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Effect of dupilumab on allergic contact dermatitis and patch testing

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

This systematic review was registered in PROSPERO (CRD42020193449) and followed PRISMA guidelines.[3] We searched Medline and EMBASE databases on June 20, 2020 using the following terms: "dermatitis," "allergic contact dermatitis," "hand dermatitis," "facial dermatitis," "patch testing," AND "dupilumab" (Supplemental Table I; available via Mendeley at https://doi.org/10.17632/b74xk7fzgy.1). 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 the effect of dupilumab on ACD/patch testing (n = 7), nonprimary research article (n = 4), or non-English article (n = 3). Original studies that reported at least 1 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 I). 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 patients with clinical results, dupilumab resulted in clearance of ACD for 9 patients, partial improvement for 31, no improvement for 4, and worsening for 3. Of the 9 patients who achieved clearance, 6 had miscellaneous personal care products and 2 had fragrances as the main clinically relevant allergens on patch testing. Notably, of 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 to, 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 II). 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[1] found that nickel had high Th1/Th17 polarization and that fragrance demonstrated strong Th2/Th22 polarization. In alignment with these findings, fragrance and balsam of Peru were 2 allergens that lost positivity post dupilumab initiation (Study 3; Table II). Moreover, fragrance and/or balsam of Peru were also clinically relevant allergens in 2 patients who achieved clearance and 7 patients with improvement on dupilumab (Study 4, 5, 8, and 18; Table I).

It is important to note that the primary management is to identify allergens and then remove them, 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, a small number of patients and patch testing results, nonstandardized 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 the 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.

Table I. 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 Hours after the 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 the 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	5 yr—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

Continued

Table I. Cont'd

Study	Age, Sex	Presentation of ACD	Clinically relevant PT results prior to dupilumab initiation*	Efficacy of dupilumab on ACD
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 a 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; **4 with complete clearance;** 2 flared after exposure to the 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, bodyACD 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] **2 mo—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 pruritus	**Propylene glycol, fragrance mix 1, patient's toothpaste, deodorant, and shaving cream**	**1 mo—clear**
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

Bold text notes the main clinically relevant patch testing allergens associated with patients who achieved complete clearance on dupilumab treatment. *AA*, Allergen avoidance; *ACD*, allergic contact dermatitis; *AD*, atopic dermatitis; *BSA*, body surface area; *d*, day; *F*, female; *FD*, facial dermatitis; *HECSI*, hand eczema severity index; *HEMA*, hydroxythylmethacrylate; *IGA*, investigator's global assessment; *M*, male; *mo*, month; *MCI/MI*, methylchloroisothiazolinone/methylisothiazolinone; *NR*, not reported; *PT*, patch testing; *yo*, years old; *yr*, year.
*The clinical relevance of an allergen is determined by history and clinical appearance of the dermatitis.

Table II. Patch testing results pre-versus 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

L, Lost; *N*, new; *NR*, not reported; *P*, persistent.
*Limited comparison as same allergens were not tested.

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Conflicts of interest

Dr Pratt has been a consultant for AbbVie, Amgen, Celgene, Eli Lilly, Janssen, Leo, Novartis, Pfizer, Sanofi Genzyme, UBC, and 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, and Xenon. Dr Mufti and authors Jo and Sachdeva have no conflicts of interest to declare.

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Disparities in melanoma stage at diagnosis in Arizona: A 10-year Arizona Cancer Registry study

To the Editor: Although there are known racial disparities concerning melanoma,[1] there is a paucity of data regarding melanoma stage at presentation between white non-Hispanics (WNH) and white Hispanics (WH) in Arizona despite a large WH population and a heavy melanoma burden.[2] The purpose of our study was to evaluate for ethnic disparities in melanoma stage at diagnosis between these 2 populations in Arizona.

We performed a retrospective analysis of patients with cutaneous melanoma from the Arizona Cancer Registry (ACR) from 2007 to 2017.[3] There were underreporting of cases to the ACR during earlier years of the study. Data points obtained included age at diagnosis, sex/gender, race/ethnicity, stage, site, year at diagnosis, and ICD-0-3 site codes C44.0 to C44.9. The ACR uses SEER Summary Staging 2000 for the staging scheme and for the purpose of our analysis, we divided the stages into 3 staging categories: 1) in situ and local; 2) regional; and 3) distant. Bivariable and multivariable polytomous logistic regressions were fitted for the 3 staging categories with in situ and local melanomas as the reference.

A total of 27,727 persons with melanoma were included from the ACR. Patient demographic information can be found in Table I. There were significant differences in age by ethnicity, with the WH population having a higher proportion of younger patients. There was nearly a 2-fold rate of lower limb melanomas in WH versus in WNH. When looking at absolute rates, 23.3% of WH present with regional or distant melanoma compared with only 8.0% of WNH.

The results of our analyses can be found in Table II and include odds ratios (OR). For the bivariable analysis, WH were found to have 2.70 (95% CI, 2.01-3.64) times greater odds of presenting with regional stage melanoma and 4.80 (95% CI, 3.61-6.37) times greater odds of presenting with distant stage melanoma compared to WNH. When looking at the primary site, the lower limb/hip had an OR of 1.93 (95% CI, 1.64-2.27) for presentation at regional stage disease and an OR of 1.45 (95% CI, 1.09-1.92) for presentation at the distant stage.

When controlling for confounders with a multivariable analysis, the disparity in stage at diagnosis between the 2 groups was also reaffirmed (Table II). WH were found to have 2.53 (95% CI, 1.83-3.48) times greater odds of presenting with regional stage