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COMMENTARY

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Use of dupilimab in pediatric atopic dermatitis: Access, dosing, and implications for managing severe atopic dermatitis

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1 | INTRODUCTION

The recent U.S. Food and Drug Administration (FDA) approval of dupilumab for atopic dermatitis (AD) has heralded "the decade of eczema," but it may take several more years before the majority of affected patients are able to gain access to this targeted treatment. Dupilumab is currently FDA approved for moderate-to-severe AD only in adults (≥ 18 years of age). For children, who represent the majority of patients with AD, FDA approval is not anticipated before 2019, beginning with those ≥ 12 years old. The first peer-reviewed data documenting use of dupilumab in six pediatric patients appear in this issue of *Pediatric Dermatology*. In both the case series performed by Treister and Lio and the phase 2a study,[1] patients treated with dupilumab had improvements in AD severity (investigator's global assessment, body surface area, Eczema Area and Severity Index, peak pruritus numeric rating scale) that were similar to those observed in adults.[2] We would like to put the results of this small case series in perspective and add a summary of our own accumulated experience with gaining off-label access, dosing/administration, and managing more than 50 pediatric patients with dupilumab.

2 | MANAGING SEVERE ATOPIC DERMATITIS

Despite recommendations by the American Academy of Dermatology[3] and the American Academy of Allergy, Asthma, and Immunology/American College of Allergy, Asthma, and Immunology[4] to avoid systemic corticosteroids, prednisolone remains the only FDA-approved systemic treatment for severe AD in pediatric patients. Given the risks of prednisolone and recognized rebound with discontinuation, pediatric dermatologists have turned to off-label treatments for their patients with moderate-to-severe AD. In a recent poll of North American pediatric dermatologists, cyclosporine (45%) and methotrexate (30%) were noted to be the most common first-line systemic medications for pediatric AD. Many children who initiate cyclosporine are transitioned to methotrexate or mycophenolate

mofetil for long-term disease control.[5] Concern for severe adverse effects is a major deterrent to using these systemic medications, including renal toxicity and hypertension for cyclosporine, hepatic toxicity for methotrexate, bone marrow suppression for mycophenolate mofetil, and the possibility for immunosuppression and malignancy for all of the currently available standard-of-care oral medications. Nevertheless, most children are able to tolerate these drugs well and the cost of these less expensive, higher risk, off-label immunosuppressant medications is generally covered by payers without prior authorization or step-edits.

Our own experience and that described by Treister and Lio suggest that dupilumab is highly effective for most children with moderate-to-severe AD, and may prove to be a safer alternative to the currently available systemic options. However, concerns have been expressed about access, dosing challenges, and potential toxicity, including unknown long-term toxicity, in pediatric patients with AD.

2.1 | Access

Access to newer, more costly medications such as dupilumab is often restricted by step-edits and age-based denials. The benefit of dupilumab has been documented to outweigh its cost by the Institute for Clinical and Economic Review (ICER), an independent, foundation-funded, nonpartisan research organization that evaluates the clinical and economic value of prescription drugs. Their 2017 review concluded that at an estimated average net price of $31 000 per year, treatment with dupilumab represents a good value for adults with moderate-to-severe AD.[6] Despite the documented value, many payers still require step-edits and often deny coverage. Patient age is one of the easiest justifications to implement for denial of coverage, placing effective systemic treatment beyond reach for many desperate pediatric patients and their caregivers.

In our experience to date, all dupilumab prescriptions for pediatric patients have required prior authorization and nearly all have required at least a first-level appeal. Many have also required a second-level appeal before being eligible for external/peer-to-peer review. To expedite the process, we have found the following steps to be helpful for gaining authorization: request peer-to-peer review as soon as possible; when speaking to the peer reviewer, request the reviewer's name and credentials, their experience with pediatric patients; state the intention to record this information in the patient record. After denied appeals by private insurers, some have successfully petitioned their state departments of insurance, although opportunities for this appeal vary by state (see https://www.naic.org/state_web_map.htm for contact information by state).

Appeal letters should include references to published data on the safety and efficacy in adults and children (see references 1 and 2, and Treister and Lio article herein), describe the severity of the patient's AD and atopic comorbidities as well as any previously failed treatments and/or any prior hospitalizations for AD, and place dupilumab treatment in the context of other systemic treatments that may be higher risk (eg, systemic corticosteroids, methotrexate, azathioprine, mycophenolate mofetil, cyclosporine), relatively contraindicated for a particular patient, or more costly (eg, hospitalization, intravenous immunoglobulin G [IVIG], interferon γ). The following language may also be helpful: "Your denial to support this treatment and thereby expose this patient to other less well-studied, and potentially higher-risk second line agents offers no added potential benefit, and is not supported by any current evidence-based guidelines. Your attempt to enforce general, age-based criteria without regard to the extenuating factors in this case is essentially the practice of medicine by an organization." Note that the so-called corporate practice of medicine such as this is prohibited by several states.[7,8]

2.2 | Dosing and Administering Dupilumab

The optimal approach to pediatric dupilumab dosing using age- and weight-based approaches is currently under investigation (Table 1). The first pediatric clinical trial included 78 patients aged 6 to < 18 years in a phase 2a open-label, ascending-dose, sequential cohort study.[1] These children received a single 2- or 4-mg/kg injection, followed 8 weeks later by the same dose given weekly for 4 weeks. Ongoing phase 3 clinical trials in children 6 years of age or older are utilizing weight-based dupilumab dose ranges, up to a maximum equivalent adult dose. Ongoing phase 2 dose-ranging trials in children < 6 years of age are utilizing a strictly weight-based dosing regimen. A long-term extension trial including children 6 months to ≤ 18 years is also exploring the safety and efficacy of these dose ranges given as often as once a week, or as infrequently as once a month.

The six-patient cohort by Treister and Lio included two 11-year-olds, each weighing 40 kg, and one 15-year-old weighing 50 kg, who received the adult dose. Three smaller patients, ages 7, 10, and 11, weighing 27 to 35 kg, were given half that dose. Using this approach, the weight-based maintenance dose ranged from 5 to 7.5 mg/kg every other week, somewhat higher than the dosage used in controlled clinical trials published thus far. The loading doses ranged from 8.6 to 15 mg/kg, somewhat higher than the weight-based dosing range in clinical trials published to date. Pending controlled clinical trial data, our consensus dosing suggestions (Table 2) are based on collective experience as investigators in clinical trials and in our clinical practices.

Regarding administration, dupilumab is currently only commercially available as a 2-mL, 300-mg, single-use, prefilled syringe. The syringe has no markings to indicate the amount of drug in the syringe to guide partial dosing, so attempts to give a fraction of this dose to children is complicated by accuracy, sterility, and drug waste.

In the absence of a well-defined pediatric dosing regimen and delivery system, Treister and Lio chose to treat their pediatric patients with either the full adult dose or an estimated half dose. The authors indicated that this dose was achieved by carefully discarding the appropriate amount into a graduated cylinder and injecting the remaining solution into the patient (personal communication). Another option would be to transfer the entire 2-mL contents of the

TABLE 1 Pediatric Dupilumab Dosing Currently Under Investigation in Controlled Clinical Trials

			Loading dose		Maintenance Dosing		
Trial	**Ages**	**Weights**	**mg**	**mg/kg**	**mg**	**mg/kg**	**Frequency**
NCT03054428 (Phase 3)[11]	≥ 12 to < 18 y	≥ 60 kg	600	≤ 10	300	≤ 5	Q2W
		≥ 30 to < 60 kg	400	6.7 to 13.3	200	3.3 to 6.7	Q2W
		All weights	600	≤ 20[a]	300	≤ 10	Q4W
NCT03345914 (Phase 3)	≥ 6 to < 12 y	N/A	Under investigation, not publicly available				
NCT02612454 (Long-term extension)	≥ 6 mo to < 18 y	N/A	Under investigation, not publicly available				
NCT02407756 (Phase 2a dose-ranging)[1]	≥ 6 to < 12 y	All weights	2 or 4 mg/kg followed 8 wk later by the same dose Q1W (×4)				
	≥ 12 to < 18 y	All weights	2 or 4 mg/kg followed 8 wk later by the same dose Q1W (×4)				
NCT03346434 (Phase 2/3 PK)	≥ 2 to < 6 y	N/A	Under investigation, not publicly available				
	≥ 6 mo to < 2 y	N/A	Under investigation, not publicly available				

N/A, not available; PK, pharmacokinetics; Q2W, every 2 wk; Q4W, every 4 wk.
[a]Based on 3rd percentile of weight for 12-y-olds (30 kg).[18]

TABLE 2 Suggested Pediatric Dupilumab Dosing Regimens

		Loading dose		Maintenance dosing		
Ages	**Weights**	**mg**	**mg/kg**	**mg**	**mg/kg**	**Frequency**
≥ 12 to < 18 y	≥ 60 kg	600	≤ 10	300	≤ 5	Q2W
	≥ 30 to < 60 kg	400	6.7 to 13.3	200	3.3 to 6.7	Q2W
≥ 6 to < 12 y	≥ 30 kg	400	≤ 13.3	200	≤ 6.7	Q2W
	< 30 kg	200	≥ 6.7	100	≥ 3.3	Q2W
≥ 6 mo to < 6 y	All weights	Not established		N/A	2 to 6	Q2W

Q2W, every 2 wk.

prefilled syringe to a 1–3-mL syringe, discarding the appropriate amount, and administering the remainder to the patient. Tragically, this necessitates wasting significant amounts of a very expensive drug, but guidelines do not exist to support a mechanism for multi-dosing from a single syringe. Regulations governing realiquoting and dispensing a partial dose fall under the FDA's guidance on Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application.[9] Of special concern is the repackaging of sterile and biologic drugs, which are particularly susceptible to contamination and degradation. This published guidance advises aseptic technique when realiquoting sterile drugs. In our experience, identification of qualified pharmacies has been difficult, and some cited additional fees for this service. For patients who are unable to access pharmacy-repackaged pediatric doses of dupilumab, clinicians should be aware of the importance of ensuring informed consent from patients and/or caregivers for use of an off-label, repackaged drug (Figure 1).

The very high cost of this drug warrants special attention to avoid additional unnecessary waste. Because of the burden of disease borne by the families of pediatric patients with severe AD, special care of this medication may require more targeted education than for adult patients. In addition to the complexities of realiquoting, the need for refrigeration is worth emphasizing.

2.3 | Potential Risks of Dupilumab in Pediatric Patients

The most frequently reported adverse events in adults treated with dupilumab compared with those treated with placebo were injection site reactions (10%), conjunctivitis (10%), oral herpes (4%), keratitis (< 1%), and eye discomfort (≤ 1%).[10] Early published data document a similar profile of adverse events in pediatric patients. Treister and Lio report that there were no adverse events in their case series, and in the phase 2a pediatric study, the most frequently reported adverse event was nasopharyngitis.[1] In the open-label phase 2a study in Europe, injection site reactions occurred in about 5% and conjunctivitis in 11% of children aged 6-11 years.[1] In the phase 3 study of patients ≥ 12 to < 18 years old, adverse events in the dupilumab versus placebo groups included injection site reactions (6-8.5% vs 3.5%) and conjunctivitis (10%-11% vs 5%).[11] Conversely, skin infections were less common in the dupilumab-treated patients (11%-13% vs 20%),[11] reflecting recent meta-analysis documenting a significantly decreased incidence of infections, including herpes simplex virus, in > 2700 adults treated with dupilumab in clinical trials for up to 52 weeks.[12]

Patients and caregivers should be encouraged to report any eye discomfort and physicians should regularly evaluate patients for ophthalmologic complaints. Patients with a history of eye discomfort

The term "on-label" refers to use of a medication for an indication or age group that has been specifically studied and approved by the US Food and Drug Administration (FDA). Conversely, a medication used "off-label" is for people with a different disease or outside of the approved age range. The great majority of medications prescribed for infants and children with skin disease are used off-label, because there are few, if any, on-label options.
In addition, dupilumab is currently available only as a single-use adult dose, and must be repackaged for pediatric use.

A physician can prescribe any medication at any dose for off-label use if, in that physician's opinion, the possible benefits of the medication are greater than the possible risks and the patient (or parent/guardian) provide consent. Signing this form indicates that I understand the risks and benefits of the recommended repackaged off-label dupilumab to treat atopic dermatitis. It does not obligate us to use the medication.

FIGURE 1 Example informed consent

may be at higher risk for developing conjunctivitis on dupilumab and should be counseled and monitored more closely. In the absence of defined pathophysiology, referral to a corneal specialist may provide the most insight for patients with objective findings.

As with any new drug, safety issues unrecognized in clinical trials may arise after approval. An emerging adverse effect recently reported as possibly related to dupilumab is a poorly characterized facial eruption, of unclear etiology.[13] In some of these cases, allergic contact dermatitis has been suspected, based on a possible drug-related increase in sensitivity toward type 1 helper T cell-biased haptens.[14] An additional concern is the risk and impact of developing anti-drug antibodies, an emerging complication of the more well-established biologic agents.[15]

2.4 | Summary

Severe AD is life altering. Early treatment and control may impact the natural history of the disease. Alternative systemic treatment options other than prednisone are all off-label and without well-defined optimal dosing or formulation. Dupilumab is the first FDA-approved targeted treatment for severe AD. Access has been delayed for children, arguably those who may derive the most benefit. Although a meeting of the Dermatologic and Ophthalmic Advisory Committee on March 9, 2015 unanimously supported early inclusion in clinical trials of children with severe AD,[16] dupilumab pediatric approval is not anticipated until 2019, beginning with patients over age 12. We applaud the pioneering effort by Regeneron to include children as young as 6 months of age in dupilumab clinical trials but lament the delay in timely access to this valuable drug for younger children.

Meanwhile, subspecialists are increasingly choosing to treat children off-label with dupilumab perhaps due to its perceived safety and efficacy. Candidates for dupilumab have included those unable to tolerate or with contraindications for treatment with a systemic immunosuppressant, those unresponsive to other systemic therapies, and those transitioning from methotrexate or cyclosporine after large cumulative doses or from much more costly IVIG. A retrospective review is being conducted by several authors of this commentary and will include results based on 50 to 100 patients at 9 centers.

Dupilumab is a welcomed addition to the AD armamentarium for children with moderate-to-severe AD who are candidates for systemic therapy. Patient selection should be individualized, and barriers to use should be minimized given the physical, emotional, and psychological comorbidities of this disease. Pediatric patients deserve timely access to new treatments given the impact of AD on growth and development, socialization, school functioning and attendance, and direct and indirect health care costs. Until optimal pediatric dupilumab dosing and administration have been defined, clinicians caring for children with severe AD that require systemic treatment are between a rock and a hard place. Fortunately, the pipeline for AD is robust and clinical trials are including pediatric patients earlier in development.[16,17] But until other options are available, dupilumab may be the best choice, despite its limitations.

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CONFLICT OF INTERESTS

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