Are blood cytokines reliable biomarkers of allergic disease diagnosis and treatment responses?

Susanne Radonjic-Hoesli, MD, PhD,[a] Nikolay Pavlov, MD,[b] Hans-Uwe Simon, MD, PhD,[c,d] and Dagmar Simon, MD[a]

Bern, Switzerland, and Neuruppin, Germany

With the development of targeted therapies for allergic diseases, the need for biomarkers supporting disease diagnosis and management has increased. Recent research has elucidated the pattern of cytokines and their distinct roles in the pathogenesis of allergic diseases. This means that cytokines should be considered as biomarkers. In this review article, we summarize published findings and critically discuss the use of cytokine measurements in association with disease diagnosis and management. Among the variety of suggested cytokines, thymus and activation-regulated chemokine (TARC) stands out and can indeed serve as a biomarker of atopic dermatitis. Both biologic characteristics and technical issues determine the reliability and limit the use of blood cytokines as biomarkers. (J Allergy Clin Immunol 2022;150:251-8.)

Key words: *Atopic dermatitis, asthma, biomarker, thymus and activation-regulated chemokine, eosinophilic esophagitis, urticaria*

Abbreviations used

AD:	Atopic dermatitis
ASST:	Autologous serum skin test
CCL:	C-C chemokine ligand
CRS:	Chronic rhinosinusitis
CSU:	Chronic spontaneous urticaria
EoE:	Eosinophilic esophagitis
TARC:	Thymus and activation-regulated chemokine
TSLP:	Thymic stromal lymphopoietin
VEGF:	Vascular endothelial growth factor

Efforts in unraveling the pathogenic mechanisms of allergic diseases have resulted in the development of novel targeted therapies. Because patient selection is crucial for the success of these therapies, reliable biomarkers that point to the correct diagnosis, objectively monitor disease activity, indicate treatment response, and define subtypes predicting disease progression are needed. A biomarker is a defined characteristic that is measured as an indicator of normal biologic processes, pathogenic processes, or responses to an exposure or intervention.[1] Blood biomarkers would be ideal, as they are easily accessible. Notably, the standards for validation of biomarkers are high.[1] Multiple clinical trials are required to demonstrate that the relationship between the change in each biomarker and the change in each outcome is generalizable.[1] Here, we critically discuss the reliability of blood cytokines as biomarkers in selected diseases.

AD

For atopic dermatitis (AD), thymus and activation-regulated chemokine (TARC), which is a key chemokine (C-C chemokine ligand 17 [CCL17]) in homing T_H2 cells to the skin, is one of the most studied markers (Table I).[2-45] Direct correlations of TARC levels in the blood with AD severity have been found in both children and adults[4-6,13,16] and confirmed by a meta-analysis.[3] In response to therapy, a decrease in TARC levels has been reported for topical corticosteroids,[5] ciclosporin,[6] mycophenolate sodium,[8] and dupilumab.[11,14] Application of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach revealed that TARC levels in blood show a high level of evidence as a biomarker for AD correlating with its severity.[2] Interestingly, after reduction of ciclosporin therapy, a rise in TARC levels preceded clinical relapse.[6] Notably, in healthy children, physiologic TARC levels are age-dependent, with the highest levels in the age group 0 to 1 year.[46] TARC levels may serve as a diagnostic tool, as they are significantly higher in patients with AD than in patients with psoriasis and healthy controls.[9] However, TARC levels are not only increased in AD, and thus, they might not discriminate from relevant differential diagnoses such as bullous pemphigoid, scabies, cutaneous T-cell lymphoma, or the lymphocytic variant of hypereosinophilic

From [a]the Department of Dermatology and [b]the Department of Pneumology, Inselspital, Bern University Hospital, and [c]the Institute of Pharmacology, University of Bern, and [d]the Institute of Biochemistry, Brandenburg Medical School, Neuruppin.

Research of H.-U.S. is supported by the Swiss National Science Foundation, Switzerland (grant 310030_184816).

Disclosure of potential conflict of interest: D. Simon reports a relationship with AbbVie, AstraZeneca, Galderma SA, LEO, Eli Lilly, Pfizer, and Sanofi that includes consulting or advising, speaking, and lecture fees. H.-U. Simon reports a relationship with GlaxoSmithKline and AstraZeneca that includes consulting or advising. N. Pavlov reports a relationship with AstraZeneca, CSL Behring, GlaxoSmithKline, Novartis, Olympus, OM Pharma, and Sanofi that includes consulting or advising and speaker fees. The remaining author declares that she has no relevant conflicts of interest.

Received for publication March 20, 2022; revised June 13, 2022; accepted for publication June 15, 2022.

Corresponding author: Dagmar Simon, MD, Department of Dermatology, Inselspital, 3010 Bern, Switzerland. E-mail: dagmar.simon@insel.ch.

0091-6749

https://doi.org/10.1016/j.jaci.2022.06.008

TABLE I. Blood cytokines as markers of diagnoses, subtypes, disease severity. and response to therapy in selected allergic diseases

		Diagnostic		Subtypes		Severity		Response to therapy	
Disease	**Cytokine**		**Ref (n)**		**Ref (n)**		**Ref (n)**		**Ref (n)**
AD	**CCL17/TARC**	*Psoriasis*	*4 (60; AD, 20)*				**3 (MA, 4 LT), 2 (R)***		**2 (R)***
						SCORAD	4 (20)	*TCS*	*5 (15)*
		Limitations:				SCORAD	5 (29)	*Ciclosporin*	*6 (7)*
		Scabies	*7 (1; AD, 0)*			LSS	6 (177)	*Ciclosporin, EC-MPS*	*8 (45)*
		Bullous pemphigoid	*9 (29; AD, 0)*			SASSAD	10 (259)	Dupilumab	11 (55)
		Cutaneous T cell lymphoma	*12 (40; AD, 0)*			SCORAD	13 (157)	Dupilumab	14 (36; 35)
		L-HES	*15 (35; AD, 9)*			SCORAD	16 (34)	Dupilumab^{+} TCS	14 (47)
	CCL18/PARC						*2 (R)*		*2 (R)*
	CCL22/MDC						*2 (R)*	*TCS*	*5 (15)*
						SCORAD	*5 (29)*	*Ciclosporin*	*17 (25)*
						SCORAD	*16 (34)*		
	CCL26/eotaxin-3						*2 (R)*		*2 (R)*
								Ciclosporin	*17 (25)*
	CCL27/CTACK						*2 (R)*		
						LSS	*6 (76)*		
						SCORAD	*13 (157)*		
						SCORAD	*16 (34)*		
	CCL13/MCP-4							*Ciclosporin*	*17 (25)*
	CCL2/MCP-1							*Ciclosporin*	*17 (25)*
	CXCL10							*Ciclosporin*	*17 (25)*
	IFN−γ							*Ciclosporin*	*17 (25)*
	IL-13					*SCORAD*	*17 (25)*	*Ciclosporin*	*2 (R)* *17 (25)*
	IL-22					*SCORAD*	*17 (25)*	*Ciclosporin*	*2 (R)* *17 (25)*
Asthma	IL-4			*Atopic vs nonatopic*	18 (77)				
				Persistence to middle age	19 (280)				
	IL-5			*Persistence into adulthood*	*20 (398)*			*Oral CS*	*21 (20)*
	IL-13			*Atopic vs nonatopic*	*18 (77)*	*Mild, moderate, severe*	*22 (128)*		
	IL-25			*Atopic v. nonatopic*	*18 (77)*				
				Corticoid-responsive	*23 (43)*				
				Aspirin-exacerbated	*24 (50)*				
	IL-33			*Allergic vs nonallergc*	*25 (128)*	*Mild, moderate, severe*	*26 (45)*		
				Eosinophilic vs noneosinophilic	*25 (128)*	*Histopathology*	*27 (45)*		
EoE	CCL17/TARC							*Budesonide*	*28 (51)*
	CCL26/eotaxin-3							*Budesonide*	*28 (51)*
	TGF-β	*EoE vs dysphagia of other origin*	*29 (58; EoE 16)*						
Rhinosinusitis	CCL17/TARC							*Dupilumab*	*30 (R)*
									31 (147)
	CCL26/eotaxin-3			*mucosal eosinophils high*	*32 (97)*				

(Continued)

TABLE I. *(Continued)*

		Diagnostic		Subtypes		Severity		Response to therapy	
Disease	**Cytokine**		**Ref (n)**		**Ref (n)**		**Ref (n)**		**Ref (n)**
	BAFF			*CRSwNP subtypes*	*33 (120)*				
				postoperative recurrence in CRSwNP	*33 (120)*				
	IL-17			*CRSwNP*	*34 (50)*	*SNOT*	*34 (50)*		
				high postoperative recurrence	*34 (50)*				
	GM-CSF	*Exacerbated CRSwNP vs sinonasal symptoms of other origin*	*35 (19; 9; 10)*			*LM score*	*35 (9)*		
	VEGF	*Exacerbated CRSwNP vs sinonasal symptoms of other origin*	*35 (19; 9; 10)*			*LM score*	*35 (9)*		
	Periostin			*CRSwNP vs CRSsNP*	*36 (23; 13; 10)*	*Imaging score*	*36 (23)*	*Dupilumab*	*37 (267); 31 (147)*
Food allergy	IL-6	*IgE vs non–IgE-mediated*	*38 (60; 37; 23*					*TED*	*38 (60);*
								OIT	*39 (28)*
	IL-10							*OIT*	*39 (28)*
	IL-2	*FPIES versus IgE-mediated*	*40 (21; 11; 10)*			*Symptomatic FPIES*	*40 (11)*		
	IL-17	*FPIES vs IgE-mediated*	*40 (21; 11; 10)*			*Symptomatic FPIES*	*40 (11)*		
	IL-22	*FPIES vs IgE-mediated*	*40 (21; 11; 10)*			*Symptomatic FPIES*	*40 (11)*		
CSU	IL-6			*Acute vs chronic*	*41 (75; 15; 60)*	*Spontaneous remission*	*42 (58)*	*Omalizumab*	*43 (8)*
	IFN-γ			*SPT^+ vs SPT^-*	*44 (60; 15;15)*			*Omalizumab*	*43 (8)*
	CCL17/TARC							*Active vs remission*	*45 (59)*
	IL-10			*Acute vs chronic*	*41 (75; 15; 60)*				
				$ASST^+$ vs $ASST^-$	*41 (60; 30; 30)*				
	IL-17	CSU vs healthy control	44 (71; 51; 20)	*$ASST^+$ vs $ASST^-$*	*41 (60; 30; 30)*	*Severe vs mild*	*44 (51; 13; 20)*		
	IL-31					*Pruritus*	*44 (51)*		
	IL-33			*IgE^+ vs IgE^-*	*44 (51; 29; 22)*	*Severe vs mild*	*44 (51; 13; 20)*		
	GM-CSF			*$ASST^+$ vs $ASST^-$*	*41 (60; 30; 30)*				

TARC is considered to be a biomarker for clinical severity of AD at baseline and during therapy (bold, roman). For other markers, the reliability has not sufficiently been proved (italic). Numbers indicate the reference, as well as size of patient cohort and subgroups when indicated. For negative data, see the text.

ASST, Autologous serum skin test; *BAFF*, B-cell–activating factor; *CRSsNP*, chronic rhinosinusitis without nasal polyps; *CRSwNP*, chronic rhinosinusitis with nasal polyps; *CTACK*, cutaneous T cell–attracting chemokine; *CXCL10*, C-X-C motif chemokine ligand 10; *FPIES*, food protein–induced enterocolitis syndrome; *L-HES*, lymphocyte-variant hypereosinophilic syndrome; *LM*, Lund-Mackay computed tomography scan score; *LSS*, Leicester severity score; *LT*, longitudinal randomized controlled trials; *MA*, meta-analysis; *MCP*, monocyte chemoattractant protein; *MDC*, macrophage-derived chemokine; *MPS*, mycophenolate sodium; *OIT*, Oral immunotherapy; *PARC*, pulmonary and activation-regulated chemokine; *R*, review; *Ref*, reference; *SASSAD*, Six Area, Six Sign of Atopic Dermatitis; *SCORAD*, Scoring Atopic Dermatitis; *SNOT*, Sino-nasal Outcome Test; *SPT*, skin prick test; *TCS*, topical corticosteroid; *TED*, therapeutic elimination diet; *VEGF*, Vascular endothelial growth factor.

*The overall evidence for TARC as a biomarker correlating with severity is based on GRADE (grading of recommendations, assessment, development, and evaluations): it is very high in adult AD and high in pediatric AD (see Renert-Yuval et al[2]).

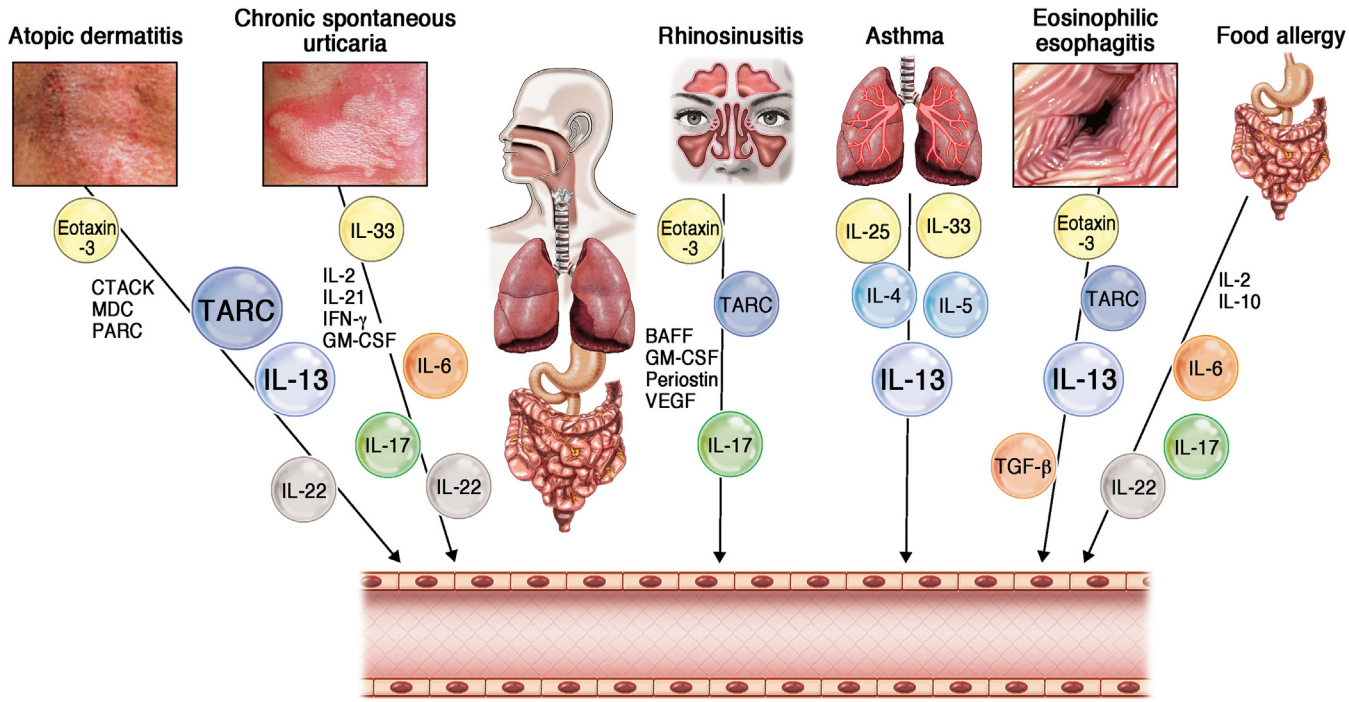

FIG 1. Patterns of potential blood cytokine biomarkers in allergic diseases. Despite disease-typical patterns, the cytokine expression is overlapping. Blood cytokines are not disease-specific and may have their origin from several diseased organs. Thus, concomitant diseases may affect the specificity of cytokines as diagnosis and treatment response markers. Examples of epithelial cells (*yellow*), T_H2 cells (*blue*), T_H17 cells (*green*), T_H22 cells (*gray*), and proinflammatory and anti-inflammatory (*orange*) cytokines are given. *BAFF,* B-Cell–activating factor; *CTACK,* cutaneous T cell–attracting chemokine; *MDC,* macrophage-derived chemokine; *PARC,* pulmonary and activation-regulated chemokine.

syndromes.[7,9,12,15] The presence of respiratory allergic disease does not seem to affect serum levels of TARC.[6]

Compared with TARC, other markers have been studied less intensively. Elevated blood levels of CCL22 and CCL27 have been detected in patients with AD as compared with in healthy controls, and they are correlated with disease severity.[2,5,6] IL-13, a key cytokine in AD pathogenesis and target of novel therapies, may also serve as a potential biomarker. Serum IL-13 and IL-22 levels are increased in patients with AD compared with in healthy controls; they are correlated with disease severity and decrease after treatment.[17,47] The identification of endotypes based on serum markers might have an implication for future precision medicine approaches.[48,49]

ALLERGIC ASTHMA

The immunopathogenesis of allergic asthma is characterized by an armory of mainly T_H2 cytokines.[50,51] Compared with healthy controls, children and adults with asthma have higher serum levels of IL-4, IL-5, IL-13, IL-25, and IL-33 (Table I).[18,25,26,52-55] Elevated IL-25 levels have been reported to indicate aspirin-exacerbated respiratory disease.[24] IL-13 and IL-33 levels are correlated with disease severity,[22,26,27] and higher IL-4, IL-13, and IL-25 levels may differentiate individuals with atopic asthma from those with nonatopic asthma.[18,22,53,54] Persistence of asthma in children and adults may be predicted by elevated levels of IL-5 and IL-4, respectively.[19,20] Clustering of blood markers, including cytokines, revealed endotypes of asthma; however, a correlation with asthma severity or symptom control did not exist.[56,57] After oral corticosteroid therapy for uncontrolled asthma, IL-5 and IL-13 serum concentrations decline, although an elevated IL-5 concentration may persist despite clinical remission.[21,58] In subjects with severe, uncontrolled asthma treated with tezepelumab, which is an anti–thymic stromal lymphopoietin (TSLP) mAb, a reduction of IL-5 and IL-13 levels was noted, suggesting their potential to serve as biomarkers for treatment response.[59] High serum levels of IL-5 are a predictor for frequent exacerbations in children and have been reported to decrease after successful treatment.[60,61] High IL-25 plasma levels have been suggested as an indicator for corticosteroid-responsive T_H2 cell–associated asthma.[23]

In spite of these observations, the reliability of blood cytokines is insufficient for them to serve as biomarkers, and thus, they are not listed among the parameters recommended for the diagnosis and management of allergic asthma.[62] On the other hand, level of fractional exhaled nitric oxide, which is considered to be a surrogate for elevated IL-4 and IL-13 levels,[63] has been proved to be a predictive biomarker for severe asthma exacerbations,[64-66] as well as for treatment responses to inhaled corticosteroids[67] and dupilumab.[68]

EoE

The diagnosis and treatment follow-up of eosinophilic esophagitis (EoE) requires repeated endoscopies and biopsies for histopathologic analysis.[69] Therefore, the need for easily accessible and reliable biomarkers (eg, blood cytokines) is great. By applying a cytokine panel, blood levels of IL-4, IL-5, IL-6, IL-

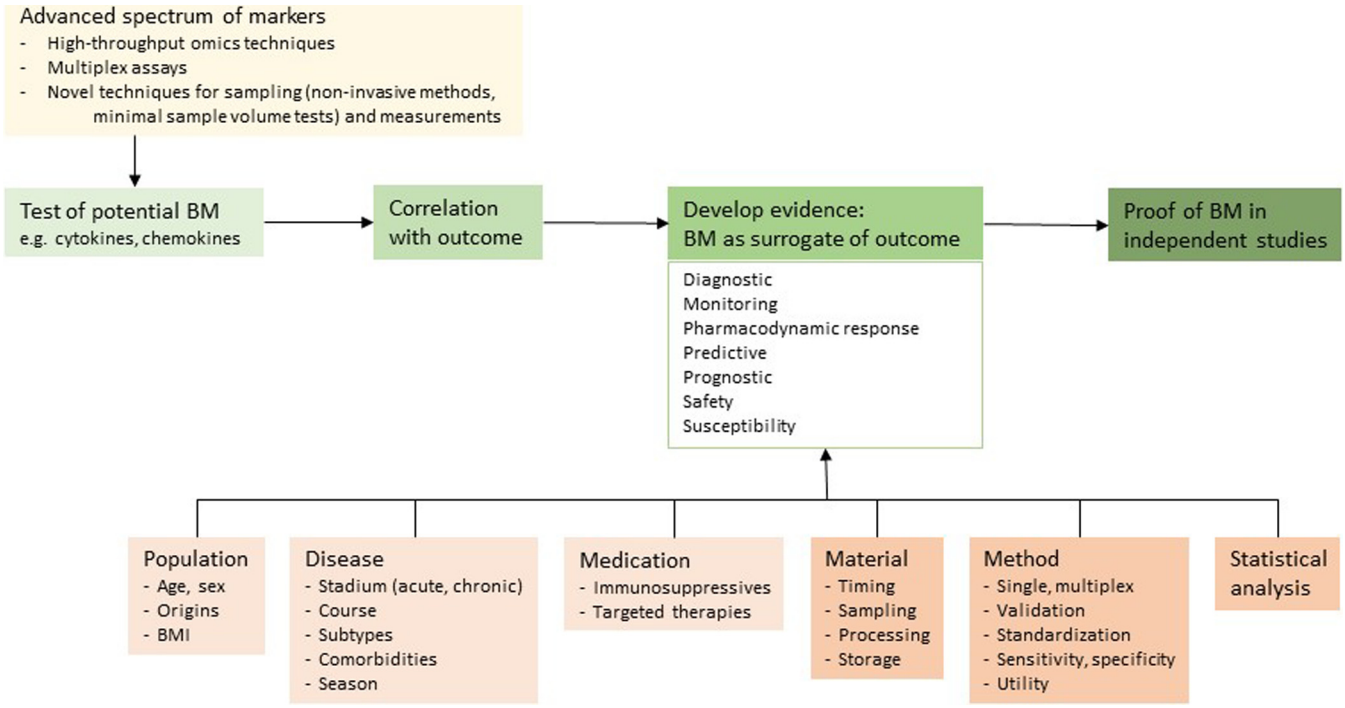

FIG 2. The process of biomarker (BM) development. The identification of potential biomarkers is promoted by novel technologies, allowing efficient screening and unbiased selection. The evaluation and proof of a biomarker require independent studies considering technical and methodologic as well as patient- and disease-related factors. For instance, during biomarker development, evaluation of associations between a biomarker and disease status, as well as demographic or clinical characteristics (such as age, sex, and body mass index [BMI]), or in patients with disease, stage, medication, or other disease characteristics, determine the design of future validation studies.

8, IL-17, IL-13, IL-12p70, CD40L, and IL-1α were found to be significantly increased in patients with EoE compared with in healthy controls, but they are unsuitable to indicate treatment response.[70] Plasma eotaxin-3 level, as well as absolute eosinophil count and eosinophil-derived neurotoxin (EDN) level, were elevated in patients with active EoE compared with in controls, whereas IL-5 level was not.[71] Strikingly, eotaxin levels increased after mepolizumab therapy.[72] Among patients with dysphagia, serum levels of TGF-β were significantly increased in patients with EoE.[29] Both IL-13 and TGF-β decreased after therapy, correlating with an improvement of fibrostenotic and inflammatory severity scores[29] (Table I). Of note, other studies investigating IL-4, IL-5, IL-6, IL-9, IL-13, TGF-α, TGF-β, TNF-α, eotaxin-1, eotaxin-2, eotaxin-3, TSLP, and periostin did not find significant differences between patients with EoE and controls or correlations with treatment response.[73-76] In children with EoE, plasma eotaxin-3 level was significantly increased in patients with EoE, but it was less accurate in distinguishing patients with EoE from controls than was a panel of eosinophil-associated biomarkers, including eotaxin-3 together with absolute eosinophil counts.[77] A systematic review of minimally invasive biomarker studies in EoE revealed inconsistent results. Only eotaxin-3 and TARC levels, as well as absolute eosinophil count, eosinophil cationic protein level, and mast cell tryptase level, could be considered as potential biomarkers discriminating patients with active versus treated EoE.[28]

RHINOSINUSITIS

A recent review concluded that blood cytokines are not applicable as biomarkers for allergic rhinitis and allergen-specific immunotherapy against inhaled allergens.[78] In chronic rhinosinusitis (CRS), mainly tissue markers have been applied to identify endotypes and monitor treatment response.[30] Higher blood levels of IL-17 and B-cell–activating factor have been reported in patients with CRS with nasal polyps than in controls.[33,34] High levels of B-cell–activating factor have been found to predict postoperative recurrence of polyps, whereas GM-CSF and vascular endothelial growth factor (VEGF) indicated disease exacerbation in patients with CRS with nasal polyps[33,35] (Table I). A decrease in blood eotaxin-3, periostin and TARC levels has been observed after dupilumab therapy.[31,37]

FOOD ALLERGY

In patients with food allergy, serum IL-6 levels were shown to discriminate between IgE-mediated and non–IgE-mediated subgroups and to also be correlated with the response to a therapeutic elimination diet.[38] After 6 months of oral immunotherapy in children with cow's milk allergy, an increase in serum levels of IL-6 and IL-10 was reported, whereas IL-4, IL-5 and IL-12p70 levels did not change.[39] A decrease in levels of IL-5 and IL-13 secreted by stimulated PBMCs has been repeatedly observed after oral or sublingual immunotherapy with food allergens, whereas the data

on IL-4, IL-10, TGF-β, and IFN-γ are inconsistent.[79-82] Of note, marked immunologic responses are often transient and have been observed during the initial phases of immunotherapy.[83] Epicutaneous immunotherapy with peanuts resulted in a decrease in the numbers of IL-4– and IL-13–producing T cells in the peripheral blood.[84]

Acute food protein–induced enterocolitis syndrome reactions are associated with a significant elevation of the numbers of T_H17 and innate inflammatory cytokines (IL-17A, IL-22, IL-17C, CCL20, IL-8, oncostatin M, leukemia inhibitory factor, TNF-α, IL-10, and IL-6), which may clearly distinguish them from the asymptomatic status and IgE-mediated food allergy.[40]

CSU

Elevated levels of T_H1 cell–/T_H2 cell– and T_H17 cell–related cytokines have been observed in the blood of patients with chronic spontaneous urticaria (CSU) compared with in the blood of healthy controls.[41-45,85] Subgroup analyses have revealed higher levels of IL-6, IL-10, and IL-13 in acute versus chronic urticaria; higher levels of GM-CSF, IL-10, and IL-17 in autologous serum skin test–positive versus autologous serum skin test–negative CSU; higher levels of IFN-γ, IL-2, IL-12p70, and IL-21 in skin prick test–positive versus skin prick test–negative CSU[41]; and higher levels of IL-33 in IgE-positive versus IgE-negative CSU[44] (Table I). Serum TARC levels were found to be increased in patients with active CSU compared with in healthy controls, with the levels decreasing in the remission phase.[45,85] IL-17 and IL-33 plasma levels were correlated with disease activity, whereas IL-31 was associated with the intensity of pruritus.[44] However, a study that aimed at verifying previous data, did not find any direct correlation between blood levels of TSLP, TNF-β, IL-6 IL-9, IL-33, IL-31, IL-18, VEGF, complement C5a, neopterin, and histamine and disease severity.[86]

CONCLUSION

Even though a number of blood cytokines have been correlated with allergic disease diagnoses and treatment responses, only TARC/CCL17 can be considered a biomarker for AD.[2] Why is the identification of blood cytokines as biomarkers challenging? Allergic diseases are complex and often not restricted to single organs; rather, they are characterized by a systemic inflammation.[17] As blood cytokine levels might be affected by concomitant allergic diseases, their relevance as markers in a certain disease should be evaluated critically[31] (Fig 1). Blood cytokines have been studied mainly in small populations. Moreover, most results have not been verified by independent investigators. As blood cytokines have a very short half-life and their blood levels are relatively low, technical issues (eg, blood sampling and processing, as well as measuring techniques) become important to guarantee quality and reliability of a biomarker (Fig 2). In the future, analyses of blood cytokine panels (eg, multiplex analyses) after a standardized process of blood sampling and/or cytokine expression in tissues obtained by noninvasive methods might overcome these difficulties.

REFERENCES

1. Califf RM. Biomarker definitions and their applications. Exp Biol Med (Maywood) 2018 Feb;243:213-21.
2. Renert-Yuval Y, Thyssen JP, Bissonnette R, Bieber T, Kabashima K, Hijnen D, et al. Biomarkers in atopic dermatitis-a review on behalf of the International Eczema Council. J Allergy Clin Immunol 2021;147:1174-90.
3. Thijs J, Krastev T, Weidinger S, Buckens CF, de Bruin-Weller M, Bruijnzeel-Koomen C, et al. Biomarkers for atopic dermatitis: a systematic review and meta-analysis. Curr Opin Allergy Clin Immunol 2015;15:453-60.
4. Kakinuma T, Nakamura K, Wakugawa M, Mitsui H, Tada Y, Saeki H, et al. Thymus and activation-regulated chemokine in atopic dermatitis: serum thymus and activation-regulated chemokine level is closely related with disease activity. J Allergy Clin Immunol 2001;107:535-41.
5. Fujisawa T, Fujisawa R, Kato Y, Nakayama T, Morita A, Katsumata H, et al. Presence of high contents of thymus and activation-regulated chemokine in platelets and elevated plasma levels of thymus and activation-regulated chemokine and macrophage-derived chemokine in patients with atopic dermatitis. J Allergy Clin Immunol 2002;110:139-46.
6. Hijnen D, De Bruin-Weller M, Oosting B, Lebre C, De Jong E, Bruijnzeel-Koomen C, et al. Serum thymus and activation-regulated chemokine (TARC) and cutaneous T cell- attracting chemokine (CTACK) levels in allergic diseases: TARC and CTACK are disease-specific markers for atopic dermatitis. J Allergy Clin Immunol 2004;113:334-40.
7. Arakawa Y, Tamagawa-Mineoka R, Masuda K, Katoh N. Serum thymus and activation-regulated chemokine levels before and after treatment for pruritic scabies. J Eur Acad Dermatol Venereol 2020;34:817-8.
8. Kwakkel-van Erp JM, Haeck IM, Paantjens AW, van de Graaf EA, van Ginkel WG, Knol MJ, et al. Differential usefulness of biomarkers thymus and activation-regulated chemokine and soluble CD30 during enteric coated mycophenolate sodium and cyclosporine therapy in atopic dermatitis. J Am Acad Dermatol 2010;63:70-7.
9. Kakinuma T, Wakugawa M, Nakamura K, Hino H, Matsushima K, Tamaki K. High level of thymus and activation-regulated chemokine in blister fluid and sera of patients with bullous pemphigoid. Br J Dermatol 2003;148:203-10.
10. Landheer J, de Bruin-Weller M, Boonacker C, Hijnen D, Bruijnzeel-Koomen C, Röckmann H. Utility of serum thymus and activation-regulated chemokine as a biomarker for monitoring of atopic dermatitis severity. J Am Acad Dermatol 2014;71:1160-6.
11. Beck LA, Thaçi D, Hamilton JD, Graham NM, Bieber T, Rocklin R, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. N Engl J Med 2014;371:130-9.
12. Kakinuma T, Sugaya M, Nakamura K, Kaneko F, Wakugawa M, Matsushima K, et al. Thymus and activation-regulated chemokine (TARC/CCL17) in mycosis fungoides: serum TARC levels reflect the disease activity of mycosis fungoides. J Am Acad Dermatol 2003;48:23-30.
13. Song TW, Sohn MH, Kim ES, Kim KW, Kim KE. Increased serum thymus and activation-regulated chemokine and cutaneous T cell-attracting chemokine levels in children with atopic dermatitis. Clin Exp Allergy 2006;36:346-51.
14. Katoh N, Kataoka Y, Saeki H, Hide M, Kabashima K, Etoh T, et al. Efficacy and safety of dupilumab in Japanese adults with moderate-to-severe atopic dermatitis: a subanalysis of three clinical trials. Br J Dermatol 2020;183:39-51.
15. de Lavareille A, Roufosse F, Schmid-Grendelmeier P, Roumier AS, Schandené L, Cogan E, et al. High serum thymus and activation-regulated chemokine levels in the lymphocytic variant of the hypereosinophilic syndrome. J Allergy Clin Immunol 2002;110:476-9.
16. Nakazato J, Kishida M, Kuroiwa R, Fujiwara J, Shimoda M, Shinomiya N. Serum levels of Th2 chemokines, CCL17, CCL22, and CCL27, were the important markers of severity in infantile atopic dermatitis. Pediatr Allergy Immunol 2008; 19:605-13.
17. Ungar B, Garcet S, Gonzalez J, Dhingra N, Correa da Rosa J, Shemer A, et al. An integrated model of atopic dermatitis biomarkers highlights the systemic nature of the disease. J Invest Dermatol 2017;137:603-13.
18. Hasegawa T, Uga H, Mori A, Kurata H. Increased serum IL-17A and Th2 cytokine levels in patients with severe uncontrolled asthma. Eur Cytokine Netw 2017;28:8-18.
19. Zhang J, Walters EH, Tang MLK, Lowe AJ, Lodge CJ, Bui D, et al. Serum cytokine concentrations and asthma persistence to middle age. Allergy 2020;75:2985-8.
20. Fong WCG, Kadalayil L, Lau L, Kurukulaaratchy RJ, Arshad SH. Blood cytokine profiles - potential biomarkers for asthma persistence into adulthood? Pediatr Allergy Immunol 2022;33:13673.
21. Sahid El-Radhi A, Hogg CL, Bungre JK, Bush A, Corrigan CJ. Effect of oral glucocorticoid treatment on serum inflammatory markers in acute asthma. Arch Dis Child 2000;83:158-62.
22. Gaye B, Sikkema D, Lee TN. Development of an ultra-sensitive single molecule counting assay for the detection of interleukin-13 as a marker for asthmatic severity. J Immunol Methods 2015;426:82-5.
23. Cheng D, Xue Z, Yi L, Shi H, Zhang K, Huo X, et al. Epithelial interleukin-25 is a key mediator in Th2-high, corticosteroid-responsive asthma. Am J Respir Crit Care Med 2014;190:639-48.

24. Lee JU, Chang HS, Lee HJ, Bae DJ, Son JH, Park JS, et al. Association of interleukin-25 levels with development of aspirin induced respiratory diseases. Respir Med 2017;123:71-8.
25. Gasiuniene E, Janulaityte I, Zemeckiene Z, Barkauskiene D, Sitkauskiene B. Elevated levels of interleukin-33 are associated with allergic and eosinophilic asthma. Scand J Immunol 2019;89:12724.
26. Bahrami Mahneh S, Movahedi M, Aryan Z, Bahar MA, Rezaei A, Sadr M, et al. Universal Scientific Education and Research Network (USERN). Serum IL-33 is elevated in children with asthma and is associated with disease severity. Int Arch Allergy Immunol 2015;168:193-6.
27. Guo Z, Wu J, Zhao J, Liu F, Chen Y, Bi L, et al. IL-33 promotes airway remodeling and is a marker of asthma disease severity. J Asthma 2014;51:863-9.
28. Hines BT, Rank MA, Wright BL, Marks LA, Hagan JB, Straumann A, et al. Minimally invasive biomarker studies in eosinophilic esophagitis: a systematic review. Ann Allergy Asthma Immunol 2018;121:218-28.
29. Sarbinowska J, Wiatrak B, Waśko-Czopnik D. Searching for noninvasive predictors of the diagnosis and monitoring of eosinophilic esophagitis-the importance of biomarkers of the inflammatory reaction involving eosinophils. Biomolecules 2021;11:890.
30. Gurrola J 2nd, Borish L. Chronic rhinosinusitis: endotypes, biomarkers, and treatment response. J Allergy Clin Immunol 2017;140:1499-508.
31. Hamilton JD, Harel S, Swanson BN, Brian W, Chen Z, Rice MS, et al. Dupilumab suppresses type 2 inflammatory biomarkers across multiple atopic, allergic diseases. Clin Exp Allergy 2021;51:915-31.
32. Yamada T, Miyabe Y, Ueki S, Fujieda S, Tokunaga T, Sakashita M, et al. Eotaxin-3 as a plasma biomarker for mucosal eosinophil infiltration in chronic rhinosinusitis. Front Immunol 2019;10:74.
33. Wang G, Li M, Zheng J, Zhan J, Zheng H, Li R, Wei X. Circulating BAFF as novel biomarker in distinguishing chronic rhinosinusitis with nasal polyps endotypes and predicting postoperative recurrence. Int Immunopharmacol 2022;104:108515.
34. Hussien HA, Habieb MS, Hamdan AM. Evaluation of serum total immunoglobulin E, interleukin-17 and pentraxin-3 as biomarkers for chronic rhinosinusitis with nasal polyposis. Am J Rhinol Allergy 2021;35:640-6.
35. Divekar RD, Samant S, Rank MA, Hagan J, Lal D, O'Brien EK, et al. Immunological profiling in chronic rhinosinusitis with nasal polyps reveals distinct VEGF and GM-CSF signatures during symptomatic exacerbations. Clin Exp Allergy 2015;45:767-78.
36. Asano T, Kanemitsu Y, Takemura M, Yokota M, Fukumitsu K, Takeda N, et al. Serum periostin as a biomarker for comorbid chronic rhinosinusitis in patients with asthma. Ann Am Thorac Soc 2017;14:667-75.
37. Bachert C, Han JK, Desrosiers M, Hellings PW, Amin N, Lee SE, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. Lancet 2019;394:1638-50.
38. Kara M, Beser OF, Konukoglu D, Cokugras H, Erkan T, Kutlu T, et al. The utility of TNF-α, IL-6 and IL-10 in the diagnosis and/or follow-up food allergy. Allergol Immunopathol (Madr) 2020;48:48-55.
39. Salmivesi S, Paassilta M, Huhtala H, Nieminen R, Moilanen E, Korppi M. Changes in biomarkers during a six-month oral immunotherapy intervention for cow's milk allergy. Acta Paediatr 2016;105:1349-54.
40. Berin MC, Lozano-Ojalvo D, Agashe C, Baker MG, Bird JA, Nowak-Wegrzyn A. Acute FPIES reactions are associated with an IL-17 inflammatory signature. J Allergy Clin Immunol 2021;148:895-901.
41. Chen Q, Zhong H, Chen WC, Zhai Z, Zhou Z, Song Z, et al. Different expression patterns of plasma Th1-, Th2-, Th17- and Th22-related cytokines correlate with serum autoreactivity and allergen sensitivity in chronic spontaneous urticaria. J Eur Acad Dermatol Venereol 2018;32:441-8.
42. Kasperska-Zajac A, Sztylc J, Machura E, Jop G. Plasma IL-6 concentration correlates with clinical disease activity and serum C-reactive protein concentration in chronic urticaria patients. Clin Exp Allergy 2011;41:1386-91.
43. Grieco T, Porzia A, Paolino G, Chello C, Sernicola A, Faina V, et al. IFN-γ/IL-6 and related cytokines in chronic spontaneous urticaria: evaluation of their pathogenetic role and changes during omalizumab therapy. Int J Dermatol 2020;59:590-4.
44. Lin W, Zhou Q, Liu C, Ying M, Xu S. Increased plasma IL-17, IL-31, and IL-33 levels in chronic spontaneous urticaria. Sci Rep 2017;7:17797.
45. Zhang L, Qi R, Yang Y, Gao X, Chen H, Xiao T. Serum miR-125a-5p and CCL17 upregulated in chronic spontaneous urticaria and correlated with treatment response. Acta Derm Venereol 2019;99:571-8.
46. Fujisawa T, Nagao M, Hiraguchi Y, Katsumata H, Nishimori H, Iguchi K, et al. Serum measurement of thymus and activation-regulated chemokine/CCL17 in children with atopic dermatitis: elevated normal levels in infancy and age-specific analysis in atopic dermatitis. Pediatr Allergy Immunol 2009;20:633-41.
47. Simon D, Vassina E, Yousefi S, Kozlowski E, Braathen LR, Simon HU. Reduced dermal infiltration of cytokine-expressing inflammatory cells in atopic dermatitis after short-term topical tacrolimus treatment. J Allergy Clin Immunol 2004;114:887-95.
48. Thijs JL, Strickland I, Bruijnzeel-Koomen CAFM, Nierkens S, Giovannone B, Csomor E, et al. Moving toward endotypes in atopic dermatitis: identification of patient clusters based on serum biomarker analysis. J Allergy Clin Immunol 2017;140:730-7.
49. Bakker DS, Nierkens S, Knol EF, Giovannone B, Delemarre EM, van der Schaft J, et al. Confirmation of multiple endotypes in atopic dermatitis based on serum biomarkers. J Allergy Clin Immunol 2021;147:189-98.
50. Zoratti E, Havstad S, Wegienka G, Nicholas C, Bobbitt KR, Woodcroft KJ, et al. Differentiating asthma phenotypes in young adults through polyclonal cytokine profiles. Ann Allergy Asthma Immunol 2014;113:25-30.
51. Bartemes KR, Kita H. Dynamic role of epithelium-derived cytokines in asthma. Clin Immunol 2012;143:222-35.
52. Alexander AG, Barkans J, Moqbel R, Barnes NC, Kay AB, Corrigan CJ. Serum interleukin 5 concentrations in atopic and nonatopic patients with glucocorticoid-dependent chronic severe asthma. Thorax 1994;49:1231-3.
53. Lama M, Chatterjee M, Nayak CR, Chaudhuri TK. Increased interleukin-4 and decreased interferon-γ levels in serum of children with asthma. Cytokine 2011;55:335-8.
54. Smolnikova MV, Smirnova SV, Freidin MB, Tyutina OS. Immunological parameters and gene polymorphisms (C-590T IL4, C-597A IL10) in severe bronchial asthma in children from the Krasnoyarsk region, West Siberia. Int J Circumpolar Health 2013 Aug;5:72.
55. Dimitrova D, Youroukova V, Ivanova-Todorova E, Tumangelova-Yuzeir K, Velikova T. Serum levels of IL-5, IL-6, IL-8, IL-13 and IL-17A in pre-defined groups of adult patients with moderate and severe bronchial asthma. Respir Med 2019;154:144-54.
56. Liang Z, Liu L, Zhao H, Xia Y, Zhang W, Ye Y, et al. A systemic inflammatory endotype of asthma with more severe disease identified by unbiased clustering of the serum cytokine profile. Medicine (Baltimore) 2016;95:3774.
57. Akiki Z, Rava M, Diaz Gil O, Pin I, le Moual N, Siroux V, et al. Serum cytokine profiles as predictors of asthma control in adults from the EGEA study. Respir Med 2017;125:57-64.
58. Busby J, Holweg CTJ, Chai A, Bradding P, Cai F, Chaudhuri R, et al. Change in type-2 biomarkers and related cytokines with prednisolone in uncontrolled severe oral corticosteroid dependent asthmatics: an interventional open-label study. Thorax 2019;74:806-9.
59. Corren J, Pham TH, Gil EG, Sałapa K, Ren P, Parnes JR, et al. Baseline type 2 biomarker levels and response to tezepelumab in severe asthma. Allergy 2022;77:1786-96.
60. Pukelsheim K, Stoeger T, Kutschke D, Ganguly K, Wjst M. Cytokine profiles in asthma families depend on age and phenotype. PLoS One 2010;5:14299.
61. Paro-Heitor ML, Bussamra MH, Saraiva-Romanholo BM, Martins MA, Okay TS, Rodrigues JC. Exhaled nitric oxide for monitoring childhood asthma inflammation compared to sputum analysis, serum interleukins and pulmonary function. Pediatr Pulmonol 2008;43:134-41.
62. Reddel HK, Bacharier LB, Bateman ED, Brightling CE, Brusselle GG, Buhl R, et al. Global Initiative for Asthma Strategy 2021: executive summary and rationale for key changes. Am J Respir Crit Care Med 2022;205:17-35.
63. Chibana K, Trudeau JB, Mustovich AT, Hu H, Zhao J, Balzar S, et al. IL-13 induced increases in nitrite levels are primarily driven by increases in inducible nitric oxide synthase as compared with effects on arginases in human primary bronchial epithelial cells. Clin Exp Allergy 2008;38:936-46.
64. Kraft M, Brusselle G, FitzGerald JM, Pavord ID, Keith M, Fageråas M, et al. Patient characteristics, biomarkers and exacerbation risk in severe, uncontrolled asthma. Eur Respir J 2021;58:2100413.
65. Busse WW, Wenzel SE, Casale TB, FitzGerald JM, Rice MS, Daizadeh N, et al. Baseline FeNO as a prognostic biomarker for subsequent severe asthma exacerbations in patients with uncontrolled, moderate-to-severe asthma receiving placebo in the LIBERTY ASTHMA QUEST study: a post-hoc analysis. Lancet Respir Med 2021;9:1165-73.
66. Shrimanker R, Keene O, Hynes G, Wenzel S, Yancey S, Pavord ID. Prognostic and predictive value of blood eosinophil count, fractional exhaled nitric oxide, and their combination in severe asthma: a post hoc analysis. Am J Respir Crit Care Med 2019;200:1308-12.
67. Kharitonov SA, Yates DH, Barnes PJ. Inhaled glucocorticoids decrease nitric oxide in exhaled air of asthmatic patients. Am J Respir Crit Care Med 1996;153:454-7.
68. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. N Engl J Med 2018;378:2486-96.

69. Dellon ES, Liacouras CA, Molina-Infante J, Furuta GT, Spergel JM, Zevit N, et al. Updated international consensus diagnostic criteria for eosinophilic esophagitis: proceedings of the AGREE conference. Gastroenterology 2018;155:1022-33.
70. Blanchard C, Stucke EM, Rodriguez-Jimenez B, Burwinkel K, Collins MH, Ahrens A, et al. A striking local esophageal cytokine expression profile in eosinophilic esophagitis. J Allergy Clin Immunol 2011;127:208-17.
71. Konikoff MR, Blanchard C, Kirby C, Buckmeier BK, Cohen MB, Heubi JE, et al. Potential of blood eosinophils, eosinophil-derived neurotoxin, and eotaxin-3 as biomarkers of eosinophilic esophagitis. Clin Gastroenterol Hepatol 2006;4:1328-36.
72. Straumann A, Conus S, Grzonka P, Kita H, Kephart G, Bussmann C, et al. Anti-interleukin-5 antibody treatment (mepolizumab) in active eosinophilic oesophagitis: a randomised, placebo-controlled, double-blind trial. Gut 2010;59:21-30.
73. Dellon ES, Rusin S, Gebhart JH, Covey S, Higgins LL, Beitia R, et al. Utility of a noninvasive serum biomarker panel for diagnosis and monitoring of eosinophilic esophagitis: a prospective study. Am J Gastroenterol 2015;110:821-7.
74. Dellon ES, Higgins LL, Beitia R, Rusin S, Woosley JT, Veerappan R, et al. Prospective assessment of serum periostin as a biomarker for diagnosis and monitoring of eosinophilic oesophagitis. Aliment Pharmacol Ther 2016;44:189-97.
75. Min SB, Nylund CM, Baker TP, Ally M, Reinhardt B, Chen YJ, et al. Longitudinal evaluation of noninvasive biomarkers for eosinophilic esophagitis. J Clin Gastroenterol 2017;51:127-35.
76. Straumann A, Conus S, Degen L, Felder S, Kummer M, Engel H, et al. Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. Gastroenterology 2010;139:1526-37.
77. Wechsler JB, Ackerman SJ, Chehade M, Amsden K, Riffle ME, Wang MY, et al. Noninvasive biomarkers identify eosinophilic esophagitis: a prospective longitudinal study in children. Allergy 2021;76:3755-65.
78. Shamji MH, Layhadi JA, Sharif H, Penagos M, Durham SR. Immunological responses and biomarkers for allergen-specific immunotherapy against inhaled allergens. J Allergy Clin Immunol Pract 2021;9:1769-78.
79. Varshney P, Jones SM, Scurlock AM, Perry TT, Kemper A, Steele P, et al. A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response. J Allergy Clin Immunol 2011;127:654-60.
80. Kulis M, Yue X, Guo R, Zhang H, Orgel K, Ye P, et al. High- and low-dose oral immunotherapy similarly suppress pro-allergic cytokines and basophil activation in young children. Clin Exp Allergy 2019;49:180-9.
81. Kim EH, Bird JA, Kulis M, Laubach S, Pons L, Shreffler W, et al. Sublingual immunotherapy for peanut allergy: clinical and immunologic evidence of desensitization. J Allergy Clin Immunol 2011;127:640-6.
82. Wisniewski JA, Commins SP, Agrawal R, Hulse KE, Yu MD, Cronin J, et al. Analysis of cytokine production by peanut-reactive T cells identifies residual Th2 effectors in highly allergic children who received peanut oral immunotherapy. Clin Exp Allergy 2015;45:1201-13.
83. Gorelik M, Narisety SD, Guerrerio AL, Chichester KL, Keet CA, Bieneman AP, et al. Suppression of the immunologic response to peanut during immunotherapy is often transient. J Allergy Clin Immunol 2015;135:1283-92.
84. Jones SM, Sicherer SH, Burks AW, Leung DY, Lindblad RW, Dawson P, et al. Epicutaneous immunotherapy for the treatment of peanut allergy in children and young adults. J Allergy Clin Immunol 2017;139:1242-52.
85. Zhang Y, Zhang H, Du S, Yan S, Zeng J. Advanced biomarkers: therapeutic and diagnostic targets in urticaria. Int Arch Allergy Immunol 2021;182:917-31.
86. Metz M, Krull C, Maurer M. Histamine, TNF, C5a, IL-6, -9, -18, -31, -33, TSLP, neopterin, and VEGF are not elevated in chronic spontaneous urticaria. J Dermatol Sci 2013;70:222-5.