

Off-label use of dupilumab for pediatric patients with atopic dermatitis: A multicenter retrospective review



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Background: Atopic dermatitis (AD) is a common, chronic type 2 inflammatory skin disease, typically starting in infancy, with increased risk for subsequent extracutaneous atopic morbidities. Dupilumab is the first biologic agent targeting type 2 inflammation approved by the U.S. Food and Drug Administration (USFDA); it was licensed in 2017 for adults with moderate to severe AD and 2 years later for adolescents. Systemic treatment for pediatric AD remains a significant unmet medical need.

Objective: To analyze off-label use of dupilumab in children with AD.

Methods: Multicenter retrospective review that evaluated children who were prescribed dupilumab for moderate to severe AD.

Results: One hundred eleven of 124 patients (89.5%) gained access to dupilumab after a mean of 9 weeks. The dosing range was 4 to 15.5 mg/kg for the loading dose and 2.0 to 15.3 mg/kg every other week for maintenance. The range was widest for 6- to 11-year-olds and was related to use of either full or half of adult dosing. Associated morbidities, treatment response, and adverse events were comparable to those in previous adolescent and adult trials.

Limitations: The retrospective design of the study limited uniform data collection.

Conclusion: Access to dupilumab was achievable for the majority of children after a mean 9-week delay because of insurance payment denial. This review supports dupilumab response and

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Funding sources: None.

Disclosure: Dr Levy—Possibly related: Regeneron: consultant. Unrelated: Castle Creek: consultant/Data Monitoring Committee (DMC); Janssen: principal investigator, study; Mayne: consultant/Data and Safety Monitoring Board (DSMB); Pfizer: study (closed); Sun Pharmaceuticals: consultant; UCB: consultant; Up to Date: author and section editor (Pedi Derm); Aldeyra: consultant (study result review). Douglas W. Kress, MD—Possibly related: Regeneron and Sanofi: speaker's bureau. Unrelated: Pfizer and Eucrisa: speaker's bureau. Lara Wine Lee, MD:

Investigator. Elaine Siegfried, MD—Possibly related: Regeneron: principal investigator, clinical trial, consulting fees, honorarium; Sanofi Genzyme: consulting fees, honorarium; UCB: consulting fees; AbbVie: consulting fees. Unrelated: Verrica: consulting fees, honorarium; Leo: consulting fees, Data Safety Monitoring Committee; Novan: consulting fees; Data Safety Monitoring Committee; Pfizer: consulting fee; Pierre Fabre: consulting fee; Janssen: principal investigator, clinical trial; Lilly: principal investigator, clinical trial. Mr Igelman; Dr Kurta; Mr Sheikh; Drs McWilliams, Armbricht, Boothe, Diaz, Fraile-Alonso, and Antaya; Ms Smith; Drs Castelo-Soccio, Treat, Cullison, Shah, Kittler, and Arkin; and Ms Patel have no conflicts of interest to declare.

Presented at the 2019 American Academy of Dermatology Annual Meeting in Washington, DC, March 2, 2019.

Reprints not available from the authors.

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Published online October 10, 2019.

0190-9622/\$36.00

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<https://doi.org/10.1016/j.jaad.2019.10.010>

tolerability in children. Optimal dosing for patients younger than 12 years has not been defined. Availability of the drug in 2 different concentrations is an important safety issue. (J Am Acad Dermatol 2020;82:407-11.)

Key words: atopic dermatitis; dupilumab access; dupilumab dosing; eczema; pediatric.

Atopic dermatitis (AD) is the most common chronic pediatric skin disease, affecting an estimated 13% of children in the United States, including at least 2% with moderate to severe disease.¹ Dupilumab (Dupixent, Regeneron Pharmaceuticals, Tarrytown, NY), a fully humanized monoclonal antibody to the alpha subunit of interleukin 4R, is the first and only targeted systemic treatment licensed to treat moderate to severe AD.² Dupilumab was first approved for adults in March 2017, and 2 years later in adolescents 12 years and older. This drug is dispensed in prepackaged, unmarked syringes, containing 300 mg in 2 mL for patients weighing ≥ 60 kg and 200 mg in 1.1 mL for patients weighing < 60 kg. To address the significant unmet medical need for younger children, industry-sponsored clinical trials in patients as young as 6 months are underway.³

Although dupilumab is not licensed for use in children < 12 years, the lack of well-defined tolerable and adequate alternative treatments has prompted off-label use of medications, including methotrexate, cyclosporine, mycophenolate, and azathioprine, in pediatric patients with moderate to severe AD. Our multicenter retrospective review analyzed several parameters among these candidates for dupilumab treatment, including access to the medication, dosing, treatment response, tolerability, and associated morbidities. Pending U.S. Food and Drug Administration (USFDA) approval for younger patients, this report may help overcome challenges related to gaining access to dupilumab and support response and tolerability of off-label use in children with moderate to severe AD who are not able to participate in a clinical trial.

METHODS

This study was conducted by board-certified pediatric dermatologists from 8 academic medical centers and was approved by each participating center's local institutional review board. All patients, from birth to 17 years, with moderate to severe AD

CAPSULE SUMMARY

- Treatment for children with moderate to severe atopic dermatitis is a significant unmet need; dupilumab is currently licensed only for patients older than 11 years.
- Off-label access to dupilumab is achievable and shows treatment success rates and tolerability similar to those in adult patients, but optimal pediatric dosing has not been defined.

from each site who received a prescription for dupilumab between March 25, 2017, and March 7, 2019, were included. Data were retrospectively collected using a standardized data collection form within the secure, central Research Electronic Data Capture (REDCap) system. Treatment response assessment was based on qualitative interpretation of improvement as documented in the medical record and translated into a 5-point

Investigator Global Assessment (IGA) score (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4 = severe).

RESULTS

Dupilumab prescribers had a median of 13 years of practice experience (range 3-27 years). Of the 19 prescribers, 13 were board certified in pediatric dermatology, and the other 6 prescribers were board-certified dermatologists practicing together with at least one board-certified pediatric dermatologist. Data were included from 124 patients who received at least one prescription for dupilumab. Thirteen patients (10.5%) were ultimately unable to gain access to treatment based on payer denial to cover the cost. For the remaining patients, the mean delay in initiating treatment, from prescription date to approval date, was 9.0 weeks (range 1 day-69 weeks). The mean age at dupilumab initiation was 13.0 ± 3.9 years (range 3.1-18.0 years). Mean follow-up was approximately 9 months (range 1-19 months). There were 54 (43%) female patients; 40 (32.3%) had prior hospitalizations for AD. Prior systemic medications included sedating antihistamines ($n = 101$; 81.5%); nonsedating antihistamines ($n = 97$; 78.2%); oral corticosteroids ($n = 87$; 70.2%); methotrexate ($n = 82$; 66.1%); cyclosporine ($n = 53$; 42.7%); mycophenolate mofetil ($n = 12$; 9.7%); intravenous immune globulin ($n = 13$; 10.5%); and azathioprine ($n = 12$; 9.7%).

Patients had a variety of associated extracutaneous morbidities. Atopic morbidities included food allergy ($n = 91$; 73.4%); allergic rhinitis ($n = 82$; 66.1%); asthma ($n = 79$; 63.7%); urticaria ($n = 36$;

Abbreviations used:

AD:	atopic dermatitis
AE:	adverse Event
IGA:	Investigator Global Assessment
USFDA:	U.S. Food and Drug Administration

29.0%); conjunctivitis (n = 33; 26.6%); and eosinophilic esophagitis (n = 11; 8.9%). Mental health morbidities included attention deficit disorder/attention deficit hyperactivity disorder (n = 16; 12.9%), and other (anxiety, depression, obsessive-compulsive disorder, and oppositional defiant disorder) (n = 39; 31.5%). History of infectious morbidities included furuncles (n = 29; 23.4%); sinusitis (n = 24; 19.4%); localized herpes simplex virus (n = 17; 13.7%); eczema herpeticum (n = 17; 13.7%); frequent otitis media, defined as >6 episodes up to 2 years of age (n = 14; 11.3%); cutaneous or pharyngeal group A *Streptococcus* infection (n = 13; 10.5%); and pneumonia (n = 7; 5.6%).

Patient dosing varied widely. Dosing for some patients was based on weight and for others by using a full or easily measurable fraction of the prefilled syringe. Patients from 3 centers received a fraction of medication from the prefilled syringe. For these patients, the entire quantity was re-aliquoted into a clean, volume-marked syringe. Excess was wasted at all centers except one that reported saving the excess for subsequent use. Weight-based dosing was retrospectively calculated for all patients. A loading dose was used in 80.2% (n = 89) of patients. The mean loading dose was 8.7 mg/kg (range 4-15.5; standard

deviation [SD] 2.6). Maintenance doses were prescribed every 2 weeks for all patients. Weight-based maintenance dosing was calculable for 106 patients, at a mean of 5.1 mg/kg/dose (range 2.0-15.3; SD 2.2) (Fig 1). Weight was not recorded for 5 patients (aged 15-17 years).

The cohort was subdivided into 3 distinct age groups to further analyze the variation in dosing: ≥ 12 years, 6-11 years, and <6 years (Table I). The weight-based loading dose (in mg/kg) was similar for the 3 age groups ($P = .1$). However, the weight-based maintenance dose for the 6- to 11-year age group was 6.4 mg/kg, significantly different from the other age groups ($P < .001$), with a wide range (2.5 to 15.3 mg/kg).

Additional subset analyses were performed to determine the proportion of patients in each age group who were treated with adult doses. Among those who received a loading dose, 66 (74%) received the full 600-mg (2-syringe) adult dose. The mean age of this group was 15.2 years (range 10.6-18.0 years; SD 2.0). The majority (92.3%) of patients older than 12 years received the full adult loading dose compared with 33.3% of children 6 to 11 years who received this dose. No patients (0%) in the birth to 5-year age group received an adult loading dose.

Eighty-one children (73%) received the 300-mg adult maintenance dose. The mean age of this group was 14.5 years (range 5.1-18.0 years; SD 2.9), including 66 (91.7%) of those >12 years, 14 (46.7%) of those 6 to 11 years, and 1 (12.5%) of those <5 years. The remaining 27% who received a lower maintenance dose had a mean age of 8.7 years

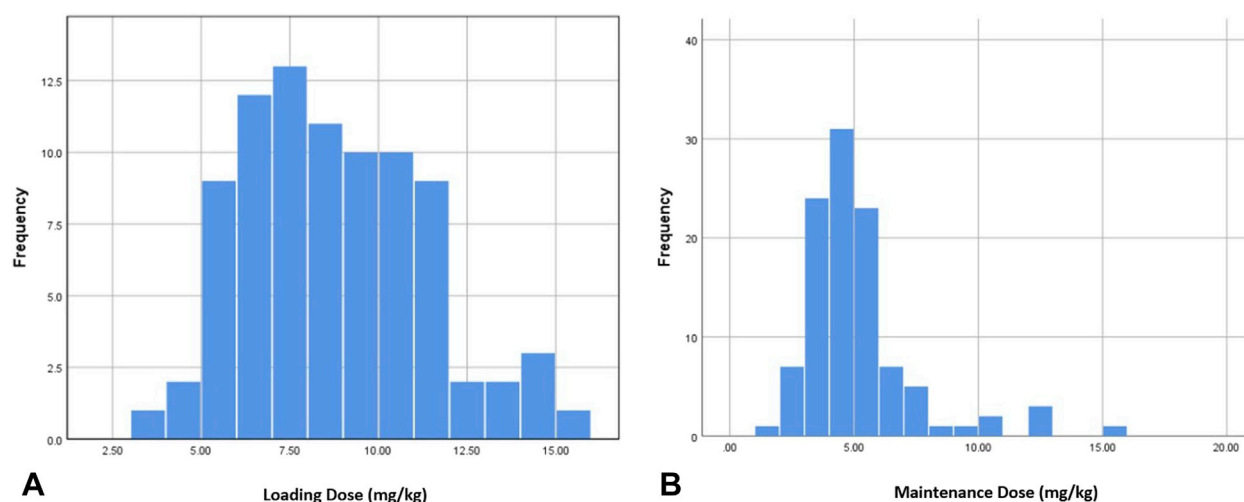


Fig 1. **A**, Loading dose. The mean weight-based loading dose was 8.7 mg/kg (range 4-15.5 mg/kg; standard deviation 2.6). **B**, Maintenance dose. The mean weight-based maintenance dose was 5.1 mg/kg (range 2.0-15.3 mg/kg; standard deviation 2.2).

Table I. Age-based dosing for dupilumab

Age (y)	No. receiving loading dose	Loading dose (mg/kg)			No. receiving maintenance dose	Maintenance dose (mg/kg)		
		Mean	Range	P value		Mean	Range	P value
12+	65	8.9	4.0-14.4	.1	72	4.5	2.0-12.2	<.001*
6-11	18	8.8	4.7-15.5		30	6.4	2.5-15.3	
0-5	6	6.5	5.0-8.0		8	4.7	2.0-7.2	

*The weight-based maintenance dose for the 6- to 11-year age group was significantly different from the other 2 age groups ($P < .001$).

(range 3.1-13.8 years; SD 3.2). The majority of these children (88%) received a maintenance dose of one-half the loading dose.

The mean number of doses received was 16.4, with a wide range (1-72 doses). Baseline and follow-up qualitative IGA scores were available for 95 treated patients. At baseline, 29.5% had disease rated as moderate and 70.5% as severe. At follow-up, 64.3% of patients experienced ≥ 2 -point IGA improvement; 22.1% reported a 1-point improvement; and 12.6% experienced no improvement. Of the 12 nonresponders, 4 received only 1 or 2 doses. IGA improvement was similar across age groups. The majority of patients in our cohort believed their eczema was improved and wanted to continue treatment.

Adverse events (AEs) were uncommon. Among the 111 treated patients, 2 had reports of a viral upper respiratory infection, 3 had injection site reactions, 10 had new or worsening conjunctivitis, and 6 had facial eruptions (Table II). No AEs prompted interruption of dupilumab treatment. There was one treatment discontinuation because of a lack of response after 6 months (12 doses of dupilumab).

DISCUSSION

Dupilumab was granted USFDA approval for adolescents 12 to 18 years of age 2 years after the March 2017 approval for adults. The pivotal clinical trial that supported adolescent approval was based on a 4-month prospective study that included 165 adolescents who received active drug.⁴ Our multicenter retrospective review includes 111 patients who were treated for an average of 9 months (and as long as 19 months). These data, collected before adolescent labeling, support positive treatment response and tolerability of long-term use of dupilumab in children as young as 3 years with moderate to severe AD. Despite the lack of pediatric-specific labeling, access to dupilumab was approved in the majority of patients, albeit after a significant delay.

The treatment response observed in our cohort was not significantly different from the data reported in the adult and adolescent trials. IGA improvement

Table II. Adverse events

Adverse event	This review No. (%)	Regeneron adolescent phase III trial ³ (%)
Injection site reaction	3 (2.7)	6.0-8.5
Conjunctivitis	10 (9.0)	9.8-10.8
Upper respiratory tract infection	2 (1.8)	7.2-11.2
Facial eruption	6 (5.4)	Not reported as an adverse event of special interest

in our cohort was somewhat comparable to a 50%, ≥ 2 -point IGA improvement reported for adults,^{5,6} but it was not directly comparable to the standard primary end point or IGA score 0 or 1 ("clear or almost clear") at week 16. For the placebo-controlled, prospective, industry-sponsored trial of dupilumab in adolescents, 24.4% of patients achieved an IGA score of 0 or 1.⁴

AEs were also not significantly different from the data reported in the adult and adolescent trials, except for the 6 patients (5%) who experienced facial dermatitis. This AE was also recognized post hoc in adults.⁷ The etiology of this eruption is currently unclear but was suspected to represent allergic contact dermatitis unresponsive to dupilumab.⁸

Associated atopic infectious and neurocognitive morbidities were common in these patients and similar to those reported in children with moderate to severe AD, supporting the need for systemic treatment. Although previously reported as AEs,^{2,4} increased cutaneous infections, including herpes labialis or eczema herpeticum, did not occur in our cohort while using dupilumab despite the high risk. Clinical trials typically include all observed potential AEs but do not recognize positive outcomes. In our cohort, unexpected, possibly drug-related, previously unreported positive outcomes included rapid resolution of long-standing warts and molluscum and marked subjective improvements in mood and mental health.

Table III. Dosing guidelines⁹

Ages	Weights (kg)	Loading dose		Maintenance dose		Frequency
		(mg)	(mg/kg)	(mg)	(mg/kg)	
≥12 to <18 y	≥60	600	≤10	300	≤5	q2wk
	≥30 to <60	400	6.7-13.3	200	3.3 to 6.7	q2wk
≥6 to <12 y	≥30	400	≤13.3	200	≤6.7	q2wk
	<30	200	≥6.7	100	≥3.3	q2wk
≥6 mo to <6 y	All weights	Not established		NA	2 to 6	q2wk

NA, Not established; q, every.

The recommended dupilumab dosing for adolescents is a 600-mg loading dose followed by 300 mg for maintenance for those weighing >60 kg, and a 400-mg loading dose followed by 200 mg for maintenance for those weighing <60 kg. The medication is dispensed in prepackaged, unmarked syringes. The smaller dose has been commercially available since October 2018 and was first approved for adults and adolescents with asthma. Optimal dosing for children <12 years and those weighing significantly <60 kg has not been defined and is important for both tolerability and treatment response. The majority of medications prescribed for children are custom-calculated based on body weight and easily administered when medications are available in liquid formulation. Clinicians not specifically trained in pediatrics are less familiar with prescribing medications that require weight-based calculations. Precise weight-based dosing is further complicated for injectable medications dispensed in premeasured syringes. This requires re-aliquoting or estimating the dose, as well as wasting excess. Saving additional medication for subsequent use is not advised. The consequence of these limitations for most of the patients in our study was either full or half-syringe dupilumab dosing, resulting in a wide range of calculated weight-based doses, especially for children in the 6- to 11-year age group. Clinicians prescribing dupilumab should be aware that the concentration of medication in the commercially available syringes is different for the 2 doses: 300 mg in 2 mL and 200 mg in 1.1 mL. Pending additional studies, pediatric weight-based dosing guidelines for younger, smaller children have been suggested (Table III).⁹

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