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Dermatology Treatments and their Effects on Patch Testing

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Introduction

Patients are often sent for patch testing to rule out allergic contact dermatitis, but it is a clinical conundrum of what to do when they are on systemic agents. The clinical question is, should the systemic agents be held for 4-5 half-lives and then patch tested to ensure there is no blunting of the immune system? The reality is that in this population without systemic treatments, patients are seldom clear enough to patch test. Their backs are covered in dermatitis and testing runs the risk of eliciting an uninterpretable "angry back". The other consideration is patients' strong preference to remain on systemic medications that control their significant itch, rash and associated sequelae. In an ideal world, it would best to patch test patients prior to the initiation of a systemic agent but clinically this is not always feasible.

We will explore various clinical scenarios involving patch testing and discuss the advice the dermatologist should provide patients regarding holding their medications.

Patch Testing on Topical Agents

Patients undergoing patch testing should avoid application of both topical corticosteroids and calcineurin inhibitors on their backs 1 week before patch testing.[1] There is a dearth of information on best practices for topical phosphodiesterase 4 inhibitors such as topical crisaborole and topical roflumilast, and recommendations for avoiding application to the patch testing site. All topicals can be used on areas that are not going to be patch tested before and during patch testing. For example, if a patient is due to be patch tested, they should be advised to stop using their topical steroid and/or topical calcineurin inhibitor on their backs. However, they can apply their topical medicaments to their hands, arms, face, chest, abdomen, legs, popliteal fossa, and feet.

Patch Testing on Phototherapy or a Tan

Tanning the skin from either phototherapy or sunlight suppresses the Langerhans cells responsible for antigen presentation. This can lead to false negatives for patch testing. It is recommended to avoid phototherapy or tanning the patch test site for 1-2 weeks prior to patch testing.[2] If patients have patch testing scheduled during the summer months it is important to remind them to avoid getting a tan on their backs. If they come for their patch testing session with

a tanned back, they will need to be reschedule to a later date in the Fall.

Patch Testing on Conventional Systemic Oral Agents

The conventional wisdom regarding patch testing on older systemic agents such as prednisone, methotrexate, cyclosporine, mycophenolate mofetil, and azathioprine is to patch ideally during a drug holiday or at the lowest possible dose given that these agents have dose-dependent inhibition.[3] Patch testing done on doses of prednisone of 20 mg or greater will decrease the accuracy results. A randomized, double-blind, clinical cross-over trial (n=24) of patients with known allergic contact dermatitis to nickel showed significantly decreased reactions if patch tested while on prednisone.[4] A total of 25% of patching positive reactions to 5% nickel in petrolatum were lost while on 20 mg of prednisone.[4] However, a case study by Olupona and Scheinman[5] in 2008 found that patch testing at a dose of prednisone of 10 mg did not interfere with patch testing results.

Patch Testing on TNF-alpha Inhibitors, IL-12/23 Antagonists, Il-17 Antagonists, Il-23 Antagonists

When discussing novel systemic treatments, the greatest amount of evidence exists for both TNF-alpha inhibitors and IL-12/23, inhibitors given that these medications have been on the market the longest. Neither of them appears to affect patch test results.[3] There is only one case report of a patient patch tested on secukinumab 300 q monthly and low-dose methotrexate 10 mg q weekly who reacted to fragrances and sorbitan sesquioleate.[6] Allergic contact dermatitis can elicit T_H1, T_H2, T_H9, T_H17, and T_H22 responses. Various allergens such as nickel induce primarily a T_H1/T_H17 response.[7] Nickel allergy patients produce Il-23 in response to nickel stimulation.[6] Fragrance and rubber induce primarily a T_H2 response.[7] The case report of the patient reacting to fragrances given Il-17 inhibition is not surprising given the mechanism of action. The key question is whether or not Il-17 and Il-23s are blunting some reactions to select allergens such as nickel. Further studies on this matter are required.

Patch Testing on Il-4/13 Antagonists and Il-13 Antagonists

Dupilumab is being used as an off-label treatment for allergic contact dermatitis with good effect. Its onset of action is 1-4 weeks. A phase 4 clinical trial on 30 participants is underway to explore dupilumab's ability to treat patients with allergic contact dermatitis who have failed allergen avoidance.[7] The ability of dupilumab to effectively treat allergic contact dermatitis raises questions regarding its impact on patch testing results. There is debate in the literature regarding the accuracy of patch testing while on dupilumab.

A systematic review of 5 studies with 28 patients by Mufti et al.[3] found that 67.9% (n=19) of who had undergone patch testing before and after starting dupilumab 67.9% (n=19 patients) maintained positive reactions. The largest study in this systematic review was a retrospective chart review (n=23 patients) by Raffi et al.[8] conducted in 2020, with 125 patch test pairs done before and after initiating dupilumab therapy. Only 10.4% of reactions were lost after initiating dupilumab therapy. Of note, all 5 studies in the systematic review by Mufti et al.[3] were case reports/series or retrospective chart reviews that have a higher rate of bias.

To date, the best data on patch testing while on dupilumab therapy comes from Bocquel et al.[9] who conducted a prospective multicentre study in France between November 2020 and January 2022. It enrolled 76 dupilumab-treated patients who had undergone patch testing at least 4 months after initiating dupilumab. Data was collected at three visits: before, during and after patch testing. All patients were patch tested to the European Baseline Series (n=36) and some were also patched to an additional French series of allergens REVIDAL-GERDA (n=15). There was a total of 1230 paired allergens. A total of 83% of patch tests results were the same (either +/+ or -/-); 2.8% were positive on dupilumab therapy (-/+); 3.6% of reactions were lost on dupilumab therapy (+/-); and 10.6% of results were uninterpretable due to either angry backs or indeterminate reaction. This study did demonstrate good reproducibility of patch test results while on dupilumab therapy. This study provides the only high-quality prospective data on the impact of dupilumab on patch testing results.

The median time to no detectable concentration is 10-11 weeks for dupilumab 300 mg q2weeks[10] Withholding dupilumab for patients requiring the medication for a variety of indications such as concomitant atopic dermatitis, asthma, nasal polyps, and eosinophilic esophagitis requires entering into a risk-benefit discussion. Pausing dupilumab for 2.5 to almost 3 months for many patients is not feasible as their underlying diseases will likely flare and cause additional harm. Given the recent study by Bocquel et al.[9] discussed above, the benefit of holding therapy is minimal, leading to capturing only 3.6% reactions that would have otherwise been blunted due to dupilumab.

It is important for patients to understand the benefit of withholding dupilumab therapy given that the best data available appears to be minimal. It is my practice to patch test patients while on dupilumab as well as Il-13 antagonists. There is a lack of information on the impact of Il-13 antagonists given that they are relatively new to the market.

Patch Testing on JAK Inhibitors

There is only one case study to date that has been published on JAK inhibitor use during patch testing by Mainville et al.[11] The patient had previously undergone patch testing while on dupilumab and was positive to fusidic acid +2, amerchol L 101 +3, thiuram +1, 4-tert butylphenol formaldehyde resin +1, corticosteroid mix +1, budesonide +1, betamethasone-17-valerate +1, clobetasol-17-propionate +1, dexamethasone-21-phosphate disodium, desoximethasone +1, betamethasone dipropionate +2 and methylprednisolone aceponate +1. When the patch testing was repeated when the patient was being treated with upadacitinib, only fusidic acid +2 and amerchol L 101 +3 remained positive (both at the same reaction levels as during testing while being treated with dupilumab).

Upadacitinib has a short half-life of 8-14 hours.[12] Considering the higher range of the half-life to be 14 hours it would take 70 hours, almost 3 days, to reach a clearance of 5 half-lives. My current practice in the patch testing clinic is, if possible, to discontinue JAK inhibitors 3 days before patch testing and to resume treatment immediately after the final patch testing readout. In many cases, patients either forget to stop taking their JAK inhibitor, or are not counselled to discontinue the medication 3 days before patch testing. In these instances, I discontinue the JAK inhibitor the day of patch testing and resume it immediately after the final readout. I have had a few instances where the patient referred for patch testing does not want to discontinue their JAK inhibitor due to the risk of eliciting a severe flare of atopic dermatitis. In these cases, I try to reduce the dose of their JAK inhibitor to the lowest dose possible (e.g., upadacitinib 15 mg po daily or abrocitinib 50 or 100 mg po daily). I still proceed with patch testing in these individuals. The patient and I have a detailed discussion that their JAK inhibitors may reduce the accuracy of the testing. They will likely experience a downgrading of reactions such as +3 to +2, a +2 to +1, or +1 to an equivocal or negative reaction. However, does it truly matter in a clinical setting if we are losing these weaker reactions? Presumably, the JAK inhibitor is doing its job and these weak allergens are not contributing to the patient's ongoing flares. The allergen is still able to elicit a positive reaction, albeit an attenuated one, while on JAK inhibitors; it is likely still relevant to the patient's ongoing flares. Additional studies are needed in this area to further elucidate this matter.

Conclusion

This paper provided real-world insights on how a dermatologist should counsel a patient who is about to undergo patch testing with respect to their topical and systemic treatments.

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