

Safety of dupilumab in a 5-month-old infant with severe atopic dermatitis

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Abstract

Dupilumab is a fully humanized monoclonal antibody that suppresses Th2-mediated inflammation by inhibiting signaling of interleukin-4 and interleukin-13 through the interleukin-4 alpha receptor subunit, and is approved by the FDA for the treatment of moderate to severe atopic dermatitis (AD) in children 6 years of age and older. While initial data from phase 2 trials in children less than 6 years are promising, dupilumab use in children less than 6 months of age is not well studied. Here we present a case of a 5-month-old boy with severe primary AD, eosinophilia, hypogammaglobulinemia, and poor weight gain, who was successfully treated with dupilumab and experienced no serious adverse effects. To our knowledge, this is the youngest patient to receive dupilumab to date.

KEYWORDS

atopic dermatitis, dupilumab, eczema, monoclonal antibody, systemic therapy

1 | INTRODUCTION

Atopic dermatitis (AD) is the most common inflammatory skin condition in pediatric patients, with 2% experiencing moderate to severe disease¹ and 45% facing onset before age 6 months.² In infants, AD can profoundly impact quality of life, leading to itching, fussiness, sleep loss, poor feeding, and poor growth.^{3–5} Treatment is largely restricted to topical corticosteroids (TCS) for patients in this age group, who are also at the highest risk for systemic absorption with resultant growth restriction and iatrogenic adrenal insufficiency due to their higher body surface area-to-weight ratio.⁶ Despite the risks of prolonged TCS use in infants with moderate to severe AD, alternative therapies including nonsteroidal topicals such as calcineurin inhibitors and systemic immunosuppressants such as methotrexate are limited in use.^{7–9}

Dupilumab, a targeted systemic therapy that suppresses Th2-mediated inflammation by inhibiting interleukin-4 (IL-4) and interleukin-13 (IL-13) through the IL-4 alpha receptor subunit, has been shown to be a safe and effective treatment for moderate to severe AD in children 6 years of age and older, leading to rapid disease improvement with minimal adverse effects.^{10,11} While results from phase 2 trials

in patients 6 months to 6 years of age show substantial clinical benefit with a similar safety profile to studies in older pediatric patients and adults, no case reports or trials have been published that describe use of dupilumab in patients younger than 6 months of age.¹² Here, we present a case of a 5-month-old boy with severe AD, eosinophilia, hypogammaglobulinemia, and poor weight gain, who was successfully treated with dupilumab after failing aggressive TCS therapy for 8 weeks. To our knowledge, this is the youngest patient in the literature to receive dupilumab to date.

2 | CASE REPORT

A 3-month-old, full-term boy with history of parental consanguinity and microretrognathia was transferred from an outside hospital for further evaluation of diarrhea, poor weight gain, severe eosinophilia, and a diffuse rash. He was noted at birth to have micrognathia, which was treated using mandibular distraction with titanium. At 1 month of life, he developed a new rash near the distractor site, concerning for infection versus allergic reaction to titanium. Complete blood count showed marked eosinophilia with a maximum absolute eosinophil



FIGURE 1 Diffuse erythematous eczematous dermatitis on the right arm at admission

count (AEC) of 42,705 cells/ μ l. Due to concern for titanium allergy, mandibular distractors were removed and replaced with polylactic acid, and methylprednisolone was started for eosinophilia. He was also transitioned to an amino acid-based formula given persistent diarrhea and poor weight gain ($<0.01\%$ ile). Three days after onset of rash, he developed a pruritic, eczematous eruption involving his face, trunk, extremities, and buttocks. Despite treatment with hydrocortisone and emollients, the rash continued to progress.

Physical exam on admission showed pink-erythematous, scaly patches and plaques across the face, extremities, and trunk (Figure 1). Multiple large erosions were present on the buttocks and inguinal folds consistent with Jacquet's dermatitis, given morphology and history of diarrhea with poor weight gain. Extreme pruritus and dysmorphic facies with micrognathia, small downslanting palpebral fissures, and large, low set ears were noted. Differential diagnosis was broad and included irritant contact dermatitis, AD (primary or in the setting of an underlying immunodeficiency given his eosinophilia, poor weight gain, and history of consanguineous parents), allergic contact dermatitis, nutritional deficiency, and Netherton syndrome or other genodermatoses. Treatment with hydrocortisone 2.5% ointment/petrolatum ointment twice daily to the face and body, and triamcinolone 0.025% ointment twice daily to the buttocks was initiated.

While his diffuse eczematous eruption and erosive diaper dermatitis improved initially, they re-worsened 1 week later in the setting of a prednisone taper. Increased potency topical steroids including triamcinolone 0.025% ointment twice daily and ultimately wet wraps with triamcinolone 0.1% ointment did not improve the eruption despite weeks of therapy. Addition of mupirocin ointment twice daily to the buttocks also did not help, and HSV and CMV PCRs from the erosions were negative. At this point, workup for an underlying immunodeficiency or nutritional deficiency by genetics, immunology, and metabolism was recommended. Metabolic workup including serum zinc, urine organic acids, acylcarnitine levels, and cystic fibrosis genetic testing was normal. Nutrition labs including vitamin D, B12, and iron studies were also normal. Thorough immunologic testing revealed hypogammaglobulinemia (IgG 12 mg/dl, IgA <6 mg/dl, IgM 5 mg/dl, and IgE 6 IU/ml) with low B cells (150 cells/ μ l) and up-trending eosinophilia (peak AEC 12,380 cells/ μ l) with suspicion for an underlying genetic disorder such as SCID with Omenn syndrome or Hyper IgE syndrome.



FIGURE 2 Resolution of eczematous patches on the bilateral lower extremities and trunk 1 year after starting dupilumab

Extensive genetic testing including whole exome sequencing and targeted sequencing of *DOCK8* failed to identify any pathogenic mutations (including normal genetics for *STAT3*, *SPINK5*, and *DSG1*). In addition, bone marrow biopsy was nondiagnostic and cardiac workup for end organ damage was negative. As such, the patient's extensive dermatitis and marked eosinophilia were deemed secondary to severe primary AD. He was started on monthly subcutaneous immunoglobulin (SCIG) 500 mg/kg/dose for hypogammaglobulinemia, and this dose was gradually increased to 500 mg/kg SCIG weekly (2 g/kg/month).

Given the severe and persistent nature of his AD, despite 2 months of treatment with multiple, aggressive topical regimens, nonformulary approval to initiate dupilumab was obtained. Based on limited studies of dupilumab in infants, the patient was started on dupilumab 4 mg/kg subcutaneously every 2 weeks. Clinical improvement was observed just 4 days after the first injection, though he was again noted to have up-trending eosinophils, which was presumed to be a side effect from dupilumab and eventually stabilized. After 1 month, dupilumab was increased to 6 mg/kg every 2 weeks to optimize disease control. His AD continued to improve markedly on this new dose, which he remained on, and topical steroids were weaned to as-needed use only by his 5-month follow-up visit. Skin prick testing to food allergens performed 3 months later was negative. He continued to remain clear more than 1 year after initiation of therapy (Figure 2).

Consent statement: Informed consent and releases from the parent(s)/guardian(s) to publish photographs was obtained.

3 | DISCUSSION

Dupilumab is the first and only targeted systemic therapy for the treatment of moderate to severe AD, which was first approved in adults in 2017^{13–15} and has since been approved for adolescents and children as young as 6 years of age.^{10,11,16,17} While off-label access to dupilumab is available for children less than 6 years of age with AD who have failed standard therapy, no studies have been published

that describe the use of dupilumab in infants younger than 6 months. Recent data from a multicenter, phase 2 trial evaluating the safety and efficacy of single-dose dupilumab in children between 6 months and 6 years of age showed that dupilumab is generally well-tolerated in infants and significantly reduced severity of AD, though slightly better responses were seen in older compared to younger patients.¹² While our patient was ultimately given the diagnosis of severe primary AD, it is possible that his eczematous dermatitis was due to an unidentified immune disorder. While he did markedly improve with dupilumab, he was also started on monthly SCIG just prior to initiating dupilumab and improvement may have been due to dupilumab, SCIG, or a combined effect from both therapies.

Trials in adults and children have demonstrated similar safety profiles. Adverse events are rarely reported with dupilumab and include conjunctivitis, injection site reaction, facial eruptions, and viral upper respiratory infections.¹⁸ Eosinophilia is a rare side effect that was seen in our patient, whose baseline eosinophilia was initially aggravated after dupilumab initiation but has since stabilized. These potential side effects from dupilumab are substantially less severe than those observed with systemic immunosuppressants like cyclosporine, methotrexate, mycophenolate, and azathioprine. Our patient experienced no serious adverse effects from dupilumab.

Studies of dupilumab in pediatrics have reiterated the need for additional studies into weight-based dosing guidelines, particularly for children who are less than 15 kg.^{12,18,19} Dupilumab has demonstrated nonlinear, target-mediated pharmacokinetics, with faster per-kilogram of total body weight clearance in smaller individuals.¹⁷ Increased per kilogram of total body weight dosing in children may be related to their higher body surface area to weight ratio or to other mechanisms, such as increased IL-13 gene expression in nonlesional AD skin among children, leading to faster drug elimination by receptor-mediated pathways.^{12,20} Our patient initially received 4 mg/kg of dupilumab, which was selected based on results from the phase 2a trial.¹⁶ After 1 month, his dose was increased to 6 mg/kg, which is comparable to the dose given for patients between 6 and 12 years of age.¹⁸

Given that nearly half of all patients with AD develop symptoms before 6 months of age, dupilumab could provide significant therapeutic benefit to other young infants with moderate to severe AD who have failed conventional therapy. While more robust studies of dupilumab in infants less than 6 months of age are warranted, potential effects of immunomodulating therapies on the developing immune system will make performing these studies challenging. Our patient was found to have immune dysregulation at baseline but responded remarkably to dupilumab.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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