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Alteration of serum thymus and activation-regulated chemokine level during biologic therapy for psoriasis: Possibility as a marker reflecting favorable response to anti-interleukin-17A agents.

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Alteration of serum Thymus and Activation-Regulated Chemokine level during Biologics therapy for psoriasis: possibility as a marker reflecting favorable response to anti-IL-17A agents

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ABSTRACT

Background

Biologics shows a great efficacy for psoriasis, a chronic inflammatory skin disease. the high cost and side effects of biologics, dose-reduction, elongation of administration-interval, and suspension are possible options. However, there has been no reliable biomarker we can use when we consider these moderations in therapy.

Objective

This study was conducted to test possibility of serum thymus and activation-regulated chemokine (TARC) level as an indicator for step down of biologics therapy.

Method

Serum TARC level was measured in 70 psoriasis patients at Asahikawa Medical University, and a correlation of TARC and severity of skin lesions was analyzed.

Results

Referring to serum TARC level, psoriasis patients can be divided into two groups. One is a population, in which serum TARC level is positively correlated with severity of skin lesions, and the other is a population with low psoriasis severity and high TARC level. Serum TARC level was higher in the group achieved PASI-clear with biologics than in the group which did not achieve PASI-clear. Among biologics, the group treated by

secukinumab, an anti-IL17A agent, showed significantly higher TARC level compared with the group treated with anti-TNF agents.

Conclusion

In certain populations achieving PASI-clear, serum TARC level might be a potent marker reflecting better response to IL-17A inhibitors, and in the case step down of treatment for psoriasis is possible.

Key words

serum thymus and activation-regulated chemokine, Biological therapy, psoriasis, immunoglobulin E levels, biomarker

INTRODUCTION

Psoriasis is a multifactorial chronic inflammatory disorder represented by scaly erythemas and plaques especially on frequently chafed body parts [1]. Both these visible skin lesions and invisible accompanied symptoms, such as itch, arthralgia, and the other comorbidities, can heavily ruin patients' quality of life (QOL) [2, 3]. Several therapeutic options have been carried out considering severity of skin lesions, the comorbidities or impairment of patients' QOL. Among them, biologics, which enable approximately 60-70% of psoriatic patients to achieve 90% improvement of psoriasis-area-and severity-index (PASI 90) [4-6], brings the greatest impact ever on therapeutic strategy of psoriasis to date, and the PASI 90 or more improvement is closely correlated with significant improvement of patients' impaired QOL [3, 7]. However, the cost of biologics therapy is generally high, and it is important to select the therapeutic options including biologics considering patient's disease activity and other personal background [8]. To minimize the economic issue and unfavorable adverse events, dose-reduction, elongation of administration-interval, and discontinuation are possible options, but biomarkers indicating deep remission of psoriasis have not been established.

Pruritus is one of bothersome symptoms in psoriasis patients, and systemic agents, such as cyclosporine, apremilast and biologics, can be effective [2]. However, recently,

persistent and increasing pruritus accompanied by increased serum level of thymus and activation-regulated chemokine (TARC), a Th2-derived cytokine, has been reported in psoriasis patients during biologics therapy [9, 10].

Here, we analyzed correlation of serum TARC and immunoglobulin E (IgE) levels with PASI, and propose the possibility of serum TARC level as an indicator for interval-elongation or suspension of biologics administration in a certain sub-population of psoriasis patients.

METHOD

This study was conducted according to the Declaration of Helsinki and the study protocol was approved by the Asahikawa Medical University (AMU) ethical committee.

Patients

Seventy outpatients who were regularly treated in the Department of Dermatology at AMU Hospital were participated in this study. The cases with present or apparent history of atopic dermatitis (AD) and other allergic disorders, such as allergic rhinitis, conjunctivitis were excluded. Patients of psoriasis vulgaris (PV), psoriatic arthritis (PsA), and generalized pustular psoriasis (GPP) were 43, 22, and five cases, respectively. The mean age was 56.2 (17-89) years old, and male-female ratio was 54:16. Severity of skin lesions were evaluated using PASI at the time of serum collection. The detail of treatment

in these 70 cases as follows: no treatment for 2 cases, topical treatment only for 3 cases, narrow band ultraviolet B irradiation for 2 cases, oral medications for 9 cases, and biologics for 54 cases. Among biologics, infliximab, adalimumab, ustekinumab, secukinumab, brodalumab, ixekizumab, and the other IL23 p19 agents were employed for 6, 12, 11, 13, 2, 2, and 8 cases, respectively.

Enzyme-linked immunosorbent assay (ELISA)

Human IgE ELISA kit (Arigo biolaboratories, Hsinchu, Taiwan) and TARC ELISA kit (Abcam, Cambridge, UK) were employed to measure serum IgE and TARC, respectively. Serum collected from the psoriasis patients was assayed using these ELISA kit following the manufactures' instructions.

Statistical analysis

Obtained data were statistically analyzed using one-way ANOVA. P value less than 0.05 was considered as a statistically significant difference. Other statistical analysis specifically employed was described for each test.

RESULT

Correlation of serum IgE and TARC levels with PASI in psoriasis

Correlations of PASI score and serum IgE or TARC levels were examined in plotted diagrams, and generally there are no close correlation (Fig 1). The correlation coefficients

(R) between PASI and IgE or TARC were 0.153 (p=0.209), and 0.321 (p=.0072), respectively. However, the samples seem to be consisted of two distinct groups. One is a group in which PASI is five or more and TARC levels and they are positively correlated with PASI (correlation coefficient (R) =0.673, p=0.006) (Fig 2). The other is a group in which PASI is four or less and TARC levels are weakly and negatively correlated with PASI (correlation coefficient=0.222, p=0.142) (Fig 3). There is no apparent correlation between PASI and serum IgE level in both groups.

Persistent pruritus during biologics therapy in psoriasis patients achieving PASI-clear and serum TARC level

Relatively persistent pruritus during biologics therapy was experienced in five cases achieving PASI 0 without a history of AD. They were consisted from four cases of PV and one case of GPP, and were treated with adalimumab, and secukinumab in one case and four cases, respectively. The cases did not present wheals suggesting urticaria. While one or two anti-histamines were administered to the cases for the pruritic symptoms, the effect was limited against the symptom compared with urticaria. Serum IgE and TARC were ranged in 0.941-18.14 ng/ml (mean 7.73), and 426.6-720.4 pg/ml (mean 583.3), respectively. In these patients, PASI score were closely and negatively correlated with serum TARC level (R=-0.794, P=0.01) (Fig 4), but not with serum IgE level (data not

shown).

Serum IgE and TARC levels in patients during treatment using biologics

Serum IgE and TARC levels were analyzed in 42 patients treated with each biologics (Infliximab (IFX): 6 cases, Adalimumab (ADA): 12 cases, Ustekinumab (UST): 11 cases, Secukinumab (SEC): 13 cases). Serum TARC levels were higher in the PASI-clear group (21 cases) than in the non-PASI-clear group with PASI less than 10 (21 cases) among cases treated with biologics (Fig 5). While serum IgE level did not show apparent difference among these groups treated with different biologics (data not shown), serum TARC level was significantly higher in the SEC-group than in the anti-TNF group (Fig 6).

DISCUSSION

As biologics show great efficacy on psoriasis, Th17-mediated inflammatory cytokine-network is essential in the pathomechanism of psoriasis [1]. Regarding the high cost in return for the effectiveness, dose-reduction, elongation of administration-interval, and suspension are potential options, but there has been no established biomarker indicating deep remission of psoriasis. This study revealed that serum TARC level increases in a certain psoriasis population achieving PASI-clear during treatment using biologics, especially anti-IL17A agent. This suggests that TARC might be a useful

biomarker for the possibility of step-down of biologics therapy.

Psoriasis is a multifactorial common inflammatory skin disease, and in the pathomechanism, dendritic cells, Th17 cells and epidermal cells-mediated inflammatory loop is essential [1]. This can be well demonstrated by extremely favorable response to biologics against tumor necrosis factor (TNF), IL-23, and IL17. The Th17 cells are differentiated from naïve CD4+ T-cells as with other Th populations [11, 12]. In the differentiation process of Th cells, several cytokines work as key regulators, and TGF-β is an essential factor in cooperation with other cytokines, such as IL-1β, IL-6, IL-21, and IL-23 [11]. These cytokines can simultaneously suppress naïve CD4+ cells to differentiate into other Th subsets. For example, TGF-β, a crucial cytokine for naïve T-cell-differentiation into Th17 cells, inhibits development of Th2 cells. The orientation of Th-differentiation can be explained by three axes of representative cytokines, TGF-β, IL-12, and IL-23 [11]. This mechanism is supported by clinical observations, such as a rare concomitance of psoriasis and AD, a Th17-mediated and a Th2-mediated inflammatory skin disease, respectively [13-15]. Recently, AD-like skin lesions are reported in psoriasis patients during anti-IL17A agents [10]. We reported that persistent pruritus accompanied by elevation of serum TARC level was experienced in moderate to severe psoriasis patients successfully treated by biologics, especially anti-IL17A agent [9]. These clinical

findings also suggest inverse relation between Th17 and Th2.

In rheumatoid arthritis (RA), up to 50 % of patients, once achieved low disease activity by biologics, kept the condition for a year following discontinuation of biologics therapy [16]. It is also suggested that deeper remission of disease can improve prognosis of RA after withdrawal of biologics, and the deep enough remission can be assessed by disease activity score, such as DAS28-ESR [16], or ultrasonographical change [17]. In psoriasis, clinical studies including withdrawal of anti-IL17A agents showed that approximately 15 % of patients who once reached PASI 75% improvement did not meet the criteria of relapse without readministration of anti-IL17A agents [18, 19]. By present, several biomarkers reflecting severity/activity of psoriasis and response to biologics therapy have been proposed. These biomarkers include genotypes of HLA, cytokine-relating genes, and inflammation signal-relating genes [20, 21], microRNAs [22], serum proteins [23], such as c-reactive protein, cytokines-relating inflammation and leucine-rich α2-glycoprotein [24]. Among them, neutrophil/lymphocyte ratio can be easily and regularly measured in daily clinical examination [25]. However, there are few studies suggesting biomarkers for suspension or interval-elongation of biologics-therapy in psoriasis.

TARC, one of the ligands of C-C chemokine receptor 4 (CCR4), is mainly

expressed on Th2 cells closely associated with allergic skin diseases represented by AD [26]. Serum TARC level was correlated with AD severity and decreased along with improvement of skin lesions by proper treatment [27]. We experienced persistently pruritic psoriasis cases, in which psoriatic skin lesions disappeared by biologics therapy [9]. These cases were accompanied by elevation of serum TARC, but, in most of these cases, apparent eczematous lesions and elevation of IgE were not observed. The present study revealed that psoriasis patients can be divided into two groups. One group is a population in which serum TARC level correlates with severity of psoriasis lesions, and another group is a population in which serum TARC level is elevated but psoriasis lesions disappear. Serum TARC is higher in PASI-clear cases than cases not achieving PASI-clear, and, in the cases with clinically persistent pruritus and PASI less than 10, serum TARC level was negatively correlated with PASI score with statistical significance. This negative correlation can be understood based on the different pathomechanism of AD, a Th2-mediated inflammatory disease and psoriasis, a Th1- and Th17-mediated inflammatory skin disease [14, 15]. Serum TARC level was higher in psoriasis cases treated with an anti-IL17A agent than in those treated with an anti-TNF agent. An anti-IL17A agent can restore abnormal gene-expression profile in psoriasis patients much more, compared with cases treated with etarnelcept, one of anti-TNF agents [27]. These

findings suggest that strong suppression of Th17 function by biologics can induce Th2-dominat cytokine-imbalance. A recent study on experimental asthma revealed that asthma, which had been considered as Th2-dominant disease, can be divided into three subtypes, a Th2-dominat type, a Th17-dominat type, and a both Th2- and Th17-low type [28]. This mixed Th-mediated inflammation can be involved in the pathomechanism of human asthma [29]. While Th2 and Th17 can inhibit each other, and inhibition of only one Th subset enhanced the other Th subsets [28], neutralization of IL-17 can suppress both Th2 and Th17 cells and induce regulatory T cells in an allergic rhinitis model [30]. These reports also support our results. Collectively, in psoriasis patients achieving PASI-clear, elevation of serum TARC might be a potential indicator for interval elongation or suspension of biologics-administration.

In terms of cost-effectiveness and safety of the treatment, dose-reduction, elongation of administration-interval, and suspension should be considered for the psoriasis patients during biologics therapy. Therefore, a biomarker which can suggest an appropriate timing to step-down psoriasis treatment is needed. While, in this study, serum markers were measured at a single point, TARC, a Th2 cytokine already established as a biomarker for AD, and biologics-inducing pruritus might be useful biomarkers at least in psoriasis patients achieving PASI-clear during treatment using IL-17A inhibitors.

Conflict of interest: none declared

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Figure legend

Fig 1: The correlation of serum IgE (left) or TARC levels (right) and severity of skin lesions (PASI). The correlation coefficients (R) between PASI and IgE or TARC were 0.153 (p=0.209), and 0.321 (p=.0072), respectively.

Fig 2: The correlation of serum IgE (left) or TARC levels (right) and severity of skin lesions (PASI) in patients with PASI five or more. TARC levels are positively correlated with PASI (correlation coefficient (R) =0.673, p=0.006). There is no apparent correlation between PASI and serum IgE level.

Fig 3: The correlation of serum IgE (left) or TARC levels (right) and severity of skin lesions (PASI) in patients with PASI four or less. TARC levels are not significantly correlated with PASI (correlation coefficient=0.222, p=0.142). There is no apparent correlation between PASI and serum IgE level.

Fig 4: The correlation of serum TARC levels and severity of skin lesions (PASI) in nine patients accompanied by relatively persistent pruritus (correlation coefficient=0.791, p=0.0111).

Fig 5: Serum TARC level in a group achieving PASI 0 and a group with PASI more than 0 and <10 during biologics therapy. Mean serum TARC levels were 592.6 and 363.1 pg/ml in the former and the latter groups, respectively. The difference was statistically

analyzed by student T-test (P=0.029).

Fig 6: Serum TARC level among groups treated with biologics (anti-TNF agents (infliximab and adalimumab), UST: ustekinumab, SEC: secukinumab). Mean serum TARC levels were 427.3, 677.2 and 737.7 pg/ml, in the anti-TNF, UST, and SEC-groups. Difference among the data was statistically analyzed by Brown-Forsythe test (p=0.021), and student T-test was employed for analyzing difference between individual data (*P=0.026).

Figure

Fig 1

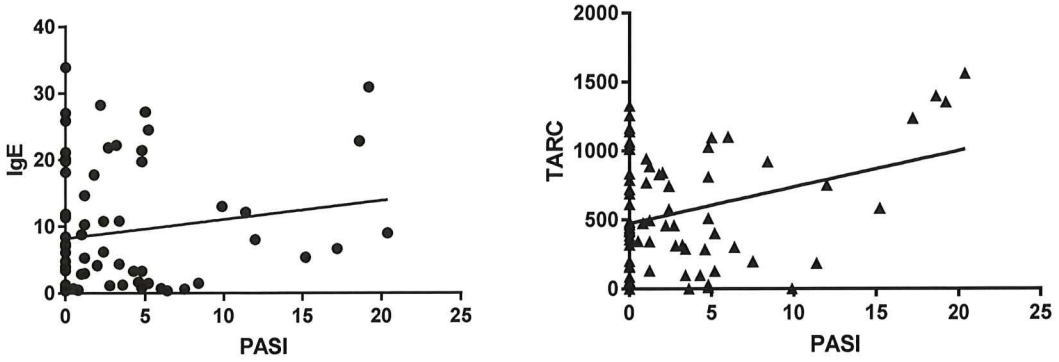

Fig 2

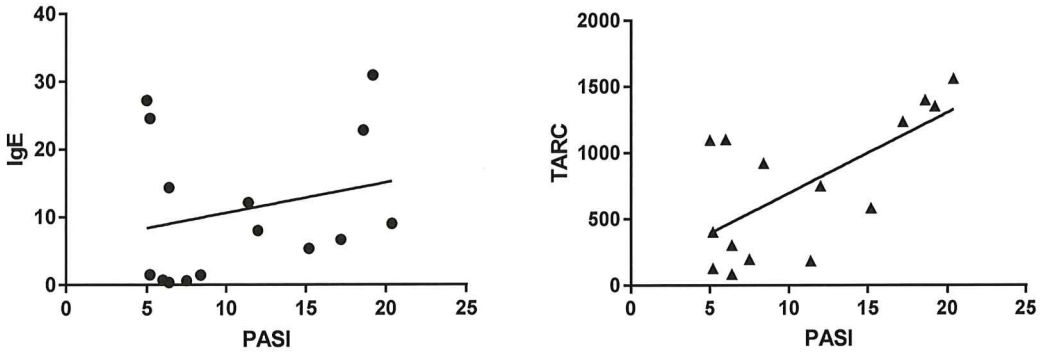

Fig 3

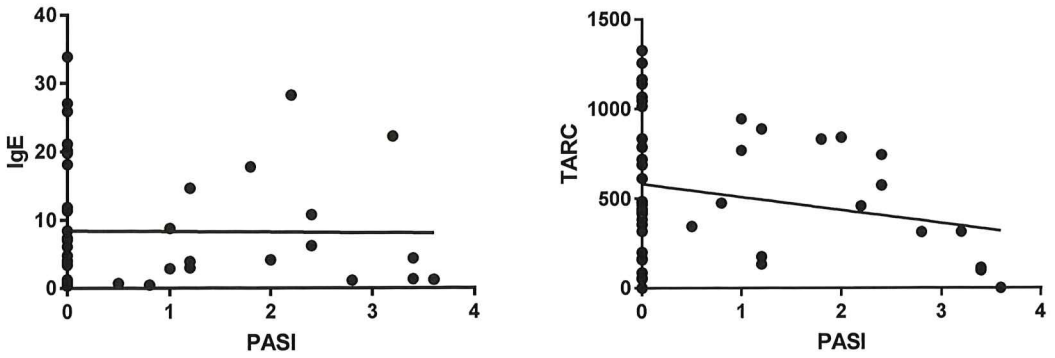

Fig 4

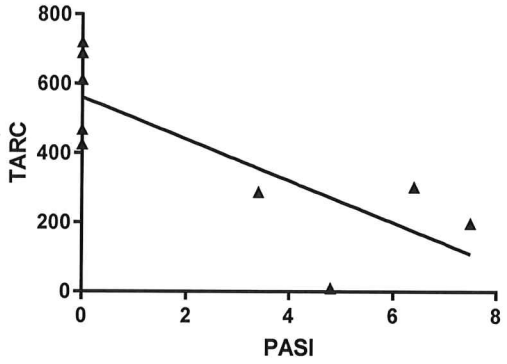

Fig 5

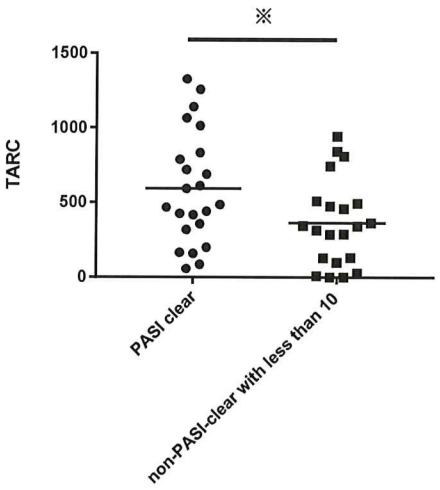

Fig 6