

IL-18 might reflect disease activity in mild and moderate asthma exacerbation

Hiroshi Tanaka, MD,^a Naomitsu Miyazaki, MD,^a Kensuke Oashi, MD,^a Shin Teramoto, MD,^a Masanori Shiratori, MD,^a Midori Hashimoto, MD,^a Mitsuhide Ohmichi, MD,^b and Shosaku Abe, MD,^a Sapporo, Japan

Background: IL-18, identified as an IFN- γ -inducing factor, is a proinflammatory cytokine that plays an important role in T_H1 cell activation. Recently, it was reported that histamine induced IL-18 and that IL-18 might act as a coinducer of T_H1 and T_H2 cytokines.

Objective: The aim was to evaluate the contribution of IL-18 to asthma exacerbation.

Methods: Serum IL-18, soluble IL-2 receptor, eosinophil cationic protein, and plasma IFN- γ levels, as well as peak expiratory flow were measured in patients with stable asthma ($n = 28$), acute mild or moderate asthma ($n = 23$), or pulmonary sarcoidosis ($n = 35$) and in healthy subjects ($n = 26$). We compared the serum IL-18 levels between patients with acute asthma and those in remission and examined the time course in acute exacerbation after asthma therapy.

Results: Significantly higher serum IL-18 levels were found in patients with acute asthma (215 ± 33 pg/mL, mean $\pm$ SE; $P = .02$) and pulmonary sarcoidosis (239 ± 27 pg/mL, $P = .008$) than in control subjects (127 ± 11 pg/mL), but the plasma IFN- γ level was significantly elevated in only pulmonary sarcoidosis ($P < .001$). In pulmonary sarcoidosis the IL-18 values significantly correlated with the IFN- γ levels ($r = 0.61$, $P < .001$), but in acute asthma they did not. The IL-18 levels during acute asthma exacerbation were significantly higher ($P = .01$) than on remission days. In acute asthma, circulating IL-18 levels significantly correlated with serum soluble IL-2 receptor levels ($r = 0.77$, $P < .0001$) but not with serum eosinophil cationic protein levels. The IL-18 level had a tendency to inversely correlate with peak expiratory flow. The elevated IL-18 levels in acute asthma quickly decreased on day 3 ($P = .02$) and day 7 ($P = .002$) after therapy.

Conclusion: It was suggested that IL-18 may play a potential role to activate immunologic responses and may reflect disease activity in mild and moderate asthma exacerbation.

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Key words: IL-18, IFN- γ , IL-2 receptor, acute asthma, sarcoidosis

IL-18 has recently been identified as a proinflammatory cytokine that induces IFN- γ in activated natural killer (NK) cells, T_H1, and CD8⁺ cytotoxic T cells.¹⁻³ Increased

Abbreviations used

ECP: Eosinophil cationic protein

NK: Natural killer

PEF: Peak expiratory flow

sIL-2R: Soluble IL-2 receptor

IL-18 expression has been detected in T_H1-mediated chronic inflammatory diseases such as Crohn's disease,⁴ rheumatoid arthritis,⁵ and acute infectious mononucleosis.⁶ Increased serum levels of IL-18 have been found in severe melioidosis⁷ and hemophagocytic lymphohistiocytosis.⁸ IL-18 and IL-12 are known to be potent inducers of IFN- γ production,^{1,9} and coadministration of IL-18 and IL-12 inhibits IgE production in helminth-infected mice in an IFN- γ -dependent manner, presenting a unique approach for the treatment of allergic diseases.¹⁰

However, in recent years it has been suggested that cytokine production induced by IL-18 may depend on the presence or absence of T_H1 cytokines. Hoshino et al¹¹ reported that strong induction of IL-13 mRNA and its protein by IL-2 and IL-18 in NK and T cells, as well as expression of this IL-13 mRNA and its protein in IFN- γ knockout mice, was greater than that in normal mice. Yoshimoto et al¹² showed that in the presence of IL-3, IL-18 causes IL-18R α chain-expressing basophils and mast cells derived by bone marrow cells to release large amounts of T_H2 cytokines (IL-4 and IL-13) both in vitro and in vivo. They also reported that injection of IL-18 and IL-12 increased IgE levels in helminth-infected IFN- γ -deficient mice and upregulated the capacity of IL-4 and IL-13 production by basophils; however, coadministration of IL-18 and IL-12 in wild-type mice induced T_H1 cytokines, not T_H2 cytokines. From these results, it was deduced that IL-18 may act as a coinducer of T_H1 and T_H2 cytokines. IL-18 seems to produce antiallergic reactions in the presence of T_H1 cytokines; however, injection of IL-18 alone also induces T_H2 cytokines. On the other hand, Kumano et al¹³ reported that IL-18 enhanced antigen-induced eosinophil recruitment into the airways of ovalbumin-sensitized mice.

Bronchial asthma is a T_H2 cytokine-dominant disease, and production of T_H1 cytokines such as IL-12 and IFN- γ is suppressed.¹⁴⁻¹⁶ In sarcoidosis, a T_H1 cytokine-dominant disease, by contrast, IL-12 and IFN- γ production is upregulated.¹⁷ Little is known about the role of IL-18 in T_H2 cytokine diseases such as bronchial asthma. Recently, Kohka et al¹⁸ reported that histamine was a strong inducer

From ^athe Third Department of Internal Medicine, Sapporo Medical University School of Medicine, and ^bthe Sapporo Hospital of Hokkaido Railway Company, Sapporo.

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Reprint requests: Hiroshi Tanaka, MD, Third Department of Internal Medicine, Sapporo Medical University School of Medicine, South-1, West-16, Chuo-ku, 060-8543, Sapporo, Japan.

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of IL-18 in human PBMCs and regulated IL-18-triggered activation of cytokine cascade without inducing IL-12 production. Hypothesizing that IL-18 might contribute to asthma exacerbation, we investigated its levels in patients with stable and acute asthma and compared them with those of patients with pulmonary sarcoidosis. We found that serum IL-18 levels were increased in patients with acute asthma and pulmonary sarcoidosis as compared with patients with stable asthma and healthy control subjects, and the elevated IL-18 levels in patients with acute asthma quickly decreased after asthma therapy.

METHODS

Study population

All patients and healthy volunteers were recruited from Sapporo Medical University Hospital and Sapporo Hospital of Hokkaido Railway Company, and all gave informed consent. We excluded patients with hepatitis to eliminate its influence.

Asthma

Twenty-eight patients with stable asthma (55 ± 6 years old, 16 women and 12 men), and 23 patients with acute disease (52 ± 7 years old, 15 women and 8 men) were recruited. Asthma was diagnosed with the American Thoracic Society guidelines,¹⁹ according to which 4 of the 23 patients had mild and 19 had moderate exacerbation. We excluded both viral and bacterial infection-induced acute asthma according to the following signs: (1) no significant elevation of serum antibodies for influenza A and B virus; parainfluenza 1, 2, and 3 virus; and respiratory syncytial virus; (2) no fever elevation; (3) no purulent sputum; and (4) no increased peripheral neutrophils and serum c-reactive protein. Stable asthma was defined as no asthma exacerbation within 6 months. The FEV₁ was $83.0\% \pm 16\%$ (mean $\pm$ SD). Seven patients with acute asthma and 9 with stable asthma were current or past smokers. Atopy was defined by 1 or more positive results on specific serum IgE tests by a commercial kit (MAST systems; Hitachi Kasei, Tokyo, Japan). The MAST system includes 16 antigens (house dust, *Dermatophagoides pteronyssinus*, ragweed, orchard grass and 2 other grasses, Japanese cedar, *Alternaria*, 4 other molds, cat and dog dander, egg, and soybean). All patients with asthma were treated with inhaled beclomethasone dipropionate, with dosages ranging from 200 to 1200 μ g/d, and an inhaled β_2 -agonist was used when required according to the international guidelines.²⁰ In addition, 21 of 28 patients with stable asthma were treated with oral long-acting theophylline.

Of the 23 patients with acute asthma, 16 were admitted to hospitals for more than 7 days because of moderate asthma exacerbation, and they were treated with methylprednisolone infusion (1–2 mg/kg/d), salbutamol inhalation (5–20 μ g/kg/d), and continuous theophylline drip infusion (400–600 mg/d) according to American Thoracic Society recommendations.²¹

Sarcoidosis

We selected 35 patients with pulmonary sarcoidosis (36 ± 17 years old, 17 men and 18 women). Nine of them were current or past smokers. All patients were diagnosed by histologic examination, and chest radiographic staging was as follows: stage I ($n = 25$), bilateral hilar lymphadenopathy; and stage II, ($n = 10$), bilateral hilar lymphadenopathy plus pulmonary infiltration. No patient had undergone prior therapy with corticosteroids.

Healthy control subjects

Serum and plasma samples were obtained from 26 healthy volunteers (51 ± 6 years old, 16 women and 10 men). Seven people

were current or past smokers. They had no history of respiratory disease, and their chest x-ray films and pulmonary function test results showed no evidence of respiratory disorders. All serum and plasma samples were stored at -80°C until assay.

Study design

We measured circulating levels of IL-18, soluble IL-2 receptor (sIL-2R), eosinophil cationic protein (ECP), and IFN- γ in all subjects. Correlations between morning peak expiratory flow (PEF) and these markers were evaluated in 23 patients with acute asthma. We also performed serial changes in morning PEF values, serum IL-18 levels, and ECP levels before (day 1) and after (days 3 and 7) asthma treatment in 16 admitted subjects with asthma.

Cytokine and mediator determinations

Determination of the IL-18, sIL-2R, and ECP content in sera and IFN- γ content in plasma was carried out by use of commercial kits: IL-18 by the Human IL-18 ELISA Kit (Medical & Biological Laboratories Co Ltd, Nagoya, Japan); IFN- γ by a high-sensitivity IFN- γ human ELISA system (Amersham Life Sciences, Buckinghamshire, England); sIL-2R by the Cellfree IL-2 receptor bead assay kit (ENDOGEN, Woburn, Mass); and ECP by the ECP RIA kit (Pharmacia Diagnostica, Uppsala, Sweden). The kits were able to detect concentrations of IL-18, IFN- γ , sIL-2R, and ECP as low as 12.5 pg/mL, 0.1 pg/mL, 85 U/mL, and 2 ng/mL, respectively. Reproducibility of the assays was good; the coefficient of variation of intra-assays and interassays was under 10% in each assay in our measurement. All assays were performed in duplicate. When cytokines and mediators were undetectable, values of half the lowest detectable concentration were assigned for statistical analysis.

Statistical analysis

Data on circulating IL-18, IFN- γ , sIL-2R, and ECP levels are presented as mean $\pm$ SEM. Comparisons of these parameters among groups were made with the Mann-Whitney U test. A paired t test was used to compare the serum levels of IL-18 between stable and acute asthma. Pearson correlation was calculated to evaluate the relationship between parameters, and the Fisher test was used to calculate P values for the correlation. Statistical significance was assumed for P values lower than .05.

RESULTS

IL-18 levels in the sera of patients with stable asthma (155 ± 80 pg/mL), patients with acute asthma (233 ± 33 pg/mL), patients with pulmonary sarcoidosis (239 ± 27 pg/mL), and healthy control subjects (127 ± 11 pg/mL) are shown in Fig 1. We found significantly higher levels of serum IL-18 in patients with acute asthma ($P = .02$) and sarcoidosis ($P = .008$) than in healthy control subjects. There was no significant difference in serum IL-18 levels between current or past smokers and nonsmokers in each group.

The results for plasma IFN- γ are shown in Fig 2. Plasma IFN- γ levels were significantly ($P < .0001$) higher in patients with pulmonary sarcoidosis (1.40 ± 0.41 pg/mL) than in healthy control subjects (0.16 ± 0.46 pg/mL) but were not elevated in patients with stable or acute asthma.

In patients with stable asthma, there were no significant differences in circulating IL-18 or IFN- γ levels between the atopic and nonatopic groups. We next compared circulating IL-18 and IFN- γ values among radiologic stages in patients with pulmonary sarcoidosis. For

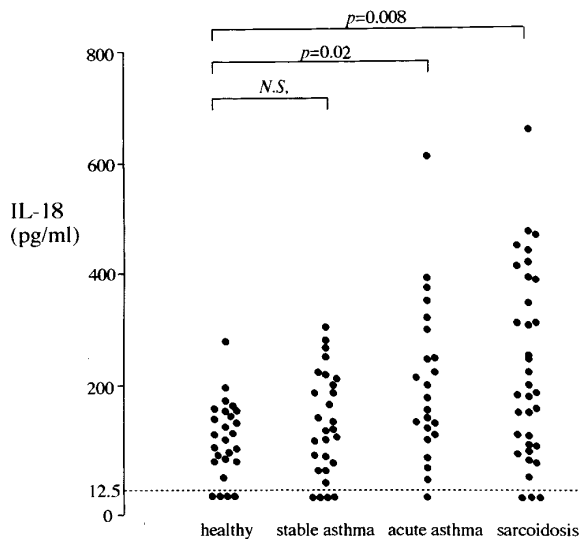


FIG 1. Serum IL-18 levels in patients with stable and acute asthma, patients with pulmonary sarcoidosis, and healthy control subjects. Dotted line represents the lower limit of the IL-18 assay. Significantly higher values of serum IL-18 were found in patients with acute asthma ($P = .02$) and patients with pulmonary sarcoidosis ($P = .008$) than in healthy control subjects.

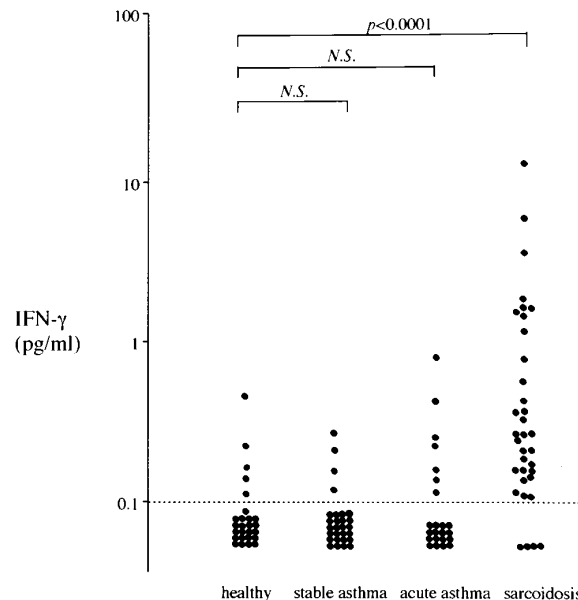


FIG 2. Circulating IFN- γ levels in patients with stable and acute asthma, patients with pulmonary sarcoidosis, and healthy control subjects. Dotted line represents the lower limit of the IFN- γ assay. Significantly higher values of serum IFN- γ were found in patients with pulmonary sarcoidosis ($P < .0001$) than in healthy control subjects.

serum IL-18, no difference was found between stage I (170 ± 25 pg/mL) and stage II (260 ± 57 pg/mL), and for plasma IFN- γ no difference was found between stage I (1.3 ± 0.5 pg/mL) and stage II (1.6 ± 0.8 pg/mL).

We analyzed the correlation between circulating IL-18 and IFN- γ values. There were no significant correlations in healthy control subjects, in patients with stable asthma, and in patients with acute asthma. Only in pulmonary sarcoidosis did circulating IL-18 values significantly correlate with circulating IFN- γ values ($r = 0.61$, $n = 35$, $P < .001$) (Fig 3).

We were able to obtain paired data on acute and stable asthma from 13 of the 23 patients with acute asthma (50 ± 6 years old, 14 women and 2 men). We measured serum IL-18 levels of the stable state when there had been no asthma exacerbation or upper respiratory infection within 3 months, and the predicted PEF in each patient was more than 80%. The IL-18 values in the acute state (285 ± 30 pg/mL) were significantly ($P = .01$) increased compared with those in the stable state (174 ± 22 pg/mL) (Fig 4).

The time course of PEF and serum IL-18 levels before (day 1) and after infusion steroid therapy (days 3 and 7) in 16 patients is shown in Fig 5. All patients' PEF values and serum ECP levels improved within 7 days. Serum IL-18 levels significantly decreased on day 3 (154 ± 25 pg/mL, $P = .02$) and day 7 (127 ± 19 pg/mL, $P = .002$) as compared with day 1 (240 ± 37 pg/mL).

There was a significant correlation ($r = 0.77$, $n = 23$, $P < .0001$) between serum IL-18 and sIL-2R levels, and the IL-18 level had a tendency to correlate inversely with PEF ($r = -0.36$, $n = 23$, $P = .09$) in acute asthma (Table

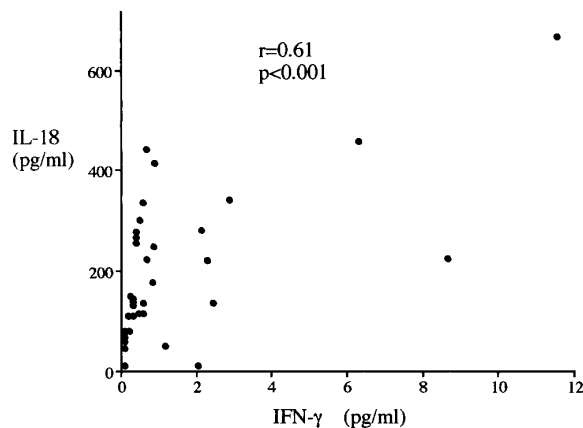


FIG 3. Relationship between circulating IL-18 and IFN- γ levels in patients with pulmonary sarcoidosis. There is a significant positive correlation ($r = 0.61$, $n = 35$, $P < .001$).

I). The PEF values also had a tendency to correlate inversely with serum ECP and sIL-2R levels (Table I). However, no correlation was found between serum IL-18 and ECP levels (Fig 6). There was no correlation between circulating IFN- γ and IL-2R levels or ECP levels in acute asthma.

DISCUSSION

We found higher circulating IL-18 levels in patients with acute asthma than in patients with stable asthma and

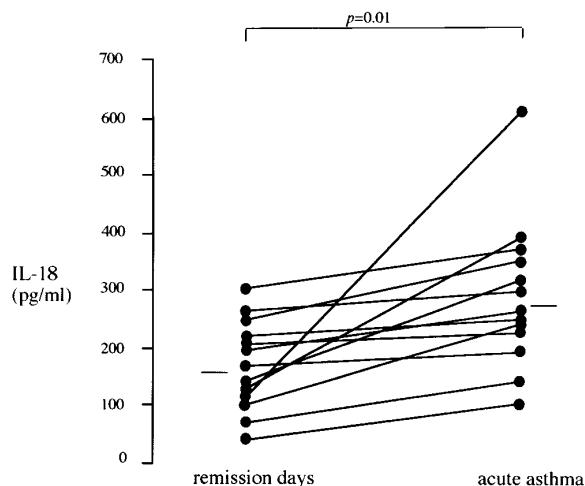


FIG 4. Paired serum IL-18 levels in 13 of 23 patients with acute asthma on exacerbation and remission days. IL-18 levels during acute asthma are significantly higher than those on remission days ($P = .01$).

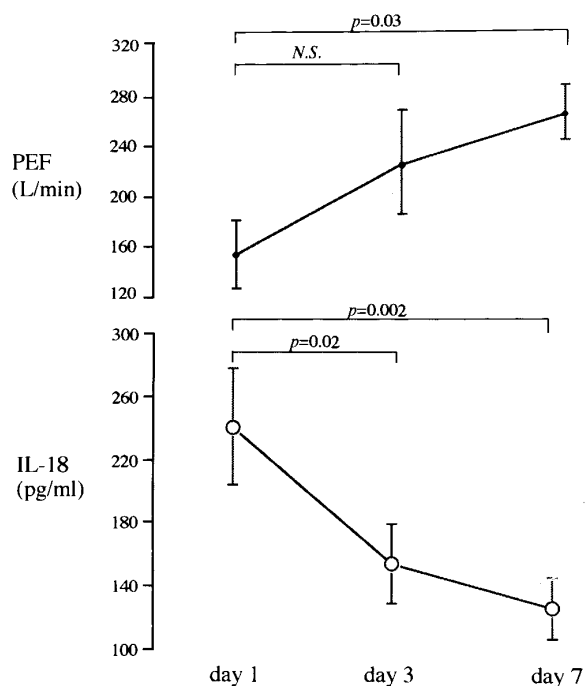


FIG 5. Serial changes in IL-18 levels in 16 of 23 patients with acute asthma treated with steroid infusion. A significantly higher PEF value is found on day 7 after asthma therapy than on day 1. There are significant decreases of serum IL-18 levels on both days 3 and 7.

healthy control subjects. The serum IL-18 value had a tendency to correlate inversely with PEF in acute asthma and decreased quickly after asthma therapy. From these results, serum IL-18 values may partly reflect disease activity in mild and moderate asthma. IL-18 is mainly secreted by activated monocytes/macrophages and also

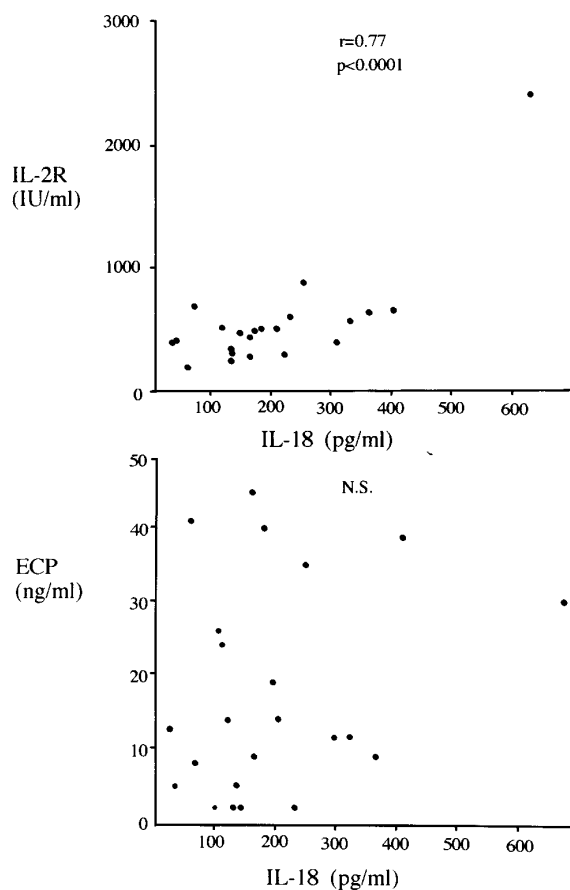


FIG 6. Relationship between circulating IL-18 levels and sIL-2R or ECP levels in acute asthma. There is a significantly positive correlation between circulating IL-18 and sIL-2R levels ($r = 0.77$, $n = 23$, $P < .0001$); however, there is no correlation between serum IL-18 and ECP values.

by Kupffer cells and other cells.^{1,22,23} IL-18 and IL-12 have both been shown to be strong cofactors for T_H1 cell activation and to stimulate T_H1 cytokines, and Krug et al²⁴ suggested that T_H1 cells might potentiate the inflammatory response in asthma by the proinflammatory effects of T_H1 cytokines. However, recently it was thought that IL-18 might act as a coinducer of both T_H1 and T_H2 cytokines. Hoshino et al¹¹ reported that IL-18 mediated IL-13 mRNA and protein from NK and T cells in IFN- γ knockout mouse. Yoshimoto et al¹² noted that a single administration of IL-18 stimulated T_H2 cytokine (IL-4 and IL-13) production and histamine release by basophils in IFN- γ -deficient mice, although coadministration of IL-18 and IL-12 induced T_H1 cytokines and inhibited IgE production, suggesting clinical applicability in the treatment of allergic diseases. In bronchial asthma, T_H1 cytokines such as IL-12 and IFN- γ were suppressed.¹⁵⁻¹⁷ In our study plasma IFN- γ levels did not increase in acute asthma, and serum IL-18 values correlated with sIL-2R levels in sera. It has been reported that activated T cells expressing IL-2R, circulating sIL-2R,

and IL-4 were significantly increased in the peripheral blood of patients with acute asthma.^{16,25} On the other hand, IL-18 was reported to induce GM-CSF, and thus the effects of IL-18 on disease conditions were not restricted to those induced by IFN- γ .²⁶ GM-CSF is a chemokine and participates in the activation of neutrophils, eosinophils, and macrophages. It was also reported that IL-18 upregulated the intercellular adhesion molecule 1 expression in a monocyte cell line through the IFN- γ -independent process.²⁷ From our results it was suggested that elevated IL-18 values in acute asthma did not affect IFN- γ production and might enhance T-lymphocyte-mediated inflammation. We speculated that IL-18 might partly reflect disease activity in asthma exacerbation through activation of T lymphocyte-, monocyte-, and granulocyte-triggered inflammation with the IFN- γ -independent pathway in asthma exacerbation. This is the first report that IL-18 might contribute to a T_H2 cytokine-dominant disease in a clinical setting.

Another possible mechanism worsening asthma by IL-18 is an eosinophil-mediated inflammation. As mentioned above, IL-18 was reported to induce GM-CSF, and GM-CSF was reported to activate eosinophils.²⁶ Kodama et al²⁸ reported that IL-18 enhanced antigen-induced eosinophil recruitment into the airways of sensitized animals, in part by increasing their antigen-induced TNF- α production. However, in this study serum IL-18 levels did not correlate with serum ECP levels. We could not investigate local inflammatory conditions in acute asthma. Further studies of IL-18 and eosinophil recruitment in bronchoalveolar lavage fluid or sputum sample are required.

IL-18 is mainly secreted from monocytes/macrophages. Recently, Kohka et al¹⁸ reported that histamine dose dependently stimulated the production of IL-18 in human PBMCs. Most of the histamine is stored in mast cells in the asthmatic airway and is released quickly into bronchial tissue during IgE-dependent asthmatic responses. Increased serum IL-18 production in acute asthma may be partly stimulated by the histamine release. Decreased IL-18 levels after asthma medication might be caused by inhibition of histamine release or direct inhibition of IL-18 production by monocytes/macrophages after asthma therapy. On the other hand, many viral and bacterial infections also may stimulate IL-18 generation^{6,7}; therefore we excluded the patients with acute asthma after these infections. Actually, IL-18 levels in sera were higher than 600 pg/mL in patients with acute asthma after influenza A virus infection (data not shown).

Sarcoidosis is a T_H1 cytokine-dominant disease, and IL-12 and IFN- γ production is upregulated.¹⁷ Our data revealed that patients with stage I and II pulmonary sarcoidosis had elevated circulating IL-18 and IFN- γ levels, and IL-18 and IFN- γ levels correlated significantly, whereas in acute asthma they did not. Lauw et al⁷ also reported that increased plasma IL-18 values were correlated with IFN- γ levels accompanied by elevation of circulating IL-12 p40 during gram-negative bacillus sepsis

TABLE I. Correlations between PEF and serum markers in acute asthma (n = 23)

PEF	IL-18	sIL-2R	ECP	IFN- γ
r	-0.36	-0.40	-0.41	-0.06
P	.09	.07	.06	.78

(*Burkholderia pseudomallei*). It was suggested that elevated IL-18 levels might produce a different immunologic response in a T_H1 and T_H2 cytokine-dominant state.

We were surprised to detect plasma IFN- γ in some of the patients with asthma because asthma is a T_H2 cytokine-dominant disease¹⁵ in which T_H1 cytokine production is suppressed.¹⁶ Recently, Fukao et al²⁹ reported that IL-4 acted synergistically with IL-12 during IFN- γ production by dendritic cells, and IL-4 enhanced IFN- γ production when dendritic cells were stimulated through CD40 or MHC class II. Purello-D'Ambrosio et al³⁰ reported that inhaled glucocorticoid (fluticasone propionate) administration significantly increased IL-12 and IFN- γ levels in either whole-blood culture supernatants or in sera of patients with asthma and that these levels reached those of the control subjects. They speculated that fluticasone propionate could have an impact on complex interactions between circulating and bronchial epithelial cells and/or on the release, by bronchial epithelium, of soluble factors capable of downregulating IL-12 and IFN- γ inhibitory factors. It was reported³¹ that clinical improvement in asthma after prednisolone treatment was associated with a reduction in the number of cells expressing IL-4 and IL-5 mRNAs and an increase in the number of cells expressing IFN- γ mRNA. In our study all asthmatic patients were treated with inhaled corticosteroids. Four subjects with stable asthma had detectable plasma IFN- γ levels, but this might have been partly due to the fact that they had been treated with 800 to 1200 μ g/d for more than 5 years. On the other hand, van Schaik et al³² reported that overproduction of IFN- γ in nasopharyngeal secretion appeared to be associated temporarily with virus-induced wheezing in children. Therefore, to leave out the effects of IFN- γ production by virus infection, we excluded patients with virus-induced asthma exacerbation.

In conclusion, we found that the serum IL-18 level was higher in acute asthma than in stable asthma and had a tendency to correlate inversely with PEF. In acute asthma, serum IL-18 levels correlated with serum sIL-2R values. Additionally, patients with pulmonary sarcoidosis (T_H1 cytokine-dominant disease) had elevated levels of both circulating IL-18 and IFN- γ and had a significant correlation. This correlation, however, was not present in patients with asthma (T_H2 cytokine-dominant disease). From these results, it was suggested that IL-18 might have a potential role in control of lymphocyte responses in acute asthma through an IFN- γ -independent pathway and that elevated IL-18 levels might induce a different immunologic response in T_H1 and T_H2 cytokine-dominant disease.

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