

Long-term off-label dupilumab in pediatric atopic dermatitis: A case series

Alison D. Treister BS, BSHS  | Peter A. Lio MD 

Department of Dermatology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois

Correspondence

Peter A. Lio, MD, Department of Dermatology, Feinberg School of Medicine, Northwestern University, Chicago, IL.
Email: peterlio@gmail.com

Abstract

Background/Objectives: Clinical trials of dupilumab have shown efficacy in treating moderate-to-severe atopic dermatitis (AD) in adult patients. While a phase 2 trial of dupilumab has shown efficacy and safety in children, the medication awaits Food and Drug Administration (FDA) approval, and off-label use is limited by dosing currently available to adults. We present this case series to describe the efficacy and safety profile of off-label dupilumab use in six pediatric patients treated by one provider in a private practice.

Methods: We conducted a retrospective chart review of all patients under the age of 18 receiving dupilumab for AD. Two dosing regimens were used as follows: adult dose for patients ≥ 40 kg and half dose for those < 40 kg. We recorded the investigator's global assessment (IGA) and body surface area (BSA) prior to dupilumab initiation and following treatment. All patients were warned of potential side effects including injection site reaction, conjunctivitis, increased risk of infection, and lack of information about use in children.

Results: Six pediatric patients were identified with an average age of 10.8 years (range: 7-15). All patients had a decrease in IGA of at least 2 points using biweekly 300 or 150 milligram (mg) doses for an average treatment duration of 8.5 months (range: 6-11). Three patients (50%) had an IGA of 1 after treatment. No side effects were reported.

Conclusions: Dupilumab appears to be an effective treatment for AD in pediatric patients. Optimal dose and delivery have yet to be determined.

KEYWORDS

atopic dermatitis, therapy-systemic

1 | INTRODUCTION

Dupilumab is a human monoclonal antibody that binds to the interleukin (IL)-4 receptor subunit alpha shared by both IL-4 and IL-13 receptors and inhibits signaling of IL-4 and IL-13.¹ These cytokines are released in type 2 helper T (Th2) cell inflammatory pathways, which are known to be dysregulated in several atopic conditions including atopic dermatitis (AD).² Clinical trials of dupilumab have shown efficacy in adult patients with moderate-to-severe AD with a significantly greater percent of treated patients achieving clear or

almost clear skin as compared to placebo.^{3,4} This medication has generally been well tolerated with less concern for toxicity as compared to other systemic medications used for AD.

Currently, the prevalence of AD is on the rise with over 20% of children affected,⁵ 33% having moderate-to-severe disease.⁶ There is an increasing need for more effective treatments in the pediatric population, especially for patients with severe disease in which treatment is limited to systemic therapies carrying the risk of immunosuppression as well as other medication-specific side effects.⁷ Additionally, there are sparse data to guide the use of these systemic

medications in pediatric patients, and some children's AD may even be recalcitrant to therapy. Currently, clinical trials are under way to investigate the efficacy and safety of dupilumab in the pediatric population. While the results seem promising, and make sense mechanistically given that Th2 inflammation drives AD in children even more so than adults,⁸ there is a pressing need to try dupilumab in pediatric patients struggling with AD prior to the dissemination of results from long-term trials and Food and Drug Administration (FDA) approval. We present this case series to describe the efficacy and safety profile of long-term, off-label dupilumab treatment in six pediatric patients in our clinical cohort.

2 | METHODS

Patients less than 18 years of age were identified from a cohort of patients treated with dupilumab for moderate-to-severe AD between March 2017 and May 2018. Because this was a case series and patients were deidentified, we did not consult the institutional review board for approval. All patients had a general consent signed by a parent stating that their information in the medical record may be used for research. This study followed the tenets of the Declaration of Helsinki.

All identified patients had received a loading dose with subsequent biweekly injection. Patients weighing less than 40 kg received half of the medication in each commercially available 2-mL syringe. Because the syringes were unmarked, these patients returned to clinic where 1 mL of the medication was wasted into a graduated cylinder prior to injection. All patients were encouraged to continue topical treatment for AD if needed and had clinical follow-up following treatment initiation. We routinely collected patient gender, age, and history of additional atopic or allergic conditions (asthma, hay fever, environmental allergies, food allergies) as well as the investigator's global assessment (IGA) and body surface area (BSA) affected with AD at the time of dupilumab initiation and most recent office visit. IGA was recorded on a scale of 0-4 (clear to severe). We further noted prescribed loading and biweekly dose, weight at the time of dupilumab initiation, as well as prior use of failed treatments for AD.

Given the increased incidence of conjunctivitis reported in clinical trials of adult patients with AD,⁹ all patients were warned of the potential for this side effect and instructed to contact the clinic if symptoms of eye irritation developed. Patients were further warned of an increased risk of infection, potential for injection site reaction, and that dupilumab had not been approved for children by the FDA.

3 | RESULTS

A total of six pediatric patients (four female) were identified with an average age of 10.8 years (range: 7-15). All patients had an IGA of 4 (severe) and an average BSA of 55% (range: 35%-70%) at the time of dupilumab initiation (Table 1).

TABLE 1 Characteristics of pediatric patients treated with dupilumab

Subject	Age at treatment initiation (y)	Gender	Onset of AD	Other atopic/allergic conditions	IGA start (%)	BSA start (%)	IGA end (%)	BSA end (%)	Months treated	Loading dose (mg)	Biweekly dose (mg)	Weight (kg)	Failed therapies
1	11	F	7 y	Asthma	4	65	2	50	8	300	150	30	TCSs, wet wraps, TCIs, NB-UVB
2	10	F	Infancy	Severe food allergies, environmental allergies	4	50	1	15	11	300	150	27	TCSs, wet wraps, TCIs, NB-UVB, cyclosporine
3	11	F	5 y	Asthma	4	70	2	25	6	600	300	40	TCSs, wet wraps, TCIs, NB-UVB, cyclosporine
4	7	M	Infancy	Asthma	4	50	1	10	11	300	150	35	TCSs, wet wraps, TCIs, NB-UVB, cyclosporine, mycophenolate, prednisone, azathioprine, inpatient admission at National Jewish hospital
5	11	M	Infancy	Hay fever	4	60	2	25	9	600	300	50	TCSs, wet wraps, TCIs, NB-UVB, cyclosporine
6	15	F	Infancy	None	4	35	1	—	6	600	300	50	TCSs, wet wraps, TCIs, NB-UVB, mycophenolate, prednisone
Mean	10.8	—	—	—	4	55	1.5	25	8.5	—	—	—	—

AD, atopic dermatitis; BSA, body surface area; IGA, investigator's global assessment; NB, narrowband; TCSs, topical corticosteroids; TCIs, topical calcineurin inhibitors.

All six patients had an average IGA and BSA of 1.5 (range 1-2) and 25% (range: 10%-50%), respectively after mean treatment duration of 8.5 months (range: 6-11 months). Three patients (50%) achieved almost clear skin (IGA = 1) (Table 1). Patient 6 opted to discontinue therapy after 6 months, when her skin was reportedly almost clear. Her skin worsened to an IGA of 3 within 2 months after discontinuing therapy, and dupilumab was subsequently restarted.

The mean loading dose for all treated patients was 11.4 mg/kg (range 8.6-15 mg/kg). The mean biweekly dose was 5.7 mg/kg (range 5-7.5 mg/kg). No patients or their families reported adverse events during the treatment period.

4 | CONCLUSION

Previously, clinical trials of dupilumab in adults with moderate-to-severe AD have demonstrated excellent treatment response. In the 52-week CHRONOS trial, 39% of patients who received dupilumab (600 mg loading dose, followed by 300 mg biweekly injection) as compared to 12% of patients who received placebo, achieved the primary endpoint of IGA 0/1 after 16-week treatment duration.⁴ Efficacy in the pediatric population has been suggested. An open-label study of children and adolescents has demonstrated up to 76% improvement in eczema area and severity index (EASI) scores, though treatment time was limited as patients received a single 2 mg/kg or 4 mg/kg dose followed by 8 weeks of observation and four subsequent weekly doses of the initial dose regimen.¹⁰ Our case series is able to expand upon this pediatric data by suggesting success of therapy with all patients having a 2-point or greater decrease in IGA after an average treatment duration of 8.5 months, including two (33%) who maintained an IGA score of 1 after 11 months of treatment. Perhaps even more importantly, our results suggest the success of dupilumab therapy in even the most severe, refractory AD patients. In the open-label phase 2 trial, 19.5% of children had a history of failed nonsteroidal systemic medications; however, outcomes measures were not been specifically stratified for this patient population. In our cohort, all had severe AD (IGA = 4) at the time of dupilumab initiation, and five out of six (83.3%) had previously failed systemic therapy, suggesting the success of this therapy in even the most recalcitrant pediatric AD patients.

The open-label phase 2 trial of dupilumab in children and adolescents stratified patients into four groups based on age (6-11 and 12-17 years) and weekly dosage (2 or 4 mg/kg). While both dose regimens had similar efficacy, as determined by improvement in EASI scores, the 4-mg/kg dose was associated with more adverse events including conjunctivitis, infections, and injection site reactions; however, these events did not lead to the discontinuation of therapy. Currently, commercially available dupilumab is supplied in unmarked, prefilled syringes containing 2 mL (300 mg) of medication, the biweekly dose FDA approved for adults. We chose to treat our

patients with either the full or measured half doses. Using this strategy, the calculated weight-based dosing was, in some cases, significantly higher than the open-label phase 2 trial as well as other trials currently under investigation. In an ongoing phase 3 study of children ages 12-18, children receive either a 600 mg loading dose followed by biweekly 300 mg doses (children $\geq$ 60 kg) or a 400 mg loading dose followed by biweekly 200 mg doses (30-60 kg). In phase 2 trials of children ages 6 months to 6 years of age, patients start with a single-dose 3 mg/kg exposure with plans to increase to 6 mg/kg pending Data and Safety Monitoring Board review (<https://clinicaltrials.gov/ct2/show/NCT03346434>). While there is currently a lack of available safety and efficacy data for dupilumab in the pediatric population, fortunately all of the patients in our small cohort responded well and tolerated treatment.

The results from our case series, along with open-label phase 2 data, suggest that dupilumab is an effective treatment option for pediatric patients with AD. Moreover, this medication seems promising with regard to both reducing pruritus and improving quality of life, as previously demonstrated in trials for adult patients.¹¹ Given the remarkable success and safety of this medication in adults, along with careful consideration of the side effects of alternative medications, many clinicians will rightfully be interested in considering the medication prior to FDA approval for pediatric patients. In the meantime, many clinicians are prescribing the medication off-label for children. Until data from multicenter, prospective trials are available to support optimal pediatric dosing, clinicians prescribing this medication for pediatric patients should alert caregivers about the unclear risks, monitor closely, and remain vigilant.

DISCLOSURES

Dr. Lio has served as a consultant and speaker for Regeneron and Sanofi Genzyme. Ms. Treister has no conflict of interest.

INSTITUTIONAL REVIEW BOARD/INFORMED CONSENT

Given that these data are presented as a deidentified case series, we did not request IRB approval. All patients had a general consent signed by a parent stating that their information in the medical record may be used for research. All patients had parental consent for dupilumab use and were made aware of off-label nature. This study followed the tenets of the Declaration of Helsinki.

ORCID

Alison D. Treister  <http://orcid.org/0000-0001-8214-1701>

Peter A. Lio  <https://orcid.org/0000-0001-7600-0152>

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How to cite this article: Treister AD, Lio PA. Long-term off-label dupilumab in pediatric atopic dermatitis: A case series. *Pediatr Dermatol*. 2018;00:1–4. <https://doi.org/10.1111/pde.13697>