Remarkable response to dupilumab in a 5-year-old patient with severe, recalcitrant atopic dermatitis

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INTRODUCTION

Atopic dermatitis (AD) is a pruritic, inflammatory skin disorder that is frequently seen in children.[1] Several factors contribute to AD development and include dysregulation of innate immune responses, enhanced type 2 immunity, altered skin microbiome, and skin barrier defects.[2,3] Research findings suggest that many of these abnormalities may be caused by the biological action of type 2 immune mediators, interleukin (IL)-4 and IL-13.[4,5]

Abbreviations used:

AD:	atopic dermatitis
CsA:	cyclosporine
IL:	interleukin
NB-UVB:	narrow-band ultraviolet B
SCORAD:	SCORing Atopic Dermatitis
QoL:	quality of life

CASE PRESENTATION

We report on a 5-year-old girl with mild, intermittent asthma, allergic rhinitis, and IgE-mediated cow's milk allergy who presented in 2018 for an excoriated, erythematous dermatitis that affected greater than 75% of her body surface area. Her AD, which began at age 1 year, worsened after she developed hand, foot, and mouth disease in 2016. Since then, her AD was never adequately controlled despite numerous topical and systemic therapies. Because of uncontrolled pruritus, the patient slept approximately 4 hours nightly, resulting in a significant impact on quality of life (QoL) for both her and the family.

While she was under our care, the patient's serum IgE ranged from 2079 to 12,275 IU/mL with total eosinophil counts ranging from 800 to 4000 cells/μL. The patient was sensitized to numerous aeroallergens, including cat, dog, horse, dust mites, silver maple tree, timothy grass, sheep sorrel, and ragweed. Evaluation for food allergy found sensitization to egg white, cow's milk, peanut, green pea, and soy. Although the family and the patient went to great lengths to avoid or reduce exposures to relevant allergens and irritants, and tried targeted as well as empiric elimination diets, the patient's AD continued to worsen.

The patient's treatment regimen in 2017 included daily emollients, bleach baths 2 to 3 times weekly, hydrocortisone 2.5% cream (to face), triamcinolone 0.1% ointment (to body), tacrolimus 0.1% ointment (to face), wet wraps for the extremities, hydroxyzine 75 mg daily (4 mg/kg/d), narrow-band ultraviolet B (NB-UVB) phototherapy, cyclosporine (CsA) up to 100 mg (5.5 mg/kg/d), multiple courses of oral corticosteroids, and suppressive doses of acyclovir to prevent recurrent eczema herpeticum, which was discontinued in March of 2018. When she presented to us in July 2018, the patient was on CsA 75 mg daily (4 mg/kg/d), Medrol 12 mg daily (0.67 mg/kg/d), desonide 0.05% ointment, triamcinolone 0.025%

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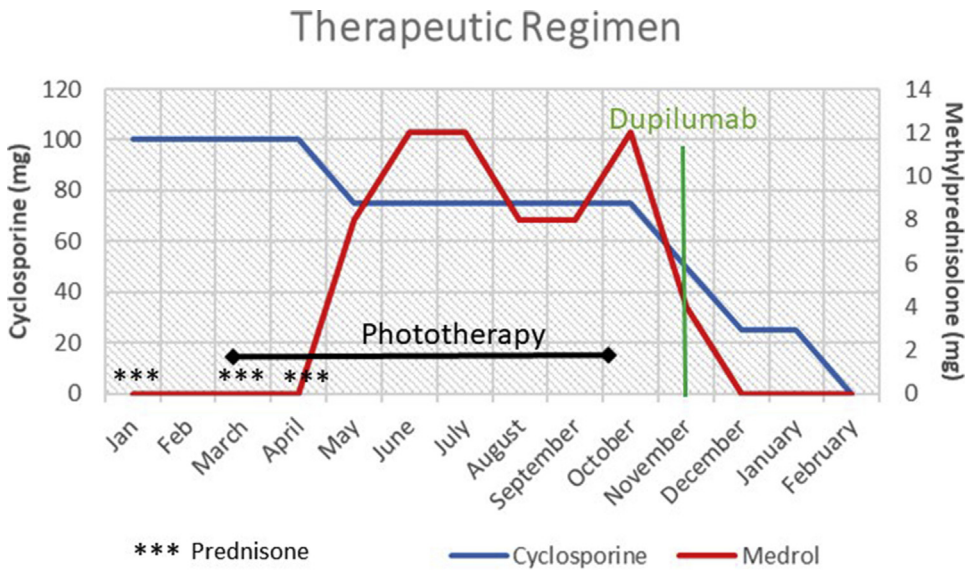

Fig 1. Therapeutic regimen from January 2018 to February 2019.

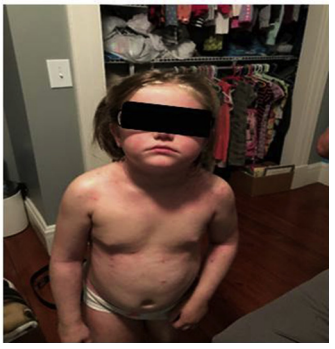

Fig 2. AD before dupilumab.

Fig 3. AD 72 hours after loading dose.

ointment, and NB-UVB phototherapy sessions 2 to 3 times per week (Fig 1). Other medications included cyproheptadine 6 mg nightly (0.33 mg/kg/d), levocetirizine 10 mg daily (0.55 mg/kg/d), and montelukast 4 mg nightly. These dosing parameters were based off her weight of 18 kg in 2017. Despite adherence with these treatments, the patient's AD failed to improve.

On examination, the patient had widespread excoriated, erythematous, and eczematous papules and plaques scattered over 75% of her body, including her face, neck, trunk, and all 4 extremities, with prominent Dennie-Morgan lines (Fig 2). Her SCORing Atopic Dermatitis (SCORAD) was 73, and her Investigator Global Assessment was 4. Additionally, she was Cushingoid in appearance and had gained roughly 10 pounds in the 5 months prior to presenting to us.

Given the severe, persistent nature of her AD despite aggressive systemic and topical therapies, a single-patient Investigational New Drug application was approved to provide dupilumab on a compassionate-use basis. The patient received a loading dose of 400 mg subcutaneously in November 2018, followed by 200 mg dose every 2 weeks. The patient weighed 25.9 kg at the initiation of dupilumab, and dosing parameters were based on ongoing clinical trials with the use of dupilumab in the pediatric population. Within 3 days after receiving the loading dose, the patient's itching significantly improved, resulting in improved sleep and QoL. Her parents reported near complete resolution of all eczematous lesions including her face, neck, back, and lower legs (Fig 3). At her 2-week follow up, her SCORAD was 12.8 and her Investigator Global Assessment was 1 (Fig 4). Within 2 weeks of her first dose of dupilumab, the patient's reliance on antihistamines decreased to only as needed. Six weeks after her loading dose, she was off systemic steroids, and her

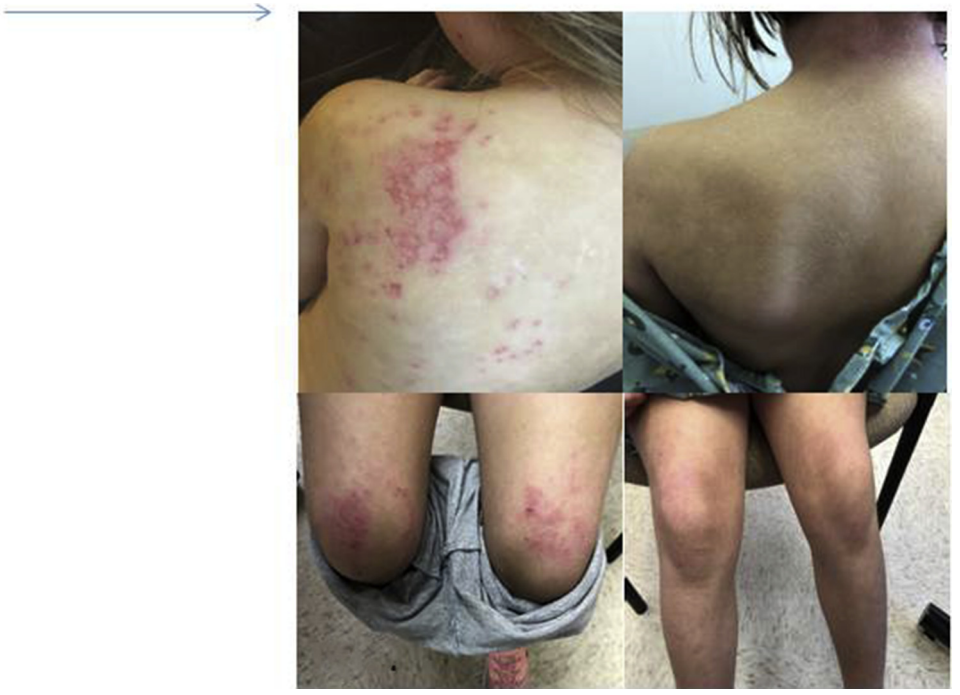

Fig 4. AD 2 weeks after loading dose.

CsA was discontinued 3 months after her loading dose (Fig 1).

DISCUSSION

In most cases, AD can be managed by minimizing exacerbating factors, good skin care, and topical therapies including corticosteroids, calcineurin inhibitors, and a phosphodiesterase-4 inhibitor, sometimes combined with antihistamines and topical or oral antibiotics as needed.[6] Patients with moderate-to-severe disease that do not improve with these conventional therapies may benefit from second-line therapies such as phototherapy and systemic medications, including systemic glucocorticoids, CsA, methotrexate, mycophenolate mofetil, or azathioprine. These systemic medications, however, require laboratory monitoring and come with potentially serious side effects, rendering them undesirable for long-term use, especially in children with developing immune systems that may be more vulnerable to systemic immunomodulatory agents.[7]

DUPILUMAB

In March 2017, the US Food and Drug Administration approved dupilumab for the treatment of adults with moderate-to-severe AD and in March 2019 approved it for adolescents aged 12 years to 17 years with moderate to severe AD. This is now considered a first-line treatment for moderate-to-severe AD in these age groups. Dupilumab is a fully humanized monoclonal antibody against the shared α subunit of IL-4 and IL-13 receptors and blocks the actions of these T-helper type 2 cytokines that are commonly found in the skin of AD patients.[8] The most common side effects associated with dupilumab are local injection site reactions and a range of ocular complaints commonly reported as dry eye, noninfectious conjunctivitis, or blepharitis. Dupilumab does not require routine laboratory monitoring, and there appears to be no increased risk of infection.[9]

CONCLUSION

Ten percent to 20% of children suffer from AD, which can adversely affect QoL for the patient and the family. Although most cases can be treated with conventional therapy, severe cases require systemic therapy, which may have significant adverse effects. We present the case of a 5-year-old girl with severe, debilitating AD despite allergen avoidance measures, good topical skin care, and systemic treatment with CsA, NB-UVB and Medrol, who responded rapidly and dramatically to dupilumab. To our knowledge, this is the first case of dupilumab in someone as young as 5 years of age. It is noteworthy that dupilumab was more effective than systemic therapy with both steroids and CsA, was steroid sparing, and allowed tapering and eventual discontinuation of CsA. This patient has not experienced a flare of her eczema herpeticum despite approximately 3 months of dupilumab treatment. We feel this case highlights the great potential of dupilumab to treat severe AD in the pediatric population.

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