

Blocking type 2 inflammation by dupilumab does not control classic (type 1-driven) allergic contact dermatitis in chronic hand eczema

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Dupilumab is an interleukin-4 receptor inhibitor whose use is indicated for the treatment of recalcitrant moderate-to-severe atopic dermatitis (AD).¹ AD is a predominantly type 2-axis immune disorder, whereas allergic contact dermatitis (ACD) is predominantly a type 1 cell-mediated process. Furthermore, evidence is scarce regarding the reliability of patch testing in patients receiving dupilumab treatment. In this case report, we describe a case of ACD with positive skin test results with a rubber additive and an associated glove source in an AD patient receiving dupilumab.

CASE REPORT

A 54-year-old surgeon with a known history of AD was referred to our department by his occupational physician because of painful, chronic hand eczema, despite systemic treatment with dupilumab. Systemic treatment was initiated for severe AD with pruritus and widespread eczema, covering the body, face, and hands, which had been refractory to topical treatment with betamethasone dipropionate ointment 0.05% and emollients. Cyclosporine had first been started, and achieved dramatic improvement, except that the hand dermatitis persisted. Therefore, it was replaced with subcutaneous dupilumab (600-mg loading dose, followed by 300 mg every other week), with comparable improvement of the body and face eczema but also with no effect on hand eczema. As ACD was suspected, patch testing was performed by the use of IQ Ultra chambers (Chemotechnique Diagnostics, Vellinge, Sweden) fixed on the back with Mefix (Mölnlycke, Göteborg, Sweden) with the European baseline series, a cosmetics series, and a rubber series (Chemotechnique Diagnostics). Two different brands of gloves were applied on the back with Tegaderm adhesive: a piece of the patient's surgical sterile rubber polyisoprene gloves (Protexis PI Classic Surgical Gloves; Cardinal Health, Dublin, Ohio) worn at work, and a piece of

accelerator-free glove (Gammex Non-Latex Sensitive Surgical Gloves; Ansell Healthcare, Iselin, New Jersey). Test results were read on day (D) 2, D3 and D10 by the same dermatologist in accordance with the recommendations of the ICDRG. Dupilumab treatment was maintained during the patch test procedure. There were positive reactions to 1,3-diphenylguanidine 1% pet. (++) (Figure 1) and to the piece of Protexis PI Classic Surgical Glove (Cardinal Health) (++) (Figure 2). The patient was advised to use accelerator-free rubber gloves, that is, Gammex Non-Latex Sensitive Surgical Gloves. His eczema healed completely, with no recurrence after 4 months of follow-up.



FIGURE 1 Positive reaction to a patch test with 1,3-diphenylguanidine 1% pet. in a patient receiving dupilumab therapy

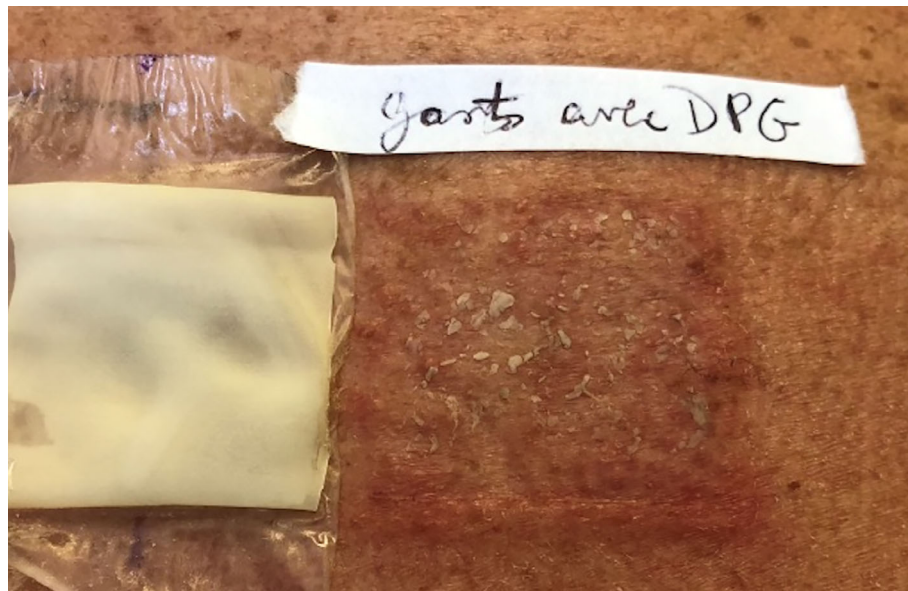


FIGURE 2 Positive reaction to a semi-open test with a piece of glove (Protexis PI Classic Surgical Gloves) in a patient receiving dupilumab therapy

DISCUSSION

Herein, we report a case in which effective dupilumab treatment of AD did not achieve control of classic ACD caused by glove compounds confirmed by patch testing. Several cases of positive patch test findings after the initiation of dupilumab therapy, used for moderate-to-severe or recalcitrant AD, have recently been reported.^{2–4} Suresh and Murase reported three cases of severe AD treated with dupilumab in patients with persistent facial eczema attributable to ACD,⁴ who improved after allergen avoidance. Two of the patients were patch tested before dupilumab initiation, and still reacted positively to the same allergens when they were patch tested when treated with dupilumab. Collantes-Rodríguez et al reported recall dermatitis at patch tests sites after dupilumab initiation in a patient with AD who was allergic to colophonium.⁵

Conversely, a few cases of severe ACD have been dramatically improved by dupilumab, and this therapy can influence patch test results in some patients. Goldminz et al reported a case series of three patients with ACD who were successfully treated with dupilumab.⁶ Two of them had no history of AD during childhood. Two of them had positive reactions to textile and rubber allergens. The third one was a hairdresser with severe hand eczema. She had positive reactions to several allergens (dyes, preservatives, fragrances, and acrylates). She remained nearly clear while receiving dupilumab, and could continue her work. Joshi and Khan reported a case of refractory ACD caused by nickel in a patient after the placement of vascular stents because of an arterial popliteal thrombus.⁷ He had no personal or family history of AD. His ACD remained refractory to high-potency topical steroids and systemic steroid therapy. After stent removal, his symptoms did not significantly improve, probably because of the persistence of many stainless steel vascular clips. Within 8 weeks after the start of dupilumab therapy, his dermatitis drastically improved. Machler et al reported 15 cases of patients treated with dupilumab for recalcitrant dermatitis.⁸ Eleven patients had a history of childhood AD. All of them had positive patch test reactions to 46 allergens. The most frequent clinically relevant allergens were cocamidopropyl betaine, nickel, oleamidopropyl

dimethylamine, *Myroxylon pereirae*, and fragrance mix I. In all cases, the dermatitis improved while the patients were receiving dupilumab. Chipalkatti and Lee reported two patients with ACD who improved significantly while receiving dupilumab.⁹ Patch tests showed positive reactions to multiple allergens (mainly biocides and fragrances). In a retrospective chart review of 64 patients who were prescribed dupilumab, by Chipalkatti et al,¹⁰ data on ACD (confirmed, suspected or unsuspected ACD) and dupilumab responses were analysed. No difference in dupilumab response rates was detected between AD patients with and without ACD. Raffi et al reported patch test results before and after treatment with dupilumab in a patient with papulovesicular dermatitis on the hands and feet.¹¹ She had positive patch test reactions to nickel, methylchloroisothiazolinone, bronopol, Compositae mix and hydroperoxides of linalool before receiving dupilumab. After 2 months of taking dupilumab, she was retested, and had positive reactions only to bronopol and methylchloroisothiazolinone.

Dupilumab is a fully human monoclonal antibody that binds to the interleukin (IL)-4 receptor- α , resulting in inhibition of both IL-4 and IL-13 signalling.¹ This blockade by dupilumab reduces the type 2 inflammatory cascade in AD patients. The normal human pathogenesis of ACD has been mainly attributed to type 1 inflammation following exposure to allergens. Interestingly, ACD responses are attenuated and differentially polarized in the skin of AD patients as compared with non-AD individuals, with decreases in the levels of type 1 cytokines and increases in the levels of type 2 and type 17 products.¹² Recent studies on allergic sensitization to common allergens in human skin have shown that different allergens have distinct molecular fingerprints, and that ACD should not be considered to be a single immunological phenomenon^{13,14}. For example, nickel promotes strong type 1 polarization, consistent with its selective binding to Toll-like receptor 4, and also significant type 17 skewing.¹⁴ On the other hand, fragrances and, to a lesser extent, rubber (carba mix and thiurams) cause type 2/type 22 skewing, which is similar to the phenotype of AD.¹⁴ Newell et al showed that, in complete contrast to the normal, non-atopic response, when individuals with AD are sensitized through

unaffected skin with 2,4-dinitrochlorobenzene, they generate a substantial type 2 response to this agent.¹⁵ They showed that the skin in humans with AD contributes to programming the adaptive T cell response towards type 2 inflammation.

Our case suggests that: (a) the type 2 inflammation was not driving the ACD in this patient with AD and associated hand eczema; (b) dupilumab is not an effective treatment for classic Th1-triggered ACD; and (c) the effect of dupilumab on patch test results has yet to be fully elucidated. Effective treatment of severe background AD with dupilumab may improve patch test detection of concomitant classic type 1 ACD.

In conclusion, our case supports patch testing of patients with refractory dermatitis undergoing dupilumab therapy for moderate-to-severe AD, and further supports the need for cytokine analysis and investigation of type 1-supported and type 2-supported ACD presentations.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

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