ア：2年未満 12.29±4.12、3年から5年未満 8.51±3.04、5年以上 10.63±3.97)。1年ごとの経年的な評価では3年以上施行した群では症状スコア、QOLスコアとも差が認められなかったが、3年以上と2年以下ではQOLが悪化した（鼻眼の症状は合計5点以下、健康関連QOLは10点以下）症例に有意差が認められた。

D.考察

QOLは2013年のパルス的な舌下免疫療法は経年的な効果を3年目以上施行している症例で、有意差が認められたのは2013年のスギ花粉飛散数が2012年より極端に多いため、2012年の経年的効果とは異なっていたものと考えらえた。これは今までの報告同様に現状のアレルゲン免疫療法では舌下免疫療法も1～2年のみの施行では最大限の効果を示してはいない事を示し、今までの報告通り3年以上の施行が望ましいことが考えられた。舌下免疫療法の施行について最適な年限については、かなり長期の症例もあるため、確定できなかったが、季節前のみパルスのように舌下免疫療法を行う場合には1～2年の少ない年限では最大限の効果は得られないと思われる。

E.結論

舌下免疫療法は、副作用の発生が極めて少なく、さらに有用性が期待される新規の治療法である。我々が行っている季節前のみの舌下免疫療法においては連続的に行う舌下免疫療法よりさらに長期の期間が必要である事が示された。連続的ではなくパルスのような季節前舌下免疫療法では確実に2シーズン以上の経年的な施行が求められる。このように疾患を根治させうる免疫療法の方法論を季節中、季節外の連日投与、あるいは季節前からの限定的パルス季節前舌下免疫療法など詳細に検討してゆくことが罹患人口の多い花粉症克服の検討課題である。

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G.知的財産権の出願・登録状況（予定も含む）

なし

厚生労働科学研究費補助金（難治性疾患等克服研究事業（免疫アレルギー疾患等予防・治療研究事業　免疫アレルギー研究分野））

（分担）研究報告書

アレルゲン舌下免疫療法に対する小児科医の認知：千葉県内小児科医へのアンケート調査

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研究要旨

千葉県小児科医会会員医師（総数450名）に郵送でスギ舌下免疫療法に関するアンケートを用いて意識調査を行い、以下の結果を得た。

1. 207 名の会員から解析可能なアンケートが回収された。このうち 90.8%が小児科で、経験年数が 21 年以上の医師が 86.5%であった。
2. 勤務先がクリニックである医師は 64.3%であり、実地医家が 2/3 を占めていた。
3. 63.8%の医師が現行のスギ花粉症の薬物療法に患者は満足していないと考えていた。
4. 83.6%はアレルギー専門医の資格を持っていなかったが、スギ舌下免疫療法には62.3%の医師が関心があると回答した。70%の医師はスギ舌下免疫療法を自ら実施することを考えていた。すなわち、スギ舌下免疫療法はアレルギー非専門の一般小児科医にも支持されて臨床で行われる可能性が高いと考えられた。
5. 舌下免疫療法に関心を持つ医師の半数以上が、非専門医が講習を受ければ実施して良いと回答した。すべての施行予定の医師は耳鼻科、アレルギー科などの専門医による講習等を十分に受ける必要があると思われる。また、患者に対しても舌下免疫療法についての情報提供を行うことが本治療法の安全で有効な施行のために望まれる。

A.　研究目的

アレルギー性鼻炎の罹患率は近年増加傾向にあり、およそ全国民の1/3が罹患していると推測されている。このようにアレルギー性鼻炎は国民病といっていいほど罹患率が高いのみでなく発症年齢も低年齢化しており、学校生活や学業にも支障を来すことが少なくない。薬物療法は有効であるが対症療法に過ぎず、根本的治療法である免疫療法の普及が望まれてきた。しかしながら、わが国で従来から行われている皮下注射によるダニやスギの免疫療法は痛みや煩雑さが妨げとなって小児のアレルギー性鼻炎の治療法としては広く行われてはいない。近年、欧米を中心に舌下免疫療法が保険診療として行われており、わが国でも近々吸入アレルゲンに対する舌下免疫療法が認可される予定である。しかしながら、アレルギー性鼻炎を診療している第一線の小児科医の舌下免疫療法に対する認知はまだ高くない可能性がある。そこで、本研究では、実地医家を中心とする小児科医のアレルゲン舌下免疫療法に対する意識調査を目的とした。

B.　研究方法

千葉県小児科医会会員医師（総数450名）に郵送でアンケートを送付し調査を行った。調査、質問項目は、以下の9つである。専門科、勤務先、医師経験年数、アレルギー専門医資格の有無、現在のスギ花粉症の薬物治療に対する患者満足度、皮下注射による免疫療法の経験の有無、スギ舌下免疫療法への関心、舌下免疫療法の実施への対応、免疫療法を実施

する医師の資格について、である。

（倫理面への配慮）
本研究はアンケート調査のみであり、また匿名であり、個人情報の保護に関しても問題ないものと考えられる。

C. 研究結果
207名の会員から解析可能なアンケートが回収された。このうち、
1) 90.8%が小児科、10.1%が内科であった（重複も含む）。(図1)
2) 勤務先はクリニックが64.3%で、病院が32.8%、その他が2.9%であり、実地医家が2/3を占めていた。(図2)
3) 経験年数では21年以上が86.5%であり、11年から20年以下が11.1%であり、以前に皮下注免疫療法の経験がある医師も多いと考えられた。(図3)
4) 83.6%は非アレルギー専門医の資格を持っていなかった。(図4)
5) 63.8%の医師が現行の薬物療法に患者は満足していないと考えていた。(図5)
6) スギ舌下免疫療法に対しては62.3%の医師が関心がある、11.6%が存在は知ってはいるが関心がない、24.2%が知らないと回答した。(図6)
7) 舌下免疫療法を自ら行う希望のない（あるいは不明な）医師はおよそ30%であった。一方で、18.5%がぜひ実施したい、51.2%が場合によっては自分での実施を考えると回答していた。すなわち、およそ70%の医師は自ら実施することを考えていた。(図7)
8) 舌下免疫療法に関心を持つ医師（129名）の52.7%が、非専門医でも講習を受ければ実施して良いと回答した。一方で31%は、専門医が行うべきと回答した。(図8)

D. 考察
千葉県小児科医会会員医師（小児科医がおよそ9割）に対するアンケート調査の結果から、およそ7割の医師はスギ舌下免疫療法に関心があり、実地医家の非アレルギー専門医にもスギ舌下免疫療法は支持されて施行される可能性が高いと思われる。
舌下免疫療法は皮下注射法に比較して安全性ははるかに高いと考えられるが、その適応、副作用などを適切に理解した上での施行が望ましい。そのためには耳鼻科、アレルギー科などの専門医による講習等を十分に行う必要があると思われる。また、患者に対しても舌下免疫療法についての情報提供を行うことが本治療法の安全で有効な施行のために望まれる。

E. 結論
千葉県小児科医会会員医師に対するアンケート調査の結果、スギ舌下免疫療法はアレルギーを専門としない一般小児科医の多くが施行を希望する可能性が高いことが明らかとなった。今後、舌下免疫療法の適正な施行の点からも一般医師ならびに患者への情報提供が必要と思われる。

F. 研究発表
1. 論文発表
なし

2. 学会発表
なし

G. 知的財産権の出願・登録状況（予定を含む）
1. 特許取得
なし
2. 実用新案登録
なし
3. その他

図 1

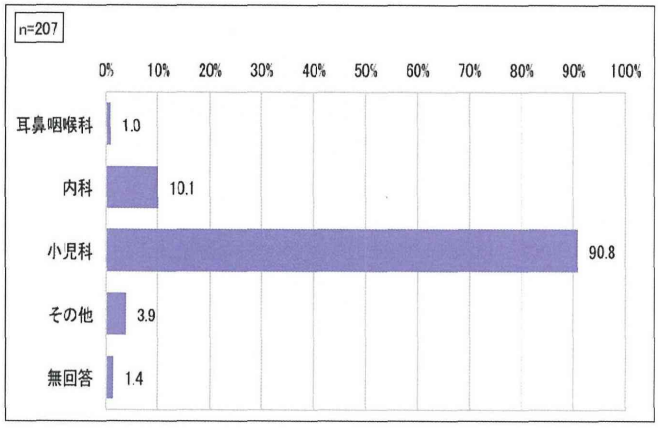


図 2

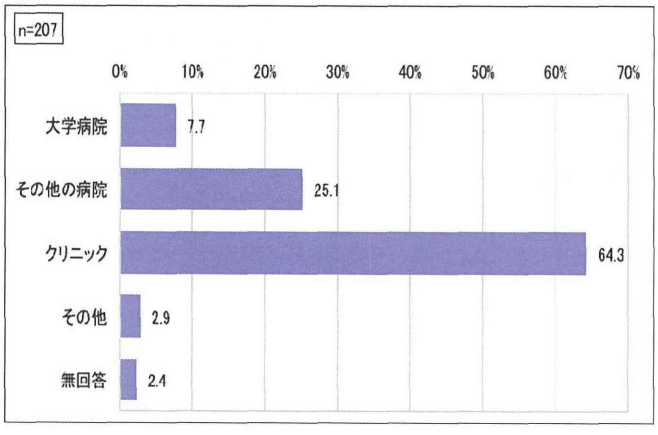


図 3

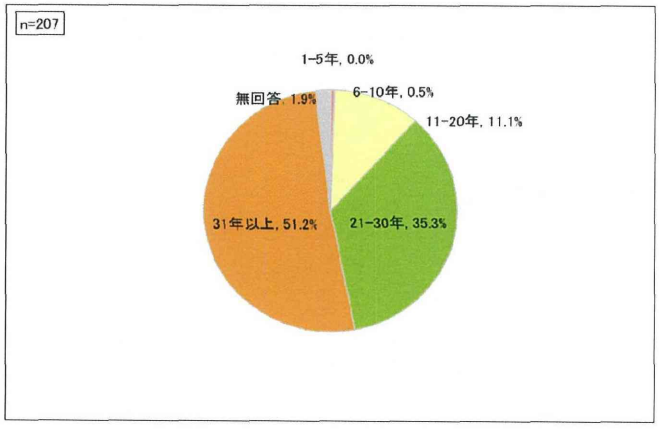


図4

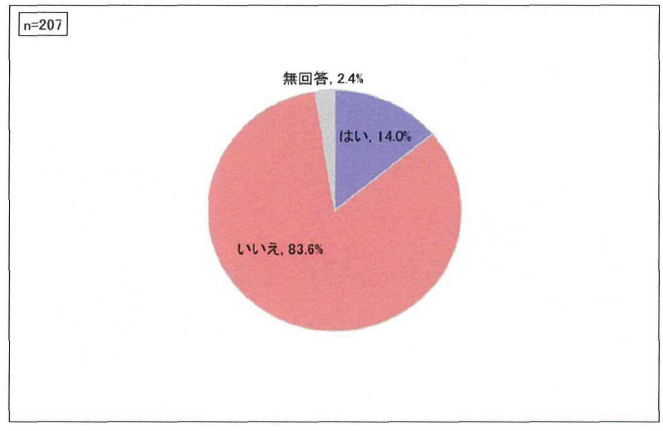


図5

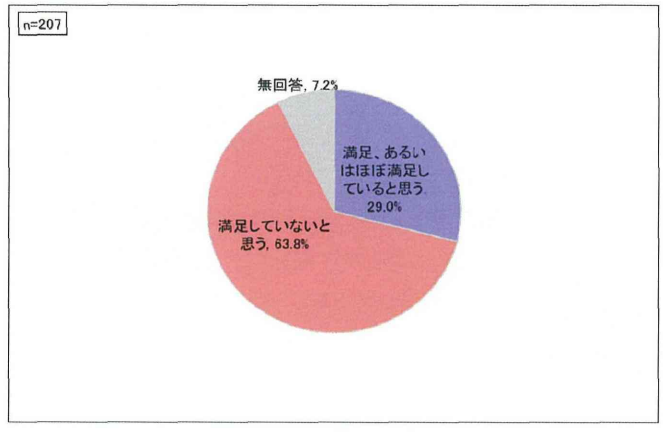


図6

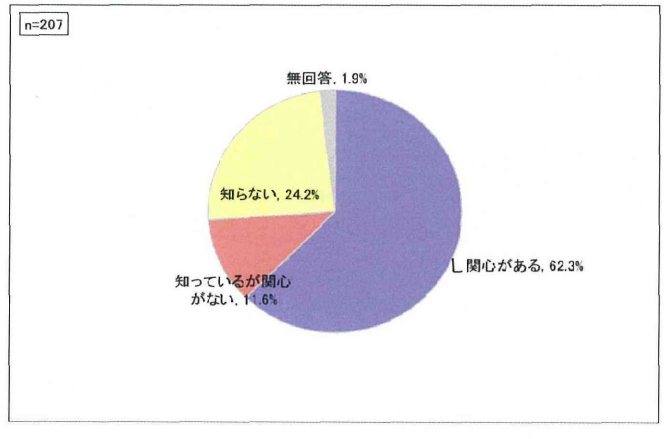


図 7

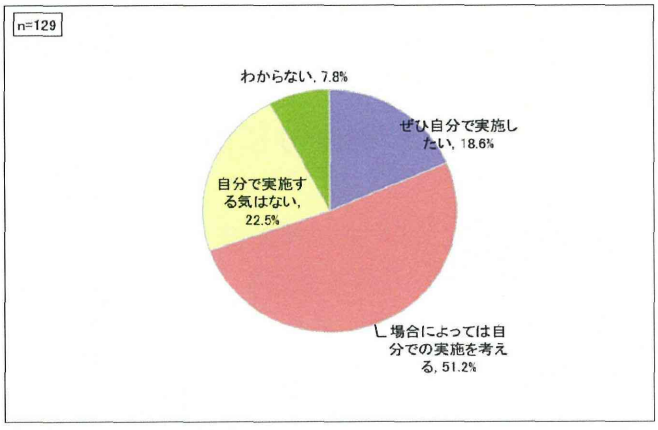
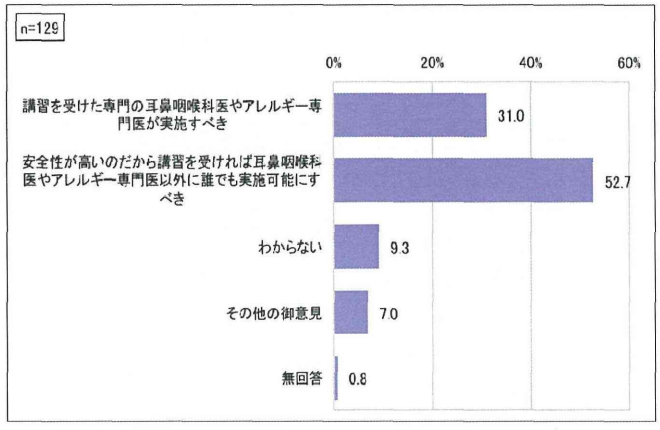

n=129
わからない, 7.8%
ぜひ自分で実施したい, 18.6%
自分で実施する気はない, 22.5%
場合によっては自分での実施を考える, 51.2%

図 8


n=129
0%
20%
40%
60%
講習を受けた専門の耳鼻咽喉科医やアレルギー専門医が実施すべき
31.0
安全性が高いのだから講習を受ければ耳鼻咽喉科医やアレルギー専門医以外に誰でも実施可能にすべき
52.7
わからない
9.3
その他の御意見
7.0
無回答
0.8

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（分担）研究報告書

スギ花粉症における minimal important difference (MCID)に関する検討

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研究協力者　野山和廉　岡山大学大学院　耳鼻咽喉・頭頸部外科学　医員

研究要旨

スギ花粉症の治療評価の解釈として、臨床的に意味のある QOL スコアの最小変動値（Minimal clinically important difference: MCID）の算出を試みた。2009 年～2013 年に実施した 6 件の臨床試験の JRQLQ データを対象とした。フェーススケールの 1 変動に応じた総 QOL スコアの変化値を算出した。2009 年での MCID は 10.469 であった。2010 年は 2 件の臨床試験を行ったが、MCID はそれぞれ 6.026 および 5.441 であった。2011 年は 6.396、2012 年は 6.953、2013 年は 5.540 であった。これらの総 QOL スコアの平均 MCID は 6.804 となり、1 項目当たりでは 0.400 となった。試験方法の違いや実薬とプラセボ薬での MCID 値に有意な差を認めなかった。さらに、総花粉飛散数と MCID 値との間には有意な相関関係を認めなかった。以上より、JRQLQ において総 QOL スコアで 6.8 の変化、1 項目当たり 0.4 の変化は臨床的に意味のある差と思われた。

A. 研究目的

スギ花粉症の治療評価すなわちエンドポイントは通常、試験薬群および対照薬群との間で統計学的な有意差を認めるか否かで評価される。一方、サンプルサイズが大きな臨床試験の場合、エンドポイントのわずかな差でも統計学的な有意性を示すことがある。

我々は、臨床的に意味のある症状スコアや QOL スコアの最小変動値（Minimal clinically important difference: MCID）検討を進めている。日本アレルギー性鼻炎標準 QOL 調査票（JRQLQ）のフェーススケールをアンカーとして 2009 年（少量飛散年）および 2010 年（大量飛散年）の MCID を計算したところ、アレルギー日記での症状スコアの MCID は花粉の飛散数に限らず一定していたが、QOL スコアは変動することが明らかとなった（Higaki T, Okano M, et al. Allergol Int 2013）。

そこで今回は、2009年から2013までに施行した6件の臨床試験のJRQLQデータを基に、QOL スコアのMCIDの算出を試みた。

B. 研究方法

2009年（総花粉飛散数3,698個/cm^2）1件、2010年（総花粉飛散数374個/cm^2）2件、2011年（総花粉飛散数1,968個/cm^2）1件、2012年（総花粉飛散数1,176個/cm^2）1件および2013年（総花粉飛散数3,643個/cm^2）1件の臨床試験（総サンプル数946）を対象とした。フェーススケールの変動に応じた総QOLスコアの変化値を算出した。

（倫理面への配慮）
被験者に対しては学術的な意義について十分な説明を行い、同意・協力が得られた上で行った。

C. 研究結果

2009 年でのフェーススケールの 1 変動（改善もしくは悪化）に対応する総 QOL スコアの変化値、すなわち MCID は 10.469 であった。2010 年は 2 件の臨床試験を行ったが、総 QOL スコアの MCID はそれぞれ 6.026 および 5.441 であった。同様に 2011 年は 6.396、2012 年は 6.953、2013 年は 5.540 であった。この 5 シーズン（6 臨床試験）の総 QOL スコアの平均

MCIDは6.804となり、1項目当たりでは0.400となった。

2010年は舌下免疫療法と鼻噴霧用ステロイド薬に関する2件の臨床試験を施行したが、試験方法によるMCID値の有意な差を認めなかった。また2011年はプラセボ対照二重盲検比較試験を施行したが、プラセボ薬および実薬の間にMCID値の有意な差を認めなかった。さらに、総花粉飛散数とMCID値との間には有意な相関関係を認めなかった（p=0.218）。

D. 考察

国際的なアレルギー性鼻炎のQOL調査票であるRQLQに関しては包括的質問票をアンカーとしたMCIDが算出され、1項目あたり約0.5のQOLの差は臨床的に有意義ということが報告されている（Juniper EF, et al. J Allergy Clin Immunol 1996）。RQLQとJRQLQは項目数や尺度に違いがあるが、ほぼ同様のMCIDを示すことが明らかとなった。

我々が渉猟し得た範囲では、MCIDと曝露抗原量との関連を検討した報告はみられない。今回の結果からは、曝露抗原量はMCIDに有意な影響を与えないことが示唆された。さらに試験薬や試験方法もMCIDには有意な影響を与えないと思われた。

E. 結論

スギ花粉症におけるQOLのMCIDは6.8であった。JRQLQにおいて総QOLスコアで6.8の変化、1項目当たり0.4の変化は臨床的に意味のある差と思われた。

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H. 知的財産権の出願・登録状況
（予定を含む。）

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

研究成果の刊行に関する一覧表

雑誌

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Guiding principles of subcutaneous immunotherapy for allergic rhinitis in Japan

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ABSTRACT

Objective: In anticipation of the development of guidelines for antigen-specific subcutaneous immunotherapy (SCIT), we present recommendations that can serve as guiding principles based on a review of the scientific literature.
Methods: Clinical questions (CQs) concerning SCIT were prepared. Literature searches for publications between January 1990 and February 2011 were performed in PubMed, the Cochrane Library, and Japana Centra Revuo Medicina Web version 4. Qualified studies were analyzed and the results were evaluated, consolidated, and codified.
Results: We present answers for 13 CQs on the indications, methods, effectiveness and mechanisms of SCIT, with evidence-based recommendations.
Conclusion: The guiding principles are intended to be applied to children (≤15 years old) and adults (≥16 years old) with allergic rhinitis (AR). These principles can be used by otorhinolaryngologists for diagnosis of AR, evaluation of severity and rhinoscopic findings, performance of antigen challenge tests, and management of systemic anaphylactic reactions associated with SCIT.

1. Introduction

The incidence of allergic rhinitis (AR) is increasing in Japan. Spontaneous resolution of AR is relatively infrequent, except in elderly individuals, and its symptoms have marked adverse effects on quality of life (QOL). Evidence-based guidelines for use of antigen-specific subcutaneous immunotherapy (SCIT) for treatment of AR have been prepared [1,2]. Antigen extracts entered the Japanese market in 1963, and subsequently SCIT for AR was initiated. The present guiding principles were prepared based on research by the Japanese Rhinologic Society (JRS) [3] to provide accurate knowledge of immunotherapy for AR and contribute to development of this therapy.

The JRS is an independent academic organization that receives no sponsorship or funding from specific organizations or businesses. The JRS has not obtained funds for preparation of the present guidelines from any businesses, including those representing the pharmaceutical industry.

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2. Criteria for determining recommendation grades

Clinical questions (CQs) were prepared concerning the methods, effects, side effects, and mechanisms of SCIT. A comprehensive literature search was performed for studies published between January 1990 and February 2011. The databases used were PubMed, the Cochrane Library, and Japana Centra Revuo Medicina Web version 4. The search was executed primarily between October 2010 and July 2011, and used the primary index words "allergic rhinitis", "pollinosis", and "SCIT". Subsequently, two members were assigned to the task of collecting scientific evidence concerning each CQ from the selected papers. After a consensus was reached by the preparation committee, the results were evaluated, consolidated, and codified.

Levels of evidence I–IV were determined as follows: Ia, meta-analysis (with homogeneity) of randomized controlled trials; Ib, at least 1 randomized controlled trial; IIa, at least 1 well-designed, controlled study, but without randomization; IIb, at least 1 well-designed, quasi-experimental study; III, at least 1 well-designed, non-experimental descriptive study (e.g., comparative studies, correlation studies, case studies); IV, expert committee reports, opinions, and/or the experiences of respected authorities. The recommendation levels of the Medical Information Distribution Service (MINDS) were adopted as follows: A, strong scientific evidence, and implementation of the treatment is strongly recommended; B, scientific evidence, and implementation of the treatment is recommended; C1: no scientific evidence, but implementation of the treatment is recommended; C2: no scientific evidence, and implementation of the treatment is not recommended; D: evidence suggesting ineffectiveness or harm, and implementation of the treatment is not recommended.

These recommendation levels are not absolute and diagnostic or therapeutic decisions should be made based on the patient's condition and wishes, and the available resources of each medical facility. However, the guiding principles presented here can be applied tentatively in clinical settings. After evaluation of the results of this process and reviews by external experts, the principles will be developed into guidelines for diagnosis and treatment. The principles and handling of conflicts of interest will be reevaluated on the basis of the results of the preparation of guidelines by the JRS.

3. Indication and methods of SCIT

AR is defined as a type I allergic disorder of the nasal mucosa with 3 major manifestations: repetitive sneezing, watery rhinorrhea, and nasal obstruction [4]. The specific antigen should be determined prior to SCIT.

3.1. CQ01: What administration methods are used for SCIT and what are their advantages and disadvantages?

Administration methods used for SCIT for AR include the 50% incremental method, 100–200% incremental method, cluster method, and rush method. All can be performed until a maintenance dose is reached.

(1) The 50% incremental method is the commonly used method, in which the antigen concentration is increased 10 times from the threshold of the intradermal reaction using 7 injections (0.05, 0.07, 0.1, 0.15, 0.2, 0.3, and 0.5 mL) at a rate of 2 injections/week. This method has a high level of safety, but it requires frequent hospital visits over a long period until the maintenance dose is reached.
(2) The 100–200% incremental method is a rapid method in which the antigen concentration is increased 10 times from the threshold of the intradermal reaction using 3 injections (0.1, 0.3, and 0.5 mL) at a rate of 1 injection/week. The therapeutic effect of the 100–200% incremental method is comparable to that of the conventional 50% incremental method. No adverse reactions were noted while using the 100–200% incremental method with house-dust antigen extract [5] (Level IIb).
(3) In the cluster method, 3 injections are performed in one day at 1 h intervals and a maintenance dose is reached by repeating the treatment once weekly for approximately 5 weeks. The maintenance dose can be reached in a short period with a high level of safety. Moderate adverse reactions have been observed with the cluster method, but their frequency was lower than that with a placebo and the safety of the method was high [6] (Level Ib).
(4) In the rush method, the maintenance dose is reached in 3 days by repeating 5–6 injections every 2 h in one day. The rush method performed in hospitalization (3 days and 2 nights) is likely to produce effects in a short period and to be effective [7] (Level IIb). The nasal symptoms score was significantly better using the rush method compared to the rapid method. Systemic adverse reactions were observed in 40% of the patients, but none of these reactions were severe [8] (Level IIb).

3.2. CQ02: How should the maintenance dose and administration period for SCIT be determined?

The effect of SCIT is insufficient at low doses, but systemic adverse events increase at high doses. For many antigens, administration as a single injection of 5–20 μg as the major antigen is recommended. If a long-term effect is required, it is generally necessary to continue the therapy for 3 years [9] (Level Ia). Three-year SCIT (32 subjects, maintenance dose 20 μg, timothy antigen) was effective for 3 years after discontinuation of treatment [10] (Level Ib). SCIT administered over 3 years (20 subjects, maintenance dose 12 μg, ragweed antigen Amb a1) suppressed antigen-evoked responses in the nasal mucosa [11] (Level Ib). One-year SCIT (35 subjects) reduced the total nasal symptom score (TSS) and medication score (MS) [6] (Level Ib). Three-year SCIT in 147 children aged 6–14 years old was effective for 7 years after the end of the therapy [12] (Level Ib). In 28 patients with a cat allergy, in whom the effects of the cat antigen Fel d 1 were compared using maintenance doses of 0.6, 3, and 15 μg, nasal symptoms were alleviated in a dose-dependent manner [13] (Level Ib). The TSS was significantly lower in 5-year SCIT (239 subjects, maintenance dose 3.6 μg, mite antigen Der p1) than in 3-year SCIT [14] (Level IIa). In patients with mite-induced asthma, the recurrence rate 3 years after discontinuation of treatment was lower in those who underwent SCIT for ≥3 years (19 patients) than in those treated for <3 years (21 patients) [15] (Level III). Recommendation level is A.

3.3. CQ03: What are the types and frequencies of the side effects of SCIT and how are they managed?

SCIT has a risk of systemic adverse reactions and anaphylaxis, with prompt treatment required after 0.13% of treatments (19/14,085 subcutaneous inoculations) [9,10] (Level Ia). Systemic adverse reactions have also been observed after 0.025% of inoculations [16] (Level Ia). Severe anaphylactic reactions due to SCIT for SAR occurred in 5.4 of 1,000,000 injections (0.0005%) and were most frequently observed during the pollen season (46%). In most cases, the cause of anaphylaxis was an error in the dose (25%) and epinephrine was administered within 20 min as a life-saving treatment [17] (Level III). The incidence of local adverse reactions to SCIT using a standardized mite or weed allergen was 10.5% and

that of systemic reactions was 4.8% (0.37% of all injections). Adverse systemic reactions occurred significantly more frequently in patients with asthma, in those sensitized to mites, and when the dose of antigen extract was increased [18] (Level III). Recommendation level is B.

3.4. CQ04: What kinds of patients are not indicated for SCIT?

Adverse reactions are more likely to occur in patients with AR complicated by asthma than in those with AR alone [19] (Level III). Malignant diseases, autoimmune disorders, patients under treatment with β-blockers, patients who are pregnant at the start of SCIT, asthmatic patients with FEV1 <70%, and patients with acute infections such as a cold are contraindicated for SCIT for AR. SCIT should also not be performed in patients aged <5 years old [20] (Level IV). Pregnancy is not a specific contraindication for SCIT, but the dose or concentration of drugs used for SCIT must not be increased during pregnancy to avoid the possibility of anaphylaxis. Initiation of new SCIT is not recommended in patients who are pregnant [21] (Level IV). SCIT is contraindicated for patients with severe cardiovascular diseases; those using β-blockers; those with severe asthma, irreversible chronic airway obstructions, hypersensitivity pneumonitis, allergic bronchopulmonary aspergillosis, and immunodeficiencies; those with psychiatric disorders, and those who cannot follow instructions concerning the therapy. Beginning SCIT during pregnancy is also a contraindication and a very young patient is a relative contraindication. Patients with mild AR that can be sufficiently managed by occasional medication and those who cannot understand explanations of SCIT are considered to be inappropriate for SCIT. In addition, patients with nasal polyps are not expected to respond markedly to SCIT [22] (Level IV). Recommendation level is C2.

4. Effectiveness of SCIT

4.1. CQ05: Can AR in children (including QOL) be improved by SCIT?

We searched the literature for randomized studies of SCIT against AR in children published since 1990 and found 2 small-scale studies: 1 on perennial AR (PAR), and the other on SAR. Symptoms were alleviated by SCIT relative to administration of a placebo [23,24] (Level Ib). SCIT for 1 year significantly lowered the TSS and MS in children with PAR [23] (Level Ib). Many of the adverse reactions were mild, but systemic adverse reactions must be managed appropriately [23,25] (Level Ia). SCIT significantly reduced symptoms and drug scores in children with AR or asthma due to a fungal allergy [26] (Level Ib). SCIT administered over 3 years significantly controlled the symptoms of SAR in children for 7 years following completion of the therapy [12] (Level IIa). The efficacy of antihistamines and topical nasal steroids was higher in children with PAR for 2 years after the start of treatment, but was surpassed by the efficacy of SCIT after 3 or more years [27] (Level IIb). Recommendation level is B.

4.2. CQ06: Can AR in adults (including QOL) be improved by SCIT?

SCIT is likely to be effective with use of a sufficient amount of standardized allergen [9,28,29] (Level Ia). For many allergens, the optimal dose of the primary allergen is 5–20 μg per administration [28,29] (Level Ia). The efficacy of SCIT as a treatment for AR is also enhanced in combination with other drug therapies [29] (Level Ia). Using the Cochrane Collaboration, 1111 papers were evaluated, and 15 of 51 papers fulfilling the criteria of scientific assessment were used in a meta-analysis, in which SCIT was found to be effective based on the TSS. Using the MS, SCIT was also found to be effective in a meta-analysis of 13 papers. However, the degree of efficacy varied and was not easily evaluated [25] (Level Ia). There is a risk of an anaphylactic reaction as a systemic side effect; although rare, appropriate management is required should this reaction occur [28,29] (Level Ia). In a domestic evaluation of SAR, SCIT was more effective than drug therapy alone for improving symptoms and QOL scores [30] (Level III). Recommendation level is B.

4.3. CQ07: Is addition of SCIT effective in patients not responding to regular drug therapy?

Drug therapy is the most widely used method for treatment of AR, but some patients do not respond to this therapy. Therefore, studies have been performed to examine whether symptoms can be alleviated and whether the quantity of drugs administered can be reduced by additional SCIT in such patients. In a randomized, double-blind, placebo controlled study (RCT) of SCIT in 40 patients with severe SAR that was poorly controlled by antihistamines, topical nasal steroids, and disodium cromoglycate in the previous year, improvements in TSS, MS, and VAS scores were observed in the active group [31] (Level Ib). In an RCT of SCIT in 36 patients with severe PAR that was not sufficiently controlled by standard antiallergic medicine, improvements in TSS and MS were observed in the SCIT group [32] (Level Ib). Recommendation level is C1.

4.4. CQ08: Does SCIT suppress the occurrence of asthma in nonasthmatic children?

The results of a 3-year open study comparing the incidence of asthma between SCIT and control drug therapy in 205 children with SAR showed that SCIT significantly suppressed the occurrence of asthma [33] (Level IIa). A 2-year follow-up of the patients in this study (183 patients) indicated that the occurrence of asthma was significantly lower in the SCIT group than in the control group [24] (Level IIa). Follow-up at 7 years after completion of SCIT (147 patients) showed that the occurrence of asthma was still significantly lower in the SCIT group, and that asthma and airway hypersensitivity were significantly alleviated [12] (Level IIa). Recommendation level is C1.

4.5. CQ09: Can sensitization to novel allergens be suppressed by SCIT in patients (children/adults)?

In children sensitized to house dust-mite antigen alone (including those with AR), the percentage of those sensitized to new antigens was significantly lower after SCIT for 2 years (22 patients) [34] and 3 years (75 patients) [35], compared to age-matched controls (Level IIa). In 147 children with AR and asthma, the percentage of those sensitized to new antigens was significantly lower in the SCIT group than in the control group [36] (Level IIa). In a retrospective study in 8396 patients with an airway allergy (asthma, AR) sensitized to house dust antigen alone, the percentages of those sensitized to new antigens at 4 years and 7 years were significantly lower in the SCIT group compared to the control group (23.8% vs. 68.0% at 4 years, and 27.0% vs. 76.8% at 7 years) [37] (Level III). Recommendation level is C1.

4.6. CQ10: How long are the effects of SCIT sustained in children?

The total symptom score was significantly lower in 13 children with SAR who underwent SCIT for 3 years than in 10 age-matched controls after 6 [38] and 12 [39] years (Level IIa). Improvements in the condition of 25 children with PAR and 12 with SAR who underwent SCIT for ≥2 years were sustained over a long period of ≥17 years, compared to children who received drug therapy [40,41] (Level III). Recommendation level is C1.

4.7. CQ11: How long are the effects of SCIT sustained in adults?

The duration of the SCIT effect after discontinuation of therapy depends on the duration of treatment and responses to a skin test [42] (Level III). The effect of the therapy in 32 patients who underwent SCIT for SAR due to grass pollen persisted for 3 to 4 years regardless of whether SCIT was continued for more than 3 years [10] (Level Ib). In 108 patients who underwent SCIT for 3 to 4 years, symptoms exacerbated in 2.7%, 16.7%, 30.6% and 32.8% of the patients at 1, 2, 3 and 4 years after therapy discontinuation, respectively [43] (Level III). The therapeutic effect in 36 patients who underwent SCIT for tree pollinosis for 3 years was maintained in 86% of those with rhinitis and 68% of those with asthma at 6 years after discontinuation of treatment [44] (Level III). In patients with AR/conjunctiva, reactivation at 2 years after discontinuation of SCIT occurred in 36% of 87 patients treated for 4 years and in 18% of 61 patients treated for 6 years [45] (Level III). Recommendation level is C1.

4.8. CQ12: Can the systemic adverse effects of SCIT be prevented by pretreatment with antiallergic drugs?

In a double-blind trial, systemic adverse reactions occurred in 7 (33%) of 21 patients who received loratadine prior to subcutaneous injection and in 19 (79%) of 24 patients who received a placebo. Thus, the incidence of severe adverse reactions was reduced by premedication with an antihistamine [46] (Level Ib). Another study showed a reduced incidence of severe adverse reactions after administration of an antihistamine before subcutaneous injection [47] (Level IV). Recommendation level is C1.

5. Mechanisms of SCIT

5.1. CQ13: What are the mechanisms underlying the effects of SCIT for AR?

Regulatory $Foxp3^+$ $CD4^+$ and $Foxp3^+$ $CD25^+$ T cells are significantly increased in the nasal mucosa in patients treated with SCIT [48]. Antigen-specific serum IgG in patients receiving SCIT inhibits binding of antigen IgE to B cells [49] and SCIT suppresses IL-4 production by $CD4^+$ T cells [50]. Expression of IL-5 mRNA in peripheral blood mononuclear cells (PBMCs) stimulated with Cry j 1 was significantly lower in patients with a marked response to SCIT compared to an untreated group and patients who did not respond to SCIT [51]. Expression of the co-inhibitory molecule BTLA in PBMCs stimulated with Cry j 1 was significantly higher in the SCIT group than in the control group. The increase in the serum cedar-specific IgE antibody level during the pollen dispersion season was suppressed by SCIT [52]. IgG antibodies (particularly IgG4) are increased by SCIT and have been reported to act as a blocking antibody and to correct the tilt to Th2 dominance by suppressing Th2 cytokines and Th2 cells. Recently, SCIT has also been reported to induce regulatory T cells and control allergic reactions via production of regulatory cytokines such as IL-10 and TGF-β.

6. Conclusion

Administration of SCIT for AR involves use of the 50% incremental, 100–200% incremental, cluster, and rush methods until a maintenance concentration is reached, but there has been no direct comparison of the effectiveness of these methods. A major antigen dose of 5–20 μg is recommended to minimize adverse reactions. The incidence of systemic adverse reactions including anaphylaxis is about 1 in 1000–4000 inoculations, and prompt and appropriate treatment is required for such reactions. The risk of systemic adverse reactions might be reduced by oral premedication with an antihistamine. SCIT administered to children with AR significantly improved the total symptom score and significantly reduced the medication score. The effect of SCIT for children with AR is also likely to continue over a long period after discontinuation of the therapy. Sensitization to new allergens can be prevented by SCIT. SCIT for adults with AR is recommended because it alleviates nasal symptoms and reduces the quantity of required drugs. In patients not responding to drug therapy, SCIT can also alleviate symptoms and reduce the use of other drugs. SCIT for AR significantly suppresses the occurrence of asthma and its effect is likely to persist after completion of SCIT. We recommend that SCIT is continued for 3 years or longer. The effect of SCIT is sustained over a long period, even after its discontinuation, and the duration of the effect of SCIT after discontinuation is related to the duration of the treatment.

Conflicts of interest

Any organizations or businesses that have provided research funding (for contract research, joint research, clinical trials, etc.), scholarship donations, and monetary compensations for lectures, manuscripts, and pamphlets to members of the guideline preparation committee are listed. (The period of interest is between January 2010 and December 2011). Astellas Pharma Inc., AstraZeneca KK, Eisai Co., Ltd., Merck & Co., Inc., Otsuka Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Kissei Pharmaceutical Co., Ltd., Kyorin Pharmaceutical Co., Ltd., Kyowa Hakko Kirin Co., Ltd., GlaxoSmithKline KK, Kowa Pharmaceutical Co., Ltd., Sanofi Aventis KK, Shionogi Co., Ltd., Senju Pharmaceutical Co., Ltd., Daiichi sankyo Co Ltd, Dainippon Sumitomo Pharma Co., Ltd., Taiho Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Co., Chugai Pharmaceutical Co., Ltd., Nikken Chemical Laboratory Co., Ltd., Nippon Shinyaku Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., Bayer Yakuhin, Ltd, Pfizer Japan Inc, Meiji Seika Pharma Co., Ltd., Taisho Toyama Pharmaceutical Co., Ltd.

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Randomized Double-Blind Study of Prophylactic Treatment with an Antihistamine for Seasonal Allergic Rhinitis

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Key Words
Prophylactic treatment · Early intervention · Seasonal allergic rhinitis · Antihistamine · Environmental challenge chamber

Abstract
Background: The efficacy of prophylactic treatment before the start of pollen dispersal for prevention of aggravation of symptoms is unclear. The aim of the present study was to examine the efficacy of prophylactic treatment with an antihistamine for seasonal allergic rhinitis (SAR) using an environmental challenge chamber (ECC). ***Methods:*** The study was performed in a randomized double-blind manner with a 3-way crossover design. The subjects were 50 patients with SAR caused by Japanese cedar pollen who were randomized for treatment with levocetirizine hydrochloride 5 mg (Xyzal®) or placebo as follows: administration of placebo for 8 days (treatment A), single administration of levocetirizine on day 8 after placebo for 7 days (treatment B) or administration of levocetirizine for 8 days (treatment C). Efficacy in each treatment arm was evaluated based on cedar pollen exposure for 3 h on day 9 in an ECC, following 1-hour exposure on day 8. The primary endpoint was the total nasal symptom score for 12 h on day 9. Other nasal and ocular symptoms were secondary endpoints. ***Results:*** The evaluation was performed in 45 subjects. The total nasal symptom score on day 9 was significantly lower with treatment B compared with treatment A. Treatment C did not show superior efficacy compared with treatment B. ***Conclusions:*** Our results suggest that early intervention with levocetirizine soon after onset of symptoms may attenuate these symptoms as effectively as prophylactic treatment before pollen dispersal. These results are important from the perspective of patient convenience and reduction of medical costs.

Introduction

Allergic rhinitis (AR) has a high prevalence in many countries and represents a global health problem [1]. In Japan, Japanese cedar *(Cryptomeria japonica)* pollen is the major allergen, and it is estimated that over 26% of the population are now affected by seasonal AR (SAR) induced by cedar pollen [2–4]. Some studies have recommended prophylactic treatment that begins prior to the pollen season to avoid aggravation of symptoms of SAR [5–9]. This treatment may increase the antiallergic effects of drugs when pollen dispersal starts and prevent priming of allergic inflammation in the nasal mucosa before the peak of pollen dispersal. Outside the pollen dispersal sea-

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son, patients with SAR who do not have rhinitis caused by other allergens tend to have normal nasal mucosa with few or no symptoms. Repeated exposure to pollen induces allergic inflammation and increases the hypersensitivity of the nasal mucosa [10], and early intervention may have a significant effect on the severity of symptoms when pollen dispersal is at its peak.

Histamine H1 receptor antagonists (antihistamines), leukotriene receptor antagonists, chemical mediator receptor antagonists and nasal steroids have been used for prophylactic treatment of SAR [5–9]. Antihistamines act as inverse agonists for histamine H1 receptors in vitro [11, 12] through stabilization of the inactive conformation of the receptor to shift the equilibrium towards the inactive state, which may downregulate constitutive receptor activity, even in the absence of histamine. This theory of inverse agonism may be one reason why prophylactic treatment with a histamine H1 receptor antagonist suppresses symptoms at the peak of pollen dispersal. However, there is no clear clinical evidence for the benefits of this treatment. In part, this is because the efficacy is difficult to evaluate due to large annual variations caused by climate changes, including the time of pollen dispersal and the amount of pollen. In addition, in evaluations performed in the pollen dispersal season, the amount of pollen to which each subject is exposed also varies due to differences in area of residence and lifestyle.

An environmental challenge chamber (ECC) can be used to expose all subjects to the same amount of pollen in a stable atmosphere and thus may be useful for evaluation of the efficacy of treatment for AR. The US Food and Drug Administration have accepted that performance of an ECC study can address the adequate prophylaxis period for a seasonal allergen [13]. Using this approach, the aim of this randomized double-blind study was to examine the efficacy of prophylactic treatment for SAR with levocetirizine hydrochloride (Xyzal®), a second-generation histamine H1 receptor antagonist.

Materials and Methods

Study Protocol

The study was performed in a randomized double-blind manner with a 3-way crossover design. Capsules of levocetirizine hydrochloride 5 mg and placebo that could not be distinguished in terms of shape, size and color were used to allow double-blind administration. The recruitment of subjects and all examinations were performed at Chiba University. A controller (Dr. Ken Toyoda of the Clinical Research Support Center Co.) who was not directly involved in the study was responsible for group allocation and preparation of test drugs. A treatment allocation number was given to each subject. To prevent leakage of information, this number was closely managed by the controller and a member of the ethical committee (who was also not directly involved in the study) until accessed with a key after completion of the study.

The study was performed from September to November 2011, a period outside the pollen dispersal season (February to May). Three examinations were performed, with washout periods of 2 weeks. The subjects took the test drugs once daily at 9 p.m. for 7 days (day 1–day 7). The time at which drugs were taken followed the package insert for levocetirizine. On day 8, a priming pollen exposure for 1 h was performed from 9 to 10 a.m., and then the subjects took the last test drug at 9 p.m. On day 9, exposure for 3 h was performed from 9 a.m. to 12 p.m. The subjects were randomized for treatment as follows: placebo from day 1 to day 8 (treatment A), levocetirizine on day 8 after having taken placebo from day 1 to day 7 (treatment B) or levocetirizine from day 1 to day 8 (treatment C). Using a rescue drug was prohibited during the study period, and only 1 levocetirizine tablet was permitted to be taken as a rescue drug after 9 p.m. on day 9, if necessary. Test drugs were delivered to each subject just before each examination to avoid an error of allocation to an incorrect group. Subjects with an upper respiratory tract infection with pyrexia, cough or throat pain were not allowed to enter the ECC.

This study was conducted at Chiba University Hospital in compliance with the Ethical Guidelines for Clinical Studies and Good Clinical Practice and the Declaration of Helsinki (2008 revision). The Ethics Committee of Chiba University approved the protocol. Each subject received a detailed explanation of the study and of the possible side effects, and written informed consent was obtained from each subject prior to their participation in the study. The clinical registration number for this study is UMIN000006318.

Subjects

The subjects were patients with SAR caused by Japanese cedar pollen. All subjects had a history of rhinitis for at least 2 consecutive cedar pollen seasons and met the following inclusion criteria: a positive allergen-specific skin test (wheal diameter more than twice the control) to standardized cedar pollen extract (Torii Pharmaceutical Co., Tokyo, Japan) and a serum cedar pollen-specific IgE score ≥2 in a CAP-radioallergosorbent test (SRL Inc., Tokyo, Japan; scores classified as follows: 6, ≥100 UA/ml; 5, 50.0–99.9 UA/ml; 4, 17.5–49.9 UA/ml; 3, 3.50–17.4 UA/ml; 2, 0.70–3.49 UA/ml; 1, 0.35–0.69 UA/ml; 0, ≤0.34 UA/ml). Subjects with moderate or severe symptoms induced by the screening cedar pollen exposure (8,000 grains/m^3) for 3 h in the ECC were selected. Exclusion criteria were nasal diseases including AR induced by other allergens and asthma that required treatment, use of antiallergic drugs within 2 weeks of screening exposure, severe renal insufficiency, women who were pregnant or planned to become pregnant during the study period and breastfeeding women.

The sample size was examined statistically for detectable differences using the Monte Carlo method. A statistical power of 87% was required to detect differences in the primary endpoint (total nasal symptom score) of 1.5 between treatments B and C and 3.0 between treatments A and C, assuming an intraindividual standard deviation of 2.54, which was estimated in preliminary repeated observations. With a power of 80%, the sample size was sufficient to detect smaller differences in the primary endpoint of 1.33 between treatments B and C and 2.67 between treatments A and C. These detectable differences were judged to be small compared

to the expected differences based on our experience. A minimum of 45 subjects with available data was required. Based on a 10% dropout rate, the sample size was set to 50.

Environmental Challenge Chamber

The examination was performed in the ECC at Chiba University, which can accommodate 50 subjects [14]. The concentration of pollen was set to 8,000 grains/m^3, and the exposure period was 3 h. The pollen concentration in the air was monitored by automatic pollen counters (Shinyei Co., Japan) [15]. Pollen levels were measured every 5 min. Symptoms were observed in all patients and reached their peaks within 3 h at this pollen concentration in a previous study [14]. Each subject recorded symptoms using a mobile communication device (Willcom Co., Japan) while in the ECC.

Assessment of Efficacy

Number of Sneezes and Nose Blows (Secondary Endpoint)

The subjects recorded the number of sneezes and nose blows during cedar pollen exposure using a mobile communication device on day 8 and day 9. On day 9, subjects recorded the number of sneezes and nose blows using an allergy diary until 9 p.m. after leaving the chamber. The numbers for 3 h in the ECC and for 9 h after leaving the chamber were counted on day 9, and the total for 12 h was calculated.

Amount of Rhinorrhea (Secondary Endpoint)

The average weight of a tissue before use was determined based on measurement of the weight of 10 tissues. The tissues used in the ECC were all of the same type. All tissues used by each subject in the ECC were collected at the end of the 3-hour cedar exposure on day 9. The number of used tissues was counted and the total weight was measured to permit calculation of the weight of nasal discharge from each subject.

Subjective Assessment of the Severity of Nasal Symptoms (Secondary Endpoint)

Subjective assessments of the severity of nasal symptoms (sneezing, rhinorrhea and nasal congestion) were recorded in the ECC every 30 min during cedar pollen exposure on day 8 and day 9. On day 9, the subjects also recorded the severity of symptoms in an allergy diary at 3, 6 and 9 p.m. after leaving the chamber. The severity of symptoms was evaluated on a 4-point scale (0–3), as follows: 0, none; 1, mild; 2, moderate, and 3, severe.

Symptom Scores for 12 h on Day 9

Nasal symptom scores for 12 h on day 9 were evaluated based on the Clinical Guidelines for the Management of Allergic Rhinitis in Japan [2]. For nasal symptoms, the severity of sneezing (number of sneezes for 12 h), nose blowing (number of times the nose is blown for 12 h) and nasal congestion were evaluated on 4-point scales (0–3). For episodes of sneezing and nose blowing for 12 h, the scores were as follows: 0, none; 1, 1–5 episodes; 2, 6–10 episodes, and 3, 11–20 episodes. For nasal congestion, the scores were as follows: 0, none; 1, mild; 2, moderate, and 3, severe. Eye symptoms and the degree of interference with daily life were also evaluated using 4-point scales (0–3). For eye itching, the scores were as follows: 0, none; 1, itching but no need to scratch; 2, scratching occasionally, and 3, scratching frequently. For eye watering, the scores were as follows: 0, none; 1, watering, but no need to wipe; 2, wiping occasionally, and 3, wiping frequently. Finally, for degree of interference with daily life: 0, none; 1, mild; 2, moderate, and 3, severe. The total nasal symptom score was defined as the sum of the scores for sneezing, nose blowing and nasal congestion (0–9). The total ocular symptoms score was defined as the sum of the scores for eye itching and eye watering (0–6). The total nasal-ocular symptoms score was defined as the sum of the total nasal and total ocular scores (0–15). The total nasal symptoms score for 12 h (9 a.m.–9 p.m.) on day 9 was defined as the primary endpoint. Other nasal and ocular symptoms were secondary endpoints.

Adverse Events

Adverse events that occurred were recorded by the subjects in an allergy diary.

Statistical Analysis

Data analysis was performed by a biostatistician (Dr. Shoji Tokunaga of Kyushu University) who was not involved in carrying out the clinical trial. A linear multilevel model was used for comparison among the 3 treatments, with each score and the treatment methods used as the continuous variable and dummy variables, respectively. The model was used based on the measurements being made repeatedly for each subject. The repeated nature of the measurements violates the assumption of mutual independence of the residuals in standard linear regression modeling. The multilevel model, also known as a mixed model or random effects model, assumes that the measurements within each subject are mutually correlated, but that measurements among subjects are independently distributed. Means of differences between treatments and their confidence intervals in each subject were estimated using this model (Stata v.11.2, Stata Corp., College Station, Tex., USA). Data analysis was performed with two-tailed tests at a significance level of 5%. Data for subjects who missed a treatment were treated as missing values and were not used for comparison of nasal or ocular symptoms. For evaluation of adverse effects, a multilevel logistic model was used with two-tailed tests at a significance level of 5%.

Results

Backgrounds of Subjects

Seventy patients were initially screened, of whom 11 were excluded because of screening failures; the serum cedar pollen-specific IgE score was <2 in 2 patients, and moderate or severe symptoms (defined as a total nasal symptom score ≥4 for 12 h) were not induced by the screening exposure in 9 patients. Of the 59 subjects who fulfilled the inclusion criteria, 50 with more severe symptoms were selected and randomized into the 3 treatment arms. These subjects included 32 females (64%) and had a mean (±SD) age of 37.8 ± 9.5 years. The mean cedar pollen radioallergosorbent test score was 3.8 ± 1.0. The distribution of classes on the test was as follows: class 2, 2 subjects; class 3, 19 subjects; class 4, 18 subjects; class 5, 7 subjects, and class 6, 4 subjects. One subject missed 1 treatment due to an upper respiratory tract infection.

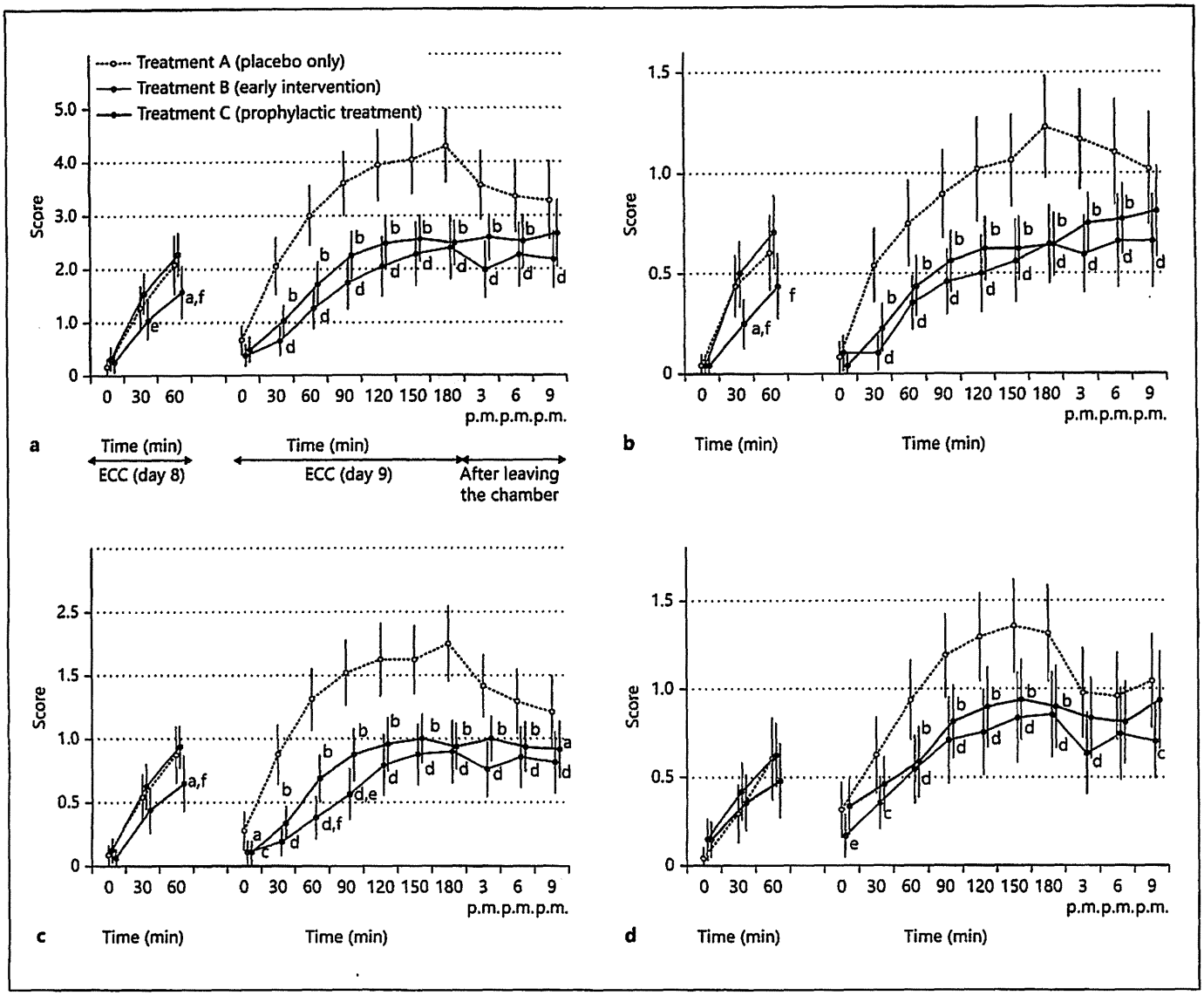

Fig. 1. Subjective assessment of the severity of nasal symptoms. **a** Total nasal symptoms. **b** Sneezing. **c** Rhinorrhea. **d** Nasal congestion. All nasal symptoms were significantly lower with treatments B and C than with treatment A on day 9. Superior efficacy was not observed with treatment C compared with treatment B, and at some time points on day 9, treatment C was less effective than treatment B. Values represent means ± 95% confidence intervals. [a] $p < 0.05$, [b] $p < 0.01$: treatment C vs. treatment A; [c] $p < 0.05$, [d] $p < 0.01$: treatment B vs. treatment A; [e] $p < 0.05$, [f] $p < 0.01$: treatment B vs. treatment C.

Three subjects missed 1 treatment and 1 subject missed 2 treatments for personal reasons. Data for these 5 patients were not used in the statistical analysis for comparison of nasal or ocular symptoms.

Subjective Assessment of the Severity of Nasal Symptoms

In the 1-hour pollen exposure from 9 to 10 a.m. on day 8, patients in the 3 treatment arms were asymptomatic at 0 min, and the scores then increased. The scores for total nasal symptoms with treatment C (prophylactic treatment) were significantly lower than those for treatment A (placebo only) at 60 min and treatment B (early intervention) from 30 to 60 min (fig. 1a). During the 3-hour pollen exposure from 9 a.m. to 12 p.m. on day 9, the scores gradually increased in all 3 treatment arms. However, the scores were significantly lower with treatments B and C than with treatment A from 30 to 180 min.

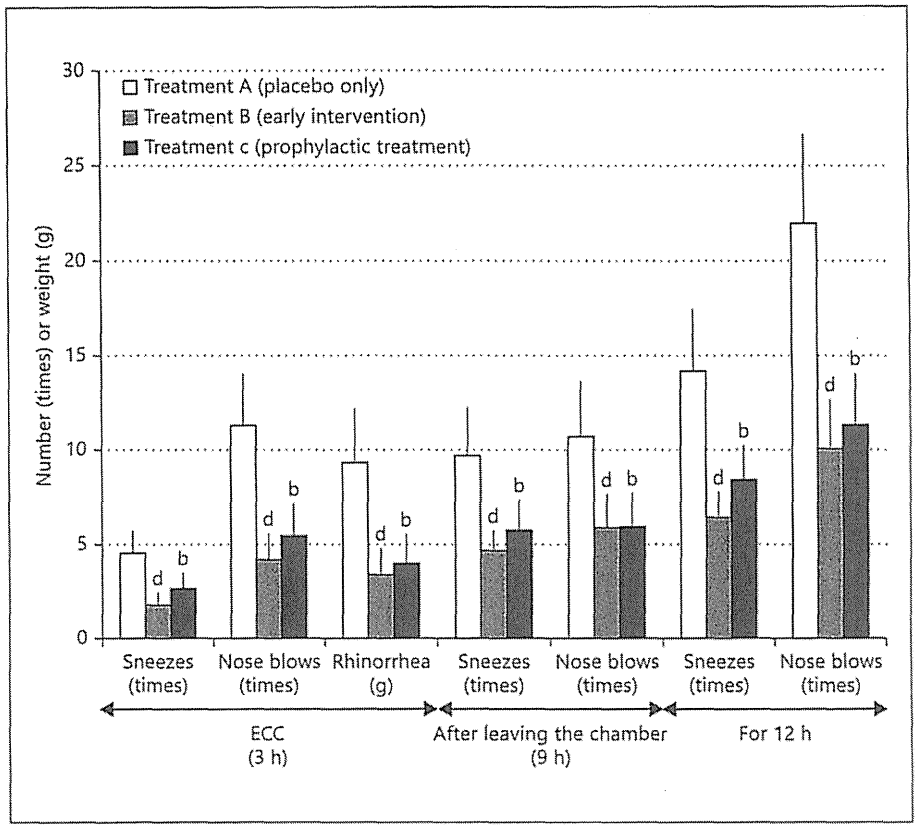

Fig. 2. Numbers of sneezes/nose blows and amount of rhinorrhea on day 9. The numbers of sneezes/nose blows and amount of rhinorrhea were significantly lower with treatments B and C compared with treatment A. There was no significant difference between treatments B and C. Values represent means ± 95% confidence intervals. [b] $p < 0.01$: treatment C vs. treatment A; [d] $p < 0.01$: treatment B vs. treatment A.

There was no significant difference between treatments B and C in the ECC. The nasal symptoms persisted after leaving the chamber on day 9, but the scores gradually decreased in the group given treatment A, and the differences compared to the other two groups became small. However, the scores with treatments B and C were still significantly lower than those with treatment A from 3 to 9 p.m. and from 3 to 6 p.m., respectively. There was no significant difference between treatments B and C after leaving the chamber.

The scores for sneezing, rhinorrhea and nasal congestion are shown in figure 1b, c and d, respectively. The changes in these symptoms were almost the same as those found in total nasal symptoms, although treatment C was less effective than treatment B at some time points for rhinorrhea and nasal congestion on day 9.

Number of Sneezes/Nose Blows and Amount of Rhinorrhea on Day 9

The number of sneezes/nose blows and the amount of rhinorrhea during cedar pollen exposure in the ECC were significantly lower with treatments B and C than with treatment A (fig. 2). There was no significant difference between treatments B and C. Similar results were obtained after leaving the chamber and for 12 h (9 a.m.–9 p.m.) on day 9. Sneezing and nose blowing clearly persisted after leaving the chamber.

Symptom Scores for 12 h on Day 9

Almost all symptoms except nasal congestion and eye itching showed significantly lower scores with treatments B and C compared with treatment A (fig. 3). Total nasal symptom scores, the primary endpoint, were also significantly lower with treatments B and C than with treatment A. For nasal congestion and eye itching, the scores with treatment B were significantly lower than with treatment A. When compared with treatment C, treatment B showed a significantly lower score for sneezing. However, there was no significant difference between treatments B and C for other symptoms.

Adverse Events

In patients in treatment arms A, B and C, sleepiness occurred in 13, 13 and 17%, respectively; thirst in 6, 11 and 15%, and fatigue in 4, 9 and 13%. Other adverse events including upper respiratory tract infection were