

Original Research Article

Assessment of the efficacy and safety of dupilumab combined with cyclosporine A in patients with atopic dermatitis

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Abstract

Purpose: To assess the efficacy and safety of dupilumab combined with cyclosporine A in patients with atopic dermatitis.

Methods: This retrospective study enrolled 100 patients with atopic dermatitis who received treatment at Beijing Luhe Hospital between November 2020 and November 2022. The patients were randomly divided into two groups, namely, treatment group and comparison group, with 50 cases in each group. Comparison group received cyclosporine A, while the treatment group received dupilumab in addition to cyclosporine A. The various efficacy scores and adverse reactions between the two groups were recorded and compared.

Results: After treatment, skin lesion area and severity, EASI score, NRS score, SCORAD score, POEM score and DLQI score in the treatment group were significantly lower than those in the comparison group ($p < 0.05$).

Conclusion: The combination of dupilumab and cyclosporine A significantly alleviates the symptoms of acne and pruritis, as well as reduce the area of skin lesions in patients with atopic dermatitis. This treatment also enhances the quality of life of the patients. However, further but larger clinical trials are required prior to adoption of this combination treatment in clinical practice.

Keywords: Dupilumab, Cyclosporine A, Atopic dermatitis, Quality of life, Drug allergy

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INTRODUCTION

Atopic Dermatitis (AD) is a chronic and recurrent skin disease characterized by itchy, dry skin and eczema [1]. The etiology of AD is multifaceted and encompasses genetic, immunological, and environmental factors. Of these, immunological dysfunction is presently regarded as the primary underlying factor in the pathogenesis of AD [2].

At the onset of AD which typically manifests in early childhood, the majority of cases are resolved by the age of 16, while a subset may persist into adulthood.

The clinical presentation of AD is characterized by intense pruritus, recurrent eczematoid lesions, and a variable disease course, which is underpinned by the interplay between immune dysregulation and skin barrier dysfunction. [3].

AD has an obvious genetic tendency, and it is not only manifested as skin symptoms and a variety of allergic comorbidities, but is also likely to be a systemic disease [4,5]. Cyclosporine is a frequently employed immunosuppressant in the field of dermatology, capable of impeding T lymphocyte-mediated immune responses and serving as a viable treatment option for a diverse range of autoimmune and chronic inflammatory cutaneous conditions [6]. Superoxidediamutase is the most important antioxidant enzyme in the body, and malondialdehyde is an important decomposition product of lipid peroxidation [7]. Studies worldwide have found that the imbalance of oxidative and antioxidant systems plays a role in the pathogenesis of AD [8]. Prior to AD treatment, symptomatic treatment aimed to relieve clinical symptoms and reduce translucency and aggravating factors [9]. For patients treated locally or not under optimal control, available systemic drugs such as cyclosporine, azathioprine, methotrexate, mycophenolate mofetil and interferon have potential long-term side effects and risks [10].

Recently, a variety of biological agents and small molecule agents that have been continuously developed provide new direction for the treatment of AD. Dupilumab is the first biological agent targeting IL-4Ra, which plays an anti-allergic role by blocking the Th2-type inflammatory pathway via inhibition of the receptor of IL-4, the core and key driver of Th2 type inflammation [11]. At present, the drug has been approved for the treatment of moderate-to-severe AD in many countries, and has good efficacy in the treatment of other allergic diseases without obvious safety problems [12]. With the development of dupilumab as a new direction in allergy treatment, patients have greater options for allergy treatment [13]. Given the limited marketing period of dupilumab in some parts of the world, the aim of this study to further investigate the drug with a view to availing clinicians broader information that would to mitigate the potential for drug-related adverse events, thereby optimizing the drug's therapeutic benefits.

METHODS

Patients

A total of 100 AD patients who were treated in Beijing Luhe Hospital from November 2020 to November 2022 were enrolled in this retrospective study, and randomly divided into treatment group and comparison group with 50 cases in each group.

Ethical approval

This study was approved by the ethics committee of Beijing Luhe Hospital, Capital Medical University. Signed written informed consents were obtained from all participants prior to commencement of the study. The study complied with the guidelines of Declaration of Helsinki [14].

Diagnostic/inclusion criteria

The diagnostic criteria for AD [15]: (1) The patient's clinical manifestations were symmetrical eczema, and the duration of eczema was greater than 6 months; (2) Laboratory examination of the patient showed that total serum IgE > 1000 IU/ml.

Inclusion and exclusion criteria

Inclusion criteria included the following: (i) patients above 12 years old with no gender difference; (ii) moderate to severe AD with IGA score of 3 and EASI score of 16; (iii) The patient's compliance was good, the severity of skin lesions was moderate to severe, and the scoring of atopic dermatitis (SCORAD) was ≥ 25 .

Exclusion criteria: (i) patients during lactation or pregnancy; (ii) comorbid diseases that interfere with the evaluation of the study results; (iii) rheumatoid patients with abnormal renal function, uncontrolled hypertension, or malignancy.

Treatments

All patients were given oral cyclosporine capsules (neosandimine) at an initial dose of 2.5 mg/kg daily. If the patient's itch was not relieved during the evaluation, the dose was increased by 0.5 mg/kg daily, subject to a maximum dose of 5 mg/kg daily. The patients were treated with glucocorticoid cream for 8 weeks. The administration of dupilumab to the treatment group was in addition to the treatment (cyclosporine A) given to the comparison group. Patients in the treatment group received 600 mg subcutaneous injections of dupilumab (Darbitux, Sanofi, approval no. S20200017, 300 mg per prefilled syringe) at week 0, followed by 300mg subcutaneous injections of dupilumab every 2 weeks for 8 weeks.

Evaluation of parameters/indices

Severity of clinical symptoms

AD (SCORAD) score [16] ranged from 0 to 103. According to the SCORAD score, the disease severity of AD patients can be divided into mild,

moderate and severe, with scores of 0 - 24 points, 25 - 50 points and > 50 points respectively. The EASI scores range from 0 to 72.

Eczema area and severity index (EASI)

At the 8th week after treatment, the percentage of improvement in the EASI score of the patient when compared with the baseline level was calculated [17].

Degree of pruritus

The NRS is a patient's rating of the worst degree of pruritus experienced in the previous 24 h, on a scale of 0 to 10, with higher scores increasing the severity of pruritus.

Patient -oriented eczema measure (POEM)

POEM is a comprehensive assessment of seven symptoms and their severity reported by the patient in the past week. The maximum score of the POEM score is 28, with higher scores indicating more severe clinical symptoms [18].

Dermatology life quality index (DLQI)

DLQI score measure in the past week skin lesions in patients with influence on the quality of life reported by the patients. Scores on the DLQI ranged from 0 to 30, with higher scores indicating a greater effect of the patient's illness on quality of life [19].

Statistical analysis

Subjects who did not receive complete treatment in this study were not statistically analyzed. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc, Cary, NC, USA). Mean, standard deviation (SD), median, minimum and maximum values were used to describe the measurement data. Frequency was used to describe count data or graded data. The normality of the parameter statistics ($\alpha = 0.10$) was assessed using Kolmogorov-Smirnov test. Changes in indicators within groups were evaluated by paired Student's t-test, while

comparisons of baseline data and changes in indicators between groups were assessed using Student's t-test. $P < 0.05$ was considered indicative of a statistically significant difference.

RESULTS

Patient's general data/profile

There were no significant differences in Mean age, Gender, Age of onset, and Duration of disease data between the two groups ($p > 0.05$).

Severity of clinical symptoms and related scores

Before treatment, there were no significant changes in relevant scores, skin lesion area and severity between the two groups ($P > 0.05$). After treatment, the skin lesion area and severity, EASI score, NRS score, SCORAD score, POEM score and DLQI score in the treatment group were significantly lower than those in the comparison group, and the difference was statistically significant ($p < 0.05$; Figure 1).

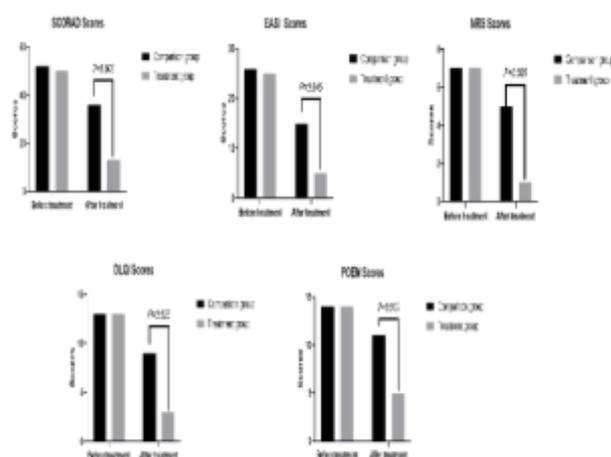


Figure 1: Comparison of severity of clinical symptoms and related scores. After dupilumab/cyclosporine A combination treatment, EASI score, NRS score, SCORAD score, POEM score and DLQI score in the treatment group were significantly lower than those in the comparison group ($p < 0.05$).

Table 1: Comparison of general patient data/profile between the two groups (mean \pm SD, n = 50)

Group	Mean age (years)	Gender (male/female)	Age of onset (years)	Duration of disease (years)
Comparison	44.63 \pm 1.32	33/17	32.31 \pm 2.51	12.34 \pm 1.25
Treatment	44.62 \pm 2.31	32/16	31.30 \pm 3.52	11.33 \pm 1.24
χ^2/t	0.037	0.044	0.025	0.009
P-value	0.970	0.834	0.980	0.993

DISCUSSION

Atopic dermatitis (AD) is a common chronic, pruritic and recurrent skin disease, which is manifested as pleomorphic rash, mossy papules, dry skin, and severe coagulation and itching. In severe cases, it lead to sleep difficulties and cause huge physical and psychological burden to patients [20]. Traditional AD treatment schemes mainly include basic moisturizing therapy, local topical drug treatment, systemic drug treatment and traditional Chinese medicine treatment, but some patients, especially those with moderate to severe AD, do not respond to the above treatments [21].

Dupilumab, when combined with cyclosporine A, significantly reduces the symptoms of acne and itching and the area of skin lesions, and improves quality of life in AD patients. The pharmacological mechanisms underlying the effectiveness of dupilumab in treating atopic dermatitis involve the inhibition of key cytokines, namely, IL-4 and IL-13, which play a critical role in the pathogenesis of allergic diseases. These cytokines are primarily produced by Th2 cells, type II innate immune cells, follicular helper T cells, and other cell types, and are also secreted by effector cells such as mast cells, basophils, and eosinophils. After binding to their receptors, IL-4 and IL-13 are involved in regulating the expression of inflammatory genes through JAK-STAT pathway. IL-4Ra is the shared receptor component of IL-4 and IL-13. Dupilumab inhibits the downstream signaling of IL-4 and IL-13 by specifically binding to I-4Ra, leading to the down-regulation of the JAK-STAT pathway signaling, blocking the Th2-type inflammatory pathway, and reducing the pathological response of Th2 type inflammation.

All the patients in this study received 600 mg of subcutaneous dupilumab in two doses, followed by 300 mg every 2 weeks. Based on the results of multiple phase II clinical trials, the efficacy and safety of dupilumab dose regimens of 300mg weekly and 300mg biweekly are similar, so 300mg bi-weekly after the first injection is the most cost-effective dose regimen [22]. The pharmacokinetic results of phase II clinical trials in China were compared with those of subjects in other countries, suggesting that changes in pharmacokinetic parameters amongst different populations may be related to differences in body weight [23]. It has been reported that although body weight has an effect on pharmacokinetic parameters, it is not necessary to adjust the dose of dupilumab according to body weight, so we did not adjust the dose of dupilumab based on the

difference in body weight of patients in this study [22,23].

The area and severity of skin lesions gradually decreased with dupilumab dose, with decreasing trends in the EASI, IGA, and SCORAD scores. NRS decreased during dupilumab treatment, and the difference was statistically significant. This demonstrates the efficacy of dupilumab in the treatment of moderate to severe AD. Clinical trials and real-world data to observe dupilumab's long-term efficacy are particularly important for AD patients with chronic and recurrent episodes. Considering the population heterogeneity of AD, reviewed the reports on the application of dupilumab in the treatment of AD in Asians, and found that the clinical efficacy results of dupilumab in Japan and other countries were significant [24]. A real-world systematic review of the efficacy and risk of adverse events of dupilumab in AD demonstrated a weighted mean reduction of 69.6 % in the EASI score after 16 weeks of dupilumab treatment. Overall, the efficacy of dupilumab in the treatment of moderate-to-severe AD was significant.

The present study revealed that the typical adverse effects associated with dupilumab therapy for atopic dermatitis comprise injection site reactions, conjunctivitis, and upper respiratory tract infections. These adverse effects are typically of mild to moderate intensity and may resolve spontaneously or with intervention. Furthermore, they seldom necessitate discontinuation of the drug. According to a cohort study, patients with a history of allergic conjunctivitis have a higher risk of this adverse reaction during treatment. None of the patients in the study had a history of allergic conjunctivitis, which may be due to the high heterogeneity of the incidence of allergic conjunctivitis in different countries and regions.

Dupilumab is a fully human monoclonal antibody directed against IL-4Ra and has a higher safety profile when compared with glucocorticoids and immunosuppressants [9]. The drug's adverse reactions vary depending on the disease being treated. As per the US FDA-approved drug instructions, the common adverse reactions comprise injection site reactions, headaches, and other infections caused by simple pox viruses. A 3-year multicenter open-label study was conducted in adult patients with AD to evaluate the safety and efficacy of dupilumab in the treatment of moderate-to-severe AD [13]. The safety study showed that the incidence of adverse events requiring urgent treatment was 6.9 %.

Limitations of the study

This study has some limitations. The sample size of the study is small and the follow-up time is short. With increase in sample size and the extension of follow-up time, the clinical efficacy and safety of dupilumab treatment in Chinese patients with moderate-to-severe AD would be more accurately evaluated. There is also the need to improve the integrity of the laboratory data during the treatment process, observe the relationship between the degree of improvement and laboratory data, and obtain the anxiety and depression scores of the patients during the treatment follow-up to observe the relationship between the changes in patients' conditions and the patient's psychological state. Further studies are needed to investigate the circumstances and causes of relapse after discontinuation of dupilumab in AD patients and how effective dupilumab retreatment would be.

CONCLUSION

Dupilumab/cyclosporine A combination for the treatment of AD patients significantly reduces the symptoms of acne and itching and the area of skin lesions, and improves the quality of life. There is, however, a need for larger multi-center trials prior to its use in clinical practice.

DECLARATIONS

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Funding

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Ethical approval

This study was approved by the ethics committee of Beijing Luhe Hospital, Capital Medical University, China.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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