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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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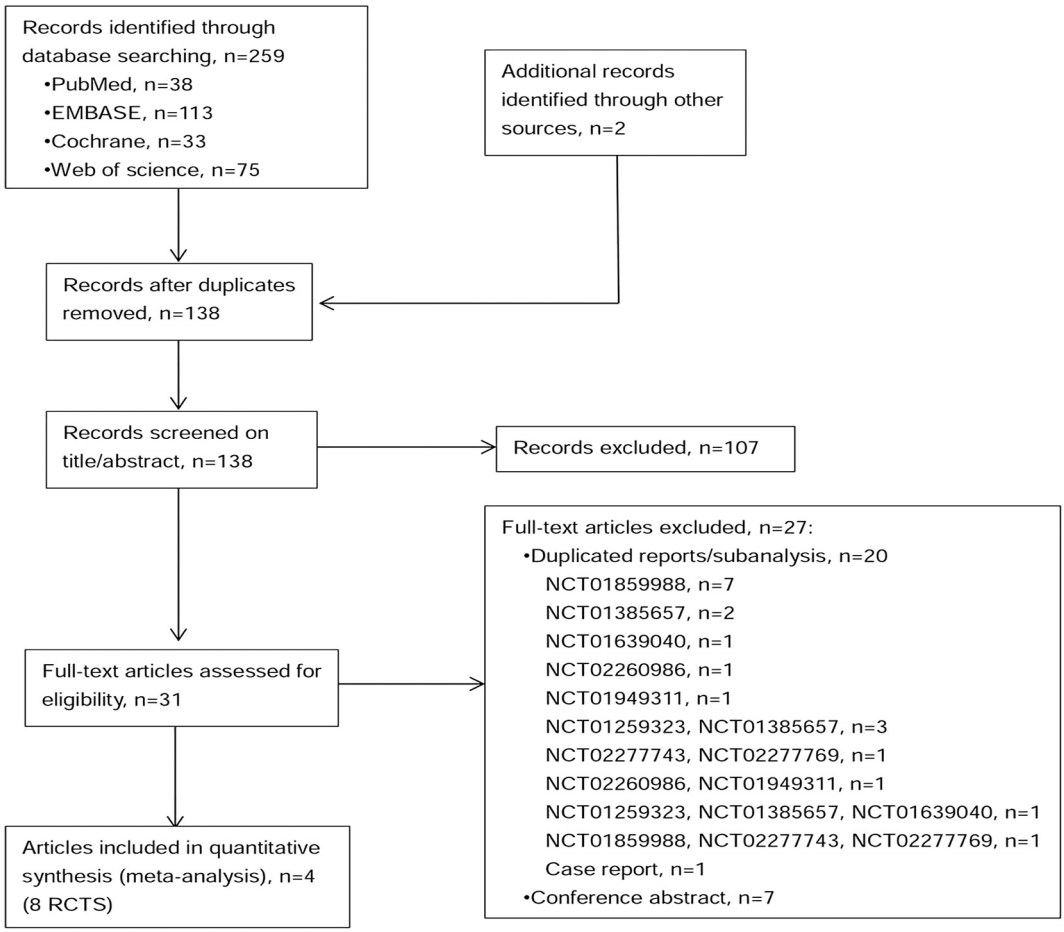

Fig. 1. Flow diagram of study selection. NCT, national clinical trial.

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