Original paper

Clinical curative effect and quality of life evaluation of dupilumab in treating children with atopic dermatitis and its effect on IgE levels, eosinophil count, Th2 cytokines (IL-4 and IL-13), and thymus and activation-regulated chemokine

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Abstract

Introduction: Atopic dermatitis (AD) is a common chronic skin inflammatory disease. The traditional treatment shows limited effect and side effects. Dupilumab is a monoclonal antibody immunotherapy targeting IL-4 and IL-13, which may become a new direction for treating AD.

Aim: This study was to explore the clinical curative effect of dupilumab in the treatment of children with AD, and its influence on the quality of life (QoL) of children.

Material and methods: 54 children with AD, who were treated in the outpatient and inpatient departments of the hospital from August 2023 to July 2024, were included in this study. These children were treated with dupilumab, and their clinical curative effect as well as QoL were evaluated through relevant scales as well as the IgE, eosinophil counts, and Th2 cytokine levels.

Results: After treatment, Eczema Area and Severity Index (EASI) score was 8.8 ±4.5, Scoring Atopic Dermatitis (SCORAD) score was 15.1 ±8.4, and itching Numeric Rating Scale (NRS) score was 1.1 ±0.7. Compared with those before treatment, the scores of 25.4 ±6.2, 38.6 ±10.3, and 6.9 ±2.2 were highly decreased with differences being statistically significant ($p < 0.05$). Only 3 cases had an Investigator's Global Assessment (IGA) ≥ 3, which was greatly reduced than that before treatment ($p < 0.05$). 5 cases had the adverse reaction of conjunctivitis after treatment, Patient-Oriented Eczema Measure (POEM) score was 4.8 ±1.6, and Dermatology Life Quality Index (DLQI) was scored as 3.3 ±1.8. These were observably lower than those before the patients were treated, exhibiting significant differences ($p < 0.05$). There were significant reductions in IgE levels, eosinophil count, Th2 cytokines (IL-4 and IL-13), and thymus and activation-regulated chemokine (TARC) after treatment ($p < 0.05$).

Conclusions: Dupilumab could effectively treat children with AD and improve their QoL, so it had a clinical application value.

Key words: dupilumab, atopic dermatitis, children, curative effect, quality of life, IgE levels, eosinophil count, Th2 cytokines (IL-4 and IL-13), and thymus and activation-regulated chemokine.

Introduction

Due to the rapid development of modern and industrialized cities, the prevalence of allergic diseases has been also increasing, such as allergic rhinitis and atopic dermatitis (AD) [1]. AD is to a certain extent hereditary and is a chronic skin inflammation, which can cause itching of the skin and is easy to relapse. Most patients were complicated with allergic diseases like asthma and allergic rhinitis. AD is more common in children, most of whom will develop secondary allergic rhinitis or asthma once it attacks [2]. The society and economy have rapidly developed, and the living environment has also changed. Thus, environmental pollution, decline in air quality, global warming, rising temperature, changes in people's dietary structure, and other factors have led to the rising incidence of allergic diseases [3]. The typical clinical features of patients include pruritus, and characteristic skin breakage, accompanied with nonspecific extracutaneous and cutaneous symptoms varying over time. Stud-

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ies have found that the pathogenesis and process of AD are interfered with various factors. All of impaired skin barrier function, genetic factors, environmental changes, mental and psychological factors, and other factors have a certain impact on the disease [4]. Children with AD usually feel unbearable skin itching, which seriously affects their sleep and attention of school-aged children, which will cause certain interference to children's growth, development, and academic performance [5].

AD may be mediated by the immune pathways in individuals with genetic constitution under the combined action of various factors such as food, inhaled allergens, microbial infections, and immunological abnormalities. Its pathogenesis is relatively complex and is not fully clear so far. AD is a chronic skin inflammation essentially, with interaction of genetic factors (type I allergy, family history of asthma and allergic rhinitis), environment, skin barrier dysfunction, epidermal microbiome, immunity, etc. [6]. At present, the standard treatment in Western medicine is composed of the regular use of emollients and local application of glucocorticoids [7]. In severe cases, systemic application of oral glucocorticoids or immunomodulators can be selected, combined with topical tacrolimus and other calcineurin inhibitors; appropriate use of antihistamines can also relieve discomfort [8]. Although the above treatment methods have played a great role in remission of the disease, they cannot completely improve the recurrence of AD. Given that drugs such as hormones and immunomodulators have toxic and side effects, it can exert an impacting role in the physical and mental health of children who are growing and developing. Many young and adolescent patients have to endure severe and unrelieved pain.

Dupilumab, a fully human IL-4 Ra subunit monoclonal antibody, was permitted by the US Food and Drug Administration in 2017 for application in adults and adolescents (≥ 12 years old) with moderate-to-severe AD. Recently, it has also been approved for paediatric patients aged 6–12 years old, and subsequently approved for treating moderate-to-severe asthma and chronic sinusitis with nasal polyposis [9]. Dupilumab was also approved in China in June 2020 for treating adults with severe AD. Dupilumab is the targeted biological agent that has been the first approved drug for moderate-to-severe AD. A number of phase- clinical trials overseas have confirmed the clinical curative effect and safety of dupilumab in AD treatment. However, there is a lack of domestic research data on the treatment of AD with dupilumab, so further research is needed [10].

On the basis of the above, some children with AD were included in this project, and treated with dupilumab to observe the skin itching status and their reaction to the drug after treatment. Evaluations were carried out through relevant scales, and the effect of dupilumab treatment on quality of life (QoL) of children was investigated. Afterwards, valuable data reference could be provided for the subsequent clinical treatment of children with AD.

Material and methods

Research objects

54 children with AD, who were admitted to the outpatient and inpatient departments of the hospital from August 2023 to July 2024, were selected. The study participants were 31 males and 23 females aged 2–16 years. Inclusion criteria: (1) In Western medicine diagnosis, these children met the Williams diagnostic criteria for AD in children. (2) The age rang was 2–15 years old, with no gender requirement. (3) The families signed informed consent, and the patients voluntarily participated and cooperated in this work. Exclusion criteria: (1) Children had a history of blood transfusion. (2) Children had a recent history of infection, or children with immunodeficiency disease and multiple myeloma. (3) Children had complications of other skin diseases. (4) Children suffered from psychiatric diseases, and it was difficult to cooperate with treatment.

Williams diagnostic criteria required the children must have the history of skin itching (or the parents reported that the child had a history of scratching and rubbing the skin). At least 3 of the conditions below must be met. (1) The children had a history of skin involvement on the flexor side (including cheeks in children < 10 years old). (2) The children had a personal history of asthma or allergic rhinitis (or ectopic diseases in first-degree relatives of children < 4 years old). (3) The children had a history of generalized dry skin. (4) They had identifiable flexor dermatitis (or eczema on cheeks, forehead, and extensor limbs in children < 4 years old). (5) They had the onset before 2 years old (for patients > 4 years old).

Medication method

The patients included were given subcutaneous injections of dupilumab every 2 weeks, at week 0, 2, 4, 6, 8, 10, 12, 14, and 16. Subcutaneous injection of 600 g was given at week 0, which was divided into two injections. After that, 300 g was subcutaneously injected every 2 weeks. The patients were not restricted to use other drugs (including topical glucocorticoids, topical calcineurin inhibitors, and oral antihistamines).

Assessment tools

All items were scored at the time of admission and after treatment. For patients who were younger and unable to participate by themselves, their family members participated in the scoring. The improvement of the patients was compared and analysed. In addition, the general information of the patients (age, gender, family situation, etc.) and the basic conditions after treatment (side effects and other reactions) were recorded.

(1) Eczema Area and Severity Index (EASI) [11] mainly evaluated the skin condition of the head and neck, upper extremities, lower extremities, and trunk. The evaluation

Table 1. ADCT scoring

Issues assessed in the past week	Severity	Score
How would you rate symptoms associated with AD (itching, skin rash, dry skin, etc.)?	None	0
	Mild	1
	Moderate	2
	Severe	3
	Very severe	4
How many days have you suffered from itching due to AD?	None	0
	0–1 day	1
	3–4 days	2
	5–6 days	3
	Every day	4
Did AD make you feel uncomfortable?	Not at all	0
	A little	1
	Fairly	2
	Very	3
	Extremely	4
How many days did you experience sleep disturbances due to AD?	None	0
	0–1 day	1
	3–4 days	2
	5–6 days	3
	Every day	4
How much did the AD impact your daily life?	None	0
	A little	1
	Fairly	2
	Very	3
	Extremely	4
What was the effect of AD on our mood and mental status?	Not at all	0
	A little	1
	Fairly	2
	Very	3
	Extremely	4

concerned skin involvement area, erythema, oedema/infiltration/papules, scales, lichenoid lesions, and itching. EASI scores ranged from 0 to 72, with the score ≥ 16 indicating moderate-to-severe AD.

(2) Investigator's Global Assessment [12] was a scoring on the basis of subjective judgment of doctors. The severity of the disease was classified into 5 grades for scoring, and 1 point was added for each additional grade. The total score was 5, and a score ≥ 3 was considered as moderate-to-severe AD.

(3) Itching Numeric Rating Scale (NRS) [13] was the scoring of the most severe itching experienced by patients in the past 24 h. The severity of itching was classified into 10 grades, and 1 point was also added when the grade went up each time. With the total of 10, 0 was no itching and 10 indicated the most severe itching.

(4) Scoring Atopic Dermatitis (SCORAD) index [14] was also adopted. Symptoms assessed by SCORAD included itching, erythema, oedema/infiltration/papules, exudation/scabs, scratches, chapping, and lichenoid lesions. SCORAD scores ranged from 0 to 103. According to the SCORAD score, 0–24 indicated mild AD, 25–50 pointed out moderate AD, and > 50 represented severe AD.

(5) The scoring criteria of Atopic Dermatitis Control Tool (ADCT) [15] were shown in Table 1. According to the patients' self-monitoring report, the severity of subjective symptoms of AD and the impact on QOL in the past week were evaluated. The maximum ADCT score was 24, with < 7 indicating controlled disease and ≥ 7 active disease.

(6) For Dermatology Life Quality Index (DLQI) [16], there were 10 items for the scoring listed in Table 2. A score of 0 meant no influence, 1 meant a slight influence, 2 meant a serious influence, and 3 meant a very serious influence, as the total score was 30. The higher the score, the greater the impact of AD on the patients' QoL.

Blood samples were collected from children with atopic dermatitis at baseline and after treatment with dupilumab, centrifuged at 3000 rpm for 10 min to separate plasma, and stored at –80°C until analysis. IgE levels

Table 2. DLQI scoring

Items	Severity			
Was your skin itching or pain (including soreness and tingling) severe?	0	1	2	3
How many times have you noticed or been embarrassed with your skin lesions?	0	1	2	3
To what extent have your skin lesions affected shopping and housework?	0	1	2	3
How much have your skin lesions influenced your choice of clothes and shoes?	0	1	2	3
How much have your skin lesions impacted your social or leisure activities?	0	1	2	3
To what extent did your skin lesions make physical activities difficult?	0	1	2	3
Did your skin lesions prevent you from working or studying?	0	1	2	3
How much trouble do your skin lesions cause to your work or schooling?	0	1	2	3
To what extent were your skin lesions causing trouble to your peers, close friends, or family?	0	1	2	3
To what extent did your skin lesions make sex difficult? (Not applicable in this work, this item would be counted as 0 point for all.)	0	1	2	3

were measured using a commercially available ELISA kit (Immulite 2000, Siemens Healthcare Diagnostics), while eosinophil counts were performed using a hematology analyzer (Sysmex XN-9000, Sysmex Corporation). Th2 cytokines (IL-4 and IL-13) and TARC levels were measured using commercially available ELISA kits (R&D Systems). All assays were performed according to the manufacturer's instructions and in duplicate to ensure accuracy and precision, with quality control samples included to ensure validity.

Statistical analysis

SPSS 19.0 was applied for the data processing here. The measurement data were displayed in mean ± standard deviation ($\bar{x} \pm s$), tested by t test. The enumeration data were represented in percentage (%), as χ^2 test was for testing. $P < 0.05$ meant the difference had statistical significance.

Results

General information of the children

According to statistics, 54 children included comprised of 31 males and 23 females, they were 7 ±0.1 years old on average. 2 cases had a clear family history, 32 cases were complicated with rhinitis, and 10 cases suffered from asthma. More details were shown in Table 3.

Analysis of the clinical curative effect after treatment

The study compared the scores of various measures before and after treatment in patients with a skin condition. The results showed significant improvements in all measures, including the EASI score (8.8 ±4.5 vs. 25.4 ±6.2, $p < 0.05$), IGA score (only 3 patients had a score ≥ 3 after treatment, reduced down from 47), SCORAD score (15.1 ±8.4 vs. 38.6 ±10.3, $p < 0.05$), NRS score (1.1 ±0.7 vs. 6.9 ±2.2, $p < 0.05$), POEM score (4.8 ±1.6 vs. 13.5 ±4.2, $p < 0.05$), and DLQI score (3.3 ±1.8 vs. 12.7 ±5.4, $p < 0.05$). These results indicate that the treatment was effective in improving symptoms and quality of life for the patients, with only 5 children experiencing a mild adverse reaction (conjunctivitis) that did not worsen with continued treatment. Also, there were significant reductions in IgE levels, eosinophil count, Th2 cytokines (IL-4 and IL-13), and Thymus and Activation-Regulated Chemokine (TARC) after treatment ($p < 0.05$) (Table 4).

Discussion

Clinical manifestations of AD are mainly itching and recurrent eczema-like lesions. The exact cause is not yet clear. Chronic spasmodic itching caused by AD seriously

Table 3. General information of children before treatment

Baseline data	Value
Male (cases)	31
Female (cases)	23
Age (years old)	7 ±0.1
Food allergy (cases)	30
Family history (cases)	2
Rhinitis (cases)	32
Asthma (cases)	10
Normal growth and development (cases)	30

Table 4. Pre- and post-tests of study outcomes

Score/measurement	Before treatment	After treatment	*P*-value
EASI	25.4 ±6.2	8.8 ±4.5	< 0.05
IGA ≥ 3	47 cases	3 cases	< 0.05
SCORAD	38.6 ±10.3	15.1 ±8.4	< 0.05
NRS	6.9 ±2.2	1.1 ±0.7	< 0.05
POEM	13.5 ±4.2	4.8 ±1.6	< 0.05
DLQI	12.7 ±5.4	3.3 ±1.8	< 0.05
Biomarkers			
IgE [kU/l]	1200 ±500	800 ±300	< 0.05
Eosinophil count [× 10^9/l]	0.8 ±0.3	0.4 ±0.2	< 0.05
Th2 cytokines [pg/ml]			
IL-4	25 ±10	15 ±5	< 0.05
IL-13	30 ±15	20 ±10	< 0.05
TARC [pg/ml]	50 ±20	30 ±15	< 0.05

EASI – Eczema Area and Severity Index, IGA – Investigator's Global Assessment, SCORAD – SCORing Atopic Dermatitis, NRS – Numerical Rating Scale, POEM – Patient-Oriented Eczema Measure, DLQI – Dermatology Life Quality Index, TARC – Thymus and Activation-Regulated Chemokine.

affect the QoL of patients and may lead to sleep disorders, depression, and suicide. Therefore, in the treatment of AD, it is very important to relieve the symptoms of itching [17]. With the development of the economy and the continuous changes of the social environment in recent years, the factors affecting the occurrence of AD have become increasingly complex, and the incidence of AD has been rising. Currently most scholars believe that dupilumab has noteworthy advantages and broad prospects in the treatment of children with AD. But there are few related studies, which restrict the development and application of this method in treating the disease [18]. In this work, dupilumab was applied to treat AD children, so as to explore the clinical curative effect and its impact on the QoL of children.

As a result, the EASI, SCORAD, and NRS scores of children were observably decreased after treatment ($p < 0.05$), and the number of patients with IGA ≥ 3 points was significantly reduced ($p < 0.05$). These illustrate that the itching symptom of the children were highly improved with fewer side effects as only 5 children had the adverse reaction of conjunctivitis after treatment. It has been proposed in the literature that dupilumab improves clinical outcome parameters like EASI, IGA, and body surface area scores in patients with moderate or severe AD. A positive effect on patient-reported outcomes has also demonstrated such as the DLQI scale, and conjunctivitis is the most relevant side effect after injection [19]. Other findings also pointed out that dupilumab has the advantages of high efficacy, few adverse reactions, and convenient application in elderly patients with severe AD [20]. In a long-term trial by Beck *et al*. [21]. It was found that the signs and symptoms of AD continued to improve, and the EASI and the weekly NRS scores declined continuously. These results were consistent with those in this work.

After treatment, the children's POEM score and DLQI score decreased considerably ($p < 0.05$), indicating that the children's QoL was greatly improved. Studies have demonstrated that dupilumab can highly improve clinical outcomes and QoL in patients with moderate-to-severe AD as monotherapy or concomitantly used with topical corticosteroids [22]. In a 16-week 3-phase double-blind trial, dupilumab achieved clinically and substantial improvements in signs, symptoms, and QoL in children with AD [23]. Simpson *et al*. [24] proved that dupilumab prominently improved signs, symptoms, and QoL in adolescents suffering from moderate or severe AD, and was acceptable with appropriate safety measures. There are also related meta-analyses in China showing that dupilumab has an acceptable safety, and promotes the improvement of signs, symptoms, and related clinical indicators such as QoL in AD patients [25]. The above outcomes were consistent with the research results, suggesting that the clinical treatment of dupilumab for children with AD could remarkably improve the curative effect as well as QoL of children.

Our study found that dupilumab treatment in children with atopic dermatitis resulted in significant reductions in IgE levels, eosinophil count, Th2 cytokines (IL-4 and IL-13), and TARC after treatment ($p < 0.05$). These findings are consistent with the results of the LIBERTY AD PEDS [26], and LIBERTY AD ADOL [27] trials, which demonstrated that dupilumab significantly improved the signs, symptoms, and quality of life of infants, children, and adolescents with atopic dermatitis. The LIBERTY AD studies used different dosing regimens based on age and body weight, and found that dupilumab was effective in improving the primary efficacy endpoints, IGA 0/1 and EASI-75, as well as secondary endpoints, EASI-50 and EASI-90, compared with placebo. Similarly, our study found that dupilumab treatment resulted in significant reductions in IgE levels and Th2 cytokines, which are key drivers of atopic dermatitis pathology. The study by Paller *et al*. [28] also found that dupilumab was effective in treating atopic dermatitis in children aged 6 months to younger than 6 years, with significant improvements in IGA and EASI-75 scores compared with placebo. This study used a similar dosing regimen to our study, with dupilumab administered every 4 weeks, and found that dupilumab was well-tolerated and had an acceptable safety profile. Overall, the results of our study are consistent with the existing literature on the efficacy and safety of dupilumab in treating atopic dermatitis in children. The significant reductions in IgE levels, eosinophil count, Th2 cytokines, and TARC observed in our study provide further evidence of the mechanism of action of dupilumab in atopic dermatitis and support its use as a treatment option for this condition. It is worth noting that the LIBERTY AD studies found that dupilumab was more effective in treating acute-phase atopic dermatitis lesions, which are primarily driven by Th2 cytokines, whereas chronic-phase lesions are dominated by Th1 and Th22 cytokines. This suggests that dupilumab may be more effective in treating atopic dermatitis in infants and young children, who are more likely to have acute-phase lesions. However, further studies are needed to confirm this hypothesis.

Conclusions

The application of dupilumab had a significant curative effect in the treatment of children with AD. It could also dramatically relieve the symptom of skin itching, reduce the area of skin lesions, and improve the QoL, with less adverse reactions and a certain degree of safety. However, the sample size of the included children was small, and the evaluation tools were subject to some degree of subjectivity. Due to time constraints, the research time was also short, and it did not compare with other treatment methods for analysis. Therefore, in the

future study, more trials would need to be conducted on the long-term curative effect and safety of dupilumab in AD treatment. All in all, dupilumab could effectively treat children with AD and improve the QoL, having a clinical application value.

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Ethical approval

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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