test at each locus. We then compared differences in allele frequencies and genotype distribution of the polymorphism between case and control subjects by using a 2×2 contingency χ^2 test with one degree of freedom, and calculated odds ratios (ORs) with 95% confidence intervals (CIs). Serum total IgE and IL-33 levels were analysed as quantitative levels, and we investigated associations between these levels and genetic variations. Log-transformed individual serum IgE levels were analysed by one-way ANOVA. When the data for IL-33 levels were not distributed normally after log-transformation, they were analysed using non-parametric equivalents and summarized using the median. Multiple comparisons were first analysed by the Kruskal–Wallis test and then by individual testing by the Mann–Whitney *U*-test if significant. Correlations were analysed by Spearman's test. A *P* value of less than 0.05 was considered statistically significant.

Results

Linkage disequilibrium of the IL-33 *gene*

A total of 22 polymorphisms with a frequency >0.10 in IL-33 were contained in the public databases available at the NCBI dbSNP website (http://www.ncbi.nlm.nih.gov/SNP/) (Table 2). Two variants including a synonymous substitution (Tyr163Tyr) were in the exons, and four variants were in the 5′-flanking region of the *IL-33* gene. Pairwise LD among the 22 SNPs was measured by different parameters, r^2 using the Haploview 3.2 program (http://www.broad.mit.edu/mpg/haploview/) (Fig. 1), and all the 22 SNPs were in strong LD ($r^2 > 0.75$). We finally selected polymorphism rs1929992 and rs10975519 (Tyr163Tyr) for association studies using tagger in the Haploview 3.2 program, and these two SNPs captured 22 of 22 alleles with a mean r^2 of 0.95 ($r^2 > 0.91$).

Association between polymorphisms in the IL-33 *gene and susceptibility of Japanese cedar pollinosis*

The locus was in Hardy–Weinberg equilibrium in the entire group. To test the association between the SNP and JC pollinosis, we compared differences in the allele frequency and genotype distribution of each polymorphism between case and control subjects by using contingency chi-square tests with one degree of freedom. ORs with 95% CIs were also calculated. In the population genotyped in this study, the MAF of rs1929992 (C = 0.49) was higher than those in the HapMap JPT data set (C = 0.46). We found a significant association between rs1929992 (T > C) and JC pollinosis (TT+TC vs. CC: OR, 1.82; 95% CI, 1.00–3.31; $P = 0.048$) (Table 3). The serum total IgE level was analysed as a quantitative level, and we investigated the association between this level and genetic variation. However, we could not find any association between the SNP and serum IgE level in this study ($P = 0.46$ by ANOVA).

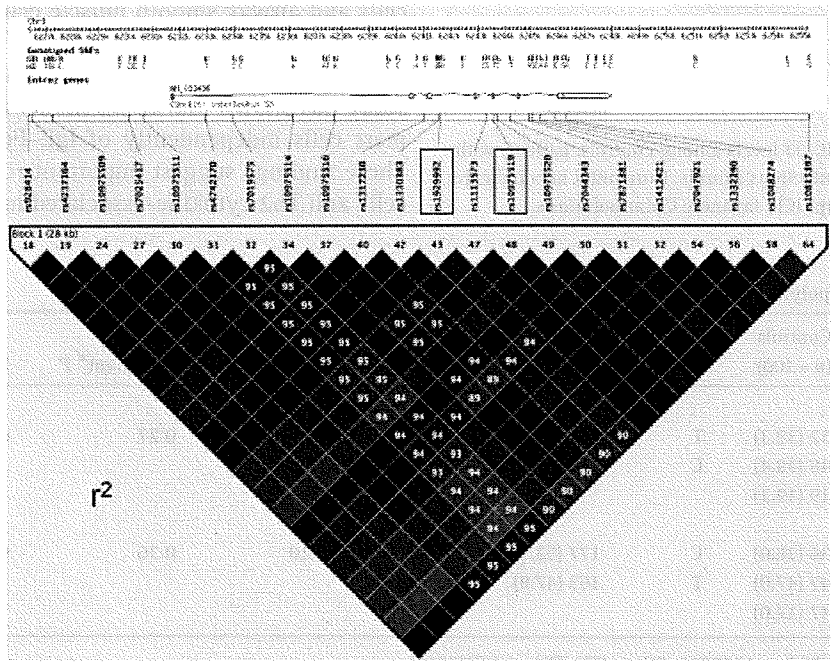

Fig. 1. Pairwise linkage disequilibrium between 22 SNPs as measured by r^2 estimated by the Haploview 3.2 program using the HapMap JPT data set. The boxed polymorphisms, rs1929992 and rs10975519, were genotyped in this study.

Patients with Japanese cedar pollinosis display higher interleukin-33 serum levels than healthy control subjects

To evaluate whether dysregulation at the IL-33 protein level might be a characteristic feature of JC pollinosis, we conducted ELISA assays of sera of patients with JC pollinosis ($n = 170$) and healthy control subjects ($n = 100$). Patients with JC pollinosis exhibited significantly higher serum levels of the IL-33 protein ($P = 0.0018$) (Fig. 2). The median serum IL-33 concentration of JC pollinosis patients was 549 pg/mL, compared with 361.8 pg/mL for controls. In addition, we examined the serum IL-33 level in infectious rhinitis as non-allergic rhinitis. The median serum IL-33 concentration of subjects with infectious rhinitis was 241.3 pg/mL. There was no significant difference of the serum IL-33 level between healthy control subjects and those with infectious rhinitis. Although total serum IgE and IL-33 levels were analysed as quantitative phenotypes, there was no significant association between the total serum IgE level and serum IL-33 level ($P = 0.095$ by Spearman's test). We also examined whether the *IL-33* genotype affected the serum level of IL-33, but we could not find any significant association between the genotype and serum IL-33 level ($P = 0.58$ by the Kruskal–Wallis test).

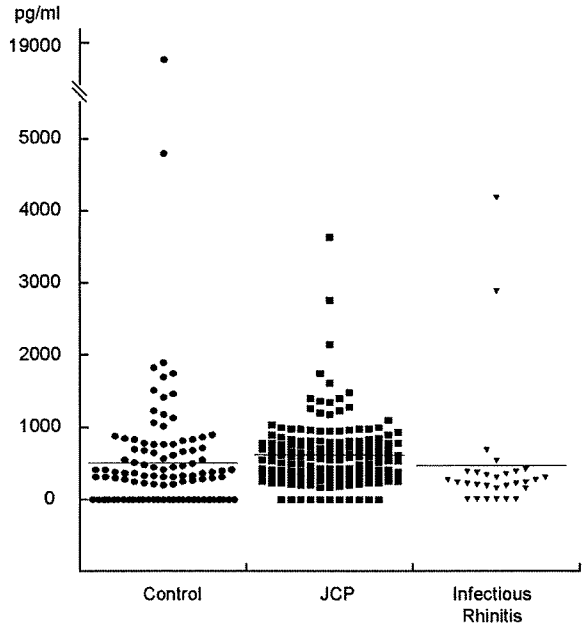

Fig. 2. Comparison of serum IL-33 levels among controls, patients with JC pollinosis and those with infectious rhinitis. Horizontal bars indicate the median value of each group. JCP, Japanese Cedar pollinosis.

Discussion

To determine the role of the *IL-33* gene in the pathogenesis of JC pollinosis, we conducted an association study using the sequence variation of the *IL-33* gene and compared serum IL-33 levels between subjects with JC pollinosis and controls. We found a significant association between JC pollinosis susceptibility and IL-33 polymorphism and higher serum IL-33 levels in subjects with JC pollinosis. Although IL-33 has been thought to play an important role in allergic diseases, this is the first study providing evidence for its involvement in such a disease. We consider the results to be hypothesis generating as the findings in this study need to be confirmed in another population with a larger size.

Recent studies have reported important roles of non-lymphoid cell-derived cytokines such as IL-33 and TSLP in the induction of Th2 differentiation [9, 19]. IL-33 is highly expressed in normal human bronchial epithelial cells and airway smooth muscle cells [9]. It induces Th2-type responses and Th2-associated cytokines IL-4, IL-5 and IL-13 by signalling through IL1RL1 [9, 20]. A recent study has shown that IL-33 induces IL-13 production by mast cells independently of IgE–FcεRI signals in mice. These findings suggest important roles for IL-33 in mast cell- and Th2 cytokine-associated immune disorders [21].

Table 3. Association between polymorphisms of *IL-33* and Japanese cedar (JC) pollinosis

Genotype	Cases ($n = 170$)	Controls ($n = 100$)	Allele	Cases ($n = 170$)	Controls ($n = 100$)	Genotype P	Dominant* P	Recessive† P	Allelic‡ P
rs1929992									
TT	44 (26.0)	32 (32.3)	T	162 (47.9)	112 (56.6)	0.13	0.27	0.048	0.053
TC	74 (43.8)	48 (48.4)	C	176 (52.1)	86 (43.4)				
CC	51 (30.2)	19 (19.2)							
rs10975519									
CC	52 (30.6)	36 (36.0)	C	177 (52.1)	119 (59.5)	0.20	0.36	0.074	0.093
CT	73 (42.9)	47 (47.0)	T	163 (47.9)	81 (40.5)				
TT	45 (26.5)	17 (17.0)							

*Dominant model (TT vs. CC+TC in rs1929992, CC vs. CT+TT in rs10975519).

†Recessive model (TT+TC vs. CC in rs1929992, CC+CT vs. TT in rs10975519).

‡Allelic model (T allele vs. C allele in rs1929992, C allele vs. T allele in rs10975519).

Structurally, IL-33 is related to IL-18, and intensive studies of the relationship between allergic inflammation and IL-18 have been conducted. IL-18 was the first cytokine demonstrated to activate T cells to produce abundant IFN-γ without T cell receptor (TCR) engagement [22]. Furthermore, genetic association studies of the *IL-18* gene have provided evidence for an association with atopic diseases [23–26]. Verhaeghe et al. reported the up-regulation of IL-18 in nasal secretions in allergic rhinitis and the persistence of elevated IL-18 concentrations until after the season [27]. Increased IL-33 concentrations were observed in subjects with JC pollinosis in the present study; however, there was no significant difference in the serum IL-33 level between controls and subjects with infectious rhinitis. Up-regulation of the IL-33 level appears to be characteristic of JC pollinosis. Further analyses of the involvement and interactions of those structurally similar cytokines in allergic inflammation should also be conducted.

Recent reports have shown that IL1RL1 is a reliable marker of Th2 lymphocytes in allergic airway inflammation [7, 13, 28]. Elevated levels of the soluble form of IL1RL1 in the circulation of patients with asthma with acute exacerbation have been reported [14]. The study has also shown that a differential rise of serum IL1RL1 level that correlates well with the severity of asthma exacerbation [14]. In a murine model of allergic airway inflammation, serum murine (m) IL1RL1 protein levels increased after allergen exposure, and pre-treatment with soluble mIL1RL1 protein significantly inhibited the Th2 cytokine production [12]. Other studies have shown that administration of either a monoclonal antibody against IL1RL1 or a recombinant IL1RL1 fusion protein attenuates eosinophilic inflammation of the airways and suppresses IL-4 and IL-5 production *in vivo* following adoptive transfer of Th2 cells [6, 7]. These findings suggest that blocking IL1RL1 pathways would be therapeutically efficacious as a new treatment for allergic diseases, and expression of soluble IL1RL1 could serve as a physiological mechanism to down-regulate Th2-driven immunopathology [10]. In this study, we did not measure the serum soluble IL1RL1 levels, and further examination of the relationship between serum IL-33 and soluble IL1RL1 is needed to clarify their functions in Th2 inflammation. The genetic factors of the *IL-33* gene or serum IL-33 level might provide valuable information for selecting appropriate therapeutic options.

We showed here a significant association between susceptibility to JC pollinosis and a polymorphism. In this study, we selected polymorphisms using HapMap information, and did not examine the functional effects of polymorphisms in strong LD with the related variant. Previous studies have shown that polymorphisms in exons often contribute to their transcript stability [29, 30]. Variants rs10975519 (Tyr163Tyr) and rs1048274 in the exon might affect the expression level or mRNA stability of the *IL-33* gene. In addition, four genetic variations were in the 5′-flanking region, which is often involved in transcriptional regulation of the gene. Several transcription factors are involved in asthmatic inflammation, including NF-κB, activator protein-1 (AP-1), nuclear factor of activated T cells (NF-AT), cyclic AMP response element-binding protein (CREB) and signal transduction-activated transcription factors (STAT) [31]. Using the TRASFAC system, we surveyed whether SNPs in the 5′ region of the *IL-33* gene create transcription factor binding sites. However, we could not find any SNP that changed the affinity of those transcription factors. The functions of these linked polymorphisms remain to be elucidated. Demonstrating the alteration of gene functions as the result of polymorphisms is necessary to further validate the involvement of the *IL-33* gene in the pathogenesis of JC pollinosis. Furthermore, there were gender differences in the population in this study, and several studies have suggested that sex affects the asthma phenotype, possibly via hormone-related events [32, 33]. If there is a sex-related difference in the association of IL-33 with JC pollinosis, looking at females only might be informative.

Our data strongly support the important role of IL-33 in JC pollinosis. Further investigation of the connections between genotypes and the functional role of IL-33 during allergic events may provide additional targets for therapeutic interventions and would be helpful to clarify the aetiology of allergic diseases.

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リアルタイムモニター飛散数の情報のあり方の研究と舌下ペプチド・アジュバント療法の臨床研究
スギ精製抗原および抗原ペプチドに対する患者末梢血T細胞反応に関する研究

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研究要旨

スギ精製抗原およびT細胞エピトープ抗原ペプチドに対するスギ花粉症患者末梢血T細胞の反応性の違いを、特異的Th2（IL-4、IL-5）細胞の出現頻度を指標に検討した。使用した精製抗原はCry j 1およびCry j 2であり、ペプチド抗原はこれまでに同定された主要7種類のT細胞エピトープ（Cry j 1（3個）、Cry j 2（4個））である。結果は、精製抗原に対するT細胞反応性とペプチド抗原に対するT細胞反応性には高い正の相関がみられた。また、精製抗原特異的Th2細胞頻度に対するペプチド特異的Th2細胞頻度は症例ごとに異なり、IL-4およびIL-5いずれにおいても30%ー80%と症例間でばらつきが認められた。ペプチド免疫療法の有効性を高めるには、多くの患者が高い反応性を示す抗原の開発が必要ではないかと考えられ、今回の測定系の有用性が示唆された。

A. 研究目的

アレルギー性鼻炎に対する抗原特異的免疫療法は、現在唯一治癒の可能性がある治療法としてWHOのポジションペーパーにも記載されている。しかしながら、従来の精製抗原ではアナフィラキシーショック等副作用の問題があり、一般的な治療法としては広く普及していないのが現状である。近年この抗原に替わり、ペプチドを用いた免疫療法が考案されている。すなわち、IgEバインディングエピトープを持たないT細胞エピトープペプチドを用いることで、アナフィラキシーショック等の副作用を来すことなく安全に治療ができるというものである。

さて、現在までにスギ花粉抗原由来のT細胞エピトープペプチドがいくつか同定されている。ペプチドを用い抗原を限定する事は副作用を軽減できるメリットがある反面、抗原タンパクの反応性（免疫原性）を低下させる可能性もある。そこで、現在までに報告されたT細胞エピトープペプチドのうち主要な7種類のペプチド（Cry j 1由来3種類・Cry j 2由来4種類）を合成し、スギ花粉精製抗原とペプチドの免疫原性の違いを、スギ花粉症患者末梢血中の特異的Th2細胞の頻度を指標に検討した。

B. 方法

同意の得られたスギ花粉症患者5症例を対象とした。患者末梢血を採取、比重遠心法によりリンパ球を分離した。また、単球を中心とした付着細胞を分離しGM-CSFとIL-4存在下で1週間培養して樹状細胞（DCs）を誘導した。現在まで報告されているスギ抗原由来T細胞エピトープペプチドから、主要7種類のペプチドを選択して合成し、スギ抗原Cry j 1、Cry j 2または7種類のスギ抗原由来ペプチドを、誘導したDCsに添加、さらに24時間培養した。抗原提示をしていないDCsをコントロールとし、これらDCsを用いて同一患者の末梢血単核球に抗原提示をさせ、ELISPOT assayを行い、Cry j 1、Cry j 2あるいはペプチド特異的IL-4、IL-5産生細胞の頻度を測定した。

C. 結果

ペプチド特異的IL-4・IL-5産生細胞とCry j 1、2特異的IL-4・IL-5産生細胞の間には高い相関が見られた。（図1）

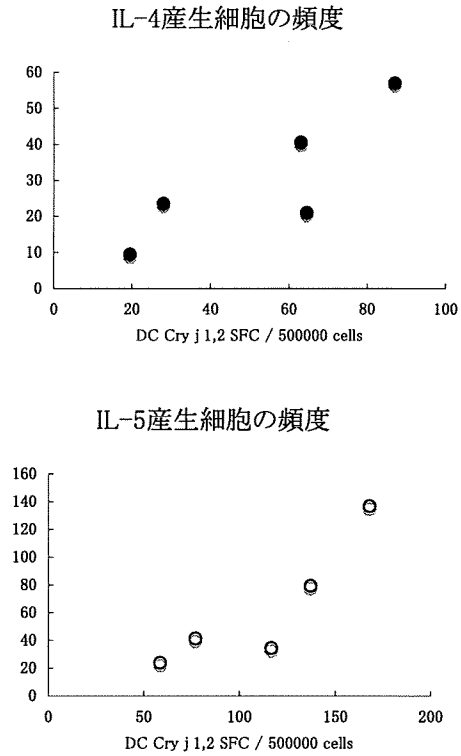

図 1. Cry j 1, 2 特異的 T 細胞とペプチド特異的 T 細胞の相関

次に、各症例ごとに、ペプチド特異的 IL-4・IL-5 産生細胞と Cry j 1、Cry j 2 特異的 IL-4・IL-5 産生細胞の頻度を測定し、抗原タンパク特異的細胞数に対するペプチド特異的細胞数の割合を算出した。症例 1 ではペプチド特異的 IL-4 産生細胞はタンパクレベルの抗原特異的 IL-4 産生細胞の 65.5%であり、IL-5 産生細胞のそれは 81.6%であった（表 1）。

各症例の Cry j 1,2 特異的 T 細胞に対するペプチド特異的 T 細胞の割合を表 1 に一覧で示す。HLA の多様性からみれば予測可能ではあるが、患者によって差があり 60%以上反応する患者もいれば 30%程度の反応しかみられない患者もいた。また、同一患者においても産生するサイトカインの種類によって差が見られた。

表 1．各症例における Cry j 1,2 特異的 Th2 細胞の頻度に対するペプチド特異的 Th2 細胞の頻度の割合

	IL-4 産生細胞の頻度 Peptide / Cry j 1, 2	IL-5 産生細胞の頻度 Peptide / Cry j 1, 2
症例 1	65.5%	81.6%
症例 2	83.9%	53.9%
症例 3	64.3%	58.0%
症例 4	48.7%	41.0%
症例 5	32.6%	29.6%
		(SFC/5×10^5 cells)

表 1.

D. 考察

抗原特異的 T 細胞を標的にした T 細胞エピトープペプチド免疫療法は、理想としては個人ごとに異なる HLA にマッチしたペプチドを用いたテーラーメイド治療を行なう必要があると考えられるが、問題点としては莫大なコストがかかることが予想される。今回スギ抗原ペプチド免疫療法の候補である 7 種類のペプチドを合成し、その免疫原性について検討を行った。抗原を 7 種類のペプチドに限定しても今回検討した 5 症例は全てレスポンダーであり、このペプチドで全ての患者はカバーされたことになる。また、図 1 で示したように Cry j 1,2 特異的 T 細胞頻度とペプチド特異的 T 細胞頻度との間には相関があり、ある程度その免疫原性は保たれていると考えられた。しかしながら、各症例におけるペプチド特異的 IL-4・IL-5 産生細胞（Th2 細胞）と精製抗原タンパク特異的 Th2 細胞の頻度を用いた検討では、症例 1、症例 2 では 7 種類のペプチドにおいて Cry j 1、2 特異的 Th2 細胞クローンの 60%から 80%が反応性を示しているが、症例 4 では 50%以下、症例 5 では 30%程度のクローンしか反応していない。つまり、この 7 種類のペプチドに限定すると反応性が高い患者と低い患者が存在することが明らかである。

ペプチド免疫療法の開発にあたっては、IgE バインディングエピトープをもたないことや、多くの患者をカバーできるよう HLA 拘束性を含めた検討は十分なされていると思われる。しかし、個々の症例に対する免疫原性についての論議は不十分である。今回の検討で、抗原を 7 種類のペプチドに限定することにより反応性が低下する患者が存在した。実際の治

療に用いるためには、より多くの患者がカバーでき、かつ高い反応性を持った抗原を開発する必要があると考えられた。

E. 結論

T 細胞エピトープペプチドを用いた免疫療法は、特にハチ毒アレルギーに対する免疫療法においてその臨床効果が報告されている。ペプチド免疫療法を含め、有効な特異的免疫療法の普及のためには、安全かつ効果的でコストバランスに優れた抗原が必要である。今後、新たな抗原を開発する上で、従来の精製抗原との免疫原性の比較検討は重要な課題であると考えられ、今回用いた測定系は有用であった。

F. 健康危険情報

なし

G. 研究発表

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H. 知的財産権の出願・登録状況

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

なし

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ORIGINAL ARTICLE

Patterns of Drug Prescription for Japanese Cedar Pollinosis Using a Clinical Vignette Questionnaire

Goro Takahashi[1], Zensei Matsuzaki[1], Takeo Nakayama[2] and Keisuke Masuyama[1]

ABSTRACT

Background: Although prescribed drugs directly affect patient outcome, the variation in physicians' attitudes towards drug therapy for cedar pollinosis has not been quantitatively assessed. This research investigated the prescription patterns of drugs for cedar pollinosis by ear, nose, and throat specialists (ENTs), general physicians (GPs) and internal medicine doctors (IMs) in Yamanashi Prefecture, Japan.

Methods: A cross-sectional study was conducted by mailing questionnaires to 532 physicians in autumn 2006. The main part of the questionnaire constituted clinical vignettes of pollinosis cases with nasal and ocular symptoms ranging from mild to severe. We requested that the physicians fill out prescription medications they considered appropriate for each vignette.

Results: Responses from 172 physicians (32%) for six clinical vignettes were analyzed. The number of drugs prescribed by ENTs was significantly higher than that by GPs and IMs for vignettes representing moderate to severe cases ($p < 0.004$). The percentage of physicians who said they would prescribe nasal corticosteroid and eye drops was higher in the ENT group compared to the other two groups in these vignettes. In terms of second-generation antihistamines, no differences were observed between the three groups for all vignettes.

Conclusions: Our investigation suggested that, compared to ENTs, GPs and IMs have a lower tendency to concomitantly prescribe drugs for localized treatment such as nasal corticosteroids and eye drops with oral medication. There may be differences in prescription patterns of drugs for pollinosis between ENTs and non-specialist physicians.

KEY WORDS

allergic rhinitis, guideline, Japan, physician's practice patterns, questionnaires

INTRODUCTION

Allergic rhinitis is not a life-threatening illness, nevertheless patients suffer from highly uncomfortable symptoms that disrupt the quality of everyday life and productivity of academic or professional work.[1] Symptoms of cedar pollinosis begin to appear around February to March every year, and it is the most common type of seasonal allergic rhinoconjunctivitis in Japan. According to a nationwide epidemiological study, the prevalence of Japanese cedar pollinosis is estimated to be 13%. However, recent studies based on statistical analyses predict potential annual increases in this figure.[2,3] Such high figures demonstrate that Japanese cedar pollinosis is indeed a large problem in society.

In recent years, variation in the medical practice of physicians has been the subject of research across many clinical fields, from the perspective of the quality of healthcare.[4-7] When considering the huge impact cedar pollinosis has on society, it is important to research the variations in medical practice for this particular illness, especially with regard to the patterns of drug prescription.

Currently, nasal corticosteroid drops are considered to be the first-line drug for patients with moderate to severe allergic rhinitis.[1] However, a cross-sectional study has suggested that, in actuality, the

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prescription of nasal corticosteroids by general physicians may be limited.[8] According to Demoly *et al.* whose research involved patients and general physicians, oral antihistamines were prescribed for 92% of the patients, whereas only 45% were prescribed nasal steroids.[9] Similarly, a patient survey conducted in Japan by Okuda *et al.* revealed a higher tendency of general physicians to singly prescribe oral medication compared to otolaryngologists.[10] Furthermore, Van Hoecke *et al.* have shown with reference to the Allergic Rhinitis and its Impact on Asthma (ARIA) guideline that 30% of medicines prescribed by general physicians for moderate or severe persistent allergic rhinitis patients were considered as undertreatment.[11] This is a problem concerning compliance with the guidelines for drug therapy. However, additional research conducted in, these previous studies on clinically prescribed medication that are often influenced by many factors such as the patients' clinical conditions, personal values, healthcare environments, medical resources and annual variance in antigen levels suggest that it is not appropriate to interpret the results simply as patterns of decision-making processes or patterns of drug prescription by individual physicians.

To date, the prescription patterns of drugs for cedar pollinosis have not been investigated. In this study, we have investigated such prescription patterns by Japanese physicians under the hypothesis that general physicians depend less on nasal steroids than otolaryngologists.

Traditionally, this type of research has been conducted using methods such as assessments involving simulated patients, or by reviewing medical records. Recently, the validity and advantages of using clinical vignettes for such research have been shown, and this is now becoming a method of interest.[12,13]

The aim of this research is to compare the prescription patterns of drugs for cedar pollinosis by ear, nose, and throat specialists (ENTs), general physicians (GPs) and internal medicine doctors (IMs) in Yamanashi Prefecture, Japan.

METHODS

RESEARCH DESIGN, SETTINGS AND SUBJECTS

This research was designed as a cross-sectional study carried out using mailed questionnaires. Subjects were ENTs, GPs and IMs working in Yamanashi Prefecture. The exact number of subjects was unknown at the time of this study, although there were 59 ENTs and 491 physicians (total number of GPs and IMs) in 2004 according to a report by the Ministry of Health, Labour and Welfare.[14]

QUESTIONNAIRE DESIGN

The questionnaire was constructed by three ENTs. It consisted of questions regarding 1) occupational background of the subjects, 2) medical consultation for allergic rhinitis, and 3) clinical vignettes for cedar pollinosis. In principle, questionnaires were answered anonymously and were self-completed. For each vignette, the most effective prescribed medication was decided by the subjects and noted together with any co-administered drugs or required medication.

RESEARCH METHODS

The names and addresses of 53 ENTs, 214 GPs and 265 IMs were found individually by searching through phone books and the Internet. Questionnaires were mailed to them on October 10, 2006. Reminders were sent twice thereafter and the questionnaires were collected by November 10, 2006. This research was conducted upon the approval of the Ethics Review Board of the University of Yamanashi Hospital.

STATISTICAL ANALYSIS

Background factors of the subjects were presented descriptively. Responses for six clinical vignettes were analyzed (Appendix). The names of prescribed medication given for each vignette were categorized and sorted into second-generation antihistamines, oral steroids, antileukotrienes, other oral medication (first-generation antihistamines, Chinese herbal medicines, chemical mediator release inhibitors etc.), nasal corticosteroid drops, non-steroidal anti-allergy nasal drops (antihistamines, chromones etc.), nasal vasoconstrictive agents and eye drops (steroids, antihistamines, chromones etc.). Fexsofenadine hydrochrorides and loratadins that were not accompanied with a product leaflet containing information on precautions for vehicular driving were categorized as non-sedative antihistamines, and analysis was carried out accordingly.

The Kruskal-Wallis test was used to compare the number of prescribed medications between the 3 groups of prescribers for each vignette. The significance level was used according to the method by Bonferroni at $\alpha = 0.008$ (two-tailed). This test was carried out for the null hypothesis: there was no difference in the number of prescribed medications between the 3 groups. For vignettes where the null hypothesis was rejected, analysis was repeated using a Mann-Whitney test between the 2 groups using a two-tailed significance level of $\alpha = 0.004$, again using the Bonferroni method.

Furthermore, for each type of drug and for each vignette, both the percentage of physicians who prescribed the drug and its 95% confidence intervals (or one-sided 97.5% confidence interval) were used to compare the 3 groups.

All statistical analyses were performed in Stata version 9.2 (StataCorp, College Station, Tx, USA).

Table 1 Characteristics of physicians included in the survey

	ENT $n = 45$	GP $n = 72$	IM $n = 55$
Male, no. (%)	39 (87)	68 (94)	48 (87)
Years since graduation from medical school, median (IQR)	20 (14–27)	25 (20–33)	13 (8–20)
Physicians with a solo practice, no. (%)	24 (53)	56 (78)	3 (5)
Greatest number of pollinosis patients per day examined in the Japanese cedar pollinosis season of 2006, no. (%)			
1–10	7 (16)	0 (0)	42 (76)
11–30	16 (36)	45 (63)	10 (18)
31–50	3 (7)	25 (35)	2 (4)
51–	19 (42)	1 (1)	1 (2)
Unknown	0 (0)	1 (1)	0 (0)
Usefulness of Japanese practical guideline for AR in the Japanese cedar pollinosis season of 2006, no. (%)			
Very useful	12 (27)	11 (15)	11 (20)
Useful	27 (60)	51 (71)	27 (49)
Neutral	5 (11)	2 (3)	4 (7)
Not useful	0 (0)	0 (0)	0 (0)
Not useful at all	0 (0)	0 (0)	0 (0)
No experience of use	1 (2)	7 (10)	13 (24)
Unknown	0 (0)	1 (1)	0 (0)

ENT, ear, nose, and throat specialists group; GP, general physicians group; IM, internal medicine doctors group; IQR, interquartile range.

RESULTS

Questionnaires were collected from 186 physicians (response rate 36%). Fourteen questionnaires in total were excluded from the analysis; this included 1 ENT, 2 GPs and 5 IMs who left the clinical vignettes blank and 6 IMs who did not examine pollinosis patients during the 2006 cedar pollen season. Overall, responses were received from 172 (32%) physicians consisting of 45 ENTs, 72 GPs and 55 IMs, and were included in the statistical analysis.

BACKGROUND OF SUBJECTS

The ENT and GP groups compared with the IM group demonstrated a trend in seeing a larger number of cedar pollinosis patients each day. Furthermore, approximately 70% of subjects in all groups approved of the validity of the Practical Guideline for the Management of Allergic Rhinitis in Japan (PGMARJ) (Table 1).[15]

REPORTED NUMBER OF PRESCRIBED DRUGS FOR EACH VIGNETTE

The number of drugs reported by physicians that they would prescribe was compared among the 3 groups for each vignette. The drugs that were included in the count were oral drugs, nasal drops, eye drops, co-administered drugs and other required medication. For vignettes 3 to 6, the numbers given by ENTs were significantly higher than for GPs and IMs ($p<0.004$) (Fig. 1).

TRENDS IN DRUG PRESCRIPTION FOR EACH TYPE OF DRUG

When comparing the percentage of physicians who reported prescribing second-generation antihistamines using the 95% confidence interval, no differences could be observed among the 3 groups for all vignettes (Fig. 2A).

The percentage of physicians who reported prescribing non-sedative antihistamines was as high as 66% (95% CI: 51%–80%) in the ENT group and 64% (95% CI: 52%–75%) in the GP group, compared with 40% (95% CI: 27%–54%) in the IM group for vignette 2 (data not shown). For all other vignettes, the percentage for non-sedative antihistamines was approximately 25% for all groups.

When the percentage of physicians who reported prescribing nasal corticosteroid drops were compared using a 95% confidence interval, an increasing trend in percentages was found with increasing severity of symptoms in all 3 groups (Fig. 2B). In vignettes 4 to 6, this percentage was clearly higher in the ENT group compared to the other 2 groups.

Comparison of the percentage of physicians who prescribed eye drops using 95% confidence intervals for vignettes 3 to 5 revealed that the percentage in the ENT group was clearly much higher than in the

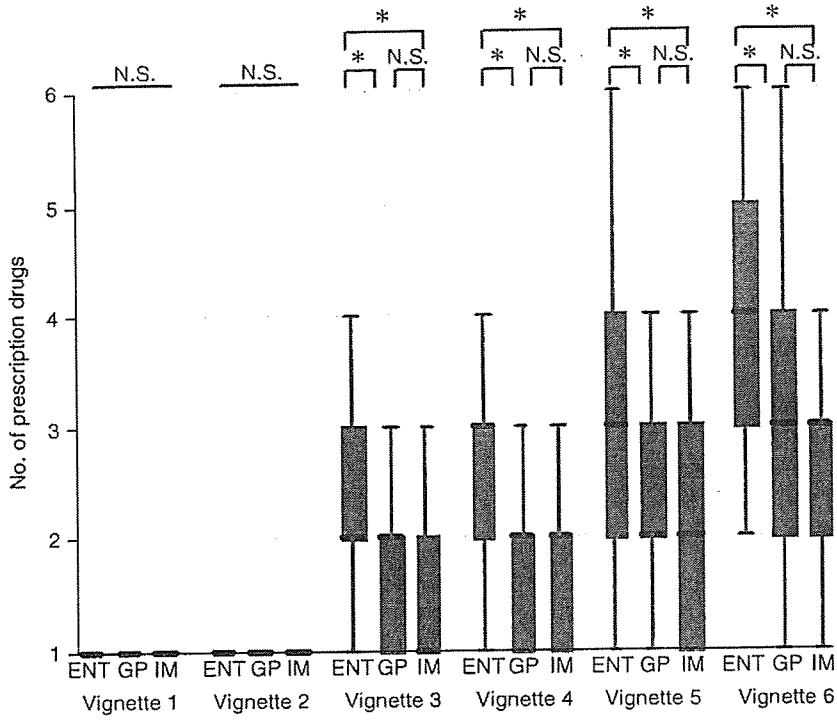

Fig. 1 Box and whisker plots of the number of prescription drugs by ear, nose, and throat specialists (ENTs), general physicians (GPs), and internal medicine doctors (IMs) for each vignette. The vertical bars indicate the range from lower to upper adjacent values. The horizontal boundaries of the boxes represent the first and third quartiles. The thick bars in the boxes indicate medians. NS means, -not statistically significant. *, $p < 0.004$.

other 2 groups (Fig. 2C).

For vignette 6, oral steroids were prescribed by 56% (95% CI: 40%–70%) of the ENT group and 45% (95% CI: 33%–57%) of the GP group, but was lower at 21% in the IM group (95% CI: 11%–34%). For all other vignettes, the percentage for oral steroids prescribed was below 20% in all 3 groups.

As for the percentage of physicians prescribing antileukotrienes and vasoconstrictive agents, there were no significant differences among the 3 groups for all vignettes.

POSSIBLE UNDERTREATMENT BY COMPARISON WITH GUIDELINES

In addition, we analyzed the possibility of some prescription patterns to be considered as undertreatment, by referring to the ARIA or PG-MARJ medical practice guidelines.[1,15] The criteria for classifying rhinitis and assessment of severity differs extensively between the 2 guidelines. The cedar pollen season in Japan lasts for approximately 2 months, and according to the ARIA, most cedar pollinosis patients will be classified as patients with persistent allergic rhinitis. According to the PG-MARJ, however, the severity of pollinosis is classified into 4 types: mild, moderate, severe, or most severe, on the basis of a patient's nasal symptoms and QOL grading. In the 2 guidelines, it is recommended to use nasal steroids as the first-choice either singularly or concomitantly for persistent moderate/severe allergic rhinitis or moderate/severe/most severe pollinosis. With reference to the above, we analyzed the answers given for vignettes 4 to 6 which represent severe cases and identified those that could potentially be considered as undertreatment.

For vignette 4 which includes severe rhinorrhea and sneezing symptoms, the prescription decided by 33% of physicians in the ENT group, 64% in the GP and 65% in the IM groups could be considered as undertreatment. For vignette 5 which includes severe nasal congestion, possible undertreatment could be identified in 13% of the ENT group, 37% of the GP group and 57% of the IM group. For vignette 6 which involves a case of severe overall symptoms, possible undertreatment could be identified for 4% of the ENT group, 25% of the GP group and 43% of the IM group (Table 2).

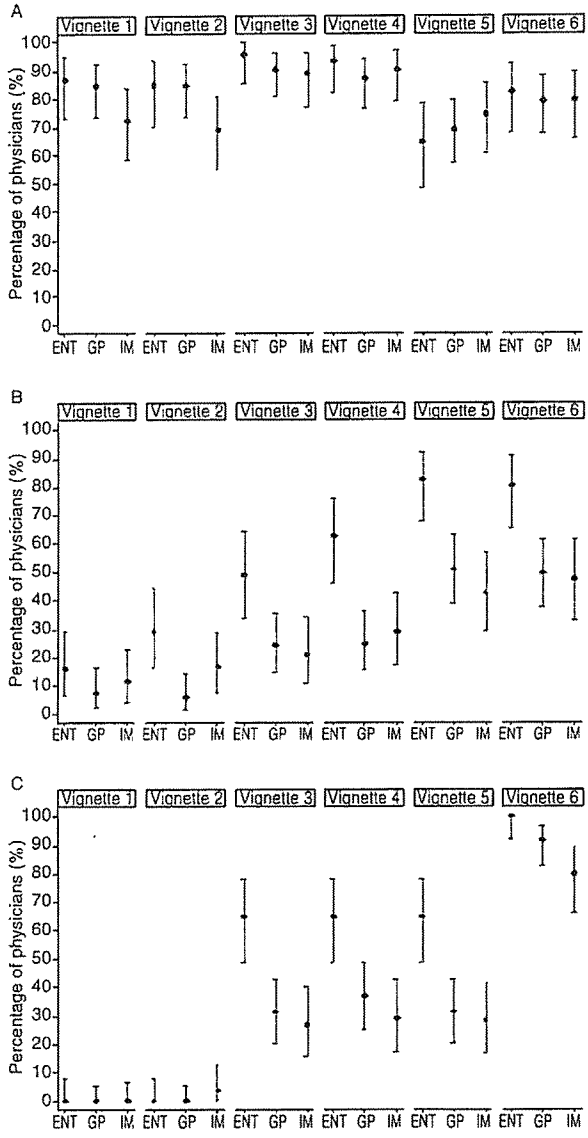

Fig. 2 Percentage of physicians prescribing each type of drug for each vignette in the 3 groups by ear, nose, and throat specialists (ENTs), general physicians (GPs), and internal medicine doctors (IMs). The black circles indicate the simple percentages. The two-tailed bars represent the 95% confidence intervals of the percentages. The one-sided bars represent the 97.5% confidence intervals of the percentages. A: Second-generation antihistamines. B: Intranasal corticosteroids. C: Antiallergic eye drops.

DISCUSSION

In this study we analyzed and compared for the first time the prescription patterns of drugs for cedar pollinosis between physicians classified as ENTs, who are specialists, and GPs and IMs through the use of clinical vignettes. The research purpose for using clinical vignettes was not to test the knowledge of physicians, but to analyze how the physicians would prescribe medication if they encountered such patients in real life as described by the vignettes. Because responses are likely to be biased in many ways, it is important to analyze the responses given by a strictly defined group of physicians rather than that of individuals.[13] Recent studies have confirmed the validity of clinical vignettes by comparing them with simulated patient studies. Clinical vignettes are advantageous in that they are more cost effective and practical compared to simulated patients, and most of all, the problem of case-mix that occurs during medical record reviews can be regulated.[12]

In Japan, many cedar pollinosis patients consult otolaryngologists and general physicians. According to past research conducted on the trend of medical consultation for cedar pollinosis patients, 40% consulted otolaryngologists and 30% consulted general physicians, and when questioned about the type of medical institutions visited, 90% of patients consulted clinics.[10] Our questionnaire has confirmed that larger numbers of cedar pollinosis patients consult ENTs and GPs compared to IMs.

Our results suggest that the most obvious differences in the prescription patterns for cedar pollinosis between ENTs, GPs and IMs are those of nasal corticosteroid drops and eye drops. In actuality, many factors including the patients themselves, features of the medical institution and the amount of airborne pollen present in a given season will affect the decision on drug prescription. Therefore, information obtained from our clinical vignettes is insufficient for use by our respondents. It may be that our results here do not represent the trends occurring in the prescription of drugs in actual clinical settings. However, our research does not focus on how well our results reflect true clinical settings, but on discovering any differences in the prescription patterns of ENTs, GPs and IMs for the same given clinical cases. What is important here is the fact that the differences discovered in the prescription patterns among the 3 groups are clearly reflected by the differences in the percentage of physicians prescribing nasal corticosteroid drops and eye drops. In order to improve the quality of cedar pollinosis treatment, it will be extremely necessary to identify the reasons why GPs tend to be reluctant in prescribing nasal corticosteroid drops and eye drops to patients with moderate/severe symptoms. This is intriguing since these GPs in particular examine a stable fraction of patients and understand the effectiveness of the guidelines. The reasons for reluctance may be that they are afraid of systemic side-effects triggered by steroids, or because patients who consult GPs often have complications and are already taking medication.[8,11] Nevertheless, the clinical vignettes used here were designed so that complica-

Table 2 Potential undertreatment of Japanese cedar pollinosis according to the Allergic Rhinitis and its Impact on Asthma guideline or the Practical Guideline for the Management of Allergic Rhinitis in Japan[15] recommendations

	Vignette 4			Vignette 5			Vignette 6		
	ENT $n = 45$	GP $n = 69$	IM $n = 52$	ENT $n = 45$	GP $n = 71$	IM $n = 54$	ENT $n = 45$	GP $n = 71$	IM $n = 53$
AH	12 (27)	29 (42)	21 (40)	1 (2)	7 (10)	14 (26)	0 (0)	7 (10)	11 (21)
AL	0 (0)	0 (0)	1 (2)	0 (0)	1 (1)	3 (6)	0 (0)	0 (0)	0 (0)
OOt	0 (0)	6 (9)	1 (2)	2 (4)	6 (9)	0 (0)	0 (0)	3 (4)	0 (0)
NsANS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)
ND	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
AH + AL	0 (0)	0 (0)	2 (4)	1 (2)	3 (4)	2 (4)	2 (4)	0 (0)	1 (2)
AH + OOt	1 (2)	6 (9)	1 (2)	0 (0)	2 (3)	1 (2)	0 (0)	4 (6)	3 (6)
AH + NsANS	2 (4)	2 (3)	8 (15)	1 (2)	3 (4)	8 (15)	0 (0)	4 (6)	7 (13)
AH + ND	0 (0)	1 (1)	0 (0)	1 (2)	4 (6)	0 (0)	0 (0)	0 (0)	0 (0)
AL + ND	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
Total	15 (33)	44 (64)	34 (65)	6 (13)	26 (37)	31 (57)	2 (4)	18 (25)	23 (43)

Number of physicians, (%); ENT, ear, nose, and throat specialists group; GP, general physicians group; IM, internal medicine doctors group; AH, second-generation antihistamines; AL, antileukotriens; OOt, other oral medications (e.g. first-generation antihistamines, herbal medications, etc); NsANS, nonsteroid antiallergic nasal spray; ND, nasal decongestants.

tions would not be included.

Furthermore, when using the medical practice guidelines as a reference, physicians of all 3 groups, including the ENTs who are specialists, may not be fully aware of the severity of symptoms of allergic rhinitis patients. In some cases, drug treatment initiated by these physicians may be insufficient for the control of symptoms. When the prescription patterns suggested by the respondents were compared with the prescriptions recommended by the ARIA guideline and PG-MARJ, a fair proportion of the suggested prescriptions were considered as possible undertreatment. The figures were 25 to 65% of GPs and IMs for the 3 vignettes representing severe cases, and 33% of even the ENT group for the vignette showing a severe case with symptoms of rhinorrhea and sneezing. The response rate of ENTs in this research was high (85%), therefore it will be interesting to know the extent of divergence of the suggested prescription patterns from the guidelines, bearing in mind that these physicians are specialists. Nevertheless, the overall degree of compliance with the guideline was higher for ENTs compared to GPs or IMs with respect to the vignettes representing severe symptoms.

Our study has several limitations. The first is that our research was not conducted during the cedar pollen season. Decisions made by physicians and its patterns may have been elicited more accurately by our vignettes if the research was conducted immediately after the end of the pollen season. Secondly, because our research was based locally in Yamanashi Prefecture, it is somewhat difficult to extend the implications of our results to a nationwide scale. Thirdly, this research was limited by the low response rate of GPs and IMs, who are non-specialist physicians. The motivation of respondents directly influences the quality of responses when using the clinical vignette method. From this standpoint, although the response rate of the GPs and IMs were 33% and 21%, respectively, it can be suggested that those who kindly responded to this complicated vignette method possessed sufficient motivation. Thus, reliability of the results from these physicians can be considered as high. Furthermore, it may be possible to speculate that GPs/IMs who did not respond, compared to those who did, are consulting the guidelines insufficiently, are prescribing simple medication such as oral medicine and have a higher potential for the undertreatment of patients. If these non-respondent physicians could be included in the statistical analysis, the difference between the prescription patterns found between ENTs and the other 2 groups might become clearer.

To conclude, our investigation of the drug prescription patterns for cedar pollinosis in Yamanashi Prefecture has shown that compared to ENTs, GPs and IMs have a lower tendency to concomitantly prescribe drugs for topical treatment such as nasal corticosteroids and eye drops with oral medication.

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APPENDIX

For the clinical vignettes shown below, please fill out the names of medications that you feel are most appropriate to prescribe.

A: Vignette 1 & 2

The amount of airborne cedar pollen is expected to be normal this season. The patient is a 34-year-old man who has visited with a major complaint of nasal symptoms which started 5 days previously. The visit was made 7 days after the beginning of cedar pollen dispersal. He mentions that he did not experience similar nasal symptoms at this time the previous year. Following medical tests and examinations, he was given a diagnosis of new-onset cedar pollinosis. He has no history of other allergies.

Vignette 1

The occupation of this patient is a clerical worker. The symptoms of rhinorrhea, sneezing and nasal congestion are all mild, and no symptoms involve the eyes.

Vignette 2

The occupation of this patient is a taxi driver. The symptoms of rhinorrhea, sneezing and nasal congestion are all mild, and no symptoms involve the eyes.

B: Vignettes 3–6

The amount of airborne cedar pollen is expected to be normal this season. The patient is a 34-year-old man who has visited with a major complaint of nasal symptoms which started 7 days previously. The visit was made 10 days after the beginning of cedar pollen dispersal. The level of airborne cedar pollen is estimated to reach its peak 1 week after his visit. He had been experiencing similar nasal symptoms around this time for the past several years, and apparently had medication prescribed by other clinics, although details are unknown. Following medical tests and examinations, he was given a diagnosis of cedar pollinosis. He has no history of other allergies.

Vignette 3

The occupation of this patient is a clerical worker. The symptoms of rhinorrhea, sneezing and nasal congestion are moderate, and symptoms involving the eyes are mild.

Vignette 4

The occupation of this patient is a clerical worker. The symptoms of rhinorrhea and sneezing are severe, but nasal congestion is mild. Symptoms involving the eyes are mild.

Vignette 5

The occupation of this patient is a clerical worker. The symptoms of rhinorrhea and sneezing are mild, but nasal congestion is severe. Symptoms involving the eyes are mild.

Vignette 6

The occupation of this patient is a clerical worker. The symptoms of rhinorrhea, sneezing and nasal congestion are all severe. Symptoms involving the eyes are also severe.

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治療薬の基礎知識

第5回

鼻噴霧用ステロイド薬

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はじめに

ステロイドは「諸刃の剣」と称されるごとく，劇的な臨床効果の一方で副作用の出現率が高いと認識されている薬物である．特に，全身投与の場合は副作用の発現には注意が必要であり，全身ステロイド薬はアレルギー性鼻炎治療の第一選択薬とはならない．しかしながら，鼻噴霧用（局所）ステロイド薬は，局所作用と全身の副作用を分離可能とした薬剤で，鼻のアレルギー性炎症を副作用をほとんど来すことなくコントロールできる非常に優れた薬物である．適切な使用法によりQOLの向上に貢献できると考える．この稿では，鼻噴霧用ステロイド薬の作用機序，副作用，使い方と今後の展望についてまとめてみたい．

鼻噴霧用ステロイド薬の作用機序

鼻噴霧用ステロイド薬の作用機序について，主に炎症細胞および構成細胞に関する作用を表1と図1に示す[1]．

炎症細胞に関しては，即時相で主役を演じる粘膜マスト細胞数を減少させる作用がある．また，遅発相でのT細胞からのサイトカイン産生の抑制ならびに好酸球数を減少させ，好酸球のアポトーシスを誘導する．加えて，好酸球の遊走に関与するケモカインの産生細胞であるマクロファージからのサイトカイン産生を抑制する．さらに，抗原提示細胞である樹状細胞数を減少させる作用がある．次に，構成細胞については，粘膜上皮細胞からのサイトカインやメディエーター遊離を抑制する．詳細には，GM-CSF，IL-8，

表1　局所（鼻噴霧用）ステロイド薬の炎症細胞と構成細胞に及ぼす効果

炎症細胞		構成細胞	
上皮マスト細胞	数↓	上皮細胞	サイトカイン メディエーター↓
T細胞	サイトカイン↓		
好酸球	数↓	血管内皮細胞	透過性↓
マクロファージ	サイトカイン ケモカイン↓	粘液腺	粘液分泌↓
		気管支平滑筋 β_2受容体	数↑
樹状細胞	数↓		

（文献1）より改変引用）

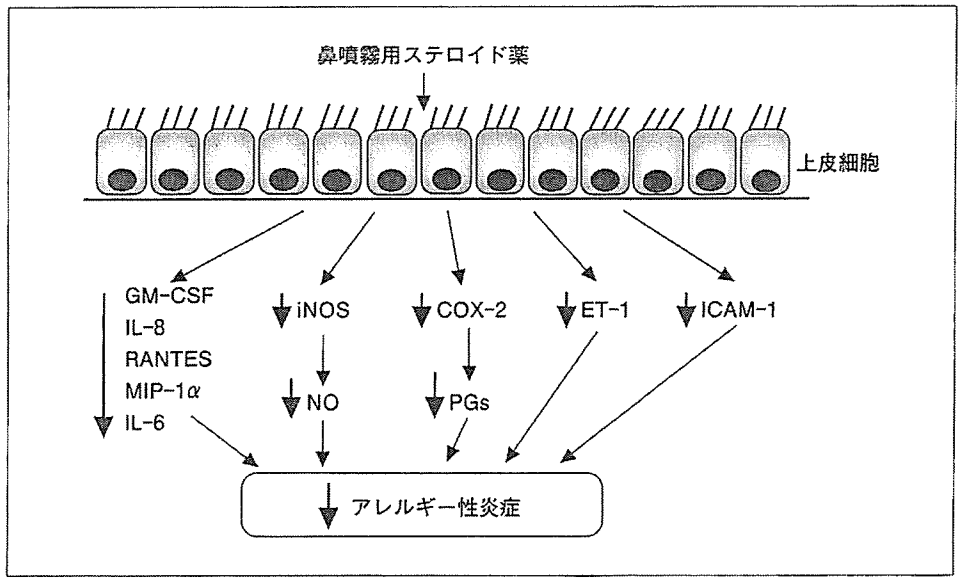

図1　鼻噴霧用ステロイド薬の上皮細胞に対する抗炎症作用

(文献1)より引用)

RANTES，MIP-1α，IL-6などのサイトカイン・ケモカイン産生抑制，アレルギー性炎症の場で発現が亢進しているiNOSの抑制ひいてはNO産生抑制，その他，COX-2，cPLA2，endothelin-1，ICAM-1などの炎症にかかわる蛋白産生の抑制など広範囲にわたっており，上皮細胞は鼻噴霧用ステロイド薬の主要なターゲットと考えていい（図1）．その他，血管内皮細胞の透過性亢進の抑制，粘液腺からの粘液分泌抑制を認める．また，喘息では気管支平滑筋のβ_2受容体の発現亢進作用なども認める．

鼻噴霧用ステロイド薬使用時の注意点ならびに副作用について

花粉症をはじめ，わが国でアレルギー性鼻炎に適応のある鼻噴霧用ステロイド薬はプロピオン酸ベクロメタゾン，プロピオン酸フルチカゾンの2種類である．最近ではそれらのジェネリックが多数存在している．欧米では，それらに加えブデソニド，トリアムシノロンアセトニド，フランカルボン酸モメタゾン，シクレソニドなどの薬剤があり，種類も豊富である．副作用は少ないが，使用の際の注意点として，有効な抗菌薬の存在しない感染症，全身真菌症，本剤過敏症の患者が禁忌となっている．原則禁忌は，結核性疾患，呼吸器感染症，高血圧，糖尿病患者（プロピオン酸ベクロメタゾンのみ）である[2]．

各薬剤の添付文書から調べた有効性は74～84％であり，副作用発現率は2％程度である（小児を除く）．局所の副作用で最も多いのは鼻出血である．これはプラセボ点鼻でも出現するので機械的な刺激によるものであろう．鼻出血が起こった場合には点鼻する方向に気をつけ，鼻中隔側ではなく外側に向けて点鼻するように指導する（右鼻には左手で，左鼻には右手で点鼻を行うという報告もある[3]）．その他，局所の刺激感や不快臭，まれに鼻中隔穿孔や発疹・浮腫などもあり，注意深い局所の観察が必要である．一方，全身の副作用としては，視床下部下垂体副腎系，骨代謝，成長に対する影響が考えられる[1]．全身への副作用は，鼻噴霧用ステロイド薬を嚥下し腸から吸収され肝臓で代謝を受けて（初回通過効果）体循環へ回ったものと，鼻粘膜局所で直接吸収されて体循環に回ったものとによる．大方は嚥下されたものであり，肝代謝による不活化が全身の副作用を左右する[4]．そこで，各薬剤のbioavailability（生物学的利用率）が異なることを知っておくべきである．プロピオン酸ベクロメタゾ

ンやブデソニドは40％を超えるが，プロピオン酸フルチカゾンは1％未満である．低値であるほうが副作用が出にくいとされる．しかしながら，健常成人を対象とした副作用の検討（点鼻4日間）で尿中コルチゾールを指標とした場合では，プロピオン酸ベクロメタゾンやトリアムシノロンアセトニドと比べ，プロピオン酸フルチカゾンで有意に低値を示している[5]．一方，アレルギー性鼻炎成人を対象とした検討では，血中・尿中のコルチゾールを指標とした場合，プロピオン酸フルチカゾン，ブデソニド，トリアムシノロンアセトニド，フランカルボン酸モメタゾンのいずれもコルチゾールに影響がなかった[6]．わが国のプロピオン酸フルチカゾンの長期投与試験（常用量）では，解析61症例中1例で血漿コルチゾールの低値がみられたが，常用量の2倍投与14症例の検討ではコルチゾールの低値は認めていない[7]．

小児においても視床下部下垂体副腎系への影響のみならず，成長への影響が懸念される．プロピオン酸フルチカゾン（常用量と倍量）およびプロピオン酸ベクロメタゾン常用量以下の検討（短期）では，いずれも血中コルチゾールおよび24時間コルチゾール排泄量に影響がみられていない[8][9]．Haye ら[10]による長期投与の報告では，16歳以上の通年性アレルギー性鼻炎患者にプロピオン酸フルチカゾン200μg の1日2回点鼻を1年間行い，血漿コルチゾール値に異常を認めなかった．

以上より，鼻噴霧用ステロイド薬は全身性副作用が極めて少ないがまったくゼロというわけではなく，投与法や吸入後のうがいなどのきめの細かい指導は非常に大事で，特に長期投与になる場合には bioavailability の低い製剤の使用が望ましい．

花粉症に対する鼻噴霧用ステロイド薬のエビデンス

花粉症の治療には，抗ヒスタミン薬，抗ロイコトリエン薬，ケミカルメディエーター遊離抑制薬そして鼻噴霧用ステロイド薬が主に使用される．多用されるのは経口抗ヒスタミン薬と鼻噴霧用ステロイド薬である．鼻アレルギー診療ガイドライン2005年版（改訂第5版）では[2]，花粉症の重症度と病型に応じて薬物の選択を示している（表2）．

それぞれの拮抗薬はピンポイントで作用し，効果を発現する．なかでも抗ヒスタミン薬は，三叉神経の末端や血管に存在するヒスタミン H_1受容体に作用し，くしゃみ反射とそれに続く鼻汁分泌を抑制，また血管に作用して鼻閉を改善し，鼻炎の3症状に効果を示す．ただし，鼻閉についてはシステイニルロイコトリエンやプロスタグランジン D_2，トロンボキサン A_2の作用が強く，その拮抗薬のほうが奏功するとされる．しかしながら，花粉症のように花粉飛散とともに症状があらわれて重症化する急性のアレルギー性炎症では，炎症の進行を早期に抑制することが治療のポイントである．本格的な症状があらわれてからでは効果は劣る．したがって，前述したような抗炎症作用に優れた鼻噴霧用ステロイド薬を早期から使用することが理にかなった治療法といえる．われわれは，初期療法として鼻噴霧用ステロイド薬を抗ヒスタミン薬と比較するパイロットスタディを行い，抗ヒスタミン薬と同等かそれ以上の効果を確認している[11]．特に鼻閉の増悪が抑制される傾向にあった．鼻噴霧用ステロイド薬の特徴を最大限に生かす努力が医師に求められる．

次に，鼻噴霧用ステロイド薬，抗ヒスタミン薬，抗ロイコトリエン薬の効果を比較したメタアナリシスの結果を述べる．

まず鼻噴霧用ステロイド薬と経口抗ヒスタミン薬の効果に関するメタアナリシスである[12]．1966～1997年までに発表された無作為比較試験を対象に，採用基準を満たした16試験である．対象合計症例数は2,267例（男性1,247例，女性1,020例）で，年齢は12～75歳，平均年齢32歳である．くしゃみ，鼻汁，鼻閉，総鼻症状に対する有効性は，いずれにおいても鼻噴霧用ステロイド薬のほうが優れている（図2）．

次に，抗ロイコトリエン薬と鼻噴霧用ステロイド薬あるいは抗ヒスタミン薬の効果に対するメタアナリシスである[13]．それぞれ4試験を対象としている．結論は，抗ロイコトリエン薬はプラセボに比較して有意に効果があるものの，抗ヒスタミン薬と効果は同等で，鼻噴霧用ステロイド薬と比較して劣るというもので

表2　重症度に応じた花粉症に対する治療法の選択

<table>
<tr><th>重症度</th><th>初期療法</th><th>軽　症</th><th colspan="2">中等症</th><th colspan="2">重症・最重症</th></tr>
<tr><th>病　型</th><th></th><th></th><th>くしゃみ・鼻漏型</th><th>鼻閉型または鼻閉を主とする充全型</th><th>くしゃみ・鼻漏型</th><th>鼻閉型または鼻閉を主とする充全型</th></tr>
<tr><td rowspan="5">治　療</td><td>①遊離抑制薬
②第2世代抗ヒスタミン薬
③抗ロイコトリエン薬

①，②，③のいずれか1つ</td><td>①第2世代抗ヒスタミン薬
②鼻噴霧用ステロイド薬

①と点眼薬で治療を開始し，必要に応じて②を追加</td><td colspan="2">鼻噴霧用ステロイド薬
＋
第2世代抗ヒスタミン薬</td><td colspan="2">鼻噴霧用ステロイド薬
＋
第2世代抗ヒスタミン薬</td></tr>
<tr><td colspan="2">鼻噴霧用ステロイド薬
＋
抗ロイコトリエン薬
＋
第2世代抗ヒスタミン薬</td><td colspan="2">鼻噴霧用ステロイド薬
＋
抗ロイコトリエン薬
＋
第2世代抗ヒスタミン薬

必要に応じて点鼻用血管収縮薬を治療開始時の7～10日間に限って用いる
鼻閉が特に強い症例では経口ステロイド薬4～7日間処方で治療開始することもある</td></tr>
<tr><td colspan="2">点眼用抗ヒスタミン薬または遊離抑制薬</td><td colspan="2">点眼用抗ヒスタミン薬，遊離抑制薬またはステロイド薬</td></tr>
<tr><td colspan="2"></td><td colspan="2">鼻閉型で鼻腔形態異常を伴う症例では手術</td></tr>
<tr><td colspan="4">特異的免疫療法</td></tr>
<tr><td colspan="4">抗原除去・回避</td></tr>
</table>

(文献2)より改変引用)

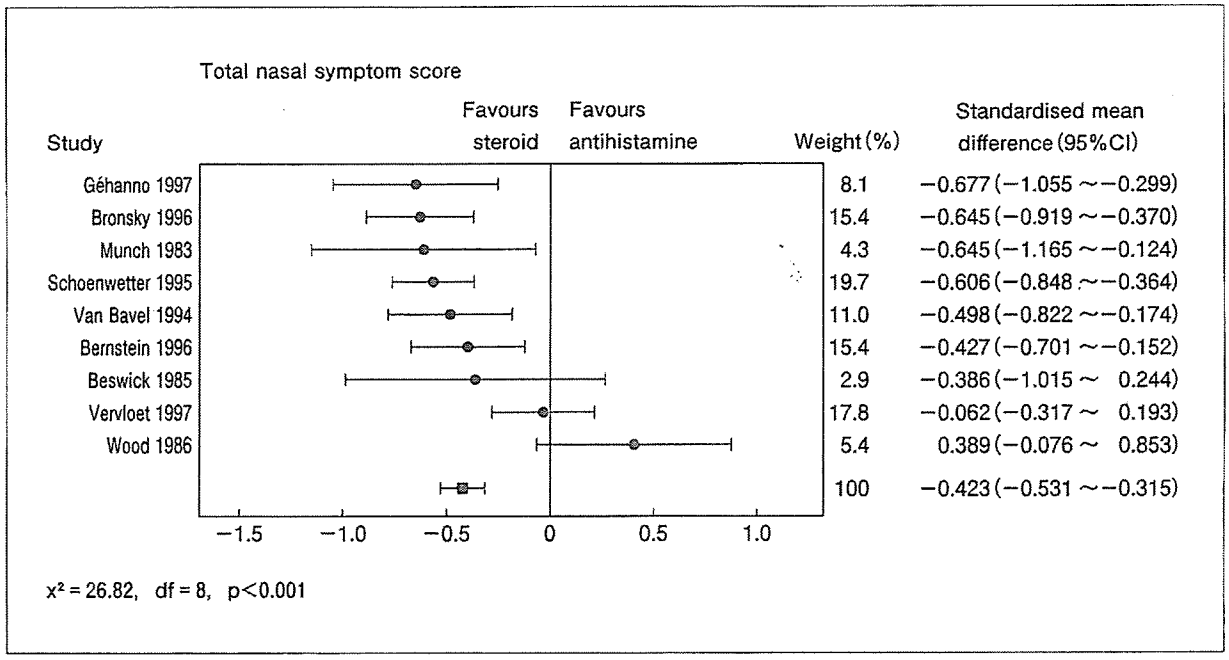

図2　総鼻症状スコアに対する鼻噴霧用ステロイド薬と経口抗ヒスタミン薬の効果の比較

(文献12)より引用)

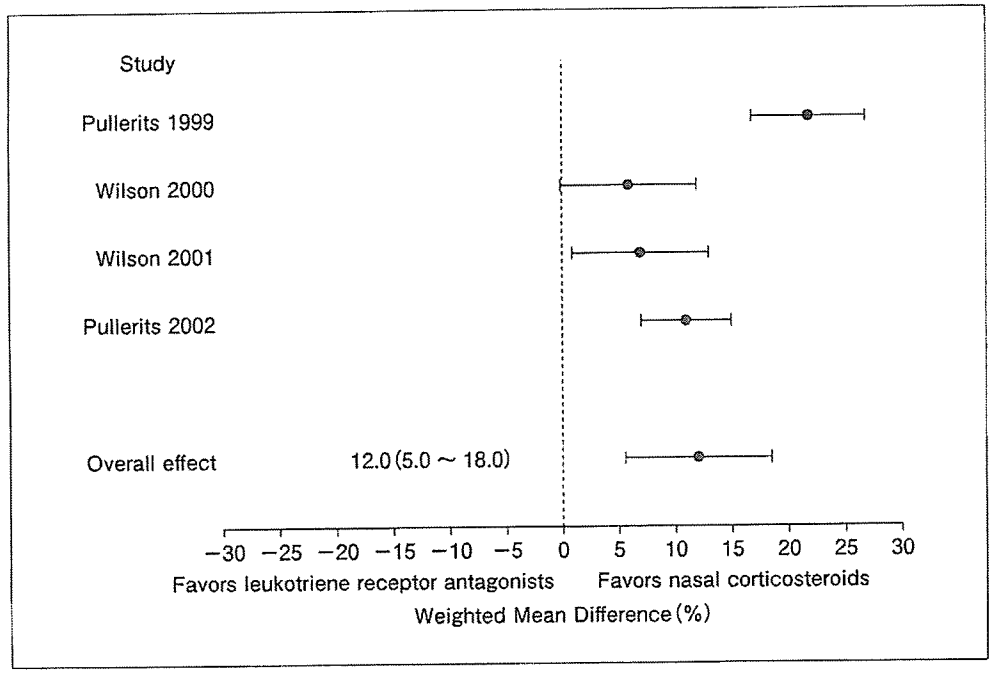

図3　鼻症状スコアに対する鼻噴霧用ステロイド薬と抗ロイコトリエン薬の効果の比較

(文献13)より引用)

あった（図3）.

メタアナリシスの対象となるトライアルは，いずれもプラセボを対照とした二重盲検試験である．日本では施行が困難であるため，いずれも海外のデータである．これらに対し一定の評価を行い，日本でも施行可能なトライアルを今後模索すべきと考える．

さて，これらのデータを受けて，花粉症治療における鼻噴霧用ステロイド薬の位置づけは，ARIAと日本においては若干異なっている．すなわち，海外においては鼻噴霧用ステロイド薬を第一選択薬として位置づけている．日本ではその作用が強力なことを考慮し，まずはマイルドな抗ヒスタミン薬あるいは鼻閉・充全型であれば抗ロイコトリエン薬が第一選択となり，鼻噴霧用ステロイド薬は中等症以上の通年性鼻炎あるいは花粉症において抗ヒスタミン薬あるいはその他の拮抗薬との併用療法として登場する．つまり，海外ではステップダウン，日本ではステップアップの考えである．

最後に，鼻噴霧用ステロイド薬とその他の薬剤の併用療法のデータを紹介する[14]．花粉症を対象に，無作為二重盲検対照群間比較試験の結果である．鼻噴霧用ステロイド薬単独群，鼻噴霧用ステロイド薬＋抗ヒスタミン薬群，鼻噴霧用ステロイド薬＋抗ロイコトリエン薬群，抗ヒスタミン薬＋抗ロイコトリエン薬群で比較した．花粉の飛散開始直前から6週間薬剤を投与した．結論は，鼻噴霧用ステロイド薬単独群はプラセボ群に比較して有意に鼻症状を改善し，抗ヒスタミン薬の併用は鼻のかゆみ，総合的鼻症状を鼻噴霧用ステロイド薬単独群に比較して有意に改善した．一方，抗ロイコトリエン薬併用群では鼻噴霧用ステロイド薬単独群に比較して有意な差を認めなかった．抗ヒスタミン薬＋抗ロイコトリエン薬群は，鼻噴霧用ステロイド薬単独群に比較して鼻閉や総合的鼻症状の改善で劣っていた．以上より，鼻噴霧用ステロイド薬との併用療法として抗ヒスタミン薬は有用である可能性がある．日本のスギ花粉症での検証が待たれる．

まとめ

鼻噴霧ステロイド薬は副作用が少なく，優れた臨床効果を示す薬剤である．正しく使用すれば，副作用なく症状を速やかに改善させる．特に，花粉症では外すことのできない薬物である．日本の市場には近い将来1日1回の鼻噴霧用ステロイド薬が続々と登場する予定である．今後，鼻噴霧用ステロイド薬に関する正確な情報提供や正しい使用法に関する啓蒙が必要と考える．

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