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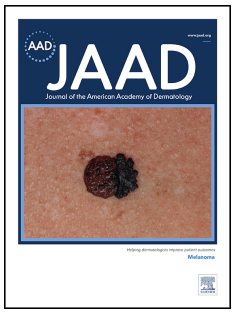

Effect of dupilumab on allergic contact dermatitis and patch testing

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PII: S0190-9622(21)00403-5

DOI: https://doi.org/10.1016/j.jaad.2021.02.044

Reference: YMJD 15713

To appear in: *Journal of the American Academy of Dermatology*

Received Date: 3 August 2020

Revised Date: 1 February 2021

Accepted Date: 15 February 2021

Please cite this article as: Jo CE, Mufti A, Sachdeva M, Pratt M, Yeung J, Effect of dupilumab on allergic contact dermatitis and patch testing, *Journal of the American Academy of Dermatology* (2021), doi: https://doi.org/10.1016/j.jaad.2021.02.044.

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Article type: Research Letter

Title: Effect of dupilumab on allergic contact dermatitis and patch testing

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Funding sources: None

Conflicts of Interest:

Ms. Jo, Dr. Mufti, and Ms. Sachdeva have no conflicts of interest to declare.

Dr. Pratt has been a consultant for Abbvie, Amgen, Celgene, Eli Lilly, Janssen, Leo, Novartis, Pfizer, Sanofi Genzyme, UBC, Valeant.

Dr. Yeung has been a speaker, consultant and investigator for AbbVie, Allergan, Amgen, Astellas, Boehringer Ingelheim, Celgene, Centocor, Coherus, Dermira, Eli Lilly, Forward, Galderma, GSK, Janssen, Leo, Medimmune, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi Genzyme, Takeda, UCB, Valeant, Xenon.

Reprint requests: None

Manuscript word count: 490
References: 5
Tables: 2
Supplemental material: DOI: 10.17632/b74xk7fzgy.1
Keywords: Dupilumab, allergic contact dermatitis, patch test, atopic dermatitis, hand dermatitis, facial dermatitis

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Although the pathogenesis of allergic contact dermatitis (ACD) has been classically thought to predominantly be Th1 driven, its complex pathophysiology is now accepted to include Th2, Th17, and Th22 pathways.[1] Due to the involvement of Th2 pathway, and concomitant ACD diagnosis in many patients with atopic dermatitis (AD), numerous reports have recently reported on the use of dupilumab in patients with ACD.[2] To better understand the effect of dupilumab on ACD and patch testing results, a systematic review was conducted.

This systematic review was registered in PROSPERO (CRD42020193449) and followed PRISMA guidelines.[3] We searched Medline and EMBASE databases on June 20th, 2020 using the following terms: "dermatitis", "allergic contact dermatitis", "hand dermatitis", "facial dermatitis", "patch testing" AND "dupilumab" (Table S1). The search yielded 1099 studies of which 1024 were excluded after title/abstract screening, and 56 were excluded after full-text screening for the following reasons: no history of ACD prior to dupilumab [n=42], study not evaluating effect of dupilumab on ACD/patch testing [n=7], non-primary research article [n=4], non-English article [n=3]. Original studies that reported at least one patient with ACD on dupilumab treatment were included.

From 19 studies, 72 patients (mean age: 54.34 years) with prior history of ACD were included (Table 1). Of the 72 patients, 44 reported on the clinical effects of dupilumab on ACD, 25 on the effects of dupilumab on patch testing, and 3 on both. Of the 47 with clinical results, dupilumab resulted in clearance of ACD for 9, partial improvement for 31, no improvement for 4, and worsening for 3 patients. Of the nine patients who achieved clearance, six had miscellaneous personal care products and two had fragrances as the main clinically relevant allergens on patch testing. Notably in the 18 patients with hand involvement, 17 improved with dupilumab use.

Between the 28 patients with additional post dupilumab patch testing results, the same allergen was tested prior and while on dupilumab in 144 occasions. Of the 144 pairs, 17 were lost and 8 were newly positive, while 71 were persistent (48 unknown) (Table 2). Dupilumab induced inhibition of the Th2 pathway resulting in Th1, Th17 or Th22 polarization may explain the inconsistent patch testing results.[4] Therefore, depending on the response pathway, certain responses may be lost, unaffected, or worsened. For example, through patch testing and subsequent genomic data analysis from biopsies, Dhingra et al. found that nickel had high Th1/Th17 polarization, while fragrance demonstrated strong Th2/Th22 polarization.[1] In alignment with these findings, fragrance and balsam of Peru were two allergens that lost positivity post dupilumab initiation (Raffi et al. -Table 2). Moreover, fragrance and/or balsam of Peru were also clinically relevant allergens in two patients who achieved clearance and seven patients with improvement on dupilumab (Goldminz et al., Jacob et al., Machler et al., and Yang et al. - Table 1).

It is important to note that the primary management is to identify and remove identified allergens especially keeping in mind the cost of dupilumab at this time. However, this review demonstrates the potential for dupilumab use in patients with recalcitrant ACD. Responses to dupilumab may also vary depending on the allergen, which was noted with fragrance and balsam of Peru in our study. Limitations of this review include reliance on case reports and series, small number of patients and patch testing results, non-standardized data and overlapping concomitant skin conditions which may have limited the ability to evaluate the isolated effects of dupilumab on ACD. Moreover, quality assessment using an established tool for case reports/series showed that majority of the studies did not discuss alternative causes that may explain the results.[5] Larger standardized trials are needed to better understand the effects of dupilumab on ACD and patch testing results and to delineate whether certain patients may be better suited for treatment based on potential patterns of allergen specific responses to dupilumab.

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Table 1: Studies reporting patients with ACD on dupilumab treatment

Study	Age, sex	Presentation of ACD	Clinically relevant PT results prior to dupilumab initiation	Efficacy of dupilumab on ACD
1	[1] 83 yo F [2] 69 yo F	[1] trunk and extremities [2] abdomen, buttocks, and all extremities	[2] propylene glycol	[1] 6 mo – IGA 1, BSA 5% [2] 4 mo – IGA 1, BSA 2%
2	[1] 90 yo M [2] 70 yo F	NR	NR – which ones are clinically relevant	[1] 13 week follow up - 90% improvement, BSA <1% [2] week 1: BSA <1%, 2 mo: development of repeated flares
3	42 yo F	Worsening eczema on hands and arms	Colophonium	24 hr after first injection – recall dermatitis to patch testing site
4	[1] 20 yo F [2] 52 yo F [3] 53 yo F	[1] BSA >80%- generalized [2] BSA 40% affecting torso, extremities [3] Hands > face, back, extremities	[1] **rubber accelerators, dyes/formaldehyde resin, cosmetic/preservatives/adhesives** [2] rubber accelerators, dyes [3] hairdresser/dyes, cosmetic/preservatives/adhesives, fragrances	All achieved >90% BSA improvement [1] **within 6 weeks – dramatic improvement, 13 mo – clear** [2] 3-4 weeks – improvement, 3 mo – near clear [3] Near clear since start
5	3M, 2F (mean age: 53)	[1] BSA 60%, mainly hands [2] Generalized dermatitis, accentuation of face, legs [3] Face and eyelid [4] BSA 65% - generalized [5] BSA 45% - eyelids, face, neck, arms, trunk	[1-4] **balsam of Peru, fragrances** [5] nickel	[1] 4 weeks – 90% improvement [2] **4 weeks – Clear** [3] 85% improvement since starting dupilumab [4] 6 weeks – 80% improvement, face recalcitrant [5] 7 days- 50% reduction in pruritus score, 2 mo – 80% resolved, 6 mo – 90% improvement, no itch *[2-5] discontinued AA*
6	44 yo M	2-4 weeks post stent insertion – generalized eczema	Nickel	8 weeks – significant improvement (*despite inability to avoid allergen)*
7	12 yo F	3 mo – severe eczematous dermatitis on face, scalp, neck	Rosin dust pieces	Couple of weeks – significant improvement (*Despite limited ability to avoid allergen)*
8	6M, 9F (mean age 52.6)	-Mean BSA 48% -11/15 – hand involvement	Cocamidopropyl betaine (40%), nickel (33%), oleamidopropyl dimethylamine (27%), myroxylon pereirae (20%), and fragrance mix 1 (20%)	Mean BSA improvement of 85% (range 70-100%)
9	50 yo F	Chronic hand eczema, HECSI score 244/360	NR – which ones are clinically relevant	Week 4 – HESCI score 115/360, Week 16 – almost clear (HESCI score 11/360)
10	63 yo F	5yr worsening of eczema	Formaldehyde	NR
11	40 yo F	3 yr- papulovesicular dermatitis on hands and feet	Nickel sulfate, bronopol, methylisothiazolinone, compositae mix, hydroperoxides of linalool	NR
12	23 patients	NR	NR – which ones are clinically relevant	NR
13	[1] 65 yo F [2] 51 yo M	[1] Sudden widespread eczema on face, arms, hands [2] Face, neck, forearms, hands	Sesquiterpene lactones	[1] 2 weeks – clear on hands and arms. Initial worsening of facial eczema, then slight improvement within 1 mo [2] 1 mo – improvement of eczema
14	3M, 3F (mean age 55.3)	Overlapping AD and ACD: BSA <15%	**Miscellaneous personal care products: hair care products (n=3), emollients and/or eczema care (n=2)**	Within 2-4 mo – all experienced major improvement. **Four with complete clearance.** Two flared after exposure to allergen. *3 completely discontinued AA.*
15	[1] 52 yo F [2] 54 yo F [3] 54 yo F	Overlapping AD and ACD: [1] body, scalp, face [2] chest, face, body ACD only: [3] FD and generalized pruritus	**[3] Sweet Baby Shampoo**	[1] few mo – dramatic improvement, but residual dermatitis on forearms, neck, and face. 2.5 mo – after additional PT, and AA – 75% improvement [2] **1 mo – significant improvement, but residual FD. 2 mo - after PT and AA – clear** [3] **2mo – clear**
16	54 yo M	Generalized photodistributed eczematous eruptions	NR – which ones are clinically relevant	Partial response
17	[1] 66 yo F [2] 28 yo F	NR	NR – which ones are clinically relevant	[1] 7 d – developed severe periocular dermatitis, exacerbation of perioral AD [2] 5.5 mo – AD flare of hands, arms, and first time periocular dermatitis

18	62 yo M	2 yr –anal and genital prur	**toothpaste, deodorant, and shaving cream**	
19	54 yo M	2 mo- hand and feet	MI, MCI/MI, nickel sulfate, 2-n-octyl-4-isothiazolin-3-one, 4,4-dithiodimorpholine	Within weeks – significant improvement

F – female, M – male, yo – years old, yr- year, mo- month, d- day, ACD – allergic contact dermatitis, AD – atopic dermatitis, facial dermatitis – FD, AA – allergen avoidance, NR – not reported, IGA – investigator's global assessment, BSA – body surface area, HECSI – hand eczema severity index, MCI/MI – methylchloroisothiazolinone/methylisothiazolinone, HEMA- hydroxythylmethacrylate, PT – patch testing

Bolded text – to note the main clinically relevant patch testing allergens associated with patients who achieved complete clearance on dupilumab treatment

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Table 2: Patch testing results pre vs post dupilumab initiation

Study	Positive patch testing results pre dupilumab	Positive patch testing results post dupilumab initiation	Comparison of pre/post dupilumab patch test result
1	Formaldehyde	Methylisothiazolinone, dimethylaminopropylamine 1% aqueous	***L**: formaldehyde
2	Multiple allergens including nickel sulfate (2+), bronopol (2+), methylisothiazolinone (3+), compositae mix (1+), and hydroperoxides of linalool (2+)	Previously positive allergens were tested: bronopol (2+) and methylisothiazolinone (3+)	**P:** bronopol, methylisothiazolinone **L:** nickel sulfate, compositae mix, hydroperoxides of linalool
3	125 allergens (fragrances, preservatives, emulsifiers and surfactants, hairdressing, sunscreen, topical therapy, metals, adhesives, varnishes, textile dyes)	Same allergens were tested	**P:** Fragrances (19), preservatives (12), emulsifiers and surfactants (11), hairdressing (2), topical therapy (5), metals (11), adhesives and varnishes (2), textile dyes (2) [64 allergies] **L:** emulsifier/surfactant (propylene glycol 10%, 100% amerchol L101, dimethylaminopropylamine) (4), fragrances (balsam of Peru, fragrance mix 1) (2), sunscreens (sulisobenzone and phenylbenzimidazole-5-sulfonic acid) (2), metals (vanadium [III] chloride and phenyl mercuric acetate) (2), preservative (iodopropynyl butyl carbamate) (1), topical medicament (Bacitracin) (1), resin (tosylamide formaldehyde) (1) [13 allergies]
4	[1] Neomycin sulfate, bacitracin, ethyl acrylate, glutaraldehyde, ammonium persulfate [2] Budesonide, alclometasone-17, 21 dipropionate	[1] Amerchol L101, lanolin alcohol, wool alcohols ointment, kanamycin sulfate, neomycin sulfate, eugenol, lyral, citral, MX-25 Fragrance Mix II, hydroperoxides of linalool, hydroperoxide of limonene, perfume mix [2] budesonide, alclometasone-17, 21 dipropionate, amerchol L101, lanolin alcohol, propylene glycol, stearyl alcohol, trace wool alcohols ointment, trace benzyl alcohol, hydroperoxides of linalool, hydroperoxide of limonene, perfume mix, patient's products (6 different allergens)	[1] ***P:** neomycin sulfate **N:** Fragrance mix, perfume mix, amerchol L101, eugenol, lyral, citral [2]***P:** budesonide, alclometasone-17, 21 dipropionate **N:** Amerchol L101, propylene glycol
5	Nickel sulfate, methylchloroisothiazolinone/ methylisothiazolinone, methylisothiazolinone, 2-n-octyl-4-isothiazolin-3-one, and 4,4-dithiodimorpholine	Repeat testing of only nickel sulfate and methylisothiazolinone: positive results for both	**P:** nickel sulfate and methylisothiazolinone

NR- Not reported, P – persistent, L – lost, N- new

***Limited comparison as same allergens were not tested**

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