

# Patch Test Results in Psoriasis Patients on Biologics

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**Objectives:** The objective of this study was to determine the prevalence of positive patch tests in patients with psoriasis receiving biologics and whether these results differ from those of patients with psoriasis not on biologics.

**Methods:** An institutional review board–approved retrospective chart review was conducted for patients with psoriasis patch tested January 2002–2012 at Tufts Medical Center. Patients had a history of psoriasis, psoriatic arthritis, and patch testing as identified by *International Classification of Diseases, Ninth Revision* codes 696.1, 696.0, and 95044, respectively, in their records. Patients were tested to a modified North American Contact Dermatitis Group standard and cosmetics series. Readings were performed at 48 hours and 72 to 96 hours. The North American Contact Dermatitis Group grading system was used to grade reactions.

**Results:** Fifteen patients with psoriasis on biologics (cases) and 16 patients with psoriasis not on biologics (control subjects) were studied. The biologics used were ustekinumab ( $n = 7$ ), etanercept ( $n = 4$ ), adalimumab ( $n = 3$ ), and infliximab ( $n = 1$ ). Eighty percent (12/15) of cases had at least 1 positive reaction compared with 81% (13/16) of the control subjects; 67% (10/15) of cases had 2+ reactions compared with 63% (10/16) of the control subjects, and 27% (4/15) of cases had 3+ reactions, compared with 38% (6/16) of control subjects. These differences were not statistically significant.

**Conclusions:** Given the limitation of small numbers of patients, biologics do not appear to influence the abilities of patients with psoriasis to mount a positive patch test.

Several population-based studies and case reports confirm that allergic contact dermatitis (ACD) can concomitantly occur in patients with psoriasis, both of which are T cell–mediated

dermatologic disorders mediated by T-cells, notably  $T_H1$  and  $T_H17$  cells.<sup>1–3</sup> Recent compiling evidence supports the significant shared role between both  $T_H1$  and  $T_H17$  pathways in the pathogenesis of important inflammatory dermatologic conditions, such as ACD and psoriasis.<sup>3</sup> Specifically, ACD is the clinical representation of a T cell–driven delayed-type hypersensitivity reaction that can be diagnosed by patch testing.<sup>4</sup> However, there is conflicting evidence on the frequency of ACD in the psoriasis population, ranging from 3.2% to 68%.<sup>5–9</sup> Some argue that the frequency of ACD among patients with psoriasis should be low because of abnormal T-cell function and high skin cell turnover in the hyperkeratotic psoriatic skin. This would ultimately lead to insufficient exposure to allergens for an immune response to occur.<sup>10</sup> On the other hand, a small cohort study showed a 68% positive patch test rate in patients with psoriasis.<sup>7</sup> The authors concluded that in those patients with psoriasis with ACD, the allergens are more easily presented to dendritic cells through a defective skin barrier and may serve as a trigger for disease exacerbation and/or treatment resistance.<sup>7</sup>

Although there is no real consensus on the association between ACD and psoriasis, tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), interleukin 23 (IL-23), and recently IL-17 are implicated in the immunopathogenesis of both ACD and psoriasis.<sup>2,11–24</sup> Tumor necrosis factor  $\alpha$  and IL-23 are targets for psoriasis therapies, and the efficacy of TNF- $\alpha$  inhibitors, including adalimumab,<sup>25–27</sup> etanercept,<sup>28–30</sup> and infliximab,<sup>31–33</sup> as well as ustekinumab,<sup>34,35</sup> an IL-12/23

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inhibitor, for psoriasis has been well documented. Of note, TNF- $\alpha$  is a major inflammatory cytokine with dual roles in both T<sub>H</sub>1- and T<sub>H</sub>17-mediated inflammation, and therefore, data suggest that TNF blockers work by affecting both pathways.<sup>36,37</sup> Furthermore, ustekinumab is a humanized monoclonal antibody that targets the p40 subunit shared by the T<sub>H</sub>17-specific IL-23 and the T<sub>H</sub>1-associated IL-12.<sup>38</sup> Today, targeted biologic therapies are frequently used for psoriasis, psoriatic arthritis, and other inflammatory diseases. Yet, currently the effect of biologics on the results of patch testing by inhibiting the pathways implicated in ACD pathogenesis is not well understood. Moreover, there are few documented cases in the literature that attest to the patch-testing outcomes of subjects on biologics.

Previous case series have demonstrated the ability of patients to show patch-test positivity on systemic immunosuppressants, including infliximab.<sup>39,40</sup> Further evidence comes from a case report of a patient on etanercept therapy who developed ACD to poison ivy.<sup>41</sup> In addition, another case report demonstrated positive patch testing for allergic contact hand dermatitis while concomitantly on infliximab for psoriasis and psoriatic arthritis.<sup>42</sup> A recent case report showed the ability of a patient with psoriasis on ustekinumab to have positive patch test reactions as well.<sup>43</sup> Nevertheless, there have not been any case series to date that investigate the prevalence of positive patch testing in patients receiving biologic therapy for their psoriasis and whether any difference in prevalence exists between patients with psoriasis on biologics compared with patients with psoriasis not on these therapies. This pilot study addressed the role of patch testing and the interpretation of results in patients with psoriasis on biologics.

## METHODS

An institutional review board–approved retrospective chart review was done of patients with psoriasis patch tested at Tufts Medical Center (TMC) between the period from January 2002 to January 2012. The included subjects had a documented diagnosis of psoriasis and/or psoriatic arthritis as well as a history of patch testing as identified by their respective *International Classification of Diseases, Ninth Revision* codes, 696.1, 696.0, and 95044, in their hospital billing records. All medical records were obtained from one of the author's (P.L.S.) Patch Test Clinic at TMC Department of Dermatology. Information from the patients' medical and billing records was reviewed in order to record demographic information, psoriasis diagnosis, and treatments, as well as patch test results. All patients were tested to a TMC standard series (a modified North American Contact Dermatitis Group [NACDG] standard series) and a cosmetics series, in addition to other supplemental series depending on history and physical examination results (Tables 1 and 2). The absolute total number of allergens included in the TMC standard plus cosmetic series varied over the course of the study period: from 2005 to 2006, there were 78 allergens, which increased to 83 between 2009 and 2010 and then to 85 allergens during 2010 to 2012. All allergens were obtained from Chemotechnique

**TABLE 1. TMC Standard Series**

### Standard Allergens

|                                                                         |
|-------------------------------------------------------------------------|
| Benzocaine 5% pet.                                                      |
| Mercaptobenzothiazole 1% pet.                                           |
| Colophony (Rosin) 20% pet.                                              |
| p-Phenylenediamine 1% pet.                                              |
| Imidazolidinyl urea 2% aq.                                              |
| Cinnamic aldehyde 1% pet.                                               |
| Lanolin alcohol (wool alcohol) 30% pet.                                 |
| Carba mix 3% pet.                                                       |
| Neomycin sulfate 20% pet.                                               |
| Thiuram mix 1% pet.                                                     |
| Formaldehyde 1% aq.                                                     |
| Ethylenediamine dihydrochloride 1% pet.                                 |
| Epoxy resin 1% pet.                                                     |
| Quaternium 15 2% pet.                                                   |
| p-tert-Butylphenol formaldehyde resin 1% pet.                           |
| Mercapto mix 2% pet.                                                    |
| N-isopropyl-n'-phenyl paraphenylenediamine (black rubber mix) 0.6% pet. |
| Potassium dichromate 0.25% pet.                                         |
| <i>Myroxylon pereirae</i> (balsam of Peru) 25% pet.                     |
| Nickel sulfate 2.5% pet.                                                |
| 4-Chloro-2-xenol (PCMX) 1% pet.                                         |
| 2-Bromo-2-nitropropane-1,3-diol (bronopol) 0.5% pet.                    |
| 4-Chloro-3-cresol (PCMC) 1% pet.                                        |
| Ethyl acrylate 0.1% pet.                                                |
| Ethyleneurea melamine-formaldehyde 5% pet., 5% SSO                      |
| Compositae mix 5% pet.                                                  |
| Paraben mix 12.0% pet.                                                  |
| Methylchloroisothiazolinone/methylisothiazolinone 0.02% aq.             |
| Fragrance mix I, 8% pet. 5% SSO                                         |
| Aluminum chloride (control) 2% pet.                                     |
| Diazolidinyl urea 2 % pet.                                              |
| Benzophenone-3 10% pet.                                                 |
| Glutaraldehyde 1% pet.                                                  |
| Benzophenone 4 10% pet.                                                 |
| Cobalt chloride 1% pet.                                                 |
| Glyceryl monothioglycolate 1% pet.                                      |
| Methyl methacrylate 2% pet.                                             |
| Tixocortal-21-pivalate 0.1% pet.                                        |
| Hydrocortisone-17-butyrate 1.0% alc.                                    |
| Budesonide 0.01% pet.                                                   |
| DMDM hydantoin 2% aq.                                                   |
| Imidazolidinyl urea 2% pet.                                             |
| Gold sodium thiosulfate 0.5% pet.                                       |
| Bacitracin 20% pet.                                                     |
| Dexamethasone 21 phosphate disodium salt 1% pet.                        |
| Lidocaine 5 % pet.                                                      |
| 4, 4'-Dithiodimorpholine 1% pet.                                        |
| Mixed dialkyl thiourea 1% pet.                                          |
| Narcissus absolute 2.0 % pet.                                           |
| Fragrance mix II 14% pet.                                               |

*Pet.* indicates petrolatum; *aq.*, aqueous; *alc.*, alcohol.

**TABLE 2. TMC Cosmetic Series****Cosmetic Series**

|                                                               |
|---------------------------------------------------------------|
| Polyethylene glycol 100% pet.                                 |
| Chlorhexidine digluconate 0.5% aq.                            |
| Abitol 10% pet.                                               |
| Amidoamine 0.1% aq.                                           |
| Hexahydro-1,3,5-tris(hydroxyethyl)triazine (Grotan BK) 1% aq. |
| Cetyl alcohol 5% pet.                                         |
| Toluene sulfonamide formaldehyde resin 10% pet.               |
| Sorbic acid 2% pet.                                           |
| Methyl-4-hydroxybenzoate (-paraben) 3% pet.                   |
| Ethyl-4-hydroxybenzoate (-paraben) 3% pet.                    |
| Propyl-4-hydroxybenzoate (-paraben) 3% pet.                   |
| Butyl-4-hydroxybenzoate (-paraben) 3% pet.                    |
| Benzalkonium chloride 0.1% aq.                                |
| Resorcinol 1% pet.                                            |
| Triclosan 2% pet.                                             |
| Methyldibromoglutaronitrile 0.5% pet.                         |
| Sorbitan sesquioleate (Arlacel 83) 20% pet.                   |
| Cetyl/stearyl alcohol 20% pet.                                |
| Amerchol L 101 50% pet.                                       |
| Resorcinol monobenzoate 1% pet.                               |
| Isopropyl myristate 20% pet.                                  |
| Triethanolamine 2% pet.                                       |
| Span 80 (sorbitan monooleate) 5% pet.                         |
| Coconut diethanolamide (cocamide DEA) 0.5% pet.               |
| Vitamin E (alpha tocopherol) 100%                             |
| Benzyl alcohol 10% pet.                                       |
| Cocamidopropyl betaine 1% aq.                                 |
| Oleamidopropyl dimethylamine 0.1% aq.                         |
| 2-Phenoxyethanol 1% pet.                                      |
| Propylene glycol 30% aq.                                      |
| BHA 2% pet.                                                   |
| BHT 2% pet.                                                   |
| Iodopropynyl butylcarbamate 0.2% pet.                         |
| 3-(Dimethylamino-1-propylamine) DMAPA 1% aq.                  |
| Lauryl glucoside 3% pet.                                      |

Diagnostics (Vellinge, Sweden). Finn chambers (Epitest Ltd Oy, Tuusula, Finland) on Scanpor tape (Norgesplaster A/S, Vennessla, Norway) were used for the patch testing. The patches were left in place and removed at 48 hours. Readings were performed at 48 hours and then 72 to 96 hours after placement. The reported results herein are based on the final readings. The NACDG grading system was applied to grade the reactions: a 3+ (extreme) reaction was defined as bullous/ulcerative lesions or papules or vesicles spreading beyond the boundaries of the Finn chambers; a 2+ (strong) reaction was papules and edema; and a 1+ (weak) reaction corresponded to erythema and papules. Macular erythema was considered to be a questionable reaction. All questionable reactions were not included in the study's analysis.

For statistical considerations, the proportion of patch test positivity in our psoriasis cases on biologics versus our psoriasis control group was compared using the Student *t* test, with  $P < 0.05$  considered statistically significant.

**RESULTS**

Thirty-one patients fulfilled the study's inclusion criteria. There were 15 patients with psoriasis who were on some form of biologic therapy before or during the time of patch testing, including the following: 7 on ustekinumab, 4 on etanercept, 3 on adalimumab, and 1 on infliximab. The average time lapse from when the patient last received an active dose of biologic treatment to when patch tests were applied was 38 days and ranged between 2 and 238 days. All time intervals from the last biologic dose given to time of patch testing were within 2 half-lives of the particular biologic, in order to suggest there would still be a measurable amount of therapy at the times of testing. Typically, in clinical trials, at least 5 half-lives must have lapsed for patients to be considered free of drug. The mean and median terminal half-lives across all clinical studies of the biologics included in the study are as follows: ustekinumab has a mean half-life of  $14.9 \pm 4.6$  to  $45.6 \pm 80.2$  days,<sup>44</sup> etanercept has a mean half-life of 4.3 days or 70 to 100 hours,<sup>45</sup> adalimumab has a mean half-life of 2 weeks or 10 to 20 days,<sup>46</sup> and infliximab has a median half-life of 7.7 to 9.5 days.<sup>47</sup> Of the patients with psoriasis on biologics (cases), there were 8 men and 7 women with ages ranging from 24 to 71 years, and the duration of their dermatitis ranged from 2 months to 4 years. Of note, within this study group, there were a few patients who were also on other systemic immunosuppressants: 2 were on methotrexate and 1 on oral prednisone (Table 3). A majority of the cases (10 of the 15 patients) had their upper extremities (hands and/or arms) involved with the dermatitis. Other areas affected with ACD, in descending order of frequency, included legs, generalized, eyelids, trunk, face, scalp, and mouth (Table 4).

On the other hand for the control group, there were 16 patients with psoriasis who had been patch tested without any history of biologics use. There were 8 men and 8 women in this study group

**TABLE 3. Basic Demographic Information for Psoriasis Patients on Biologics (Cases) and Not on Biologics (Control Subjects)**

| Categories                     | Cases       | Control Subjects |
|--------------------------------|-------------|------------------|
| Sex                            |             |                  |
| Male                           | 8           | 8                |
| Female                         | 7           | 8                |
| Age                            |             |                  |
| Range                          | 24–71 y     | 42–71 y          |
| Mean                           | 49 y        | 57 y             |
| Median                         | 46 y        | 63 y             |
| Duration of dermatitis         |             |                  |
| Range                          | 2 mo to 4 y | 4 mo to 10 y     |
| Mean                           | 12.5 mo     | 69 mo            |
| Median                         | 6.5 mo      | 36 mo            |
| Concomitant immunosuppressants |             |                  |
| Prednisone                     | 2           | 1                |
| Methotrexate                   | 1           | 2                |
| Cyclosporine                   | 0           | 1                |

**TABLE 4. Location of Dermatitis for Psoriasis Patients on Biologics (Cases)**

| Location of Dermatitis                | Cases |
|---------------------------------------|-------|
| Upper extremities (hands and/or arms) | 10    |
| Lower extremities                     | 5     |
| Generalized                           | 4     |
| Eyelids                               | 2     |
| Trunk                                 | 1     |
| Face                                  | 1     |
| Scalp                                 | 1     |
| Mouth                                 | 1     |

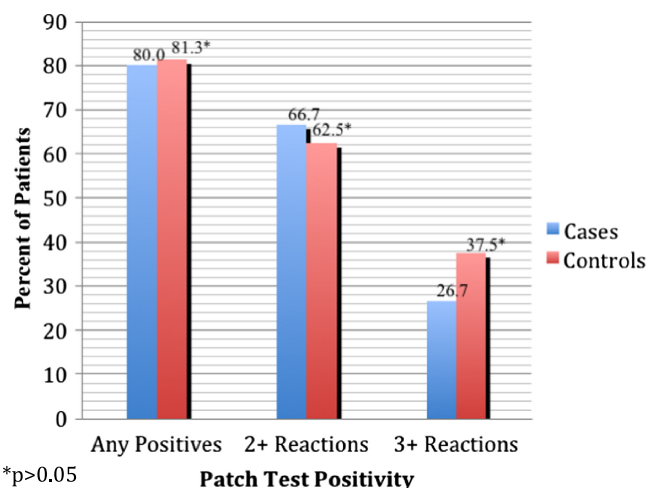
with ages ranging from 42 to 71 years. The duration of the dermatitis for the patients in the control group was between 4 months and 10 years. Few of the included patients in the control group also were on systemic immunosuppressants, such as 2 patients on methotrexate, 1 on oral prednisone, and 1 on cyclosporine (Table 3). Nine of the 16 patients had their upper extremities, specifically the hands, affected by their dermatitis with other locations, in descending order of frequency, being lower extremities, generalized, trunk, face, eyelids, neck, scalp, tongue, and perianal (Table 5).

Overall, 80.0% (12/15) of the cases had at least 1 positive patch test reaction compared with the 81.3% of the control subjects ( $P = 0.933$ ). These reactions included all 1+ to 3+ reactions based on the final readings. Among the cases, 66.7% (10/15) had at least one 2+ reaction in their patch-testing results versus the 62.5% (10/16) of the control subjects ( $P = 0.816$ ). Fewer patients had records of a 3+ patch test reaction: 26.7% (4/15) of the cases compared with 37.5% (6/16) of the control subjects ( $P = 0.534$ ). As denoted by the  $P$  values, there were no significant differences found in the patch test response percentage as well as the absolute number of positive reactions between the 2 study groups (Fig. 1).

Among the cases, there were no significant differences noted in the frequency of patch test positivity between the patients who were on different biologic treatments. All the patients with psoriasis on ustekinumab had at least 1 positive patch test reaction (7/7), 85.7% (6/7) had at least one 2+ reaction, and 28.6% (2/7) had at least one 3+ reaction. Half of the patients with psoriasis on

**TABLE 5. Location of Dermatitis for Psoriasis Patients Not on Biologics (Control Subjects)**

| Location of Dermatitis    | Control Subjects |
|---------------------------|------------------|
| Upper extremities (hands) | 9                |
| Lower extremities         | 5                |
| Generalized               | 2                |
| Trunk                     | 2                |
| Face                      | 1                |
| Eyelids                   | 1                |
| Neck                      | 1                |
| Scalp                     | 1                |
| Tongue                    | 1                |
| Perianal                  | 1                |

**Figure 1.** Percentage of patients with psoriasis with positive patch tests on biologics (cases) and not on biologics (control subjects).

etanercept had at least 1 positive reaction (2/4); 25.0% (1/4) of them had at least one 2+ reaction, and 25.0% (1/4) had at least one 3+ reaction. Two (66.7%) of the 3 patients with psoriasis on adalimumab had at least 1 positive reaction and at least one 2+ reaction. None of those on adalimumab had a 3+ reaction according to their patch testing results. The 1 patient with psoriasis on infliximab had at least one 1+, 2+, and 3+ reaction (Table 6).

The frequencies of positive allergic reactions to our standard and cosmetics allergens were compiled. Some of these allergens are aligned with the top 10 most common allergens found by the NACDG according to their pooled 2009-2010 data, such as nickel sulfate, neomycin sulfate, fragrance mix I, bacitracin, *Myroxylon perei*, cobalt chloride, formaldehyde, quaternium 15, and fragrance mix II.<sup>48</sup> Compared with the NACDG data, 4 particular allergens were found to be frequently positive in our cases, including propylene glycol, paraben mix, ethylenediamine dihydrochloride, and lanolin alcohol.<sup>48</sup> Of note, gold sodium thiosulfate and benzalkonium chloride are not tested by the NACDG standard allergen tray. Some of the allergens within the list of commonly positive allergens found among the cases showed 3+ reactions. These consisted of nickel sulfate, bacitracin, and quaternium 15 (Table 7).

For the control psoriatic group, allergens found to be among the top 10 NACDG allergens included nickel sulfate, neomycin, fragrance mix I, *M. perei*, cobalt chloride, formaldehyde, quaternium 15, and paraphenylenediamine.<sup>48</sup> Of this control group, allergens commonly found but not present in the top 10 of the NACDG allergens included dithiodimorpholine, carba mix, methylidibromoglutaronitrile, potassium dichromate, and MCI/MI. Of note, dithiodimorpholine is not on the NACDG standard series, and methylidibromoglutaronitrile is tested in a mixture together with phenoxyethanol on the NACDG series.<sup>48</sup>

The patients in the control psoriatic group also showed 3+ reactions to some of the commonly positive allergens, such as fragrance mix I, paraphenylenediamine, nickel, neomycin, and

**TABLE 6. Psoriasis Patients on Biologics and Patch Testing Results**

| Patient No. | Biologic    | Time Interval From Last Dose to Patch Testing, d | Patch Testing Results to the Standard and Cosmetic Series                                                                                                                                                                                                                                             |
|-------------|-------------|--------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1           | Ustekinumab | 28                                               | Standard: 2+ Gold sodium thiosulfate                                                                                                                                                                                                                                                                  |
| 2           | Ustekinumab | 37                                               | Standard: 2+ Lanolin alcohol<br>2+ Balsam of Peru<br>3+ Nickel sulfate<br>2+ Methylchloroisothiazolinone/methylisothiazolinone<br>1+ Fragrance mix II<br>Cosmetic: 2+ Iodopropynyl butylcarbamate                                                                                                     |
| 3           | Ustekinumab | 28                                               | Standard: 2+ Balsam of Peru<br>Cosmetic: 1+ Propylene glycol                                                                                                                                                                                                                                          |
| 4           | Ustekinumab | 112                                              | Standard: 2+ Nickel sulfate<br>1+ Bacitracin                                                                                                                                                                                                                                                          |
| 5           | Ustekinumab | 42                                               | Standard: 1+ benzophenone 4<br>1+ Bacitracin<br>1+ Fragrance mix II<br>1+ Fragrance mix I<br>Cosmetic: 1+ Benzalkonium chloride<br>1+ Amerchol L 101<br>1+ Propylene glycol                                                                                                                           |
| 6           | Ustekinumab | 238                                              | Standard: 1+ Neomycin<br>2+ Ethylenediamine                                                                                                                                                                                                                                                           |
| 7           | Ustekinumab | 28                                               | Standard: 2+ Formaldehyde<br>3+ Quaternium 15<br>2+ Balsam of Peru<br>2+ Methylchloroisothiazolinone/methylisothiazolinone<br>2+ Fragrance mix II                                                                                                                                                     |
| 8           | Etanercept  | 5                                                | —                                                                                                                                                                                                                                                                                                     |
| 9           | Etanercept  | 8                                                | Standard: 2+ Neomycin sulfate<br>1+ Quaternium 15<br>2+ Balsam of Peru<br>3+ Bacitracin                                                                                                                                                                                                               |
| 10          | Etanercept  | 7                                                | —                                                                                                                                                                                                                                                                                                     |
| 11          | Etanercept  | 6                                                | Standard: 1+ Nickel sulfate<br>1+ Paraben mix<br>1+ Gold sodium thiosulfate<br>Cosmetic: 1+ Abitol<br>1+ Oleamidopropyl dimethylamine                                                                                                                                                                 |
| 12          | Adalimumab  | 6                                                | Standard: 2+ Balsam of Peru<br>1+ Glutaraldehyde<br>2+ Cobalt chloride<br>2+ Gold sodium thiosulfate<br>1+ Dithiodimorpholone<br>Cosmetic: 1+ Amidoamine<br>1+ Benzalkonium chloride<br>2+ Methylidibromoglutaronitrile<br>1+ Sorbitan monooleate<br>1+ Cocamidopropyl betaine<br>1+ Laurel glucoside |
| 13          | Adalimumab  | 2                                                | Standard: 1+ Methylchloroisothiazolinone/methylisothiazolinone<br>2+ Gold<br>Cosmetic: 1+ Benzalkonium chloride<br>1+ Euxyl K 400                                                                                                                                                                     |
| 14          | Adalimumab  | 7                                                | —                                                                                                                                                                                                                                                                                                     |

*(Continued on next page)*

**TABLE 6.** (Continued)

| Patient No. | Biologic   | Time Interval From Last Dose to Patch Testing, d | Patch Testing Results to the Standard and Cosmetic Series                                                                                                                                                                                                                                                                        |
|-------------|------------|--------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 15          | Infliximab | 14                                               | Standard: 1+ Benzophenone 3<br>1+ Cobalt<br>1+ Gold Sodium thiosulfate<br>2+ Bacitracin<br>2+ Lanolin alcohol<br>3+ Carba mix<br>3+ Thiuram mix<br>2+ Formaldehyde<br>1+ Ethylenediamine<br>1+ Potassium dichromate<br>2+ Nickel sulfate<br>1+ Paraben mix<br>1+ Fragrance mix I<br>Cosmetic: 1+ Benzalkonium chloride<br>1+ BHT |

tixocortol-21-pivalate. Again, some of the less common allergens according to the NACDG were found to be relatively common in this study population; these included lanolin and the 2 corticosteroid screening chemicals: hydrocortisone-17-butyrate and tixocortol-21-pivalate<sup>48</sup> (Table 8).

In addition, 53.0% (8/15) of the cases had at least 1 positive reaction to an allergen in a supplemental series compared with 38.0% (6/16) of the control subjects, although the difference was not statistically significant.

## DISCUSSION

Overall, a majority of both study groups of patients with psoriasis, including those on various biologic therapies, had at least 1 positive patch test reaction to an allergen, showing that biologics do not influence the ability of patients with psoriasis to have a positive patch test. In addition, we found no statistically significant difference in the prevalence of positive patch tests between those patients with psoriasis on biologics compared with those who are not; however, the numbers of patients were small. This is important as our study shows that concomitant biologic therapy may not be a contraindication to have patch testing performed. In fact, previous studies have concluded that other immunosuppressants, specifically prednisone, may decrease the number of positive patch test reactions in patients with previously strong positive reactions, as well as decrease the number of 3+ reactions compared with those on placebo.<sup>49,50</sup> The contrast in conclusions may relate to different immune-suppressing treatments producing different effects on the immune system or influences on the balance of immune response to an allergen. Our study suggests preliminary observations that the ability to generate positive patch test

reactions does not differ between the patients who were on different biologics, including patients on both TNF blockers and ustekinumab. However, the numbers of patients were small, and a larger series of patients is needed to make a definitive statement. It will be interesting to add results of patients who are on the emerging class of newer biologics that are currently in clinical trials targeted specifically against IL-17.

**TABLE 7. Top Allergens for Psoriasis Patients on Biologics (Cases)**

| Allergens                                             | Percentage of Cases (n = 15) |
|-------------------------------------------------------|------------------------------|
| <i>M. pereirae</i> (balsam of Peru)*                  | 33.3 (5/15)                  |
| Gold sodium thiosulfate                               | 33.3 (5/15)                  |
| Nickel sulfate*†                                      | 26.7 (4/15)                  |
| Bacitracin*†                                          | 26.7 (4/15)                  |
| Benzalkonium chloride                                 | 26.7 (4/15)                  |
| Fragrance mix II*                                     | 20.0 (3/15)                  |
| Methylchloroisothiazolinone/<br>methylisothiazolinone | 13.3 (2/15)                  |
| Quaternium 15*†                                       | 13.3 (2/15)                  |
| Neomycin sulfate*                                     | 13.3 (2/15)                  |
| Formaldehyde*                                         | 13.3 (2/15)                  |
| Cobalt chloride*                                      | 13.3 (2/15)                  |
| Propylene glycol                                      | 13.3 (2/15)                  |
| Paraben mix                                           | 13.3 (2/15)                  |
| Ethylenediamine dihydrochloride                       | 13.3 (2/15)                  |
| Lanolin alcohol                                       | 13.3 (2/15)                  |
| Fragrance mix I*                                      | 13.3 (2/15)                  |

\*Top 10 NACDG allergen.

†Had 3+ reaction.

**TABLE 8. Top Allergens for Psoriasis Patients Not on Biologics (Control Subjects)**

| Allergens                                             | Percentage of Control Subjects (n = 16) |
|-------------------------------------------------------|-----------------------------------------|
| Fragrance mix I*†                                     | 31.3 (5/16)                             |
| Paraphenylenediamine*†                                | 31.3 (5/16)                             |
| Dithiodimorpholine                                    | 31.3 (5/16)                             |
| Nickel sulfate*†                                      | 25.0 (4/16)                             |
| Carba mix                                             | 25.0 (4/16)                             |
| <i>M. pereirae</i> (balsam of Peru)*                  | 18.8 (3/16)                             |
| Quaternium 15*                                        | 18.8 (3/16)                             |
| Neomycin*†                                            | 18.8 (3/16)                             |
| Methyldibromoglutaronitrile                           | 18.8 (3/16)                             |
| Potassium dichromate                                  | 18.8 (3/16)                             |
| Lanolin                                               | 18.8 (3/16)                             |
| Formaldehyde*                                         | 12.5 (2/16)                             |
| Cobalt chloride*                                      | 12.5 (2/16)                             |
| Cinnamic aldehyde                                     | 12.5 (2/16)                             |
| Methylchloroisothiazolinone/<br>methylisothiazolinone | 12.5 (2/16)                             |
| Hydrocortisone-17-butyrate                            | 12.5 (2/16)                             |
| Tixocortal-21-pivalate†                               | 12.5 (2/16)                             |
| Diazolidinyl urea                                     | 12.5 (2/16)                             |
| Imidazolidinyl urea                                   | 12.5 (2/16)                             |

\*Top 10 NACDG allergen.

†Had 3+ reaction.

Despite the suppression of the  $T_H1$  and  $T_H17$  arms of the immune system by biologics, our study demonstrates that patients with psoriasis on biologics are able to mount a range of weak to extreme positive patch test reactions. These findings are notable given the commonalities in immunologic pathways between psoriasis and ACD and the vital role the very immune modulators that are targeted by the biologics play in the ACD cascade. Although prior research has demonstrated reduced ear swelling to contact allergen in IL-17-deficient mice,<sup>51</sup> our study demonstrates strong positive patch test reactions in patients on biologics including those on ustekinumab. Our study thus implicates the role of other immunologic pathways in the pathogenesis of ACD. Interestingly, mouse models have shown increased expression of  $T_H2$  cytokines, IL-4, IL-5, and IL-13, from lesional skin of the ear after contact hypersensitivity induced by either 2,4,6-trinitrochlorobenzene or nickel.<sup>52,53</sup> In addition, there is evidence of increased production of IL-4, IL-5, and IL-13 from the peripheral blood mononuclear cells of patients who have patch test-proven contact allergy to MCI/MI compared with those not allergic to the allergen.<sup>54</sup> Increasing levels of IL-5 in the peripheral mononuclear blood cells correlate with the intensity of the positive patch test reactions to nickel in patients with ACD.<sup>55</sup> Studies will be needed to uncover what cytokines and pathways do play a role in the pathogenesis of the ACD response in patients with psoriasis on biologics, elucidating further the complexity of the immune system and potentially providing novel therapeutic targets.

Although many of our case and control positive allergens aligned with the top 10 NACDG allergens,<sup>48</sup> less common allergens were also found among our patients, both cases and control subjects. This could be explained by decreased skin barrier and exposure to numerous topical medicaments and emollients in our patients with psoriasis. For example, the corticosteroid screening chemicals, hydrocortisone-17-butyrate and tixocortal-21-pivalate, may be more common in our data as patients with psoriasis likely have prolonged exposure to both the over-the-counter (tixocortal type) and prescription corticosteroids; therefore, they are at risk for sensitization to these allergens. Similar to patients with chronic leg ulcers, we found lanolin and parabens, generally weak sensitizers, commonly positive in our cases, and lanolin plus corticosteroids commonly positive in our control subjects.<sup>56</sup>

In addition, both our case and control psoriatic groups had a higher prevalence of patch test reactions (80% and 81%, respectively) than those reported by the NACDG (61%).<sup>48</sup> Our greater number of allergens tested (78-85 during study period) compared with the NACDG<sup>48</sup> 70 might explain our increased prevalence of sensitization in our patients. In addition, several of the allergens commonly positive in our cases (gold, benzalkonium chloride) and in our control subjects (dithiodimorpholine) are not tested in the NACDG standard tray. Also, given the tertiary care nature of our patients with psoriasis, they may have had particularly severe disease and may have had more contact sensitizations than a typical patient with psoriasis.

In terms of localization of dermatitis for our patients, there was a predilection for the upper and lower extremities, mirroring the regions typically affected by psoriasis, that is, elbows, knees, hands, and feet. In contradistinction to dermatitis patients reported by the NACDG,<sup>48</sup> our case and control patients with psoriasis had uncommon involvement of the face. This could be explained by the relative lack of facial involvement in patients with psoriasis, in general.

Our study was confounded by several limitations. First, as this was a retrospective chart review, we were limited by how many cases already existed that fulfilled the inclusion criteria; therefore, there was a small sample size. The study would have benefited from a larger number of included patients to help with the study's statistical significance. Also the total number of tested allergens on our standard and cosmetics trays varied over the course of the study period. Moreover, different biologics with different mechanisms of action and therapeutic targets were included in the same study group. It would have been ideal to have had a standardized number of total allergens as well as compared the 2 study arms using the same biologic treatment to limit the number of variables within the study design. Furthermore, there was no directly matched comparison control group that might have strengthened the hypothesis that patients with psoriasis who are on various immunosuppressing therapies have intact immune responses to mount positive patch tests. All the patients included in the study analysis were evaluated and managed at a tertiary referral center and typically exhibited severe disease burden; therefore, the results may not be

representative of the general psoriasis population. Nevertheless, this study is the first case series to document that various types of biologics, including ustekinumab, do not impair the ability of a patient with psoriasis to have a positive patch test.

The utility of patch testing in patients with psoriasis, particularly among those with recalcitrant disease, can have enormous therapeutic potential and impact on the quality of life of these patients. Finding clinically meaningful positive patch tests to allergens in these patients can alleviate the symptom burden of those with dual diagnoses or discover that they are, in fact, allergic to the very treatment that they may be receiving, therefore guiding management decisions.

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