Efficacy and safety of nemolizumab for adult atopic dermatitis treatment: A meta-analysis of randomized clinical trials

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To the Editor:

Nemolizumab is a recently developed human monoclonal antibody targeting the interleukin-31 receptor (IL-31R). [1-3] In this meta-analysis, we aimed to explore the efficacy and safety of nemolizumab for the treatment of atopic dermatitis (AD).

On 2020 Oct 15, we conducted a systematic search of Embase, Medline, PubMed, and Web of Science databases for randomized controlled trials (RCTs) using the search terms "nemolizumab" and "atopic dermatitis" or "eczema". A total of 4 randomized, double-blinded, and placebo-controlled clinical trials (one phase I, two phase II, and one phase III) were included in our meta-analysis enrolled 729 patients diagnosed with moderate-to-severe AD(Supplementary Figure 1). [4-7] In the phase I trial, nemolizumab doses of 0.3, 1.0, and 3.0 mg/kg were administered to patients. The two later phase II trials, were independent trials with identical clinical design, to evaluate the consistency of nemolizumab safety and efficacy profiles, where patients received nemolizumab 0.1 mg/kg once 4 every weeks (0.1 mg/kg q4w), 0.5 mg/kg once 4 every weeks (0.5 mg/kg q4w), 2.0 mg/kg once every 4 weeks (2.0 mg/kg q4w), 2.0 mg/kg once every 8 weeks (2.0 mg/kg q8w), 10 mg every 4 weeks (10mg q4w), 30 mg every 4 weeks (30mg q4w), and 90 mg every 4 weeks (90mg q4w). In the phase III trial, the treatment group received a 60 mg dose of nemolizumab(Supplementary Table 1). All patients were adults, had EASI scores > 10 or SCORAD scores > 25, and a diagnosis of AD for > 1 year. All studies included in this systematic review exhibited a low risk of bias using the Cochrane collaboration tool, and funnel plot and Egger test analyses showed there was no significant publication bias(Supplementary Figure 2). Furthermore, the quality of each RCT was estimated using the Jadad scale, and all 4 RCTs were found to be of high quality(Supplementary Table 2).

A pooled analysis of all 4 RCTs indicated that nemolizumab treatment resulted in significant improvements in efficacy and safety based on various clinical indices. As shown in Figure 1, treatment with nemolizumab led to significantly decreased EASI scores compared with the placebo group (SMD = -0.31; 95% CI = -0.45 to -0.17; p < 0.001). A meta-analysis of the two phase II RCTs suggested a significant reduction of SCORAD score in the nemolizumab-treated group compared with the placebo group (SMD = -0.56; 95% CI = -1.05 to -0.07; p = 0.025). A reduction in pruritus VAS indicates relief for patients and a significant improvement in quality of life. In the pooled nemolizumab-treated group the SMD of pruritus VAS was -3.95 (95% CI -5.56 to -2.37; p < 0.001). The results showed a significant decrease in the SMD BSA score in the nemolizumab group compared with the control group (SMD = -0.19; 95% CI = -0.35 to -0.03; p = 0.019). There was a significant difference in the percentage of IGA response in the nemolizumab treatment group compared with the placebo group (RR = 0.81; 95% CI = -0.65 to -1.01; p = 0.064). In addition to the overall efficacy of nemolizumab, the dose-dependent efficacy of nemolizumab treatment was also investigated in this systematic review. Doses of 60 mg q4w, 3.0 mg/kg q4w, and 2.0 mg/kg q4w resulted in the most effective clinical improvement; while doses of 30 mg q4w and 90 mg q4w were less effective, but led to significant improvements; and doses of 0.1 mg/kg q4w, 0.5 mg/kg q4w and 10mg q4w resulted in barely significant improvements. Galbraith radial plot confirmed that nemolizumab regimens with doses (0.1 mg/kg q4w, 0.5 mg/kg q4w and 2.0 mg/kg q8w) were not as safe as those with doses (0.3 mg/kg q4w and 60 mg q4w) (Supplementary Figure 3). Based on the results of efficacy and safety, the optimal dose of nemolizumab for the treatment of patients with moderate-to-severe AD is likely to be 60mg q4w.

Overall, the results of the included RCTs demonstrate that nemolizumab has an acceptable safety profile, as there was no significant difference in adverse events (AEs) or SAEs compared with the placebo group. The rate of AEs did not differ significantly among the four trials (RR = 0.84; 95% CI 0.69 to 1.01; p = 0.069). Furthermore, the rate of SAE did not differ significantly between the placebo control and nemolizumab groups (RR = 1.27; 95% CI 0.97 to1.66; p = 0.079) (Supplementary Figure 4).

Our findings clearly demonstrate that nemolizumab is a promising anti-AD medication, and provide evidence that it can be used to treat AD efficiently and specifically. Further studies should be conducted to assess the long-term stability, efficacy, and safety of nemolizumab for treatment of AD.

Conflicts of Interest: None declared.

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Figure legends

Fig 1. Forest plot of the efficacy of nemolizumab treatment in the 4 RCTs based on the four clinical outcomes: (A) Eczema Area and Severity Index (EASI) score; (B) Scoring Atopic Dermatitis (SCORAD) score; (C) pruritus visual analogue scale (VAS); (D) Body surface area (BSA) score. Horizontal lines stand for 95%Cls of the standardized mean difference(SMD) estimates. Green dots represent the SMD and diamonds represent the meta-analysis summary effect estimate.