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Elevation of serum soluble tumour necrosis factor (TNF) receptor and IL-1 receptor antagonist levels in bronchial asthma

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SUMMARY

The specific inhibitor for TNF-α activity, soluble form of the 55-kD TNF receptor (sTNF-RI) and soluble form of the 75-kD receptor (sTNF-RII), and the specific inhibitor for IL-1 activity, IL-1 receptor antagonist (IL-1Ra), have been identified. It has been shown that the levels of these inhibitors are elevated in plasma/serum and biological fluids in several diseases, and the protective and inhibitory effect of these inhibitors exist in several inflammatory diseases. In the present study, we measured serum levels of sTNF-RI, STNF-RII and IL-1Ra by ELISA in 36 patients with bronchial asthma (16 atopic and 20 non-atopic) during asthma attacks and in stable conditions in order to assess the state of these inhibitors in allergic inflammation. The levels of sTNF-RI, sTNF-RII and IL-1Ra in sera obtained during bronchial asthma attacks were higher than those in sera obtained in stable conditions. These findings were obtained regardless of atopic status. These results suggest that higher levels of serum sTNF-RI, sTNF-RII and IL-1Ra may reflect up-regulation of TNF-R expression and IL-1Ra production in allergic inflammation, and sTNF-RI, sTNF-RII and IL-1Ra may contribute to regulating TNF-α- and IL-1-mediated production and development of allergic inflammation.

Keywords bronchial asthma soluble TNF receptor IL-1 receptor antagonist

INTRODUCTION

Bronchial asthma is a disease that is characterized by episodic reversible airway obstruction, airway hyperresponsiveness to exogenous and endogenous stimuli, and allergic inflammation in the airway [1]. The pathogenesis of allergic inflammation is complex and involves multiple inflammatory cells and mediators [2,3]. The involvement of macrophages and macrophage-derived cytokines such as TNF-α and IL-1 in the production of allergic inflammation has been described [4,5].

TNF-α and IL-1 exhibit a number of biological activities and play an important role in the pathogenesis of inflammatory disease [6]. In allergic inflammation, an increased expression of TNF-α and IL-1β mRNA in cells from bronchoalveolar lavage fluid (BALF) [7–10], elevated levels of TNF-α in BALF only in patients exhibiting a late asthmatic response [11], and an increased expression of TNF-α mRNA in cutaneous and nasal late-phase response have been demonstrated [10]. Increased production of these cytokines and IgE-mediated production of these cytokines by alveolar macrophages and peripheral blood monocytes were found in patients with bronchial asthma [11–13]. Furthermore, several lines of evidence point to the possibility that these cytokines contribute to the production of allergic inflammation: inhalation of TNF-α and administration of IL-1β cause bronchial hyperreactivity [14,15]; anti-TNF-α antibody suppresses leucocyte accumulation following IgE-dependent cutaneous late-phase reactions [16], and administration of IL-1 receptor antagonist (IL-1Ra) results in suppression of bronchial hyperreactivity and inflammatory cell infiltration following allergen challenge in sensitized guinea pigs [17] and suppression of human cutaneous allergic late-phase responses [18]. These results suggest that IL-1β and TNF-α play an important role in the production of allergic inflammation and the development of late asthmatic responses.

The specific inhibitor for IL-1 activities, designated IL-1Ra [19,20] and the specific inhibitor for TNF-α activities, soluble forms of the 55-kD TNF receptor (sTNF-RI) and the 75-kD receptor (sTNF-RII) [21–23], have been identified. The elevation of these cytokine inhibitors in serum/plasma and biological fluids in several diseases [24–28], and the inhibitory and protective effects of these cytokine inhibitors against IL-1- and TNF-α-mediated diseases, have been demonstrated [17,18,29–31]. Although up-regulation of TNF-α and IL-1β in bronchial asthma has been demonstrated, serum sTNF-R and IL-1Ra levels have not been elucidated.

In the present study, we measured two types of sTNF-R and IL-1Ra in sera from patients with bronchial asthma during asthma attacks and in stable conditions in order to analyse the change in serum sTNF-RI, sTNF-RII and IL-1Ra levels, and evaluate a

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potential role of these cytokine inhibitors in regulating the allergic inflammation.

PATIENTS AND METHODS

Study population

The study group comprised 16 patients with atopic bronchial asthma (10 women and six men) with a mean age of 38·4 years (range 20–69 years), 20 patients with non-atopic bronchial asthma (12 women and 8 men) with a mean age of 45·9 years (range 20–70 years), and 25 normal subjects (14 women and 11 men) with a mean age of 34·8 years (range 24–46 years). All patients with bronchial asthma met the American Thoracic Society's definition of asthma [1]. The patient characteristics have been published previously elsewhere [32].

Briefly, all asthmatic patients had a history of episodic wheeze and dyspnoea, reversible bronchoconstriction, and airway hyperresponsiveness measured by direct writing the dose–response curve of respiratory resistance (Rrs) during the continuous inhalation of the methacholine in stepwise incremental concentrations [33]. Atopic or non-atopic bronchial asthma was defined by a history of bronchoconstrictive response after allergen exposure, total serum IgE levels ($>$ 250 U/ml), and specific IgE levels against house dust mite (*Dermatophagoides farinea* (*Df*)) ($>$ 0·34 PRU/ml) and/or skin prick tests to *Df*. At the time of this study, 23 patients (10 were atopic and 13 were non-atopic) were taking inhaled beclomethasone dipropionate (BDP) (200-400 μg/day), but none of the patients was taking oral corticosteroids. Severity of asthma was defined as follows: mild, dyspnoea attacks less than three times a week; moderate, dyspnoea attacks more than three times a week; and severe, daily dyspnoea attacks. All patients were mild cases. Asthma attacks and stable conditions (asymptomatic period) were defined on the basis of the presence of clinical symptoms and values of peak expiratory flowrate (PEFR). The patients had wheeze, chest tightness and decreased values of PEFR during asthma attacks, whereas they were asymptomatic and their PEFR values were $>$ 70% of that predicted in stable conditions. Blood samples were obtained from patients with asthma attacks on day 1 and additionally on day 7 or 14 in stable conditions when they visited the out-patient clinic. After initial blood samples were obtained, all patients were treated with systemic hydrocortisone succinate (300 $\sim$ 600 mg) or inhaled β_2 agonists on day 1 once only. Differential leucocyte counts were performed by an automated blood cell analysis. Healthy normal control subjects had no history of allergy and bronchial asthma, had normal total and specific IgE levels, and were not taking any medication. Informed consent was obtained from all patients and normal control subjects.

Measurement of serum sTNF-RI, sTNF-RII and IL-1Ra levels

Serum sTNF-RI, sTNF-RII and IL-1Ra levels were measured by commercially available ELISA kits (Amersham International plc, Aylesbury, UK). ELISA was performed according to the manufacturer's instructions. The sensitivity of sTNF-RI ELISA, sTNF-RII ELISA and IL-1Ra ELISA is 25 pg/ml, 5·0 pg/ml and 22·0 pg/ml, respectively. All samples were assayed in duplicate.

Measurement of serum TNF-α and IL-1β levels

Serum levels of TNF-α (T Cell Science Inc., Cambridge, MA) and IL-1β (Ohtsuka Pharmaceutical Co. Ltd., Osaka, Japan) were measured by commercially available ELISA kits. ELISA was performed according to the manufacturer's instructions. The sensitivity of TNF-α ELISA and IL-1β is 1·5 pg/ml and 5·0 pg/ml, respectively. All samples were assayed in duplicate.

Statistical analysis

Statistical significance was analysed using the Mann–Whitney *U*-test. Spearman's test was used for correlation analysis. $P < 0{\cdot}05$ was considered significant.

RESULTS

Serum sTNF-RI levels

Sera from patients with atopic bronchial asthma during asthma attacks contained more sTNF-RI ($n = 16$; $0{\cdot}70 \pm 0{\cdot}22$ ng/ml (mean $\pm$ s.d.); 0·65 (0·40–1·05) ng/ml (median (range)) than those in stable conditions ($0{\cdot}42 \pm 0{\cdot}19$ ng/ml; 0·37 (0·10–0·68) ng/ml; $P < 0{\cdot}001$) (Fig. 1a). Similar observations were obtained in patients with non-atopic bronchial asthma: i.e. sera from patients with non-atopic bronchial asthma during asthma attacks contained more sTNF-RI ($n = 20$; $0{\cdot}72 \pm 0{\cdot}31$ ng/ml; 0·72 (0·38–1·64) ng/ml) than those in stable conditions ($0{\cdot}54 \pm 0{\cdot}19$ ng/ml; 0·54 (0·30–1·02) ng/ml; $P < 0{\cdot}001$) (Fig. 1b). Sera from all patients with bronchial asthma during asthma attacks contained more sTNF-RI ($n = 36$; $0{\cdot}77 \pm 0{\cdot}28$ ng/ml; 0·71 (0·38–1·64) ng/ml) than those in stable conditions ($0{\cdot}48 \pm 0{\cdot}19$ ng/ml; 0·45 (0·10–1·00) ng/ml; $P < 0{\cdot}0001$). There was no significant difference in serum sTNF-RI levels during asthma attacks between atopic asthmatics and non-atopic asthmatics. Similarly, there was no significant difference in serum sTNF-RI in stable conditions between groups (Table 1).

Serum sTNF-RII levels

Sera from patients with atopic bronchial asthma during asthma attacks contained more sTNF-RII ($n = 16$; $2{\cdot}55 \pm 0{\cdot}77$ ng/ml; 2·39 (1·56–3·85) ng/ml) than those in stable conditions ($1{\cdot}65 \pm 0{\cdot}38$ ng/ml; 1·60 (1·02–2·39) ng/ml; $P < 0{\cdot}001$) (Fig. 2a). Similar observations were obtained in patients with non-atopic bronchial asthma: i.e. sera from patients with non-atopic bronchial

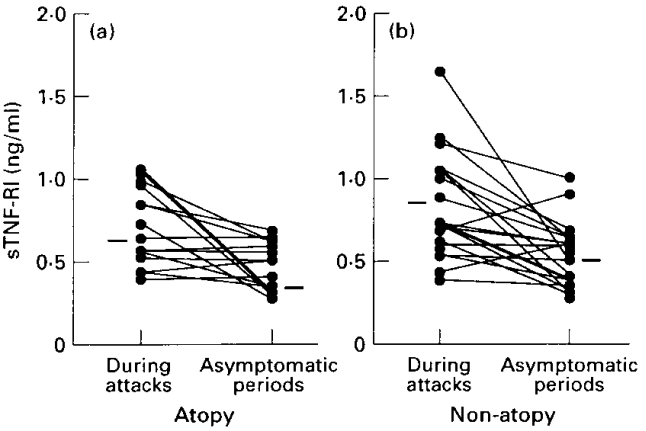

Fig. 1. Serum soluble form of the 55-kD TNF receptor (sTNF-RI) levels in patients with bronchial asthma during asthma attacks and in stable conditions. Serum sTNF-RI levels in patients with atopic bronchial asthma (a) and patients with non-atopic bronchial asthma (b) during asthma attacks and in stable conditions were measured. Horizontal short lines represent median of each group. Median of serum sTNF-RI levels in normal control subjects ($n = 19$) was 0·43 ng/ml.

Table 1. Serum levels of soluble form of the 55-kD TNF receptor (sTNF-RI), soluble form of the 75-kD TNF receptor (sTNF-RII) and IL-1 receptor antagonist (IL-1Ra) in patients with bronchial asthma and normal control subjects

	Atopic asthmatics		Non-atopic asthmatics		
	Attack (+)	Attack (−)	Attack (+)	Attack (−)	Normal controls
sTNF-RI	0·65* (0·40–1·05)	0·37 (0·10–0·68)	0·72* (0·35–1·64)	0·54 (0·30–1·02)	0·43 (0·24–0·67)
sTNF-RII	2·39* (1·56–3·85)	1·60 1·02–2·39)	2·87* (1·43–4·86)	1·64 (0·79–3·52)	1·22 (0·73–1·95)
IL-1Ra	218* (104–480)	145 (124–308)	208* (108–384)	151 (64–281)	109 (20–375)

Results are expressed as median values (range).
* $P < 0·001$ compared with normal controls.

asthma during asthma attacks contained more sTNF-RII ($n = 20$; $2·99 \pm 1·02$ ng/ml; 2·87 (1·43–4·86) ng/ml) than those in stable conditions ($1·79 \pm 0·69$ ng/ml; 1·64 (0·79–3·52) ng/ml; $P < 0·001$) (Fig. 2b). Sera from all patients with bronchial asthma during asthma attacks contained more sTNF-RII ($n = 36$; $2·80 \pm 0·93$ ng/ml; 2·85 (1·43–4·86) ng/ml) that those in stable conditions ($1·73 \pm 0·57$ ng/ml; 1·64 (0·79–3·52) ng/ml; $P < 0·0001$). There was no signifi-cant difference in serum sTNF-RII levels during asthma attacks between atopic asthmatics and non-atopic asthmatics. Similarly, there was no significant difference in serum sTNF-RII in stable conditions between groups (Table 1).

Serum IL-1Ra levels

Sera from patients with atopic bronchial asthma during asthma attacks contained more IL-1Ra ($n = 16$; $246·7 \pm 113·1$ ng/ml; 218 (104–480) pg/ml) than those in stable conditions ($165·8 \pm 51·2$ ng/ml; 145 (124–308) pg/ml; $P < 0·05$) (Fig. 3a). Similar observations were obtained in patients with non-atopic bronchial asthma: i.e. sera from patients with non-atopic bronchial asthma during asthma attacks contained more IL-1Ra ($n = 20$; $227·2 \pm 84·1$ pg/ml; 208 (108–384) pg/ml) than those in stable conditions ($158·7 \pm 55·7$ pg/ml; 151 (64–281) pg/ml; $P < 0·005$) (Fig. 3b). Sera from all patients with bronchial asthma during asthma attacks contained more IL-1Ra ($n = 36$; $235·9 \pm 97·0$ pg/ml; 212 (104–480) pg/ml) than those in stable conditions ($161·8 \pm 53·1$ pg/ml; 145 (64–308) pg/ml; $P < 0·001$). There was no significant difference in serum IL-1Ra levels during asthma attacks between atopic asthmatics and non-atopic asthmatics. Similarly, there was no significant difference in serum IL-1Ra in stable conditions between groups (Table 1). Serum levels of sTNF-R during asthma attacks did not correlate with the degree of airway hyperresponsiveness (values of minimum dose of methacholine (D_{min}) and slope of respiratory conductance (sGrs), peripheral eosinophil counts, percentage of predicted values of PEFR before asthma attacks, and percentage of decrease in values of PEFR during asthma attacks (data not shown). Serum levels of sTNF-R and the value of PEFR during asthma attacks were compared with those in stable conditions. Of

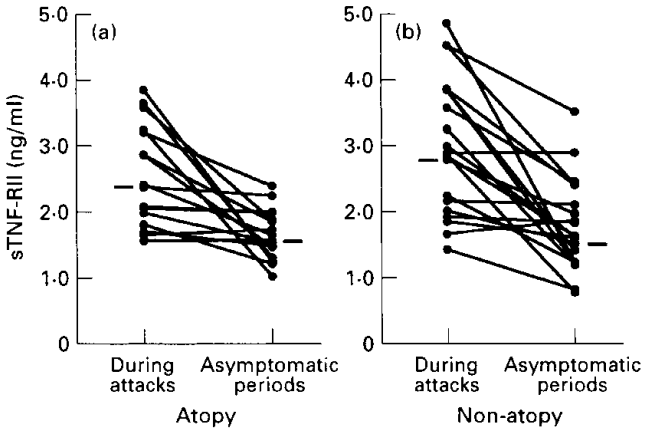

Fig. 2. Serum soluble form of the 75-kD TNF receptor (sTNF-RII) levels in patients with bronchial asthma during asthma attacks and in stable conditions. Serum sTNF-RII levels in patients with atopic bronchial asthma (a) and patients with non-atopic bronchial asthma (b) during asthma attacks and in stable conditions were measured. Horizontal short lines represent median of each group. Median of serum sTNF-RII levels in normal control subjects was 1·22 ng/ml.

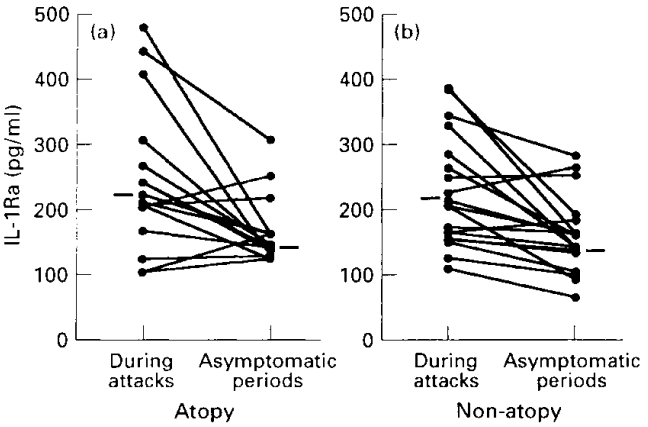

Fig. 3. Serum IL-1Ra levels in patients with bronchial asthma during asthma attacks and in stable conditions. Serum IL-1Ra levels in patients with atopic bronchial asthma (a) and patients with non-atopic bronchial asthma (b) during asthma attacks and in stable conditions were measured. Horizontal short lines represent median of each group. Median of serum IL-1Ra levels in normal control subjects was 108·9 pg/ml.

36 bronchial asthmatics, 32 patients and 32 patients showed a decrease in serum sTNF-RI levels and in serum sTNF-RII levels in stable conditions, respectively, whereas the values of PEFR in all patients were improved and greater than 70% of that predicted in stable conditions. In addition, the percentage of decrease in serum levels of sTNF-RI and sTNF-RII did not correlate with the percentage of improvement in values of PEFR (changes were calculated by a percentage of the values on day 1 during asthma attacks). There was no difference in the percentage of decrease in serum levels and sTNF-RI and sTNF-RII levels between patients treated with hydrocortisone sodium succinate and patients treated with inhaled β_2 agonists on day 1 (data not shown). Similar observations were obtained for IL-1Ra.

Relationship between serum sTNF-RI levels and serum sTNF-RII levels

There was a significant correlation between serum sTNF-RI levels and serum sTNF-RII levels in patients with bronchial asthma ($r = 0{\cdot}97$, $P < 0{\cdot}0001$) (Fig. 4).

Relationship between serum sTNF-RI levels or serum sTNF-RII levels and serum IL-1Ra levels

There was a significant correlation between serum sTNF-RI levels or serum sTNF-RII levels and serum IL-1Ra levels in patients with bronchial asthma ($r = 0{\cdot}69$, $P < 0{\cdot}0001$; $r = 0{\cdot}68$, $P < 0{\cdot}0001$, respectively) (Fig. 5).

Serum sTNF-RI, sTNF-RII and IL-1Ra levels in bronchial asthmatics and normal controls

Serum levels of sTNF-RI, sTNF-RII and IL-1Ra in bronchial asthmatics and normal control subjects and statistical differences between study groups are summarized in Table 1. Serum levels of sTNF-RI during asthma attacks were higher in atopic bronchial asthmatics than those in normal control subjects, whereas sTNF-RI levels in sera from atopic bronchial asthmatics in stable conditions were comparable to those from normal subjects. Similar observations were obtained in sTNF-RII and IL-1Ra. In the case of non-atopic bronchial asthmatics, similar observations were obtained.

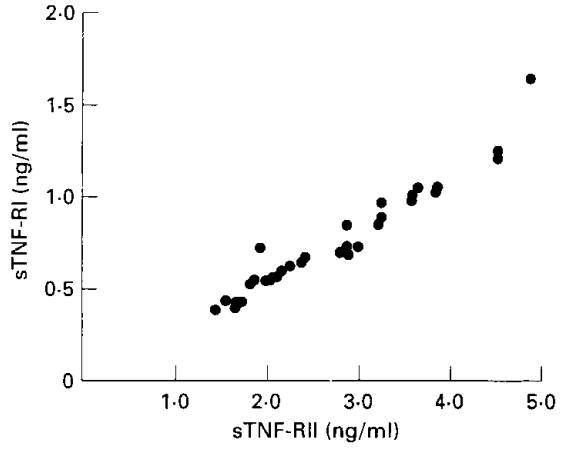

Fig. 4. Relationship between serum soluble form of the 55-kD TNF receptor (sTNF-RI) levels and serum soluble form of the 75-kD TNF receptor (sTNF-RII) levels in patients with bronchial asthma. Relationship between serum sTNF-RI levels and serum sTNF-RII levels during asthma attacks was analysed in 36 patients with bronchial asthma.

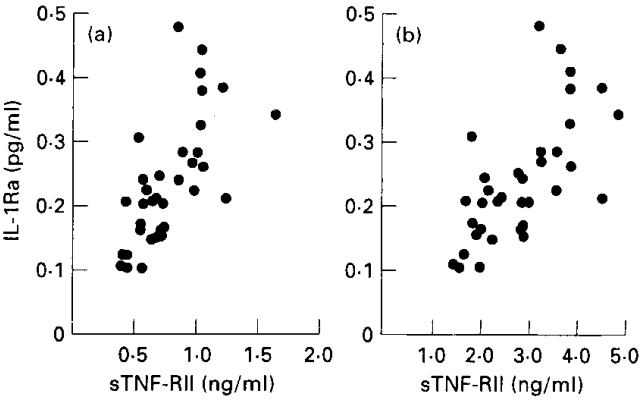

Fig. 5. Relationship between serum soluble form of the 55-kD TNF receptor (sTNF-RI) levels or serum soluble form of the 75-kD TNF receptor (sTNF-RII) levels and serum IL-1Ra levels in patients with bronchial asthma. Relationship between serum sTNF-RI levels and serum IL-1Ra levels (a), and serum sTNF-RII levels and serum IL-1Ra levels (b) during asthma attacks was analysed in 36 patients with bronchial asthma.

Serum TNF-α levels

The results with serum TNF-α levels as shown in Fig. 6 were reported previously [32]. Since it was of interest to clarify the relationship between the magnitude of changes in serum levels of sTNF-RI and sTNF-RII during asthma attacks and in stable conditions, and the magnitude of change in serum levels of TNF-α, we show here the results with serum TNF-α levels.

Sera from patients with atopic bronchial asthma during asthma attacks contained more TNF-α ($n = 16$; $61{\cdot}6 \pm 25{\cdot}0$ pg/ml; 64·6 (27·9–107·0) pg/ml) than those in stable conditions ($30{\cdot}7 \pm 15{\cdot}2$ pg/ml; 27·3 (9·3–63·3) pg/ml; $P < 0{\cdot}01$) (Fig. 6a). Similar observations were obtained in patients with non-atopic bronchial asthma: i.e. sera from patients with non-atopic bronchial asthma during asthma attacks contained more TNF-α ($n = 20$; $67{\cdot}9 \pm 39{\cdot}1$ pg/ml; 63·3 (24·0–159·0) pg/ml) than those in stable conditions ($38{\cdot}2 \pm 21{\cdot}6$ pg/ml; 39·3 (0–80·6) pg/ml; $P < 0{\cdot}01$) (Fig. 6b). Serum IL-1β levels were below the levels of reliable assay sensitivity limit.

Serum sTNF-RI, sTNF-RII and IL-1Ra levels in patients with bronchial asthma receiving inhaled BDP and those in patients with bronchial asthma not receiving inhaled BDP

It was of interest to compare serum levels of sTNF-RI, sTNF-RII and IL-Ra in patients with bronchial asthma during asthma attacks who were receiving inhaled BDP with those in patients with bronchial asthma who were not receiving inhaled BDP, since inhaled corticosteroids have been shown to be effective in controlling allergic inflammation in the asthmatic airway [34]. The results are summarized in Table 2. There was no significant difference in serum levels of sTNF-RI, sTNF-RII and IL-1Ra between study groups.

DISCUSSION

Our results showed that levels of sTNF-RI, sTNF-RII and IL-1Ra in sera from patients with bronchial asthma obtained during asthma

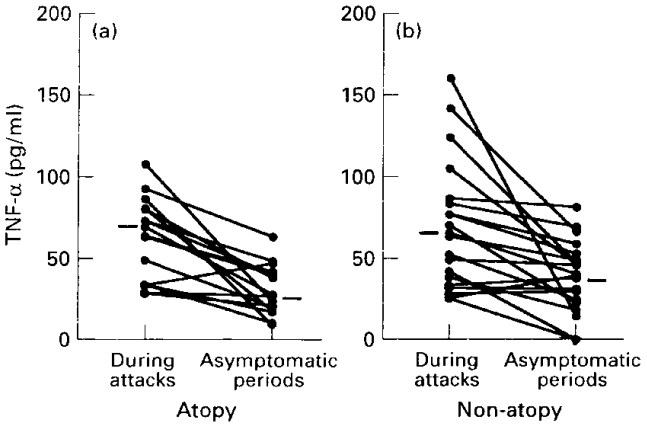

Fig. 6. Serum TNF-α levels in patients with bronchial asthma during asthma attacks and in stable conditions. Serum TNF-α levels in patients with atopic bronchial asthma (a) and patients with non-atopic bronchial asthma (b) during asthma attacks and in stable conditions were measured. Horizontal short lines represent median of each group. Median of serum TNF-α levels in normal control subjects was 24·4 pg/ml.

attacks were higher than those in sera in stable conditions. These findings were obtained regardless of atopic status.

Serum sTNF-RI and sTNF-RII levels in patients with bronchial asthma were elevated during asthma attacks and decreased in stable conditions to levels comparable to normal control subjects. The nature of change in serum sTNF-R levels was similar to the results where serum TNF-α levels were elevated during asthma attacks and decreased in stable conditions. Similarly, serum IL-1Ra levels were elevated during asthma attacks and decreased in stable conditions. These results indicate that serum IL-1Ra levels as well as serum sTNF-R levels were elevated in bronchial asthma during asthma attacks. These results show that the change in serum sTNF-R and IL-1Ra levels were closely related with clinical improvement of asthma attacks.

Involvement of TNF-α and IL-1 in the production of allergic inflammation and the development of late asthmatic responses has been shown. Functional activities of sTNF-R and IL-1Ra have been investigated and described. Competition of sTNF-R with TNF-R on the surface of cells and binding of IL-1Ra to IL-1 receptors on the surface of cells result in interference with TNF activities [22,35] and IL-1 activities [19,20], respectively. The elevation of sTNF-R and IL-1Ra in plasma/serum and biological fluids reflecting a variety of inflammatory disorders has been shown in several diseases [24–28]. In addition, protective and inhibitory effects of sTNF-R and IL-1Ra against several inflammatory diseases have been shown [17,18, 29–31]. In allergic inflammatory disease, inhibitory effects of IL-1Ra against bronchial hyperreactivity [17], IgE synthesis and allergen-specific production of cytokines such as IL-1β, TNF-α, IL-6 and granulocyte-macrophage colony-stimulating factor (GM-CSF) [36] have been shown. Taken together with inhibitory effects of sTNF-R and IL-1Ra, and our results demonstrating the elevation of serum sTNF-R and IL-1Ra levels during asthma attacks, sTNF-R and IL-1Ra may serve to limit the activity of TNF-α and IL-1, and thus may regulate allergic inflammation in bronchial asthma.

Serum sTNF-RI, sTNF-RII and IL-1Ra levels during asthma attacks did not correlate with the percentage of decrease in PEFR, indicating that serum levels of these cytokine inhibitors were not related with severity of asthma attacks. Although we measured serum sTNF-R and IL-1Ra levels in mild asthmatics in this study, it might be of interest to compare serum sTNF-R and IL-1Ra levels during asthma attacks with the degree of airway hyperresponsiveness and the percentage of predicted value of PEFR before asthma attacks. There was no correlation between them. These results indicate that serum sTNF-R and IL-1Ra levels were not related with severity of asthma in our mild asthmatics. Taking all the data into account, serum sTNF-R and IL-1Ra levels were apparently elevated during asthma attacks, whereas their levels were not related with severity of asthma and asthma attacks. In addition, no significant difference in percentage of decrease in serum sTNF-R and IL-1Ra between patients treated with inhaled β_2 agonists and patients treated with systemic hydrocortisone succinate indicates that therapeutic agents did not affect serum levels of sTNF-R and IL-1Ra in stable conditions. Finally, we compared serum sTNF-R and IL-1Ra levels in patients during asthma attacks who were receiving inhaled BDP with those in patients who were not receiving inhaled BDP. There was no significant difference in serum sTNF-R and IL-1Ra levels between them. A dosage effect of inhaled BDP on serum sTNF-R and IL-1Ra levels should be examined.

In conclusion, our study demonstrates elevation of serum levels of sTNF-RI, sTNF-RII and IL-1Ra in bronchial asthma during asthma attacks. These results suggest that higher levels of serum

Table 2. Serum levels of soluble form of the 55-kD TNF receptor (sTNF-RI), soluble form of the 75-kD TNF receptor (sTNF-RII) and IL-1 receptor antagonist (IL-1Ra) in bronchial asthmatics receiving inhalated beclomethasone dipropionate (BDP) and those in bronchial asthmatics not receiving BDP

	Atopic asthmatics		Non-atopic asthmatics	
	BDP (+)	BDP (−)	BDP (+)	BDP (−)
sTNF-RI	0·60 (n = 10; 0·43–1·05)	0·76 (n = 6; 0·40–0·98)	0·72 (n = 13; 0·38–1·24)	0·72 (n = 7; 0·54–1·64)
sTNF-RII	2·22 (n = 10; 1·56–3·85)	2·61 (n = 6; 1·64–3·57)	2·85 (n = 13; 1·43–4·53)	2·88 (n = 7; 2·01–4·87)
IL-1Ra	208 (n = 10; 104–443)	233 (n = 6; 124–308)	212 (n = 13; 108–384)	204 (n = 7; 148–342)

Results are expressed as median values (number; range).

sTNF-RI, sTNF-RII and IL-1Ra may reflect up-regulation of sTNF-RI, sTNF-RII and IL-1Ra production in allergic inflammation, and sTNF-RI, sTNF-RII and IL-1Ra may contribute to regulating TNF-α- and IL-1-mediated production of allergic inflammation and development of late asthmatic reaction in bronchial asthma.

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