/B because the studies had a similar design and similar patient populations. Risk ratios (RRs) with 95% confidence interval (CI) were calculated for all dichotomous outcomes. Heterogeneities between studies were assessed by using the chi-square ($\chi 2$) test; a $p\chi 2$ value < 0.1 was considered as significant heterogeneity. The I^2 statistic, which calculates the percentage of total variation among trials, was used to further assess heterogeneity between studies. A fixed-effects model was used to perform the meta-analysis if I^2 was < 0.5; otherwise, a random-effects model was chosen. A subgroup analysis was performed on the intervals between the ends of the studies and the ends of assessment. A post hoc sensitivity analysis was undertaken by changing the effects model from a random effects model to a fixed effects model. Publication bias was evaluated qualitatively by constructing a funnel plot when there were at least 10 trials for an outcome. All data were analysed with the Review Manager (RevMan) software version 5.3. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

2.6. Definition of adverse effects

‘Adverse effects’ refers to any untoward medical occurrence in a

Table 1
Characteristics of trials included in the work.

Reference (study, year)	Study design	Patients	Diagnosis of AD (course)	Outcomes	Time points of assessment	Intervention (patients)	Control
Beck et al. 2014 (M4A, 2012)	RCT DB PC	30 adults (≥ 18 y, 58.2% male) with IGA ≥ 3, BSA ≥ 10%	Hannifin and Rajka (≥ 3 years)	Skin infection	The day after the end-day	Dupilumab:75 mg qw (8), 150 mg qw (8), 300 mg qw (8) for 4 weeks	Placebo
Beck et al. 2014 (M4B, 2012)	RCT DB PC	37 adults (≥ 18 y, 58.2% male) with IGA ≥ 3, BSA ≥ 10%	Hannifin and Rajka (≥ 3 years)	Skin infection	The day after the end-day	Dupilumab:150 mg qw (14), 300 mg qw (13) for 4 weeks	Placebo
Beck et al. 2014 (M12, 2013)	RCT TB PC	109 adults (≥ 18 y, 53.2% male) with IGA ≥ 3, BSA ≥ 10%	Hannifin and Rajka (≥ 3 years)	Skin infection	The day after the end-day	Dupilumab: 300 mg qw (55) for 12 weeks	Placebo
Beck et al. 2014 (C4, 2013)	RCT TB PC	31 adults (≥ 18 y, 41.9% male) with IGA ≥ 3, BSA ≥ 10%	Hannifin and Rajka (≥ 3 years)	Skin infection	The day after the end-day	Dupilumab + TGC:300 mg qw (21) for 4 weeks	Placebo + TGC
Thaci et al. 2015 (Phase IIb, 2014)	RCT TB PC	379 adults (≥ 18 y, 61.7% male) with IGA ≥ 3, BSA ≥ 10%	ND (≥ 3 years)	Infections[b]; exacerbation of AD; injection-site reaction; headache	The 16th—week after end-day	Dupilumab: 300 mg qw (63), 300 mg q2w (64), 200 mg q2w (61), 300 mg q4w (65), 100 mg q4w (65) for 16 weeks	Placebo
Simpson et al. 2016 (SOLO 1, 2015)	RCT TB PC	671 adults[a] (≥ 18 y, 58.1% male) with IGA ≥ 3, BSA ≥ 10%	AADCC(≥ 3 years)	Infections[b]; exacerbation of AD; injection-site reaction; headache	The day after the end-day	Dupilumab: 300 mg qw (218), 300 mg q2w (229) for 16 weeks	Placebo
Simpson et al. 2016 (SOLO 2, 2016)	RCT TB PC	708 adults[a] (≥ 18 y, 57.6% male) with IGA ≥ 3, BSA ≥ 10%	AADCC (≥ 3 years)	Infections[b]; exacerbation of AD; injection-site reaction; headache	The day after the end-day	Dupilumab: 300 mg qw (237), 300 mg q2w (236) for 16 weeks	Placebo
Blauvelt et al. 2017 (CHRONOS, 2016)	RCT TB PC	740 adults[a] (≥ 18 y, 60.0% male) with IGA ≥ 3, BSA ≥ 10%	AADCC (≥ 3 years)	Infections[b] except urinary tract infection; exacerbation of AD; injection-site reaction; headache	The day after the end-day	Dupilumab + TGC: 300 mg qw (315), 300 mg q2w (110) for 52 weeks	Placebo + TGC

TB, triple blind; DB: double blind, PC, placebo controlled; IGA, Investigator's Global Assessment; BSA, body surface area; ND, not determined; AADCC, American Academy of Dermatology Consensus Criteria; qw, once a week; q2w, every 2 weeks; q4w, every 4 weeks; TGC, topical glucocorticoids, a standardized regimen of topical glucocorticoids.

[a] Patients are listed according to the randomization group, which may differ from study drug received.

[b] Infections mentioned here refer to skin infections, herpes viral infections, upper respiration tract infections, nasopharyngitis, conjunctivitis, and urinary tract infection.

patient who had been administered a medicinal product, including occurrences that are not necessarily related to or caused by that product.

3. Results

3.1. Search results

The electronic searches retrieved 261 articles, of which 138 remained after removing duplicates. Two authors screened these articles and excluded 107 records based on title and abstract information. Finally, four articles (eight trials) were included for full analysis (Fig. 1). A total of 27 studies were excluded because they were duplicate reports/subanalyses (n = 20) or were only published in conference abstracts (n = 7).

3.2. Character of included studies

All studies included in this work were placebo-controlled randomised controlled trials (RCTs). Except for study M4A, which was conducted in the United States, all studies were multinational. All patients were adults (≥ 18 years old), had an Investigator's Global Assessment (IGA) score of ≥ 3, affected body surface area of ≥ 10%, and a diagnosis of AD for ≥ 3 years. As for AD diagnostic criteria, four studies were diagnosed according to the criteria of Hanifin and Rajka, three studies were diagnosed according to the American Academy of Dermatology Consensus Criteria and one was not specified. In M4A, the patients received weekly doses of 75, 150, or 300 mg of dupilumab or placebo for 4 weeks. In M4B, the patients received weekly doses of 150 or 300 mg of dupilumab for 4 weeks. In M12, the patients received 300 mg of dupilumab weekly for 12 weeks. In C4, the patients received a combination treatment of 300 mg of dupilumab and topical glucocorticoids for 4 weeks. In the Phase IIb study, the patients received 300 mg of dupilumab once a week, 300 mg every 2 weeks, 200 mg every 2 weeks, 300 mg every 4 weeks, 100 mg every 4 weeks, or placebo once a week for 16 weeks. In the remaining three phase III trials, patients received 300 mg of dupilumab or placebo either weekly or biweekly for 16 weeks in SOLO 1 and SOLO 2, or combined with topical glucocorticoids for 52 weeks in CHRONOS. The placebos used in these trials were prepared according to the same formulation as dupilumab, but without the addition of the active agent, by the same pharmaceutical company. All adverse events were assessed until 1 day after the last day of the study, except in the Phase IIb study, which was assessed up until the 16th week after the last day of the study. The other trial characteristics are shown in Table 1 and the inclusion criteria are detailed in Table S1 in the Supplementary Appendix.

3.3. Risk of bias in included studies

All the studies included in this work were randomised trials with details on the method of randomisation. Blinding of participants, investigators, and outcome assessor was considered adequate in all studies. Four of the studies had a high risk of selective reporting because they only provided the conclusions, but no details, for some adverse events. The results of each risk-of-bias item for the included studies are summarized in Fig. 2.

3.4. Skin infection

The data on skin infections were pooled. A total of 1790 patients were included in the dupilumab group, and 912 were included in the placebo group. A fixed-effect model pooling the results showed that the incidence of skin infection was 6.7% (120/1790) in the dupilumab group and 13.3% (121/912) in the placebo group (RR 0.54, 95% CI 0.42–0.69, $p < 0.00001$, $p\chi2 = 0.62$, $I^2 = 0\%$; Fig. 3). Visual inspection of the forest plot and statistical test showed that there was no heterogeneity among the studies. A sensitivity analysis found similar results in both effects models (data not shown).

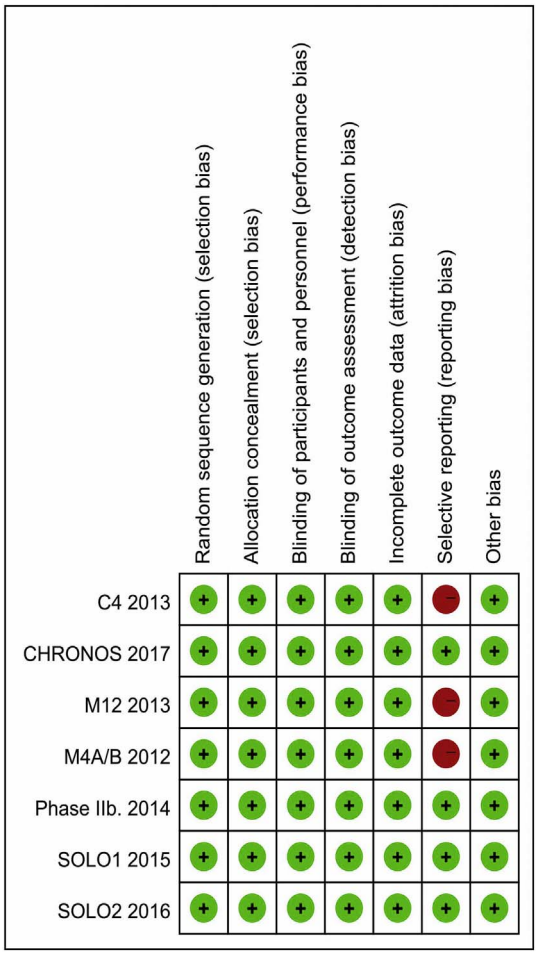

Fig. 2. Risk-of-bias summary. Our judgment of each risk-of-bias item for each included study.

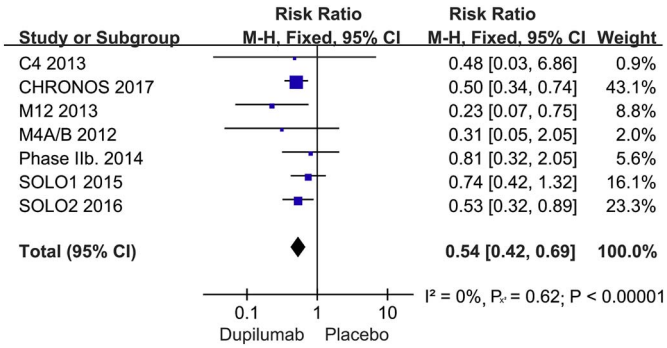

Fig. 3. Meta-analysis (pooled data) of studies of skin infections in patients treated with dupilumab or a placebo. CI, confidence interval.

3.5. Herpes virus infection

Four trials (SOLO1, SOLO2, CHRONOS, and the Phase IIb trial) involving 2495 participants reported herpes virus infection in 102/1663 (6.1%) of the participants treated with dupilumab and 43/832 (5.2%) of the participants treated with a placebo (RR 1.21, 95% CI 0.84–1.74, $p = 0.30$, $p\chi2 = 0.32$, $I^2 = 15\%$; Fig. 4). A sensitivity analysis found similar results in both effects models (data not shown).

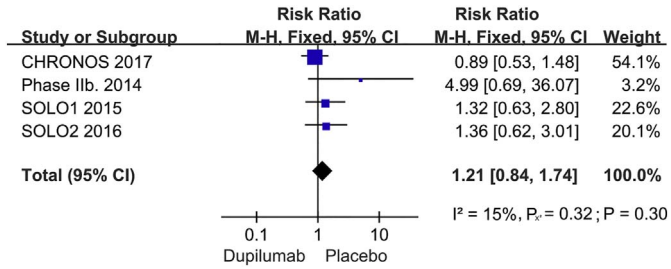

Fig. 4. Meta-analysis (pooled data) of studies of herpes virus infections in patients treated with dupilumab or a placebo. CI, confidence interval.

3.6. Non-skin infections

SOLO1 reported a higher incidence of non-skin infections in the dupilumab group than in the placebo group (136/447 = 30.4% and 49/222 = 22.1%, respectively; RR 1.38, 95% CI 1.04–1.83, p = 0.03), whereas SOLO2 reported similar incidences of non-skin infections in both groups (119/473 = 25.2% and 57/234 = 24.4%, respectively; RR 1.03, 95% CI 0.79–1.36, p = 0.82). No meta-analysis of non-skin infections was undertaken because there was moderate/substantial heterogeneity (51%) between the two trials and a wide variety of different infections. The specific infections were analysed as follows.

3.6.1. Upper respiratory tract infections

We pooled the data on upper respiratory tract infections and also performed a subgroup analysis according to the interval between the end of the study and the end of assessment. The Phase IIb trial was included in the subgroup with an interval of 16 weeks, in which we found a lower incidence of upper respiratory tract infections in the dupilumab group than in the placebo group (23/318 = 7.2% and 11/61 = 18.0%, respectively; RR 0.40, 95% CI 0.21–0.78, p = 0.007; Fig. 5sa). SOLO1, SOLO2, and CHRONOS were included in the second subgroup because there were no such intervals in these three studies. We found that the incidence of upper respiration tract infections was similar in the dupilumab group and placebo group in this subgroup (87/1345 = 6.5% and 42/771 = 5.4%, respectively; RR 1.34, 95% CI 0.94–1.91, p = 0.11, pχ2 = 0.81, I^2 = 0%; Fig. 5sa). The total combined results for the four studies showed a similar incidence of upper respiratory infections in the dupilumab group and the placebo group (110/1663 = 6.6% and 53/832 = 6.4%, respectively; RR 1.03, 95% CI 0.53–2.01, p = 0.94, pχ2 = 0.01, I^2 = 71%; Fig. 5sa). A sensitivity analysis found similar results in both effects models (data not shown).

3.6.2. Nasopharyngitis

In four trials (SOLO1, SOLO2, CHRONOS, and the Phase IIb trial) with 2495 participants, nasopharyngitis was reported in 261/1663 (15.7%) of the participants treated with dupilumab and in 116/832 (13.9%) of the participants treated with a placebo (RR 1.06, 95% CI 0.87–1.31, p = 0.55, pχ2 = 0.71, I^2 = 0%; Fig. 5sb). A sensitivity analysis found similar results in both effects models (data not shown).

3.6.3. Conjunctivitis

In four trials (SOLO1, SOLO2, CHRONOS, and the Phase IIb trial) with 2495 participants, conjunctivitis was reported in 133/1663 (8.0%) of the participants treated with dupilumab, but in only 30/832 (3.6%) of the participants treated with a placebo (RR 2.64, 95% CI 1.79–3.89, p < 0.0001, pχ2 = 0.46, I^2 = 0%; Fig. 5sc). A sensitivity analysis found similar results in both effects models (data not shown).

3.6.4. Urinary tract infection

In three trials (SOLO1, SOLO2, and the Phase IIb trial) with 1755 participants, urinary tract infection was reported in 25/1238 (2.0%) of the participants treated with dupilumab and in 12/517 (2.3%) of the participants treated with a placebo (RR 0.58, 95% CI 0.28–1.19,

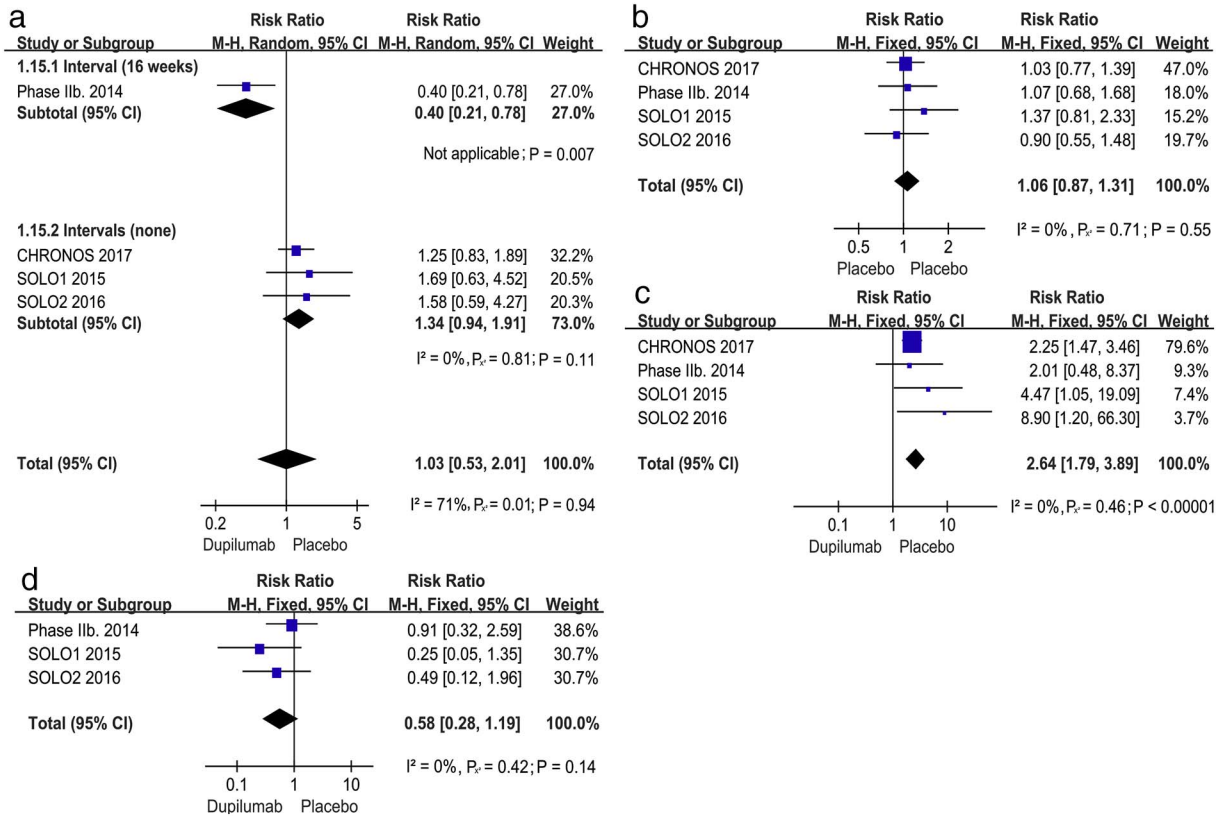

Fig. 5s. Meta-analysis (pooled data) of studies of non-skin infections in patients treated with dupilumab or a placebo. (a) Upper respiratory tract infection; (b) nasopharyngitis; (c) conjunctivitis; (d) urinary tract infection. CI, confidence interval.

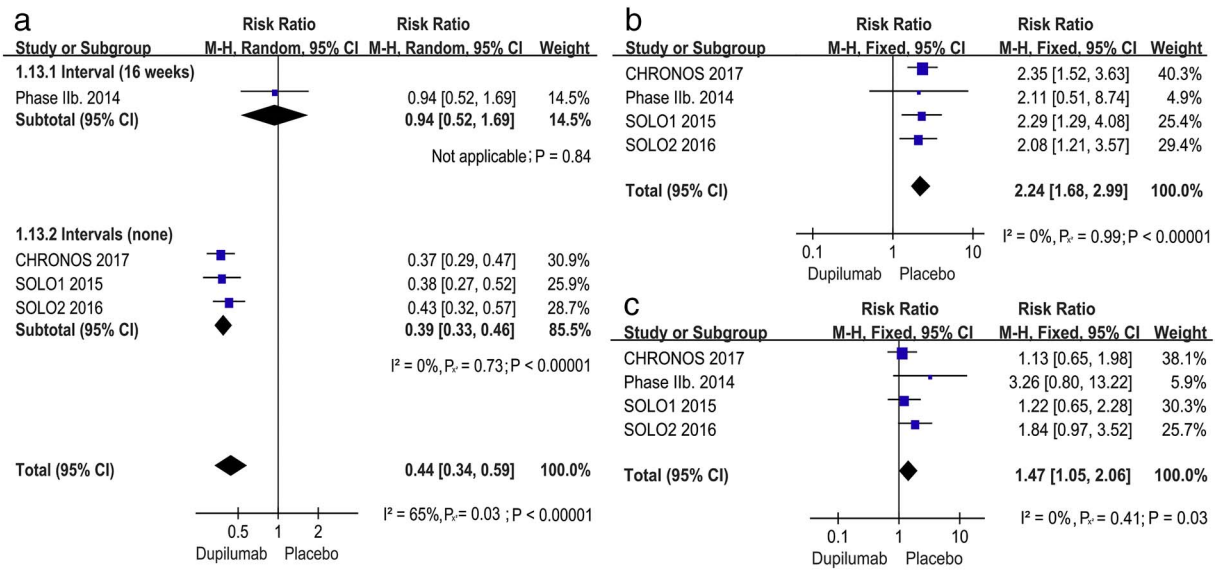

Fig. 6s. Meta-analysis (pooled data) of studies of other adverse effects in patients treated with dupilumab or a placebo. (a) Exacerbation of atopic dermatitis; (b) injection-site reaction; (c) headache. CI, confidence interval.

p = 0.14, pχ2 = 0.42, I^2 = 0%; Fig. 5sd). A sensitivity analysis found similar results in both effects models (data not shown).

3.7. Other adverse events

We also pooled the data on the exacerbation of AD and performed a subgroup analysis according to the interval between the end of each study and the end of assessment. The Phase IIb trial was included in the subgroup in which the interval was 16 weeks. In this subgroup, the exacerbation of AD did not differ in the dupilumab and placebo groups (54/318 = 17.0% and 11/61 = 18.0%, respectively; RR 0.94, 95% CI 0.52–1.69, p = 0.84; Fig. 6sa). The SOLO1, SOLO2, and CHRONOS trials were included in the second subgroup, in which there were no interval between the end of each study and the end of assessment. In this subgroup, the incidence of AD exacerbation was lower in the dupilumab group than in the placebo group (193/1345 = 14.3% and 292/771 = 37.9%, respectively; RR 0.39, 95% CI 0.33–0.46, $p < 0.00001$, pχ2 = 0.73, I^2 = 0%; Fig. 6sa). The total combined results of the four studies demonstrated that dupilumab significantly reduced the exacerbation of AD relative to that in the placebo-treated group (247/1663 = 14.9% and 303/832 = 36.4%, respectively; RR 0.44, 95% CI 0.34–0.59, $p < 00001$, pχ2 = 0.03, I^2 = 65%; Fig. 6sa). A sensitivity analysis found similar results in both effects models (data not shown).

The four trials (SOLO1, SOLO2, CHRONOS, and the Phase IIb trial) with 2495 participants reported an injection-site reaction in 221/1663 (13.2%) of the participants treated with dupilumab and 54/832 (6.5%) of the participants treated with a placebo (RR 2.24, 95% CI 1.68–2.99 $p < 0.0001$, pχ2 = 0.99, I^2 = 0%; Fig. 6sb). A sensitivity analysis found similar results in both effects models (data not shown). The four trials (SOLO1, SOLO2, CHRONOS, and the Phase IIb trial) also reported headache in 136/1663 (8.2%) of the participants treated with dupilumab and 45/832 (5.4%) of the participants treated with a placebo (RR 1.47, 95% CI 1.05–2.06, $p = 0.03$, pχ2 = 0.41, I^2 = 0%; Fig. 6sc). A sensitivity analysis found similar results in both effects models (data not shown).

Low-incidence adverse effects and those reported in only one study are listed in Table 2. Asthma ($p = 0.003$) and back pain ($p = 0.05$) were reported less frequently in the dupilumab-treated group than in the placebo-treated groups, whereas the incidences of the other adverse effects were similar in the two groups.

4. Discussion

Previous therapies for adult patients with moderate-to-severe AD have had limited efficacy, with many adverse effects and an increased risk of infection [6,8,9]. Dupilumab, a new therapy, has shown significantly reduced symptoms and signs in previous studies [6,13,14,18], but its adverse effects remain controversial [6,13,14].

We previously considered that secondary infections were the most worrying side effect of dupilumab. However, we found that dupilumab reduced the risk of skin infection in adults with moderate-to-severe AD. This result could be attributable to the fact that IL-4 and IL-13 suppress the production of lipids and the differentiation of keratinocytes, disrupting the epidermal barrier and increasing the risk of skin infection. However, this process is inhibited by dupilumab [20–22]. We also found that conjunctivitis occurred more frequently in the dupilumab-treated groups than in the placebo-treated groups. In contrast to early studies of dupilumab, the incidence of conjunctivitis was similar in the dupilumab-treated and placebo-treated patients with asthma [15] or chronic sinusitis with nasal polyposis [23], which suggests that dupilumab exerts different mechanistic effects on asthma, and chronic sinusitis than on AD. Further studies are required to explain this observation. The incidence of other infections, such as herpes virus infection, upper respiratory tract infection, nasopharyngitis, and urinary tract infection, was similar in the two groups, suggesting that dupilumab does not directly affect the ability of the normal immune system to protect against the invasion of microorganisms. Heterogeneity was observed in the entire-group analysis of upper respiratory tract infections, but in the subgroup in which there was no interval between the end of the experiment and the date of assessment, there was 0% heterogeneity (I^2), so we consider that the Phase IIb trial [13] was the main source of heterogeneity. A subgroup analysis of dupilumab (300 mg per week) showed a slightly reduction in heterogeneity from 71% to 49% (data not shown). Therefore, we suspect that the heterogeneity in this meta-analysis was much more closely related to the interval between the end of the trial and the end of the assessment, as well as to the unspecified method of AD diagnosis, than to differences in the doses of dupilumab given. A sensitivity analysis was undertaken by exchanging the two effects models and showed that our results are robust.

We also found that dupilumab protected adults with moderate-to-severe AD from exacerbation ($p < 0.00001$, I^2 = 65%). This was not unexpected because dupilumab was designed to treat AD, and in

Table 2
Infrequent adverse events and those reported in only one study.

Events	Dupilumab group n (incidence)	Placebo group n (incidence)	RR	95%CI	*p* value
Bacterial infection	25(7.9%)	7(11.5%)	0.69	0.31–1.51	0.35
Viral infection	17(5.3%)	6(9.8%)	0.54	0.22–1.32	0.18
Dermatitis and eczama	63(19.8%)	12(19.7%)	1.01	0.58–1.75	0.98
Nausea and vomiting symptoms	10(3.1%)	4(6.6%)	0.48	0.16–1.48	0.20
Musculoskeletal and connective tissue pain and disorder	15(4.7%)	5(8.2%)	0.58	0.22–1.52	0.27
Back pain	9(2.8%)	5(8.2%)	0.35	0.12–0.99	0.05
Sinusitis	23(1.7%)	15(1.9%)	0.68	0.10–4.68	0.70
Influenza	19(1.4%)	19(2.5%)	0.68	0.36–1.28	0.23
Asthma	7(1.6%)	19(6.0%)	0.27	0.12–0.64	0.003

RR, risk ratio; CI, confidence interval.

previous trials, it improved almost all the signs and symptoms of AD [6,24,13,14]. In this meta-analysis, we observed high heterogeneity in the entire group, but in the subgroup in which there was no interval between the end of the experiment and the end of assessment, heterogeneity (I^2) was 0%, so we consider that the Phase IIb trial [13] was the main source of heterogeneity. A subgroup analysis of 300 mg of dupilumab given every 2 weeks showed no difference in heterogeneity (data not shown). We suspect that the interval between the end of trial and the end of assessment, as well as the unspecified method of AD diagnosis, was the source of the observed heterogeneity, rather than the differences in the doses given. A sensitivity analysis was undertaken by exchanging the two effects models and showed that our results are robust.

Injection-site reactions were not only occurred more frequently in the dupilumab groups in our study, but also in a study of dupilumab in patients suffering chronic sinusitis with nasal polyposis [23]. Therefore, we suspect that dupilumab aggravates the reaction at the injection site, although the mechanism is still unclear. Further studies are required to explore this phenomenon.

Each individual study included in this research reported a similar incidence of headache in the dupilumab- groups and placebo-treated groups [6,24,13,14], but interestingly, the pooled data demonstrated a slightly higher incidence of headache in the dupilumab-treated group. This is a new finding and warrants further research.

Meta-analyses always play an important role in assessing treatment effects related to controversial items. To our knowledge, this is the first meta-analysis of the adverse effects of dupilumab in the treatment of moderate-to-severe AD, and resolves many of the controversies around these effects that have arisen from the discrepant results of many trials. A unique strength of this meta-analysis is that all the studies were placebo-controlled RCTs. Another strength was the low heterogeneity in most outcomes between the individual studies.

Our study had several limitations. First, the analysis included trials C4 and CHRONOS, which were steroid-combining studies, so any skin infections may have been affected by the use of steroids, compared with their spontaneous occurrence in M4A, M4B, M12, Phase IIb trial, SOLO 1, and SOLO 2 [6,24,13,14]. However, a sensitivity analysis that excluded C4 and CHRONOS showed similar results to the analysis from which they were not excluded. Second, only eight clinical trials were included in the study and all of them were funded by the pharmaceutical industry.

The signals of IL-4 and IL-13 can be inhibited by dupilumab, a monoclonal antibody aimed at IL-4 receptor alpha that has been proven effective in patients suffering from chronic sinusitis with nasal polyposis and asthma with elevated eosinophil levels, as well as moderate-to-severe AD [6,24,13,23,14,18,15,16]. In this study, we have found dupilumab to have few side effects, even decreasing the risk of skin infection and the exacerbation of AD in adults with moderate-to-severe AD. In summary, dupilumab possesses many significant advantages over current therapies for patients with moderate-to-severe AD. However, the long-term safety and effect on the most commonly affected population, children, need to be explored in future clinical research.

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Table S1: Details of inclusion criteria of included studies.

Inclusion Criterion	Study							
	M4A	M4B	M12	C4	Phase IIb	SOLO 1	SOLO 2	CHORONOS
Male/female patients≥18 years	√	√	√	√	√	√	√	√
Diagnosis of AD for ≥3 years	√	√	√	√	√	√	√	√
EASI score ≥12	√	√	—	—	—	—	—	—
EASI score ≥16	—	—	√	—	√	√	√	√
IGA score ≥3	√	√	√	√	√	√	√	√
BSA affected by AD ≥10%	—	√	√	√	√	√	√	√
BSA affected by AD ≥15%	√	—	—	—	—	—	—	—
Inadequate response to treatment with topical medication within 3 months	√	√	—	√	—	—	—	—
Inadequate response to treatment with topical medication within 6 months	—	—	—	—	√	√	√	√

AD, atopic dermatitis; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; BSA, body surface area; inadequate response

represented failure to achieve and maintain remission or a low disease activity state (comparable to Investigator's Global Assessment [IGA] 0 [clear] to 2 [mild]) despite treatment with a daily regimen of topical corticosteroids (TCS) of medium to high potency (with or without topical calcineurin inhibitors [TCI] as appropriate), applied for at least 28 days or for the maximum duration recommended by the product prescribing information (eg, 14 days for super-potent TCS), whichever was shorter.