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RESEARCH LETTER

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Effects of dupilumab treatment on patch test reactions: A retrospective evaluation

To the Editor,

Atopic dermatitis (AD) and allergic contact dermatitis (ACD) are complex immunological conditions. ACD is a type IV T cell-mediated hypersensitivity reaction that is usually diagnosed through epicutaneous patch testing.[1] Although varying reproducibility rates are reported (56%–96%), it is thought that allergy patch testing is reasonably reproducible as long as methodologic inconsistencies are minimized.[2,3] The relation between AD and ACD is complex and multifactorial.[4] Factors that might play a role include the potentially shared immunological pathways and the downstream effects of Th2 cytokines.[5] Recently, dupilumab, the first biologic for the treatment of AD which inhibits the effects of IL-4 and IL-13, has been approved. Literature about the impact of dupilumab on patch testing is sparse and controversial.[6] However, the reliability might be of clinical relevance in patients developing a paradoxical head and neck erythema during dupilumab treatment.[7] Distinction of ACD from other causes of the erythema (e.g., dupilumab-induced skin reactions; or *Malassezia furfur* and Demodex associated dermatitis) in these patients and patients with a general sub-optimal response to dupilumab treatment might be of great clinical interest.[7] Here, we report on the reliability of patch testing in dupilumab treated AD patients.

We conducted a retrospective cohort study in the Erasmus MC (Rotterdam) and Northwestern Medicine (Chicago). This study was not subjected to evaluation by the local Medical Research Ethics Committees because all data were collected as part of the standard of care. Adult AD patients who had at least 1 positive reaction in a PT conducted before the start of dupilumab treatment, elicited by an allergen that was re-tested during dupilumab treatment (≥12 weeks) were eligible. Detailed results of both PTs including strength of reactions (ICDRG criteria: +++; ++; +;?+; –) had to be available. Patients were treated with dupilumab according to the product label. Patients were excluded if they used systemic glucocorticosteroids or had sun(bed) exposure 2 weeks prior to patch testing; used topical therapy on the test site 48 h prior to testing; or when having eczema on the intended PT area. The use of any other relevant concomitant drugs was recorded. All PTs during dupilumab treatment (second PT), were conducted in our clinics. Allergens that tested positive in the first PT are reported. Details on the allergens and materials that were used can be found in Appendix 1. All tests were interpreted by the same medical team (i.e., ACD-experienced dermatologist and specialized nurses). Possible reactions were read on day 2 and day 3, in accordance with ICDRG recommendations. On day 2, the patches were removed and readings were performed. Patients with patches on their arm could optionally remove the patches themselves. They were asked to mark the patch sites and e-mail standardized photographs directly after removing the patches. On day 3, all patients consulted our dermatologist who determined present reactions. Test results defined as ?+ were considered indeterminate. Patients were informed of the possibility of a delayed reaction and were instructed to make an appointment for day 7 or to (let someone) check the tested sites on day 5–7 and visit our dermatologist the same day in case of (doubtful) signs or symptoms (e.g., itch/burning sensations/erythema/papules/vesicles). Additionally, patients were instructed to continue allergen avoidance during dupilumab treatment, even if all reactions turned negative in the second PT.

Patient characteristics of the 20 patients that were included in our study are shown in Table 1. In the first PT, a total of 37 different allergens elicited 56 positive reactions (+ or stronger), with a median number of 2.5 positive reactions per patient (Table 2, Appendix 2). The median time between PTs was 5.5 years. During the first PT, 2 patients were treated with systemic immunosuppressants (patients 2 and 7).

In the second PT, a total of 13 different allergens elicited a total of 16 positive reactions in 10 patients, with a median number of 0.5 positive reactions per patient (delayed reactions: n = 1, Appendix 2). These allergens included bacitracin, balsam of peru, carbamix, colophony, fragrance mix I and II, mercaptobenzothiazole, mercapto mix, methyldibromo glutaronitrile, methylisothiazolinone, nickel sulphate hexahydrate, potassium dichromate and sesquiterpene lactone (Appendix 2). The second PT was conducted after a mean of 36 weeks of dupilumab treatment, with 3 patients using concomitant systemic immunosuppressants (patient 4, 7 and 15). During the second PTs, 11 patients had recalcitrant eczematous lesions, mainly located in the head-neck area (Table 1). Table 2 shows that 37 (/56 = 66%) reactions that were initially positive turned negative at re-testing. Twelve of these reactions changed from ++ to –, and 25 reactions showed a change from + to –. More than 75% of the reactions of wool alcohols (5/5), food ingredients (2/2), hair products (1/1 = 100%), fragrances

TABLE 1 Patient characteristics

Characteristic	Cohort (*n* = 20)
Age, mean (SD)–years	51 (16)
Female sex–*n* (%)	14 (70)
BMI, mean (SD)[a]	26.4 (6)
Race–*n* (%)	
White	16 (80)
Asian	4 (20)
Age of onset AD	
Median age of onset (IQR)–years	0 (0–12)
0–<2 years–*n* (%)	11 (55)
2–<6 years	2 (10)
6–<18 years	3 (15)
≥18 years	4 (20)
Atopic/allergic conditions–*n* (%)	
Asthma	12 (60)
Allergic (rhino)conjunctivitis	16 (80)
Food allergy	10 (50)
Family history–*n* (%)	
Atopic dermatitis[b]	9 (45)
Asthma[b]	8 (40)
Allergic (rhino)conjunctivitis[c]	11 (55)
Time between patch tests, median (IQR)–years	5.5 (2–8)
Duration of dupilumab treatment at time of second patch test, mean (SD)–weeks	36 (15)
Clinic (second patch test)	
Erasmus MC University Medical Center, Rotterdam	16 (80)
Northwestern Medicine, Chicago	4 (20)
Distribution of recalcitrant dermatitis prior to dupilumab treatment–*n* (%)[d]	
Generalized	4 (20)
Hand	9 (45)
Head-neck	10 (50)
Feet	4 (20)
Distribution of recalcitrant dermatitis during dupilumab treatment–*n* (%)[d]	
Generalized	1 (5)
Hand	2 (10)
Head-neck	7 (35)
Feet	2 (10)
No recalcitrant dermatitis[e]	9 (45)

Note: Missing data: [a]*n* = 6 (6%), [b]*n* = 2 (13%), [c] *n* = 3 [d]Multiple recalcitrant locations in one patient possible (prior to dupilumab: 2 locations: *n* = 5; 3 locations: *n* = 1 / during dupilumab: 2 locations: *n* = 1) [e]Reason for repeated testing is concern for ongoing contact hypersensitivity by the patient and physician.

Abbreviations: AD, atopic dermatitis; BMI, body mass index; IQR, interquartile range; SD, standard deviation.

Key message

- Patch test reactions during dupilumab treatment showed a reproducibility rate of 29%.
- Reproducibility rates were higher for initially extreme (+++) or strong positive (++) reactions.
- Patch test reactions might be suppressed during dupilumab treatment, possibly leading to false-negative reactions.

(10/13) and topical medications (4/5) turned negative at re-testing. In contrast, metals (6/10), preservatives (5/7), rubber (2/6), fabric dyes (0/1) and adhesives (1/3) turned negative in <75% of the reactions (Appendix 2). Additionally, 7 reactions remained the same (+: *n* = 6, ++: *n* = 1). Nine patients showed a decrease in reaction intensity from +++ to ++ (*n* = 2) and ++ to + (*n* = 7). Three initially positive reactions turned into an indeterminate (?+) reaction. None of the patients had stronger patch test reactions during dupilumab treatment. The reproducibility rate for reactions that were determined extreme positive (+++) in the first PT was 100% (2/2), although reactions turned out to be weaker (both ++) in the second PT (Table 2). Additionally, 40% (8/20) of the strong positive reactions (++, *n* = 20) in the first PT, remained positive in the second PT, with a weak positive reaction (+) in 88% (7/8). The weak positive reactions (+, *n* = 34) in the first PT showed a lower reproducibility rate in the second PT, namely 18% (6/34). Patients who had recalcitrant lesions during dupilumab treatment showed higher reproducibility rates (36%) compared to patients without recalcitrant lesions (17%).

In our study, only 16 (16/56 = 29%) positive reactions could be replicated upon repeated patch testing during dupilumab treatment. Although positive patch test reactions in patients using dupilumab and conventional systemic immunosuppressants have been reported, the effect of these drugs on the accuracy of patch testing has not been well-established.[8] The high percentage (71%) of positive patch test reactions that could not be replicated during dupilumab treatment in our patients might be the result of the anti-inflammatory effect of dupilumab treatment, resulting in false-negative patch test reactions. Although Dhingra et al.[5] reported on distinct T cell polarization responses to different allergens, we did not observe different reaction patterns between allergens thought to be Th1/Th17 versus Th2 inducing (Appendix 3). Our observation that weak positive reactions (+) showed a lower reproducibility rate compared to stronger reactions (++,+++) is in line with results from a recent study.[3]

Recent literature about clinical effects of dupilumab on ACD varies from complete clearance of ACD to continuing recalcitrant lesions.[8,9] Although the underlying immunological pathways in ACD and AD are not the same, they are largely overlapping. This might explain why targeting the shared Th2 pathway could reduce ACD severity.

TABLE 2 Results of epicutaneous patch tests conducted prior to (PT1) and during dupilumab treatment (PT2)–stratified by results of PT1

		Patch test during dupilumab (PT2)					
		–	+	++	+++	?+	Total
Patch test prior to dupilumab (PT1)	+	25	6	0	0	3	34
	++	12	7	1	0	0	20
	+++	0	0	2	0	0	2
Total		37	13	3	0	3	56

Note: Presentation of results is in accordance with the recommendations of the ICDRG criteria: –, negative reaction; +, weak positive reaction; ++, strong positive reaction; +++, extreme positive reaction; ?+, doubtful reaction.

This suggests that there could be a therapeutic role for dupilumab in the treatment of patients with (comorbid) ACD who are not able to avoid their allergens, for example, due to work circumstances. Future studies investigating patch test reactions in patients who discontinued dupilumab treatment and evaluation of the effect of dupilumab in patients with recalcitrant ACD would be of added value.

Limitations of this study include the retrospective and unblinded design, the absence of a control group, and the variable period of time between the PTs. However, the period of time between repeated PTs does not (statistically) influence reproducibility rates according to available literature, which was also confirmed in our study.[3] Although we were not able to include an appropriate control group, we compared our rates with reproducibility rates reported in literature (with variable periods between tests), which could serve as a control group. This revealed that our reproducibility rates were much lower compared to the rates reported in literature (Appendix 3). Another possible limitation could be that PTs prior to and during dupilumab are not always conducted in the same hospital. However, reproducibility rates of patients who were patch tested by the same dermatologist before and during dupilumab treatment (n = 12, reproducibility: 28%) or different dermatologists (n = 8, reproducibility: 30%) were comparable. This suggests that our findings could not be explained by a discrepancy in applied reading qualities or—techniques or different staff involved in reading the patch tests. Although patients with recalcitrant lesions showed higher reproducibility rates (36%) compared to patients without recalcitrant lesions (17%), none of the positively tested allergens was unavoidable or of relevance in daily life for these patients which made a relevant contact allergy as a source for these recalcitrant lesions unlikely.

We showed that only 29% of positive patch test reactions observed before dupilumab treatment, could be re-elicited in AD patients using dupilumab treatment. Consequently, this study suggests that patch test reactions in dupilumab treated AD patients might be suppressed, possibly leading to false-negative reactions. Further prospective studies are warranted to elucidate the effect of dupilumab and other systemic immunosuppressive agents on patch testing in patients with AD.

KEYWORDS

allergens and epitopes, allergic contact dermatitis, atopic dermatitis, dermatology

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CONFLICT OF INTEREST

LdW, JvdW, TN and AK declare to have no conflict of interest; JS was a consultant or advisory member for AbbVie, Anaptysbio, Arena, Asana, Boehringer-Ingelheim, Dermira, Dermavant, DS Biopharma, Eli Lilly, Galderma, GlaxoSmithKline, Glenmark, Incyte, Kiniksa, LEO Pharma, Menlo, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., and Sanofi, and a speaker for Regeneron Pharmaceuticals, Inc., and Sanofi; DH was an investigator for LEO pharma, MedImmune/Astrazeneca, Novartis, Sanofi/Regeneron, a consultant for Regeneron/Sanofi, LEO pharma, MedImmune/AstraZeneca, Novartis, Incyte, Janssen, and Pfizer.

AUTHOR CONTRIBUTIONS

Conceptualization: LDW, JVD, TN, JI, AK, DH; Data curation: LDW, JVDW, JI; Formal analysis: LDW; Funding acquisition: N/A; Investigation: LDW, JVDW, JI, AK, DH; Methodology: LDW, DH; Project administration: LDW, JVDW; Resources: LDW, JVDW; Software: LDW; Supervision: DH, TN, AK; Validation: LDW; Visualization: LDW; Writing – original draft: LDW; Writing—review & editing: LDW, JVDW, TN, JI, AK, DH.

ETHICAL APPROVAL

This study was not subjected to evaluation by the local Medical Research Ethics Committees because all data were collected as part of standard of care. Data collection was exempted from evaluation by the local medical research ethics committees (MEC-2017–1123).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in our manuscript (Table 2, Appendix 2). Additional data are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.