

CLINICAL MANAGEMENT RECOMMENDATIONS

The Role of Dupilumab In Managing Allergic Contact Dermatitis

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Allergic contact dermatitis (ACD) is an inflammatory skin disease caused by a type IV, delayed hypersensitivity reaction to an allergen. It is a common condition that affects 15 to 20% of the general population and significantly decreases quality of life in affected patients.^{1,2} It demonstrates considerable variation in its clinical presentation and level of severity. The diagnosis of ACD is further complicated because it can occur concomitantly with irritant contact dermatitis, contact urticaria, atopic dermatitis (AD) as well as other primary dermatoses.³ While for many decades ACD was considered a cell-mediated process that occurred exclusively via the TH1 pathway, recent evidence suggests that contact sensitization is a hapten-specific, multifaceted process that involves adaptive cellular, humoral, and innate immune systems, involving TH2, TH17, and TH22 cytokines.⁴⁻⁹ For example, nickel is typically a potent inducer of the TH1 pathway, while fragrance and rubber tend to demonstrate classic “allergic” TH2 polarizations with smaller TH1 contributions.⁹ Interestingly, frequent and recurrent exposure to an allergen can lead to stronger elicitation of TH2-predominant responses over time.¹⁰

This deeper understanding of the varying mechanistic processes contributing to ACD has led to new targets of therapy. Systemic and topical steroids remain the most widely used agents to treat ACD and act by nonspecifically inhibiting TH0, TH1, and TH2 inflammation.¹¹ Antimetabolites (e.g. methotrexate, azathioprine), IFN- γ antagonists, and TNF- α antagonists have been used to block signaling cascades involved in innate immunity and the TH0 and TH1 pathways.¹¹ Recently, there has been vigorous debate about the value of using dupilumab, a biologic that targets TH2-mediated processes, in the management of recalcitrant ACD.

WHAT IS DUPILUMAB?

Dupilumab is a human monoclonal immunoglobulin G4 (IgG4) antibody approved by the US Food and Drug Administration for the treatment of recalcitrant moderate to severe AD.¹² By binding to the interleukin-4R α (IL-4R α) subunit shared by the IL-4 and IL-13 receptor complexes, it inhibits IL-4 and IL-13 cytokine-induced responses, preventing the production and release of IgE,

proinflammatory cytokines, and chemokines.¹² This downregulates genes associated with epidermal proliferation and blocks the differentiation of naïve T cells via the TH2 pathway.¹³

IS THERE DATA SUPPORTING DUPILUMAB AS A TREATMENT FOR ALLERGIC CONTACT DERMATITIS?

In 2018, Puza and Atwater reported a weakened patch test response in a patient taking dupilumab.¹⁴ A few months later, Joshi and Khan reported a patient with allergic contact dermatitis that appeared to be controlled by dupilumab after failing other systemic therapies. The patient had no personal or family history of AD but interestingly had a predominantly TH2-mediated response to endovascular stents containing nickel.¹⁵ Chipalkatti et al later presented two patients with recalcitrant ACD, multiple positive allergens on patch testing, and significant improvement with dupilumab.¹⁶

The remaining case reports and studies investigating dupilumab's efficacy in treating ACD involved patients with concomitant AD. The distinction between dupilumab's use in ACD patients with and without underlying AD is important, as ACD responses are polarized toward a TH2 response in the skin of AD patients.¹⁷ Four studies demonstrated significant improvement in recalcitrant ACD with dupilumab in a series of predominantly AD patients. Three of these studies showed mean improvements ranging from 85 to 90% in the percentage of body surface area affected by ACD; 17 of the 23 patients included in these studies had a history of AD.^{18–20} The fourth study, a retrospective chart review, demonstrated improvement with dupilumab in 64 AD patients, 31 of whom had confirmed or suspected ACD. AD

patients with and without ACD responded equally well to dupilumab.²¹ In the context of underlying AD, the allergens that cause ACD in dupilumab-responsive patients include balsam of Peru, carba mix, cobalt, cocamidopropyl betaine, colophonium, formaldehyde, fragrance mixes 1 and 2, mercapto mix, methylchloroisothiazolinone, mixed diakyl thiourea, nickel, oleamidopropyl dimethylamine, propylene glycol, rubber, and textile dyes.^{15,18–20,22–24} Further investigations are required to determine the full range of allergens that evoke significant type 2 immune responses in patients with and without AD.

ARE THERE POTENTIAL PROBLEMS WITH CHOOSING DUPILUMAB TREATMENT?

1. Not all patients with ACD respond to dupilumab.

Crepy and colleagues reported a case in which an AD patient had ACD that was driven primarily by type 1 inflammation and was not improved with dupilumab, suggesting that, even in AD patients, dupilumab is ineffective against classic TH1-triggered ACD.²⁵ Stout and Silverberg provided further evidence that dupilumab is not always an effective treatment for ACD in AD patients. They presented seven cases: four patients no longer experienced flares of ACD with allergen contact, while three patients continued to develop flares with allergen exposure.²⁶ Finally, if dupilumab “turned off” ACD like a light switch, patch testing in AD patients controlled by this drug would be uniformly negative, and this is not the case.^{14,27} Further, it is uncertain if dupilumab's efficacy in treating ACD in

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AD patients is due to improvement of the underlying AD and improving the skin's barrier function against offending allergens.²¹

2. Dupilumab has significant side effects.

A meta-analysis of eight randomized controlled trials that compared dupilumab to a placebo for the treatment of AD found that patients receiving dupilumab had statistically significant increases in the incidences of conjunctivitis (RR 2.64), injection-site reactions (RR 2.24), and headache (RR 1.47).²⁸ These effects are not likely due to an immunosuppressive mechanism since this medication has had no known immunosuppressive activity and incidences of nasopharyngitis, upper respiratory infections, urinary tract infections, and herpes virus infections were not increased with dupilumab when compared to placebo.^{28,29}

3. Dupilumab is expensive.

For ACD patients who are responsive to dupilumab and are unable to avoid relevant allergens, the cost of long-term dupilumab treatment can be prohibitive. A recent study evaluating the cost of dupilumab for the treatment of AD estimated the lifetime cost for patients to be \$509,600 (i.e. \$267,800 in drug costs and \$241,800 in other healthcare costs), exceeding the cost of usual care with emollients by \$238,100.³⁰

HOW SHOULD PHYSICIANS DISCUSS DUPILUMAB WITH PATIENTS WITH ACD?

- The cytokine polarity of the immunologic response in ACD depends upon the inciting allergen, so the therapeutic approach to ACD must be individualized.
- A single allergen can elicit different immunological responses in patients with and without underlying AD.
- There is limited evidence in support of using dupilumab for ACD in patients without concomitant AD.
- The cost of this drug further argues against its use in all patients with ACD.
- Dupilumab's benign side effect profile, particularly its lack of immunosuppression, relative to other systemic therapies make it a reasonable option in AD patients with systemic ACD to certain allergens known to elicit a significant type 2 immune response who have failed other treatments.

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References:

1. Peiser M, Tralau T, Heidler J, et al. Allergic contact dermatitis: epidemiology, molecular mechanisms, in vitro methods and regulatory aspects. Current knowledge assembled at an international workshop at BfR, Germany. *Cell Mol Life Sci*. 2012;69(5):763-781.
2. Kadyk DL, McCarter K, Achen F, Belsito D V. Quality of life in patients with allergic contact dermatitis. *J Am Acad Dermatol*. 2003;49(6):1037-1048.
3. Nixon RL, Mowad CM, Marks JG. Allergic contact dermatitis. In: Bologna J, Schaffer J, Cerroni L, eds. *Dermatology*. 4th ed. Philadelphia: Elsevier; 2018:242-261.
4. Rowe A, Bunker CB. Interleukin-4 and the interleukin-4 receptor in allergic contact dermatitis. *Contact Dermatitis*. 1998;38(1):36-39.
5. Traidl C, Jugert F, Krieg T, Merk H, Hunzelmann N. Inhibition of allergic contact dermatitis to DNCB but not to oxazolone in interleukin-4-deficient mice. *J Invest Dermatol*. 1999;112(4):476-482.
6. Nagai H, Ueda Y, Ochi T, et al. Different role of IL-4 in the onset of hapten-induced contact hypersensitivity in BALB/c and C57BL/6 mice. *Br J Pharmacol*. 2000;129(2):299-306.
7. Campos RA, Szczepanik M, Itakura A, et al. Interleukin-4-dependent innate collaboration between iNKT cells and B-1 B cells controls adaptative contact sensitivity. *Immunology*. 2006;117(4):536-547.
9. Niiyama S, Tamauchi H, Amoh Y, et al. Th2 immune response plays a critical role in the development of nickel-induced allergic contact dermatitis. *Int Arch Allergy Immunol*. 2010;153(3):303-314.
10. Dhingra N, Shemer A, Correa da Rosa J, et al. Molecular profiling of contact dermatitis skin identifies allergen-dependent differences in immune response. *J Allergy Clin Immunol*. 2014;134(2):362-372.
11. Kitagaki H, Ono N, Hayakawa K, Kitazawa T, Watanabe K, Shiohara T. Repeated elicitation of contact hypersensitivity induces a shift in cutaneous cytokine milieu from a T helper cell type 1 to a T helper cell type 2 profile. *J Immunol*. 1997;159(5):2484-2491.
12. Sung CT, McGowan MA, Machler BC, Jacob SE. Systemic treatments for allergic contact dermatitis. *Dermatitis*. 2019;30(1):46-53.
13. Dupixent (dupilumab) injection. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761055lbl.pdf.
14. Hamilton JD, Suárez-Fariñas M, Dhingra N, et al. Dupilumab improves the molecular signature in skin of patients with moderate-to-severe atopic dermatitis. *J Allergy Clin Immunol*. 2014;134(6):1293-1300.
15. Puza CJ, Atwater AR. Positive patch test reaction in a patient taking dupilumab. *Dermat contact, atopic, Occup drug*. 2018;29(2):89.
16. Joshi SR, Khan DA. Effective use of dupilumab in managing systemic allergic contact dermatitis. *Dermat contact, atopic, Occup drug*. 2018;29(5):282-284.
17. Chipalkatti N, Lee N, Zancanaro P, Dumont N, Donovan C, Rosmarin D. Dupilumab as a treatment for allergic contact dermatitis. *Dermat contact, atopic, Occup drug*. 2018;29(6):347-348.
18. Correa da Rosa J, Malajian D, Shemer A, et al. Patients with atopic dermatitis have attenuated and distinct contact

- hypersensitivity responses to common allergens in skin. *J Allergy Clin Immunol.* 2015;135(3):712-720.
19. Machler BC, Sung CT, Darwin E, Jacob SE. Dupilumab use in allergic contact dermatitis. *J Am Acad Dermatol.* 2019;80(1):280-281.e1.
 20. Goldminz AM, Scheinman PL. A case series of dupilumab-treated allergic contact dermatitis patients. *Dermatol Ther.* 2018;31(6):e12701.
 21. Jacob SE, Sung CT, Machler BC. Dupilumab for systemic allergy syndrome with dermatitis. *Dermat contact, atopic, Occup drug.* 2019;30(2):164-167.
 22. Chipalkatti N, Lee N, Zancanaro P, Dumont N, Kachuk C, Rosmarin D. A retrospective review of dupilumab for atopic dermatitis patients with allergic contact dermatitis. *J Am Acad Dermatol.* 2019;80(4):1166-1167.
 23. Collantes-Rodríguez C, Jiménez-Gallo D, Ossorio-García L, Villegas-Romero I, Linares-Barrios M. Recall dermatitis at patch test sites in an atopic dermatitis patient treated with dupilumab. *Contact Dermatitis.* 2019;80(1):69-70.
 24. Huynh T, Hadi S, Tan K, Guttman-Yassky E. Dupilumab therapy for chronic refractory hand dermatitis [abstract]. *Exp Dermatol.* 2018;27(S2):33.
 25. Zhu GA, Chen JK, Chiou A, Ko J, Honari G. Repeat patch testing in a patient with allergic contact dermatitis improved on dupilumab. *JAAD Case Reports.* 2019;5(4):336-338.
 26. Crepy M-N, Nosbaum A, Bensefa-Colas L. Blocking type 2 inflammation by dupilumab does not control classic (Type 1-driven) allergic contact dermatitis in chronic hand eczema. *Contact Dermatitis.* March 2019.
 27. Stout M, Silverberg JI. Variable impact of dupilumab on patch testing results and allergic contact dermatitis in adults with atopic dermatitis. *J Am Acad Dermatol.* March 2019.
 28. Hoot JW, Douglas JD, Falo LD. Patch testing in a patient on dupilumab. *Dermatitis.* 2018;29(3):164.
 29. Ou Z, Chen C, Chen A, Yang Y, Zhou W. Adverse events of dupilumab in adults with moderate-to-severe atopic dermatitis: a meta-analysis. *Int Immunopharmacol.* 2018;54:303-310.
 30. 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.
 31. Zimmermann M, Rind D, Chapman R, Kumar V, Kahn S, Carlson J. Economic evaluation of dupilumab for moderate-to-severe atopic dermatitis: a cost-utility analysis. *J Drugs Dermatol.* 2018;17(7):750-756.