Variable impact of dupilumab on patch testing results and allergic contact dermatitis in adults with atopic dermatitis

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Background: Previous case reports and series suggested that dupilumab may be an effective treatment for allergic contact dermatitis (ACD). Little is known about the impact of dupilumab on patch test results and comorbid ACD in patients with atopic dermatitis (AD).

Objective: Determine the impact of dupilumab on patch testing results and improvement of ACD in patients with AD.

Methods: A retrospective study of patients with AD treated with dupilumab who underwent patch testing (n = 7) or had concomitant ACD (n = 6).

Results: In all, 7 patients with AD were patch tested while taking dupilumab; in all of these patients, at least 1 positive patch test reaction was observed, with a total of 25 different allergens having a reaction graded as 1+ or stronger and few irritant reactions. In 1 patient, multiple previously positive relevant patch test results were not duplicated upon repeat patch testing. In the 6 patients with AD and concomitant ACD, dupilumab and allergen avoidance resulted in substantial or complete resolution of AD signs and symptoms but resolution of ACD in only 3 patients. However, 3 patients had at least 1 flare of ACD upon re-exposure to relevant allergens.

Limitations: Retrospective and uncontrolled study.

Conclusions: Dupilumab had variable impact on patch testing results and resolution of comorbid ACD in adult patients with AD. (J Am Acad Dermatol 2019;81:157-62.)

Key words: allergic contact dermatitis; atopic dermatitis; biologic; eczema; treatment.

Patients with atopic dermatitis (AD) have multiple risk factors for developing allergic contact dermatitis (ACD), including the following: skin barrier disruption[1-3]; frequent topical application of emollients and anti-inflammatories that contain contact sensitizers[4,5]; and a potentially shared immune pathway, such as type 1 helper T cell (Th1), Th2, Th9, and/or Th17 cytokines.[6] ACD is a

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Dr Stout and Dr Silverberg had full access to all of the data in the study and take responsibility for the integrity of the data. Dr Stout and Dr Silverberg take responsibility for acquisition, analysis, and interpretation of data; drafting of the article; and critical revision of the article for important intellectual content. Dr Silverberg takes responsibility for the study concept and design.

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common clinical problem in patients with AD, particularly in response to allergens in personal care products and topical medications,[7] with approximately one-third of children with AD who were patch tested having at least 1 contact allergy.[8] A systematic review and meta-analysis of 74 studies found that patients with AD had increased prevalence of contact sensitization compared with the general population.[9]

Some treatments may also be effective for treating ACD in patients with AD. Dupilumab is a monoclonal antibody that targets the interleukin 4 (IL-4) receptor-α subunit, thereby inhibiting the signaling of IL-4 and IL-13. Dupilumab is approved in the United States and many other countries worldwide for the treatment of moderate-to-severe AD with inadequate response or contraindication to topical therapy. However, little is known about the efficacy of dupilumab in patients with AD and comorbid ACD. In addition, little is known about the impact of dupilumab on patch testing results in patients with AD. We present a case series of 13 patients with AD and comorbid ACD who were patch tested either before or while undergoing dupilumab treatment.

CAPSULE SUMMARY

- This study identified variable impact of dupilumab on patch testing results and variable efficacy for comorbid allergic contact dermatitis in adult patients with atopic dermatitis.
- These results should be incorporated into the interpretation of patch testing results and clinical decision making in patients with atopic dermatitis.

METHODS

Study design

We performed a retrospective chart review of 13 adults (age ≥18 years) who were patch tested at the Northwestern Medicine patch testing clinic in 2017-2018. Patients routinely completed a questionnaire that assessed demographics and historical elements related to the diagnosis of their AD and ACD. Patients also had their medical history taken and underwent physical examination by a dermatologist (J.S.) before patch testing. Current AD was diagnosed by using the Hanifin and Rajka criteria.[10] Distribution of skin lesions was recorded for each patient.

Patients were patch tested with the North American Contact Dermatitis Group 75 standard series. Expanded series contained l allergen beyond what was included in the standard series to allow for a more complete evaluation. Patches were applied to patients' upper back and removed after 48 hours. Patches were evaluated initially at 48 hours and again at 72 to 80 hours, at which time final patch test results were recorded. Negative reactions included weak or irritant responses. Positive reactions were further classified as 1+, 2+, or 3+ per the International Contact Dermatitis Research Group scoring system.[11] Allergen source was established by patient history and/or improvement with allergen avoidance. At the time of patch testing, patients were washed out from topical corticosteroids, calcineurin inhibitors, and phosphodiesterase E4 inhibitors at the site of patch testing for at least 1 week, and oral systemic immunosuppressants or phototherapy for at least 4 weeks. No active dermatitis was present at the site of patch testing during patch placement.

The institutional review board of Northwestern University approved the study, and informed consent was waived.

RESULTS

Patch testing results during dupilumab treatment

In all, 7 patients were patch tested while undergoing dupilumab treatment; they included 4 males and 3 females aged 24 to 68 years (Table I). All met the Hanifin and Rajka criteria for AD, with a personal and/or family history of atopic disease, and they all had documented histories of AD for at least 7 years. All had generalized dermatitis, which flared immediately upon discontinuation of topical corticosteroids and/or systemic immunosuppressants, thereby precluding reliable patch testing. All patients were treated with dupilumab, 600 mg subcutaneously (loading dose), followed by 300 mg subcutaneously every 2 weeks thereafter (maintenance dose). All patients experienced almost clear skin with major improvements of their itch and other AD symptoms by 4 to 16 weeks of dupilumab therapy. However, all had persistent localized dermatitis that was refractory to dupilumab and concomitant midpotent to superpotent topical corticosteroids with or without topical calcineurin inhibitors. Recalcitrant lesions were localized to the hands and/or digits (n = 3), face and/or neck (n = 5), or feet (n = 1).

Epicutaneous patch testing was performed to determine whether the patients had overlapping ACD. At the time of patch testing, patients had been receiving a stable dose of dupilumab for 4 to 24 months, with no active dermatitis at the site of patch testing and a total body surface area (BSA) of dermatitis involvement less than 5%. In all 7 cases, at least 1 positive patch test reaction was observed, with a total of 25 different allergens eliciting a 1+ or stronger reaction. Of note, few irritant reactions were

Abbreviations used:

ACD: allergic contact dermatitis
AD: atopic dermatitis
BSA: body surface area
IL: interleukin
Th: helper T cell

observed. The source of allergen exposure was miscellaneous personal care products in 5 patients, including sunscreen in 2 and cosmetics in 3, as well as boots in 1 and other occupational exposure in 1. Of note, in case 3, the patient had severe airborne contact dermatitis on the face secondary to occupational nickel exposures. His facial dermatitis actually worsened with dupilumab treatment despite clearance of all his typical signs and symptoms of AD on the rest of the body.

In case 7, the patient was patch tested 2 years before starting dupilumab treatment under the same conditions and using the same NACDG standard series and was found to have reactions graded 2+ to nickel sulfate hexahydrate, methylchloroisothiazolinone/methylisothiazolinone, cinnamal, and balsam of Peru, with no irritant or weak reactions. The reactions to nickel had past relevance (ie, they were relevant to the adverse reactions that she had to jewelry when she was a child but not to her current dermatitis). The reactions to methylchloroisothiazolinone/methylisothiazolinone, cinnamal, and balsam of Peru had definite relevance; the patient experienced clinical improvement with their avoidance. However, upon repeat patch testing while she was undergoing dupilumab treatment, the patient only had a 2+ reaction to nickel sulfate hexahydrate.

Improvement of cases of overlapping AD and ACD after dupilumab treatment

A total of 6 patients underwent patch testing before dupilumab treatment, including 3 males and 3 females aged 49 to 61 years. All met the Hanifin and Rajka criteria for AD, had a personal and/or family history of atopic disease, and had documented histories of AD for at least 1 year. All had generalized dermatitis; 1 patient had sparing of the face, fingers and feet, whereas another had a lesional predilection for the hands and face.

Epicutaneous patch testing was performed to determine whether the patients had overlapping ACD. At the time of patch testing, their total BSA of dermatitis involvement was less than 15%. In all 6 cases, at least 1 positive patch test reaction was observed, with a total of 24 different allergens having a 1+ or stronger reaction, and numerous irritant reactions. Relevance was established in all cases by positive patch test reactions to personal care products containing the allergen (n = 4) and/or a positive use test result (n = 3). The source of allergen exposure was miscellaneous personal care products in 5 patients, including hair care products in 3 and emollients and/or eczema care in 2. In case 10, there were numerous weak reactions that were deemed to be irritant reactions owing to their very high frequency and disparate allergen classes, as well as the contrasting few strong relevant allergens.

All 6 patients were provided with detailed recommendations for allergen avoidance and subsequently treated with dupilumab, 600 mg subcutaneously, followed by 300 mg subcutaneously every 2 weeks thereafter. All patients experienced major improvement of their dermatitis within 2 to 4 months of dupilumab treatment. Four patients experienced complete clearance of all active dermatitis and were able to discontinue prescription topical therapy. Over time, 3 of these patients (50%) completely discontinued allergen avoidance (ie, when reintroduced to the allergens positive on patch testing, they did not experience any flares). One patient experienced an 83% reduction of the eczema area and severity index after 4 months of dupilumab treatment but experienced a generalized dermatitis flare after exposure to a scented body lotion. One patient experienced complete clearance of dermatitis on the body but less than 50% improvement of hand dermatitis that required intermittent use of superpotent topical corticosteroids and localized narrowband ultraviolet B phototherapy. His hand dermatitis flared intermittently upon exposure to soft soap containing lanolin in the workplace.

DISCUSSION

This case series demonstrates the variable impact of dupilumab on patch testing results in adult patients with AD. Positive patch tests were elicited in all 7 cases. ACD should be considered as a comorbid diagnosis in patients with AD with only a partial therapeutic response to dupilumab. In particular, ACD should be considered in patients with AD who experience clinical improvement of their typical AD signs and symptoms but have refractory localized dermatitis. In addition, patch testing may provide useful and relevant information about contact allergens in patients with AD treated with dupilumab. In 1 patient, however, there were multiple relevant positive patch test reactions that were observed before dupilumab treatment but were no longer positive while the patient was undergoing dupilumab therapy. Thus, dupilumab may cause false-negative patch test reactions in some patients. It is

Table I. Patient characteristics

Characteristic	During dupilumab therapy (n = 7)	Before dupilumab therapy (n = 6)
Mean age ± SD, y	46.4 ± 13.8	55.3 ± 4.9
Female sex, n (%)	3 (42.9%)	4 (66.7%)
Distribution of recalcitrant dermatitis, n (%)		
Generalized	7 (100.0%)	6 (100.0%)
Hands	3 (42.9%)	1 (16.7%)
Face and/or neck	5 (71.4%)	1 (16.7%)
Other	1 (14.3%)	0 (0.0%)
Mean duration of atypical or recalcitrant dermatitis ± SD, y	5.4 ± 4.7	5.5 ± 4.1
Mean age of AD onset ± SD, y	10.4 ± 22.4	40.8 ± 20.1
Mean duration of AD ± SD, y	35.7 ± 16.4	13.6 ± 17.7
Personal history, n (%)		
Asthma	5 (71.4%)	3 (50.0%)
Seasonal allergies	6 (85.7%)	3 (50.0%)
Food allergies	4 (57.1%)	2 (33.3%)
Family history, n (%)		
AD	5 (71.4%)	4 (66.7%)
Asthma	6 (85.7%)	4 (66.7%)
Seasonal allergies	6 (85.7%)	5 (83.3%)
Food allergies	4 (57.1%)	2 (33.3%)
Mean duration of dupilumab treatment ± SD, mo	12.9 ± 7.2	N/A
Positive reaction to allergens (1+, 2+, 3+) identified during patch testing, n (%)		
Lanolin, 50% pet	2 (28.6%)	1 (16.7%)
Propolis, 10.0% pet	1 (14.3%)	1 (16.7%)
Fragrance mix I, 8.0% pet	2 (28.6%)	1 (16.7%)
Citral, 2.0% pet	1 (14.3%)	
Farnesol, 5.0% pet	1 (14.3%)	
Fragrance mix II, 14.0% pet	1 (14.3%)	
Amyl cinnamyl alcohol, 5.0% pet	1 (14.3%)	
Anise alcohol, 10.0% sof	1 (14.3%)	
Benzophenone-4, 10.0% pet	1 (14.3%)	1 (16.7%)
Neomycin sulfate, 20.0% pet	1 (14.3%)	1 (16.7%)
Bacitracin, 20.0%	1 (14.3%)	1 (16.7%)
Gentamicin sulfate, 20.0% pet	1 (14.3%)	
Ethylenediamine dihydrochloride, 1.0% pet	1 (14.3%)	
Naphthyl mix, 1.0% pet	1 (14.3%)	
N,N′-Diethylthiourea, 1.0% pet	1 (14.3%)	
Mixed dialkyl thioureas, 1.0% pet	1 (14.3%)	
Nickel sulfate hexahydrate, 2.5.0% pet	2 (28.6%)	1 (16.7%)
Thimerosal, 1.0% pet	2 (28.6%)	
Phenyl mercuric acetate, 0.01.0% aq	1 (14.3%)	
Ethyl cyanoacrylate, 10.0% pet	1 (14.3%)	
Amidoamine, 0.1.0% aq	1 (14.3%)	
Sorbitan sesquioleate, 20% pet	1 (14.3%)	
Ammonium persulfate, 2.5.0% pet	1 (14.3%)	
Formaldehyde, 1.0% aq		2 (33.3%)
Diazolidinyl urea, 1.0% pet		1 (16.7%)
Potassium dichromate, 0.25.0% pet		1 (16.7%)
Hydroperoxides of linalool, 1.0% pet		1 (16.7%)
Isoeugenol, 1.0% pet		1 (16.7%)
Musk xylene, 1.0% pet		1 (16.7%)
Jasmine synthetic, 2.0% pet		1 (16.7%)
Benzyl salicylate, 10.0% pet		1 (16.7%)
Cinnamal 1.0% pet		1 (16.7%)
Methyldibromo glutaronitrile/phenoxyethanol, 2.0% pet		1 (16.7%)
Cocamide DEA, 0.5.0% pet		1 (16.7%)

Continued

Table I. Cont'd

Characteristic	During dupilumab therapy (n = 7)	Before dupilumab therapy (n = 6)
Thiuram mix, 1.0% pet		1 (16.7%)
Diphenylguanidine, 1.0% pet		1 (16.7%)
2-Hydroxyethyl methacrylate, 2.0% pet		1 (16.7%)
Chlorhexidine digluconate 0.5.0% aq		1 (16.7%)
Allergen sources, n (%)		
Personal care products	5 (71.4%)	6 (83.3%)
Clothing or shoes	2 (28.6%)	2 (33.3%)
Jewelry		1 (16.7%)
Other	1 (14.3%)	5 (83.3%)

aq, Aqueous; *DEA*, diethanolamine; *pet*, petrolatum; *SD*, standard deviation; *sof*, Softisan 649.

important for clinicians to recognize the possibility of false-negative reactions and consider repeat patch testing if dupilumab is discontinued.

In addition, we found that dupilumab had variable efficacy on comorbid ACD in patients with AD. Some patients with AD who were treated with dupilumab did not flare despite discontinuing avoidance of their relevant allergens. It may be that dupilumab successfully treated the ACD. However, we were unable to safely discontinue dupilumab and re-expose patients to the positive allergens. Thus, it is possible that these patients were sensitized but did not have ACD per se. In contrast, other patients experienced good control of AD signs and symptoms while taking dupilumab but experienced 1 or more flares of ACD upon exposure to their relevant allergens. Previous case reports or series demonstrated clearance of ACD in patients treated with dupilumab. Dupilumab was found to be effective in a middle-aged man with systemic contact dermatitis to nickel from endovascular stents and vascular clips.[12] In contrast, we found that dupilumab was not effective in treating ACD in response to nickel despite it being highly effective in treating the patient's AD (case 3). A case series showed that 2 patients with AD and ACD had similar patch testing results during and before taking dupilumab.[13] In contrast, we had 1 patient with multiple relevant positive reactions before dupilumab treatment that were not duplicated during dupilumab treatment (case 7). This suggests that dupilumab may result in false-negative patch test reactions and that patch testing results should be interpreted with caution in patients who are taking dupilumab. A case series of 15 patients with a history of AD and comorbid ACD found that dupilumab led to substantial reductions of BSA involvement.[14] However, that series did not determine whether clinical improvement was due to improvement of the AD, the ACD, or both. We found that dupilumab did indeed result in dramatic improvements of patients' typical signs and symptoms of AD but had variable effects on lesions attributed to ACD. Further, some of our patients had localized flares of dermatitis upon provocation with relevant allergens. Thus, it appears that patients with AD and ACD treated with dupilumab should be counseled to continue appropriate allergen avoidance. A trial of re-exposure to contact allergens can be considered cautiously in patients experiencing good clinical response during dupilumab therapy. Other case series have suggested that dupilumab successfully treated ACD (without any mention of past or present AD).[15,16] It is important to recognize that all of these previously published reports are anecdotal and subject to publication bias. Our case series suggests that indeed dupilumab may be effective for some cases of ACD, but not predictably so. Clinicians considering off-label use of dupilumab in ACD should recognize that patients may not achieve adequate clinical improvement. Such patients may benefit from shorter intervals and longer duration of follow-up, use of standardized assessments to monitor for clinical improvement, and continued allergen avoidance. In addition, randomized controlled trials are needed to provide evidence supporting the efficacy of dupilumab in ACD.

ACD is thought to be primarily driven by a Th1 immune response.[17] However, Th2, Th17, and Th22 responses also appear to play a role in ACD, sometimes depending on the allergen.[18-20] One study found that nickel was a potent inducer of the innate immune Th1, Th17, and Th22 pathways, whereas fragrance and rubber promoted Th2 activity with less Th1 and Th17 involvement.[21] Different cytokine responses may explain (1) why dupilumab is effective in treating ACD in some but not all patients and (2) why dupilumab may result in false-negative patch testing reactions for some but not all allergens. Future research is needed to better understand the cytokine responses of different contact

allergens and to better predict which ACD patients would benefit from dupilumab or other targeted therapies.

In conclusion, dupilumab had a variable impact on patch testing results and resolution of comorbid ACD in adult patients with AD.

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