Patch Testing in Patients With Severe Atopic Dermatitis Treated With Dupilumab: A Multicentric Approach in Spain

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Abstract: ***Background:*** **Persistent localized dermatitis (PLD) or eczema flare-ups (EF) may occur in atopic dermatitis (AD) patients treated with dupilumab. They may reflect concomitant allergic contact dermatitis (ACD) exposed by the inhibition of the Th2 pathway by dupilumab in some cases.**

Objective: **To evaluate the prevalence and etiology of these events and the impact of dupilumab on patch test outcome.**

Methods: **We performed patch tests on 54 AD patients treated with dupilumab and evaluated the prevalence and final diagnosis of EF and PLD as well as the patch test results.**

Results: **The patch test results were positive in 20/54 (37.0%). 21/54 patients (38.9%) had PLD and 12/54 (22.2%) had EF. Ten of 54 (18.5%) had both conditions and 11/54 (20.4%) had neither PLD nor EF. 64.5% of PLD involved the face. 83.9% patients with PLD and 90.9% patients with EF were diagnosed with inadequately controlled AD. 9.7% patients with PLD and 4.5% patients with EF were finally diagnosed with ACD. Nine of 21 (42.9%) patients patch tested twice were positive either before and/or during dupilumab. Patch tests results changed over time in all of them.**

Conclusions: **Patch testing assisted us to exclude ACD as the cause of PLD/EF in AD patients treated with dupilumab. Most PLD and EF were, however, diagnosed as poorly controlled AD. Dupilumab appeared to impact the patch test outcomes.**

Capsule Summary

- The main cause of persistent localized dermatitis (PLD) and eczema flare-ups (EF) during dupilumab treatment is poorly controlled atopic dermatitis.
- Patch testing, although there were various results, it is useful to detect some cases of allergic contact dermatitis as a cause of EF and PLD.

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BACKGROUND

Atopic dermatitis (AD) is a chronic inflammatory disorder caused by the combination of alterations in the cutaneous barrier with an inflammatory reaction generally mediated by T-helper 2 (Th2) lymphocytes.[1,2]

The relationship between AD and allergic contact dermatitis (ACD) is controversial. Traditionally, ACD has been considered to be a delayed-type hypersensitivity reaction mediated by Th1 lymphocytes,[2] unlike AD, mainly mediated by Th2 lymphocytes. Therefore, it was traditionally believed that patients with AD were less likely to have ACD.[3] This assumption has been refuted by some studies.[4] Furthermore, some allergens (eg, fragrances, rubber chemicals, and preservatives) tend to elicit ACD reactions with a more pronounced Th2 participation.[5,6] A subset of Th2 cells that produces interleukin (IL) 9 is upregulated in both AD and ACD,[7] and Th17 involvement may be present in both conditions,[8] although the inflammatory profile may be a variable depending on the duration of the lesion.[8]

Dupilumab is the first monoclonal antibody approved for the treatment of severe AD. It blocks the IL4RA receptor, preventing the IL-4 and IL-13 from binding and inhibiting the Th2 signaling pathway.[9] In addition, dupilumab has been used with acceptable efficacy in refractory ACD involving individuals sensitized to a wide variety of allergens.[10,11]

The response of ACD to therapy with dupilumab is, however, heterogeneous. An association with the allergens that produce Th2-mediated inflammation was not observed as would be expected, as a result of the dupilumab inhibitory effect on the Th2 pathway.[12]

Frequently, patients treated with dupilumab for severe AD present with eczematous flare-ups (EF) or with areas particularly refractory to treatment, usually on the face. They are usually called persistent localized dermatitis (PLD). Although they can affect any location,[13–15] most studies on EF and PLD have focused exclusively on those involving the head and neck. According to these studies, although the inclusion criteria are heterogeneous and the data are retrospectively reviewed, EF and PLD involve between 4.2% and 23% of patients treated with dupilumab, respectively.[16–18] Both events could represent an indication to perform patch tests to rule out ACD as its underlying cause.[19] In addition, the application of patch tests and their interpretation in patients with severe AD presenting with active diffuse inflammation is very challenging. These drawbacks may be overcome by performing patch tests during treatment with dupilumab once lessening of the inflammation and recovery of disease-free areas is achieved.

The main aim of this research is to evaluate the frequency and underlying diagnosed cause of EF and PLD in patients treated with dupilumab for severe AD and to evaluate the impact of dupilumab on the outcome of the patch tests.

METHODS

We evaluated 54 consecutive patients treated with dupilumab for severe AD (Eczema Area and Severity Index >21 before the initiation of treatment) who agreed to participate in the study (in 15 dermatology departments across Spain), from September 2019 until March 2020. They were patch tested with the Spanish Contact Dermatitis Research Group (GEIDAC) Baseline Series[20] (Table 1). Patch tests were applied on lesion-free skin of the back for 48 hours, read on days (D)2 and D4, and interpreted by each researcher following the European Society of Contact Dermatitis criteria.[21] All patients avoided systemic immunosuppressive drugs other than dupilumab or topical medications applied on their backs for at least 2 weeks before the patch tests were performed.

In addition, we evaluated the features of the population (age, gender, clinical features, evolution, anatomical distribution, exposure to allergens, etc.), variables related to treatment with dupilumab (total cumulative dose and duration), as well as the results of the patch tests (positive results, strength of the reactions, clinical relevance, and time passed from the initial dose of dupilumab to the patch tests). If the patients had patch tests before starting dupilumab, these were also evaluated (including time passed from the prior patch tests to the initial dose of dupilumab).

TABLE 1. Allergens in the GEIDAC Baseline Series

1.	Nickel sulfate 5% pet
2.	Wool alcohols 30% pet
3.	Neomycin sulfate 20% pet
4.	Potassium dichromate 0.5% pet
5.	Caine mix 7% pet
6.	Fragrance mix I 8% pet
7.	Colophony 20% pet
8.	Epoxy resin, bisphenol A 1% pet
9.	Methylisothiazolinone 0.2% aq (2000 ppm)
10.	Myroxylon pereirae 25% pet
11.	Ethylenediamine dihydrochloride 1% pet
12.	Cobalt chloride 1% pet
13.	*p-tert*-Butylphenol formaldehyde resin 1% pet
14.	Paraben mix 16% pet
15.	Carba mix 3% pet
16.	*N*-Isopropyl-*N*-phenyl-*p*-phenylenediamine 0.1% pet
17.	Methylchloroisothiazolinone/methylisothiazolinone 0.02% aq (200 ppm)
18.	Quaternium 15 1% pet
19.	Mercaptobenzothiazole 2% pet
20.	Paraphenylenediamine 1% pet
21.	Formaldehyde 2% aq
22.	Mercapto mix 2% pet
23.	Imidazolidinyl urea 2% pet
24.	Thiuram mix 1% pet
25.	Diazolidinyl urea 2% pet
26.	Sesquiterpene lactone mix 0.1% pet
27.	Tixocortol-21-pivalate 0.1% pet
28.	Budesonide 0.01% pet
29.	Methyldibromo glutaronitrile 0.5% pet
30.	Fragrance mix II 14% pet
31.	Hydroxyisohexyl 3-cyclohexene carboxaldehyde 5% pet
32.	2-Phenoxyethanol 1% pet

GEIDAC, Spanish Contact Dermatitis and Skin Allergy Research Group; aq, aqueous solution; pet, petrolatum; ppm, parts per million.

The prevalence of PLD and EF was evaluated. PLD was defined as eczematous reactions involving areas previously affected by the disease that did not clear up following the administration of dupilumab and, were still present, at the time of evaluation. EF was defined as new lesions arising on previously unaffected or healed skin. Underlying causes of PLD and EF were diagnosed by each researcher according to clinical criteria (clinical features, evolution, anatomical distribution, exposure to allergens, etc.) and patch test investigations. The frequency of ACD according to the patch test results was evaluated.

The program Statistical Package for the Social Sciences (SPSS, IBM Corp., Armonk, NY) version 25.0 was used to analyze the data. Continuous variables were expressed as median and interquartile ranges and categorical variants in percentages.

Informed consent for participation was obtained from all patients who also agreed to the publication of the results. This study has been reviewed and approved by the Drug Research Ethics Committee (CEIm) of the Guadalajara University Hospital.

RESULTS

Prevalence of PLD and EF

We included 54 patients treated with dupilumab: 38.9% female, mean age: 40.0; interquartile range (IQR): 22.7. Features such as gender, median age, age of onset of AD as well as dupilumab treatments, duration, and total cumulative dose are summarized in Table 2.

Thirty-one patients (57.4%) presented with PLD (Table 3). In 20 of them (64.5%) PLD was localized on the face. After performing patch tests, PLD was attributed to AD in 26 patients (83.9%), to ACD in 3 patients (9.7%), and to other diagnoses in 2 patients (6.5%).

Twenty-two patients (40.7%) presented with EF (Table 3). Eleven (50.0%) of them had facial involvement. After patch testing, EF was attributed to AD in 20 patients (90.9%), to ACD in 1 patient (4.5%); and to protein contact dermatitis in 1 patient (4.5%).

Ten patients (18.5%, included in the previous 2 groups) presented with both PLD and EF during dupilumab treatment. Eleven patients (20.4%) had neither PLD nor EF.

TABLE 2. Epidemiological and Clinical Features of the 54 Patients with Severe Atopic Dermatitis Treated with Dupilumab

Features	N (%) Patients (N = 54)
Gender	
Male	33 (61.1)
Female	21 (38.9)
Other Features	**Median (IQR)**
Age (years)	40.0 (21.8)
AD age of onset (years)	6.0 (19)
Dupilumab total cumulative dose (mg)	11100 (6900)
Dupilumab treatment duration (months)	18 (12)
Time passed from the initial dose of dupilumab to the patch tests performed thereafter (months)	20.5 (12.3)
Time passed from the prior patch tests to the initial dose of dupilumab (months, N = 21)	26 (54.25)

AD, atopic dermatitis; N, number; IQR, interquartile range.

TABLE 3. Persistent Localized Dermatitis and Eczema Flare-Ups Features

Features	N (%) Patients (N = 54)
PLD (patients who also had EF are included)	31 (57.4)
Body sites (there may be different body sites involved concomitantly)	
Face	20 (64.5)
Trunk	6 (11.1)
Lower limbs	6 (11.1)
Antecubital fold	5 (16.1)
Popliteal fold	4 (7.4)
Hands	4 (7.4)
Eyelids	2 (6.5)
Underlying cause	
Atopic dermatitis	26 (83.9)
Allergic contact dermatitis	3 (9.7)
Protein contact dermatitis	1 (3.2)
Rosacea	1 (3.2)
EF (patients who also had PLD are included)	22 (40.7)
Body sites (several may coexist in the same patient)	
Face	11 (50.0)
Trunk	8 (36.4)
Popliteal fold	5 (22.7)
Antecubital fold	4 (18.2)
Eyelids	3 (13.6)
Hands	2 (9.1)
Lower limbs	2 (9.1)
Underlying cause	
Atopic dermatitis	20 (90.9)
Protein contact dermatitis	1 (4.5)
Allergic contact dermatitis	1 (4.5)

EF, eczema flare-ups; PLD, persistent localized dermatitis.

Patch Tests Performed During Dupilumab Treatment

Twenty-one of 54 (38.9%) patients had at least 1 positive reaction, with a total of 32 positive patch test reactions. Sensitization and their relevance are summarized in Table 4. Nickel sulfate, methylchloroisothiazolinone/methylisothiazolinone 200 ppm, and potassium dichromate were the most frequent positive allergens. Two patients were positive to allergens belonging to the sphere of fragrances (*Myroxylon pereirae* and hydroxyisohexyl 3-cyclohexene carboxaldehyde, respectively).

Patch Tests Previous to Dupilumab Treatment

Twenty-one patients of 54 (38.9%) had been additionally patch tested with the GEIDAC baseline series before the initiation of

TABLE 4. Patch Test Results

Features	N (%) of Patients (N = 54)
Patch tests during dupilumab	54 (100)
Results	
At least one positive patch	21 (38.9)
Negative	33 (61.1)
Relevance of positive patch test reactions*	N (%) of positive reactions (N = 32)
Current	4 (12.5)
Past	22 (68.8)
Unknown	6 (18.8)
Allergens	No. of positive reactions
Nickel sulfate 5% pet	7
Methylchloroisothiazolinone/methylisothiazolinone 200 ppm aq	6
Potassium dichromate 0.5% pet	5
Carba mix 3% pet	3
Methylisothiazolinone 2000 ppm aq	3
Budesonide 0.01% pet	2
Sesquiterpene lactone mix 0.1% pet	2
Cobalt chloride 1% pet	1
Methyldibromoglutaronitrile 0.5% pet	1
Myroxylon pereirae 25% pet	1
Hydroxyisohexyl 3-cyclohexene carboxaldehyde 5% pet	1
Patch tests before initial dose of dupilumab	N (%) of patients, 21 (38.9)
Results	
At least one positive patch test reaction	6 (28.1)
Negative	15 (71.4)
Relevance of positive patch test reactions	N (%) of positive reactions (12)
Current	3 (25.0)
Past	5 (41.7)
Unknown	4 (33.3)
Allergens	No. of positive reactions
Potassium dichromate 0.5% pet	3
Nickel sulfate 5% pet	2
Cobalt chloride 1% pet	2
N-Isopropyl-*N*-phenyl-*p*-phenylenediamine 0.1% pet	1
Mercaptobenzothiazole 2% pet	1
p-tert-Butylphenol formaldehyde resin 1% pet	1
Tixocortol 21 pivalate 0.1% pet	1
Methyldibromoglutaronitrile 0.5% pet	1

**Clinical relevance of the patches during dupilumab is referred to eczema flare-ups and PLD.*

dupilumab. Before dupilumab, we observed 12 positive patch tests to 8 different allergens involving 6 (28.6%) patients (Table 4). Three of them were considered to have current relevance regarding past contact reactions. Before dupilumab treatment, sensitizations to potassium dichromate, nickel sulfate, and cobalt chloride were more frequent than during the treatment. Methylchoroisotiazolinone/methylisothiazolinone 200 ppm, methylisothiazolinone 2000 ppm, and fragrance allergy markers were negative in all.

In 9 patients (9/21; 42.8%) with a double set of patch tests, the results of the patch tests performed before the introduction of dupilumab differed from the results of those performed during dupilumab: in 4 patients, new positive allergens were detected in the patch tests during dupilumab; in 4 patients, previously positive allergens became negative during dupilumab; and, in 1 patient, some previously positive patch reactions were not reproducible, whereas other allergens became positive. The only cases with no changes in the patch tests over time involved 12 individuals of whom the patch tests were negative both times.

Before dupilumab, we found 12 positive patch tests to 8 different allergens involving 7 patients. Of them, 8/12 (66.7%) became negative after dupilumab was initiated. In addition, among patients with a double set of patch tests, we found, after the initiation of dupilumab, 11 positive patch tests to 6 different allergens involving 4 patients. Of them, 7/11 (63.6%) became positive after initiating dupilumab. Pairs of allergens patch tested twice with positive results either before or during dupilumab are summarized in Tables 5 and 6.

Among newly positive patch test reactions, we detected novel responses to nickel sulfate that had not been detected previously, involving 4 patients. Three of them recalled long-term episodic eczematous reactions from jewelry starting before dupilumab initiation, thus past relevance was established.

TABLE 5. Allergens With At Least One Positive Result Among Patients Investigated With Two Sets of Patch Tests (Patch Tested Both Before and After Dupilumab Initiation)

Patient	Allergen	Patch Tests Before Dupilumab Initiation	Patch Tests After Dupilumab Initiation	Relevance	Type and Location of Lesions	Final Diagnosis
1	Mercaptobenzothiazole 2% pet	++	–	Past	EF legs	AD
2	Nickel sulfate 5% pet	–	++	Past	EF face, trunk	AD
	Carba mix 3% pet	–	+	Past		
3	Potassium dichromate 0.5% pet	++	+++	Past	PLD face	AD
	p-tert-Butylphenol formaldehyde resin 1% pet	++	–	Past		
4	Nickel sulfate 5% pet	–	++	Current	PLD face, hands, EF trunk	AD + ACD hands Improved with avoidance
5	Nickel sulfate 5% pet	–	+++	Unknown	PLD legs, EF arms	AD
6	Tixocortol 21 pivalate 0.1% pet	++	–	Unknown	PLD face, EF trunk	AD
	Carba mix 3% pet	–	+	Unknown		
	Sesquiterpene lactone mix 0.1%pet	–	+	Unknown		
7	Nickel sulfate 5% pet	++	–	Current	PLD face, EF trunk	AD+ACD
	Cobalt chloride 1% pet	++	++	Current		Improved with avoidance
	Potassium dichromate 0.5% pet	++	++	Current		
8	Nickel sulfate 5% pet	–	++	Past	No lesions	—
	Methyldibromoglutaronitrile 0.5% pet	++	++	Unknown		
9	Nickel sulfate 5% pet	++	–	Past	No lesions	—
	Cobalt chloride 1% pet	++	–	Past		
	Potassium dichromate 0.5% pet	++	–	Unknown		
	N-Isopropyl-*N*-phenyl-*p*-phenylenediamine 0.1% pet	++	-	Unknown		

Intensity of the reactions is graded according to the International Contact Dermatitis Research Group[34] and the European Society of Contact Dermatitis criteria.[21]

ACD, allergic contact dermatitis; AD, atopic dermatitis; EF, eczema flare-ups; PLD, persistent localized dermatitis.

DISCUSSION

Diagnosed Underlying Cause of PLD and EF

We observed that PLD predominantly involving the face, as previously published,[22] was also a frequent phenomenon in our study population. AD was, after performing patch test investigations, the most frequently diagnosed cause of PLD among our patients. In only 3 patients, (9.7%) PLD was finally attributed to ACD. Raffi et al,[23] in contrast, observed that 91.4% of 35 patients with AD treated with dupilumab had concomitant ACD that improved with allergen avoidance measures. These differences could be due to methodological and regional factors, as well as

TABLE 6. Number of Positive Patch Tests of Allergens With At Least One Positive Result Among Patients Tested Both Before and After Dupilumab Initiation

Allergen	N Only Positive Before Dupilumab	N Only Positive After Dupilumab	N Positive Both Before and After Dupilumab
Potassium dichromate 0.5% pet	1	0	2
Nickel sulfate 5% pet	2	4	0
Carba mix 3% pet	0	2	0
Cobalt chloride 1% pet	1	0	1
N-Isopropyl-*N*-phenyl-*p*-phenylenediamine 0.1% pet	1	0	0
Mercaptobenzothiazole 2% pet	1	0	0
p-tert-Butylphenol formaldehyde resin 1% pet	1	0	0
Tixocortol 21 pivalate 0.1% pet	1	0	0
Methyldibromoglutaronitrile 0.5% pet	0	0	1
Sesquiterpene lactone mix 0.1%pet	0	1	0

N, number of patches.

diverse interpretations of patch tests. We performed patch tests in our AD patients treated with dupilumab, regardless of whether they had active lesions or not, and not only in those who presented PLD/EF. We have not detected a high frequency of sensitization to fragrance and rubber allergens and a low frequency of sensitization to metals as shown by other research.[24–26]

PLD has also been proposed to be related to exacerbations of other disorders (eg, rosacea-like eruptions or seborrheic dermatitis) caused by the inhibition of Th2[17,22,27] pathway induced by dupilumab, which would generate a dominance of other inflammatory pathways. These diagnoses have, however, been exceptional among our patients.

Most of our patients had been receiving long-term treatment at the time PLD was identified (median 18 months, IQR 12.7). Thus, we do not believe PLD is related to a slow response to dupilumab.

In our opinion, PLD and EF may result from the inability of dupilumab to achieve a total and permanent clearance of AD lesions in the majority of our patients.[28]

Influence of Dupilumab on the Patch Test Outcomes

Patch tests usually show a certain degree of variability. Thus, when patch tests are performed twice, only 66.8% of positive results observed the first time can be reproduced overtime.[29] Regarding our AD patients treated with dupilumab, we observed even higher discrepancies between the results of the patch tests performed before the initiation of dupilumab and the patch tests performed during treatment with dupilumab. Only 33.3% of previously positive patch tests remained unchanged during treatment, similar to the frequency reported by Wijs et al.[30]

Unlike that study, we could not find evidence of a positive relationship between the intensity of patch tests performed before the initiation of dupilumab and their reproducibility, since all initial tests involved strong responses ("++"). Raffi et al[23] observed that 51.2% of previous positive patch tests before dupilumab persisted without changes. Likewise, a recent systematic review[12] showed that 49.3% of patch tests persisted unaltered after dupilumab. According to these findings, the authors of both studies conclude that dupilumab does not have a significant influence on the results of patch tests. We, however, consider that a change involving 49%–66% of the patch tests could reflect at least some impact of dupilumab on the test.

There could be at least 3 potential explanations for newly discovered positivity to allergens during treatment with dupilumab. First, false negative patch tests before dupilumab initiation (variations in reproducibility). Second, patients could have become sensitized at some point in time between the first and second patch tests. And third, patients could have already been sensitized before dupilumab was initiated, but the intense polarization toward Th2 during active severe AD would hypothetically have prevented positive reactions from being elicited (initial false-negative patch tests).[17] If this was true, inhibition of Th2-mediated inflammation by treatment with dupilumab may promote the appearance of predominantly Th1-mediated patch test reactions.

Interestingly, we found 4 new patch test reactions to nickel sulfate, which has traditionally been considered the Th1-allergen prototype.[5] Three of 4 patients with newly detected positive patch tests to nickel sulfate recalled a history of intolerance to metallic objects before the initial negative patch test. We believe that these patients were already sensitized to nickel before the first (false negative) patch tests were performed, and thus dupilumab would have contributed to unmasking sensitization to this allergen.

In contrast, patch tests becoming negative with dupilumab have also been previously published.[16] This could be due to a mistaken interpretation of prior irritative tests as allergic (prior false-positive). We could also consider that sensitization to some allergens develops through activation of the Th2 pathway, and dupilumab would inhibit these Th2-mediated ACD reactions. We would expect that the allergens with higher involvement of the Th2 pathway (fragrances, rubber additives, etc.)[9] would become negative during treatment with dupilumab more often than allergens with an apparently higher Th1/Th17 pathway participation (eg, nickel).[9] In this study, we found the loss of positivity to 2 rubber additives. The sample was, however, too small to conclude that dupilumab is able to suppress patch test reactivity to any particular allergen subclass.

Dupilumab has been published as a therapy for ACD with a great response variability regardless of the allergens involved.[31] The changes over time in patch test results were heterogeneous and did not align with the recently proposed paradigm that certain allergens elicit specific immune polarization.

It is possible that polarization toward a certain inflammatory pathway depends not only on the allergen characteristics but also on patient-specific circumstances (such as the status of the AD), as the higher tendency to develop Th2-mediated reactions in atopic patients seems to suggest.[32] The improvement of the cutaneous barrier induced by dupilumab could indirectly lead to clinical improvement regardless of the involved pathway.[31]

The Usefulness of Patch Testing Patients With Severe AD During Treatment With Dupilumab

Despite the results, variability patch tests proved to be a useful tool to detect some cases of concomitant ACD among our patients. Allergen avoidance recommendations contributed to a clinical improvement in said cases as previously reported.[23,31,33] Although dupilumab may impact the outcome of patch tests, it is possible that positive results detected during treatment specifically corresponded to allergens that could still cause clinical ACD reactions despite dupilumab. Thus, theoretically, adherence to avoidance measures regarding these particular allergens would improve the clinical manifestations and quality of life.

Limitations of the Study

The main limitation of this study is the absence of control groups without treatment with dupilumab and without AD to compare the patch test reproducibility. Furthermore, the results may not be completely extrapolated because of the relatively small sample size. In addition, patients who presented with EF and/or PLD lesions during treatment may have been more likely willing to participate in the study and undergo patch tests, generating a potential bias involving the overestimation of the prevalence of EF, PLD, and ACD among AD patients. However, this bias is likely to be less essential than in retrospective chart review studies. Being a multicenter retrospective study, the manufacturers of patch tests were heterogeneous across centers and, unfortunately, not mentioned in all cases.

CONCLUSIONS

Although most cases of PLD and EF were attributed to poorly controlled (dupilumab-refractory) AD, after patch testing ACD was diagnosed as the underlying cause in some patients. Accordingly, it is worthwhile to patch test patients with severe AD treated with dupilumab presenting with PLD or EF to detect concomitant ACD, which may significantly improve through allergen avoidance. Patch test interpretation under these circumstances may, however, be complex.

Treatments that inhibit Th2 pathway (such as dupilumab) as well as the inflammation generated by AD seem to impact the patch test results. This modification in the patch test response induced by dupilumab is highly variable and, according to the results of this study, could be independent of the allergen.

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