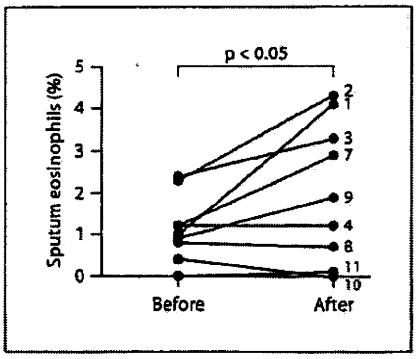

Fig. 1. Changes in sputum eosinophil ratios (%) after ICS cessation. Sputum was obtained from adult asthmatics (n = 9) during the run-in period (before cessation of ICS) or at the end of the study (after ICS cessation). Eosinophils were identified by May-Giemsa staining and morphologically. Patient numbers are shown on the right.

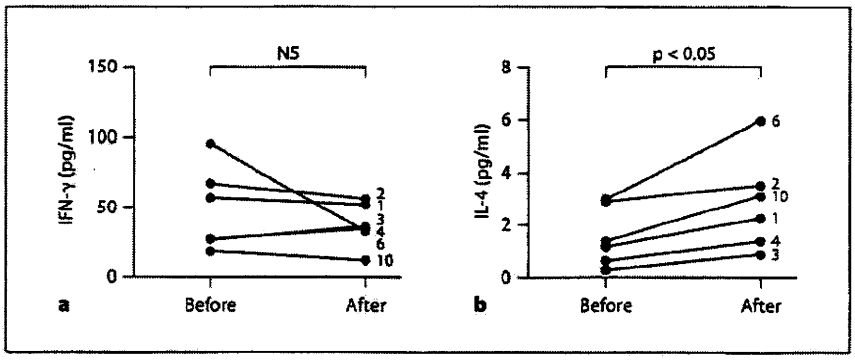

Fig. 2. Changes in IFN-γ (**a**) and IL-4 concentrations (**b**) in sputum after ICS cessation. Sputum was obtained from adult asthmatics (n = 6) during the run-in period (before cessation of ICS) or at the end of the study (after ICS cessation). Concentrations of IFN-γ or IL-4 in sputum supernatant are shown. Patient numbers are shown on the right. NS = Nonsignificant.

tion of ICS resulted in an increase in AHR in all 7 *Df*-sensitized adult asthmatics and asthma relapse in 4 (57.1%). The 4 who clinically relapsed were all sensitized to *Df*. Eosinophil numbers and IL-4 concentrations increased in sputum immediately before asthma relapse or AHR induction. These results indicate that remission in adult patients with allergic asthma, especially among those who are sensitized to house dust mites, is rare. The results also suggest that the eosinophil count or IL-4 concentration in sputum after ICS cessation could be an important predictive factor for relapse in adult asthma.

There is no standardized definition about complete remission or clinical remission in adult asthma. In this study, we used the term 'remission', but not 'complete remission' or 'clinical remission', according to the definition by the Japanese Pediatric Guidelines for the Treatment and Management of Asthma [1], as we evaluated patients only 1 year after ICS cessation. Our results demonstrated that only 1 patient (9.1%) achieved remission with normal airway response to MCh (no AHR) even 1 year after ICS cessation (table 2). Six patients had AHR without asthma symptoms for 1 year (54.5%), and asthma relapsed in 4 (36.4%) patients, all of whom relapsed within 4 months (table 2). Panhuysen et al. [20] studied 181 asthma patients aged 13–44 years at enrolment and found that only 11% remained in remission with no AHR and normal lung function after 25 years. Moreover, recent reports suggest that about 50% of adult asthmatics relapse within 1 year after ICS cessation [21–23], and that most clinical relapses occur within 3 months [21, 24]. Therefore, our results were consistent with these previous studies and confirmed that remission with no AHR in adult asthma would be more difficult to achieve. As increasing evidence indicates that airway inflammation is present during the remission of allergic asthma [25], our results might support the significance of an anti-inflammatory strategy, such as ICS therapy for asymptomatic adult asthmatics, but further studies are required.

AHR worsened in 10 (90.9%) of the 11 patients with allergic asthma after ICS cessation, and asthma recurred in 4 (36.4%) of them (table 2). Of the 7 *Df*-sensitized adult asthmatics, AHR was aggravated in all of them and asthma recurred in 4 (57.1%). Therefore, the atopic status, especially sensitization to house dust mites, may play an important role in the pathogenesis of asthma relapse, leading to the hypothesis that relapse in allergic asthma might be inevitable unless allergen avoidance is completely achieved. In childhood asthma, Bjerg-Bäcklund et al. [26] reported that the frequency of remission was significantly higher in non-allergic asthmatics than in allergic asthmatics. Limb et al. [11] reported that lower IgE levels and fewer positive allergy skin tests in addition to milder symptoms were factors predictive of remission of moderate-severe asthma. Sears et al. [27] reported that factors predictive of relapse were childhood sensitization to house dust mites as well as AHR and early age at onset. Our results in adult asthma were consistent with these findings in childhood asthma. Moreover, sensitization to

inhalant allergens, e.g. house dust mites, increases the risk of developing asthma [28, 29]. Toelle et al. [6] demonstrated that in addition to a low FEV_1 and AHR, atopy in childhood is a predictive factor for having asthma in adulthood. In a study by Visser et al. [7] the increase in AHR after ICS withdrawal was associated with more atopic features (positive RAST and high IgE) as well as lower FEV_1 levels, indicating that continued sensitization to house dust mites could trigger the development of asthma or the increase in AHR.

Eosinophils and IL-4 concentrations in sputum increased immediately before asthma relapse or AHR induction (fig. 1, 2), suggesting that the Th2-mediated immune response played an important role in these processes. Eosinophils release various lipid mediators, cytokines and growth factors involved in the pathogenesis of asthma [30]. IL-4 drives B-cell isotype switching from IgM to IgE [31] and augments eosinophil adhesion to and transmigration of eosinophils through the endothelium by enhancing the expression of adhesion molecules on endothelial cells [32], thus initiating eosinophil infiltration into the airways. In a report by Masuyama et al. [33], intranasal corticosteroid inhibited eosinophilic nasal inflammation and mRNA expression of IL-4 in the nasal mucosa, suggesting that IL-4 would mediate the development of eosinophilic inflammation in the airways. In a mouse model of allergic airway inflammation, To et al. [34] reported that antigen systemic sensitization could induce AHR and increase IL-4 concentration in bronchoalveolar lavage fluid before or at the early phase of eosinophilic airway inflammation. Therefore, IL-4 played an essential role in the increase in AHR at the early phase of eosinophilic airway inflammation, which was consistent with our results.

The effect of eosinophil counts in sputum on the prevention of asthma exacerbation has recently been highlighted [35], and Deykin et al. reported that asthma relapse in children is associated with an increased number of eosinophils in sputum [36]. Furthermore, Giannini et al. [23] reported that sputum eosinophil ratios significantly increase during symptom recurrence in adult asthmatics after ICS cessation. Therefore, evaluation of eosinophils in sputum would be a reasonable strategy for monitoring and preventing asthma relapse. Serial measurements of Th2 cytokines such as IL-4 in sputum might also be useful for monitoring.

However, limitations of this study were the small study cohort (only 11 patients participated in this study) and the allergic type of their asthma. Therefore, caution should be applied when extrapolating the findings of this study to all asthmatics. Further studies are required to clarify changes in eosinophil ratios and IL-4 concentrations in sputum after ICS cessation in all types of asthma, including non-allergic asthma.

In conclusion, we demonstrated that remission in adult patients with allergic asthma, especially those who are allergic to house dust mites, is difficult to achieve. Eosinophil ratios and IL-4 concentrations in sputum increased immediately before asthma relapse or AHR induction. Therefore, ICS cessation should be carefully considered in *Df*-sensitized adult asthmatics. Serial examination of eosinophil counts or IL-4 concentrations in sputum might provides a reasonable and useful strategy for monitoring and preventing asthma relapse.

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Disclosure Statement

The authors declare that no financial or other conflict of interest exists in relation to the content of this article.

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REVIEW ARTICLE

Allergen Immunotherapy in Asthma: Current Status and Future Perspectives

Makoto Nagata[1,2] and Kazuyuki Nakagome[1,2]

ABSTRACT

Allergen immunotherapy targets Th2 cells activated by specific allergens, which constitutes the basis of allergic disease. Therefore, this approach has therapeutic potential for a variety of allergic diseases, including asthma, and may modify their natural course. Immunotherapy results in systemic immunological changes to allergens, thereby providing clinical benefits in allergic asthma. For example, immunotherapy attenuates T-cell-mediated airway inflammation by down-modulating Th2 and inducing Th1 differentiation. In addition, immunotherapy induces regulatory T cells, which produce IL-10. Meta-analysis has demonstrated that allergen immunotherapy improves clinical symptoms and non-specific airway hyperresponsiveness in asthma, and decreases drug requirements. Clinical studies have supported the usefulness if immunotherapy in mild to moderate asthma cases, particularly in patients with concomitant rhinitis. Several promising novel approaches have emerged as future immunotherapeutic strategies for the treatment of asthma. Current pharmacotherapy, including inhalational corticosteroids, provides powerful anti-symptomatic benefits in asthma; however, pharmacotherapy cannot cure or modify the natural course of asthma. As immunotherapy targets the background immunological state in asthma, it is expected to lead to long-term amelioration or cure. It is hoped that the positioning of allergen immunotherapy as a treatment option will allow the comprehensive management of symptoms in allergic individuals, and the modification of disease course.

KEY WORDS

allergic asthma, allergic conjunctivitis, allergic rhinitis, immunotherapy, Th2 responses

INTRODUCTION

Allergen immunotherapy constitutes a treatment method that modifies immunoreactive responses to specific allergens by administrating allergens that cause allergic diseases such as asthma. According to the WHO position paper,[1] immunotherapy is effective for diseases that are associated with type I allergic reactions, such as allergic rhinitis and allergic bronchial asthma. As a result of anti-symptomatic therapies, including the use of inhalational corticosteroids (ICS), management of asthma has markedly improved. Consequently, the use of allergen immunotherapy has been reduced. However, there is increasing evidence that ICS does not affect the natural course of asthma.[2-4] Furthermore, ICS does not provide therapeutic benefits for symptoms caused by rhinoconjunctivitis, which is commonly observed in asthmatic patients. In contrast to ICS, allergen immunotherapy targets the Th2 cells pathophysiologically activated by specific allergens, thus providing therapeutic potency for the variety of allergic diseases observed simultaneously in allergic individuals, and possibly modifying the natural course of allergic diseases.[1] In this article, the authors review the current understanding of the role of allergen immunotherapy in asthma and discuss future perspectives of this treatment modality in this field.

MECHANISMS OF ALLERGEN IMMUNOTHERAPY

Airway inflammation is a key feature of asthma. For example, infiltration of activated eosinophils is an important factor and is known to be associated with disease severity. In successful cases of immunotherapy in asthma, indexes of airway inflammation, including

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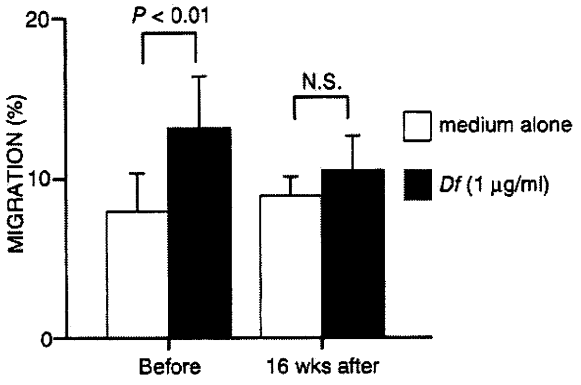

Fig. 1 Eosinophil transendothelial migration induced by culture supernatants of peripheral blood mononuclear cells (PBMC) obtained from *Dermatophagoides farinae* (*Df*)-sensitive atopic asthmatics treated by rush immunotherapy (n = 5). *Df* (-); eosinophil migration in response to supernatants of PBMC cultured with medium alone. *Df* (+); eosinophil migration in response to supernatants of PBMC cultured with *Df*-antigen. Data are expressed as mean ± SEM.

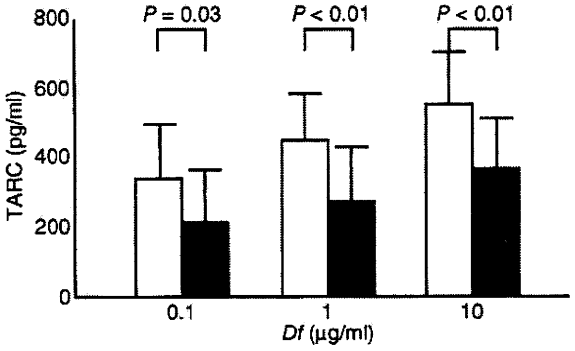

Fig. 2 Effects of rush immunotherapy on production of TARC by peripheral blood mononuclear cells obtained from house dust mite-sensitive asthmatics. Open bars represent data before immunotherapy, and closed bars represent data at 16 weeks following induction of allergen immunotherapy. Data are expressed as mean ± SEM from 8 donors.

the number of infiltrated eosinophils and/or concentrations of eosinophil specific-granule proteins, are reduced.[5-7] For circulating eosinophils to accumulate in asthmatic airways, they must adhere to and then migrate across vascular endothelial cells. These processes are largely regulated by cytokines/chemokines produced by various cells, including Th2 cells. During the allergen exposure period in birch pollen asthma, increased adhesiveness of peripheral blood eosinophils and increased chemotactic activity for eosinophils in bronchoalveolar lavage fluid are observed, and these actions are blocked by immunotherapy.[5,8]

The authors previously confirmed that stimulation of mononuclear leukocytes from house dust mite-sensitive allergic asthmatics with mite-allergen results in productions of eosinophil adhesion-inducing activity, eosinophil chemotactic activity, and eosinophil transendothelial migration-inducing activity and the increases of those parameters were attenuated in patients treated with allergen immunotherapy (Fig. 1).[9-11] These findings suggest that modification of the responsiveness of T cells, particularly Th2 cells, to specific allergens by immunotherapy results in the suppression of eosinophil accumulation in the airways. These effects are likely to involve down-regulation of Th2 cells.

It has been demonstrated that the production of Th2 cytokines, such as IL-4 and IL-5, is decreased by immunotherapy.[8,12] We recently found that immunotherapy attenuates the house dust mite allergen-specific production of TARC, a potent chemokine activator of Th2 cells, from peripheral blood mononuclear cells obtained from patients with house dust mite-sensitive allergic asthma, thus suggesting that immunotherapy can reduce accumulation of Th2 cells during allergen exposure (Fig. 2). Therefore, immunotherapy results in systemic immunological changes in response to allergens, and provides some clinical benefits in allergic asthma. In addition to modulating effects on the Th2 cascade, immunotherapy induced differentiation to the Th1, rather than the Th2, phenotype in Th0 cells.[13]

It has been reported[13] that allergen-challenge-induced expression of IL-12 mRNA in the skin was augmented by immunotherapy. These findings support the notion that immunotherapy attenuates T-cell-mediated airway inflammation via down-modulation of Th2 and induction of Th1 differentiation. There is also increasing evidence that immunotherapy induces regulatory T cells (Treg), which produce IL-10 and down-modulate allergic inflammation.[14-16] For example, in bee venom allergy, immunotherapy increases the production of IL-10, which is associated with inhibitory effects in response to specific allergens. However, recent investigations using immunotherapy with Th1 adjuvants, such as CpG-motif, have shown some clinical benefits without production of IL-10, thus indicating the need for further research to elucidate the significance of Treg/IL-10. Involvement of Treg/IL-10 in immunotherapy for Th2 suppression may be regulated by multiple factors, including allergen, adjuvant and time of assessment.

CURRENT STATUS OF ALLERGEN IMMUNOTHERAPY IN ASTHMA

The clinical indications for immunotherapy in asthma are not fully established; however, this therapy should be considered for allergic asthma patients who have identified environmental aero allergens that

Table Clinical effects in terms of step-down rate after rush immunotherapy in house dust mite-sensitive asthmatics

	FEV_1%		Duration	
	≧70%	<70%	≧10 y	<10 y
Unchanged:	15 (39.5%)	8 (66.7%)	18 (54.5%)	5 (29.4%)
Improved:	23 (60.5%)	4 (33.3%)	15 (45.5%)	12 (70.6%)
	$P = 0.009$		$P = 0.043$	

are difficult to avoid or for cases that are not severe and present normal pulmonary function. This approach was outlined in the recent US asthma guideline Expert Panel 3.[17] In asthma, meta-analysis has demonstrated that allergen immunotherapy improves clinical symptoms and non-specific airway hyperresponsiveness, and decreases drug requirements.[18] For immunotherapy to be successful, the maintenance allergen dose to be administered should be sufficiently high. In rush immunotherapy, patients are hospitalized and repeatedly injected under clinically controlled conditions, and the target concentration is easily achieved in several days, with clinical effects being seen rapidly[19]; improvement in symptom medication scores and allergen-specific bronchial hyperresponsiveness typically appears within several weeks. Using this method, we observed that clinical effects, based on the rate of obtaining step-down of asthma severity, is significantly less in patients with more than 10 years of disease or FEV1% of less than 70% (Table). Therefore, it is conceivable that immunotherapy would be beneficial for asthmatics with early-stage allergic asthma, without development of airway remodeling.

What happens if immunotherapy is prescribed in addition to ICS? Current pharmacotherapy, including ICS, recommended by the latest guidelines tends to rapidly improve symptoms in mild to moderate asthma. Maestrelli *et al.*[20] investigated the additional effects of immunotherapy when it was combined with pharmacotherapy according to the Global Initiative for Asthma (GINA) guidelines in mild to moderate disease in mite-sensitive asthmatic patients. The immunotherapy group showed partial suppression in mite-induced immediate skin reactions, decreased frequency of rescue use of short-acting β2-agonist, and improved peak expiratory flow rate, thus suggesting immunotherapy provides additive effects in patients treated with ICS. More recently, Garcia-Robaina *et al.*[21] investigated the effects of a depigmented polymerized allergen vaccine containing a 50% mixture of *Dermatophagoides pteronyssinus* and *Dermatophagoides farina* on mild to moderate asthma, and found that the median improvement in total symptom and medication scores in the active versus placebo group was 53.8% and 58.1%, respectively. This study also demonstrated that this immunotherapy improves symptoms of rhinoconjunctivitis, thereby confirming that immunotherapy acts as an active systemic therapy for allergic individuals. In this context, Marogna *et al.*[22] compared the effects of sublingual immunotherapy (SLIT) and ICS in patients with mild asthma and concomitant rhinitis due to grass pollen allergy. After a run-in season, patients were randomized to either 800 μg/day budesonide, an ICS, during the pollen season or continuous grass SLIT for 5 years. Asthma symptoms decreased significantly in both groups; however, improvements were greater in the SLIT patients at 3 and 5 years. Furthermore, a decrease in both nasal symptoms and nasal eosinophils was observed only in the SLIT group. These results indicate that SLIT is equally effective as ICS in treating seasonal asthma and provides benefits in treating rhinitis symptoms.

Taken together, these clinical studies confirmed the rationale of current US guideline EPR3, and support the usefulness of immunotherapy in mild to moderate asthma, particularly in those with rhinoconjunctivitis.

MODIFICATION OF NATURAL HISTORY BY IMMUNOTHERAPY

What about the significance of immunotherapy in its original role of modification of the natural history of allergic diseases such as asthma? The approaches described in the following section provide promising data. As noted above, it is speculated that immunotherapy would be less effective in asthmatic patients with longer disease period because of development of airway remodeling. Moller *et al.*[23] investigated the effects of immunotherapy on onset of asthma in pollen allergy rhinitis patients. Non-specific airway hyperresponsiveness during the pollen season improved only in the active treatment group. After three years of follow up, the ratio of asthma development was significantly lower in the immunotherapy treatment group (21%) than in the control group (44%). These results suggest that immunotherapy is more effective when introduced at early stages.

Thus, Di Rienzo *et al.*[24] investigated whether mite-allergen immunotherapy using SLIT can improve the natural course of children suffering from mite allergy. At the end of a 4- to 5-year course of SLIT treatment and a further 4 to 5 years after SLIT discontinuation, there was a significant reduction in the presence of asthma in the treated patients, as compared with baseline. On the other hand, in the control group, no clinical changes were observed after 5 and 10 years of follow-up. There was a highly significant difference between the two groups, at both the end of SLIT and after 5 years. This study demonstrates that SLIT improves the prognosis of children with mite allergy, and that clinical efficacy is maintained for 4 to 5 years after discontinuation.

NEW APPROACHES FOR ALLERGEN IMMUNOTHERAPY

The following novel approaches constitute promising future immunotherapy modalities for asthma. It has been demonstrated that Th1 adjuvants, such as liposome, monophosphoryl lipid A (MPL) or the immunostimulatory DNA sequence CpG motif, may facilitate the action of allergen immunotherapy. For example, Basomba *et al.*[25] conducted a double blinded comparative study of immunotherapy using liposomal mite allergen on mild to moderate asthma. Approximately half (46%) of the immunotherapy group showed a decrease in symptom-medication scores of more than 60%, while fewer patients (only 12%) in the placebo group showed such improvement. In the active treatment group, mite-specific IgG4 was increased, while allergen-specific bronchial responsiveness was improved. It was meaningful to demonstrate that liposome, which is known to be a Th1 adjuvant, can be used for allergen immunotherapy in asthma; however, it is unclear whether this modification can overcome current treads in conventional immunotherapy.

Drachenberg *et al.*[26] examined whether a grass pollen-specific vaccine containing MPL, a potent Th1 adjuvant and a ligand for toll-like receptor 4, would modify allergic symptoms in grass pollen-sensitive subjects. Tyrosine-absorbed glutaraldehyde-modified grass pollen extract containing MPL adjuvant was used. After only four preseasonal injections, the vaccine containing MPL reduced nasal symptoms, ocular symptoms, and combined symptom and medication scores.

Tulik *et al.*[27] investigated whether a conjugate of the major ragweed allergen Amb a 1 and CpG motif (A1C) would modify asthma and rhinitis due to ragweed hay fever. No severe side effects were observed, and the active treatment was well tolerated. In the active group, nasally administered allergen induced IL-4 producing cells were blocked while IFN-γ was increased, confirming an immunological shift from the Th2 to Th1 system. During the pollen season, the AIC group showed significantly fewer asthma and rhinitis symptoms as compared with the control group. Creticos *et al.*[28] also reported that a 6-week regimen of the AIC vaccine appeared to offer long-term clinical efficacy in the treatment of ragweed allergic rhinitis: During the first ragweed season, the AIC group had better peak-season rhinitis scores than the placebo group and a clinical benefits were again observed in the subsequent ragweed season. These studies are important for demonstrating that induction of Th1 and reduction of Th2 response act as mechanisms of immunotherapy, thus raising the future possibility of additional Th1 adjuvants.

There is increasing evidence that recombinant DNA technology has the potential to produce allergen-specific immunotherapy vaccines.[29,30] Pauli *et al.*[29] evaluated the effectiveness of a recombinant birch pollen allergen vaccine in patients with birch pollen allergy. A randomized, double-blind, placebo-controlled trial was undertaken in order to compare the following three vaccines in 134 adults with birch pollen allergy: recombinant birch pollen allergen vaccine (rBet v 1a), licensed birch pollen extract, natural purified birch pollen allergen (nBet v 1), and placebo. Significant reductions (about 50%) in rhinoconjunctivitis symptoms, rescue medication, and skin sensitivities were observed in the three actively treated groups, as compared with the placebo. No severe systemic adverse events were observed in the rBet v 1-treated group. These results indicate that the rBet v 1-based vaccine is safe and effective in treating birch pollen allergy.

FUTURE PERSPECTIVES

Application of immunotherapy upon onset of asthma is clinically feasible in Japan with the aim of prevention. Patients with Japanese cedar pollinosis, for example, may be candidates for immunotherapy in terms of preventing development of asthma. The present study also suggests the usefulness of early intervention in producing improvements. The study on mite allergy using SLIT strongly suggests that immunotherapy can improve the natural course of allergic diseases, including asthma, in children. However, it remains to be elucidated whether such effects can also be achieved in adult asthmatics.

Among recent progress and newly developed approaches regarding allergen immunotherapy, liposomal allergen vaccination is promising; however, it should be clarified whether this method is better than conventional allergen immunotherapy. On the other hand, selective Th1 adjuvants, such as CpG motif or MPL, have the potential to become useful therapies for allergic asthma, such as in mite allergy. In any case, the application of Th1 system adjuvant may be useful as a modified vaccine approach in immunotherapy. Immunotherapy using recombinant allergen would provide a further possibility to improve this form of therapy. The results of a study by Pauli *et al.*[29] are extremely promising, and suggest the possible use of this approach in dust mite allergy.

Current pharmacotherapy, such as ICS, provides powerful anti-symptomatic benefits in asthma; however, it does not cure or modify the natural disease course. As immunotherapy targets the immunological background in asthma, including pathological activation of Th2 cells, it is expected to lead to long-term amelioration of asthma. It is hoped that the novel approaches described in this article will become more sophisticated and provide better efficacy, and that the positioning of allergen immunotherapy as a treatment option for comprehensive management of allergy symptoms and for modification of disease course.

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原　著

鼻炎症状と喘息症状の連関についてのアンケート調査

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【背景】アレルギー性鼻炎などの鼻疾患と気管支喘息は，互いに影響することがよく知られている．しかし特に我が国で，鼻疾患と喘息の連関に関する疫学的データは少ない．今回我々は，鼻症状と喘息症状の連関の頻度及び特徴を調査する目的で，アンケートを行った．
【方法】鼻疾患（アレルギー性鼻炎・花粉症・慢性副鼻腔炎）と喘息を合併する126名を対象に，アンケート調査により，鼻症状と喘息症状の連関の頻度を検討した．またどのような患者で，鼻症状の変化によって，喘息症状が影響されるかについても，同時に検討した．
【結果】38名（30%）で，鼻疾患の悪化に伴って喘息が悪化することを自覚していた．一方，28名（22%）で，鼻治療により喘息が改善した．鼻症状の変化が喘息症状に与える影響は，喘息コントロールが良くない患者で有意に強かった．また，副鼻腔炎のある患者で両者の連関はより強い傾向にあった．
【結語】鼻疾患と喘息を合併する患者において，約30%で両者の連関を自覚していた．鼻に対する治療は，通年的に喘息症状がある患者で特に，喘息コントロールに重要と考えられた．上下気道にわたる包括的なアレルギー診療の重要性が示唆された．

Key words: allergic rhinitis —— bronchial asthma —— one airway one disease

緒　言

アレルギー性鼻炎と気管支喘息が合併する割合は高く，アレルギー性鼻炎の30-40%に気管支喘息が，気管支喘息の50-80%にアレルギー性鼻炎が合併するとされている[1]．アレルギー性鼻炎患者は，健常者と比較し，約3倍喘息に移行しやすいことが報告され[2]，気管支喘息発症の独立した危険因子と認識されている．アレルギー性鼻炎患者では，気管支喘息の有無と無関係に，気道過敏性亢進[3]や好酸球の気管支への集積[4]が見られる．また鼻粘膜へのアレルゲン曝露が，下気道の平滑筋収縮，好酸球浸潤，気道過敏性亢進を誘導することも報告されている[5]．さらに，アレルギー性鼻炎の治療を行うことで，喘息症状や気道過敏性を改善させ[6-9]，急性増悪頻度を減少させうることも報告されている[10]．一方で，気管支喘息患者においても，アレルギー性鼻炎の有無と無関係に，好

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Abbreviations: ICS "inhalational corticosteroid", H1RA "histamine 1 receptor antagonist", LABA "long acting beta2-agoist", LTRA "leukotriene receptor antagonist"
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Table 1 Clinical characteristics of patients

Number of the subjects	
1. Sex: Male	49
Female	75
Not described	2
2. Age: < 20 yr	1
20-29 yr	16
30-39 yr	26
40-49 yr	23
50-59 yr	21
60-69 yr	29
70-79 yr	8
80 < yr	1
Not described	1
3. Atopy: Atopic	106
House-dust-mite	53
Japanese cedar	83
Non-atopic	7
Unknown	13
4. Treatment: ICS	113
LABA	60
SABA	22
Theophylline	40
LTRA	75
Nasal conticosteroid	34
H1RA	44
Immunotherapy	22
5. Step: Step1	7
Step2	24
Step3	46
Step4	41
Unknown	8

Table 2 Pre-existing nasal disease

Number of the subjects	
Allergic rhinitis (AR)	28
Japanese cedar pollinosis (JCP)	26
Chronic sinusitis	5
AR + JCP	32
AR + chronic sinusitis	7
JCP + chronic sinusitis	2
AR + JCP + chronic sinusitis	14
Unknown	12

酸球の上気道への集積が見られる[11]．また経気管支鏡的気管内アレルゲン投与が，鼻炎症状と鼻粘膜組織への好酸球浸潤を誘導することも報告されている[12]．このように上気道と下気道は，共通の進行する炎症性反応の影響を受け，連動するメカニズムにより持続・増幅すると考えられている[13]．

また副鼻腔炎も，喘息の増悪因子の一つであることがよく知られている[14]．近年では，従来のマクロライド治療が有効な慢性副鼻腔炎に加え，アレルギー性副鼻腔炎や好酸球性副鼻腔炎などが提唱され，病態の多様性が認識されるようになった[15][16]．その中でも，好酸球性副鼻腔炎では，ポリープがロイコトリエンなどの化学伝達物質の産生源とされており，ポリープ切除により喘息コントロールが改善することがしばしば経験される[17]．

しかしながら，鼻疾患と喘息の合併例における上気道症状と下気道症状の連関は，日常臨床において，すべての患者で観察されるものではない．また，両者の連関がどのような患者で観察されやすいかについては，今まであまり検討されてこなかった．今回我々は，鼻疾患（アレルギー性鼻炎・花粉症・慢性副鼻腔炎）と気管支喘息・咳喘息を合併する患者において，鼻炎症状と喘息症状の連関についてアンケート調査を行い，その連関の頻度および特徴について検討したので，ここに報告する．

研究対象と方法

2007年11月から12月にかけて，埼玉医科大学病院アレルギー・喘息センター，あるいは耳鼻咽喉科に通院中の，鼻疾患（アレルギー性鼻炎・花粉症・慢性副鼻腔炎）と喘息を持ち，鼻炎症状と喘息症状を合併した患者を対象に，両者の連関についてアンケート調査を行った．本試験の公表について同意を得られた，126人を対象とした（Table 1）．性別は，男性49名，女性75名，記載なし2名であり，平均年齢は48.1歳であった．基礎疾患の内訳は，アレルギー性鼻炎81名，花粉症74名，慢性副鼻腔炎28名，気管支喘息113名，咳喘息16名であった（Table 2；重複有り）．アンケート質問内容は，①鼻炎症状からみた喘息症状との連関に

Table 3　Questionnaire for determining relationship between nasal and asthma symptoms

1-1　以下と診断されたことはありますか？ 診断されたものに○をつけてください.
　アレルギー性鼻炎（1年中不定期に続く，原因　カビやダニ，ホコリ）
　花粉症（春や秋などの花粉で鼻症状がある）
　蓄膿や鼻茸（慢性副鼻腔炎）
　喘息
　咳喘息（ゼイゼイはしないけれど，咳が出る）
1-2　鼻の症状と，喘息症状に対して日常，連続して使用している薬に○をつけてください.
　飲み薬　オノン，シングレア
　　セレスタミン，プレドニゾロン，プレドニン，リンデロン
　　テオドール，テオロング，ユニフィル，スピロペント
　　アレジオン，クラリチン，アレグラ，アレロック，ジルテック，ニポラジン，
　　タリオン，ザジテン，アゼプチン，セルテクト，エバステル
　　クラリス，クラリシッド，ルリッド，その他（　　）
　貼付薬　ホクナリンテープ
　点鼻薬　フルナーゼ，アルデシン，スカイロン，リノコート，インタール点鼻薬，ザジテン点鼻薬，
　　その他（　　）
　吸入薬　フルタイド，キュバール，パルミコート，セレベント，アドエア，
　　オルベスコ，メプチン，サルタノール，スピリーバ，その他（　　）
　免疫（減感作）療法　スギ，ダニ，ハウスダスト
　手術　下鼻甲介切除，下鼻甲介焼灼（レーザーなど）その他（　　）
2-1　かぜをひいているときでなくとも，喘息に関連する症状（息苦しさ，咳，ゼイゼイ，胸の違和感）がありますか
　しばしばある，ときどきある，ほとんどない
2-2　かぜをひいている時でなくとも，鼻の症状（鼻水，鼻汁，くしゃみ，鼻つまり）がありますか？
　しばしばある，ときどきある，ほとんどない
3-1　鼻症状が悪くなると喘息症状はどうなりますか？
　悪くなる，変化しない，良くなる
3-2　喘息症状が悪くなると鼻症状はどうなりますか？
　悪くなる，変化しない，良くなる
4-1　鼻症状を薬で治療すると，喘息症状はどうなりますか？
　良くなる，変化しない，悪化する
4-2　喘息症状を薬で治療すると，鼻症状はどうなりますか？
　良くなる，変化しない，悪化する

ついて（鼻症状が悪化すると喘息症状は悪化するか？鼻症状を治療すると喘息症状は改善するか？）②喘息症状からみた鼻炎症状との連関について（喘息症状が悪化すると鼻症状は悪化するか？喘息症状を治療すると鼻症状は改善するか？）③鼻炎症状と喘息症状の程度（頻度）について（しばしばある，ときどきある，ほとんどない）④普段の治療内容について，などである（Table 3）．統計学的解析として，異なる2群における検討には$\chi 2$乗検定を用いた．

結　果

①全症例（126例）における鼻炎症状と喘息症状の連関の検討

（1）鼻炎症状の変化に伴う喘息症状の変化

初めに，鼻疾患と喘息を合併し，鼻炎症状と喘息症状を呈する126症例における，鼻炎症状の変化に伴う喘息症状の変化について，検討した．全症例のうち30%（38/126）で，鼻炎症状が悪化すると，喘息症状が悪化すると自覚していることがわかった（Table 4）．一方で，鼻を治療すると，22%

Table 4 Effect of exacerbated nasal disease on asthma symptoms.

		Exacerbated nasal disease
Asthma symptoms	Deteriorated	38 (30%)
	Unchanged	59 (47%)
	Improved	2 (2%)
	Unknown	27 (21%)
Total		126 (100%)

Table 5 Effect of nasal treatment on asthma symptoms.

		Nasal treatment
Asthma symptoms	Improved	28 (22%)
	Unchanged	71 (57%)
	Deteriorated	0 (0%)
	Unknown	27 (21%)
Total		126 (100%)

Table 6 Effect of exacerbated asthma on nasal symptoms.

		Exacerbated asthma
Nasal symptoms	Deteriorated	28 (22%)
	Unchanged	60 (48%)
	Improved	1 (1%)
	Unknown	37 (29%)
Total		126 (100%)

Table 7 Effect of asthma treatment on nasal symptoms.

		Asthma treatment
Nasal symptoms	Improved	24 (19%)
	Unchanged	83 (66%)
	Deteriorated	0 (0%)
	Unknown	19 (15%)
Total		126 (100%)

(28/126)で，喘息症状が改善すると自覚していた(Table 5)．

また，鼻炎症状が悪化すると喘息症状が悪化すると回答した38名の中で，鼻を治療すると19名(50%：全体の15%)で喘息症状が改善をすると自覚しており，"鼻を治療すると喘息症状が改善し，鼻症状が悪化すると喘息症状も悪化する"という強い連関を自覚する一群が存在することが示された．

(2) 喘息症状の変化に伴う鼻炎症状の変化

次に，鼻炎症状と喘息症状を合併する126症例における，喘息症状の変化に伴う鼻炎症状の変化について，検討した．全症例のうち22%(28/126)で，喘息症状が悪化すると，鼻炎症状が悪化すると自覚していることがわかった(Table 6)．また，喘息を治療すると19% (24/126)で，鼻炎症状は改善すると自覚していた (Table 7)．

これらの結果から，鼻炎症状及び喘息症状のある患者の約30%で，両者の相関を自覚していることがわかった．

②鼻炎症状と喘息症状の連関が高い群の検討

今回のアンケートでは，鼻炎症状の変化によって喘息症状が変化する割合の方が，喘息症状の変化によって鼻炎症状が変化する割合と比較し，より高率であった．そこで，両者の連関がどの患者でより強く観察されるかについての解析は，鼻炎症状の変化によって喘息症状が変化する割合に絞って施行した．アンケートの回答が得られた99人を対象とした．

(1) 基礎疾患による違い

初めに，鼻の基礎疾患の違いによって，鼻炎症状が変化したときの喘息症状の変化が異なるか検討した．初めにTable 2における7群で，鼻炎症状の悪化に伴う喘息症状の悪化を自覚する頻度及び鼻治療に伴う喘息症状の改善を自覚する頻度を検討した．副鼻腔炎の存在は，両者の連関を強める可能性が示唆されたが，各群間で有意差はなかった (Table 8 and data not shown)．

Table 8 Influence of pre-existing nasal disease on association between exacerbated nasal disease and asthma symptoms.

		Exacerbation of asthma by exacerbated nasal disease (+)	Exacerbation of asthma by exacerbated nasal disease (−)	Total
Pre existing nasal disease	AR	8 (33%)	16 (67%)	24
	JCP	7 (35%)	13 (65%)	20
	Sinusitis	0 (0%)	3 (100%)	3
	AR + JCP	10 (36%)	18 (64%)	28
	AR + sinusitis	4 (57%)	3 (43%)	7
	JCP + sinusitis	1 (50%)	1 (50%)	2
	AR + JCP + sinusitis	6 (55%)	5 (45%)	11
	Unknown	2 (50%)	2 (50%)	4
Total		38	61	99

Table 9 Influence of asthma control on association between exacerbated nasal disease and asthma symptoms

		Exacerbation of asthma by exacerbated nasal disease (+)	Exacerbation of asthma by exacerbated nasal disease (−)	Total
Asthma control	Good (symptom-free or minimal symptoms)	31 (53%)	28 (47%)	58
	Not good (occasional or frequent symptoms)	7 (17%)	34 (83%)	41
Total		38	61	99

そこで，副鼻腔炎がある群（23 人）と副鼻腔炎がない群（72 人）で，両者の連関について検討した．副鼻腔炎がある群と副鼻腔炎のない群とでは，鼻炎症状の悪化による喘息症状の悪化を自覚する割合に差が無かったが（副鼻腔炎あり 47.8%（11/23）：副鼻腔炎なし 34.7%（25/72）；$p=0.26$）．副鼻腔炎がある群では，有意ではないが，鼻治療によって喘息症状が改善すると自覚する傾向にあった（副鼻腔炎あり 39.1%（9/23）：副鼻腔炎なし 22.2%（16/72）：$p=0.11$）．

（2）鼻炎・喘息の症状（頻度）による違い

日常的に鼻炎症状がある群（ときどき・しばしば）と鼻炎症状がない群（ほとんどない）で，両者の連関に差があるか検討した．日常的に鼻炎症状がある群と鼻炎症状がない群とでは，鼻炎症状の悪化による喘息症状の悪化を自覚する割合は，差が無かった（鼻炎あり 38.8%（33/85）：鼻炎なし 35.7%（5/14）；$p=0.82$）．また，日常的に鼻炎症状がある群と鼻炎症状が無い群とでは，鼻治療による喘息症状の改善を自覚する割合も差が無かった（鼻炎あり 27.1%（23/85）：鼻炎なし 14.3%（2/14）；$p=0.30$）．次に，通年的に喘息症状がある群（ときどき・しばしば）と喘息症状がない群（ほとんどない）で，鼻炎症状と喘息症状の連関に差があるか検討した．通年的に喘息症状がある群では，喘息症状がない群と比較し，鼻炎症状の悪化により喘息症状が悪化するとより自覚していることがわかった（喘息あり 53%（31/58）：喘息なし 17%

Table 10 Influence of asthma control on association between nasal treatment and asthma symptoms.

		Improvement of asthma by nasal treatment (+)	Improvement of asthma by nasal treatment (−)	Total
Asthma control	Good (symptom-free or minimal symptoms)	21 (36%)	37 (64%)	58
	Not good (occasional or frequent symptoms)	7 (17%)	34 (83%)	41
Total		28	71	99

Table 11 Influence of asthma severity on association between exacerbated nasal disease and asthma symptoms.

		Exacerbation of asthma by exacerbated nasal disease (+)	Exacerbation of asthma by exacerbated nasal disease (−)	Total
Asthma Severity	Step 1	2 (40%)	3 (60%)	5
	Step 2	3 (16%)	16 (84%)	19
	Step 3	14 (41%)	20 (59%)	34
	Step 4	18 (55%)	15 (45%)	33
	Unknown	1 (13%)	7 (87%)	8
Total		38	61	99

(7/41)；$p=0.0002$；**Table 9**)．さらに，通年的に喘息症状のある群では，鼻症状の治療により喘息症状がより改善すると自覚していた（喘息あり 36% (21/58)；喘息なし 17% (7/41)；$p=0.03$；**Table 10**)．したがって，喘息症状のコントロールが悪い群では，鼻炎症状の悪化に伴い喘息症状が悪化しやすく，鼻治療により喘息が改善しやすいと認識していることが示唆された．

また，喘息重症度によって，鼻炎症状と喘息症状の連関に差があるか検討した．喘息の重症度は我が国のガイドラインに準じ[14]，ステップ1(軽症間欠型)，ステップ2（軽症持続型)，ステップ3(中等症持続型)，ステップ4(重症持続型)に分類した．鼻炎症状の悪化に伴う喘息症状の悪化を自覚する頻度及び鼻炎治療に伴う喘息症状の改善を自覚する頻度は，各ステップ間で有意差はなかったが(**Table 11**)，「現在の治療を考慮した喘息重症度の分類」[14]の最重症持続型（ステップ4でコントロール不良)に相当する5名においては，5名全員が，鼻炎症状が悪化すると喘息症状が悪化すると回答しており（data not shown)．重症度が高くなると両者の連関を認識しやすくなる可能性が示唆された．

考 察

今回我々は，アンケート調査により，鼻疾患と喘息を持ち，鼻炎症状と喘息症状を合併した患者の約30% で，両者の連関を自覚していることを明らかにした．さらにその中で，全体の約15% の患者で鼻炎症状が悪化すると喘息症状が悪化し，鼻炎の治療により喘息症状が改善するという強い連関を自覚していることがわかった．また，通年的に喘息症状のある患者，すなわち喘息コントロールの悪い患者で，喘息症状が鼻症状の影響を受け

やすいと自覚していた．今回の検討はアンケートによるものであり，実際の病態を反映していない可能性は否定できないが，自覚症状から見た場合，普段から喘息コントロールを良くすることが，鼻炎症状と喘息症状を合併している患者の管理において特に重要と考えられる．

鼻炎症状と喘息症状を合併した患者の約30%で，鼻炎症状と喘息症状の連関を自覚していた(Table 4〜7)．副鼻腔炎単独の5名を除き，アレルギー性鼻炎または花粉症を合併していることを考慮すると，今回の結果から，アレルギー性鼻炎症状と喘息症状の連関を，約3割の患者で自覚していると解釈することが可能と思われる．今までにもアレルギー性鼻炎症状と喘息症状の連関に関しては，多々報告されている[18)-23)]．Yamauchiらは，アレルギー患者10009名(成人喘息2781名，小児喘息3283名，アレルギー性鼻炎3945名)に対し，気管支喘息とアレルギー性鼻炎の連関頻度についてのアンケート調査を行った．アレルギー性鼻炎症状のある成人喘息1693名の中で52.3%，アレルギー性鼻炎症状のある小児喘息2238名の中で62.2%の患者が，気管支喘息が悪化する際に，鼻症状も悪化すると認識していた[18)]．さらに，喘息症状のあるアレルギー性鼻炎1935名の中で74.9%の患者が，アレルギー性鼻炎が悪化する際に，喘息症状も悪化すると認識していることを報告した[18)]．また，Matsunoらは，大分県の喘息患者246名を対象とし，アレルギー性鼻炎を合併する129名(全体の52.4%)の中で，35.7%の患者が，気管支喘息が悪化する際に鼻症状の悪化を伴うと認識していることを報告した[19)]．増田らは，鼻アレルギーを合併する小児気管支喘息患者155名にアンケート調査を行い，38.7%が，喘息と鼻症状が同時に悪化することを明らかにした[20)]．スギ花粉症の気管支喘息に及ぼす影響については，上野らは，スギ花粉症合併成人喘息患者116名のうち，41名(35.3%)がスギ花粉時期に何らかの喘息症状が増悪し，さらに13名(11.2%)の患者においては花粉飛散時期にピークフロー値が平均10%以上低下することを報告した[21)]．また我々は以前，スギ花粉症合併成人慢性気管支喘息患者71名を対象としてスギ飛散時期の喘息症状悪化の有無についてのアンケート調査を行い，スギ飛散時期に花粉症のある患者では約半数が喘息への悪化を感じたことを報告した[22)]．さらに徳安らは，スギ花粉症の罹患率が関東地方より少ない山陰地方で我々と同じアンケート調査を行い，スギ飛散時期の喘息悪化の自覚は，我々の調査(関東地方)と同等の割合であったことを報告した[23)]．すなわち，アレルギー性鼻炎またはスギ花粉症を合併する喘息患者の1/3〜2/3で，鼻症状の悪化により喘息症状が悪化すると認識しており，実際にピークフロー値が低下する症例も存在すると要約されよう．鼻炎症状に伴って喘息症状が悪化する機序としては，①アレルゲンが直接下気道に到達し喘息症状を誘発する②鼻閉塞によってアレルゲンが下気道に侵入しやすくなる③鼻局所でロイコトリエンなどの化学伝達物質が産生・放出され，一部が下気道に下降する④アレルゲン曝露に伴いIL-5などのTh2サイトカインの産生が亢進し，骨髄に作用し好酸球を増加または活性化させ，気道への好酸球浸潤が増加する，などが想定されている[13)]．実際には，これらが複合的に病態形成に関与していると考えられるが，それぞれの関与の割合は不明である．

これまでに，アレルギー性鼻炎の治療のみで喘息症状や気道過敏性亢進が改善するかについて，多々検討されてきた．Welshらは季節性アレルギー性鼻炎患者(48%で季節性喘息を合併)に点鼻ステロイド治療を行ったところ，喘息スコアが有意に改善したことを報告した[6)]．またHenriksenらは，アレルギー性鼻炎＋気管支喘息患者(ICS使用なし)に，点鼻ステロイド治療を行ったところ，咳や喘息重症度の改善が見られたことを報告した[7)]．さらに，Foresiらは季節性アレルギー性鼻炎患者(喘息合併なし)に点鼻ステロイド治療を行ったところ，気道過敏性亢進が改善したことを報告した[8)]．Correnらは，季節性アレルギー性鼻炎＋気管支喘息患者(ICS使用なし)に点鼻ステロイド治療を行ったところ，症状やピークフロー値は不変であったが気道過敏性が改善したことを報告した[9)]．これらの報告は，点鼻ステロイド

治療が，鼻だけではなく，喘息症状にも有効であることを示唆している．しかし近年では，点鼻ステロイド治療が喘息症状や気道過敏性亢進に対して効果が無いとする報告も散見される[24)25)]．結果の乖離の原因として①合併する喘息症状の程度の違い（喘息が重いほど，点鼻ステロイドによる喘息治療効果が少ないことが考えられる）②喘息に対するICS治療の有無の違い（ICS治療が無い群で，より点鼻ステロイドによる喘息治療効果が期待される）③原因抗原の違いなどが想定される．

鼻の基礎疾患の中で，副鼻腔炎の存在は，鼻炎症状と喘息症状の連関を強める傾向にあることが示唆された(**Table 8** and data not shown)．副鼻腔炎は，喘息の増悪因子の一つであることが知られている[14]．近年では，慢性副鼻腔炎の病態の多様性が認識されるようになった．従来型のマクロライド療法が効果的な慢性副鼻腔炎だけでなく，アレルギー性副鼻腔炎や好酸球性副鼻腔炎などの概念が提唱され，知見が集積している[15)16)]．アレルギー性副鼻腔炎は，アレルギー性鼻炎に合併し，膿性鼻汁など感染の関与がない副鼻腔炎と考えられており，一般に好酸球浸潤は軽度である[15]．好酸球性副鼻腔炎は，マクロライド治療抵抗性の副鼻腔炎であり，鼻茸中に大量の好酸球の浸潤を伴い，鼻汁は粘稠である[16]．また，好酸球性副鼻腔炎は，アスピリン喘息や好酸球性中耳炎を合併しやすいことが知られている[16]．今回のアンケートで，病理組織より好酸球性副鼻腔炎と診断，または病歴（好酸球性中耳炎の合併またはアスピリン喘息の合併）より好酸球性副鼻腔炎が強く推測された症例は15例（15/28：54%）であった（data not shown）．残りは，特徴的な病歴が無く，組織所見があっても好酸球浸潤は中等度であり，好酸球性副鼻腔炎とアレルギー性副鼻腔炎の鑑別が難しい症例であった．従って，今回の解析における副鼻腔炎の主体は，好酸球性副鼻腔炎であり，アレルギー性鼻炎と関連したアレルギー性副鼻腔炎ではないと考えられる．好酸球性副鼻腔炎では，ポリープがロイコトリエンなどの化学伝達物質の産生源と考えられ，ポリープ切除により喘息コントロールが改善することが知られている[17]．今回の結果からは，副鼻腔炎の存在は，有意ではないが，鼻炎症状と喘息症状の連関を強める可能性が示唆され，副鼻腔炎合併喘息では，特に鼻症状の管理が重要と考えられた．今後は副鼻腔炎の病態によって，喘息悪化への関与が異なるかなどの解析が重要と考えられる．

また，喘息コントロールの悪い患者で，鼻炎症状の悪化に伴い喘息症状が悪化し，鼻治療により喘息症状が改善しやすいと，自覚していることがわかった(**Table 9, 10**)．喘息コントロールの悪い患者では，わずかな増悪因子（鼻症状の悪化）でも，喘息症状が悪化することは容易に想定される．我々は同時に，喘息の重症度によって，鼻炎症状と喘息症状の連関に差があるか検討したが，最重症持続型の喘息患者では全例（5名中5名）で，鼻炎症状の悪化に伴い喘息症状が悪化すると自覚していた（data not shown）．我が国のガイドラインでは，最重症持続型は重症持続型（ステップ4）でコントロール不良例と定義されており[14]，喘息コントロール不良患者では，鼻炎症状の悪化に伴い喘息症状が悪化しやすいと自覚していることが，再確認された．従って，鼻炎及び気管支喘息に対するベースの治療が重要と考えられる．

一方で，今回我々は，ベースの治療薬剤の有無が，鼻炎症状と喘息症状との連関に与える影響についても，検討を試みた．鼻炎症状の変化によって喘息症状が変化する割合について，他剤の有無を考慮せずに，単にその薬を使用しているかいないかで，両者の連関にどのように影響を与えるかについて調査した．結果からは，①ベースにICSを使用していない患者では，鼻治療により喘息症状も改善すると自覚しやすい②ベースに点鼻ステロイドを使用している患者では，鼻治療により喘息症状も改善すると自覚しやすいことなどが考えられた．しかし，今回の検討は単剤使用による影響の検討ではなく，本当にその薬による影響かについては，将来のさらなる精査を必要とすると考えられる．

今回のアンケート調査は，対象が少ない．医師の診察の確認もない解析であり，全体として，結論を述べることに限界があると考えられる．アン

ケートの初めの症状コントロールに関する質問部分では，"かぜをひいているときでなくとも" と記載し，感冒を除外するように努めたが，両者の連関に関する質問部分では，"かぜをひいているときでなくとも" との記載はしておらず，感冒による鼻症状や喘息の悪化を完全には除外できていないと考えられる．さらに今回のアンケートでは，"鼻症状" について質問しており，慢性副鼻腔炎単独の5名を除き，鼻症状はアレルギー性鼻炎症状を意味するものと推定することが可能ではあるが，本当に鼻症状がアレルギー性鼻炎症状であるかは明らかではない．病態の異なる鼻疾患をまとめて，気管支喘息との関連を調べている点でも問題がある．従って，今回の結果が，実際の病態を反映していない可能性は否定できない．しかしながら，患者が今回のアンケート結果のように自覚していることは事実と考えられ，上気道下気道の連関を念頭に置きながら，診療に当たることは重要と考えられた．

今回我々は，鼻疾患と喘息を合併する患者において，約30% で両者の症状の連関を自覚していることを確認した．通年的に喘息症状がある患者では，鼻治療により喘息症状が改善すると自覚しており，鼻治療は喘息コントロールに重要と考えられた．従って，鼻症状と喘息症状のある患者に対しては，上下気道にわたる包括的なアレルギー診療が重要と考えられた．

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QUESTIONNAIRE FOR DETERMINING RELATIONSHIP BETWEEN NASAL AND ASTHMA SYMPTOMS

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Background: The interaction between allergic rhinitis and bronchial asthma is well known. However, there is little epidemiological data on the relationship between nasal diseases and asthma, especially in Japan.
Methods: We administered a questionnaire to 126 patients to examine the frequency of associations between nasal and asthma symptoms in patients with both nasal disease and asthma. We also investigated in which type of patients the asthma symptoms were affected by changes in nasal symptoms.
Results: Thirty-eight patients (30%) were aware that their asthma was worsened by exacerbated nasal disease, and nasal treatment improved asthma in 28 patients (22%). The influence of changes in nasal symptoms on asthma symptoms was stronger in patients lacking good asthma control. The relationship between nasal and asthma symptoms tended to be stronger in patients with sinusitis.
Conclusion: About 30% of patients with nasal disease and asthma reported an association between their nasal and asthma symptoms. Nasal treatment is considered to be important for asthma control, especially in patients with asthma symptoms. These results suggested the important role of comprehensive allergy care in controlling both nasal disease and asthma.

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厚生労働科学研究費補助金(免疫アレルギー疾患等予防・治療研究事業)
分担研究報告書

リアルタイムモニター花粉数の情報のあり方の研究と舌下ペプチド・アジュバンド療法の臨床研究

複数地点におけるスギ花粉飛散数測定の意義と重症スギ花粉症患者の局所病態および花粉抗原の共通抗原性に関する研究

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研究要旨

スギ花粉症は、通年性アレルギー性鼻炎とは異なり、特定の時期に大量の花粉が飛散することによって非常に強い局所症状のみならず全身症状を引き起こす。近年スギ花粉症の患者数は急増し、国民の約20%を超えると報告されており、現代社会においてこの疾患の治療は重要性を増している。スギ花粉症に罹患する患者層は若年層が多く、治療はくしゃみ、鼻汁、鼻閉などの鼻、眼の症状だけではなく、倦怠、集中力の低下など日中のパフォーマンスが労働や就学に及ぼす影響があるためにQOLを考慮した治療が求められている。この治療にあたってはスギ花粉飛散数の把握が極めて重要であり、重症のスギ花粉症患者の局所での病態を解明することが新しい治療方法の展開に必須である。また、免疫療法で使用する抗原を選択するためには、花粉抗原の特性特に共通抗原性に関する検討が極めて重要である。そこで今回、われわれは山形市、甲府市、福井市の3市のスギ花粉飛散数について検討した。また、重症スギ花粉症患者の鼻粘膜におけるステロイド受容体、ペンドリン、ペリオスチンなどの分子の発現について検討した。さらに、コナラ、ヤナギ、クルミ、シラカバ、ヒメシイバ等の花粉抗原の共通性について検討した。その結果、3都市のスギ花粉飛散数の値は異なる地点でもおおむね一致していた。また、重症のスギ花粉症患者の鼻粘膜にはステロイドβ受容体、ペリオスチン、ペンドリンが過剰に発現しており、このためステロイド抵抗性、リモデリングおよび鼻汁の過剰分泌が生じ、これらの変化が重症化の一因と考えられた。また、種々の花粉抗原は共通抗原性を有しており、花粉飛散が重なる初夏にはこの点を念頭に置き治療戦略を立てる必要があると考えられた。

A. 研究目的

スギ花粉症は、通年性アレルギー性鼻炎とは異なり、特定の時期に大量の花粉が飛散することによって非常に強い局所症状のみならず全身症状を引き起こす。近年スギ花粉症の患者数は急増し、国民の約20%を超えると報告されており、現代社会においてこの疾患の治療は重要性を増している。スギ花粉症に罹患する患者層は若年層が多く、治療はくしゃみ、鼻汁、鼻閉などの鼻、眼の症状だけではなく、倦怠、集中力の低下など日中のパフォーマンスが労働や就学に及ぼす影響があるためにQOLを考慮した治療が求められている。この治療にあたってはスギ花粉飛散数の把握が極めて重要であり、重症のスギ花粉症患者の局所での病態を解明することが新しい治療方法の展開に必須である。また、免疫療法で使用する抗原を選択するためには、花粉抗原の特性特に共通抗原性に関する検討が極めて重要である。そこで今回、われわれは山形市、甲府市、福井市の3市のスギ花粉飛散数について検討した。また、重症スギ花粉症患者の鼻粘膜におけるステロイド受容体、ペンドリン、ペリオスチンなどの分子の発現について検討した。さらに、スギ、イネ科花粉、コナラ、ヤナギ、クルミ、シラカバ等の花粉抗原の共通性について検討した。

B. 研究方法

スギ花粉飛散数の測定：スギ花粉飛散数は、リアルタイムモニター（KH3000）を用いて山形市（山形大学医学部および山形県衛生研究所の屋上）、福井市（福井大学および福井県大気汚染測定局の屋上）、および甲府市（山梨大学および山梨県衛生研究所の屋上）にて測定した。ステロイド受容体、ペリオスチンおよびペンドリンの測定：重症スギ花粉症患者の鼻粘膜におけるステロイド受容体（αおよびβ受容体）、ペリオスチンおよびペンドリンの発現を免疫組織学的に検討した。ペンドリンおよびペリオスチンの発現は、Real Time PCRおよびWestern blottingを用いた検討も行った。

RASTインヒビション：ヒメシイバ、コナラ、ヤナギ、クルミ、シラカバ等の花粉抗原の共通性に