CASE REPORT

Dupilumab: One therapy to treat multiple atopic diseases

Fatima Bawany, BA, Abigail I. Franco, MD, and Lisa A. Beck, MD
Rochester, New York

Key words: allergic rhinitis; asthma; atopic dermatitis; chronic sinusitis; dupilumab; eosinophilic esophagitis.

INTRODUCTION

Dupilumab is a fully humanized monoclonal antibody targeting the interleukin (IL)-4Ra subunit of the IL-4 and IL-13 receptors. IL-4 and IL-13 are type 2 cytokines involved in the pathogenesis of atopic dermatitis (AD) and allergic diseases including asthma, food allergy, allergic rhinitis (AR), eosinophilic esophagitis (EoE), and chronic rhinosinusitis with nasal polyposis (CRwNP). Therefore, dupilumab has been hypothesized as a potential treatment for all of these atopic conditions, but is currently only approved by the US Food and Drug Administration for patients 6 years and older with moderate-to-severe AD, 12 years and older with moderate-to-severe asthma, and adults with CRwNP. It is not uncommon for AD patients to have a history of multiple allergic conditions; it is less common to have all of them coexisting (ie, active) concurrently. To our knowledge, this is the first case report of a pediatric AD patient with multiple comorbid allergic conditions who experienced objective improvements in all of his conditions (AD, EoE, asthma, AR, and chronic sinusitis [CS]) with dupilumab treatment.

CASE REPORT

A 9-year-old boy presented to the dermatology clinic for management of severe lifelong AD. His family history was significant for seasonal allergies (parents/siblings), AR and CS (mother), and asthma and EoE (father), the latter of which required esophageal dilations. The patient’s comorbid conditions included extensive EoE, asthma, food/environmental allergies, AR, and CS, each of which will be discussed separately. His mother reported that his skin disease did not respond to moisturizers, topical prescriptions (corticosteroids, tacrolimus, crisaborole), oral antibiotics (7 courses), narrow-band ultraviolet B phototherapy (2 years), methotrexate (4 months), and oral steroids (15 courses). Examination found diffuse xerosis and widespread erythematous and excoriated papules and plaques, most notable on the antecubital fossae, knees, and popliteal fossae. Cyclosporine, 100 mg/d (3.2 mg/kg/d) was initiated, along with triamcinolone 0.1% cream plus ointment for the body, tacrolimus 0.1% ointment for the face, and bleach baths. After 11 months of cyclosporine, he experienced improvement in symptoms but had hyperkalemia, necessitating a reduction in cyclosporine dosage. After 11 months of cyclosporine, he experienced improvement in symptoms but had hyperkalemia, necessitating a reduction in cyclosporine dosage. Ultimately, the patient and his mother decided to enroll in a randomized, double-blinded, placebo-controlled trial.
controlled phase 3 trial of dupilumab for children 6 to 12 years old (R668-AD-1652/NCT03345914). He was randomly assigned to dupilumab, 200 mg, or placebo bi-weekly for 16 weeks, followed by an open-label extension (OLE) of dupilumab, 200 mg biweekly (R668-AD-1434/NCT02612454). He turned 12 during the OLE and, because the US Food and Drug Administration approved dupilumab for adolescents with AD, was transitioned to dupilumab through his commercial insurance.

Although the randomization during the first 16 weeks remains unknown, he experienced substantial improvements in AD during his 57 weeks in the trial (Fig 1, A). At the end of the trial, his only remaining lesions were on the antecubital/popliteal fossae and neck. His disease severity and quality-of-life measures also improved markedly (Fig 1, B).

Before dupilumab treatment, he missed many school days and complained of constant pruritus, sleep disturbances, difficulty focusing, and low self-esteem. After treatment, he had substantially reduced pruritus, slept uninterrupted through the night 95% of the time, found it easier to concentrate, and felt more confident. The dupilumab was well tolerated with the exception of conjunctivitis (a known adverse effect of the drug), which resolved with 3 weeks of 1% prednisolone acetate eye drops.

Several months after the trial ended, he had only scattered excoriations on the right antecubital and popliteal fossae (Fig 1, A). Additionally, his mother reported dramatic improvements in his other allergic conditions, as discussed below.

The patient had a 5-year history of EoE, which had caused dysphagia, gastroesophageal reflux, and dental erosions. Previous esophageal biopsies at 21, 24, and 26 cm found active esophagitis with 5 to 25 intraepithelial eosinophils per high-power field and mild-to-moderate squamous hyperplasia (Fig 2). Treatment with omeprazole and fluticasone yielded some symptomatic improvement but only limited histologic improvement. After 32 weeks in the dupilumab study, the patient and his mother noticed significant improvement in symptoms and discontinued his EoE medications. Remarkably, repeat biopsies after 70 weeks of treatment showed only mild reactive changes with up to 5 eosinophils per high-power field at 34 cm and rare-to-absent eosinophils at 28 cm and 31 cm (Fig 2).

The patient also had a long history of moderate, persistent asthma, food/environmental allergies, AR, and CS. Treatment of these conditions before the dupilumab study included a daily fluticasone-salmeterol inhaler, avoidance of allergens, daily antihistamines, daily intranasal corticosteroids, and sinusplasty, respectively. After 32 weeks in the trial, he discontinued his inhaler entirely and reduced his antihistamines and intranasal corticosteroids to an as-needed basis, given the significant improvement in symptoms he experienced while taking dupilumab.

**DISCUSSION**

This case highlights that dupilumab may benefit patients with multiple coexisting allergic diseases. In
trials of dupilumab in moderate-to-severe AD, 60% of adults and 75% to 92% of adolescents had at least 1 comorbid allergic condition. Of adolescents, 45% to 66% had comorbid AR, 30% to 54% had asthma, and 0.4% had EoE. However, nearly all trials have only evaluated the effects of dupilumab on a single disease entity per trial. In these studies, dupilumab dramatically improved disease severity and quality of life in AD, asthma, and CRwNP with minimal side effects. Although dupilumab is not yet approved for EoE, phase 2 trials showed improved dysphagia, intraepithelial eosinophil counts, and histologic grade in adults. A trial with adolescents (NCT03633617) is currently enrolling subjects.

The few studies that have examined the efficacy of dupilumab on comorbid allergic diseases have found promising results. One study on adolescents with AD found improved asthma symptoms (measured by the Juniper Asthma Control Questionnaire), AR symptoms (measured by the Total Nasal Symptom Score), and IgE levels for cow’s milk, egg white, peanut, and aeroallergens. Similarly, a post hoc analysis of 2 phase 3 asthma trials noted that dupilumab reduced severe asthma exacerbations by 47.7%, increased forced expiratory volume in 1 second (FEV1) by 0.18 L, and improved AR symptoms (nasal blockage, runny nose, sneezing, and postnatal discharge).

The case we present here highlights the potential for dupilumab to provide relief to patients who suffer from multiple concurrent allergic diseases. With its well-tolerated safety profile and ease of administration, dupilumab offers a safe, effective, and long-term therapeutic option for these highly atopic individuals.

The authors acknowledge James Prezzano, MD, Brian L. Johnson, MD, Abigail I. Franco, MD, Alicia Papalia, BA, and Susan Proe, BA for their roles in coordinating the trials mentioned in this report. We also acknowledge Philip Katzman, MD and Maria C. Reyes, MD for providing us with the surgical pathology images from the patient’s esophagogastroduodenoscopy.

REFERENCES
1. Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. N Engl J Med. 2018;378(26):2486-2496.
2. Hirano I, Dellon ES, Hamilton JD, et al. Efficacy of dupilumab in a phase 2 randomized trial of adults with active eosinophilic esophagitis. Gastroenterology. 2020;158(1):111-122.e10.
3. Bachert C, Han JK, Desrosiers M, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. Lancet. 2019;394(10209):1638-1650.
4. Cork MJ, Thaci D, Eichenfield LF, et al. Dupilumab in adolescents with uncontrolled moderate to severe atopic dermatitis: results from a phase IIa open-label trial and subsequent phase III open-label extension. Br J Dermatol. 2020;182(1):85-96.
5. Simpson EL, Paller AS, Siegfried EC, et al. Efficacy and safety of dupilumab in adolescents with uncontrolled moderate-to-severe atopic dermatitis: a phase 3 randomized clinical trial. JAMA Dermatol. 2019;156(1):44-56.
6. Simpson EL, Bieber T, Guttman-Yassky E, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. N Engl J Med. 2016;375(24):2335-2348.
7. Weidinger S, Beck LA, Bieber T, Kabashima K, Irvine AD. Atopic dermatitis. Nat Rev Dis Primers. 2018;4(1):1.
8. Weinstein SF, Katial R, Jayawardena S, et al. Efficacy and safety of dupilumab in perennial allergic rhinitis and comorbid asthma. J Allergy Clin Immunol. 2018;142(1):171-177.e1.