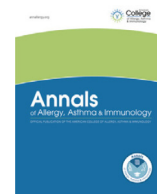




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Letters

Impact of vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on the atopic dermatitis serum proteome



Vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is currently recommended for patients with atopic dermatitis (AD), including those managed with immunomodulatory therapy.^{1,2} Dupilumab, an interleukin (IL)-4R α inhibitor, is most often used in the treatment of moderate-to-severe AD.³ Although available data are limited,^{2,4} there is no evidence to suggest that dupilumab may interfere with the immune response to coronavirus disease 2019 (COVID-19) vaccination, and dupilumab has, in fact, been associated with reduced symptom severity and mortality in patients hospitalized with COVID-19.⁵ Conversely, understanding of the effects of COVID-19 vaccines on AD also remains limited, particularly after the 2-week period, with one study reporting transient AD exacerbations in patients taking dupilumab less than or equal to 2 weeks after vaccination.⁶ It is therefore important to characterize the molecular mechanisms underlying the longer-term effects of immunization against SARS-CoV-2 on AD in the context of dupilumab therapy, which we aim to elucidate in this proteomic study of the blood.

Patients were enrolled with institutional review board–approved consent, and serum samples were collected before and at least 14 days after full vaccination (2 doses of Pfizer-BioNTech or Moderna or 1 dose of Janssen/Johnson & Johnson) between June 2020 and

February 2022. Inclusion criteria included age above or equal to 12 years and a diagnosis of moderate-to-severe AD (defined as currently or previously on systemic therapy [oral or injected immunomodulatory medications or phototherapy] or candidate for systemic therapy), as previously reported.⁴

Serum samples were centrifuged and stored at -80°C . Aliquots were subsequently processed with the OLINK Proseek multiplex ultrasensitive platform using the following 7 custom panels: inflammation, cardiovascular disease II, cardiovascular disease III, neuroinflammation, cardiometabolic, oncology II, and development (644 measured protein products), similar to prior work.⁷

Analyses were performed using R language (R-project.org) and bioconductor project packages (www.bioconductor.org), as previously described.⁷ Protein expression profiles were fitted to linear models using the R limma framework.⁸ *P* values were adjusted for multiple hypotheses using the Benjamini-Hochberg procedure to control for false discovery rates (FDRs). Differentially expressed proteins (DEPs) were defined with an absolute fold-change greater than 1.2 and an FDR less than 0.1.

A total of 119 samples were obtained from 68 patients. Treatment groups were defined as follows (*n* denotes number of samples): limited (topicals/no treatment; prevaccine [Sample 1], *n* = 8; postvaccine [Sample 2], *n* = 9) and dupilumab (prevaccine, *n* = 52; postvaccine, *n* = 50). Patients on dupilumab had been receiving treatment between 3.3 and 45.7 months at the time of vaccine series completion. No significant differences between treatment groups were found in age, time between completion of vaccine series and sample 2 collection, sex, or vaccination type (Pfizer-BioNTech, Moderna, or Janssen/Johnson & Johnson). In patients for whom clinical severity data were available (investigator's global assessment [IGA] and body surface area [BSA] [%]), average IGA was significantly greater in the limited treatment group (*n* = 7) than in the dupilumab group (*n* = 45), whereas BSA was similar between groups. Further demographic information is provided in Table 1.

A total of 2 DEPs (IL-4R, IL-4) were found in intra- and inter-treatment group comparisons. No markers were significantly modulated with vaccination in either treatment group (Fig 1), though direction of change was noted to be positive postvaccination for more markers in the limited group than in the dupilumab group. There were also a small number of significant prevaccination intertreatment group comparisons: IL-4 and IL-4R were up-regulated in patients receiving dupilumab relative to limited therapy (Fig 1), and IL-4R was also found to be up-regulated in the dupilumab group relative to the limited group postvaccination. A subgroup analysis with patients with clinical severity scores, adjusted for IGA and BSA, was consistent with these results.

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Table 1
Patient Demographics

Parameter	Limited n = 10		Dupilumab n = 58		P value
Age (y)					
Mean (SD)	37.5 (14.4)		43.4 (19.3)		.28
Range	19-61				
Time between sample collection (mo)					
Mean (SD)	6.5 (3.7)		7.2 (2.9)		.58
Range	1-12				
Time between vaccine series completion and sample 2 collection (mo)					
Mean (SD)	3.8 (1.9)		3 (2.7)		.31
Range	0.7-6		0.1-11.6		
Duration of treatment at vaccine series completion (mo)					
Mean (SD)	N/A		21.6 (9.5)		
Range	N/A		3.3-45.7		
Duration of treatment at sample 2 (mo)					
Mean (SD)	N/A		26.3 (11.7)		
Range	N/A		6-57		
IGA ^a					
Mean (SD)	2.9 (0.7)		1.1 (0.8)		1.73E-04
Range	2-4		0-3		
BSA (%) ^a					
Mean (SD)	10.9 (11.2)		4.8 (5.2)		.21
Range	1-35		0-28		
Sex	n	%	n	%	
Female	6	60.0%	25	43.1%	.49
Male	4	40.0%	33	56.9%	
Vaccine type	n	%	n	%	
Pfizer	8	80.0%	38	65.5%	.13
Moderna	1	10.0%	19	32.8%	
Janssen/Johnson & Johnson	1	10.0%	1	1.7%	
Race	n	%	n	%	
White	7	70.0%	36	62.1%	.59
Asian	0	0.0%	3	5.2%	
Black	1	10.0%	12	20.7%	
Other	2	20.0%	7	12.1%	
Sample size by treatment group	n	%	n	%	
Prevaccination	8	47%	52	51.0%	.92
Postvaccination	9	53%	50	49.0%	

NOTE. *P* values for age, IGA, BSA, and time between sample collection determined by unpaired *t* tests. *P* values for sex, vaccination type, race, and sample size by treatment groups were calculated with Fisher's exact tests. "Other" race indicates unknown race or that patient declined to specify.

^aIGA and BSA were available for 7 patients in the limited group and 45 patients in the dupilumab-dupilumab group. Subgroup analysis with patients with clinical severity data, adjusting for IGA and BSA, was consistent with unadjusted analysis with the whole cohort.

To summarize, patients on dupilumab, relative to patients on topical or no therapeutics, expressed significantly more IL-4R and IL-4 prevaccination and more IL-4R postvaccination, and no markers, including other T_H2 markers (eg, IL-4, IL-13, IL-10, CCL7, CCL18), were significantly modulated relative to baseline in either treatment group after full vaccination. The increased expression of IL-4R in the dupilumab-treated group relative to the limited-therapy group may, in fact, be an effect of dupilumab itself as internalization of the IL-4R receptor in immune cells⁹ and a compensatory up-regulation of serum IL-4R with prolonged inhibition. The absence of otherwise significant immune modulation in the serum at least 2 weeks after vaccination suggests that COVID-19 vaccination does not seem to induce

proteomic changes relevant to AD pathogenesis, regardless of treatment. Prior work in AD has revealed that pronounced inflammatory protein expression in the skin is accompanied by more modest modulation in the blood,⁷ which may, in part, explain the similarity in limited and dupilumab serum proteomic phenotypes despite differences in baseline severity scores. Additional studies evaluating changes in the skin in the context of COVID-19 vaccination, therefore, may capture more proteomic changes. In conclusion, our report provides molecular context supportive of vaccination against SARS-CoV-2 in patients with AD, without discontinuation of dupilumab. Future studies may expand on our findings with comparisons with more patients, healthy controls, and the inclusion of skin samples.

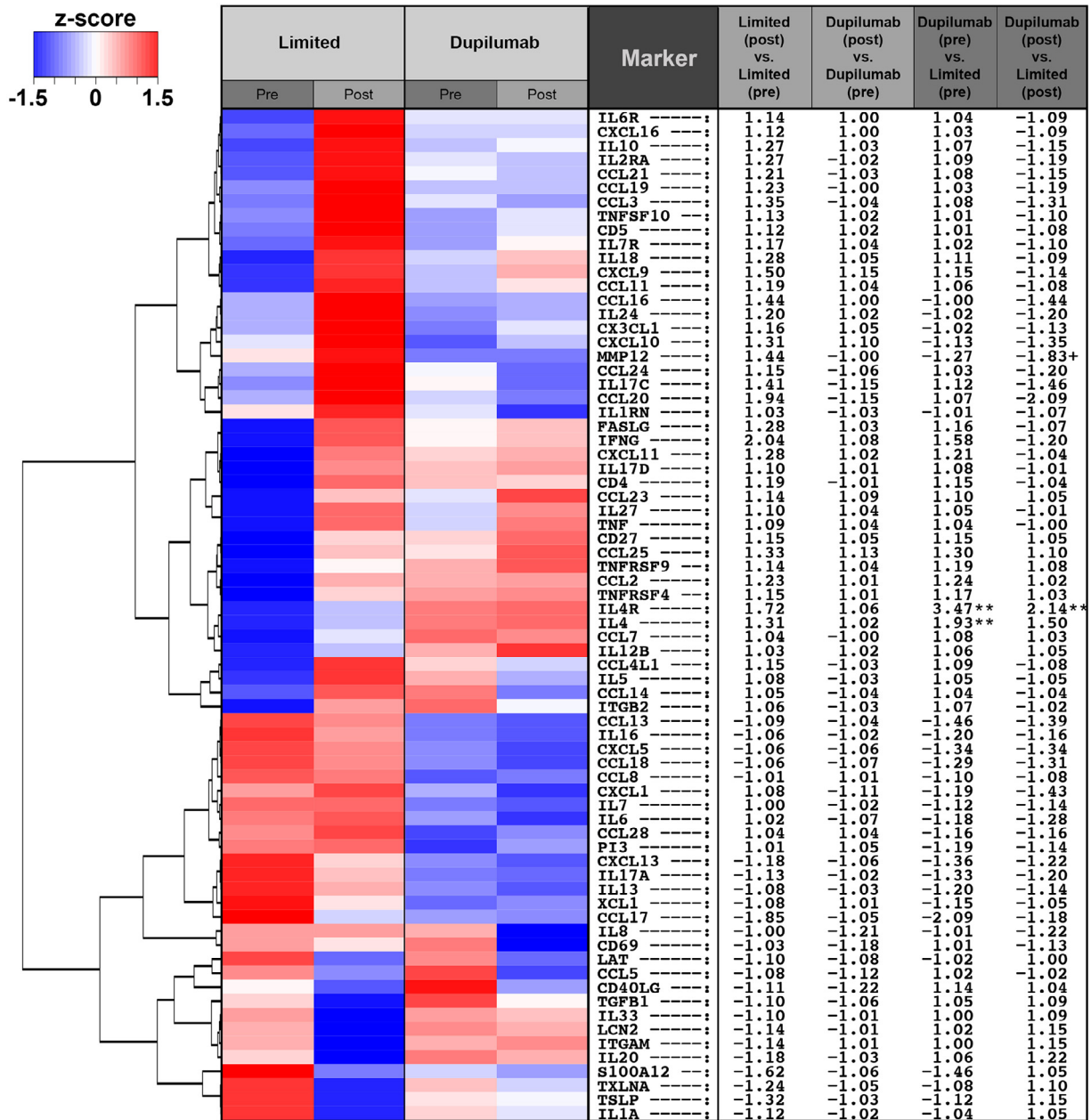


Figure 1. Expression of a subset of previously published immune markers^{7,10} by treatment group and vaccination status for the limited group (n = 10) and dupilumab group (n = 58). Protein expression profiles were fitted to linear regression models, and *P* values were adjusted for multiple comparisons using the Benjamini-Hochberg procedure. Asterisk denotes FDR < 0.05; double asterisks denote FDR < 0.01. FDR, false discovery rate; post, postvaccination; pre, prevaccination.

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Systemic contact dermatitis to peanut ingestion



Delayed cutaneous hypersensitivity with ingestion of an allergen (a form of systemic contact dermatitis) involves a noncutaneous exposure to an allergen that has already been sensitized through the cutaneous route.¹ The exact mechanism for systemic contact dermatitis remains unclear, but it is believed to be mediated by type IV hypersensitivity involving T-cell activation to a hapten.¹ Ingestion of Balsam of Peru and nickel is most frequently implicated in systemic contact dermatitis, with Balsam of Peru most often found in citrus fruits, tomatoes, and spices, and nickel most often found in grains, chocolate, and canned foods.^{1,2} However, typical food triggers for immunoglobulin (Ig)E-mediated hypersensitivity are generally not implicated in systemic contact dermatitis. We present a case of convincing systemic contact dermatitis to peanut ingestion, which has not previously been reported in the literature.

A 26-month-old boy with no significant past medical history presented to allergy clinic for rash after peanut consumption. He had no prior history of atopic dermatitis, asthma, or food allergy.

His first introduction to peanut was Bamba (Osem Food Industries, Shoham, Israel) at 8 months old with no reaction. On the following day, he again consumed Bamba and developed a red, papular, pruritic rash on the face and neck 5 hours after ingestion without associated respiratory, gastrointestinal, or other allergic symptoms. The rash resolved after 2 days and did not require any treatment. At 12 months old, he ate peanut flour and developed a similar delayed rash on the back several hours after ingestion without systemic symptoms. At 24 months of age, he was given peanut butter on bread for 2 consecutive days. On the second day, he developed pruritic, erythematous papules coalescing into plaques on the chin, neck, and back approximately 5 hours after ingestion (Fig 1). The rash resolved after 4 days without any treatment. Before each of the peanut ingestions, he was well and without concurrent illness. There was no reported cutaneous exposure of the peanut product during any episodes of ingestion. He regularly eats and tolerates other major food allergens.

During his allergy visit at 26 months of age, he was well and without any cutaneous findings on examination. Serum and skin prick testing to peanut was performed, and the results revealed low levels of IgE sensitization. The result of his peanut ImmunoCAP (Thermo Fisher Scientific/Phadia, Uppsala, Sweden) was 0.91 kUA/L, Ara h1 0.30 kUA/L, Ara h2 0.53 kUA/L, Ara h3 0.18 kUA/L, and negative Ara h6, Ara h8, and Ara h9 (<0.10 kUA/L). Skin prick testing to peanut resulted in a wheal of 4 mm and a flare of 15 mm with a positive histamine control (4 mm/6 mm). Interestingly, 48 hours after testing, he developed dermatitis at the site of peanut skin prick testing. At a subsequent visit, patch testing was performed on the lower back with peanut, which was prepared with 2 g of peanut powder mixed with 4 mL of sterile water. At 48 hours after application, there



Figure 1. Pruritic, erythematous papules coalescing into plaques on the nape of neck and postauricular regions approximately 5 hours after ingestion of peanut.

was a positive reaction with erythema, infiltration, and papules with persistent papules and erythema at 76 hours after application.

Although the patient had low levels of peanut IgE sensitization on serum and skin prick testing, the clinical symptoms were not consistent with an immediate IgE-mediated hypersensitivity. The presentation was also unique from fixed food eruption to peanut, which has previously been reported.^{3,4} In both previously reported cases of fixed food eruption, the patient presented with a fixed urticarial rash within 2 hours after peanut exposure, which differs from the delayed and more diffuse nature of the rash noted in our patient.^{3,4} The presentation was most consistent with a delayed hypersensitivity, which was confirmed with positive patch testing result. Because the patient did not have a history of atopic dermatitis, we have low suspicion that the positive patch test result was due to exacerbation of eczematous skin lesions. Although peanut can contain nickel, a more common trigger of systemic contact dermatitis, the patient did not develop dermatitis with ingestion of any other high-nickel-containing foods.⁵ This suggests that the delayed hypersensitivity was specific to peanut. To our knowledge, this is the first report of systemic contact dermatitis to peanut ingestion.

Currently, avoidance of the known trigger is the mainstay of therapy for systemic contact dermatitis. The patient's family was interested in pursuing oral challenge and oral immunotherapy as a potential interventional treatment. We found several studies that reported some improvement in symptoms after oral hyposensitization in patients with systemic contact dermatitis to cobalt⁶ and nickel.^{7,8} Mansfield et al⁶ report a patient who developed cobalt systemic contact dermatitis after shoulder joint replacement surgery, who underwent successful oral cobalt desensitization with daily

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