

Dupilumab for Allergic Contact Dermatitis: An Overview of Its Use and Impact on Patch Testing

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PRACTICE POINTS

- Dupilumab is approved by the US Food and Drug Administration for the treatment of moderate to severe atopic dermatitis.
- Multiple reports have suggested that dupilumab may be effective in the treatment of allergic contact dermatitis, and a phase 4 clinical trial is ongoing.
- The accuracy of patch testing after dupilumab initiation is unclear, as reactions may remain positive, change to negative, or become newly positive after its administration.

Allergic contact dermatitis (ACD) has been estimated to affect up to 20% of the general population. Patch testing is the gold standard for identification of causative allergens. When allergen avoidance fails, current treatment options include topical and oral corticosteroids, systemic immunosuppressants, and phototherapy. Dupilumab, a monoclonal antibody targeting IL-4/IL-13, is approved by the US Food and Drug Administration for the treatment of moderate to severe atopic dermatitis. It also has been used off label with some success in the treatment of ACD. This article discusses the evidence for using dupilumab to treat ACD as well as considerations for patch testing in patients who are taking this medication.

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Dupilumab is a humanized monoclonal antibody approved by the US Food and Drug Administration (FDA) for the treatment of moderate to severe

atopic dermatitis. Through inhibition of the IL-4R α subunit, it prevents activation of the IL-4/IL-13 signaling cascade. This dampens the T_H2 inflammatory response, thereby improving the symptoms associated with atopic dermatitis.^{1,2} Recent literature suggests that dupilumab may be useful in the treatment of other chronic dermatologic conditions, including allergic contact dermatitis (ACD) refractory to allergen avoidance and other treatments. Herein, we provide an overview of ACD, the role that dupilumab may play in its management, and its impact on patch testing results.

Pathogenesis of ACD

Allergic contact dermatitis is a cell-mediated type IV hypersensitivity reaction that develops through 2 distinct stages. In the sensitization phase, an allergen penetrates the skin and subsequently is engulfed by a cutaneous antigen-presenting cell. The allergen is then combined with a peptide to form a complex that is presented to naïve T lymphocytes in regional lymph nodes. The result is clonal expansion of a T-cell population that recognizes the allergen. In the elicitation phase, repeat exposure to the allergen leads to the recruitment of primed T cells to the skin, followed by cytokine release, inflammation, and resultant dermatitis.³

Historically, ACD was thought to be primarily driven by the T_H1 inflammatory response; however, it is now known that T_H2, T_H9, T_H17, and T_H22 also may play a role in its pathogenesis.^{4,5} Another key finding is that the

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The eTable is available in the Appendix online at www.mdedge.com/dermatology.

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immune response in ACD appears to be at least partially allergen specific. Molecular profiling has revealed that nickel primarily induces a T_H1/T_H17 response, while allergens such as fragrance and rubber primarily induce a T_H2 response.⁴

Management of ACD

Allergen avoidance is the mainstay of ACD treatment; however, in some patients, this approach does not always improve symptoms. In addition, eliminating the source of the allergen may not be possible in those with certain occupational, environmental, or medical exposures.

There are no FDA-approved treatments for ACD. When allergen avoidance alone is insufficient, first-line pharmacologic therapy typically includes topical or oral corticosteroids, the choice of which depends on the extent and severity of the dermatitis; however, a steroid-sparing agent often is preferred to avoid the unfavorable effects of long-term steroid use. Other systemic treatments for ACD include methotrexate, cyclosporine, mycophenolate mofetil, and azathioprine.⁶ These agents are used for severe ACD and typically are chosen as a last resort due to their immunosuppressive activity.

Phototherapy is another option, often as an adjunct to other therapies. Narrowband UVB and psoralen plus UVA have both been used. Psoralen plus UVA tends to have more side effects; therefore, narrowband UVB often is preferred.^{7,8}

Use of Dupilumab in ACD

Biologics are unique, as they can target a single step in the immune response to improve a wide variety of symptoms. Research investigating their role as a treatment modality for ACD is still evolving alongside our increasing knowledge of its pathophysiology.⁹ Of note, studies examining the anti-IL-17 biologic secukinumab revealed it to be ineffective against ACD,^{10,11} which suggests that targeting specific immune components may not always result in improvement of ACD symptoms, likely because its pathophysiology involves several pathways.

There have been multiple reports demonstrating the effectiveness of dupilumab in the treatment of ACD (eTable).¹²⁻²⁰ The findings from these studies show that dupilumab can improve recalcitrant dermatitis caused by a broad range of contact allergens, including nickel. This highlights its ability to improve ACD caused by allergens with a T_H1 bias, despite its primarily T_H2 -dampening effects. Notably, several studies have reported successful use of dupilumab for systemic ACD.^{12,18} In addition, dupilumab may be able to improve symptoms of ACD in as little as 1 to 4 weeks. Unlike some systemic therapies for ACD, dupilumab also benefits from its lack of notable immunosuppressive effects.⁹ A phase 4 clinical trial at Brigham and Women's Hospital (Boston, Massachusetts) is recruiting participants, with a primary goal of investigating dupilumab's impact on ACD in patients who have not improved

despite allergen avoidance (ClinicalTrials.gov identifier NCT03935971).

There are a few potential disadvantages to dupilumab. Because it is not yet FDA approved for the treatment of ACD, insurance companies may deny coverage, making it likely to be unaffordable for most patients. Furthermore, the side-effect profile has not been fully characterized. In addition to ocular adverse effects, a growing number of studies have reported face and neck erythema after starting dupilumab. Although the cause is unclear, one theory is that the inhibition of IL-4/IL-13 leads to T_H1/T_H17 polarization, thereby worsening ACD caused by allergens that activate a T_H1 -predominant response.²¹ Finally, not all cases of ACD respond to dupilumab.²²

Patch Testing While on Dupilumab

Diagnosing ACD is a challenging process. An accurate history and physical examination are critical, and patch testing remains the gold standard when it comes to identifying the source of the contact allergen(s).

There is ongoing debate among contact dermatitis experts regarding the diagnostic accuracy of patch testing for those on immunomodulators or immunosuppressants, as these medications can dampen positive results and increase the risk for false-negative readings.²³ Consequently, some have questioned whether patch testing on dupilumab is accurate or feasible.²⁴ Contact dermatitis experts have examined patch testing results before and after initiation of dupilumab to further investigate. Puza and Atwater²⁵ established that patients are able to mount a positive patch test reaction while on dupilumab. Moreover, a retrospective review by Raffi et al²⁶ found that out of 125 before therapy/on therapy patch test pairs, only 13 were lost after administration of dupilumab. Although this would suggest that dupilumab has little impact on patch testing, Jo et al²⁷ found in a systematic review that patch test reactions may remain positive, change to negative, or become newly positive after dupilumab initiation.

This inconsistency in results may relate to the allergen-specific pathogenesis of ACD—one allergen may have a different response to the mechanism of dupilumab than another.^{28,29} More recently, de Wijs et al³⁰ reported a series of 20 patients in whom more than two-thirds of prior positive patch test reactions were lost after retesting on dupilumab; there were no clear trends according to the immune polarity of the allergens. This finding suggests that patient-specific factors also should be considered, as this too could have an impact on the reliability of patch test findings after starting dupilumab.²⁹

Final Interpretation

Given its overall excellent safety profile, dupilumab may be a feasible off-label option for patients with ACD that does not respond to allergen avoidance or for those who experience adverse effects from traditional therapies; however, it remains difficult to obtain through insurance

because it is not yet FDA approved for ACD. Likewise, its impact on the accuracy of patch testing is not yet well defined. Further investigations are needed to elucidate the pathophysiology of ACD and to guide further use of dupilumab in its treatment.

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APPENDIX

eTABLE. Studies Demonstrating Improvement of ACD With Dupilumab Use

Reference (year)	Country	Age, y/sex	Contact allergen(s)	Previously failed medications	Time to improvement on dupilumab
Joshi and Khan ¹² (2018)	US	44/M	Nickel	Topical and oral corticosteroids, mycophenolate mofetil	8 wk
Goldminz and Scheinman ¹³ (2018)	US	20/F	Rubber accelerators, dyes, formaldehyde resin, cosmetics, preservatives, adhesives, tea tree oil	Topical and oral corticosteroids	6 wk
		52/F	Rubber accelerators, dyes	Topical and oral corticosteroids, azathioprine	3–4 wk
		53/F	Hair dyes, cosmetics, preservatives, adhesives, fragrances, neomycin	Topical and oral corticosteroids, cyclosporine	NA; patient remained nearly clear for 6 mo
Chipalkatti et al ¹⁴ (2018)	US	83/F	Unclear (multiple positive reactions without a clear exposure source)	Topical and oral corticosteroids	6 mo
		69/F	Propylene glycol	Methotrexate, mycophenolate mofetil	4 mo
Zhu et al ¹⁵ (2019)	US	54/M	Nickel, methylisothiazolinone, methylchloroisothiazolinone/methylisothiazolinone, octylisothiazolinone, 4,4'-dithiodimorpholine	Topical and oral corticosteroids, phototherapy, acitretin	Within weeks
Machler et al ¹⁶ (2019)	US	15 total patients (average age, 52.6 y; 6 M, 9 F)	46 distinct allergens: most frequently cocamidopropyl betaine, nickel, oleamidopropyl dimethylamine, balsam of Peru, fragrance mix 1	Average of 2.9 prior medications, including prednisone, cyclosporine, mycophenolic acid, methotrexate, apremilast, azathioprine, ustekinumab, etanercept	70%–100% BSA improvement at 10–12 wk follow-up
Chipalkatti et al ¹⁷ (2019)	US	17 patients with confirmed ACD (average age, 44 y; 5 M, 12 F)	NA	Average of 4 prior medications, including corticosteroids, immunosuppressants, phototherapy	NA
		14 patients with suspected ACD (average age, 44 y; 8 M, 6 F)	NA		

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eTABLE. (continued)

Reference (year)	Country	Age, y/sex	Contact allergen(s)	Previously failed medications	Time to improvement on dupilumab
Jacob et al ¹⁸ (2019)	US	60/M	Ethylenediamine dihydrochloride, benzalkonium, cocamidopropyl betaine, balsam of Peru, Carba mix	Mycophenolate mofetil, cyclosporine, prednisone	4 wk
		53/M	Caine mix, dithiodimorpholine, shellac, benzalkonium, balsam of Peru, disperse blue mix, formaldehyde	Cyclosporine	4 wk
		69/F	Balsam of Peru, fragrance mix 1, bronopol, benzalkonium, carba mix, euxyl K 400, formaldehyde, neomycin, palladium, quaternium 15, sandalwood, thimerosal, thiuram	Cyclosporine, prednisone, mycophenolate mofetil	85% BSA improvement within 10–12 wk
		29/M	Fragrance mix, balsam of Peru	Cyclosporine, mycophenolate mofetil, prednisone	6 wk
		54/F	Nickel	Cyclosporine, mycophenolate mofetil, methotrexate, UVB phototherapy, prednisone, fluconazole	7 d
Ruge et al ¹⁹ (2020)	Denmark	65/F	Sesquiterpene lactones	Topical and oral corticosteroids, azathioprine	2 wk for hands/arms, 1 mo for face after initial worsening
		51/M	Sesquiterpene lactones	Topical and oral corticosteroids, mycophenolate mofetil, methotrexate, azathioprine, cyclosporine, ustekinumab	1 mo
Wilson et al ²⁰ (2021)	US	55/M	Chromate	Topical corticosteroids	Complete resolution at 2 mo follow-up

Abbreviations: ACD, allergic contact dermatitis; BSA, body surface area; F, female; M, male; NA, not available; US, United States.