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INVESTIGATIVE REPORT

Increased Levels of Serum Interleukin-16 in Adult Type Atopic Dermatitis

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Interleukin (IL)-16 serves as a natural ligand of CD4 molecules and induces chemotaxis in CD4-expressing cells such as T cells, eosinophils, dendritic cells and monocytes. We examined the serum levels of IL-16 in patients with adult atopic dermatitis when their eruptions were aggravated and in non-atopic healthy controls, and then analysed the possible correlation between these values and the levels of several clinical markers. The serum levels of IL-16 were significantly higher in patients with atopic dermatitis than in the controls – both in exacerbation status and after conventional treatment. Multiple regression analyses showed that serum IL-16 was a predictor of the eosinophil count. Circulating IL-16 levels decreased significantly in patients with atopic dermatitis after topical treatment with corticosteroids or tacrolimus. These findings provide evidence that IL-16 plays a role in the exacerbation of chronic adult atopic dermatitis. ***Key words: clinical marker; exacerbation; Th2 cells.***

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Atopic dermatitis (AD) is a chronic inflammatory skin disease frequently seen in individuals with a genetic predisposition to increased IgE synthesis and IgE-mediated allergic reactions, i.e. allergic rhinitis or asthma (1–3). Accumulated evidence suggests that CD4+ helper T cells infiltrating the lesional skin play a pivotal role in the pathogenesis of AD (2). Acute skin lesions have significantly larger numbers of Th2 cells producing interleukin (IL-4), IL-5 and IL-13, whereas chronic AD skin lesions reveal increased numbers of Th1 cells expressing interferon-γ (4–7). Using soluble CD30 and CD26 as predictors for Th2 and Th1 we observed that the exacerbation of AD eruption is driven by Th2 cells, while the maintenance of chronic lesions is associated with both Th1 and Th2 cells (8). It is therefore assumed that chemotactic factors that recruit CD4+ T cells at inflammation sites play an important role in the pathomechanism of AD.

IL-16, originally described as a lymphocyte chemoattractant factor, serves as a natural ligand of CD4 molecules and induces chemotaxis in CD4-expressing cells such as T cells, eosinophils, dendritic cells and monocytes (9, 10). In addition to being a chemoattractant factor, IL-16 amplifies the inflammatory reaction by stimulating cytokine production in monocytes (11) and activating T cells (12). IL-16 is found in the bronchial mucosa of asthmatic patients (13), and IL-16 mRNA-positive cells in the epidermis and dermis are increased in acute lesions compared with chronic lesions in patients with AD (14). These facts suggest that IL-16 is involved in allergic inflammation. Indeed, Frezzolini et al. (15) recently reported that the serum levels of IL-16 were elevated in paediatric patients with AD and correlated with AD severity. However, no information is available concerning the possible correlation between the serum levels of IL-16 and several clinical markers that represent atopy and disease activity in AD, such as peripheral eosinophil counts and serum levels of IgE and lactate dehydrogenase (LDH). More importantly, there has been no study in which the serum IL-16 values have been followed repeatedly during the course of AD.

In this study, we examined the serum levels of IL-16 in patients with exacerbated AD and non-atopic healthy controls, and then analysed the possible correlation between these values and the levels of several clinical markers. We also evaluated whether the IL-16 values could change in association with improved AD eruptions after treatment with topical corticosteroids or tacrolimus.

MATERIALS AND METHODS

Patients

Sixty patients (aged 14–52 years, median 22) with chronic AD (duration of AD: median 22 years, range 6–35) diagnosed according to the criteria of Hanifin & Rajka (16) were selected for this study. Patients with active symptoms of asthma and/or allergic rhinitis and who were not receiving any drug treatment for their symptoms were excluded from the study. Patients who had other diseases were also excluded. The patients had not been treated with any topical steroid, immunosuppressant or systemic anti-histamine agents within at least one month prior to the study. Peripheral blood samples were obtained and eruption scores of the patients were calculated at their first visit to our hospital, when they felt their symptoms, such as eruptions and itch, were most severely aggravated. The median serum IgE level

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was 4,280 IU/ml (range 20–88,300 IU/ml; reference value <380 IU/ml). Patients with severe AD were then divided randomly for treatment with one of the following ointments: 0.12% betamethasone valerate (Rinderon V, Shionogi Pharmaceutical, Osaka, Japan) or 0.1% tacrolimus (Protopic, Fujisawa Pharmaceutical, Osaka, Japan) for 6 months. None of the patients had been treated with systemic steroids or other systemic immune suppressive agents. Serum was again obtained after 6 months from 10 of the patients with severe AD treated with corticosteroids and 10 treated with tacrolimus. AD activity was calculated using a modified version of a scoring system (8). Twenty-five healthy controls with no history of atopic diseases, including AD, bronchial asthma or allergic rhinitis (median serum IgE level 25 IU/ml, range 1–183), and 12 patients with chronic plaque psoriasis also participated in this study. Informed consent was obtained from all subjects or from their parents.

ELISA

Serum levels of IL-16 were measured by sandwich ELISA using monoclonal antibodies against human/mouse IL-16 (17.1 and 14.1, Endogen, MA, USA). This ELISA system cannot distinguish pro-IL-16 from bioactive IL-16. All serum samples, stored at −80°C until use, were assayed in duplicate.

Statistics

Data are expressed as the mean±SD unless otherwise indicated. Mann-Whitney U tests were performed for comparison analysis between patients with AD and the control subjects, between patients with mild, moderate and severe AD and between patients with AD alone and with AD and asthma or with AD and rhinitis. Pearson's correlation analyses were carried out to determine a possible correlation between the IL-16 values and clinical markers such as eruption score, total serum IgE levels, lactate dehydrogenase and peripheral blood eosinophil counts using log-transformed values except for eruption scores. Simple and multiple regression analyses were performed to analyse which of the clinical predictors accounts for the level of serum IL-16. The transition of log IL-16 in patients with AD in association with treatment was analysed using Wilcoxon's signed-rank test. All statistical analyses were assessed using StatView Version 5 (SAS Institute Inc. NC) on a Macintosh computer. A p value less than 0.05 was regarded as significant.

RESULTS

Serum levels of IL-16 in patients with atopic dermatitis

We first examined the serum levels of IL-16 in patients with AD when their eruptions were aggravated. The serum levels of IL-16 were significantly higher in patients with AD (median 7,554 pg/ml, range 520–69,354 pg/ml) than in the control subjects (median 480 pg/ml, range 120–5,250 pg/ml) ($p<0.0001$, Fig. 1A) and in patients with psoriasis (median 1,115 pg/ml, range 491–2,137 pg/ml) ($p=0.0003$; vs. AD, $p=0.0067$; vs. control). As shown in Fig. 1B, the increase in IL-16 levels was still significant (mild vs. moderate, $p<0.0001$, moderate vs. severe, $p=0.0017$) when patients were subdivided into mild, moderate and severe AD according to the eruption score. Of 60 patients with AD, 20 had a history of asthma during childhood, 16 had seasonal rhinitis except in the study period and 12 of these had both. However, the levels of IL-16 were not significantly different between the patients with AD alone and those with AD and a history of asthma ($p=0.1993$) or those with AD and a history of rhinitis ($p=0.5334$).

Correlation between IL-16 concentration and other predictors of disease activity in atopic dermatitis

We next examined the association between the levels of log IL-16 and the values of several clinical markers in patients with AD when their eruptions were aggravated (Table I). The correlation between the logarithmic values of peripheral eosinophilic counts (log Eos) and log IL-16 are significant. The values of log IgE and log IL-16 showed a positive correlation too, while no correlation was found between log LDH and log IL-16. The values of the eruption score also correlated significantly with log IL-16. Simple regression analyses also showed a positive relation between log IL-16 and log IgE, log Eos, and the eruption score. These findings indicate that elevated levels of IL-16 are associated with the clinical markers of AD disease activity. Multiple

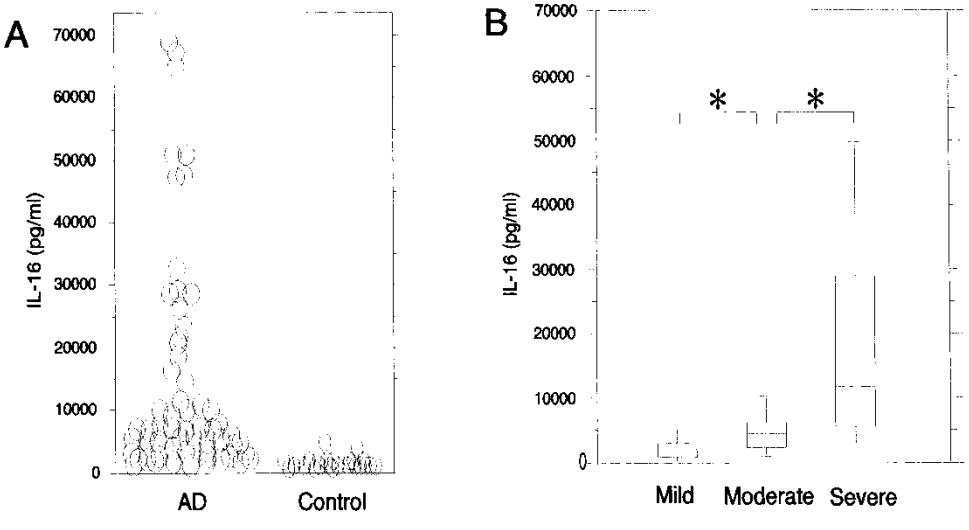

Fig. 1. (A) Serum levels of IL-16 in patients with atopic dermatitis (AD, $n=60$) and non-atopic healthy subjects ($n=25$). (B) Serum levels of IL-16 in patients subdivided by disease severity according to our scoring methods; mild (score<20, $n=10$), moderate (20–50, $n=19$) and severe (>50, $n=31$). The Kruskal-Wallis test was performed to compare three groups followed by the Mann-Whitney U-test (*$p<0.05$).

regression analyses showed that peripheral eosinophil counts exhibited the strongest correlation to the serum IL-16 concentration.

Changes in serum levels of IL-16 associated with treatment of atopic dermatitis

Finally, we asked if the values of serum IL-16 can change in association with improvement of AD. In principle, the elevated levels of IL-16 in patients with AD are either due to the disease activity itself or to a genetic predisposition to enhanced production of IL-16. Among the patients with severe AD ($n=31$), 20 agreed to participate in the 6-month treatment course with topical steroid or tacrolimus. The remaining 11 patients wanted to take both topical steroid and tacrolimus and were excluded from this part of the study. Median values of the eruption score fell from 75 to 25 and from 78 to 24, respectively in the betamethasone- and tacrolimus-treated groups after 6 months of treatment. In both groups, a significant reduction in the peripheral eosinophil counts and serum LDH was observed, although this was not the case for the serum IgE values (data not shown). As shown in Fig. 2, the serum concentration of IL-16 was significantly reduced in patients with AD after treatment with betamethasone ($p=0.0051$) and tacrolimus ($p=0.0069$). The serum levels of IL-16 in these patients were still significantly higher after treatment than in the non-atopic controls and patients with psoriasis (data not shown).

DISCUSSION

In this study, a positive correlation was demonstrated between the serum levels of IL-16 and the disease activity and severity of AD when the patients' eruptions were aggravated. Several cell types have been demonstrated to express IL-16 mRNA, including lymphocytes (CD4+, CD8+), eosinophils (17), mast cells (18), Langerhans' cells (19), monocytes/macrophages (20) and keratinocytes (21), all of which are involved in the pathogenesis of AD. This suggests that IL-16 produced by these cells plays a role not only in the development of acute skin lesion but also in the aggravation of chronic lesions in AD. One of the major events that exacerbates AD eruptions is increased exposure to allergens. Allergen exposure followed by the activation of Langerhans' cells in an IgE/FcεRI-mediated fashion has been demonstrated to up-regulate the production of IL-16 by these cells (19). The increased expression of IL-16 by keratinocytes in acute AD lesions (14) and in delayed-type hypersensitivity reactions (21) suggests that keratinocytes in the skin lesions of aggravated AD would also be activated. IL-16 produced by these epidermal cells is considered to play an important role in the initial accumulation of CD4+ T cells.

Besides IL-16, many chemokines have been described as the chemotactic factors able to induce recruitment and activation of T cells and eosinophils at sites of atopic inflammation (22). Many studies demonstrated an enhanced expression of CC chemokine receptor (CCR) 3 and CCR4 preferentially on Th2 cells as well as the β-chemokine ligands of CCR3 such as eotaxin, RANTES, and of CCR4, as there are thymus and activation-regulated chemokine and macrophage-derived chemokine in skin lesions of AD (23–30). In addition to lesional CD4+ T cells, peripheral CD4+ T cells from patients with AD highly express CCR4 and it was also shown that CCR4+ T cells migrate to human skin in response to CCR4 ligands (24, 30). Enhanced production of IL-16, a chemotactic factor for CD4+ cells (14), and β-chemokines bound to CCR3 and CCR4 in AD skin lesion may contribute cooperatively to the preferential recruitment of Th2 cells and to exacerbation of eruption in AD. It is of interest to note that IL-16 promotes RANTES and eotaxin release from human eosinophils via CD4-mediated signalling, which then induces CCR3-mediated IL-4 release in an autocrine fashion (31). If this CD4- and CCR3/eotaxin-mediated signalling pathway is present and functional in T cells, it is possible that IL-16 not only recruits CD4+ T cells but also activates preferentially the CCR3+ Th2 cells in an autocrine manner.

Peripheral numbers of eosinophils often increase in association with exacerbation of AD. Involvement of

Table I. *Correlation, simple and multiple regression analyses between IL-16 concentrations and other predictors of disease activity in atopic dermatitis**

		Correlation analysis		Coefficient of determination		Regression coefficient	
	Median value (range)	*r*	*p*	r^2	*p*	*r*	*p*
Serum IgE (U/ml)	9380 (1–88300)	0.436	0.004	0.190	0.0044	0.05	0.7511
Serum LDH (U/l)	253 (140–426)	0.154	0.441	0.024	0.3373	0.014	0.9183
Eosinophil (counts/μl)	800 (100–3400)	0.634	<0.0001	0.402	<0.0001	0.448	0.0128
Eruption score	60 (22–108)	0.557	0.0001	0.310	0.0002	0.32	0.0408

Reference values: serum IgE, <380 U/ml; serum lactate dehydrogenase (LDH), 114–243 U/l; peripheral eosinophil counts, <420/μl.
The values, with the exception of eruption scores, were log-transformed simple and multiple regression analyses.
*The results of simple and multiple regression analyses are described as the coefficient of determination and the regression coefficient, respectively.

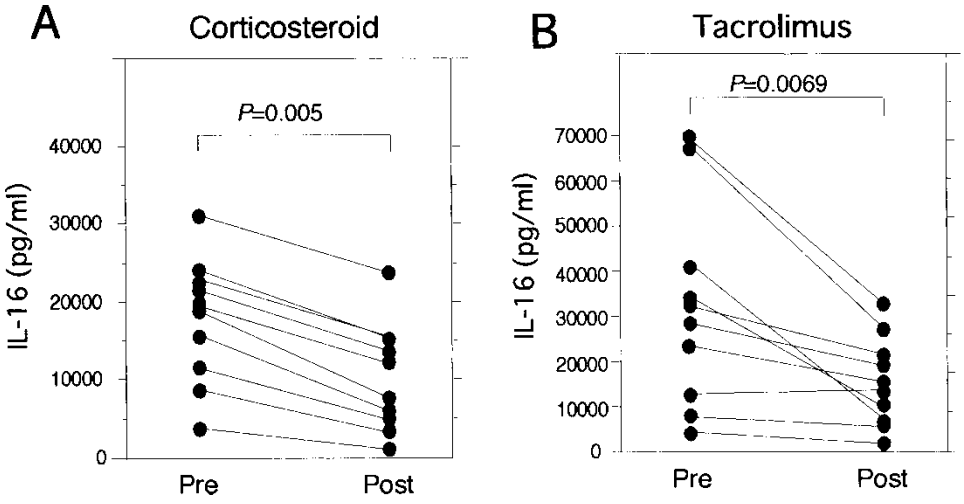

Fig. 2. Change in serum IL-16 levels in association with exacerbation (Pre) followed by treatment (Post) with topical corticosteroids (A) or tacrolimus (B). Concentrations of serum IL-16 were examined using ELISA and analysed using the Wilcoxon signed-rank test.

Th2-type cytokines IL-5 and IL-3 in this phenomenon is generally accepted (1–3, 32). Some studies have shown that an exposure to allergen, a representative exacerbating factor of AD, up-regulates IL-16 production by eosinophils (13, 17, 33). Interestingly, of the several clinical AD markers tested in this study, the best correlation was found with serum IL-16 levels and peripheral eosinophil counts. Thus, allergen induced IL-16 production by eosinophils may be an underlying mechanism explaining this good correlation. It is also possible that IL-16 produced by the activated eosinophils recruits more eosinophils, induces IL-4 release (31) and contributes to further exacerbation of eruption in AD. It would be of interest to determine serum IL-16 levels and peripheral eosinophil counts at the time of initial response to treatment because this might increase our understanding of the relevant role of IL-16 and the relationship between IL-16 and eosinophils in the pathomechanism of AD.

The serum IL-16 levels were much lower in patients with psoriasis than in patients with AD, although still higher than in control subjects. The dermal infiltrate in AD contains fairly numerous monocytes/macrophages, which are found only rarely in psoriasis. Monocytes from patients with AD show a significantly lower apoptosis rate *in vitro* than those from patients with psoriasis because of their autocrine production of cytokines and growth factor (34, 35). Increased monocyte/macrophage counts in dermal lesions may account for the abundant IL-16 in AD. Alternatively, the difference in a Th1/Th2 balance between psoriasis and AD may result in the disparity of IL-16 levels in the circulation. However, the literature does not demonstrate that Th2 cells preferentially produce IL-16. To determine whether serum IL-16 level in AD is simply interchangeable with other cytokine levels reflecting T-cell activation, it would be interesting to test serum IL-16 values in other chronic inflammatory skin diseases with Th2 bias, such as late-stage mycosis fungoides.

The circulation levels of IL-16 were significantly reduced after 6 months of treatment with corticosteroids or tacrolimus; the latter is an immunomodulator that provides an alternative to corticosteroids in the topical treatment of AD and other inflammatory dermatoses (36). Tacrolimus forms a complex with cytosolic immunophilins, blocking calcineurin and inhibiting transcription of the nuclear factor for activated T cells and nuclear factor-κB-independent proinflammatory cytokine genes (37). Tacrolimus has been shown to inhibit IL-16 production by human peripheral T cells via the down-regulation of calcineurin activity (38). It has also been demonstrated that tacrolimus treatment reduces IL-16 expression in Langerhans' cells in the epidermis of AD (39). Suppression of the IL-16-producing capacity by these cells in the lesional AD skin should be added to the modes of action by which this agent improves AD eruptions.

We conclude that IL-16 contributes to the aggravation of AD, and that the serum value of AD can be a useful marker of AD disease activity.

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