

Patch-Testing While on Systemic Immunosuppressants

David Rosmarin, Alice B. Gottlieb, Adam Asarch, and Pamela L. Scheinman

Background: Occasionally, the need arises to patch-test patients while they are on immunomodulators. Little is known about how these systemic agents affect the results of patch testing.

Objective: To present data on 11 patients who underwent patch testing while under the effects of immunosuppressants.

Methods: Retrospective chart reviews were performed on 11 patients who underwent patch testing while they were taking various systemic immunosuppressants or within 48 hours of cessation of various systemic immunosuppressants.

Results: Patients had been taking prednisone ($n = 6$), cyclosporine ($n = 2$), combination cyclosporine and prednisone ($n = 1$), mycophenolate mofetil ($n = 1$), and infliximab ($n = 1$) up to 48 hours prior to and/or during patch testing. Seven patients showed at least one strong (++) or extreme (+++) patch-test reaction. Three patients had at least one weak (+) reaction. One patient showed only questionable reactions. The patient on mycophenolate was eventually retested while off immunosuppressants and showed strong clinically relevant patch-test reactions. Overall, 8 of the 11 patients reported some improvement in their dermatitis, including all the patients with strong or extreme reactions.

Conclusion: While it is optimal for patch testing to be performed when patients are off immunosuppressants, immunosuppressive therapies should not be an absolute contraindication to patch testing.

THE “GOLD STANDARD” for determining allergens in patients with allergic contact dermatitis is patch testing. Ideally, patch testing is performed when patients are not taking systemic immunosuppressants or using topical medications. In a sensitized individual, a contact allergen causes keratinocytes and Langerhans’ cells to release cytokines, which activate adhesion molecules on endothelial cells attracting leukocytes and T-effector cells. These T-effector cells are activated by antigen presentation and induce other cytokines, attracting inflammatory cells and leading to the manifestations of contact dermatitis.

Glucocorticoids^{1,2} can suppress cytokines and impair dendritic cells needed for type IV delayed-type hypersensitivity. Because tumor necrosis factor- α (TNF- α) is involved in delayed-type hypersensitivity,³ TNF- α inhibi-

tors can suppress allergic contact dermatitis. On a mechanistic level, many immunomodulators interfere with the delayed type IV hypersensitivity elicited during patch testing.

Occasionally, however, the need arises to test patients while they are on immunomodulators, either because they are on such medication for an unrelated disease or because they have a generalized dermatitis and do not have sufficient area on their body on which to perform patch testing. Although little is known about how immunosuppressants affect the results of patch testing, it is of crucial importance to understand their effects on such results, given the increasing number of patients taking these medications.

Methods

Retrospective chart reviews were performed from January 2006 to September 2007 for patients who underwent patch testing at Tufts Medical Center while under the effects of immunosuppressants or within 48 hours of ceasing to take immunosuppressants. Eleven patients met the criteria.

All patients were tested with a modified North American Contact Dermatitis Group (NACDG) standard series, fragrance series, and preservative series, in addition to other series depending on history and physical examination results. All allergens were obtained from

From the Tufts Medical Center, Department of Dermatology, Boston, MA.

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Chemotechnique Diagnostics (Vellinge, Sweden), with the exception of individual fragrance mix I components, which were purchased from Hermal (Reinbek, Germany). Finn Chambers (Epitest Ltd Oy, Tuusula, Finland) on Scanpor tape (Norgesplaster A/S, Vennesla, Norway) were used for the patch tests. The patches were removed at 48 hours, and readings were performed at 48 and 72 hours. The results reported herein represent the reactions at the 72-hour reading.

Reactions were graded according to the NACDG grading system: an extreme (+++) reaction is defined as bullous ulcerative lesions or papules or vesicles spreading beyond the boundaries of the Finn Chambers; a strong (++) reaction is one that yields papules and edema; and a weak (+) reaction is one that shows erythema and papules.

Macular erythema was considered questionable only. The highest-graded reactions are reported in Table 1. Improvement was judged on the basis of either the patient's report of clinical improvement via phone interview or the results of examination by one of the investigators in the clinic.

Results

Eleven patients met the criteria and were on immunosuppressants, including prednisone, cyclosporine, combination prednisone and cyclosporine, mycophenolate, and infliximab (see Table 1).⁴ While most of the patients were on their immunosuppressant during patch testing, one patient had discontinued cyclosporine 2 days prior to

Table 1. Medications, Doses, and Patch-Test Results

Pt	Medication	Dose* (mg/d)	Reaction	Allergens	Improved
1	Prednisone	10	+++	Balsam of Peru	Yes
2	Prednisone + cyclosporine	10 200	+++	Cobalt chloride, neomycin, nickel	Yes
3	Cyclosporine	200 [†]	+++	Cobalt chloride	Yes
4	Infliximab	5 [‡]	+++	Carba mix; thiuram mix; tetraethylthiuram disulfide; n,n'-diphenyl-4-phenylenediamine; zinc diethyldithiocarbamate	Yes
5	Prednisone	10	++	p-Phenylenediamine, Disperse Orange 3	Yes
6	Prednisone	10	++	Formaldehyde, Grotan BK, benzalkonium chloride	Yes
7	Cyclosporine	300 [§]	++	Cinnamyl alcohol	Yes
8	Prednisone	10	+	Benzophenone-4, Grotan BK, cocamide DEA, cocamidopropyl betaine, oleamidopropyl dimethylamine, Reactive Black 5, dimethylol dihydroxyethyleneurea (aq), dimethylol dihydroxyethyleneurea (FIX NF), dimethylol dihydroxyethyleneurea modified (Fix ECO), melamine formaldehyde	No
9	Prednisone	5	+	Euxyl K400 (methyl dibromoglutaronitrile/ phenoxyethanol), oleamidopropyl dimethylamine, carba mix, potassium dichromate, balsam of Peru, nickel	No
10	Mycophenolate	2,000	+	Cobalt, gold, triethanolamine	No
10	(Off immunomodulator)	—	++ +	Formaldehyde MCI/MI; diazolidinylurea, DMDM hydantoin, melamine formaldehyde	Yes
11	Prednisone	10	?	Fragrance mix, methyl methacrylate	Yes

? = questionable; aq = aqueous; DEA = diethanolamine; DMDM = dimethylol dimethyl; MCI/MI = methylchloroisothiazolinone/methylisothiazolinone; Pt = individual patient's number.

*All medications were continued during testing unless otherwise indicated.

[†]Discontinued 2 days prior to testing.

[‡]5 mg/kg/d. Patient received infusion every 8 weeks; last dose was 3 weeks prior to testing.

[§]Discontinued the day of testing.

testing, and one patient discontinued cyclosporine on the day of testing. A patient who was receiving infliximab (5 mg/kg/d) was receiving an infusion every 8 weeks, his last infusion having been 3 weeks prior to patch testing.

The patients included four males and seven females, with ages ranging from 24 to 69 years and duration of dermatitis ranging from 2 months to 7 years (Table 2). Ten of the 11 patients had a generalized dermatitis. Only the patient on infliximab had a dermatitis localized to the hands. The 10 patients with generalized dermatitis were on immunosuppressants to make their backs clear enough for patch testing. The patient on infliximab needed the infusions for psoriatic arthritis and has been previously reported.⁴

Four patients had extreme reactions (see Table 1). Two of the patients who had +++ reactions had metal allergens (cobalt and nickel), one had a fragrance screening allergen (balsam of Peru), one had a topical antibiotic allergen (neomycin), and one had rubber additive allergens (carba mix, thiuram mix, tetraethylthiuram disulfide, *n,n'*-diphenyl-4-phenylenediamine, and zinc diethyldithiocarbamate). Three patients had ++ reactions: one to hair dye (*p*-phenylenediamine) and a clothing dye allergen (Disperse Orange 3); one to formaldehyde, a formaldehyde-releasing preservative (Grotan BK, Schülke&Mayr GmbH, Norderstedt, Germany), and the preservative benzalkonium chloride; and one to a fragrance allergen (cinnamyl alcohol). All of these reactions were believed to be clinically relevant, and all seven patients—the four patients with extreme reactions and the three patients with

strong reactions—improved as compared to prior to patch testing.

Of the patients with weak reactions, one reacted to numerous allergens, including textile formaldehyde resins (dimethylol dihydroxyethyleneurea and melamine formaldehyde), a preservative (Grotan BK), surfactants (cocamide diethanolamine and cocamidopropyl betaine), a textile dye (Reactive Black 5), an emulsifier (oleamido-propyl dimethylamine), and a sunscreen allergen (benzophenone-4), but did not improve with avoidance of these chemicals. One patient's allergens included a preservative (Euxyl K400, Schülke&Mayr), an emulsifier (oleamido-propyl dimethylamine), a fragrance screening chemical (balsam of Peru), metals (potassium dichromate and nickel), and a rubber additive mixture (carba mix); this patient did not improve with avoidance of these chemicals.

The patient on mycophenolate had + reactions to cobalt, gold, and triethanolamine. She was noted to have had past dermatitis underneath costume jewelry, so her metal reactions were felt to be of past relevance. After patch testing, the patient did not improve; however, suspicion for allergic contact dermatitis persisted. The patient was therefore retested 1 year later while off mycophenolate. On this subsequent patch testing, the patient had a ++ reaction to formaldehyde and + reactions to formaldehyde-releasing preservatives (FRPs) and the preservative methylchloroisothiazolinone/methylisothiazolinone. This patient improved when she avoided skin care products containing FRPs, avoided textiles likely to be finished with formaldehyde, and avoided eating foods with synthetic sweeteners (such as aspartame, which can be converted to formaldehyde).

One patient on prednisone (10 mg daily) had only questionable reactions to fragrance mix and methyl methacrylate. Her reaction to methyl methacrylate was not considered clinically relevant. Her symptoms did not resolve with the use of fragrance-free products nor with a low-balsam diet. Therefore, her reaction to fragrance mix was not felt to be clinically relevant either.

Overall, 8 of the 11 patients reported some improvement in their dermatitis. All patients with ++ or +++ reactions improved somewhat. Of the 7 patients who had strong or extreme reactions, 4 were believed to have systemic allergic contact dermatitis (2 from metals and 2 from fragrance). Two patients had reactions to textile and skin care products, and one had an occupational dermatitis from the rubber additives in the gloves he wore. In comparison, only a quarter of those who had weak or questionable reactions improved.

Table 2. Patient Demographics

Category	No. of Patients, Months, or Years
Gender	
Male	4
Female	7
Age	
Range	24–69 yrs
Mean	59 yrs
Median	49 yrs
Duration of dermatitis	
Range	2 mo–7 yrs
Mean	2.4 yrs
Median	2 yrs
Distribution of dermatitis	
Generalized	10
Localized	1

Discussion

In our study, the patients with the best clinical outcomes were the ones who had strong or extreme reactions on patch testing. In contrast, only 2 of 4 patients with questionable or weak patch-test reactions clinically improved. There was also a high percentage of systemic contact dermatitis (4 of 7 patients) in those who had strong or extreme reactions. Systemic contact dermatitis can occur when a patient sensitized to an allergen ingests foods or medications containing that allergen or is exposed to it parenterally. Such patients can develop a generalized rash or sometimes rashes localized to the hands or feet or to the genitalia.⁵⁻⁷

It is particularly interesting that patient 10, who was patch-tested while on mycophenolate without relevant allergens, was found to have clinically relevant allergens when retested while not taking any systemic immunosuppressant. Of note, the patient was retested 14 months after the original patch testing, so it is possible that there was an interval change in the patient's condition. It is possible that, had the patient been tested while not on systemic immunosuppressant originally, the results would have been the same.

There are several limitations to our study. First, only 11 patients were in the study. Our results would carry more weight if there were more patients. Also, because the different immunosuppressants have different mechanisms of action, our evaluations would be better if the patients had been on the same immunosuppressants at the same doses. If patients had been patch-tested both while on and while off their immunomodulator, a comparison would have yielded more useful results. Additionally, some patients requiring systemic immunosuppressants to make the skin clear enough for patch testing may have residual background dermatitis when the patches are placed. Therefore, weak reactions can be difficult to interpret as true positives versus just extensions of some baseline dermatitis. Although it is not ideal to place patches when patients have residual dermatitis (especially if patients are unable to remain clear without systemic immunosuppressants), it seems beneficial to investigate whether any strong or extreme contact reactions might be present. If contact allergens can be defined and then avoided, patients can potentially be cured.

Studies looking at the effects of prednisone on patch-test reactivity have been performed. Feuerman and Levy analyzed patients who had previous positive or strongly positive patch-test reactions to various allergens and retested 12 patients who were on prednisone 40 mg per

day, 18 patients on prednisone 30 mg per day, and 16 patients on prednisone 20 mg per day.⁸ Of the 16 patients who were on prednisone 20 mg per day, 15 (94%) still had some reaction. Increasing doses of prednisone suppressed more reactions so that, of the 12 patients who were on 40 mg, 3 patients experienced a complete suppression of their reaction, 8 had a diminished response, and only 1 had no change.

In a multicenter double-blinded placebo-controlled study by Anveden and colleagues, 19 patients with known nickel allergy were placed on placebo or prednisone (20 mg per day) and patch-tested with nickel 5% in petrolatum.⁹ Four of the patients had no patch-test reactions while on placebo or prednisone; 12 patients had some positive reaction while on 20 mg of prednisone per day; and 15 patients had a positive reaction while on placebo. Of note, there was a significant decrease in extreme (+++) patch-test reactions when comparing the patients when on prednisone to when they were on placebo. The patients in the studies by Feuerman and Levy⁸ and Anveden and colleagues⁹ were on higher doses of prednisone than the patients listed in our chart review. Five of our patients were on prednisone 10 mg per day, one was on prednisone 5 mg per day, and one was on a combination of cyclosporine 200 mg per day and prednisone 10 mg per day. Successful patch-testing with delineation of multiple clinically relevant contact allergens in a patient taking prednisone 10 mg per day during testing has been previously reported.¹⁰

To study the effects of cyclosporine on allergic contact dermatitis, 15 patients with severe allergic contact dermatitis were treated with cyclosporine 5 mg/kg/d for 4 weeks and then 3 mg/kg/d, with good response. One month after treatment, the patients were patch-tested; the strong to extreme responses remained unchanged, whereas the weak responses (15%) became negative.¹¹ A study examining six patients with chronic contact dermatitis treated with cyclosporin A (5 mg/kg/d) showed that responses were reduced over the range of allergen concentration used and that the threshold for exhibiting a reaction was increased.¹² In our study, two patients on cyclosporine and combination cyclosporine and prednisone had extreme reactions to allergens, and a patient on cyclosporine had strong reactions to allergens. These three all gained clinical benefit from patch testing.

There is a case report of a patient who was on azathioprine (100 mg per day) and who had aphthous ulcers, initially diagnosed with Behçet syndrome. Because the patient had metal dental restorations, a potential metal allergy was suspected as the cause of her chronic recurrent

oral ulcers. When the patient was patch-tested with both the standard and dental series, she showed a strong (++) reaction to nickel; however, she declined the removal of her intraoral metal alloys.¹³ There is also a case report of a patient on etanercept who developed contact dermatitis due to urushiol exposure.¹⁴

We believe that patch testing can often overcome the suppressive effects of immunomodulators in a sensitized individual because the dose per unit area of allergens used for patch testing is high enough to exceed the threshold necessary to generate a delayed-type hypersensitivity response. It has been shown in vitro that the co-stimulatory effects of interleukin-2 and CD28 can abrogate the suppressive action of dexamethasone on T-cell proliferation acting via mitogen-activated protein kinase.¹⁵

Studies have also shown that the topical application of corticosteroids can lead to the partial or total suppression of patch-test reactions,^{16,17} which further emphasizes the importance of the conditions in the local milieu in promoting the development of effector T cells. However, other studies show minimal, if any, effect of topical midpotency steroids¹⁸ and topical cyclosporine¹⁹ on patch-test reactions.

Conclusion

Recent use of immunomodulators should not be an absolute contraindication to patch testing. However, the lowest possible dose of immunosuppressant should be used. In our study, patients with ++ or +++ patch-test reactions had the best clinical outcomes. If the suspicion of allergic contact dermatitis persists, the patient should be retested while off the immunosuppressant. Further studies are needed to determine if (1) certain immunosuppressants may be preferable to others for patch testing, (2) patients can be patch-tested in nonconventional locations if no area on the back is clear enough for testing, and (3) the concentration of allergen in petrolatum can be adjusted to allow a dose per unit area high enough to exceed the threshold and elicit a response.

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