Journal of Dermatological Science xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Journal of Dermatological Science

journal homepage: www.jdsjournal.com

Dupilumab treatment in moderate-to-severe atopic dermatitis: A systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 24 November 2017
Received in revised form 28 December 2017
Accepted 29 January 2018

Keywords:
Atopic dermatitis
Dupilumab
Meta-analysis
Systematic review

ABSTRACT

Background: Dupilumab, a fully human monoclonal antibody against the interleukin-4-receptor α subunit, has been developed and used in clinical trials to treat atopic dermatitis (AD).
Objective: We aimed to assess the overall efficacy and safety of dupilumab treatment in AD.
Methods: PubMed, Embase, Cochrane library databases, and the Chinese Biological Medicine (CBM) published up to September 2017 were searched. All randomized controlled trials (RCTs) of dupilumab treatment on adult patients with AD were included. Fixed- or random-effects models were used to calculate pooled standard mean differences or relative risks (SMD or RR, respectively).
Results: Six trials involving 2447 patients were identified. Pooled analysis revealed significant improvements in Eczema Area and Severity Index (EASI) score (SMD = −0.89, 95% CI: −1.0 to −0.78), percentage of body surface area (BSA) (SMD = −0.83, 95% CI: −0.90 to −0.75), pruritus numeric rating scale (NRS) scores (SMD = −0.81, 95% CI: −0.96 to −0.66), and Dermatology Life Quality Index (DLQI) scores (SMD = −0.78, 95% CI: −0.89 to −0.66). Dupilumab treatment was also associated with a significant increase in the proportion of patients achieving Investigator's Global Assessment (IGA) response (RR = 3.82; 95% CI: 3.23 to 4.51) and a similar incidence of adverse events (RR = 1.0; 95% CI: 0.96 to 1.04).
Conclusions: Our analysis provided evidence that dupilumab had an acceptable safety profile and resulted in clinically relevant improvements in signs and symptoms of AD. Dose regimens of 300 mg qw and q2 w seemed to have similar benefits. Further long-term trials are required for confirmation.

1. Introduction

Atopic dermatitis (AD) is a common chronic skin condition with a worldwide prevalence of 1 to 20% in adults, approximately 20% of patients have moderate-to-severe disease [1–4]. It is characterized by the T-helper (Th)-2-mediated skin inflammation, epidermal barrier dysfunction and increased Staphylococcus aureus colonization [5,6]. Despite the high prevalence of AD, treatments are limited, especially for patients with moderate to severe disease, only 3 (depending on country) systemic therapeutic options approved for patients with severe disease who are not controlled by topical medications, including oral corticosteroids, oral cyclosporin, and UVA/narrow-band UVB phototherapy [7]. However, these treatments often have limited efficacy and unfavorable safety. Thus, there remains a significant need for more effective and safe therapies.

Immunologically, upregulation of the Th2 immune response seems to play a crucial role in the pathogenesis of AD. The key Th2 cell cytokines of interleukin-4(IL-4) and IL-13 are key drivers of atopic or allergic diseases such as atopic dermatitis and asthma [8,9]. Dupilumab, a fully human monoclonal antibody, binds specifically to the shared α chain subunit of the interleukin-4 and interleukin-13 receptors, thereby blocking the signaling of both IL-4 and IL-13. Dupilumab is a novel therapeutic approach for atopic/allergic diseases such as atopic dermatitis and asthma [10]. Several early-phase and phase 3 randomized, placebo-controlled studies (RCTs) have shown convincing efficacy in adults with moderate to severe AD. However, the evidence is inadequate for drawing robust conclusions, as the sample sizes of these studies are varied and their dosages are inconsistent. We therefore conducted a meta-analysis to assess the robustness of the results from the available trials and determine the optimal dosage.

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https://doi.org/10.1016/j.jdermsci.2018.01.016
0923-1811/

2. Methods

2.1. Literature searches and study selection

We carried out a systematic literature review search using the PubMed, Embase, the Cochrane Library, and the Chinese Biological Medicine (CBM), published up to September 5, 2017, using the search terms "dupilumab" and "atopic dermatitis" or "atopic eczema". No language restrictions were applied. In addition, the relevant review articles and their references were also screened. Two authors independently selected trials for inclusion. Any discrepancy was resolved by discussion and consensus.

2.2. Inclusion and exclusion criteria

We included all randomized clinical trials on dupilumab administration to treat AD based on the following inclusion criteria: 1) patients were adults (age ≥18 years) with moderate-to-severe AD at least 3 years before the screening visit; Investigator's Global Assessment (IGA, scores range from 0 to 4, with higher scores indicating more severe disease) score of 3 (moderate) or 4 (severe); Eczema Area and Severity Index (EASI) score 12 or higher at screening and baseline visits; body surface area (BSA) affected of more than 10%; documented history within 6 months before screening of inadequate response to topical treatments. Moderate-to-severe disease was defined based on: IGA scores of 3 or higher at screening and baseline, consistent with the categories of moderate (IGA = 3) and severe (IGA = 4); and EASI scores of 12 or higher at screening and 16 or higher at baseline; 2) double-blind, RCTs; 3) As 300 mg once weekly (qw) and 300 mg every 2 weeks (q2w) were the most common dosagees among the studies, we only analyzed the effects of dupilumab 300 mg qw and q2 w in this meta-analysis; 4) reporting the following outcomes: EASI, IGA, the pruritus numeric rating scale (NRS), percent BSA affected with AD, Dermatology Life Quality Index (DLQI) and adverse events. Abstracts of trials were excluded because the data could not be fully analyzed. We also excluded non-randomized, observational, cohort, case-control and non-blinded clinical studies.

2.3. Data extraction and quality assessment

Using a standardized data extraction form, we extracted data concerning reference of study, publication year, study design, patient characteristics, selection criteria, dupilumab dosages used, numbers of participating subjects, duration of study periods, and outcome measures. Efficacy outcomes were improvement in EASI from baseline, the proportion of patients achieving IGA response from baseline (IGA = 0 [clear] or IGA = 1 [almost clear]), the percentage reduction in the BSA, percentage change from baseline in peak NRS scores, DLQI. Safety outcome included adverse events. The Cochrane Collaboration's domains which included adequate sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data, selective reporting, and other bias, were used to assess the risk of bias [11].

2.4. Statistical analyses

Data collected were pooled to calculate summary estimates. We calculated standardized mean differences (SMD) for continuous data and relative risk (RR) for dichotomous outcomes. Heterogeneity was calculated using I^2 statistic and the chi-squared test. I^2 value of 50% was considered as a significant heterogeneity [12]. The fixed-effects model was used if no heterogeneity was present, and random-effects were used for analyses with high heterogeneity ($I^2 > 50\%$) [13]. As a priori subgroup analysis, we explored the influence of different doses. Meta-regression was performed to explore potential sources of heterogeneity. Publication bias was tested using funnel plot with the Begg's and Egger's tests [14]. Review Manager (Version 5.3, The Cochrane Collaboration) and Stata (Version 12.0, Stata Corporation, USA) were used for data management and statistical analyses, and statistical significance was set at 0.05 for the I^2 test for heterogeneity and the Z-test for RR.

3. Results

3.1. Search results

The searches retrieved 288 potential relevant publications (Fig. 1). Among these, we identified 214 articles of which 20 on RCTs compared dupilumab versus placebo. 7 potentially relevant RCTs which had been published as an abstract only were excluded owing to data unavailable. Three articles were excluded because they were a quality-of-life study or patient burden or patient-reported outcomes on RCTs that were already included [15–17]. Ultimately, six clinical trials published in four articles were included in the analysis [18–21].

3.2. Study characteristics

The six trials that included a total of 2447 (1547/900) patients were enrolled. Detailed characteristics of included studies are shown in Table 1. The duration of treatment ranged from 4 to 52 weeks. All trials administered drugs used subcutaneous injection. A single intervention group dupilumab 300 mg qw was presented in one trial [18], while the remaining trials presented two interventions (dupilumab 300 mg qw and 300 mg q2w) [19–21]. The treatment groups received dupilumab monotherapy in four trials [18,20], while in the rest trials received combination therapy with topical corticosteroids [18,21].

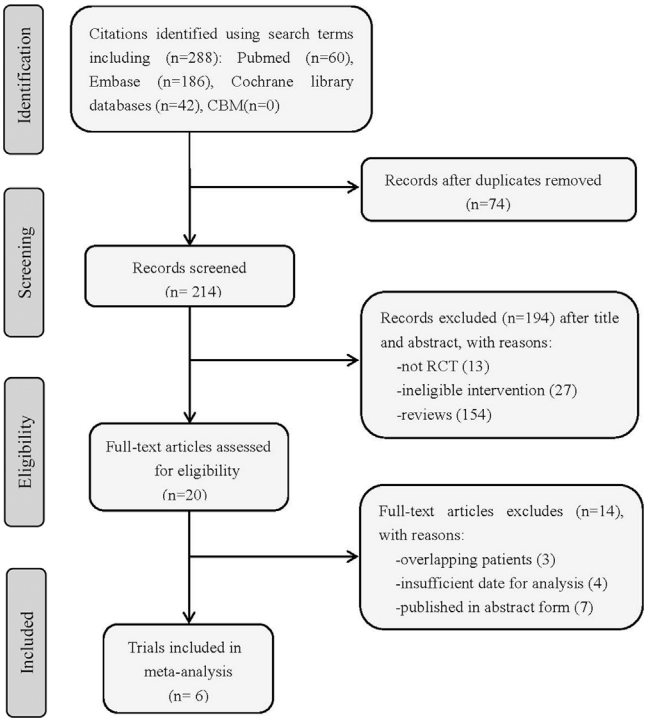

Fig. 1. Flow chart of identification of studies included.

Please cite this article in press as: F.-P. Wang, et al., Dupilumab treatment in moderate-to-severe atopic dermatitis: A systematic review and meta-analysis, J Dermatol Sci (2018), https://doi.org/10.1016/j.jdermsci.2018.01.016