

The Application of Dupilumab to Pediatric Patients Aged 6–11 yrs with Moderate-to-Severe Atopic Dermatitis Whose Disease is Not Adequately Controlled: The Clinical Data so Far

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Background: While dupilumab has shown efficacy in improving atopic dermatitis, few studies have assessed the long-term clinical data of dupilumab use in pediatric patients.

Objective: In the present study, we reviewed the current literature to assess reported efficacies, side effects, and risks of using dupilumab to treat atopic dermatitis in pediatric populations.

Methods: Using PRISMA guidelines, the authors searched PubMed/MEDLINE and Embase for studies related to dupilumab treatment for atopic dermatitis in pediatric patients aged 6–11 years old.

Results: A total of 512 pediatric patients (ages 6–11) were included. Outcome measures assessed by EASI, SCORAD, P-NRS, IGA and C-DLQI showed significant improvements in scores from those observed at baseline to the last treatment of dupilumab. Most reported adverse effects on dupilumab were conjunctivitis and infection site reactions. All studies reported that dupilumab was well-tolerated.

Limitations: Limitations include the low number of studies available and observation periods of up to 16 weeks, which may be too short to evaluate the drug's effectiveness and occurrence of adverse effects. This also limits our knowledge on whether there are sustained benefits and/or diminished efficacy as well as long-term side effects.

Conclusion: Thus far, the data demonstrates dupilumab to be safe and effective in the management of moderate-to-severe atopic dermatitis in children aged 6–11 years. Future studies should evaluate long-term dupilumab use and sustained effects.

Keywords: pediatric, pediatric dermatology, atopic dermatitis, dupilumab

Introduction

Atopic dermatitis (AD) is one of the most common inflammatory skin diseases affecting approximately 15–25% of children.¹ It is characterized by outbreaks of pruritic skin lesions and xerosis that classically manifest in early childhood.² Comorbid conditions including asthma, food allergies, eosinophilic esophagitis, sleep impairment, as well as mental health and behavioral problems that negatively impact the quality of life of both those affected and their families.³ Food allergies and eosinophilic esophagitis are early components of atopic march, where such cutaneous manifestations may precede the onset of secondary pathologies and dermatologists represent the sentinels for the early identification of this group of patients with AD.⁴ Significant medical, personal, societal, and financial burdens are also associated with AD. Estimated annual costs for families to care for a child with AD are comparable to those of a child with insulin-dependent diabetes and much higher than those of a child with asthma.⁵ AD can be difficult to treat, however, there are a number of available treatment options that aim to reduce symptoms, prevent exacerbations, and minimize therapeutic risks.¹

Initial treatment for pediatric AD consists mostly of topical emollients and corticosteroids (TCs).⁶ TCs are typically well-tolerated medications when used properly; however, TCs pose higher risks in the pediatric population given increased absorption due to a higher body surface area-to-weight ratio.^{1,6} Alternative treatments include topical calcineurin inhibitors (TCIs), particularly for sensitive skin sites such as the face and skin folds. While TCIs have the advantage of not imposing risk for cutaneous atrophy, TCIs are not as effective as TCs and are more costly.¹ Although phototherapy is another treatment option available, it is not commonly used in pediatric populations as it requires biweekly visits to the doctor's office and not all healthcare facilities have access to the equipment.¹ Systemic corticosteroids and off-label drugs (cyclosporine, methotrexate, azathioprine) can also be used, but management with these is challenging. These medications require forewent lab morning, increase the risk of systemic adverse effects, and are not recommended for long-term use.^{7,8}

Emerging drug therapies for AD target its immune response elements. AD is characterized by an immune response that increases the expression of cytokines IL-4-, IL-13, and IL-5 secreted from Th2 helper T-cells. Dupilumab is a fully human monoclonal antibody that blocks the shared receptor for IL-4 and IL-13, thereby blocking the signaling cascade for these cytokines.⁹ Dupilumab is approved for the treatment of moderate-to-severe AD, and has been shown to improve AD symptoms and quality of life with an acceptable safety profile.¹⁰ Given the majority of patients suffering from AD are children, dupilumab holds great promise in providing a safe, effective therapy for pediatric patients. At present, there are few studies evaluating the long-term clinical data of dupilumab use in pediatric patients aged 6–11 years with moderate-to-severe atopic dermatitis. The most prevalent side effects of dupilumab included conjunctivitis, nasopharyngitis, headaches, and injection-site reaction.^{11–14} This study aims to investigate the current literature and further compare the use of dupilumab to leading treatments in terms of efficacy, side effects, and risks.

Methods

A systematic literature search of PubMed/MEDLINE and Embase was conducted using the following terms: “atopic dermatitis”, “eczema”, “children”, “pediatric patients”, “Dupixent”, “dupilumab”. Terms were combined using appropriate Boolean operators. No limitations in language, publication type, or publication period were applied.

This systematic review was performed in accordance with guidelines provided by Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist. The inclusion criteria were: (1) studies looking at patients who were between the ages of 6 and 11 years old, (2) the article was a randomized controlled trial or clinical review. The following exclusion criteria were then applied: (1) the article was not in English (or no English-translated versions were available from the publisher), (2) the article was a conference abstract, letter, or note, (3) studies looking at the infant, adolescent, or adult populations. Ultimately, four studies met all criteria and were used for analysis. The reporting of this systemic review was guided by the standards of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement ([Supplement 1](#)).

Results

The four trials included a total of 512 patients whose detailed characteristics ([Table 1](#)). All trials administered dupilumab using subcutaneous injection. Treatment groups received dupilumab monotherapy in two trials^{12,13}, while the other two by Paller et al and Yang et al included patients applying concomitant TCs.^{14,15} Measures used to assess disease severity in these studies included the Eczema Area Severity index (EASI), SCORing Atopic Dermatitis (SCORAD), and Investigator's Global Assessment (IGA). Three of the studies included patient reported outcomes such as the Dermatology Life Quality Index (DLQI) and the Pruritic Numeric Rating Scale for itch (P-NRS). Change in mean EASI score from baseline to the final 16th week of treatment showed significant improvement for the following studies; Paller ($p < 0.0001$); Napolitano ($p < 0.001$); Yang ($p < 0.001$). Significant improvements in average SCORAD were reported by; Paller ($p < 0.0001$); Yang ($p < 0.0001$); Losek ($p < 0.0001$). Similarly, improvements in patient reported outcomes assessed by DQLI and P-NRS were significant; Paller (DQLI $p < 0.0001$, P-NRS $p < 0.0001$); Napolitano (DQLI $p < 0.0001$, P-NRS $p < 0.001$); Yang (DQLI $p < 0.001$). Rate of adverse effects on dupilumab was generally low, however, the most reported were conjunctivitis and injection site reactions. All studies reported that dupilumab was well-tolerated.

Table 1 Characteristics of Studies Included

| Author, Year | Patients (Ages 6–11) | Treatment Arms | Prior Medications | Results with Dupixent | Other Notes |
|--|---|--|--|---|--|
| Paller et al, 2020¹² Phase III Randomized double blinded placebo controlled phase 3 trial | n = 362 | Placebo + TCS (n=123) Dupilumab 300mg q4w + TCS (n=122) Dupilumab 100mg or 200mg q2w + TCS (n=122) (weight-based) | Placebo + TCS (n=120) - CS - 17/120 (14.2%) - ST - 22/120 (18.3%) Dupilumab 300mg q4w + TCS (n=122) - CS - 25/120 (20.8%) - ST - 23/120 (19.2%) Dupilumab 100mg or 200mg q2w + TCS (n=122) - CS - 30/122 (24.6%) - ST - 16/122 (13.1%) | Both q4w and q2w dupilumab + TCS regimens resulted in statistically significant improvement in signs, symptoms, and quality of life versus placebo + TCS in all pre specified endpoints: - IGA score of 0 or 1 at week 16 - ≥75% in EASI (EASI-75) from baseline to week 16 - % change in EASI and weekly average P-NRS from baseline to week 16 | Most prevalent adverse effects: - Conjunctivitis - Injection-site reactions |
| Napolitano et al, 2022¹¹ Multicentre real-life study Retrospective observational | n = 55 | Day 1: Dupilumab 300mg Day 15: Dupilumab 300mg Subsequent Dupilumab 300mg q4w (up to 16wk) (n=55) | TCs - 41/55 TCI - 27/55 ST - 35/55 Off-label treatment - 18/55 | Significant improvement in EASI, P-NRS, S-NRS, AND c-DLQI scores observed from baseline to W16 of dupilumab treatment | Most prevalent adverse effects: - Conjunctivitis - Injection-site reactions - Headaches |
| Yang et al, 2022¹⁴ Real-world study Retrospective observational | n = 15 (4–12 years old) Mean age 7.80 ± 2.60 | Dupilumab 600mg initial dose - 9/15 - Dupilumab 300mg maintenance dose q4w over 4 months Dupilumab 300mg initial dose - 6/15 - Dupilumab 300mg maintenance dose q4w over 4 months | At least 1 antihistamine medicine - 15/15 > 2 antihistamine medicines - 8/15 | Significant improvement in EASI, c-DLQI, and SCORAD scores observed from baseline to W16 of dupilumab treatment | Topical drugs type during treatment TCS and TCI - 4/15 Only TCS - 8/15 Only TCI - 2/15 Most prevalent adverse effects: - Conjunctivitis |
| Lasek et al, 2022¹⁵ Retrospective observational multicentre cohort study | n = 80 | Patients (ages 6–11) diagnosed with AD who received at least one injection of dupilumab Dupilumab doses not specified Observational Mean duration (days) of Dupilumab = 99 ± 10.7 | Previous general treatments for AD, n Cyclosporine - 30/80 (37.5%) Methotrexate - 21/80 (26.3%) Phototherapy - 3/80 (3.8%) Omalizumab - 1/80 (1.3%) Azathioprine - 1/80 (1.3%) Acitretin - 5/80 (6.3%) | After 3 months of treatment, there was a significant decrease in SCORAD and IGA: 68.4% of children (n = 39) had reached 0–I IGA at 3 months. | Most prevalent adverse effects: - Conjunctivitis - Pain or reaction at injection site |

Abbreviations: AE, adverse event; CDLQI, Children's Dermatology Life Quality Index; CS, corticosteroids; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; NRS, Numerical Rating Scale; P-NRS, Peak Pruritus Numerical Rating Scale; SCORAD, SCORing Atopic Dermatitis; TCI, topical calcineurin inhibitors; TCs, topical corticosteroids; ST, systemic treatment (nonsteroidal); OLE, open label extension; QOL, quality of life; q2w, every 2 weeks; q4w, every 4 weeks.

Discussion

Our findings demonstrate that the use of dupilumab improves symptoms and quality of life in children aged 6–11 years with moderate-to-severe AD. All scoring metrics used to assess disease severity and impact showed statistically significant improvement for patients given dupilumab when compared to baseline before starting treatment. Most children achieved mild or absent pruritus and improvement of severity or extent of AD, as measured through P-NRS, EASI, SCORAD, and IGA, by the end of the specified treatment period. By reducing pruritic skin lesions, dupilumab resulted in improved quality of life for these children as measured through c-DLQI.^{11,12,14,15}

Of the studies included, no patients discontinued dupilumab due to severe treatment-emergent adverse events (TEAEs) related to dupilumab. Most prevalent side effects included conjunctivitis, nasopharyngitis, headaches, and injection-site reaction. While conjunctivitis was the most frequent side effect of dupilumab, most cases were of mild-to-moderate severity, resolved during treatment, and did not lead to discontinuation of treatment. Overall, dupilumab was well-tolerated and had an acceptable safety profile across all studies.^{11,12,14,15}

This review has some limitations. Results were limited due to the low number of studies available. Additionally, observation periods for most of the included studies were up to 16 weeks, which may be too short to evaluate the drug's effectiveness and occurrence of adverse events. The treatment arms used in the study by Paller et al 2020 included concurrent TC use in addition to dupilumab in both the control group and groups receiving dupilumab. While results from this study highlight dupilumab's efficacy in treating pediatric AD, it is important to consider this variation in treatment arms when comparing results between the different studies reviewed.

These results support the use of dupilumab as a safe treatment for children aged 6–11 years with moderate-to-severe AD. Among all studies included, dupilumab results in clinically and statistically significant improvements in EASI, SCORAD, P-NRS, IGA, and c-DLQI. Dupilumab is shown to be effective for use in pediatric patients and improves the intensity of AD symptoms and quality of life, with a favorable safety profile and no severe adverse events such as serious infection or systemic hypersensitivity.

Conclusion

AD is a complex disorder that poses a significant financial burden and a negative impact on quality of life on those affected. Traditional treatment modalities can be difficult to access and can pose side effects with long-term use. This review demonstrates that dupilumab is an effective treatment for moderate-to-severe AD that improves both AD symptoms and quality of life. The adverse effects of dupilumab were not severe enough to discontinue treatment and were generally well-tolerated among the patients in each of the studies.

Results were limited due to the low number of studies available and the short-term observation period of 16 weeks in most studies included. As the use of dupilumab becomes more common, future studies can evaluate long-term use in pediatric populations.

IRB Status

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