Patch Testing During Immunosuppressive Therapy: A Systematic Review

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Abstract: **Patch testing, used in the assessment of allergic contact dermatitis, is ideally avoided in patients receiving immunosuppressive therapy because of concerns with reductions in accuracy; however, this is not well characterized in the literature. This systematic review summarizes patch testing results in patients receiving immunosuppressive therapy. We identified 16 studies, comprising 195 patients with dermatitis or psoriasis, who were patch tested while receiving immunosuppressants. Of these, 7 studies, comprising 85 patients with dermatitis, patch tests were performed before and during immunosuppression. Overall, 67.9% (n = 19) of the dermatitis patients receiving dupilumab maintained positive reactions to an allergen that previously graded as a 2+/3+ reaction. Several immunosuppressants were also associated with positive patch test results for various allergens. These include dupilumab, cyclosporine, and low-dose prednisone (≤10 mg/d) for dermatitis, and tumor necrosis factor α inhibitors, ustekinumab, and methotrexate for psoriasis. Ideally, it is preferable to patch test when patients are not receiving oral immunosuppressants or immunomodulators. However, clinicians may choose to assess the risks and benefits of patch testing for each patient given the impact of allergic contact dermatitis on patient quality of life.**

Patch testing is commonly conducted in patients with suspected allergic contact dermatitis and is ideally performed when patients are not taking systemic immunosuppressants or using topical medications on the site of patch testing, which may suppress allergic responses. Numerous allergens are used for patch testing, including baseline or screening series, other series of allergens selected by the clinician, and the patients' own personal and occupational products.[1] Common screening series include the European Standard Series, T.R.U.E. TEST, North American Contact Dermatitis Group screening series, and the American Contact Dermatitis Society Core Allergen series.

It is unclear whether patch tests can be conducted for patients receiving immunosuppressive therapy. Multiple factors, such as the type of immunosuppressant as well as the dosage, may impact patch test results. Dupilumab, a monoclonal antibody and the first biologic approved by the US Food and Drug Administration for the treatment of atopic dermatitis, targets the α chain of the interleukin 4 (IL-4) receptor, inhibiting T helper cell 2 (T_H2) inflammation, including IL-4 and IL-13.[2] Positive patch test results while on dupilumab have been reported,[3] along with psoriasis patients on biologics or methotrexate,[4,5] demonstrating that patients are capable of mounting acute reactions during allergen exposure. In addition, dosage may impact patch test results, as a multicenter, randomized, double-blind, crossover study found that prednisone (20 mg/d) suppressed extreme patch test reactions when compared with placebo,[6] and another study found successful patch testing results when using a lower dose (≤10 mg/d) of prednisone.[7]

These findings suggest that there is uncertainty with respect to the effect of immunosuppressive therapy and patch testing. An expert opinion by the North American Contact Dermatitis Group members on the effects of immunomodulatory agents on patch testing reported the following: (1) topical corticosteroids should be avoided on the patch test site for 3 to 7 days; (2) it is acceptable to patch test a patient receiving 10 mg of oral prednisone; however, it is best if discontinued; (3) if patient uses intramuscular triamcinolone 40 mg, wait until 4 weeks after injection; (4) there is little to no effect on patch test results for tumor necrosis factor α (TNF-α) inhibitors, methotrexate, and ustekinumab; and (5) there is dose-dependent inhibition for azathioprine, cyclosporine, mycophenolate mofetil, and tacrolimus; however, more data are needed.[8]

In an attempt to address this uncertainty, we conducted a systematic review on patch testing in patients receiving immunosuppressants and evaluated studies that conducted both patch tests

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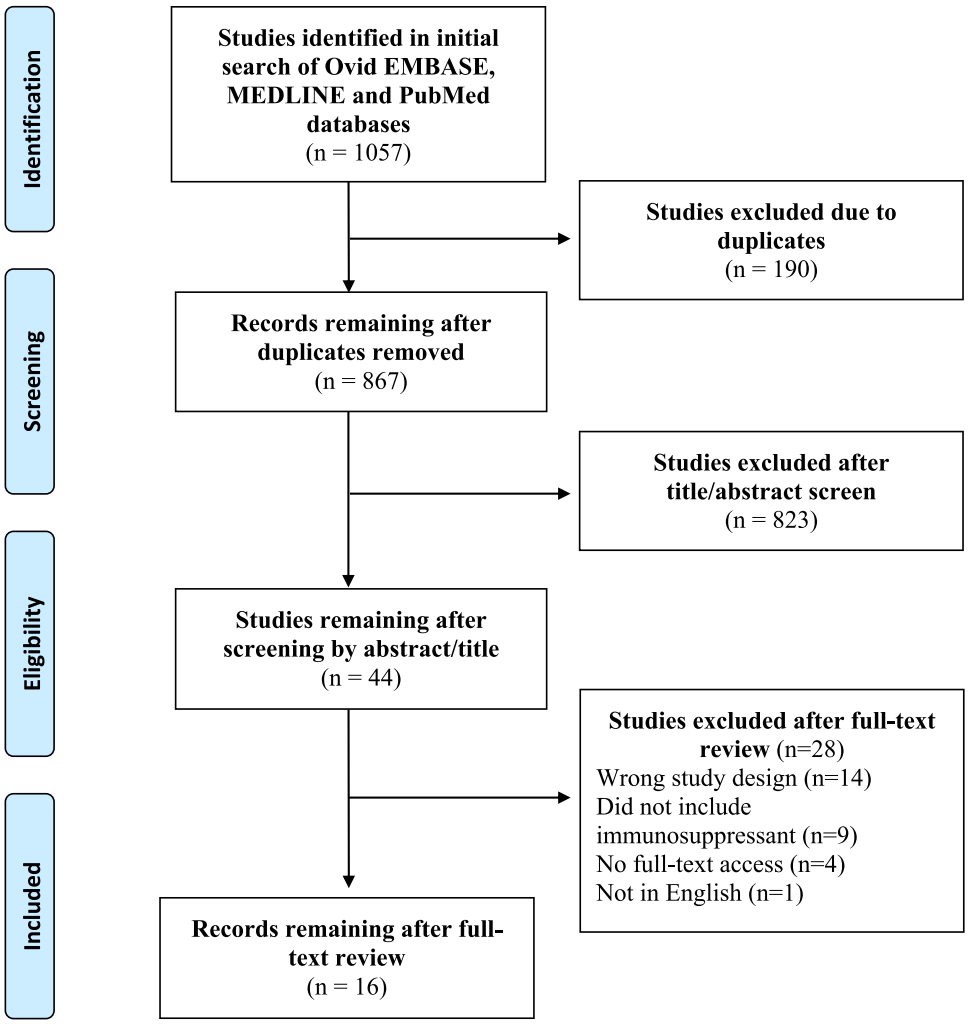

Figure 1. Flow diagram of literature screening using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

either before and during immunosuppression or only during immunosuppression.

METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Fig. 1).

Study Identification

OVID Embase and OVID MEDLINE databases were systematically searched from inception to June 28, 2020, using variations of the following search key words: "patch test" and specific immunosuppressants (Fig. 1). Using the predetermined inclusion criteria, titles/abstracts and full texts of retrieved articles were independently screened by 2 reviewers (A.M. and M.S.), and conflicts were resolved by a third reviewer (J.Y.). A reviewer (M.S.) manually searched the reference lists of relevant reviews and studies to identify articles missed by the initial database search.

Inclusion Criteria

Eligibility for inclusion of articles was established a priori. Original articles written in the English language were included if they (1) involved the appropriate study population (ie, patients receiving immunosuppressants), (2) used patch testing, (3) had an observational (ie, case reports, case series, cross-sectional, or cohort studies) study design, and (4) were accessible through researchers' affiliated institution. Conference abstracts and studies with irretrievable full texts were excluded.

Data Extraction and Analysis

Abstract screening and data extraction were conducted by 2 authors working independently of each other (H.Z. and M.S.). Disagreements were resolved by discussion between the 2 authors. Data extraction included the following: study characteristics, patient

information (age, sex, comorbidities, family history of dermatitis or allergies), medication information (type, dosage, duration, frequency), and patch testing information (when patch testing was conducted, the baseline series used, positive allergens, and lost allergens). All allergens that tested positive were grouped into broad source categories (eg, antibiotics, metals, fragrances, etc). For the dupilumab studies, maintenance of positive reactions was assessed by looking at baseline 2+/3+ reactions because of variability in patch test results for weaker reactions.

RESULTS

Literature Search Results

A total of 1057 studies were identified through database searching (Fig. 1). Of these, 190 articles were duplicates, leaving 867 articles for title and abstract screening. From this, 823 studies were excluded as not meeting the eligibility criteria, leaving 44 studies to be analyzed for full-text review. Of these, 29 were excluded because of a nonapplicable study design (n = 15), lack of inclusion of immunosuppressants (n = 9), no access to full text (n = 4), and absence of English language (n = 1). After full-text review, 16 studies were included for analysis.[3–5,9–21] Of these, 3 were cohort studies, 6 were retrospective chart reviews, 6 were case reports, and 1 was a case series.

Study and Patient Characteristics

Overall, 195 patients (mean age = 48.9, n = 115) underwent patch testing, of which 46.6% (n = 54) were male and 53.4% (n = 62) were female; age and sex were not reported for 80 patients (Table 1). Of the 16 studies included for analysis, 7 comprising 85 patients conducted patch tests before and during immunosuppression therapy in patients with dermatitis. However, none of the studies evaluated repeat patch testing in a control group of patients without immunosuppression. The remaining 9 studies evaluated patch tests only during immunosuppression, in patients with psoriasis (n = 43) and dermatitis (n = 49). Patient comorbidities, known allergies, and family history of dermatitis or allergies were generally not reported.

Patch Testing Results Before and During Immunosuppressant Use

Five studies, consisting of 28 patients with dermatitis, evaluated patch tests before and during treatment with dupilumab.[3,9–12] The most common dose was 300 mg every other week. The duration of immunosuppression before patch testing was not reported for the largest study (n = 23)[9] but ranged from 2 to 9 months with a mean of 5 months for the remaining 5 patients.[3,10–12] A total of 67.9% (n = 19) of the patients on dupilumab maintained positive reactions to standard allergen concentrations. Allergens included the following: fragrances, preservatives, emulsifiers and surfactants, hairdressing agents, topical therapy, metals, adhesives, varnishes, textile dyes, and antibiotics. Lost allergens included the following: emulsifiers and surfactants, fragrances, sunscreens, metals, preservatives, topical medication, and resin. Diminished reactions were not reported for the largest study (n = 23),[9] but of the remaining 5 patients, 2 had diminished reactions (1 to formaldehyde[3] and 1 to nickel[11]). A total of 28.6% (n = 8) of the patients had completely suppressed reactions (ie, lost reactions) to standard allergen concentrations after immunosuppressive therapy initiation, which were all originally 2+/3+ reactions. However, 3 of these patients had documented immunodeficiencies due to malignancies, lymphocytopenia, and hypogammaglobulinemia, leading to low immunoglobulin G1 and immunoglobulin G2 levels.[9] No study evaluated the use of a higher concentration of lost allergens during immunosuppressant patch testing in an attempt to elicit a positive reaction.

The largest study was by Raffi et al[9] in 2020, who conducted a retrospective chart review of 23 patients with 125 paired patch tests before and after dupilumab. Dupilumab led to 13 lost reactions in 7 patients, resulting in 10.4% of patch test pairs.[9] However, 38.4% of the pairs were labeled "unknown" effect and included any 1+ reaction that became doubtful or negative.

The 13 lost reactions were as follows: 4 emulsifiers/surfactants (propylene glycol 10% and 100%, Amerchol, dimethylaminopropylamine), 2 sunscreens (sulisobenzone, phenylbenzimidazole-5-sulfonic acid), 2 metals (vanadium [III] chloride and phenyl mercuric acetate), 2 fragrances (balsam of Peru and fragrance mix I), 1 preservative (iodopropynyl butylcarbamate), 1 topical medication (bacitracin), and 1 resin (tosylamide formaldehyde). However, 3 of the 7 patients had preexisting immunodeficient conditions and accounted for 5 of the 13 lost allergens. Furthermore, some of the lost allergens (vanadium chloride, phenyl mercuric acetate, propylene glycol 100%, Amerchol, balsam of Peru, and fragrance mix) are associated with weak irritant reactions and may test negative upon retesting even in patients who are not immunosuppressed.[22] Consequently, it is difficult to delineate persistent versus lost patch test results for weaker reactions. The remaining 4 studies comprising a total of 5 patients were small case series or case reports.[3,10–12]

Two studies evaluated patch test results in dermatitis patients before and during treatment on azathioprine and cyclosporine, respectively.[13,14] For azathioprine, 95.7% (n = 45) of the patients maintained positive reactions to *Parthenium hysterophorus* after 6 months' treatment with either 300 mg of weekly azathioprine (n = 25) or 100 mg daily orally (n = 22); however, the only allergen tested was parthenium.[13] Diminished reactions were not reported. In a separate study with cyclosporine, 10 patients were on 5 mg/kg per day, and the repeat patch test was conducted 1 month after resolution.[14] Fifty-six percent of the reactions were lost, although it was not specified what exact reactions were conducted or lost.

Positive Allergens in Dermatitis Patients With Immunosuppression

Dermatitis patients with patch tests conducted during immunosuppression and associated positive allergens are summarized (Table 2). For dermatitis, the drugs evaluated during immunosuppression included dupilumab (n = 7), azathioprine (n = 2), cyclosporine (n = 2), azathioprine and prenisolone (n = 1), systemic

TABLE 1. Dermatitis Treated With Immunosuppressants Before and During Patch Testing

Study Characteristics and Demographics				Drug Information		Patch Testing					
Author, Year	Type of Study	Sample Size	Age, y/Sex	Drug	Dose, Frequency, and Duration Before Patch Test	Type of Patch Test	Positive Patients Before Immunosuppression	Positive Patients During Immunosuppression	Positive Patients Became Negative	Negative Patients Became Positive	Positive Allergens
Raffi et al,[9] 2020	Retrospective chart review	23	NR/NR	Dupilumab	300 mg, frequency, and duration: NR	NACDG screening, fragrances, textile colors and finish, sunscreens, eye medicaments, corticosteroids, and dietary additives	23/23	16/23	7/23 (13 lost reactions of 125, but 48 reactions were "unknown" where 1 or both patch test results were questionable)	NR	Fragrances (19) Preservatives (12) Emulsifiers and surfactants (11) Hairdressing (2) Topical therapies (5) Metals (11) Adhesives (2) Textile dyes (2)
Suresh and Murase,[10] 2018	Case series	2	53 mean/ both F	Dupilumab	600-mg loading dose followed by 300 mg EOW, duration: patient 1 for 6 mo, patient 2 for 9 mo	NACDG standard series in addition to patients' products, sunscreen series, corticosteroid series, and F-1000 fragrance series	2/2	2/2	0	0	Fragrances (8) Antibiotics (1) Emulsifiers and surfactants (6) Corticosteroids (2) Others (1)
Zhu et al,[11] 2019	Case report	1	54/M	Dupilumab	NR, NR, and for 2 mo	NR	1/1	1/1	0	0	Metals (1) Preservatives (1)
Raffi and Botto,[12] 2019	Case report	1	40/F	Dupilumab	NR, NR, and for 2 mo	NR	1/1	0	1/1 (lost 3 reactions)	0	Preservatives (2)
Puza and Atwater,[3] 2018	Case report	1	63/F	Dupilumab	300 mg EOW for 6 mo	NACDG, the corticosteroid series, and 50 additional allergens (129 total allergens tested)	1/1	1/1	0	0	Preservatives (2)
Verma et al,[13] 2016	Prospective cohort	47	NR/NR	Azathioprine	2 groups: 300 mg, weekly as a pulse dose (n = 25), 100 mg daily orally (n = 22), and both for 6 mo	NR and only tested parthenium	47/47	45/47	2/47 (1 patient from each group)	0	Others (1)
Vena et al,[14] 1994	Prospective cohort	10	NR/NR	Cyclosporine	5 mg/kg per day, duration: NR, but patch test was done 1 mo after resolution	European standard series	10/10	NR	NR (56% of reactions were lost)	NR	NR

EOW, every other week; F, female; M, male; NACDG, North American Contact Dermatitis Group; NR, not reported.

TABLE 2. Dermatitis Patients with Patch Tests Conducted during Immunosuppression and Associated Positive Allergens

Author, Year	Type of Study	Age, y/Sex	Drug	Dose, Frequency, and Duration	When Patch Testing Was Done	Type of Patch Test	Positive Patients Out of Patients Tested	Positive Allergens
Stout and Silverberg,[15] 2019	Retrospective chart review	46.4 mean/4 M, 3 F	Dupilumab	600-mg loading dose, 300 mg EOW, and 12.9 mo	After 4–24 mo of treatment	NACDG standard series	7/7	Antibiotics (3) Rubber-related allergens (2) Fragrances (6) Metals (1) Toiletry-related allergens (2) Sunscreens (1) Preservatives (3) Glue-related allergens (1) Emulsifiers/ surfactants (2) Others (2)
Hoot et al,[16] 2018	Case report	26, F	Dupilumab	NR and 10 wk	After 10 wk of treatment	NR	1/1	Antibiotics (2) Rubber-related allergens (2) Others (2)
López-Jiménez and Marrero-Alemán,[17] 2019	Retrospective chart review	34 mean/6 M, 6 F	8 with systemic corticosteroids, 3 with cyclosporine or azathioprine and 1 with narrowband ultraviolet B	NR	NR	Spanish baseline series and T.R.U.E. test	12/22	Fragrances (5) Antibiotics (1) Metals (4) Rubber-related allergens (2) Preservatives (7) Emulsifiers and surfactants (3) Others (4)
Wentworth and Davis,[18] 2014	Retrospective chart review	65.3 mean/3 M	Methotrexate	15, 20, and 25 mg weekly (per patient) and duration: NR	NR	NACDG	2/3	Fragrances (1) Preservatives (2) Others (1)
Yfanti et al,[19] 2018	Case report	38, F	Methotrexate	25 mg weekly and for 3 mo	After 3 mo of treatment	European baseline series	1/1	Fragrances (1) Metals (1)

(Continued on next page)

TABLE 2. *(Continued)*

Author, Year	Type of Study	Age, y/Sex	Drug	Dose, Frequency, and Duration	When Patch Testing Was Done	Type of Patch Test	Positive Patients Out of Patients Tested	Positive Allergens
Wee et al,[5] 2010	Prospective cohort	36 mean/3 M, 2 F	Azathioprine	50–200 mg/d and duration: NR	NR	European baseline patch test series with Trolab allergens (NR)	1/5	Metals (1)
		37.4 mean/2 M, 7 F	Cyclosporine	2–3 mg/kg per day and duration: NR			4/9	Fragrances (2) Metals (1) Rubber-related allergens (1) Sunscreens (1) Preservatives (1) Others (1)
		77 M	Azathioprine and prednisolone	100 mg, 10 mg, and duration: NR	NR	European baseline patch test series with Trolab allergens (NR)	1/1	Antibiotics (1)
Rosmarin et al,[20] 2009	Retrospective chart review	NR/NR	Cyclosporine	200–300 mg/d and duration: NR	NR	NACDG standard series, fragrance series, and preservative series, in addition to other series depending on history and physical examination results.	2/2	Fragrances (1) Metals (1)
			Prednisone	5–10 mg/d and duration: NR			6/6	Fragrances (2) Metals (2) Sunscreens (1) Rubber-related allergens (1) Emulsifiers (3) Preservatives (2) Others (5)
			Prednisone and cyclosporine	10 mg/d; 200 mg/d, and duration: NR			1/1	Antibiotics (1) Metals (2)
			Mycophenolate	2000 mg/d and duration: NR			1/1	Metals (2) Others (1)

EOW, every other week; F, female; M, male; NACDG, North American Contact Dermatitis Group; NR, not reported.

corticosteroids (n = 8), prednisone (n = 1), prednisone and cyclosporine (n = 1), methotrexate (n = 2), mycophenolate (n = 1), and unspecified (n = 1).

Patients with the most positive allergens were receiving treatment with dupilumab (n = 28/35), cyclosporine (n = 6/11), and low-dose prednisone (<10 mg/d, n = 6/6). Patients receiving dupilumab had a broad range of positive allergens including antibiotics, rubbers, fragrances, toiletries, preservatives, emulsifiers and surfactants, topical therapies, metals, adhesives, and textile dyes. For cyclosporine patients, positive allergens included fragrances, metals, rubber, sunscreen, and preservatives. Prednisone also had a variety of positive allergens including antibiotics, fragrances, metals, rubber, sunscreen, emulsifiers, surfactants, and preservatives. Although 88% (n = 46/52) of azathioprine and 75% (n = 3/4) of methotrexate patients were positive both before and during immunosuppression, there was a smaller range of positive allergens tested or reported. For example, from the 2 azathioprine studies, patients had positive reactions only to cobalt (n = 1/5) and parthenium (n = 45/47). The study testing parthenium did not evaluate any other allergen, whereas patients in the cobalt study were tested with the European baseline patch test series (Table 2). For the 2 methotrexate studies, persistent positive patch test reactions were reported to fragrances (n = 3/4), nickel (n = 1/4), and preservatives (n = 2/4); however, the number of patients tested was small. One patient on mycophenolate reported positive allergens to cobalt, gold, and triethanolamine.

Positive Allergens in Psoriasis Patients With Immunosuppression

Psoriasis patients with patch tests conducted during immunosuppression and associated positive allergens are summarized (Table 3). For psoriasis, the drugs evaluated during immunosuppression included infliximab (n = 3), infliximab and methotrexate (n = 1), adalimumab (n = 2), etanercept (n = 1), etanercept and methotrexate (n = 1), secukinumab and methotrexate (n = 1), ustekinumab (n = 1), methotrexate (n = 2), and cyclosporine and fumaderm (n = 1).

Patients with the most positive allergens were receiving TNF-α inhibitors (infliximab [n = 4/4], adalimumab [n = 3/4], and etanercept [n = 3/5]), ustekinumab (n = 7/7), and methotrexate (n = 3/4). Patients receiving TNF-α inhibitors (n = 10) had a broad range of positive allergens including antibiotics, rubbers, fragrances, preservatives, emulsifiers and surfactants, corticosteroids, and metals. Patients receiving ustekinumab (n = 7) had positive allergens to fragrances, antibiotics, metals, preservatives, sunscreen, and emulsifiers and surfactants. Patients on methotrexate (n = 3) had positive allergens to fragrances, metals, antibiotics, preservatives, glue, and nail polish. Drugs with fewer reported positive allergens included secukinumab (n = 1), which reported only allergens to fragrances, and cyclosporine and fumaderm (n = 1), with allergens to antibiotics. However, this could be due to the small sample size.

DISCUSSION

We conducted a systematic review and identified 16 studies that performed patch tests while patients were receiving immunosuppresive therapy. Overall, dupilumab did not drastically affect patch test results in patients who originally had 2+ and 3+ reactions, with only 13 reactions (10.4%) of 125 patch test allergens being lost after immunosuppression for the largest study (n = 23).[9] However, an "unknown" effect was observed in 38.4% of patch test allergens, which described any 1+ reaction that became doubtful or negative.[9] Several immunosuppressants were also associated with positive patch tests for various allergens, including cyclosporine and low-dose prednisone for dermatitis, and TNF-α inhibitors, ustekinumab, and methotrexate for psoriasis, suggesting that they do not generally dampen patch test results.

Dupilumab did not seem to selectively block specific allergens or allergen classes based on patch test results conducted before and during immunosuppression. Dhingra et al[23] found that nickel was a potent inducer of the T_H1, T_H17, and T_H22 pathways, whereas fragrance and rubber promoted T_H2 activity with less T_H1 and T_H17 involvement, suggesting that dupilumab would dampen the T_H2 pathway and associated allergens such as fragrance and rubber while not affecting T_H1-specific allergens such as nickel. However, Raffi et al[9] showed that between patch test results before and during dupilumab, 13 lost allergens spanned a variety of allergen subtypes (4 emulsifiers, 2 fragrances, 1 topical medication, 1 preservative, and 1 resin). This is also supported by patch test results during immunosuppression, as there was a variety of positive allergens recorded for dupilumab, which included fragrances and rubber (Table 2). Raffi et al[9] also reported 3 immunodeficient patients and contributed to 5 of the 13 lost allergies. Another 5 allergies occurred in a patient who was believed to be hyperirritable in his initial patch test, with 16 of 125 positive results.[9] These results support patch testing for patients taking dupilumab for their dermatitis, as patch testing may provide useful information about contact allergens. However, a risk of false-negative patch test results remains, and it is important for clinicians to recognize potential false negatives and consider repeat patch tests when dupilumab is discontinued. Another consideration is that if dupilumab is potent enough to suppress relevant patch tests, it may also suppress the allergic contact dermatitis associated with those allergens in a given patient; however, further studies are needed to support this hypothesis.

Azathioprine and cyclosporine were also assessed in dermatitis with patch tests before and during immunosuppression.[13,14] Although each treatment was limited to 1 study, both showed no overt dampening effects for allergic responses. Of the 47 patients who were positive for parthenium, only 2 lost their allergens after 6 months of azathioprine; however, the study assessed only the parthenium allergen.[13] Cyclosporine produced similar results, although 56% of reactions were lost, those that were relevant based on the patient's history were exactly reconfirmed.[14] Furthermore, this study was limited to excited skin syndrome, and patients with initial patch test results may have been more sensitive to various allergens.[24] This suggests that strongly positive reactions would be more likely to be captured with patch tests conducted during immunosuppression. In addition, we found various positive allergens reported for cyclosporine in patients with dermatitis (Table 2).

TABLE 3. Psoriasis Patients With Patch Tests Conducted During Immunosuppression and Associated Positive Allergens

Author, Year	Type of Study	Age, y/Sex	Drug	Dose, Frequency, and Duration	When Patch Testing Was Done	Type of Patch Test	Positive Patients out of Patients Tested	Positive Allergens
Wee et al, 2010[5]	Prospective cohort	63 F	Infliximab	5 mg/kg and duration: NR	NR	European baseline patch test series with Trolab allergens (NR)	1/1	Fragrances (3)
		38 F	Infliximab, methotrexate	5 mg/kg, 10 mg/wk, and duration: NR	NR	European baseline patch test series with Trolab allergens (NR)	1/1	Metals (1)
		38 F	Adalimumab	40 mg/wk and duration: NR	NR	European baseline patch test series with Trolab allergens (NR)	1/1	Metals (1)
		60 F	Etanercept, methotrexate	25 mg ×2/wk, 10 mg/wk, and duration: NR	NR	European baseline patch test series with Trolab allergens (NR)	1/1	Corticosteroids (1) Preservatives (1)
		49 F	Methotrexate	5–7.5 mg/wk and duration: NR	NR	European baseline patch test series with Trolab allergens (NR)	1/1	Fragrances (1) Metals (2)
		62 M	Cyclosporine, fumaderm	150 mg once daily, 720 mg, and duration: NR	NR	European baseline patch test series with Trolab allergens (NR)	1/1	Antibiotics (1)
Kim et al,[4] 2014	Retrospective chart review with control	NR/NR	Infliximab	NR	14 d from last dose	Modified NACDG standard series, cosmetics series, other supplemental series depending on history and physical examination results	1/1	Fragrances (2) Antibiotics (1) Metals (4) Rubber-related allergens (2) Sunscreens (1) Preservatives (4) Others (1)
		NR/NR	Adalimumab	NR	Mean: 5 d (2–7 d from last dose)	Modified NACDG standard series, cosmetics series, other supplemental series depending on history and physical examination results	2/3	Fragrances (1) Metals (3) Rubber-related allergens (1) Preservatives (4) Emulsifiers and surfactants (5) Others (1)
		NR/NR	Etanercept	NR	Mean: 6.5 d (5–8 d from last dose)	Modified NACDG standard series, cosmetics series, other supplemental series depending on history and physical examination results	2/4	Fragrances (1) Antibiotics (2) Metals (2) Preservative (2) Emulsifiers and surfactants (1) Others (1)
		NR/NR	Ustekinumab	NR	Mean: 85.5 d (28–238 d from last dose)	Modified NACDG standard series, cosmetics series, other supplemental series depending on history and physical examination results	7/7	Fragrances (3) Antibiotics (2) Metals (2) Preservatives (5) Sunscreen (1) Emulsifiers and surfactants (2) Others (2)

Wentworth and Davis,[18] 2014	Retrospective chart review	48 mean/ 2 M, 1 F	Methotrexate	7.5, 15, and 20 mg weekly (per patient)	NR	NACDG	2/3	Antibiotics (2) Metals (2) Preservatives (6) Glue-related allergens (1) Nail polish–related allergens (1) Others (5)
Rosmarin et al,[20] 2009	Retrospective chart review	NR/NR	Infliximab	5 mg/d and duration: NR	NR	NACDG standard series, fragrance series, and preservative series, in addition to other series depending on history and physical examination results	1/1	Rubber-related allergens (3) Others (2)
Hamann and Ziwas,[21] 2017	Case report	66 M	Secukinumab and methotrexate	300 mg monthly, 10 mg weekly, and duration: NR	NR	NR	1/1	Fragrances (3)

EOW, every other week; F, female; M, male; NACDG, North American Contact Dermatitis Group; NR, not reported.

However, only metals and parthenium were reported for azathioprine, and more data are needed for azathioprine.

Although we only found patch tests conducted during immunosuppression for psoriasis patients, TNF-α inhibitors, ustekinumab, and methotrexate were associated with a variety of positive allergens. Kim et al[4] conducted a retrospective chart review with a control group (without biologics) and treatment group (with biologics) for patients with psoriasis and/or psoriatic arthritis. There was no significant difference between the frequency of positive patch tests between patients on biologics and those without; however, the sample size was small and limited to 31 patients.[4] In addition, we found a report on only 1 patient on secukinumab who was patch tested, with reported positive tests to fragrances.[21] More data are needed on patch tests for psoriasis patients and more recently approved biologics.

Limitations

We were limited to 7 studies that evaluated patch tests conducted before and during immunosuppression, and most studies were limited to case studies or case series. In addition, most studies did not conduct repeat patch tests, so we could not account for variations between patch test results. The clinical relevance of positive patch test results varies greatly because of the lack of standardization for assessing clinical relevance, as patch testing interpretation is based on clinical judgments that can vary with knowledge and experience.[25] Because of minimal data, we could not report the dose thresholds at which immunosuppressive therapies may begin to diminish positive patch test reactions.

CONCLUSIONS

Our findings suggest that patch tests generally benefit patients receiving immunosuppressive therapy, particularly dupilumab, cyclosporine, and low-dose prednisone (≤10 mg/d) for dermatitis and TNF-α inhibitors, ustekinumab, and methotrexate for psoriasis. However, because of limited data, clinicians should provide the lowest dose of immunosuppressant if possible. Further studies are needed to determine patch test results before and during biologic use for psoriasis and whether there are specific classes of allergens that may be affected. Because of limited data including clinical relevance of lost reactions, the conservative approach would be to patch test before immunosuppression when practical. However, clinicians may choose to assess the risks and benefits of patch testing on a case-by-case basis in patients on immunosuppressants, given that the information obtained could greatly impact their quality of life.

REFERENCES

1. Lazzarini R, Duarte I, Ferreira AL. Patch tests. *An Bras Dermatol* 2013;88(6): 879–888.
2. Sastre J, Dávila I. Dupilumab: a new paradigm for the treatment of allergic diseases. *J Investig Allergol Clin Immunol* 2018;28(3):139–150.

3. Puza CJ, Atwater AR. Positive patch test reaction in a patient taking dupilumab. *Dermatitis* 2018;29(2):89.
4. Kim N, Notik S, Gottlieb AB, et al. Patch test results in psoriasis patients on biologics. *Dermatitis* 2014;25(4):182–190.
5. Wee JS, White JM, McFadden JP, et al. Patch testing in patients treated with systemic immunosuppression and cytokine inhibitors. *Contact Dermatitis* 2010;62(3):165–169.
6. Anveden I, Lindberg M, Andersen KE, et al. Oral prednisone suppresses allergic but not irritant patch test reactions in individuals hypersensitive to nickel. *Contact Dermatitis* 2004;50(5):298–303.
7. Olupona T, Scheinman P. Successful patch testing despite concomitant low-dose prednisone use. *Dermatitis* 2008;19(2):117–118.
8. Fowler JF Jr., Maibach HI, Zirwas M, et al. Effects of immunomodulatory agents on patch testing: expert opinion 2012. *Dermatitis* 2012;23(6):301–303.
9. Raffi J, Suresh R, Botto N, et al. The impact of dupilumab on patch testing and the prevalence of comorbid allergic contact dermatitis in recalcitrant atopic dermatitis: a retrospective chart review. *J Am Acad Dermatol* 2020; 82(1):132–138.
10. Suresh R, Murase JE. The role of expanded series patch testing in identifying causality of residual facial dermatitis following initiation of dupilumab therapy. *JAAD Case Rep* 2018;4(9):899–904.
11. Zhu GA, Chen JK, Chiou A, et al. Repeat patch testing in a patient with allergic contact dermatitis improved on dupilumab. *JAAD Case Rep* 2019;5(4): 336–338.
12. Raffi J, Botto N. Patch testing and allergen-specific inhibition in a patient taking dupilumab. *JAMA Dermatol* 2019;155(1):120–121.
13. Verma KK, Bhari N, Sethuraman G. Azathioprine does not influence patch test reactivity in parthenium dermatitis. *Contact Dermatitis* 2016;74(1): 64–65.
14. Vena GA, Foti C, Piazzola L, et al. Can cyclosporin A help distinguish allergic from irritant patch test reactions? *Contact Dermatitis* 1994;31(4):256–257.
15. Stout M, Silverberg JI. Variable impact of dupilumab on patch testing results and allergic contact dermatitis in adults with atopic dermatitis. *J Am Acad Dermatol* 2019;81(1):157–162.
16. Hoot JW, Douglas JD, Falo LD Jr. Patch testing in a patient on dupilumab. *Dermatitis* 2018;29(3):164.
17. López-Jiménez EC, Marrero-Alemán G. One-third of patients with therapy-resistant atopic dermatitis may benefit after patch testing. *J Eur Acad Dermatol Venereol* 2019;33(10):e377–e378.
18. Wentworth AB, Davis MD. Patch testing with the standard series when receiving immunosuppressive medications. *Dermatitis* 2014;25(4):195–200.
19. Yfanti I, Nosbaum A, Berard F, et al. Methotrexate does not impede the development of contact allergy. *Contact Dermatitis* 2018;78(3):223–224.
20. Rosmarin D, Gottlieb AB, Asarch A, et al. Patch-testing while on systemic immunosuppressants. *Dermatitis* 2009;20(5):265–270.
21. Hamann D, Zirwas M. Successful patch testing of a patient receiving anti–interleukin-17 therapy with secukinumab: a case report. *Contact Dermatitis* 2017;76(6):378–379.
22. Burkemper NM. Contact dermatitis, patch testing, and allergen avoidance. *Mo Med* 2015;112(4):296–300.
23. Dhingra N, Shemer A, Correa da Rosa J, et al. Molecular profiling of contact dermatitis skin identifies allergen-dependent differences in immune response. *J Allergy Clin Immunol* 2014;134(2):362–372.
24. Duarte I, Almeida FA, Proença NG. Excited skin syndrome. *Am J Contact Dermatitis* 1996;7(1):24–34.
25. Ale IS, Maibacht HA. Diagnostic approach in allergic and irritant contact dermatitis. *Expert Rev Clin Immunol* 2010;6(2):291–310.