Original Article

Changes in thymus- and activation-regulated chemokine (TARC) associated with allergen immunotherapy in patients with perennial allergic rhinitis

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Abstract. *Background.* Thymus- and activation-regulated chemokine (TARC), which is a CC chemokine receptor (CCR) 4 ligand with ability to recruit Th2 cells to inflammatory sites, is pathogenetically important in allergic rhinitis. Specific immunotherapy (IT), among the most effective therapies for allergic rhinitis, has incompletely understood mechanisms of action. TARC might be involved in some benefits of IT.
Methods. TARC in sera was assayed, obtained from 50 patients with house dust mite allergic rhinitis before and 1 year after beginning IT. Their ages ranged from 6 to 34 years (mean, 10), 30 were male and 20 were female.
Results: In patients whose nasal obstruction responded to IT, TARC decreased significantly with IT, while when response was defined in terms of sneezing or rhinorrhea, TARC did not change significantly.
Conclusion: TARC might be an important target of IT in reducing obstructive allergic rhinitis.

Key words: thymus- and activation-regulated chimokine (TARC), immunotherapy, allergic rhinitis, house dust mite.

Introduction

Allergen-specific immunotherapy (IT), in use for about 100 years in the treatment of allergic rhinitis, remains among the most important therapies. The efficacy of IT has been shown in many controlled studies.

IT appears to confer immunomodulatory benefits by converting T-helper (Th) 2-dominated immune responses to Th1-dominant responses. Aiming to further clarify the mechanism of IT, several studies have examined IT-related changes cytokines such as interleukin (IL)-4, IL-5, IL-6, and IL-10 [1-3]. However, the mechanisms underlying IT effects remain incompletely understood.

Thymus- and activation-regulated chemokine (TARC) was recently found to act as a highly specific ligand at type 4 C-C chemokine receptors (CCR4) [4]. TARC, most likely produced by monocytes and dendritic cells, appears to facilitate recruitment, activation, and development of Th2-polarized cells that express CCR4 [5-11]. TARC has begun to attract the attention of many investigators because Th2-dominant status may be induced by TARC, while the mechanism of IT might involve reduction of this chemokine.

In the present study, we measured serum concentrations of TARC in subjects with house dust-related allergic rhinitis before and after initiation of IT with house dust allergen extracts. We examined relationships betweens TARC concentrations and clinical responses to IT.

Methods

Patients

Fifty subjects (30 male, 20 female; ages, 6 to 34 years) were selected for immunotherapy on the basis of a history of perennial allergic rhinitis associated with immediate skin-test reactivity to house dust mite antigen and/or demonstrable specific serum IgE for house dust (HD). Subjects received subcutaneous injections of aqueous extracts of HD (Torii Inc., Tokyo, Japan), with individual initial doses determined by a threshold skin test. Doses were increased weekly until the highest dose tolerated was reached, usually in about 6 months. Weekly injections were continued for 4 weeks after attaining this maintenance dose. The interval between injections was then gradually lengthened until it reached 1 month, about 1 year after initiating IT.

Study design

For each symptom considered individually, subjects were assigned to a responder group or a nonresponder group according to the efficacy of IT as defined in the following section. Values for total IgE, HD- and *Dermatophagoides farinae*- specific IgE, and TARC were compared between serum samples obtained before and during IT in each group.

Venous blood was collected twice from each subject: just before starting immunotherapy and again when the interval between injections had reached 1 month, about 1 year after starting IT. All serum samples were separated and stored at –35ºC. All subjects gave informed consent, and experimental protocols were approved by the Tottori University Hospital Ethics Committee.

Clinical evaluation of nasal symptoms

Subjects were queried concerning severity of nasal symptoms by the same interviewer at the time of each injection. Sneezing, nasal discharge, and nasal obstruction were graded individually on a four-point scale (Table). For each symptom, responders were designated according to marked or moderate responses, while nonresponders were designated on the basis of unchanged symptom severity or worsening of the symptom.

Quantitation of total IgE, antigen-specific IgE, and TARC

Amounts of total IgE in sera from subjects were determined by an enzyme-linked immunosorbent assay (ELISA). Antigen-specific serum IgE (to HD and D. farinae) was determined using CAP RAST. TARC were measured by an ELISA (sensitivity, 15.6 pg/ml).

Statistical analysis

Results for IgE, HD- and D. farinae- specific IgE, and TARC are given as group medians and interquartile ranges. The Wilcoxon signed-rank test was used for comparisons within groups. The Mann-Whitney U test was used for comparisons between groups. A p value of <0.05 was considered to indicate significance.

Results

Considering all patients together, total serum IgE, HD- and D. farinae-specific IgE, and TARC did not differ significantly between samples obtained before and during IT. When patients were assigned to responder and nonresponder groups according to changes in each symptom associated with IT, TARC was decreased significantly during IT only in responders with respect to nasal obstruction (Fig. 1). None of the other symptoms showed a significant change in TARC related to IT, in either responders or nonresponders.

Table 1. Scoring of nasal symptoms.

Score	Sneezing	Nasal discharge	Nasal obstruction
0	no sneezing attack	no nose blowing	no nasal obstruction
1	< 6 attacks/day	nose blowing<6 times/day	no mouth breathing
2	6-10 attacks/day	nose blowing 6-10 times/day	sporadic mouth breathing
3	≥ 11 attacks/day	nose blowing ≥ times/day	mouth breathing all day

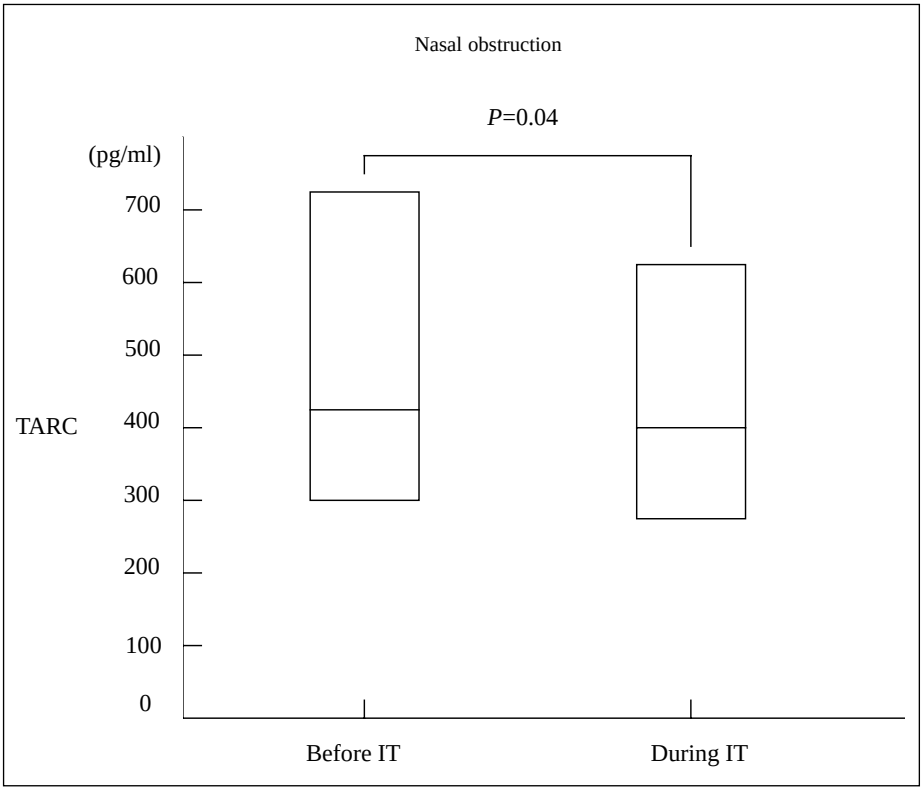

Figure 1. Serum thymus- and activation-regulated chemokine (TARC) before and during immunotherapy (IT) in responders and nonresponders concerning sneezing, nasal discharge, and nasal obstruction. Horizontal bars and squares in the lettered panels show median values and interquartile ranges, respectively. Median values before and during IT (with interquartile ranges) respectively were as follows: Sneezing, 436 pg/ml (351) and 461 pg/ml (227) in responders (p=0.63) and 362 pg/ml (221) and 390 pg/ml (284) in nonresponders (p=0.26); nasal discharge, 357 pg/ml (420)and 461 pg/ml (420) in responders (p=0.09) and 383 pg/ml (181) and 418 pg/ml (203) in non responders (p=0.50); and nasal obstruction, 423 pg/ml (412) and 399 pg/ml (351) in responders (p=0.04) and 356 pg/ml (253) and 431 pg/ml (218) in nonresponders (p=0.97).

Discussion

Many investigations have already shown that TARC could play an important role in the pathogenesis of allergic diseases, e.g. asthma, allergic rhinitis, and atopic dermatitis. Those studies, however, included only a few clinical ones. Only in atopic dermatitis, Kakinuma et al [6] showed that the TARC level decreased after the treatment with topical corticosteroid and oral antihistamines. Recently, Hijnen et al [12] showed that serum TARC levels paralleled disease severity during treatment with cyclosporin A in patients with atopic dermatitis.

This study is the first to quantitate changes in TARC with respect to IT in patients with perennial allergic rhinitis. The most important result was that TARC significantly decreased after IT only in responders as defined by nasal obstruction; TARC was essentially unchanged by IT in responders and in nonresponders as defined by either sneezing or nasal discharge.

To explain our results (Fig. 2), we hypothesized the existence of two pathways causing nasal obstruction in allergic rhinitis, both intensified by TARC. One of these would be the so-called “immediate reaction” in which chemical mediators such as histamine are released from mast cells following antigen-antibody reactions. Vasodilation and edema induced by the chemical mediator would cause relatively brief, reversible nasal obstruction. The other pathway would involve eosinophilic chronic inflammation induced by Th2 cytokines and chemokines, causing nasal obstruction with little fluctuation [13-16]. TARC has been identified as a ligand specific for CCR4 that can induce chemotaxis of Th2 lymphocytes [5-8, 17, 18]. If IT can reduce production of TARC, it might decrease numbers of Th2 lymphocytes and/or suppress function in these cells. As a result, IT might decrease eosinophilic chronic inflammation and relieve chronic nasal obstruction.

One might expect that if the function of Th2 lymphocytes is suppressed by IT, sneezing and nasal discharge also should be suppressed. In this study, no significant changes in TARC were evident with respect to sneezing and nasal discharge. More subjects and a longer study period might be necessary to better define the relationship between efficacy of IT and change in TARC.

In conclusion, the present study suggests that effects upon TARC may contribute to the response to IT in allergic rhinitis.

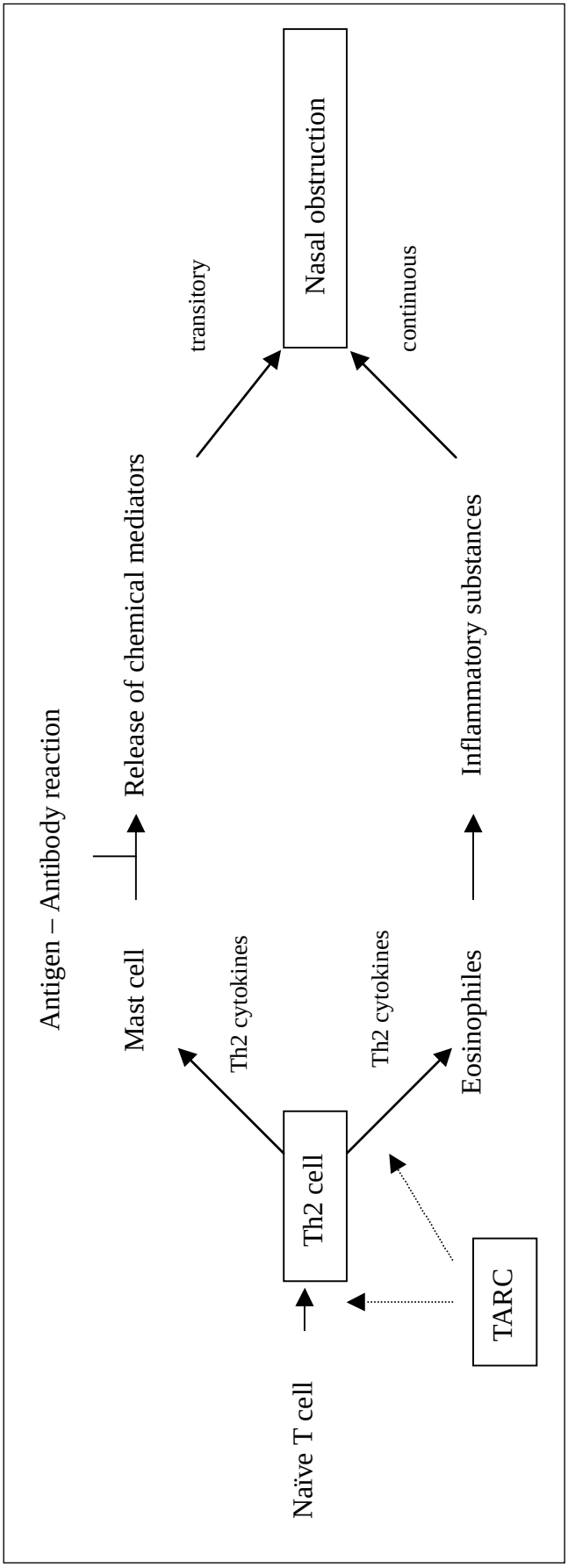

Figure 2. Proposed pathways leading to nasal obstruction in allergic rhinitis. Th, T-helper; TARC, thymus- and activation-regulated chemokine.

References

1. Luster AD. Antichemokine immunotherapy for allergic diseases. Curr Opin Allergy Clin Immunol 2001;1:561-567.
2. Lukacs NW. Role of chemokines in the pathogenesis of asthma. Immunology 2001;1:108-116.
3. Keskin G, Inal A, Ali Sari R, Sengül A, Sahin M, Turgay M, and Kinikli G. Serum IFN-γ and IL-10 levels before and after specific immunotherapy in patients with allergic rhinitis. Allergol et Immunopathol 1999;27:261-264.
4. Imai T, Baba M, Nishimura M, Kakizaki M, Takagi S, and 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.
5. Kawasaki S, Takizawa H, Yoneyama H, Nkayama T, Fujisawa R, Izumizaki M, Imai T, Yoshie O, Homma I, Yamamoto K, and Matsushima K. Intervention of thymus and activation-regulated chemokine attenuates the development of allergic airway inflammation and hyperresponsiveness in mice. Immunol 2001;107: 2055-2062.
6. Kakinuma T, Nakamura K, Wakugawa M, Mitsui H, Tada Y, Saeki H, Torii H, asahina A, Onai N, Matsushima K, and Tamaki K. 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;107:535-541.
7. Panina-Bordignon P, Papi A, Mariani M, Lucia PD, Casoni G, Bellettato C, Buonsanti C, Miotto D, Mapp C, Villa A, Arrigoni G, Fabbri LM, and Sinigaglia F. The C-C chemokine receptors CCR4 and CCR8 identify airway T cells of allergen-challenged atopic asthmatics. Clinical Invest 2001;107:1357-1364.
8. Terada N, Nomura T, Kim WJ, Otsuka Y, Takahashi R, Kishi H, Yamashita T, Sugawara N, Fukuda S, Ikedaito T and Konnno Y. Expression of C-C chemokine TARC in human nasal mucosa and its regulation by cytokines. Clinical and Exp Allergy 2001;31:1923-1931.
9. Sandoval-Lopez G , Teran LM TARC: novel mediator of allergic inflammation. Clin Exp allergy 2001;31:1809-1812.
10. Leung T, Wong C, Chan IHS, Ip W, Lam KWK, and Wong GWK. Plasma concentration of thymus and activation-regulated chemokine is elevated in childhood asthma. J Allergy Clin Immunol 2002;110:404-409.
11. Fujisawa T, Fujisawa R, Kato Y, Nakayama T, Morita A, Katsumata H, Nishimori H, Iguchi K, Kamiya H, Gray PW, Chantry D, Suzuki R and Yoshie O. Presence of high contents of thymus and activation-regulated chemokine in platelets and elevated plasma levels of thymus activation-regulated chemokine and macrophage-derived chemokine in patients with atopic dermatitis. J Allergy Clin Immunol 2002;110:139-146.
12. Hijnen D, Bruin-Weller M, Oosting B, Lebre c, Jong E, Bruijnzeel-Koomen C, and Knol E. Serum thymus and activation-regulated chemokine (TARC) and cutaneous T cell-attracting chemokine (CTACK) level in allergic diseases. TARC and CTACK are disease-specific markers for atopic dermatitis. J Allergy Clin Immunol. 2004; 113: 334-340.
13. MacGlashan D Jr. Inflammatory mechanisms in allergic disease. Clin Allergy Immunol 2002;16:519-532.
14. Goebeler M, Trautmann A, Voss A, Bröcker E, Toksoy A, and Gillitzer R. Differential and sequential expression

of multiple chemokines during elicitation allergic contact hypersensitivity. Am J Pathol 2001;158:431-440.
15. Vestergaard C, Yoneyama H, Murai M, Nakamura K, Tamaki K, Terashima Y, Imai T, Yoshie O, Irimura T, Mizutani H, and Matsushima K. Overproduction of Th2-specific chemokines in NC/Nga mice exhibiting atopic dermatitis-like lesions. Clin Invest 1999;104:1097-1105.
16. Kaplan AP. Chemokines, chemokine receptors and allergy. Int Arch Allergy Immunol 2001;124:423-431.
17. Vestergaard C, Bang K, Gesser B, Yoneyama H, Matsushima K, and Larsen CG. A Th2 chemokine, TARC, produced by keratinocytes may recruit CLA^+CCR4^+ lymphocytes into lesional atopic dermatitis skin. Invest Dermatol 2000;115:640-646.
18. Abi-Younes S, Si-Tahar M, Luster AD. The CC chemokines MDC and TARC induce platelet activation via CCR4. Thromb Res 2002;101:279-289.

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