Reduction of serum TARC levels in atopic dermatitis by topical anti-inflammatory treatments

Yumi Yasukochi,[1] Takeshi Nakahara,[1] Takeru Abe,[2] Makiko Kido-Nakahara,[1] Futoshi Kohda,[1] Satoshi Takeuchi,[1] Akihito Hagihara[2] and Masutaka Furue[1]

Summary

Background: **Serum thymus and activation-regulated chemokine (TARC) levels are associated with the disease activity of patients with atopic dermatitis (AD) and sensitively reflect short-term changes in skin conditions. The main treatment for AD is topical agent application.**

Objective: **This study investigated the relationship between serum TARC levels and the dosage of topical agents, including corticosteroids and/or tacrolimus, in patients with AD.**

Methods: **The serum TARC levels of 56 AD patients and the amounts of topical agents prescribed to them were investigated retrospectively. The weekly reduction in serum TARC levels and weekly dosage of topical agents among AD patients were compared and their associations were evaluated.**

Results: **The dosage of topical agents was closely related to serum TARC levels. One gram of strong rank steroid or the equivalent amount of steroid/tacrolimus is required to reduce serum TARC levels by 9.94 pg/mL weekly in moderate to severe AD patients. Higher initial TARC levels require more topical agent, which results in a more rapid decrease in TARC levels. The serum TARC levels and eosinophil numbers in peripheral blood are significantly correlated.**

Conclusion: **Serum TARC level improvement and topical agent dosage are strongly correlated. TARC and eosinophil numbers are significantly correlated, but the wider range of TARC levels seems to be clinically more useful for monitoring AD severity. The serum TARC level is a very sensitive biomarker for monitoring the severity and treatment response in AD. *(Asian Pac J Allergy Immunol 2014;32:240-5)***

Keywords: *atopic dermatitis, serum thymus and activation-regulated chemokine (TARC) levels, topical corticosteroids, topical tacrolimus, total equivalent amounts (TEA)*

From 1. Department of Dermatology, Graduate School of Medical Sciences
2. Department of Health Services Management and Policy Kyushu University, Fukuoka, Japan
Corresponding author: Yumi Yasukochi
E-mail: yummy@dermatol.med.kyushu-u.ac.jp
Submitted date: 25/7/2013
Accepted date: 11/10/2013

Introduction

Atopic dermatitis (AD) is a common, chronic or chronically relapsing, severely pruritic, eczematous skin disease that manifests not only in humans but also in other mammals, such as dogs.[1,4] The waxing and waning clinical course of AD results in deterioration in patients' quality of life because of spontaneous or seasonal flare-up.[2,3] The most important clinical symptom is intolerable itch. By scratching, patients easily fall into a vicious circle called the "itch-scratch cycle", resulting in chronic sleep disturbance.[6] The main treatment of AD is skin moisturization with emollients and topical anti-inflammatory agents, such as corticosteroids and tacrolimus.[2,3]

Thymus and activation-regulated chemokine (TARC), a chemokine involved in Th2 cell migration, was recently found to be closely associated with AD.[7,8] The measurement of TARC was recently covered by medical insurance in Japan. Serum TARC levels are significantly elevated in patients with AD, particularly in those severely affected by the disease, compared with patients with other inflammatory skin diseases and healthy controls.[7-12] The TARC levels are significantly correlated with the clinical severity scores of AD. Therefore, serum TARC level is now considered a specific and objective indicator of AD disease activity.[7-12] Another feature of serum TARC level that makes it

a useful and reliable biomarker is its wide range of values - 100 to 50000 or more pg/mL - allowing it to sensitively correspond to the waxing and waning of AD severity.[11,12] Tamaki et al. reported that it is now feasible to quantify a patient's AD severity according to the serum TARC level (mild state: ≤700 pg/mL, moderate/severe state: >700pg/mL).[12] This is very advantageous because both dermatologists and their patients can evaluate the severity state of AD by using the same measures. Dermatologists can confidently ask the patients to change treatment strategy to reduce his/her TARC level to ≤700 pg/mL or 450 pg/mL (the normal control level); this greatly increases patients' adherence to treatment in routine clinical practice.

The concept of finger-tip units is a useful application method and is recommended in therapeutic guidelines.[2,13] In general, doses of topical steroids and tacrolimus are closely related to the severity of AD.[14,15] However, how topical dosage affects serum TARC levels is not well understood. This study statistically assessed the influence of topical agent dosage on the reduction of serum TARC levels.

Methods

Patients

Patients were diagnosed as AD according to the diagnostic criteria of the Japanese Dermatological Association.[2] A total of 349 patients with AD (184 men and 165 women), whose serum TARC levels were measured between April 2008 and October 2012, were initially enrolled. The following patients were excluded: patients whose TARC levels were measured only once (n = 188), those taking oral immunosuppressants such as cyclosporine and prednisolone and/or receiving ultraviolet therapies (n = 54), children aging 14 years and under (n = 13), those whose TARC levels were checked at an interval exceeding 3 months (n = 36), and mild patients with TARC levels ≤700 pg/mL (n = 2). Finally 56 moderate/severe patients out of 349 patients (16.05%, 31 men and 25 women, mean age 34.75±12.76, range 15-73 years) whose TARC levels were examined before and after treatment within 3 months were included. If a patient had multiple TARC measurements, only the first pair was used. All 56 patients were treated with topical anti-inflammatory treatments continuously during those periods and all of them received oral anti-histamines and emollients in addition.

Methods

We divided the patients into 2 groups; those with TARC levels ≥3001 pg/mL (severe AD group) and 701 to 3000 pg/mL (moderate AD group). To calculate the weekly reduction in TARC levels, the difference between the pre- and post-treatment TARC levels was divided by the number of weeks in the intermediate periods. Meanwhile, the amounts of topical steroids and/or topical tacrolimus prescribed for each patient were checked during these periods by asking how much topical agents the patient used or by checking the number of used tubes and the weekly dosages of topical agents were calculated. The amounts of topical agents per week are expressed as the total equivalent amount (TEA) and were calculated by multiplying by potency equivalent factors as follows[16]: strong rank steroids, x1; mild rank steroids, x0.5; very strong rank steroids, x2, and strongest rank steroids, x4. For example, 1g of the strongest rank steroid represented 4 TEA. Tacrolimus ointments (0.1% and 0.03%) were classified as strong rank (x1) and mild rank (x0.5) steroids, respectively. Among the 56 patients, 31 (55.4%) used topical steroids only and 25 patients (44.6%) used both topical steroids and tacrolimus but there were no patients treated with tacrolimus only. The study was approved by the ethical committee of Kyushu University Hospital.

Statistical analysis

Statistical analysis was performed using the Microsoft Excel software under the Windows 7 operating system, and the SPSS statistical software package for Windows (Version 11.0, SPSS Inc., Chicago, IL, USA). Data are expressed as means±standard error (SE). The weekly TARC reduction, weekly TEA and the rate of change in TARC levels between the moderate and severe AD groups were analyzed using unpaired *t*-tests. The factors affecting the serum TARC levels were analyzed using analysis of covariance (ANCOVA). A *P*-value of <0.05 was considered to indicate statistical significance.

Results

Serum TARC levels of patients with moderate/ severe AD

The overall pre-treatment serum TARC levels of the 56 moderate/severely affected patients with AD ranged from 829 to 52000 pg/mL (mean±SE; 7076.48±1336.73 pg/mL). Post-treatment TARC levels within 3 months after topical treatment ranged

Table 1. Weekly TARC reduction and weekly TEA in all the patients and those patients with TARC levels 701-3000 and ≥3001 pg/mL

	TARC (701-3000 pg/mL) mean ± SE/frequency(%)	TARC (≧3001 pg/mL) mean ± SE/frequency(%)	TARC (≧701 pg/mL) mean ± SE/frequency(%)	*p*-value
Age(years)	35.46 ± 2.39	34.03 ± 2.47	34.75 ± 1.71	0.679306
Gender(M)	15(53.6%)	16(57.1%)	31(55.3%)	0.788077
Pre-treatment TARC(pg/mL)	1847.89 ± 137.60	12305.07 ± 2246.94	7076.48 ± 1336.73	0.000097
Post-treatment TARC(pg/mL)	971.11 ± 113.88	2138.32 ± 342.48	1554.71 ± 198.07	0.003205
TARC reduction per week(pg/mL)	143.67 ± 24.34	2089.67 ± 411.25	1116.68 ± 245.78	0.000079
TEA per week	61.85 ± 7.96	104.57 ± 14.45	83.21±8.77	0.013490

from 159 to 6740 pg/mL (1554.71±198.07 pg/mL) (Table 1, Figure 1A). The pre-treatment TARC levels in the moderate AD group (1847.89±137.60 pg/mL) decreased significantly to 971.11±113.88 pg/mL post-treatment (Figure 1B). The pre-treatment TARC levels of the severe AD group (12305.07±2246.94 pg/mL) decreased rapidly to 2138.32±342.48 pg/mL within 3 months (Figure 1C). The rate of change in the severe AD group was significantly faster than in the moderate TARC group ($p < 0.001$).

Weekly dosage of topical agents and reduction in serum TARC levels

The weekly TEA of the overall moderate/severely affected patients ranged from 10 to 340 (83.21±8.77) (Table 1). The weekly TARC reduction of the study group as a whole ranged from 3.1 to 7765 (1116.68±245.78 pg/mL). The weekly TARC reduction was significantly correlated with weekly TEA (Figure 2). The weekly TARC reduction (2089.67±411.25 pg/mL) of the severe AD group was significantly larger than that of the moderate AD group (143.67±24.34 pg/mL) ($p < 0.001$). Accordingly, the weekly TEA (104.57± 14.45) of the severe AD group was significantly larger than that of the moderate AD group (61.85±7.96) ($p < 0.001$) (Table 1).

Factors affecting the reduction of serum TARC levels

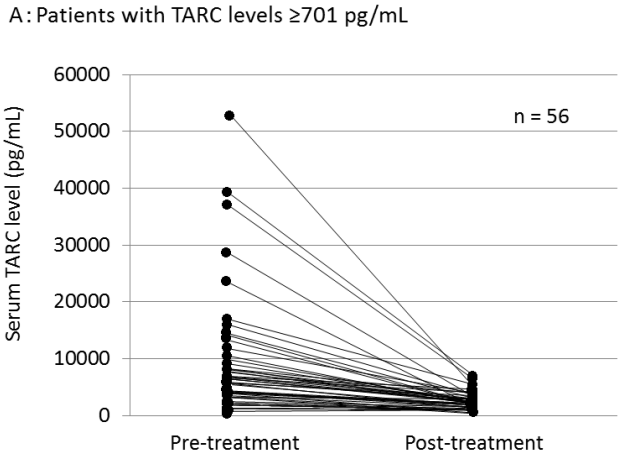
Next we analyzed whether the following factors affected the serum TARC levels using regression analysis: age, gender, treatment duration (weeks), TEA values, and initial severity (TARC ≤3000 or ≥3001 pg/mL). The TEA values ($p < 0.01$) and initial severity ($p < 0.001$) were significantly related to the reduction of TARC levels (Table 2). The results of ANCOVA demonstrated that 1 TEA per week reduced serum TARC levels by 9.94 pg/mL.

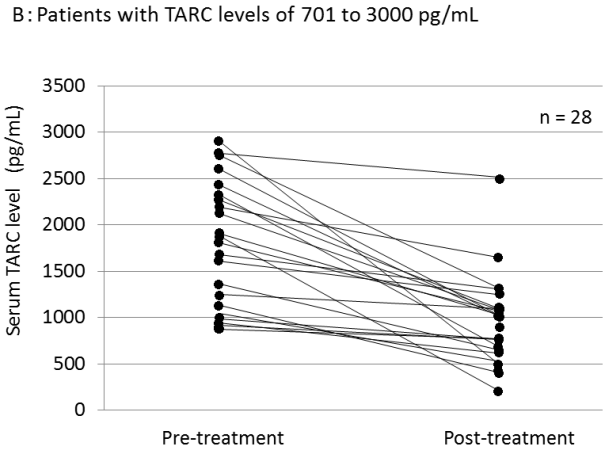
Correlation between TARC and eosinophil number

There was a moderate and significant correlation between pre-treatment TARC levels and eosinophil numbers ($R^2 = 0.2822$, $P = 0.000003585$), as has been reported by Kakinuma et al.[7] A significant correlation was also observed between the pre- and post-treatment reduction of TARC levels and the reduction of eosinophil numbers ($R^2 = 0.236$, $P = 0.0002978$). The pre-treatment values of TARC and eosinophil numbers ranged from 829-52000 and 162-7634, respectively, and the pre- and post-treatment reduction of TARC levels and eosinophil numbers ranged from 28-48140 and 1571-7295, respectively, confirming that the wider range of TARC levels seemed to be clinically more useful for evaluating AD activity than eosinophil numbers.

Discussion

Although the topical application of steroids and tacrolimus is the mainstay of the treatment of AD, dosages of topical agents prescribed in daily clinical practice were actually small, possibly reflecting patients' aversion to steroid use which is spreading worldwide.[14,15,17] As documented previously, up to 75% of adolescent/adult patients with AD are prescribed a total of less than 180g topical steroids per 6 months (7.5g/week) and less than 59g topical





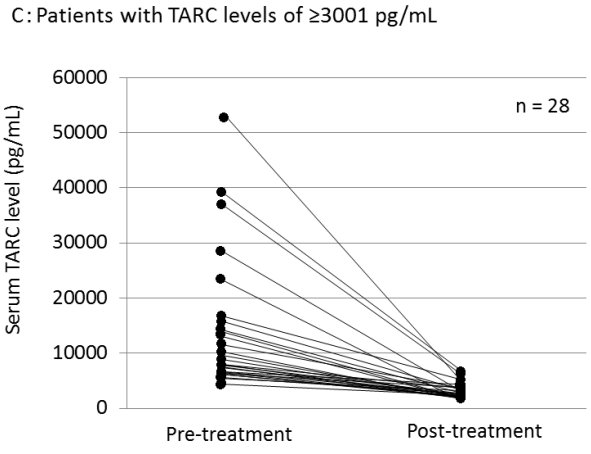


Figure 1. Serum TARC levels pre- and post-treatment. A: Patients with TARC levels ≥ 701 pg/mL. B: Patients with TARC levels 701 to 3000 pg/mL. C: Patients with TARC levels ≥3001pg/mL.

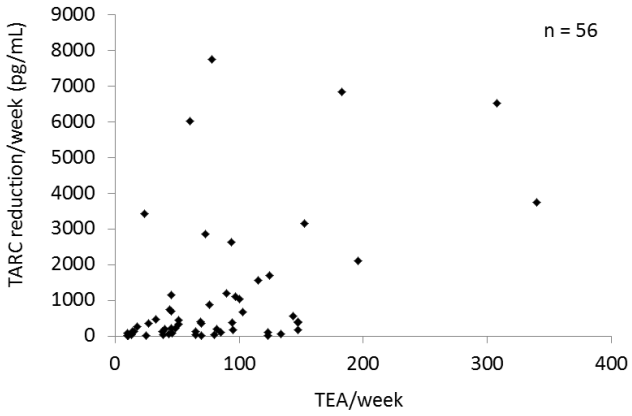


Figure 2. Correlation between weekly TARC reduction and weekly TEA

tacrolimus per 6 months (2.5g/week).[14,15] Treatment outcomes were unsatisfactory in this situation because 19% of adolescent and adult AD patients remained in a very severe or severe state or experience exacerbation.[14] Since Japanese medical insurance began to cover the monthly measurement of serum TARC levels in AD patients, monitoring TARC levels has been recognized as a very useful tool for setting treatment goals through mutual discussion between a patient and a dermatologist. Kimura et al.[18] stresses the importance of bringing TARC levels down and keeping them under 500 pg/mL. However, considering patients' aversion to steroids, it is difficult to persuade or negotiate with a patient to use a suitable amount of topical agents.

The present study examined the dose impact of topical agents on the reduction of TARC levels. The TEA was calculated by summing up the amounts of different topical agents multiplied by their respective potency equivalent factor. As expected, a greater increase in the TEA resulted in a greater decrease in TARC levels. One TEA contributed to a roughly 10 pg/mL reduction in TARC levels per week. Patients in the severe AD group exhibited a more rapid decrease in TARC levels than those in the moderate AD group. Although the exact reason for this remains unknown, we assume that more severely affected patients with more damaged skin may absorb topical agents to a greater extent, consequently inducing a dramatic reduction of TARC levels.

Intrinsic and extrinsic AD have recently received attention.[19-21] In this study, 4 female patients with normal IgE levels (104 to 138 IU/mL) were identified; their pre- and post-treatment TARC

Table 2. Regression analysis of factors affecting serum TARC level reduction

Factors affecting TARC reduction	*B*	SE	*p*-value	
Age	-19.57	15.62	0.2159	
Gender	467.00	394.87	0.2425	
Weekly TEA	9.94	3.44	0.0056	<0.01
Weeks	48.53	79.35	0.5436	
Initial TARC3000 (ref.:<3000 pg/mL)	-1626.71	436.44	0.0005	<0.001

levels changed from 839 to 394, 2778 to 1040, 4980 to 748, and 12300 to 847 pg/mL, respectively. These findings indicate TARC is likely to be a reliable biomarker of AD irrespective of IgE level.

In addition, the TARC levels significantly correlated with the number of eosinophils, as has been documented previously.[7] However, due to wider range of the values, the TARC levels seemed to be more advantageous than the number of eosinophils in evaluating the disease activity.

Oral anti-histamines are effective therapeutic adjuncts in AD.[2,3] Interestingly, Shoji et al.[22] demonstrated that antihistamines inhibit TARC production by human CD14+ monocytes/macrophages *in vitro*. Concordant with this evidence, Kimura et al.[18] found that the addition of oral antihistamines to topical steroids decreases TARC levels to a significantly greater extent than topical therapy alone. Since all patients in the present study received antihistamines simultaneously, we were unable to investigate the effect of antihistamines on the reduction of TARC levels.

This study has the following limitations; (1) the TEA may not represent the actual consumption of topical agents, (2) 3 months of post-treatment duration may be too long to adequately investigate the dose-effect relationship, and (3) we cannot exclude the beneficial effects of antihistamines and emollients, etc.

In conclusion, the results of the present study suggest that the weekly application of 1 TEA reduces TARC levels by 10 pg/mL in AD patients with serum TARC≥701 pg/mL.

Acknowledgement

This work was partly supported by grants from the Ministry of Health, Labour and Welfare, the Ministry of Education, Culture, Sports, Science and Technology, and the Environment Technology Development Fund of the Ministry of the Environment, Japan.

References

1. Furue M, Chiba T, Takeuchi S. Current status of atopic dermatitis in Japan. Asia Pac Allergy. 2011;1:64-72.
2. Saeki H, Furue M, Furukawa F, Hide M, Ohtsuki M, Katayama I, et al.; Committee for guidelines for the management of atopic dermatitis of Japanese Dermatological Association. Guidelines for management of atopic dermatitis. J Dermatol. 2009;36:563-77.
3. Rubel D, Thirumoorthy T, Soebaryo RW, Weng SC, Gabriel TM, Villafuerte LL,et al.; Asia-Pacific Consensus Group for Atopic Dermatitis.Consensus guidelines for the management of atopic dermatitis: An Asia-Pacific perspective. J Dermatol. 2013;40:160-71.
4. Terada Y, Nagata M, Murayama N, Nanko H, Furue M. Clinical comparison of human and canine atopic dermatitis using human diagnostic criteria (Japanese Dermatological Association, 2009): proposal of provisional diagnostic criteria for canine atopic dermatitis. J Dermatol. 2011;38:784-90.
5. Hachisuka J, Takeuchi S, Kido M, Fukiwake N, Furue M. Severity of disease, rather than xerosis, correlates with pruritus in patients with atopic dermatitis. Int J Dermatol. 2009;48:374-8.
6. Anuntaseree W, Sangsupawanich P, Osmond C, Mo-suwan L, Vasknanonte P, Choprapawon C. Sleep quality in infants with atopic dermatitis; a community-based, birth cohort study. Asian Pac J Allergy Immunol. 2012;30:26-31.
7. 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.
8. Furusho N, Takeoka H, Toyoda K, Murata M, Maeda S, Ohnishi H, et al. Thymus and activation regulated chemokines in children with atopic dermatitis: Kyushu University Ishigaki Atopic Dermatitis Study (KIDS). Eur J Dermatol. 2007;17:397-404.
9. 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.
10. 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.
11. Tamaki K, Kakinuma T, Saeki H, Horikawa T, Kataoka Y, Fujisawa T, et al. Serum levels of CCL 17/TARC in various skin diseases. J Dermatol. 2006;33:300-2.
12. Tamaki K, Saeki H, Kadono T, Sato S, Yata N, Hasegawa M, et al. Serum TARC/CCL 17 levels as disease marker of atopic dermatitis. Jpn J Dermatol. 2006;116:27-39. (in Japanese)

13. Long CC, Finlay AY. The finger-tip unit—a new practical measure. Clin Exp Dermatol. 1991;16:444-7.
14. Furue M, Terao H, Rikihisa W, Urabe K, Kinukawa N, Nose Y, et al. Clinical dose and adverse effects of topical steroids in daily management of atopic dermatitis. Br J Dermatol. 2003;148:128-33.
15. Furue M, Terao H, Moroi Y, Koga T, Kubota Y, Nakayama J, et al. Dosage and adverse effects of topical tacrolimus and steroids in daily management of atopic dermatitis. J Dermatol. 2004;31:277-83.
16. Kobayashi H, Ishii M, Takeuchi S, Tanaka Y, Shintani T, Yamatodani A, et al. Efficacy and safety of a traditional herbal medicine, Hochu-ekki-to in the long-term management of Kikyo (delicate constitution) patients with atopic dermatitis: a 6-month, multicenter, double-blind, randomized, placebo-controlled study. Evid Based Complement Alternat Med. 2010;7:367-73.
17. Charman CR, Morris AD, Williams HC. Topical corticosteroid phobia in patients with atopic eczema. Br J Dermatol. 2000;142:931-6.
18. Kimura U, Matsuba S, Chikenji T, Haruna K, Kamano M, Suga Y, et al. Usefulness of TARC in serum as treatment marker and combination treatment with Loratadine and steroid ointment for atopic dermatitis. Skin Research. 2009;8:125-31.
19. Bieber T. Atopic dermatitis 2.0: from the clinical phenotype to the molecular taxonomy and stratified medicine. Allergy. 2012;67:1475-82.
20. Kabashima-Kubo R, Nakamura M, Sakabe J, Sugita K, Hino R, Mori T, et al. A group of atopic dermatitis without IgE elevation or barrier impairment shows a high Th1 frequency: possible immunological state of the intrinsic type. J Dermatol Sci. 2012;67:37-43.
21. Kulthanan K, Chularojanamontri L, Manapajon A, Nuchkull P. Prevalence and clinical characterestics of adult-onset atopic dermatitis with positive skin prick testing to mites. Asian Pac J Allergy Immunol. 2011;29:318-26.
22. Shoji N, Asano K, Furuta A, Hirano K, Suzaki H. Effect of histamine H1 receptor antagonists on TARC/CCL17 and MDC/CCL22 production from CD14+ cells induced by antigenic stimulation in vitro. Int Arch Allergy Immunol. 2011;155:38-51.