The role of expanded series patch testing in identifying causality of residual facial dermatitis following initiation of dupilumab therapy

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INTRODUCTION

Dupilumab is a biological agent that addresses the pathophysiology of atopic dermatitis (AD) by modulating signaling of interleukin-4 and interleukin-13, the primary interleukins involved in the type 2 helper T-cell response. Dupilumab was approved by the US Food and Drug Administration on March 28, 2017, for moderate-to-severe AD not adequately controlled with topical prescription therapy in adults.

Dalia and Marchese Johnson published the first report of a persistent facial dermatitis after initiation of dupilumab therapy and resolution of dermatitis on the body.1 The authors hypothesized that the facial dermatitis was a side effect of the medication. Importantly, this patient was not patch tested. We report 3 cases of severe AD treated with dupilumab in which patch testing was critical to unmasking an underlying allergic contact dermatitis (ACD).

These cases highlight the following three key principles:

1. Patch testing dupilumab candidates before initiation of therapy helps identify potential underlying ACD, thereby decreasing the chances of falsely identifying treatment as failed.

2. Patients can be patch tested on dupilumab; prior positives in previous testing should act as controls whenever possible, as seen in patients 1 and 2 of this series.

3. Patients with residual facial dermatitis on dupilumab may benefit from further comprehensive patch testing.

Before dupilumab initiation, all patients in this series attempted similar treatment regimens including topical Vaseline, bleach baths, corticosteroids, and calcineurin inhibitors; systemic antihistamines, intramuscular triamcinolone, prednisone, and periodic oral antibiotics for any identified bacterial infections; and phototherapy. Before patch testing, patients were treated with soak and smear regimens of twice-daily applications of Vanicream (Pharmaceutical Specialties, Inc., Rochester, MN) and clobetasol. Patch testing was only initiated at least 4 weeks after the most recent dose of oral prednisone and at least 3 months after the most recent dose of intramuscular triamcinolone.

CASE 1

A 52-year-old woman with a lifelong history of severe AD presented with pruritus and eczematous dermatitis covering the body, scalp, and face. Her disease was refractory to multiple therapies, and...
### Table I. Timing and results of comprehensive patch testing

| Patient | Patch test time relative to dupilumab initiation | Trays/allergens tested | Positives at 2 d/5-6 d |
|---------|-------------------------------------------------|------------------------|------------------------|
| 1       | 2 y prior                                       | NACDG standard series (75 allergens) (SmartPractice, Calgary, Alberta, Canada) | -/2+: neomycin sulfate 20%  
-/+ bacitracin 20%  
Trace/2+: ethyl acrylate 0.1%  
1+/2+: glutaraldehyde 1%  
-/2+: ammonium persulfate 2.5% |
|         |                                                 | TF-1000 textile colours & finish series (33 allergens) (Chemotechnique Diagnostics, Tygelsjö, Sweden) | None |
| 1       | 6 mo after                                      | Corticosteroid series (9 allergens) (SmartPractice, Canada)  
External agents/emulsifiers series (35 allergens) (SmartPractice)  
Eye medicaments series (26 allergens) (Smartpractice)  
F-1000 fragrance series (Dormer Laboratories, Rexdale, Ontario, Canada) | None  
-/2+: Amerchol L101 50%  
-1+: lanolin alcohol 30%  
-1+: wool alcohols ointment 100%  
-1+/2+: kanamycin sulfate 10% |
|         |                                                 | Sunscreen series (21 allergens) (Dormer Laboratories)  
Cosmetics tray (47 allergens; custom designed with allergens from SmartPractice and Dormer Laboratories, See Table II) | None |
| 2       | 6 y prior                                       | NACDG standard series (75 allergens) (SmartPractice)  
Sunscreen series (20 allergens)  
Corticosteroid series (13 allergens)  
Patient’s products (18 allergens) (SmartPractice) | Trace/1+: budesonide 0.1%  
None  
Trace/1+: budesonide 0.01%  
Trace/1+: budesonide 0.1%  
-1+: alclometasone-17,21 dipropionate 1% |
| 2       | 9 mo after                                      | Control: budesonide 0.1% (SmartPractice)  
Corticosteroid series (9 allergens)  
External agents/emulsifiers series (35 allergens)  
F-1000 fragrance series (44 allergens) | -1+/2+: budesonide 0.1%  
-1+/2+: budesonide 0.01%  
-1+: alclometasone-17,21 dipropionate 1%  
-1+: budesonide 0.1%  
-1+: budesonide 0.1%  
-1+: lanolin alcohol 30%  
-1+: propylene glycol 30%  
-1+: stearyl alcohol 30%  
-1+: lanolin alcohol 30%  
-1+: wool alcohols ointment 100%  
-1+: benzyl alcohol 1%  
-1+: hydroperoxides of linalool 1% |

Continued
patch testing was undertaken to identify potential ACD (Table I). She tested positive for 5 allergens, including neomycin sulfate 20%, and began allergen avoidance. She experienced inadequate relief, and 2 years later began dupilumab therapy (600 mg loading dose followed by 300-mg subcutaneous doses every other week). Dramatic improvement was noted within a few months, but residual dermatitis persisted on the forearms, neck, and face. Advanced series patch testing was performed as seen in Tables I and II. The patient remained allergic to neomycin sulfate 20%, demonstrating patch testing remained effective after initiation of dupilumab. The patient also tested positive for perfume mix and fragrance mix, which was undetected on prior testing—notably she was using a fragranced shampoo. She began allergen avoidance, and 2.5 months later, the forearm, neck, and face dermatitis was 75% improved as noted by both the patient and clinician. Because mild residual disease was noted, topical tacrolimus to the face was initiated. She is on topical tacrolimus and dupilumab maintenance therapy.

**CASE 2**

A 54-year-old woman with a history of lifelong mild-to-moderate AD presented with eczematous dermatitis consisting of numerous edematous plaques on the chest, red papules on the face, and thin plaques on the body (Fig 1, A). Her disease was refractory to multiple therapies, and patch testing was performed revealing allergies to budesonide and alclometasone (Table I). After 6 years of allergen avoidance and additional attempts of topical

**Table I. Cont’d**

| Patient | Patch test time relative to dupilumab initiation | Trays/allergens tested                                                                 |
|---------|---------------------------------------------------|---------------------------------------------------------------------------------------|
| 3       | 3 mo prior                                        | -/1+ hydperoxide of limonene 0.3%                                                     |
|         |                                                   | -/1+ Perfume Mix                                                                      |
|         |                                                   | None                                                                                  |
|         |                                                   | -/1+ CeraVe sunscreen                                                                  |
|         |                                                   | Trace/2+ La Roche-Posay Anthelios 50 Mineral Sunscreen                                 |
|         |                                                   | -/1+ Apothecare Essentials Shampoo 10%                                                |
|         |                                                   | -/Trace Shea Moisturizer Daily Hydration Shampoo                                      |
|         |                                                   | 10%                                                                                  |
|         |                                                   | -/1+ Under the Canopy White Citrus & Lime Conditioning Shampoo                        |
|         |                                                   | -/1+ Nexxus Therappe Shampoo 10%                                                      |
|         |                                                   | None                                                                                  |
|         |                                                   | 1+ /Trace hexylene glycol 10%                                                        |
|         |                                                   | 2+/1+ propylene glycol 100%                                                          |
|         |                                                   | Trace/1+ propylene glycol 20%                                                        |
|         |                                                   | Trace/1+ propylene glycol 30%                                                        |
|         |                                                   | 1+/1+ sodium lauryl sulfate 0.25%                                                    |
|         |                                                   | 1+/Trace hydroperoxides of linalool 1%                                               |
|         |                                                   | 2+/1+ Bare Minerals Gel Cream SPF 30                                                   |
|         |                                                   | 2+/2+ Sweet Baby Shampoo 10%                                                         |
|         |                                                   | 2+/2+ Sweet Baby Shampoo 1%                                                          |

Note. The timing of the patients’ patch testing relative to the initiation of dupilumab is noted. The trays used for each patient are indicated. Patch testing was performed and read 2 days postplacement, and again 5 to 6 days postplacement. The scale is indicated on the table, ranging from negative (−) to 3+ for most severe reaction. Allergens used as controls were underlined and bolded to demonstrate positivity both before and after dupilumab initiation.
therapy, disease remained inadequately controlled and she began taking dupilumab. She experienced significant improvement 1 month into treatment, but the facial rash persisted. Additional patch testing was performed while on dupilumab as seen in Table I, including a retest of budesonide and alclometasone as controls. She remained positive to budesonide and alclometasone, again demonstrating dupilumab did not affect the ability to repeat prior positive patch tests. The patient was allergic to limonene, which was present in her shampoo. She continued dupilumab and began allergen avoidance. Her dermatitis cleared, and she remained clear at a follow-up examination 2 months after patch testing with dupilumab monotherapy (Fig 1, B).

CASE 3
A 54-year-old woman with a history of mild AD from childhood presented with severe facial dermatitis and significant pruritus. On physical examination, lichenified erythematous plaques were noted over the eyelids, cheeks, forehead, chin, and lateral neck with milder involvement of the extremities and trunk (Fig 2, A). Because of the distribution of disease, it was thought the patient had a mild AD with superimposed ACD. She underwent patch testing with multiple series as seen in Table I. When testing personal products, an allergy to Sweet Baby shampoo (Paradise Island Organics LLC, Pocatello, Idaho) was identified. Upon allergen avoidance, the patient noted improvement of facial dermatitis, but 1 month later experienced a flare on the face and continued to have mild generalized pruritus. She began taking dupilumab. The combination of allergen avoidance and dupilumab therapy provided the patient significant relief. The patient’s facial dermatitis resolved 2 months after dupilumab initiation and she remained clear on dupilumab monotherapy at a 3-month follow-up examination (Fig 2, B).

DISCUSSION
When caring for patients with suspected AD, patch testing is recommended when dermatitis:
- Worsens or fails to improve with topical therapy
- Rebounds upon topical therapy discontinuation
- Is controlled with high doses of corticosteroids but flares when only low potency corticosteroids are used
- Has an atypical or changing distribution
- Is resistant on the hand in the working population
- Begins in adulthood or adolescence,

Table II. Custom-designed cosmetics tray

| Ingredient                                        | Percentage |
|--------------------------------------------------|------------|
| Abietic acid                                     | 10%        |
| Abitio1 (hydroabietyl alcohol)                    | 10%        |
| Aluminum (III) chloride hexahydrate               | 2%         |
| Arnica Montana (mountain tobacco)                 | 0.5%       |
| Sulisobenzone (2-hydroxy-4-methoxy-benzophenone-5- sulfonic acid, 5-Benzoyl-4-hydroxy-2-methoxybenzenesulfonic acid) | 10%       |
| Benzophenone-4                                    | 2%         |
| Benzy1 alcohol                                    | 10%        |
| Bithionol                                        | 1%         |
| Butylhydroxyanisole                               | 2%         |
| Butylhydroxytoluene                               | 2%         |
| Captan                                           | 0.5%       |
| Cetyl alcohol                                     | 5%         |
| Chloroacetamide/2-chloroacetamide                 | 0.2%       |
| Chlorhexidine digluconate                         | 0.5%       |
| p-Chloro-m-cresol/4-Chloro-3-cresol               | 1%         |
| Clioquinnol (chinoform, Vioform)                  | 3%         |
| Dichlorophene                                     | 1%         |
| 2,6-Di-tert-butyl-4-cresol                        | 2%         |
| Dodecyl gallate                                  | 0.25%      |
| Drometrizole trisiloxane/(2-(2'-hydroxy-5’-methyl-penyl)-benzotriazol) | 10%       |
| Hexachloropropene                                 | 1%         |
| Hexahydro-1,3,5-tris-(2-hydroxyethyl) triazine    | 1%         |
| Hexamethylenetetramine (methenamine)              | 2%         |
| Lauryl polyglucose                                | 3%         |
| Methylol chloroacetamide                          | 0.1%       |
| Musk mix                                         | 3%         |
| Octyl gallate                                    | 0.25%      |
| Peppermint oil (mentha piperita oil)              | 2%         |
| 2-Phenoxyethanol                                  | 1%         |
| Phenylpheno1 (o-phenylenophenol)                  | 1%         |
| Phenyl mercuric acetate                           | 0.01%      |
| Phenyl salicylate (Salol)                         | 1%         |
| Propyl gallate                                   | 1%         |
| Quaternium-15 (Dowicil 200)/1-(3-Chloroallyl)-3,5,7-triaz-1-azoniadamantane chloride | 2%         |
| Shellac                                          | 20%        |
| Sodium benzoate                                   | 5%         |
| Sodium disulfite                                  | 1%         |
| Sodium metabisulfate                              | 1%         |
| Sodium-2-pyridinethiol-1-oxide (sodium omadine)   | 0.1%       |
| Sorbic acid                                      | 2%         |
| Turpentine oil oxidized                           | 0.4%       |
| Tert-butylhydroquinone                            | 1%         |
| 3,3’/4‘/5-Tetrachloro salicylanilide              | 0.1%       |
| Tocopheryl acetate                               | 10%        |
| Tocopherol (DL alpha tocopherol)                  | 100%       |
| 3,4,5-Tribromosalicylanilide tribromosalan, TBS   | 1%         |
| Triclocarban (3,4,4-Trichlorocarbanilide)         | 1%         |

Note. The cosmetics tray was custom designed with allergens from SmartPractice and Dormer to include cosmetic allergens not already present in the NACDG, fragrance, and emulsifier series.
Is severe or widespread and systemic immuno-suppressants are being considered

Comprehensive patch testing before induction of dupilumab as seen in patient 3 of this series is recommended because it further delineates potential allergens, decreasing the chance of falsely identifying treatment as having failed. It appears patch testing can be performed when patients are on dupilumab as well, and initial or additional patch testing should be performed in instances of

Fig 1. A, Patient 2, pictured at baseline (A) before dupilumab with full facial eczematous dermatitis that extended onto the neck, trunk and extremities. Additional patch testing with advanced series was performed because despite initiation of dupilumab therapy and resolution of disease on the body, there was persistent dermatitis on the forehead and cheeks. B, Two months after the second round of patch testing and allergen avoidance, the patient’s facial dermatitis resolved.

Fig 2. A, Patient 3 is pictured at the time of initial patch testing with full facial involvement. B, Marked resolution of the dermatitis and pruritus after 5 months of allergen avoidance and 2 months of dupilumab.
persistent head and neck dermatitis after initiation of dupilumab. In these instances, we recommend use of a control when patch test results are available as seen in patients 1 and 2 of this series. Successful patch testing on dupilumab has also been reported by other groups.3,4

Patch testing is unlikely to be helpful in patients for whom2:
- There is good control of dermatitis or no recent change in dermatitis distribution or severity
- There have been topical steroids recently applied to patch test sites
- Ultraviolet therapy or excessive solar radiation has been performed within 2 to 3 weeks
- Oral prednisone has been given within the last 4 weeks
- Intramuscular triamcinolone has been given within the last 3 months
- The patch test battery is inadequate

Baseline series such as the North American Contact Dermatitis Group (NACDG) standard series appear inadequate in the identification of ACD, as seen in patients 1 and 2 of this series. Studies found 21% to 34% of ACD diagnoses would have been missed by the NACDG standard series without testing supplemental allergens.5,6 Moreover, patients with positive patch tests were found to have additional allergens when more extensive testing was performed.5,6 Comprehensive patch testing has a higher probability of yielding specific allergy diagnosis compared with limited patch testing, leading to a much higher probability of cure.7 Thus, it is recommended that patients receive comprehensive patch testing, which consists of a baseline series such as the NACDG Standard Series, advanced series, and the patient’s personal products.

Ultimately, with the increased availability of treatment options for atopic dermatitis, it is important for providers to:
- Be aware of the potential for concomitant ACD
- Recognize indications for patch testing in atopic dermatitis patients
- Perform patch testing with adequate allergens
- Educate patients regarding allergen avoidance to reduce the chances of mistakenly classifying persistent dermatitis as treatment failure or drug reaction
- Increase the number of patients successfully treated with systemic agents

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