

ORIGINAL ARTICLE

Utility of serum thymus and activation-regulated chemokine as a biomarker for monitoring of atopic dermatitis severity

Janneke Landheer, MD,^a Marjolein de Bruin-Weller, MD, PhD,^a Chantal Boonacker, PhD,^b DirkJan Hijnen, MD, PhD,^a Carla Bruijnzeel-Koomen, MD, PhD,^a and Heike Röckmann, MD, PhD^a
Utrecht, The Netherlands

Background: Serum thymus and activation-regulated chemokine (sTARC) levels reflect disease severity of atopic dermatitis (AD) in small study populations. It remains unclear whether sTARC is a reliable outcome measurement for AD severity in heterogeneous AD populations in daily practice.

Objective: We sought to assess the utility of sTARC as a biomarker for monitoring AD severity in adults in daily practice.

Methods: sTARC, clinical skin score (Six Area, Six Sign AD [SASSAD]), and body surface area measurements were collected from all adult patients with AD visiting our clinic between March 2009 and March 2012, at first visit or exacerbation (baseline). In addition, data from short-term and long-term follow-up visits were collected.

Results: At baseline sTARC levels ranged widely ($n = 320$; minimum-maximum: 3-50,400 pg/mL) and sTARC and SASSAD or body surface area correlated moderately. In the majority of patients, sTARC and SASSAD or body surface area changed congruently during follow-up.

Limitations: Data were collected retrospectively.

Conclusion: sTARC may represent a suitable biomarker for monitoring of AD severity in daily practice. (J Am Acad Dermatol <http://dx.doi.org/10.1016/j.jaad.2014.07.031>.)

Key words: atopic dermatitis; body surface area; disease severity; follow-up; serum thymus and activation-regulated chemokine; Six Area; Six Sign Atopic Dermatitis.

Atopic dermatitis (AD) is a chronic inflammatory skin disease with high prevalence,¹⁻³ considerable morbidity, and profound effect on quality of life.⁴ Treatment options include topical steroids, topical immunomodulatory agents, ultraviolet therapy, and systemic immunosuppressive drugs. The choice of therapy depends on different factors, such as disease severity, previous treatment responses, and side effects.⁵

Assessment of AD disease severity is important for evaluating therapy effectiveness and is currently

Abbreviations used:

AD:	atopic dermatitis
BSA:	body surface area
SASSAD:	Six Area, Six Sign Atopic Dermatitis
SCORAD:	SCORing Atopic Dermatitis
sTARC:	serum thymus and activation-regulated chemokine

determined by clinical disease severity scores. There are a large number of AD severity scores (eg, SCORing

From the Department of Dermatology and Allergology^a and Julius Center for Health Sciences and Primary Care,^b University Medical Center Utrecht.

Funding sources: None.

Conflicts of interest: None declared.

Presented in part as a poster (IDEA, Malmö, Sweden, August 26-28, 2012).

Accepted for publication July 17, 2014.

Reprint requests: Heike Röckmann, MD, PhD, Department of Dermatology, University Medical Center, Heidelberglaan 100, G 02.124, 3584 CX Utrecht, The Netherlands. E-mail: h.rockmann@umcutrecht.nl.

Published online September 4, 2014.

0190-9622/\$36.00

© 2014 by the American Academy of Dermatology, Inc.

<http://dx.doi.org/10.1016/j.jaad.2014.07.031>

AD [SCORAD]; Three Item Score; Eczema Area and Severity Index; Six Area, Six Sign AD [SASSAD]). These severity scores weighted measures of the intensity of clinical lesions and/or the extent of clinically involved skin expressed as body surface area (BSA).^{6,7} Unfortunately, these scores are subjective, characterized by high interobserver and intraobserver variations and studies comparing validity and reliability are lacking.⁶⁻⁸ Disease severity scores are, therefore, less reliable in daily practice where different clinicians may monitor a single patient.

For these reasons, there is a need for an objective biomarker. To date, several serum cytokines and chemokines have been suggested as biomarkers for AD. Serum thymus and activation-regulated chemokine (sTARC) was found to correlate well with disease severity.⁹⁻¹² Thymus and activation-regulated chemokine is produced by different cell types, including dendritic cells and endothelial cells.¹³⁻¹⁵ Thymus and activation-regulated chemokine is a chemoattractant for CCR4⁺ T cells, which are known to play an important role in the pathogenesis of AD.¹⁶⁻¹⁸ Elevated sTARC levels have also been described in other skin diseases such as cutaneous T-cell lymphoma and staphylococcal scalded skin syndrome.¹²

sTARC levels were found increased in patients with AD, but not in healthy control subjects or in patients with asthma, allergic rhinitis, or both.^{9,11,19} This specificity within the atopy syndrome makes sTARC an attractive biomarker for AD. Furthermore, sTARC levels are significantly higher in patients with severe AD compared with mild or moderate AD.⁹⁻¹² Previously reported correlation coefficients between sTARC and disease severity scores (mainly SCORAD or SASSAD) varied between 0.39 and 0.99,^{9,19-28} but were investigated in small study populations^{9,20,21,23-26,29} predominantly in children.^{20,23-28} Only a few small studies investigated sTARC in AD longitudinally.^{9,19,20,22,29,30}

The aim of the current study was to validate sTARC as a biomarker for monitoring AD severity in adult patients in daily practice.

METHODS

Patient population

This study is based on information gathered via the standard treatment protocol for patients with AD

visiting our department. sTARC levels, clinical disease severity score SASSAD,³¹ and BSA are determined routinely at baseline (first visit and/or exacerbation), short-term follow-up, and/or long-term follow-up visits. Exacerbation is defined as increased disease severity, requiring escalation of therapy.³²

CAPSULE SUMMARY

- In small selected study populations, serum thymus and activation-regulated chemokine reflects atopic dermatitis (AD) severity.
- In this large heterogeneous AD population, serum thymus and activation-regulated chemokine levels and AD severity scores changed congruently during follow-up.
- In daily practice, serum thymus and activation-regulated chemokine may represent a suitable biomarker for monitoring AD severity.

Medical records of all 579 patients visiting our department between March 2009 and March 2012 were screened. The following inclusion criteria were used: (1) diagnosis of AD, according to the criteria of Hanifin and Rajka³³; and (2) sTARC level measurement and concomitant SASSAD and BSA determined at baseline. Exclusion criteria were: (1) systemic immunosuppressive treatment (other than systemic corticosteroids) in the 3 months before baseline; and (2) systemic corticosteroids 2 weeks before

baseline. Of the 579 patient files screened, 259 patients were ineligible: 220 (85%) because of use of systemic immunosuppressive treatment within 3 months before baseline; 10% because of missing SASSAD and BSA scores at baseline; and 5% because of another diagnosis.

Follow-up

Short-term follow-up was defined as 1 to 6 weeks, and long-term follow-up as 7 to 36 weeks after baseline. In patients with multiple measurements within the defined periods, an interpolation algorithm was used to determine 1 time point within the short-term follow-up interval closest to 4 weeks, and within the long-term follow-up interval closest to 24 weeks.

Measurements

sTARC was determined using the human thymus and activation-regulated chemokine immunoassay (Quantikine, R&D Systems, Minneapolis, MN) according to the manufacturer's instructions. The reference range in healthy control subjects was 71 to 848 pg/mL.

The compiled data on SASSAD and BSA were determined by different doctors and nurses, who were trained in using SASSAD and BSA. Pearson correlation coefficient between SCORAD and SASSAD, and between SCORAD and BSA, was

Table I. Baseline characteristics

	(A) Total study population	(B) No. of follow-up visits		
	Total (n = 320)	Baseline only (n = 120)	Baseline + 1 follow-up visit (n = 140)	Baseline + 2 follow-up visits (n = 60)
sTARC, pg/mL, median (IQR)	1733 (696-4742)	1383 (465-2638)	2133 (995-5231)	5444 (2158-8683)
SASSAD (0-108), median (IQR)	26 (18-36)	22 (14-29)	30 (23-39)	33 (24-47)
BSA, %, median (IQR)	40 (24-60)	30 (18-48)	48 (33-60)	63 (42-75)

sTARC, SASSAD, and body surface area at baseline: of the total study population (A), differentiated by treatment (B), and by no. of follow-up visits.

BSA, Body surface area; IQR, interquartile range; SASSAD, Six Area, Six Sign Atopic Dermatitis; sTARC, serum thymus and activation-regulated chemokine.

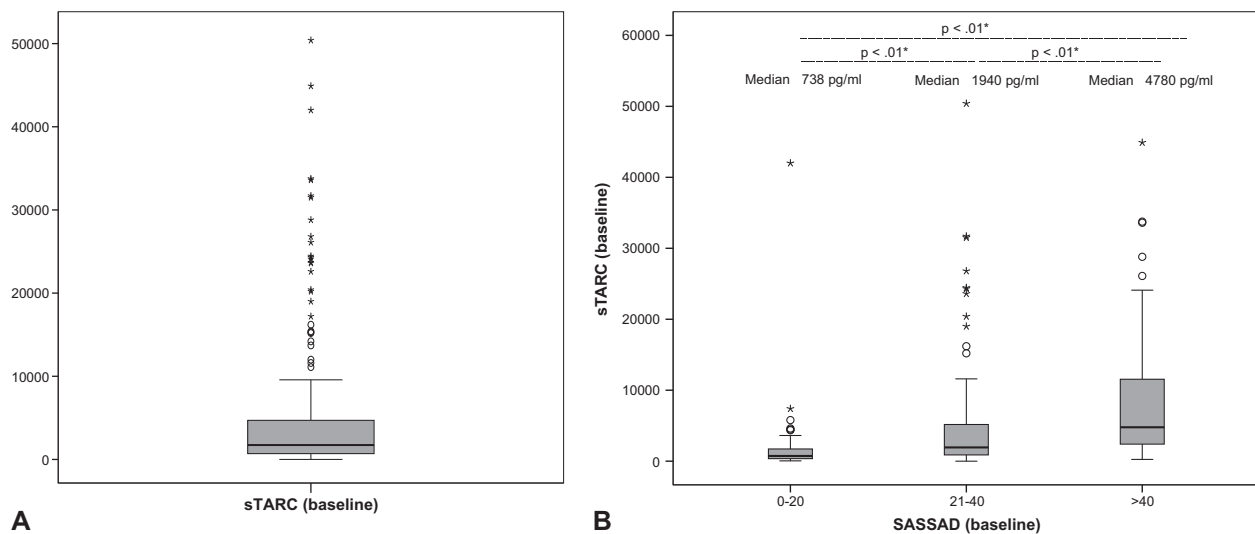


Fig 1. Distribution of serum thymus and activation-regulated chemokine (sTARC) at baseline in the total study population (n = 320) (A) and per atopic dermatitis (AD) severity category (B) presented as basic box plot. AD severity is categorized by Six Area, Six Sign AD (SASSAD) (<20, 20-40, >40). Box plot: median (middle horizontal bar), interquartile range (IQR) (box), 3 IQR (whiskers), outliers (○), and extremes (*). Differences were analyzed by Mann-Whitney U test.

$r = 0.80$ ($P < .01$) in 55 patients with AD from a recently published randomized clinical trial.²⁹

Statistical analyses

Statistical analyses were performed using software (SPSS, IBM Statistics for Windows Version 20.0, IBM Corp, Armonk, NY). Spearman correlation coefficients between sTARC and SASSAD, and between sTARC and BSA, were calculated after logarithmic transformation of sTARC levels.

This study was approved by the local medical ethics committee.

RESULTS

Patient characteristics

We included 320 adult patients with AD with a mean age of 34.8 years (SD 15.2). In all, 40.3% were male. The median short-term follow-up interval was

3.5 weeks (interquartile range 2.8-4.1) and the median long-term follow-up interval was 14.6 weeks (interquartile range 9.6-23.0).

sTARC and disease severity at baseline

The median sTARC level at baseline was 1733 pg/mL (interquartile range 696-4742) (Table I). Disease severity scores (SASSAD and BSA) were normally distributed, however, sTARC levels were not normally distributed and ranged widely (minimum-maximum: 3-50,400) (Fig 1, A). Table II shows that 9% (29 of 320) of all patients had sTARC levels higher than 10,000 pg/mL, and 30% (99 of 320) had sTARC levels below the upper reference margin of 848 pg/mL.

Spearman correlation coefficients between logarithmic transformation of sTARC levels and SASSAD, and logarithmic transformation of sTARC

Table II. Patient distribution according to categorized Six Area, Six Sign Atopic Dermatitis and serum thymus and activation-regulated chemokine at baseline

		Mild AD	Moderate AD	Severe AD	Total, n
sTARC		SASSAD <20	SASSAD 20-40	SASSAD >40	
Low	sTARC <848 pg/mL	53*	39	7	99
Intermediate	sTARC 849-5000 pg/mL	41	82*	23	146
High	sTARC >5000 pg/mL	3	43	29*	75
Total (n)		97	164	59	320

Patient distribution according to categorized SASSAD and sTARC. Study population categorized according to SASSAD score (<20; 21-40; >40) and sTARC level (<848 pg/mL; 849-5000 pg/mL; >5000 pg/mL). The no. of patients per category at baseline is shown.

AD, Atopic dermatitis; SASSAD, Six Area, Six Sign Atopic Dermatitis; sTARC, serum thymus and activation-regulated chemokine.

*Agreement.

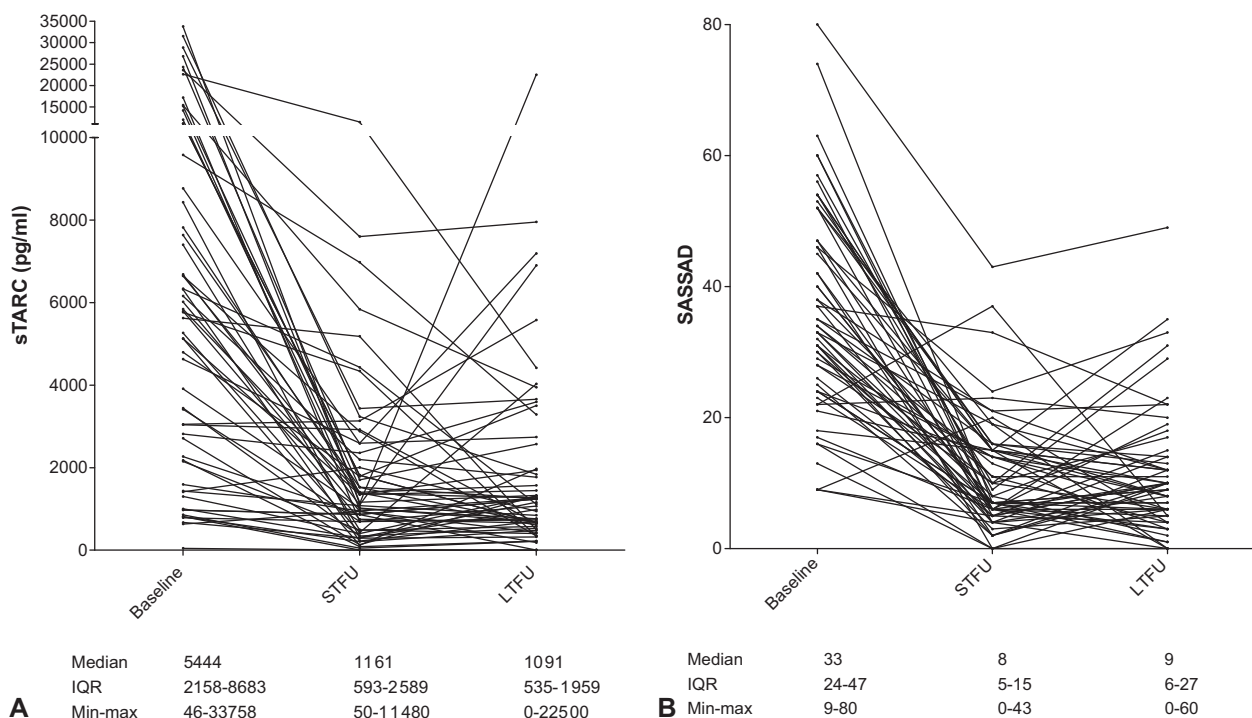


Fig 2. Serum thymus and activation-regulated chemokine (sTARC; pg/mL) and Six Area, Six Sign Atopic Dermatitis (SASSAD) during follow-up (FU). Serum TARC (**A**) and SASSAD (**B**) per individual patient ($\times 2$ follow-up group, $n = 60$) at baseline, short-term (ST) FU, and long-term (LT) FU are shown. Medians, interquartile range (IQR), and minimum (min)-maximum (max) are presented.

levels and BSA, were $r = 0.48$ and $r = 0.65$, respectively. Patients were divided into 3 groups based on SASSAD score being mild, moderate, or severe (Fig 1, B). Median sTARC levels differed significantly among the 3 SASSAD categories; however, within each category the range of sTARC levels remained wide.

Subsequently, sTARC levels were divided into 3 categories: low, intermediate, and high. Distribution of patients across sTARC and SASSAD categories was analyzed (Table II). In 164 patients (51.3%) sTARC

and SASSAD categories corresponded (eg, low sTARC concentration and mild SASSAD severity). In all, 146 patients (45.6%) did not correspond and differed by 1 category. Ten patients (3.1%) did not correspond and differed even by 2 categories.

Changes in sTARC and disease severity during follow-up

The frequency of follow-up visits in daily practice is influenced by multiple factors, including disease severity. Therefore, we differentiated patients by

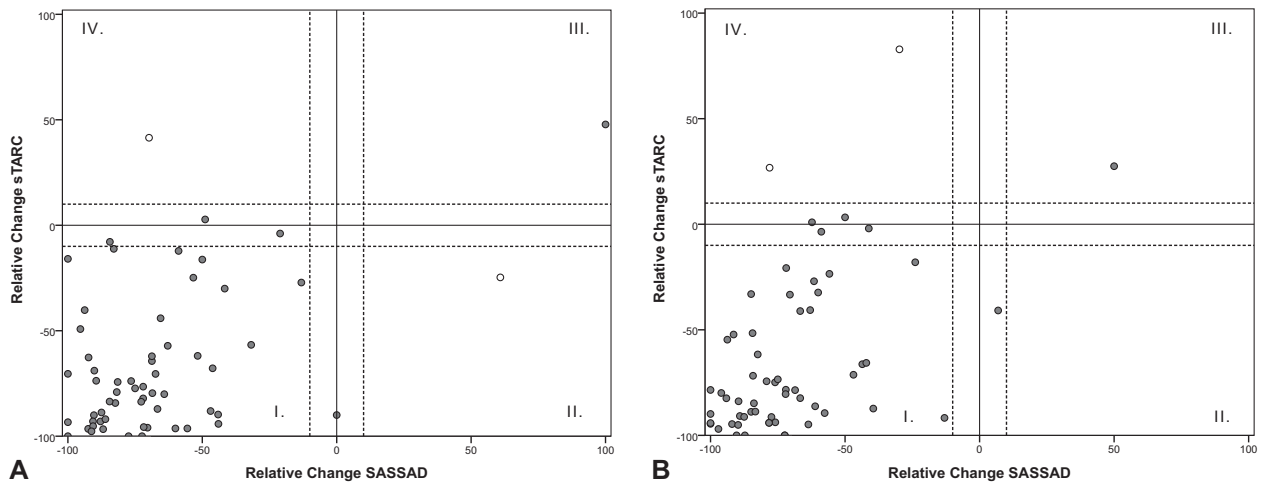


Fig 3. Relative change in serum thymus and activation-regulated chemokine (sTARC) and Six Sign Atopic Dermatitis (SASSAD) in individual patients. The $\times 2$ follow-up (FU) group (n = 60) is depicted in baseline and short-term (ST) (A) and long-term (LT) (B) FU. Patients with congruent decrease (quadrant I) and increase (quadrant III) in TARC and SASSAD (●). Quadrant II: increase in serum TARC but decrease in SASSAD (○). Quadrant IV: decrease in TARC and increase in SASSAD (○). Change <10% (---) was defined as negligible.

the number of follow-up visits: (1) baseline only; (2) baseline and 1 follow-up visit; or (3) baseline and 2 follow-up visits (Table 1). Indeed, median sTARC (and SASSAD) levels at baseline differed significantly (Kruskal-Wallis test; $P < .001$) between patients with 2 follow-up visits and those with only 1 or no follow-up visits.

Intraindividual absolute and relative changes in sTARC and SASSAD were analyzed in patients with 2 follow-up visits and are shown in Figs 2 and 3, respectively. Compared with baseline, median sTARC levels and SASSAD at short-term follow-up decreased by 79% and 76%, respectively, and by 80% and 73% at long-term follow-up (Fig 2). sTARC and SASSAD decreased congruently in the majority of patients over the short-term (53 of 60; 89%) and long-term (52 of 60; 87%) follow-up intervals (Fig 3, quadrant I/III). Incongruent changes in sTARC and SASSAD were observed in only 4 patients over the short-term (2 of 60; 3%) or long-term (2 of 60; 3%) follow-up intervals (Fig 3, quadrant II/IV). All 4 patients had been clinically unstable, requiring treatment adjustments. Changes in BSA were similar to changes in SASSAD (data not shown).

Intraindividual absolute and relative changes in sTARC and SASSAD were similar in patients with only 1 follow-up visit (n = 140) (data not shown).

DISCUSSION

To our knowledge, this is the first study investigating the suitability of sTARC as a biomarker

for monitoring AD disease severity in a large adult population in daily practice.

In the majority of patients, changes in sTARC during follow-up were congruent with changes in SASSAD and BSA. This interrelation has not been reported before in such a large study population. These findings show that sTARC represents a suitable biomarker for monitoring AD disease severity in daily practice, being a substitute for clinical severity scores with high interobserver and intraobserver variability.

We configured 3 SASSAD categories at baseline (mild, moderate, severe). Between the SASSAD categories median sTARC levels differed significantly, which is in agreement with other studies.⁹⁻¹² However, within each of the 3 SASSAD categories sTARC levels demonstrated a wide range. This variation in sTARC levels may explain the intermediate strength correlation between sTARC and SASSAD or BSA as shown previously.^{9,19,20-28}

In addition, we analyzed the relation between disease severity and sTARC at baseline, using the 3 categories of SASSAD (mild, moderate, severe) and sTARC (low, intermediate, high). sTARC reflects indeed the disease severity in the majority of patients. However, the accordance was only moderate, because of patients with high SASSAD but low sTARC or vice versa.

The moderate degree of accordance between sTARC and SASSAD severity categories may be the result of different AD phenotypes in our large unselected daily practice patient population.³⁴⁻³⁶

Patients with AD and the same clinical severity but with large differences in sTARC levels may represent different immunologic phenotypes. This needs additional study.

In conclusion, sTARC may represent a suitable biomarker for monitoring AD severity in daily practice.

Limitations

In this large daily practice study population, sTARC, SASSAD, and BSA data have been retrospectively collected. Interobserver and intraobserver variations of SASSAD and BSA measurements have not been determined. The studied AD population was recruited from a university tertiary center, which may result in a selection bias.

We thank Charlotte Cremers for her assistance with data collection.

REFERENCES

- Herd RM, Tidman MJ, Prescott RJ, Hunter JA. Prevalence of atopic eczema in the community: the Lothian atopic dermatitis study. *Br J Dermatol* 1996;135:18-9.
- Silverberg JL, Hanifin JM. Adult eczema prevalence and associations with asthma and other health and demographic factors: a US population-based study. *J Allergy Clin Immunol* 2013;132:1132-8.
- Vartiainen E, Petays T, Haahtela T, Jousilahti P, Pekkanen J. Allergic diseases, skin prick test responses, and IgE levels in North Karelia, Finland, and the Republic of Karelia, Russia. *J Allergy Clin Immunol* 2002;109:643-8.
- Finlay AY. Quality of life in atopic dermatitis. *J Am Acad Dermatol* 2001;45(Suppl):S64-6.
- Flohr C, Irvine AD. Systemic therapies for severe atopic dermatitis in children and adults. *J Allergy Clin Immunol* 2013;132:774.
- Schmitt J, Langan S, Williams HC. What are the best outcome measurements for atopic eczema? A systematic review. *J Allergy Clin Immunol* 2007;120:1389-98.
- Schmitt J, Langan S, Deckert S, Svensson A, von Kobyletzki L, Thomas K, et al. Assessment of clinical signs of atopic dermatitis: a systematic review and recommendation. *J Allergy Clin Immunol* 2013;132:1337-47.
- Oranje AP, Glazenburg EJ, Wolkerstorfer A, de Waard-van der Spek FB. Practical issues on interpretation of scoring atopic dermatitis: the SCORAD index, objective SCORAD and the three-item severity score. *Br J Dermatol* 2007;157:645-8.
- 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.
- Saeki H, Tamaki K. Thymus and activation-regulated chemokine (TARC)/CCL17 and skin diseases. *J Dermatol Sci* 2006;43:75-84.
- Shimada Y, Takehara K, Sato S. Both Th2 and Th1 chemokines (TARC/CCL17, MDC/CCL22, and Mig/CXCL9) are elevated in sera from patients with atopic dermatitis. *J Dermatol Sci* 2004;34:201-8.
- Tamaki K, Kakinuma T, Saeki H, Horikawa T, Kataoka Y, Fujisawa T, et al. Serum levels of CCL17/TARC in various skin diseases. *J Dermatol* 2006;33:300-2.
- Berlin MC, Eckmann L, Broide DH, Kagnoff MF. Regulated production of the T helper 2-type T-cell chemoattractant TARC by human bronchial epithelial cells in vitro and in human lung xenografts. *Am J Respir Cell Mol Biol* 2001;24:382-9.
- Fukuda K, Fujitsu Y, Seki K, Kumagai N, Nishida T. Differential expression of thymus- and activation-regulated chemokine (CCL17) and macrophage-derived chemokine (CCL22) by human fibroblasts from cornea, skin, and lung. *J Allergy Clin Immunol* 2003;111:520-6.
- Vestergaard C, Bang K, Gesser B, Yoneyama H, Matsushima K, Larsen CG. A Th2 chemokine, TARC, produced by keratinocytes may recruit CLA⁺CCR4⁺ lymphocytes into lesional atopic dermatitis skin. *J Invest Dermatol* 2000;115:640-6.
- Bonecchi R, Bianchi G, Bordignon PP, D'Ambrosio D, Lang R, Borsatti A, et al. Differential expression of chemokine receptors and chemotactic responsiveness of type 1 T helper cells (Th1s) and Th2s. *J Exp Med* 1998;187:129-34.
- Imai T, Baba M, Nishimura M, Kakizaki M, Takagi S, Yoshie O. The T cell-directed CC chemokine TARC is a highly specific biological ligand for CC chemokine receptor 4. *J Biol Chem* 1997;272:15036-42.
- Imai T, Nagira M, Takagi S, Kakizaki M, Nishimura M, Wang J, et al. Selective recruitment of CCR4-bearing Th2 cells toward antigen-presenting cells by the CC chemokines thymus and activation-regulated chemokine and macrophage-derived chemokine. *Int Immunol* 1999;11:81-8.
- 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.
- 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.
- Jahnz-Rozyk K, Targowski T, Paluchowska E, Owczarek W, Kucharczyk A. Serum thymus and activation-regulated chemokine, macrophage-derived chemokine and eotaxin as markers of severity of atopic dermatitis. *Allergy* 2005;60:685-8.
- Kou K, Aihara M, Matsunaga T, Chen H, Taguri M, Morita S, et al. Association of serum interleukin-18 and other biomarkers with disease severity in adults with atopic dermatitis. *Arch Dermatol Res* 2012;304:305-12.
- Leung TF, Ma KC, Hon KL, Lam CW, Wan H, Li CY, et al. Serum concentration of macrophage-derived chemokine may be a useful inflammatory marker for assessing severity of atopic dermatitis in infants and young children. *Pediatr Allergy Immunol* 2003;14:296-301.
- Machura E, Rusek-Zychma M, Jachimowicz M, Wrzask M, Mazur B, Kasperska-Zajac A. Serum TARC and CTACK concentrations in children with atopic dermatitis, allergic asthma, and urticaria. *Pediatr Allergy Immunol* 2012;23:278-84.
- Mostafa GA, Tomoum HY, Salem SA, Abd El-Aziz MM, Abou El-Maged DI, El-Sayed El-Far I. Serum concentrations of CCR4 ligands in relation to clinical severity of atopic dermatitis in Egyptian children. *Pediatr Allergy Immunol* 2008;19:756-62.
- 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.
- 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.
28. van Velsen SG, Knol MJ, Haeck IM, Bruijnzeel-Koomen CA, Pasmans SG. The self-administered Eczema Area and Severity Index in children with moderate to severe atopic dermatitis: better estimation of AD body surface area than severity. *Pediatr Dermatol* 2010;27:470-5.
 29. Haeck IM, Knol MJ, Ten Berge O, van Velsen SG, de Bruin-Weller MS, Bruijnzeel-Koomen CA. Enteric-coated mycophenolate sodium versus cyclosporin A as long-term treatment in adult patients with severe atopic dermatitis: a randomized controlled trial. *J Am Acad Dermatol* 2011;64:1074-84.
 30. 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.
 31. Charman CR, Venn AJ, Williams HC. Reliability testing of the Six Area, Six Sign Atopic Dermatitis severity score. *Br J Dermatol* 2002;146:1057-60.
 32. Langan SM, Thomas KS, Williams HC. What is meant by a "flare" in atopic dermatitis? A systematic review and proposal. *Arch Dermatol* 2006;142:1190-6.
 33. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol Suppl(Stockh)* 1980;92:44-7.
 34. Abuabara K, Margolis DJ. Do children really outgrow their eczema, or is there more than one eczema? *J Allergy Clin Immunol* 2013;132:1139-40.
 35. Bieber T, Cork M, Reitamo S. Atopic dermatitis: a candidate for disease-modifying strategy. *Allergy* 2012;67:969-75.
 36. Bieber T. Atopic dermatitis 2.0: from the clinical phenotype to the molecular taxonomy and stratified medicine. *Allergy* 2012;67:1475-82.