

Short communication

Up-regulation of IL-18 in allergic rhinitis

Background: This paper reports a study on the concentrations of the pro-inflammatory cytokines IL-18 and IL-1 β in nasal secretions of allergic rhinitis patients in relation to ECP and nasal symptoms.

Methods: We measured IL-18 and IL-1 β concentrations using ELISA, and eosinophilic cationic protein (ECP) using the CAP system, in nasal secretions of 15 seasonal allergic rhinitis (SAR) patients at six visits throughout the pollen season. Pollen exposure, nasal and ocular symptoms were monitored daily. Furthermore, we measured IL-18, IL-1 β and ECP concentrations in nasal secretions of 19 controls and 20 symptomatic persistent allergic rhinitis (PAR) patients with house dust mite allergy.

Results: In SAR, the increase of IL-18, IL-1 β and ECP paralleled the pollen flight with a time delay. IL-18 and IL-1 β significantly increased during the pollen season compared to baseline, and differently from ECP, remained elevated until 4 weeks after the season. In PAR, the concentrations of IL-18 and ECP, but not IL-1 β , were significantly higher compared to controls, with IL-18 concentrations also being significantly higher than in SAR.

Conclusion: This is the first study to demonstrate the up-regulation of IL-18 in nasal secretions in allergic rhinitis. The persistence of elevated IL-18 concentrations until after the season and the high concentrations in PAR compared to SAR suggests its role in persistent allergic inflammation.

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Key words: ECP; IL-1 β ; IL-18; persistent allergic rhinitis; pollen count; seasonal allergic rhinitis.

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Accepted for publication 15 April 2002

Allergic rhinitis is the result of an immunologically mediated hypersensitivity reaction of the nasal mucosa, initiated by exposure to specific allergens (1, 2). The reaction is characterized by the infiltration of various inflammatory cell populations. Eosinophils are major effector cells with basophils, monocytes, neutrophils and lymphocytes also playing a significant role (3–6). It has become clear that in IgE mediated allergic rhinitis, Th2 cells drive the inflammation, initiating and sustaining the allergic response through the production of a network of Th2 cytokines. Pro-inflammatory cytokines such as IL-1 β and TNF- α also contribute to the inflammation by acting on endothelial cells and lymphocytes. They might be secreted from a variety of cells, including immune and non-immune cells, and increase the severity of the reaction (7).

In previous studies we demonstrated that pro-inflammatory cytokines are released into nasal secretions of allergic rhinitis patients under natural and artificial conditions inducing the expression of adhesion receptor molecules (8–10). In addition we assessed the up-regulation of the cytokine IL-1 β in seasonal allergic rhinitis patients during and after the pollen season, supporting

the concept of a persistent inflammation stimulated by pro-inflammatory cytokines (8).

IL-18, formerly called the IFN- γ -inducing factor, is a pro-inflammatory cytokine closely related to the IL-1 family in terms of structure and pro-inflammatory properties. IL-18 and IL-1 β have an analogue signalling pathway and both cytokines are produced as inactive precursors, which need cleavage by IL-1 beta converting enzyme (ICE or caspase-1) into the active protein (10, 11).

IL-18 was first described as an important factor in the Th1 response by its ability to induce IFN- γ production in T-cells, B-cells and NK cells, in collaboration with IL-12 (13, 14). IFN- γ is known as a potent inhibitor of the Th2-driven allergic processes.

However, recent reports demonstrated a pleiotropic role for IL-18 in Th1 and Th2 responses dependent on the cytokine milieu (15, 16). IL-18 can also induce Th2 cytokines such as IL-13, IL-10 and IL-4 (17–19) and may amplify inflammation, as demonstrated by the recruitment of eosinophils in mouse models of IgE-mediated allergic asthma (18–20). Because of its relationship to IL- β and its broad-spectrum pro-inflammatory functions, we focused on the possible role of IL-18 in IgE-mediated inflammation of the nose.

This study aimed to investigate the release of IL-18 under natural conditions in patients with seasonal and persistent (house dust mite) allergic rhinitis and to

determine whether its secretion pattern would be related to the production of IL-1 β or to the activation of eosinophils. Therefore, we assessed the concentrations of IL-18, ECP and IL-1 β in nasal secretions of persistent allergic rhinitis patients and seasonal allergic patients before, during and after the pollen season, together with pollen exposure and symptom data.

Material and methods

Patient recruitment

The patients suffering from allergic rhinitis were free of other clinically significant illness or other nasal disease as determined by their medical history, physical examination and rhinoscopy. Patients with mild allergic asthma were included if they did not need medication chronically. Systemic and nasal corticosteroids were excluded 4 weeks before and during the study. The use of oral antihistamines was only excluded 4 weeks before the study; however, they were allowed as rescue medication during the season. Fifteen seasonal allergic rhinitis patients (SAR group; 5 F/10 M, mean age 31 years and range 22–54 years) were included, based on a positive history and skin prick tests (Allergopharma, Reinbek, Germany) positive for birch and grass pollen (mixture of five common grasses), and monitored every 4 weeks before the beginning of the birch pollen season until the end of the grass pollen season (from mid March to mid August 1999). All patients came to the centre within a 2-week period, and data obtained at visit 1 were used as baseline. Twenty patients suffering from persistent allergic rhinitis (PAR group; 9 F/11 M, mean age 34 years and range 18–55 years) were selected based on a positive history, a skin prick test positive for at least one perennial allergen (*Dermatophagoides pteronyssinus*) and present symptoms at inclusion, with nasal obstruction being at least moderate on a 0–3 point score (one visit in December 1999).

Simultaneously, 19 volunteers (Controls; 9 F/10 M, mean age 31 years and range 24–48 years) without nasal disease or asthma, free of any clinically significant illness, and with negative skin prick test to a standard panel of allergens, formed the control group. The local Ethical Committee approved the study, and informed consent was obtained from each individual before inclusion in the study.

Pollen data and symptom scores

Daily birch and grass pollen concentrations were provided from local pollen information services and were registered from mid March to mid August. Concentrations are expressed as the number of pollen/m³/day.

Seasonal allergic rhinitis patients evaluated daily nasal symptoms (rhinorrhoea, blockage, sneezing, itching) and eye symptoms (itchy, red eyes) using a 0–3 point score (none, mild, moderate, severe) daily in the morning and documented all in a diary.

Collection of nasal secretion samples

Nasal secretion samples were collected by means of pre-weight paper disks of 6 mm in diameter (Shandon Inc., Pittsburgh). Three disks were gently inserted bilaterally in the nose and placed on the nasal septum, opposite to the inferior turbinate, for 1 min. The secretion weight was determined as the difference compared to before insertion, and the disks were transferred into 4 mL 0.9% saline solution for 2 h at 4°C. After centrifugation at 1500 g for 15 min, supernatants were aliquoted and stored at –70°C until further analysed.

Measurements of IL-1 β , IL-18 and ECP

All supernatants were assayed for IL-18 (sensitivity 12.5 pg/mL, mean recovery 86%; MBL, Naka-ku, Nagoya, Japan) and IL-1 β (sensitivity 0.1 pg/mL, mean recovery 93%; R & D System, Minneapolis, USA) by ELISA using commercially available kits. ECP was measured in duplicate by the CAP system (sensitivity 0.5 μ g/L, mean recovery 86%; Pharmacia, Uppsala, Sweden) according to the guidelines of the manufacturer and recalculated on the basis of the secretion weight.

Statistical analyses

Data are expressed as means with the standard error of mean (SEM). Normal distribution of the data was confirmed by the Kolmogorov–Smirnov test. One-way analysis of variance (ANOVA) was used to compare the data of the SAR patients at the different visits. Unpaired samples *t*-test was used to detect significant changes between patients with PAR and controls. Pearson's correlation coefficient (*r*) and test were used to assess the relationship between the parameters. *P*-values less than 0.05 were considered statistically significant.

Results

Pollen count and symptom scores of seasonal allergic rhinitis patients

Birch and/or grass pollen exposure was demonstrated from the end of March until beginning of August (Fig. 1). Maximum concentrations of birch pollen were seen in April (439/m³/day) and of grass pollen in June and July (visits 4 and 5, 100 and 74/m³/day, respectively). The last day with an exposure of more than 20 pollen/m³/day was 21st of July.

Rhinoconjunctivitis symptoms initiated at the start of the season and intensified over time in relation to pollen exposure (Fig. 1). Interestingly, daily nasal and ocular symptoms peaked at the end of May and in June, although maximum pollen exposure was more than four times higher in April. Furthermore, symptoms persisted until mid-August, despite a very low or absent pollen exposure.

Expression pattern of IL-18, IL-1 β and ECP in seasonal allergic rhinitis patients

In nasal secretions, IL-18 concentrations increased from visit 1 (March) to visit 3 (May), with a plateau until visit 6 (August) (Fig. 2). Compared to visit 1 (= baseline visit), concentrations of IL-18 were significantly elevated at visits 3, 5 and 6 (*P* < 0.05). IL-1 β followed the same secretion patterns, with concentrations significantly increased compared to baseline at visits 3 and 5 (*P* < 0.05). The increase of both cytokines paralleled the daily symptoms and remained high up to 4 weeks after the last pollen peak with > 20 pollen/m³/day. Moreover, IL-18 and IL-1 β were significantly correlated at visits 2 (*r* = 0.6822, *P* < 0.01), 3 (*r* = 0.6194, *P* < 0.05) and 6 (*r* = 0.7420, *P* < 0.01). The secretion of ECP was up-regulated throughout the season

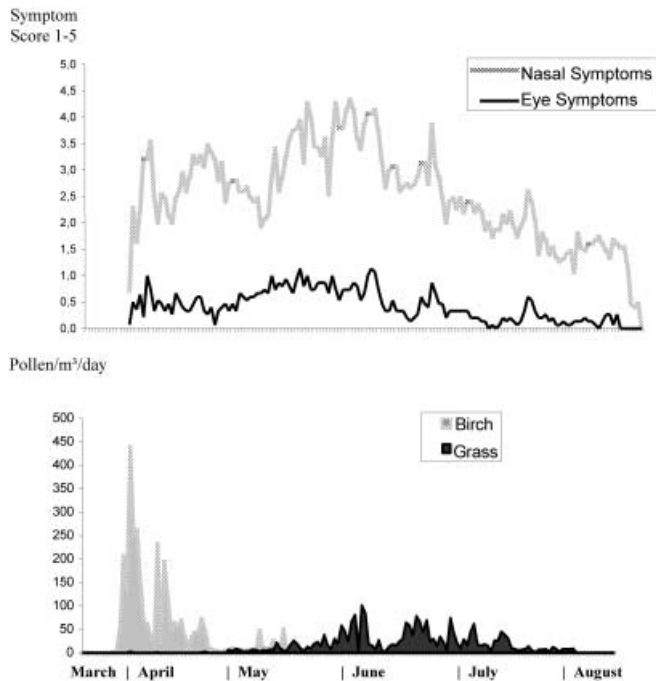


Figure 1. Relation between rhinoconjunctivitis symptoms and the pollen count registered at the same time points. In the beginning of April, we noted the highest birch pollen peaks of 450/m³ and 350/m³ a day. Maximum concentrations of grass pollen were measured in June and July with 100/m³ and 74/m³ a day, respectively. The last grass pollen peak (>20 pollen/m³/day) was seen at the end of July. Nasal (upper line) and eye symptoms (lower line), evaluated daily by symptom scores, were initiated at the start of the pollen flight and intensified over the time in relation to pollen exposure.

and reached significance at visits 3 and 4 ($P < 0.05$) compared to baseline, but decreased at the end of season. At all visits, ECP was correlated to IL-1 β ($r = 0.530$ – 0.849 , $P < 0.05$ – 0.001). Correlations between IL-18 and ECP were significant at visits 3 ($r = 0.698$, $P < 0.01$) and 6 ($r = 0.7394$, $P < 0.01$) only.

Concentrations of IL-18, IL-1 β and ECP in persistent allergic rhinitis patients

Concentrations of IL-18 in nasal secretions of PAR patients were significantly higher compared to healthy controls ($P = 0.0002$) (Fig. 3) and to any visit during seasonal allergen exposure ($P < 0.01$), whereas IL-1 β concentrations were not increased. ECP data were also significantly increased in comparison to control patients ($P = 0.0314$), but not in comparison to seasonal allergic subjects. ECP was not correlated to IL-1 β nor to IL-18.

Discussion

This is the first clinical study providing evidence for the involvement of IL-18 in nasal allergic inflammation.

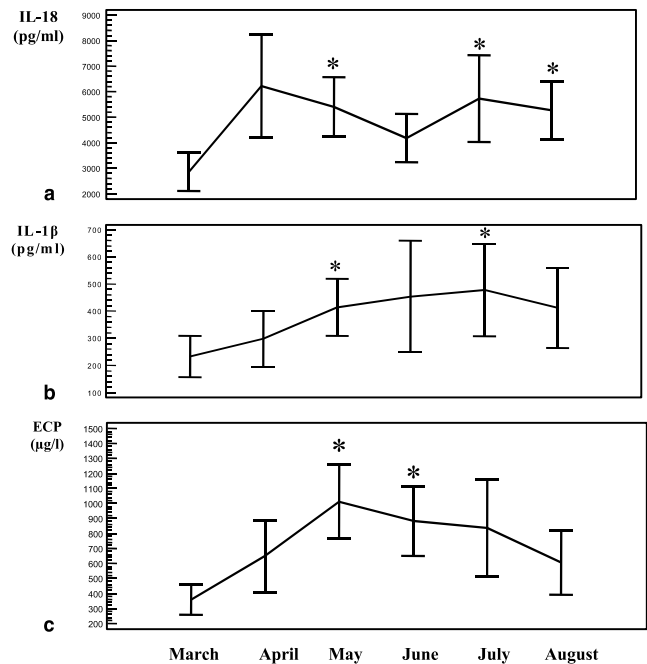


Figure 2. Concentrations of IL-18, IL-1 β and ECP in nasal secretions of seasonal allergic rhinitis patients ($n = 15$) measured at 4-week intervals before the season throughout the pollen season (end of March – mid August). Values of IL-18, IL-1 β and ECP are compared to the baseline visit (visit 1) and are expressed as mean $\pm$ SEM. ANOVA was used to detect significant changes. The increase of IL-18 and IL-1 β paralleled the pollen flight with a delay and remained high up to 4 weeks after the last pollen peak. Concentrations of IL-18 were significantly elevated at visits 3, 4 and 6 ($P < 0.05$) (a). The production of IL-1 β was significantly enhanced at visits 3 and 5 ($P < 0.05$) and followed the same secretion pattern as IL-18 (b). The secretion of ECP was up-regulated throughout the season and reached significance at visits 3 and 4 ($P < 0.05$) (c).

The pro-inflammatory cytokine IL-18 is up-regulated because of natural allergen exposure in nasal secretions of seasonal allergic rhinitis patients, showing a similar pattern to IL-1 β , with a slow, but persistent increase during the course of the pollen season. In contrast to ECP, which was increased during the season, but tended to normalize shortly after the season, IL-18 remained increased. ECP was strongly correlated to IL-1 α throughout the season, whereas only limited correlations between IL-18 and ECP were found, suggesting a rather weak impact of IL-18 on the eosinophilic inflammation. In nasal secretions of PAR patients, IL-18 concentrations were significantly higher compared to controls and seasonal rhinitis subjects, but did not correlate to ECP, which was increased compared to controls only. The finding that there was no correlation between IL-18 and ECP again questioned the role of IL-18 in eosinophil regulation. However, the persistence of elevated IL-18 concentrations until after the season and the even higher concentrations in PAR compared to SAR suggest its likely role in long-term persistent allergic inflammation.

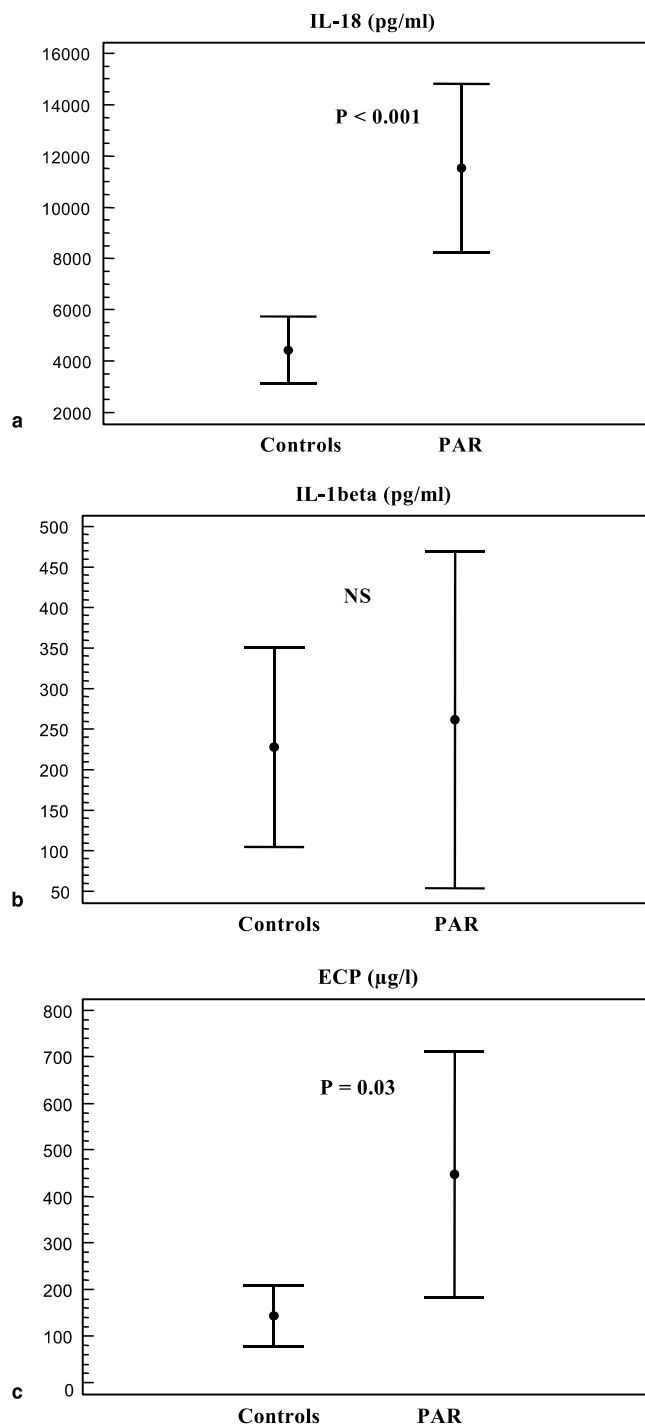


Figure 3. Concentrations of ECP, IL-1 β and IL-18 measured in nasal secretions of symptomatic persistent allergic rhinitis patients ($n = 20$) and controls ($n = 19$) on one visit in December. Data are expressed as means $\pm$ SEM. Unpaired samples t -tests were used to detect significant changes. Concentrations of IL-18 were significantly higher compared to healthy controls ($P < 0.001$) (a). IL-1 β was not increased in nasal secretions of PAR patients (b). ECP showed a significant up-regulation in PAR in comparison to controls ($P < 0.05$) (c).

IL-18 is a new member of the IL-1 family, to which it is closely related in terms of structure and pro-inflammatory properties (12). IL-1 is the prototype of the

pro-inflammatory cytokines, enhancing the severity of inflammation in different unspecific and specific ways (7). The receptors of IL-18 and IL-1 β belong to the IL-1R/TOLL-like receptor superfamily and have analogue signalling pathways, such as the recruitment of IL-1R-activating kinase and NFkappaB-inducing kinase. Moreover, both cytokines are produced as inactive precursors, which need cleavage by IL-1 beta converting enzyme (ICE or caspase-1) into the active protein (11–13). Pro-inflammatory activities of IL-18 have been demonstrated by *in vitro* experiments, showing the induction of gene expression and synthesis of IL-1 α , IL-1 β , TNF α , IL-8, IL-6 and ICAM-1 (7, 18, 21). The ability to stimulate the expression of adhesion molecules, cytokines and chemokines places IL-18 in a commanding role for amplifying the immune response. Previous studies demonstrated a persistent up-regulation of the pro-inflammatory cytokines IL-1 β , TNF-alpha and IL-6 in nasal secretions of seasonal allergic rhinitis patients (8, 22). A similar persistent up-regulation of IL-18 is illustrated in this study.

Apart from its pro-inflammatory properties, IL-18 was originally discovered as a potent inducer of IFN- γ in collaboration with IL-12 (14). However, recent studies demonstrated a more pleiotropic role for IL-18, highlighting its importance in both Th1 and Th2 driven pathways, depending on the cytokine milieu (15–17). The possible functions of IL-18 at different levels of the allergic mechanisms have mainly been analysed by *in vitro* and mice studies. It was shown that, in the absence of IL-12, IL-18 has the capacity to induce the production of IL-4, IL-10 and IL-13 and thus strongly promotes Th2 differentiation (17, 19, 23, 24). Wild et al. (19) found that the administration of IL-18 increased the production of ragweed-specific IgE and IgG1 in serum in a mouse model of allergic asthma, effects consistent with the support of a Th2 phenotype. Furthermore, transgenic mice over-expressing human caspase-1 in keratinocytes – resulting in high serum levels of mature IL-18 – spontaneously develop chronic dermatitis with high serum levels of IgE and IgG1 (16). Other studies provided further evidence for the contribution of IL-18 in the eosinophilic inflammation (19, 20). Intra-pulmonary administration of IL-18 in mice was associated with increased eotaxin levels and eosinophilic recruitment in the airways (19, 20). Furthermore, intranasal application of IL-18 together with ragweed increased the production of BAL eosinophilia, suggesting the stimulation of an allergic sensitization when co-administered with an allergen (19). Thus, IL-18 seems to drive the allergic inflammation by its ability to stimulate eosinophilia and IgE production in mice models.

This study suggests that there is an enhanced expression of IL-18 in allergic rhinitis, modulated directly or indirectly by allergen exposure. The exact mechanisms leading to the induction of IL-18 in allergic diseases are unknown. It is well accepted that the major source of IL-18 is the macrophage, but other immune and

non-immune cells such as dendritic cells, airway epithelial cells and keratinocytes are able to produce IL-18 constitutively (25, 26). Dendritic cells can increase the release of IL-18 by interaction with antigen-specific T-cells, and keratinocytes secrete IL-18 along with IL-12 in response to stimulation with contact allergens (27, 28).

In patients with seasonal allergic rhinitis, IL-1 β , IL-18 and ECP all were significantly up-regulated during seasonal allergen exposure, with a remarkably high correlation between IL-1 β and ECP throughout the study period. The increased concentrations of ECP highlight an eosinophilic inflammation, which, however, diminished shortly after the end of the season. In contrast to ECP, IL-18 remained up-regulated up to 4 weeks after the last pollen peak in our study. A further enhanced expression of IL-18, but not IL-1 β , in persistent inflammation was illustrated in patients suffering from PAR, suggesting a different

regulation of pro-inflammatory cytokines in seasonal vs persistent allergic inflammation and a possible role of IL-18 in persistent inflammation. However, the only weak correlation of IL-18 with ECP in SAR and the absence of any correlation in PAR do not suggest a direct impact of IL-18 on the regulation of eosinophilic inflammation.

To conclude, this is the first study demonstrating an increased expression of IL-18 in nasal secretions of allergic rhinitis patients due to allergen exposure (29). Although IL-18 belongs to the IL-1 superfamily, both pro-inflammatory cytokines demonstrated different release patterns in PAR, with IL-18 possibly linked to persistent inflammatory processes. However, our data do not support a direct role of IL-18 in the regulation of eosinophil activation. Further *in vivo* studies are needed to clarify the impact of IL-18 in the induction and maintenance of allergic inflammation.

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