

Patch Testing With the Standard Series When Receiving Immunosuppressive Medications

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Background: Debate surrounds the validity of patch testing for allergic contact dermatitis in patients taking immunosuppressants and the extent to which these medications suppress patch test reactions. Previous studies have demonstrated that corticosteroids can suppress immune reactions measured in patch testing. Because immunomodulators are increasingly used, their impact on patch testing also requires evaluation.

Objectives: This study aimed to report patch test results in patients taking specific immunosuppressants and to review relevant literature.

Methods: A retrospective review of patients patch tested with the standard series at Mayo Clinic in Rochester, Minnesota, between January 1, 2008, and December 31, 2011, was conducted.

Conclusions: Positive patch test results occur during methotrexate therapy. How reactions would differ with no immunosuppression is unclear.

Patch testing is an important component in the assessment of patients with suspected allergic contact dermatitis (ACD).¹ In general, the testing is avoided in patients with recent application of topical corticosteroids to test sites or use of systemic immunosuppressants unless these therapies have been discontinued for a designated time before the testing.² The utility of patch testing in patients receiving immunosuppressive therapy is uncertain, given that accuracy may be affected by the impact of these medications on the immune response evaluated in the tests.^{3,4} Patch testing has thus been recommended after a patient has permanently or temporarily ceased the use of immunosuppressants.⁵ Yet, immunosuppressant discontinuation is not possible for all patients because of concern for exacerbating or flaring controlled disease.³ Consequently, the testing may be indefinitely deferred in such patients, delaying their evaluation.^{3,5}

To determine whether patch testing of patients taking immunosuppressants provides valid and clinically useful information, researchers have studied the impact of corticosteroid treatments

on patch test results for the past 6 decades.^{3,6} Although results varied depending on the dose and vehicle of corticosteroid therapy, most studies found that some patients could maintain positive reactions to standard allergen concentrations after initiation of immunosuppressive therapy. However, a substantial number of patients had reactions that were either diminished or completely suppressed.⁴⁻⁸ When compared, reaction strength was often weaker than the response before immunosuppressive treatment, and the use of more diluted allergen concentrations led to decreased sensitivity.⁴⁻⁸

Although the consequences of corticosteroid use on patch test results have been evaluated, other forms of immunosuppressive therapy increasingly used to treat autoimmune and inflammatory medical conditions are relatively unexplored. As such, these immunomodulating agents have only recently been examined in several studies^{3,9,10} and case reports^{11,12} as well as in a retrospective review.¹³ The findings of these studies show potential for positive patch results in patients taking various immunomodulators, but further study needs to be performed for precise determination of immunomodulator effects.

At our institution, we attempt to patch test patients who are not taking immunosuppressive medications, seeking to minimize the chances of false-negative patch test results. However, in specific instances, patch testing is performed when it is impractical for the patient to stop immunosuppressive treatment, leading to the question of whether patch test reactions can occur in these patients. In an attempt to answer this query, we retrospectively examined patch test results in patients taking azathioprine, methotrexate, or mycophenolate mofetil, or a combination, during the evaluation. We thus performed a

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retrospective review of patients tested with the standard series at our institution between January 1, 2008, and December 31, 2011, to report on patch test results of patients who were immunosuppressed with 1 or more of these agents at the time of testing.

METHODS

Patient Data Collection

After study approval by the Mayo Clinic Institutional Review Board, data were electronically retrieved from an institutional Sybase (Sybase Inc) database of all patients tested with the standard series at Mayo Clinic in Rochester, Minnesota, from January 1, 2008, through December 31, 2011. Patients without documented consent for use of data in medical research were excluded. The outpatient medication lists of all patients were electronically queried to identify those who were treated with azathioprine, methotrexate, or mycophenolate mofetil, or a combination, within 5 years before their patch testing. The medical records of the identified patients were then reviewed manually to confirm medication use at the time of testing and to acquire information regarding medication dose and conditions for prescription as well as indications for patch testing. Patients who held their daily or weekly dose of medication during the period of patch testing were included.

Interpretation of Patch Test Results

Patch testing was performed in accordance with the process described in previous publications from our institution.^{14,15} Finn Chambers (SmartPractice, formerly Epitest Ltd Oy) on Scanpor tape (Alpharma AS, Norgesplaster Aksjeselskap) were used in testing. Allergens were purchased from Chemotechnique Diagnostics AB and allergEAZE (SmartPractice Canada) or compounded by the Mayo Clinic pharmacy. Patches were applied to the upper back of the patients and removed 48 hours later. Reactions were generally read at 48 and at 96 hours after application. The ordering physician performed final readings, interpretation of findings, and evaluation of relevancy.

In reaction definitions, the following 5 categories were used: negative, erythema only, weak (featuring erythema, infiltration, or papules, or a combination), strong (containing edema or vesicles, or both), and extreme (spreading or featuring bullae or ulceration). This study categorized positive allergic patch test results as weak, strong, or extreme reactions at the final reading or as reactions featuring macular erythema when the result was deemed relevant with irritant reactions excluded.

Relevancy assessment involved evaluation for history of definite contact with substances containing the suspected allergen or situations involving exposures to such substances. The categories were as follows: I, irritant; N, allergic, not relevant (no history of exposure to products with allergen); Q, allergic, questionably relevant (current exposure to products that could contain allergen); P, allergic, formerly relevant (prior exposure to products containing allergen); and R, allergic, relevant (the patch test with

TABLE 1. Characteristics of the 8 Immunosuppressed Patients

Characteristic	Patients
Sex	
Male	5 (62.5)
Female	3 (37.5)
Age, median (range), y	56 (32–67)
Race	
Unknown	1 (12.5)
White	6 (75.0)
Other	1 (12.5)
Family history of atopy	
Unknown	1 (12.5)
No	5 (62.5)
Yes	2 (25.0)
Occupation	
Administrative assistant	1 (12.5)
Carpenter	3 (37.5)
Factory worker	1 (12.5)
Guard	1 (12.5)
Homemaker	1 (12.5)
Nurse	1 (12.5)
Site of dermatitis*	
Anal/genital	1 (12.5)
Arm	2 (25.0)
Back	2 (25.0)
Chest	1 (12.5)
Face	2 (25.0)
Feet	2 (25.0)
Hands	2 (25.0)
Head	1 (12.5)
Lower extremities	2 (25.0)
Neck	2 (25.0)
Scalp	1 (12.5)
Upper extremities	2 (25.0)

Values are presented as number and percentage unless specified otherwise.

*Because multiple sites are listed for some patients, the total is more than 100%.

an allergen-containing substance is positive, or the allergen is a confirmed ingredient in a product with definite patient use).

RESULTS

From January 1, 2008, through December 31, 2011, a total of 1416 unique patients were patch tested with the standard series. Among them, 8 patients were identified as being immunosuppressed because of treatment with azathioprine, methotrexate, or mycophenolate mofetil, or in combination, at the time of patch testing. Five (62.5%) patients were men; the median age of the 8 patients was 56 years (range, 32–67 years). Demographic characteristics are summarized in Table 1.

Seven patients were receiving treatment with methotrexate at patch testing; 1 patient was taking mycophenolate mofetil. In 4 instances, the patients held their weekly dose of methotrexate during the patch testing. Patch testing for suspected ACD was indicated either for

TABLE 2. Final Diagnoses and Combined Patch Test Results for the 8 Patients Receiving Immunomodulator Therapy

Results	Patients
Final diagnosis	
Dermatitis, allergic	3 (37.5)
Dermatitis, atopic	1 (12.5)
Dermatitis, NOS	1 (12.5)
Neurodermatitis	1 (12.5)
Psoriasis	1 (12.5)
Vulvitis	1 (12.5)
No. standard series allergens tested, median (range)	74 (70–75)
No. allergic reactions	
0	4 (50.0)
2	3 (37.5)
18	1 (12.5)
Total no. allergic reactions among patients	24
No. irritant reactions	
0	6 (75.0)
1	1 (12.5)
2	1 (12.5)
Total no. irritant reactions among patients	3

Values are presented as number and percentage unless specified otherwise.
NOS indicates not otherwise specified.

evaluation of a newly diagnosed dermatitis or because of concern for a component of ACD in recalcitrant dermatitis. The duration of dermatitis before patch testing ranged from 7 months to 4 years. The sites of distribution were varied (Table 1).

Four of the identified patients had 1 or more positive patch test reactions. A total of 24 allergic reactions and 3 irritant reactions occurred among all patients (Table 2). Individual patch test results are featured in Table 3. One patient receiving methotrexate (25 mg/wk) had positive reactions to *Myroxylon pereirae* resin (balsam of Peru; 25%) and to benzoic acid (5%). These reactions featured erythema only but were judged relevant. Both patients taking methotrexate at 15 mg/wk had 2 positive patch test reactions. One of these patients reacted to formaldehyde (1% aqueous [aq]; erythema only) and methylchloroisothiazolinone/methylisothiazolinone (100 ppm aq; weak); each reaction was considered relevant. The other patients had weak reactions to benzoic acid (5%) and cobalt chloride (1%). Both reactions had past relevancy. The patient taking methotrexate at 7.5 mg/wk showed 18 positive patch test reactions (3 strong, 7 weak, and 8 macular erythema), and all were relevant. No positive patch test results were manifested in the patient taking methotrexate at 30 mg/wk or by either of the patients taking 20 mg/wk. The patient taking mycophenolate mofetil at 1000 mg/d had no positive patch test results.

None of the patients had their patch testing performed before immunosuppression was initiated or after completion of therapy. Follow-up information was available for 2 patients with positive patch test results. The patient receiving methotrexate at 25 mg/wk and having positive reactions to *M. pereirae* resin (25%) and to benzoic acid (5%) reported resolution of his symptoms after

avoidance of these allergens. He had 1 flare treated with a course of prednisone and reinitiation of methotrexate therapy. The patient taking methotrexate at 7.5 mg/wk and with 18 positive reactions had responded well to allergen avoidance at follow-up appointments.

Discussion

The impact of corticosteroid therapy on the ability of sensitized patients to mount positive allergic patch test results has been well evaluated. An early study of 5 patients manifesting positive reactions to 1 or more allergens before starting therapy with 150 mg/d oral cortisone showed a trend of decreased sensitivity because patients were tested with more diluted allergen during immunosuppression, but the patients ultimately maintained their positive reactions to allergen standard concentrations.⁶

A later report found that the use of prednisone in doses of 30 mg/d or greater resulted in partial to complete suppression of formerly positive responses among most patients tested with standard concentrations.⁸ A similar range in suppression of previously positive results has been described in patients tested with standard concentrations during a course of prednisone at 40 mg/d, with an elevated threshold of allergen concentration required for response.⁵ Comparably, in another study of patients taking prednisone at 40 mg/d, a majority maintained positive, but frequently diminished, reactions at standard concentrations. Once again, greater threshold doses of allergen were required to generate the same response observed before immunosuppression.⁷

A randomized, double-blinded, crossover study recently showed a significant decrease in the total number of positive results in the patients who took prednisone at 20 mg/d compared with placebo.⁴ The authors also reported that immunosuppression commonly resulted in comparatively weaker reactions and in increased threshold concentrations required to elicit a reaction. The influence of topical corticosteroid medication on patch testing sites continues to be indefinite because several studies have shown evidence for partial to complete suppression in patients with known positive results,^{16–18} yet others have found little to no effect on patch test results.^{19,20} In general, these studies show that corticosteroid use causes partial to complete suppression of positive patch test results in many patients; however, some patients may maintain positive reactions.

With the advent and increasing use of immunomodulating therapies to treat such medical conditions such as inflammatory bowel disease, psoriasis, and rheumatoid arthritis, there is a growing need to assess the effects of these medications on patch testing. In a recently published study, 38 patients in whom new or worsening ACD was suspected were patch tested while also taking an immunosuppressant (adalimumab, azathioprine, cyclosporine, etanercept, infliximab, methotrexate, mycophenolate mofetil, or tacrolimus).³ One or more patients taking each of these medications manifested at least 1 positive response. Given that the patients were not tested before or after their course of immunosuppressive therapy, the

TABLE 3. Medications, Doses, and Patch Test Results of the 8 Patients Receiving Immunomodulator Therapy

Patient Number	Age, y	Sex	Medication	Dose, mg*	Indication for Immunomodulation	Allergens Causing Positive Results	Strength of Day 5 Reaction† (Relevance)
1	51	F	Methotrexate	30 weekly	Rheumatoid arthritis	None	
2	67	M	Methotrexate	25‡ weekly	Eczematous dermatitis	Benzoic acid, 5% <i>M. pereirae</i> resin (balsam of Peru), 25%	1 (R) 1 (R)
3	32	M	Methotrexate	20 weekly	Palmoplantar psoriasis	None	
4	62	M	Methotrexate	20‡ weekly	Atopic dermatitis	None	
5	67	M	Methotrexate	15‡ weekly	Chronic generalized dermatitis	Formaldehyde, 1% aq MCI/MI, 100 ppm aq	1 (R) 2 (R)
6	64	M	Methotrexate	15‡ weekly	Pustular psoriasis	Benzoic acid, 5% Cobalt chloride, 1%	2 (P) 2 (P)
7	48	F	Methotrexate	7.5 weekly	Palmoplantar psoriasis	Bacitracin, 20% DMDM hydantoin, 1% DMDM hydantoin, 2% aq Diazolidinyl urea, 1% Diazolidinyl urea, 1% aq Dimethylol dihydroxyethyleneurea, 4.5% aq Ethylene urea/melamine formaldehyde mix, 5% Formaldehyde, 1% aq Hexahydro-1,3,5-tris(2-hydroxyethyl)triazine, 1% Hexylresorcinol, 0.25% Imidazolidinyl urea, 2% Imidazolidinyl urea, 2% aq Methyltribromo glutaronitrile/phenoxyethanol, 1.5% Neomycin sulfate, 20% Nickel sulfate hexahydrate, 2.5% Phenol formaldehyde resin, 1% Quaternium-15, 1% Toluenesulfonamide formaldehyde resin, 10%	3 (R) 1 (R) 1 (R) 2 (R) 2 (R) 2 (R) 2 (R) 2 (R) 1 (R) 1 (R) 1 (R) 3 (R) 3 (R) 1 (R) 2 (R) 1 (R)
8	40	F	Mycophenolate mofetil	1000 daily	Inflammatory arthritis	None	

*Medications continued during testing unless noted.

†Reaction gradings are as follows: 1, erythema only; 2, weak; 3, strong.

‡Dose held during the period of patch testing.

DMDM indicates 1,3-dimethylol-5,5'-dimethyl; F, female; M, male; MCI/MI, methylchloroisothiazolinone/methylisothiazolinone; P, formerly relevant; R, relevant.

investigators were unable to determine whether the patient's medications affected the number and degree of positive reactions.

Another recent study reviewed the patch test results of 11 patients taking cyclosporine, prednisone, combined cyclosporine and prednisone, infliximab, or mycophenolate mofetil at the time of testing.¹³ Seven patients had 1 or more strong or extreme patch test reactions, 3 patients had at least 1 weak reaction, and 1 patient had multiple questionable reactions. One patient who showed a weak reaction to 3 allergens when taking mycophenolate mofetil later had a strong, clinically relevant reaction to a different allergen after discontinuing therapy. The influence of cyclosporine was studied in a report that evaluated patients before and after initiating daily treatment at 5 mg/kg.¹⁰ In general, the patients who showed strong or extreme reactions before treatment maintained these results, whereas the reactions of those with formerly weak responses were read as negative. Two case reports have also described patients taking azathioprine¹² and infliximab¹¹ who were able to show positive patch test results.

Most of these studies suggest potential for positive response during immunomodulation. However, a study examining 6 patients who previously had positive patch results showed almost complete suppression of these reactions in all patients after initiating cyclosporine daily treatment at 5 mg/kg, along with an increase in threshold concentrations required to generate response.⁹

Through several mechanisms, immunosuppressive therapies may affect the response mediating the ACD and measured in patch testing. In ACD, patients have a T-cell-mediated, delayed-type hypersensitivity reaction to contact allergens.^{1,21} These allergens initiate sensitization through interactions with Langerhans cells in the epidermal layer, leading to release of interleukin (IL)-1 β and IL-18 from the Langerhans cells. Keratinocytes then generate IL-1 α , tumor necrosis factor α (TNF- α), and granulocyte-macrophage colony-stimulating factor, which guide migration of Langerhans cells containing allergen-protein complexes to associated lymph nodes. Allergens are shown to naive T cells in these lymph nodes and activate them, which leads to IL-2 production by the activated T cells. Subsequent contact with the allergen prompts proinflammatory cytokine production, resulting in the clinical presentation associated with ACD and elicited in patch testing.

Various immunosuppressive agents affect 1 step or more in the process that mediates this immune response. Corticosteroids impede IL-1, IL-2, TNF- α , and granulocyte-macrophage colony-stimulating factor, whereas they also inhibit dendritic cell activation of T cells.²² Azathioprine interrupts nucleic acids, reduces the amount of Langerhans cells, and impairs T cells.²³ Methotrexate affects DNA synthesis, decreases IL-1 activity and TNF- α release, and leads to activated T-cell apoptosis.²⁴ Mycophenolate mofetil reduces T-cell proliferation, blocks dendritic cell function, and limits cytokine inducement.²⁵ Given that most studies have shown the ability of some patients to mount an immune reaction while taking suppressive therapies, the high concentration of allergen used during patch testing has been hypothesized to overwhelm immune suppression.^{7,11,13}

Recommendations

At our institution, patch testing is generally recommended only after patients have discontinued their use of topical corticosteroids or systemic immunosuppressants for approximately 1 week or 1 month, respectively, before patch testing.¹⁵ However, the persistence of positive reactions in patients tested while they were taking immunosuppressive therapies has led some authors to question whether the use of these medications should be a contraindication for patch testing.^{3,6,11,13} Our results suggest that positive, clinically relevant patch test results are possible during immunosuppression with methotrexate. Unfortunately, because none of the patients who were tested during the 4-year period were taking azathioprine, we are unable to comment on the ability of patients receiving azathioprine to mount positive reactions. Similarly, because only 1 patient was taking mycophenolate mofetil and no response was elicited, we cannot confidently conclude about the effect of this immunosuppressant.

When conducting patch testing in immunosuppressed patients, health care providers should use the lowest dose of therapy possible and retest after therapy discontinuation.¹³ In considering the patch test results of patients taking immunosuppressants, providers also must be aware that mild or irritant reactions could represent suppression of stronger positive reactions.^{5,13}

Limitations and Further Study

The limitations of this study include its retrospective nature and inability to compare with results obtained when patients are not in an immunosuppressed state. Prospective studies evaluating patients before and during immunosuppression with immunomodulating agents are required to further define their effects on patch test results. A comparison among immunomodulators to determine whether their consequences significantly differ also needs to be performed. Dose thresholds at which immunomodulators may begin to diminish positive reactions have yet to be determined.⁸ Whether the duration of immunosuppressive therapy before testing significantly affects the impact of these medications deserves exploration.⁷ A lingering question for test administration involves whether allergen concentrations should increase when testing immunosuppressed patients to elicit a positive reaction in sensitized persons.

CONCLUSIONS

During 4 years at our institution, 8 patients were patch tested while taking methotrexate or mycophenolate mofetil. Four patients taking methotrexate had positive patch test reactions, generating 24 total allergic reactions (3 strong, 10 weak, and 11 macular erythema only). Our experience echoes the findings of other investigators, showing that patch test reactions can occur when receiving immunosuppressive medications. The open question is to what extent the patch test results would have been different if the patients were not taking these immunosuppressive treatments.

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