

Dupilumab for Systemic Allergy Syndrome With Dermatitis

Sharon E. Jacob, MD,* Calvin T. Sung, BS,† and Brian C. Machler, MD‡

Allergic contact dermatitis (ACD) has been traditionally identified as T_H1-mediated delayed-type hypersensitivity reactions. There is currently no Food and Drug Administration–approved systemic therapy indicated for ACD. Among patients with ACD, there is a subgroup that experience not only concomitant atopic dermatitis and ACD but also systemic allergic dermatitis driven by allergens encountered through dietary consumption. Basic science and clinical studies have supported the notion that ACD involves a complex interaction between both T_H1 and T_H2 axes of the secondary immune system on an allergen-by-allergen basis. Herein, we report the patients with systemic allergy syndrome with dermatitis to either Balsam of Peru or nickel who achieved remarkable improvement and regained their quality of life without continuing adherence to strict diets. Our study suggests that dupilumab may be an efficacious solution for a particular subgroup of patients with recalcitrant ACD when first- and second-line therapies have failed.

Allergic contact dermatitis (ACD) is a common yet complex cutaneous disease within the family of delayed hypersensitivity reactions. The diagnosis is typically established through a high index of clinical suspicion and confirmed epicutaneous patch testing. The successful treatment of and remission from ACD are achieved through avoidance of proven allergens. In more severe and complex cases of ACD with multiple allergens or situations where culprit avoidance is difficult, such as cases with systemic involvement, topical anti-inflammatories may prove insufficient.¹ A number of systemic therapies have demonstrated efficacy when used in patients with recalcitrant disease; however, withdrawal of these agents becomes a challenge because ACD often recurs, but by the same token, continued use of these systemic agents can lead to significant morbidities. Although contact dermatitis is traditionally designated as an exclusive cell-mediated T_H1 process for many decades, current evidence suggests that ACD is a multifaceted disease involving aspects of the adaptive cellular, humoral, and innate immune system.²

The US Food and Drug Administration has approved dupilumab for the treatment of adult patients with moderate-to-severe atopic dermatitis (AD) that is insufficiently controlled with topical therapies or when those therapies are not advisable.³ Dupilumab is a human monoclonal antibody that binds to the α subunit of the

interleukin-4 receptor (IL-4R α) and inhibits the signaling of the IL-4 and IL-13 pathways responsible for T_H2-mediated humoral immunity proliferation.

Our findings suggest that the T_H2/IL-4 immunological paradigm, traditionally associated with AD, is involved in the development of contact sensitization against certain, as in some, haptens. We present five cases of recalcitrant systemic contact dermatitis (SCD) treated with dupilumab to (1) discuss the role of IL-4 as a proinflammatory agent associated with SCD, and (2) highlight the possibility of allowing patients to achieve a remarkable quality of life without having to undergo drastic and absolute lifestyle modification to avoid allergens completely.

Case Presentations

Case 1 is a 60-year-old white office worker with adult-onset dermatitis, affecting 60% body surface area (BSA), who was evaluated by patch testing and treated with systemic immunomodulators (cases detailed in Table 1). He had minimal improvement with strict avoidance of his allergens topically and recognized balsam of Peru (BOP) food triggers as causing flares within 60 minutes of ingesting them. He was seen 26 times in one year and has been seen only once since starting dupilumab for the past 11 months, with 90% improvement noted within four weeks of initiation. Of note, he recalled an episode of a nonspecific dermatitis during childhood, but denied a history consistent with AD.

Case 2 is a 53-year-old white salesman with no history of childhood eczema who had developed a recalcitrant generalized dermatitis with accentuation on his face and legs. The patient achieved partial clearance upon allergen avoidance and, although successfully treated with cyclosporine A (CysA), had to discontinue the medication because of prolonged use. He noted flares associated with drinking wine

*From the *Department of Dermatology, Loma Linda University, CA; †School of Medicine, University of California, Riverside; and ‡Ronald O. Perelman Department of Dermatology, New York University, New York City.*

Address reprint requests to Sharon E. Jacob, MD, Department of Dermatology, Loma Linda University, 11370 Anderson St, Ste 2600, Loma Linda, CA 92354. E-mail: sjacob@contactderm.net.

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TABLE 1. Dupilumab for Systemic Allergy Syndrome With Dermatitis

Age of Subject When Dupilumab Was Initiated	Sex (M/F)	History of Childhood Atopic Dermatitis	Predominant Hand Involvement (Yes/No)	Percent BSA at Onset of Dupilumab	Estimated % Improvement Within 10–12 wk on Dupilumab	Recalcitrant Dermatitis Sites While on Dupilumab (eg, Face, Arm, Legs, Trunk)	Positive Patch Test Allergens 96-h Read	Previously Failed Systemic Therapies
60	M	Yes	Yes	60%	90%	Scalp, face, torso, arms, legs, hands	Ethylenediamine dihydrochloride (3+) Benzalkonium (2+) Cocamidopropyl betaine (2+) Balsam of Peru (1+) Carba mix (1+) Caine mix (2+) Dithiomorpholine (2+) Shellac (2+) Benzalkonium (2+) Balsam of Peru (1+) Disperse blue mix (1+) Formaldehyde (1+) Balsam of Peru (1+) Fragrance mix I (1+) Bronopol (2+) Benzalkonium (1+) Carba (1+) Euxyl K 400 (1+) Formaldehyde (3+) Neomycin (2+) Palladium (2+) Quaternium-15 (1+) Sandalwood (1+) Thimerosal (1+) Thiuram (1+) Fragrance mix (1+) Balsam of Peru (2+)	• MM • CysA • Pred
53	M	No	No	65%	100%	Generalized, face, legs		• CysA
69	F	Yes	No	65%	85%	Face, breasts, eyelids		• CysA • Pred • MM
29	M	Yes	No	65%	80%	Generalized		• CysA • MM • Pred
54	F	Yes	No	45%	80%	Face, eyelids, neck, torso, and arms	Nickel (1+)	• CysA • MM • Methotrexate • UVB • Pred • Fluconazole trial

Abbreviations: CysA, cyclosporine A; F, female; M, male; MM, mycophenolate mofetil; Pred, prednisone.

and eating tomato-based products, but had a difficult time adhering to a BOP-restriction diet due to business travel. Within four weeks of dupilumab administration, he achieved 100% BSA clearance of his dermatitis and, most notably on a return visit, was pleased to disclose that he could now “eat with reckless abandon.”

Case 3 is a 69-year-old white homemaker with a history of childhood AD who developed a severe adult-onset dermatitis recalcitrant to both topical and systemic therapies. She noted flares of her facial and eyelid dermatitis associated with BOP-containing foods. After starting dupilumab, she achieved an 85% clinical improvement from baseline. When asked about her dietary triggers, she estimated a 75% improvement but stated that she no longer restricted her diet.

Case 4 is a 29-year-old Asian shipping-warehouse employee with a history of childhood AD and recalcitrant dermatitis affecting 65% of his BSA in a generalized distribution. The severity of his recalcitrant dermatitis affected his quality of life to the extent that he considered changing occupations and disengaged socially. He had significant improvement with allergen avoidance but was not able to maintain a low-Balsam diet. The patient was treated with multiple immunosuppressive medications. Within 6 weeks of initiating dupilumab, his recalcitrant dermatitis resolved by 80%. Notably, although the patient achieved substantial pruritus relief clinically, his face remained recalcitrant to treatment. Similar to the other cases, he also successfully resumed his normal diet regaining a marked improvement in quality of life.

Case 5 is a 54-year-old white school teacher with a long-standing history of AD. She presented with an intractable pruritic dermatitis affecting 45% of her BSA, primarily involving her eyelids, face, neck, arms, and trunk. She had been preemptively treated with a four-week trial course of weekly fluconazole without improvement. A biopsy confirmed ACD. After patch testing, allergen avoidance was prescribed and she notably experienced 50% improvement on a “low-nickel diet,” but she was not able to remain compliant because of dietary difficulties. She was treated with CysA, which was discontinued when she experienced a decline in renal functions; ultraviolet B; mycophenolate mofetil on which she continued to flare; and a 3-week course of methotrexate that was discontinued because of fatigue. She was observed to have a 50% reduction in pruritus score within 7 days after starting dupilumab. Within 2 months of starting dupilumab, her recalcitrant dermatitis resolved by 80%. At the 6-month follow-up, she was more than 90% improved and had no itch, and notably, she was no longer following a nickel restriction diet.

These five patients had all previously failed some type of oral or systemic therapy, notably prednisone and CysA, followed by mycophenolic acid and methotrexate. Three of five patients had experienced childhood AD, four had recalcitrant facial dermatitis, one had predominant hand involvement. Two patients, notably, did not have a childhood history of AD. Five patients had allergen-proven patch tests to various allergens, four with definite clinical relevance to BOP and fragrances and one with definite clinical relevance to nickel. The patients reported symptoms consistent with food-induced SCD to BOP triggers or high-nickel

foods, respectively, which they stated occurred typically from 1 to 12 hours after ingestion. Percent BSA at baseline before treatment ranged from 45% to 95%. There was a remarkable clinical response to dupilumab, and all 5 patients reverted to an unrestricted diet after several months on therapy.

DISCUSSION

Conventionally, the adaptive cell-mediated (T_H1) and humoral-mediated (T_H2) responses have been thought to be mutually exclusive.⁴ The remarkable improvement of our patients with recalcitrant SCD highlights the potential therapeutic value of dupilumab and provides further evidence for the role of IL-4 and IL-4 α R in the development of ACD against some allergens in certain individuals.^{5,6} Our findings support the concept that hapten sensitization properties may be distinguishable on the basis of whether there is a polarized $T_H1/CD8 + IFN\gamma$ or $T_H2/IL-4$ cytokine signature, noting that inflamed atopic skin may predispose patients to developing sensitization to less potent contact allergens due to the upregulation of the T_H2 signature already associated with patients with AD.^{7,8} Biologics inhibiting the T_H2 pathway may provide a subgroup of patients with ACD against certain allergens and those with systemic balsam allergy syndrome and systemic nickel allergy syndrome an option when strict avoidance or lifestyle-altering diets fail.

Systemic contact dermatitis is a subset of ACD that involves a $T_H2/IL-4$ - and IL-5-mediated hypersensitivity reaction. Systemic contact dermatitis creates another magnitude of challenges for management through avoidance, particularly for nickel and BOP.^{9,10} Balsam allergy syndrome and systemic nickel allergy syndrome have been associated with uncontrolled ACD despite prudent contact allergen avoidance. The study by Salam and Fowler¹¹ (n = 75 patients with positive patch test to BOP or FM) revealed that following a BOP-reduced diet resulted in significant to complete dermatitis improvement.¹¹ The systemic balsam allergy syndrome diet involves avoiding a wide range of flavorful foods and has been described as “cruel and unusual punishment” by Dr. Belsito, because proper dietary adherence necessitates the complete avoidances of all prepared fruits and vegetables along with an extensive list of deserts, spices, and beverages.^{12–14} Notably, the low-nickel diet for the patients with systemic nickel allergy syndrome is almost equally cumbersome, especially for vegetarians where the mainstay protein sources are seeds, nuts, and legumes, which are all high-nickel foods.

Although the extent of allergen sensitivities identified among our patients is by no means comprehensive to suggest a treatment of recalcitrant dermatitis to all contact allergens, it may serve as a reference point to highlight a potential therapeutic value of dupilumab for ACD in a certain subset of patients.¹⁵ One limitation of this report is the small number of patients. Although there remains the possibility that our observation in three patients with AD reflects systemic exacerbations of underlying AD induced by contact sensitization, the two patients without AD who had a remarkable clinical response to dupilumab further speak to a potential efficacy of the drug in the management of SCD.^{16,17} By reporting these findings,

we hope to stimulate discussion surrounding our perceptions of AD, ACD, and SCD as well as systemic allergy syndromes; encourage research; and promote awareness of the need for treatments of ACD.

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