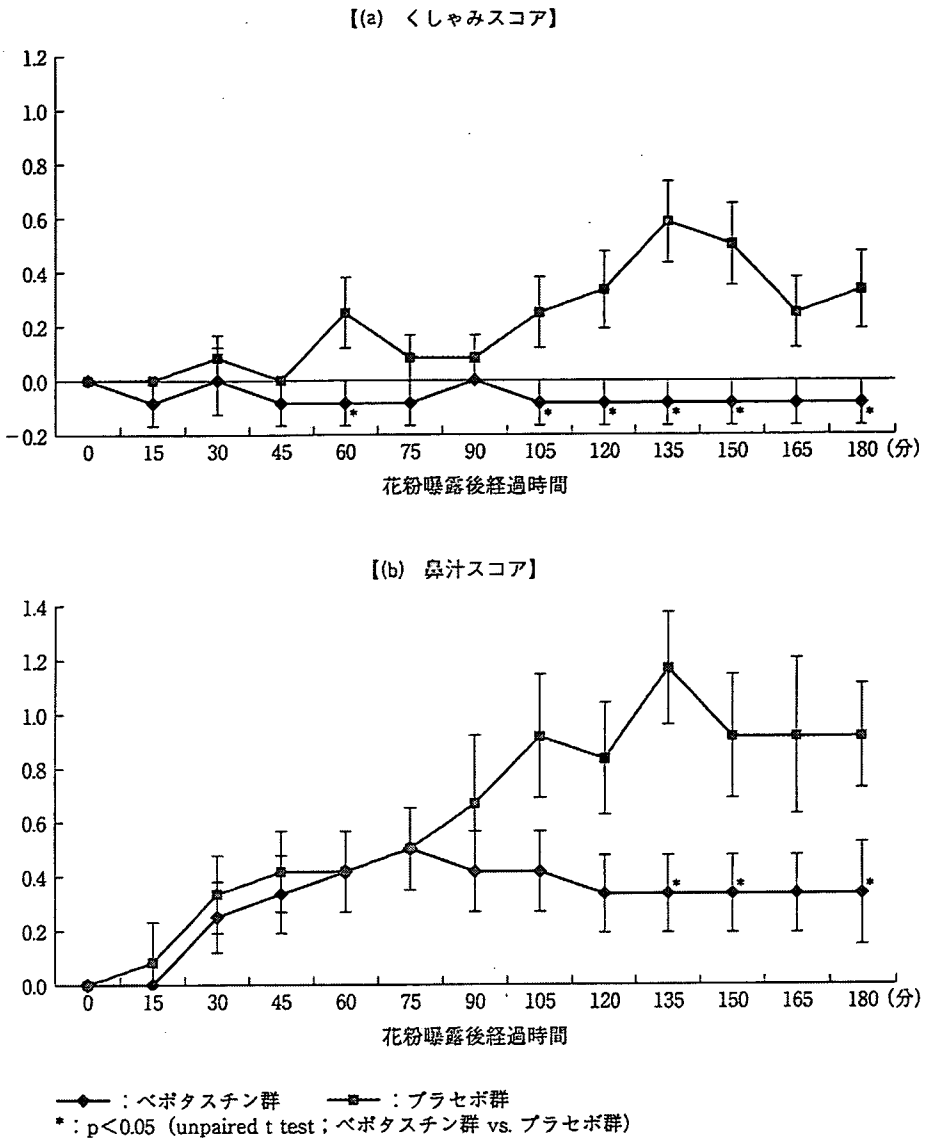
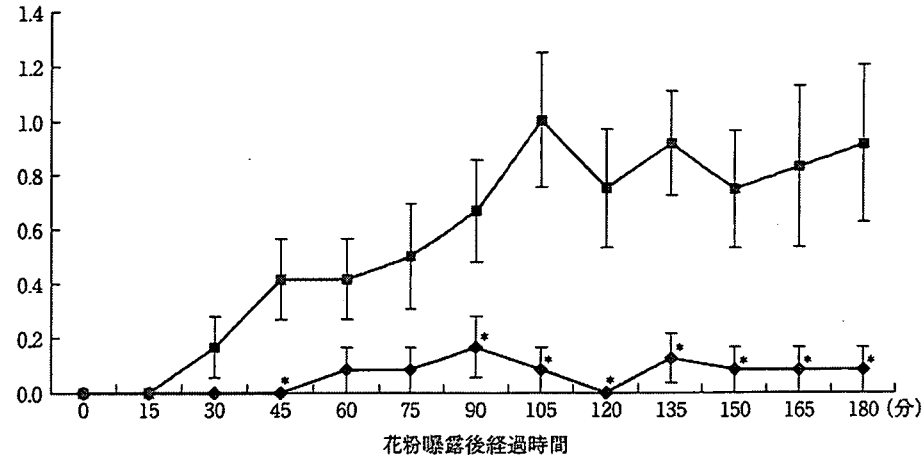
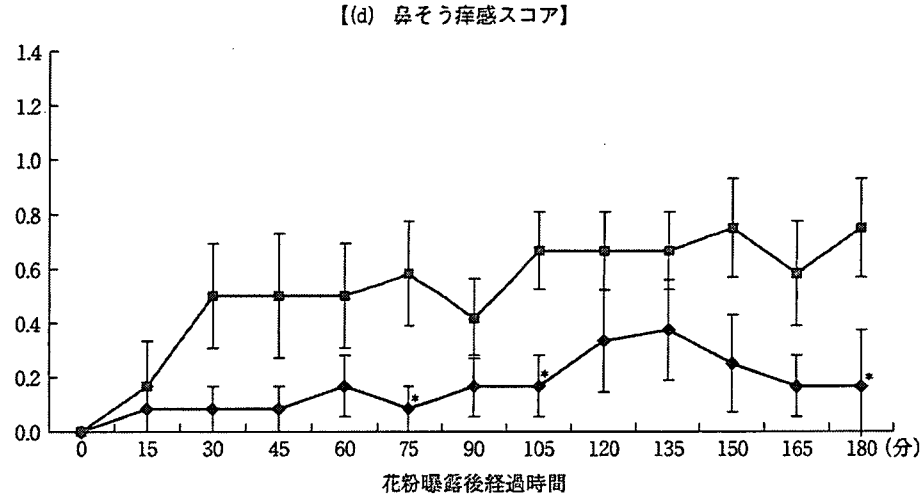


図4　入室時値に対する

Wakayama EEUもスギ花粉曝露が可能な施設であり，榎本らはその施設で塩酸セチリジンを投与し鼻症状に対する効果についてプラセボを対照として検討している[9]。われわれの結果と同じように，鼻閉に対して効果を示していた。ただし評価方法としてVASを使用していたことから，今回の結果と比較することは難しい。一般に抗ヒスタミン薬は鼻閉症状には効果が少ないと考えられているが，今回の結果から，第2世代の抗ヒスタミン薬の鼻閉に対する効果に関してさらに検討していく必要があると考えられた。

ベポタスチンOD錠は，服用後最高血中濃度到達時間が1.0時間であることから，効果発現が早いことが示されている[10]。本試験ではスギ花粉曝露10分前に1回だけ服用したが，プラセボ群は全例で症状発現が認められたのに対し，ベポタスチンを服用した12例中6例では





鼻症状スコア（変化量）の推移

症状発現が認められなかった。この結果は，本剤をスギ花粉飛散前に服用することにより症状抑制が可能であるという予防投与の有効性の可能性を示している。

本試験においてはImpaired Performanceの評価として，D-CATを用いた作業試験を実施した。この結果，プラセボ群では作業量が減少傾向を示したが，ベポタスチン群では逆に試験とともに作業量が上昇した。花粉症は，日常のQOLに悪影響を及ぼすとともに，作業能率の低下を招くことが知られており，それによる経済的損失は社会問題になっている[11]。本試験の結果でも，プラセボ群で作業能率が低下傾向を示したことは，花粉症に伴う諸症状がImpaired Performanceを引き起こすことの裏づけになった。一方，ベポタスチン群で作業量の増加が認められた理由として，花粉曝露による症状を抑制したことと，本剤由来

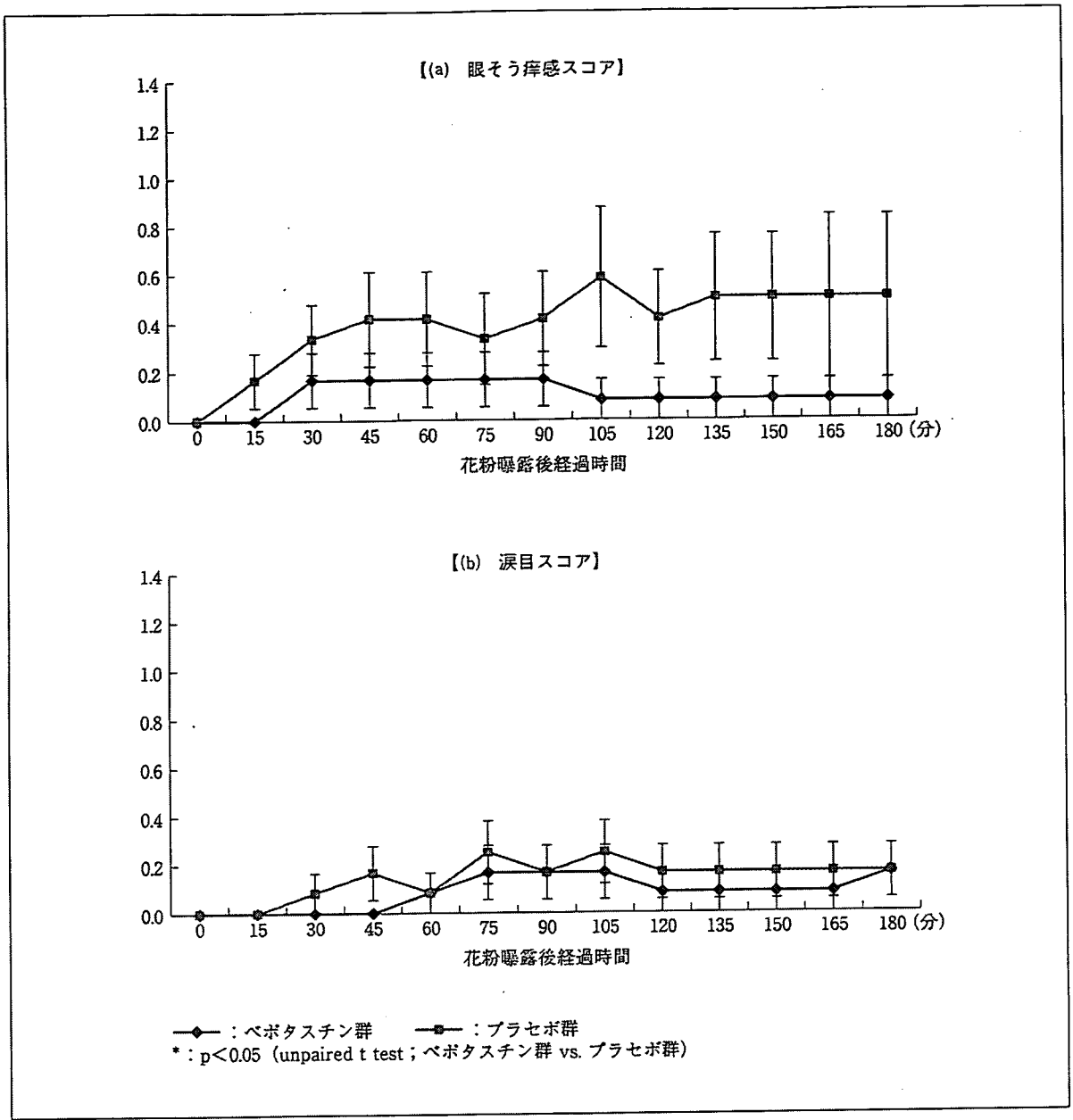


図5 入室時値に対する眼症状スコア（変化量）の推移

のImpaired Performanceが認められなかったことによるものと考えられる。これまでの検討は健康成人に対する薬剤由来のImpaired Performanceの評価が中心であったが，本試験のように実際の臨床状況に即した形で検証することも重要であると考える。

本剤は，p糖蛋白の基質となることから脳内移行が低く抑えられることが確認されている[12]。またTashiroらによるPETを用いた脳内移行の研究から鎮静作用が少ない抗ヒスタミン薬であることも確認されている[13]。本試験の結果はこれらの特徴を支持する結果となった。

結論として，われわれはOHIO Chamberを用い，スギ花粉症患者においてベポタスチンOD錠10mgをスギ花粉曝露10分前に1回投与することにより，スギ花粉曝露による症状発現抑制効果と作業能率の維持ができることを示した。またその作用は即効性があることと

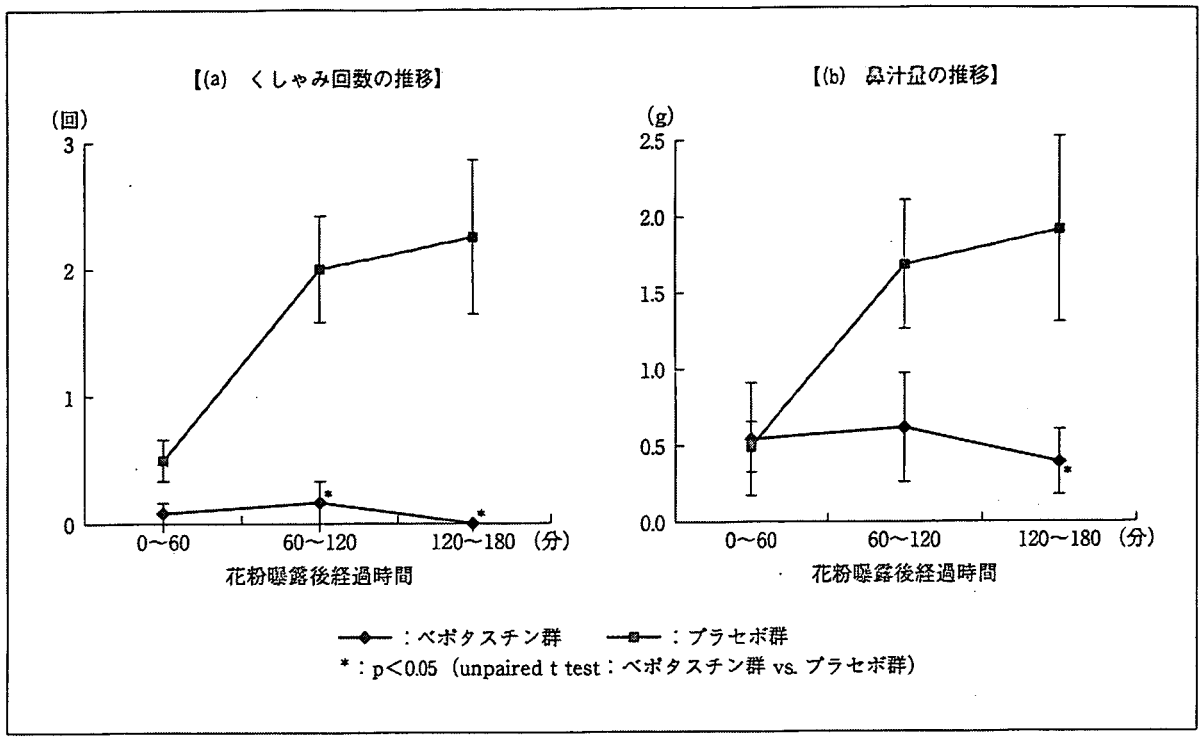


図6 くしゃみ回数および鼻汁量の推移

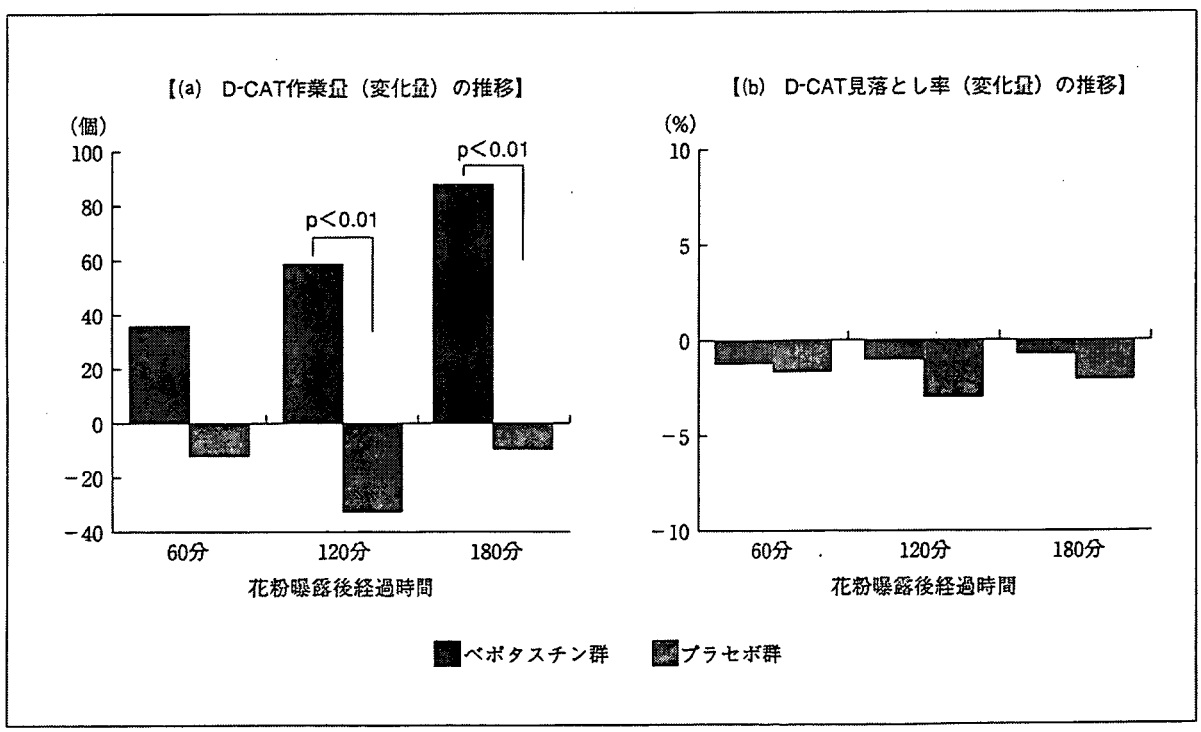


図7 Impaired Performanceの推移

安全であることも示した。さらに，ベポタスチンOD錠は水なしで服用できる利便性を有しており，スギ花粉症に対し，非常に有用な薬剤であるものと推察する。

◎本試験は財団法人パブリックヘルスリサーチセンターの臨床支援研究として実施した。

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

リアルタイムモニター飛散数と現状の治療によるQOLの関連性の評価研究と花粉症根治療法の開発
スギ花粉症に対する経年的な舌下免疫療法と丸山ワクチン免疫療法の臨床研究

主任研究者　大久保公裕　日本医科大学耳鼻咽喉科

研究要旨
現在、スギ花粉症の治療は一般的に薬物療法がおこなわれている。しかし発症年齢が低下し、罹患人口が増加している現状で、また薬物療法の効果が限界になっている今日では治癒を目標とした治療法の開発が急務である。このため我々は昨年度から始めた舌下免疫療法の経年的ＲＣＴを評価した。1年目の効果はやはり2005年時と同じくＱＯＬを悪化を抑制した、しかし2年目はプラセボと差がなかった。これは方法論の失敗と考えられた。投与ルートを変更するのではなく、アジュバントを用いる方法も開発し、丸山ワクチンを用いた皮下注射による抗原特異的免疫療法検討を検討したが、これはまだ結果が出ていない。今後さらに治癒的な免疫療法を追求する。

A. 研究目的
アレルギー疾患の治療においては現在、一般臨床医で多く行われている薬物療法が主体をなしている。薬物療法は対症療法であり、症状の軽快のみで治癒を導くことはできない。アレルギー反応そのものを起きにくくするという視点に立てば、唯一根治的治療と認識されているのはアレルゲン免疫療法のみである。つまり、アレルギーの感作にかかわる誘導相に治療効果が作用する。1911年にNoon Lがlancetにイネ科花粉症に報告して以来の治療法であり二重盲検比較試験でも臨床効果が確立されている。しかし皮下注射の方法論は現状でも当時のそのままであり、進歩が少なかった。このため我々の研究班では根治的免疫療法の臨床応用を目標としてスギ花粉症患者に対する舌下免疫療法の応用を行ってきた。これは2年のプラセボ対照二重盲検比較試験であり2006年、2007年の経年的な効果を検証した。免疫療法はT細胞への効果発現機序が考えられており、Th2の抑制とTh1の誘導が主たる目標となる。Th1の誘導として我々は今回、丸山ワクチンを使用し、抗原と組み合わせた免疫療法の試験を少人数ではあるが、倫理委員会の承認を受けて検討した。

B. 方法
①日本医科大学耳鼻咽喉科と研究班の分担研究者の施設において109名の試験参加を受け付けた。試験はランダム化プラセボ対照比較試験で2006年(109名)と2007年(93名)の効果について検討した。検討した項目はアレルギー日記による症状スコアとJRQLQによるQOLスコアである。舌下免疫療法の方法は1年目までは2005年と同じで季節中まで1週間に1回の維持量2000JAU/mlを20滴あり、季節後から2年目の季節まで2週間に1回の投与として行った。評価はアレルギー日記とＪＲＱＬＱによるＱＯＬの評価を行った。
②日本医科大学耳鼻咽喉科において12名の試験参加を受け付けた。試験はランダム化プラセボ対照比較試験でプラセボ群と丸山ワクチン単独群、丸山ワクチンと抗原の混合群の3群で各群として4症例を行った。方法は急速法であり、抗ヒスタミン薬を前もって服用し1週間に混合薬を投与した。結果は2008年の花粉症季節時の症状スコア、QOLスコアで評価する予定である。

C. 結果
①1年目である2006年は全国的にスギ花粉の飛散は少なかった。この年の症状スコアは実薬とプラセボで鼻閉に差が認められた。QOL平均スコアでも3月に実薬0.6プラセボ1.2であった。1年目の効果は2005年と同じく、スギ花粉症に対して効果が認められた。しかし2年目の2007年は平年並みとなりの年の症状スコアは実薬でプラセボより鼻閉で有意に良い時期があったが、QOLスコアでは実薬1.0プラセボ1.0であり、2年目の効果は確認されなかった。
②丸山ワクチン併用免疫療法の効果は2008年の花粉症季節時の症状スコアでの評価である。このためまだ結果は出ていないが、現在投与時期に関してはアレルゲンによる副反応は生じていない。効果判定は2008年5月以降になる。

D. 考察
舌下免疫療法は欧州で始まった免疫療法の新しい方法であるが、その方法論はまだ定型的なものはない。欧米では季節前の短期的な舌下免疫療法が主体であるが、今回我々は経年的に非季節時もブースト効果を狙い免疫療法を持続させ、2年目の症状を判定した。日本のスギ花粉症では1年目の効果が2年目の

効果より良く、今後1年目から2年目に移るときに2週間に1回と減少させたためかどうか検討しなければならない。免疫療法には抗原特異的なTh2の抑制とTh1の増加免疫療法の効果発現に重要と考えられている。通常の免疫療法でこの作用を増強するにはTh1誘導のアジュバントを使用する方法が考えられ始めている。丸山ワクチンを併用させた免疫療法では入院ではない急速法での可能性を示唆した。現状ではまだ季節中の効果は出ていないが、今後季節の効果を判定し、新たな免疫療法の可能性を見出したい。

E. 結論

免疫療法の効果はすでに実証されているが、一般医療として広げるにはさらに副作用を減少させ、治療期間を減少させる必要がある。今回我々は一般的に言われるように舌下免疫療法が経年的に行うことによりその効果が増強する事は見出せなかった。今後その原因を検証し、経年的な効果を得られるように検証しなければならない。Th1アジュバントである丸山ワクチンを用いてスギ花粉症の患者に急速法でのアレルゲン免疫療法として実施した。現在まだ施行中の免疫療法では副作用は生じていないが、今後の副作用の確認と症状の抑制効果を見なければならない。

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G．知的所有権

なし

実用新案登録

なし

H．健康安全情報

なし

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ORIGINAL PAPER

Omalizumab is more effective than suplatast tosilate in the treatment of Japanese cedar pollen-induced seasonal allergic rhinitis

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Clinical and Experimental Allergy

Summary

Background Seasonal allergic rhinitis (SAR) induced by Japanese cedar pollens is a major problem in Japan. Omalizumab, a humanized monoclonal anti-IgE antibody, improves symptoms associated with SAR, but a comparative study with an anti-allergy drug has not yet been conducted.

Objective To compare the efficacy and safety of omalizumab with suplatast tosilate, a selective T-helper type 2 (Th2) cytokine inhibitor, in patients with Japanese cedar pollen-induced SAR.

Methods A randomized, double-blind, double-dummy study was conducted in 308 Japanese patients with a history of moderate-to-severe SAR who showed a CAP-RAST value ($\geqslant 2+$) specifically to Japanese cedar pollens. Patients were treated for 12 weeks with omalizumab plus placebo of suplatast tosilate or suplatast tosilate plus placebo of omalizumab.

Results The mean daily nasal symptom medication scores (sum of the daily nasal symptom severity score and daily nasal rescue medication score) were significantly lower in the omalizumab group than in the suplatast tosilate group during three evaluation periods ($P < 0.001$). The omalizumab group also had significantly lower mean daily nasal severity scores, each of the mean daily nasal and ocular symptom severity scores (sneezing, runny nose, stuffy nose, itchy nose, itchy eyes, watery eyes, and red eyes). Omalizumab reduced rescue medication requirements, and the proportion of days with any rescue medication use in the omalizumab group was significantly lower. Serum-free IgE levels markedly decreased in the omalizumab group and it was associated with clinical efficacy. The adverse reaction profiles were similar between the two groups. The overall incidence of injection site reactions was higher in the omalizumab group than in the suplatast tosilate group, but all these events were of mild degree. No anti-omalizumab antibodies were detected.

Conclusion Omalizumab showed significantly greater improvements than suplatast tosilate in the treatment of SAR induced by Japanese cedar pollens.

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Keywords anti-IgE antibody, omalizumab, seasonal allergic rhinitis, suplatast tosilate
Submitted 20 March 2007; revised 6 September 2007; accepted 26 September 2007

Introduction

Seasonal allergic rhinitis (SAR), especially Japanese cedar pollen-induced SAR, is a major medical problem in Japan, afflicting approximately 20% of the Japanese people [1]. Symptoms can range from mild to serious debilitating and can affect quality of life (QOL) by causing fatigue, headache, cognitive impairment, and other systemic symptoms. Such symptoms can result in loss of work productivity and school days [2].

Omalizumab is a recombinant humanized monoclonal anti-IgE antibody currently approved in the United States and Europe for treating allergic asthma that specifically binds to the Cε3 domain of IgE that interacts with IgE receptors on effector cells [3]. This antibody blocks the binding of IgE to high-affinity receptors (FcεRI), thereby preventing the IgE-mediated cellular responses, such as allergen-induced histamine release from basophils and mast cells [4, 5]. It also inhibits allergen-induced T-helper type 2 (Th2) cytokine production, IL-4, IL-5 [6], IL-13 [7],

leucotriene release [8], human IgE synthesis [4, 9], and reduces eosinophil counts in patients with allergic rhinitis (AR) or bronchial asthma [10–12]. Because it does not bind to effector cell-bound IgE, omalizumab is non-anaphylactogenic, which is crucial in its clinical application.

We had demonstrated previously the prominent clinical effects of this novel antibody on Japanese cedar pollen-induced SAR against placebo [13]. Therefore, we have further tried to investigate the clinical benefits of omalizumab by comparing with a current clinical medication. Although omalizumab has new and unique modes of action, we have chosen suplatast tosilate as a controller for comparison of the clinical efficacy. Suplatast tosilate is a new dimethylsulphonium agent that has been shown to be effective for allergic disease, such as bronchial asthma [14], AR [15], and atopic dermatitis [16]. It is classified into a selective Th2 cytokine inhibitor and is included in the list of drugs that can be used in the treatment of AR on clinical guidelines in Japan [17]. This anti-allergic agent has some modes of action similar to omalizumab; it suppresses the production of IL-4 and IL-5 from human and mouse Th2 clones [18], IgE synthesis [14, 19, 20], and eosinophil infiltration in patients with AR or bronchial asthma [15, 21, 22]. The other clinical medications for AR such as anti-histamine [23], topical corticosteroids [24], cromones [25], and anti-leukotriene [26] do not have such modes of action especially on IgE production.

Therefore, we compare the clinical effects of omalizumab with suplatast tosilate in patients with moderate to severe Japanese cedar pollen-induced SAR in a randomized, double-blind manner.

Materials and methods

Participants

Patients who met the following criteria were considered to be eligible for enrollment: (1) age (20–64 years); (2) a history of SAR induced by Japanese cedar pollens in at least 2 consecutive years; (3) presentation of at least four out of eight moderate-to-severe symptoms (sneezing, itchy nose, runny nose, stuffy nose, itchy eyes, watery eyes, red eyes, and itchy throat), with two or more nasal symptoms among these four or more symptoms that persisted for 1 or more weeks during the last Japanese cedar pollen season; (4) the presence of IgE specific to Japanese cedar pollens (CAP-RAST: $\geqslant 2+$) at baseline; (5) serum total IgE levels of 30–700 IU/mL and body weights of 30–150 kg at baseline; and (6) no symptoms of AR at 1 month before the onset of the screening period.

Patients who had a history or clinical status of the following were excluded from the study: (1) specific immunotherapy (SIT) to Japanese cedar pollens in the previous 2 years; (2) severe anaphylactoid or anaphylactic reactions; (3) active or recent development (within 3 months before the study onset) of any other type(s) of rhinitis; (4) a positive reaction to omalizumab in the skin test at screening; (5) pregnant/nursing women; and (6) serious medical conditions (e.g. cancer, hepatic failure, and renal failure).

The present study was conducted in compliance with the current good clinical practice, and the protocol was approved by each institutional ethical committee. Before the onset of the study, written informed consent was obtained from all the patients who were enrolled.

Study design

This randomized, double-blind, double-dummy, parallel-group study was conducted in two regions of Japan (Tokyo and Osaka) between October 2002 and April 2003 and consisted of a 4-week screening period, a 12-week treatment period, and a 12-week follow-up period after the final dosing. Following screening, eligible patients were assigned to the omalizumab group or the suplatast tosilate group at a 1 : 1 ratio.

Daily pollen counts were measured in Tokyo and Osaka. The start day of the pollen period was defined as the first of 2 consecutive days when $\geqslant 1$ grain/cm^2 were counted; the end day of the pollen period was the first of 3 consecutive days when no grain was counted. The severe pollen period was defined as the span between the first and last days when $\geqslant 30$ grains/cm^2 were counted.

Doses and administration

Patients received either omalizumab plus placebo of suplatast tosilate (omalizumab group) or suplatast tosilate plus placebo of omalizumab (suplatast tosilate group).

Omalizumab (150, 225, 300, or 375 mg) or the matching placebo was administered to patients subcutaneously every 2 or 4 weeks based on their serum total IgE level and body weight at baseline, which ensured a minimum dose of 0.016 mg/kg/IgE (IU/mL) every 4 weeks. Suplatast tosilate (100 mg) or the matching placebo was administered orally three times a day. The initial dose was administered at least 1 month before the expected starting date of the pollen period.

The following drugs were allowed as rescue medications: for nasal use [clemastine fumarate (tablet), sodium cromoglycate (nose drop), naphazoline nitrate (nose drop)] and for ocular use [sodium cromoglycate (eye drop)]. Agents that were prohibited from use as concomitant drugs were leucotriene antagonists, corticosteroids, antihistamines (except for rescue medications), anticholinergic agents, nasal vasoconstrictors (except for rescue medications), tricyclic antidepressants, and monoamine oxidase inhibitors. SIT was prohibited.

Evaluation of efficacy

The patients who were enrolled were requested to fill in the patient diary in order to describe their seven rhinoconjunctival symptoms (sneezing, itchy nose, runny nose, stuffy nose, itchy eyes, watery eyes, and red eyes) according to the 4-point scale (0: none; 1: mild; 2: moderate; and 3: severe) and to document their rescue medication use, if any. Regarding each rescue medication, its usage was scored 1 point regardless of dose and frequency.

The primary efficacy variable was the mean of the daily nasal symptom medication scores. The daily nasal symptom medication score (0–15 points) consisted of the sum of the daily nasal symptom severity score (0–12 points) and the daily nasal rescue medication score (0–3 points).

Secondary efficacy variables included the daily ocular symptom medication score (0–10 points) [sum of the daily ocular symptom severity score (0–9 points) and the daily ocular rescue medication score (0–1 point)]; the daily nasal symptom severity score; each of the mean daily nasal and ocular symptom severity scores (sneezing, runny nose, stuffy nose, itchy nose, itchy eyes, watery eyes, and red eyes); the daily nasal rescue medication score; the daily ocular rescue medication score; the consumption per day of rescue medications; and the proportion of days on which any rescue medication was taken.

The primary and secondary variables were evaluated over three evaluation periods (the treatment period, the pollen period, and the severe pollen period).

Estimation of serum-free immunoglobulin E levels

Blood samples were collected for measurement of free IgE at baseline and at 4 and 12 weeks of the treatment period. Free IgE was measured using a solid-phase ELISA [27].

Evaluation of safety

Adverse events were examined throughout the treatment period. Clinical laboratory tests were conducted at baseline and at 2, 4, 8, and 12 weeks of the treatment period. Anti-omalizumab antibodies (IgG subtype) were measured using solid-phase ELISA at baseline and 12 weeks post-final dosing [28].

Statistical analysis

Three hundred patients were planned to be assigned to the omalizumab group or to the suplatast tosilate group at a 1 : 1 ratio. The sample size was calculated under the assumption of 80% power, significance level of 0.05 (two-sided), and at a standard deviation of 1.50 for the difference. The non-inferiority margin was set to 0.5.

The mean daily nasal symptom medication scores were evaluated as the primary efficacy variables to demonstrate the non-inferiority of omalizumab compared with suplatast tosilate in the per protocol set (PPS). Statistical analysis for the non-inferiority was confirmed using a confidence interval for the difference. Once the non-inferiority was confirmed, the superiority of omalizumab was tested in the full-analysis set (FAS). The primary efficacy variable was evaluated using a mixed-effect model under the null hypothesis of no difference between the study groups and a two-sided significant level of 0.05. The mixed-effect model included covariates of the study group as a fixed effect, and location and administration interval (2- or 4-week interval) as random effects. The least-squares mean (LSM) for each study group and the difference in LSM between the study groups were estimated.

The mean daily ocular symptom medication scores, each of symptom severity scores, were also analysed similar to the analysis of the mean daily nasal symptom medication scores. The consumption per day of rescue medications and the proportion of days on which any rescue medication was taken were analysed using the Wilcoxon test.

The safety and tolerability of the study drugs were summarized by appropriate descriptive methods.

Results

Three hundred and seven of 308 randomized patients received either of the study drugs: 154 received omalizumab (155 randomized) and 153 received suplatast tosilate. The remaining patients in the omalizumab group withdrew during the screening period due to use of prohibited concomitant medicine. The patient characteristics were comparable between the study groups (Table 1).

Table 1. Patient characteristics

	Omalizumab ($n = 154$)	Suplatast tosilate ($n = 153$)
Gender		
Male	69	75
Age (years)		
Mean ± SD	35.3 ± 13.0	34.9 ± 12.0
Range	20–64	20–62
History of SAR induced by Japanese cedar pollens (years)		
Mean ± SD	12.0 ± 6.6	12.2 ± 6.4
Range	2–38	3–34
Specific IgE levels against Japanese cedar pollens (CAP-RAST)*		
Class 2 (0.70–3.49 UA/mL)	11	18
Class 3 (3.50–17.49 UA/mL)	70	71
Class 4 (17.50–49.99 UA/mL)	60	56
Class 5 (50.00–99.99 UA/mL)	13	8
Serum total IgE levels at baseline (IU/mL)		
Mean ± SD	169.2 ± 139.8	159.9 ± 133.5
Range	31.0 ± 610.0	30.0 ± 560.0

*Specific IgE levels against Japanese cedar pollens at baseline were categorized into seven groups (classes 0–6), and a ⩾2 class group was assessed to be positive against the allergen.
SAR, Seasonal allergic rhinitis.

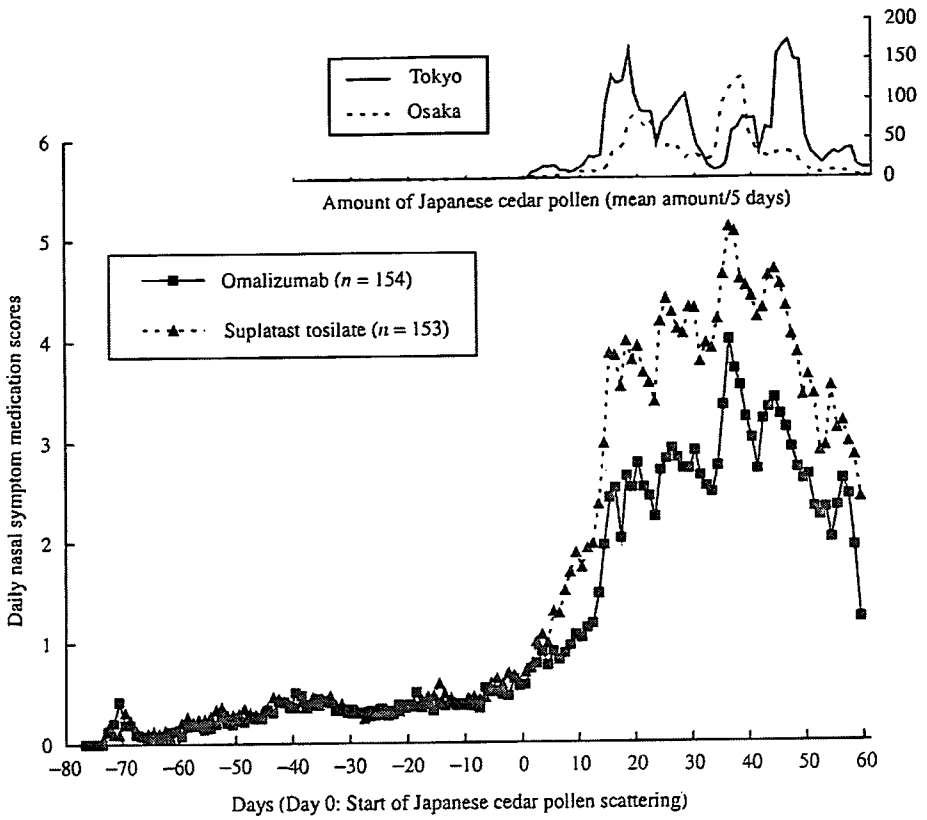

Fig. 1. Time-course changes in daily nasal symptom medication score [full analysis set (FAS)] and in the amount of Japanese cedar pollen. Day 0 represents the start day of the pollen period in Tokyo and Osaka.

Six patients (one receiving omalizumab and five receiving suplatast tosilate) discontinued the study prematurely; among them, four patients in the suplatast tosilate group ceased the study due to protocol deviations. One suplatast tosilate-treated patient discontinued because of adverse events, and one omalizumab-treated patient withdrew consent. None of the patients discontinued the study because of an unsatisfactory therapeutic effect.

The pollen period started at the beginning of February and continued till the end of April (Fig. 1). All patients received the first administration at least 3 weeks before the starting date of the pollen period.

Daily nasal symptom medication score

Time-course changes in daily nasal symptom medication scores are shown in Fig. 1. The daily nasal symptom medication scores throughout the pollen period were consistently lower in the omalizumab group than in the suplatast tosilate group.

The omalizumab group showed significantly lower mean daily nasal symptom medication scores compared with the suplatast tosilate group in the PPS during the three evaluation periods (e.g. LSM ± SE, 1.517 ± 0.348 for the omalizumab group and 2.215 ± 0.347 for the suplatast tosilate group; $P<0.001$, the treatment period). Statistical analyses revealed similar results with respect to the relevant scores in the FAS during the three evaluation periods (Fig. 2a). During the pollen period, patients with lower mean nasal symptom medication scores were distributed predominantly in the omalizumab group than in the suplatast tosilate group, with greater numbers of patients with scores of 0–1 and >2–3 in the former and latter groups, respectively. Over half of the patients in the omalizumab group had mean daily nasal symptom medication scores of ⩽2 (mild or less severe symptoms) in contrast to 27% in the suplatast tosilate group. More than 10% of the patients in the suplatast tosilate group had scores of >6 (severe symptoms) compared with 4.6% in the omalizumab group (Fig. 2b).

As shown in Fig. 1, although the amount of Japanese cedar pollens in Tokyo was approximately twice as much as that of Osaka (3542 grains/cm^2 for Tokyo and 1855 grains/cm^2 for Osaka), the mean daily nasal symptom medication scores were consistently lower in the omalizumab group than in the suplatast tosilate group in Tokyo and Osaka, respectively (mean ± SE, 1.931 ± 0.140 and 2.398 ± 0.163 for Tokyo, 1.313 ± 0.138 and 2.164 ± 0.152 for Osaka, the treatment period).

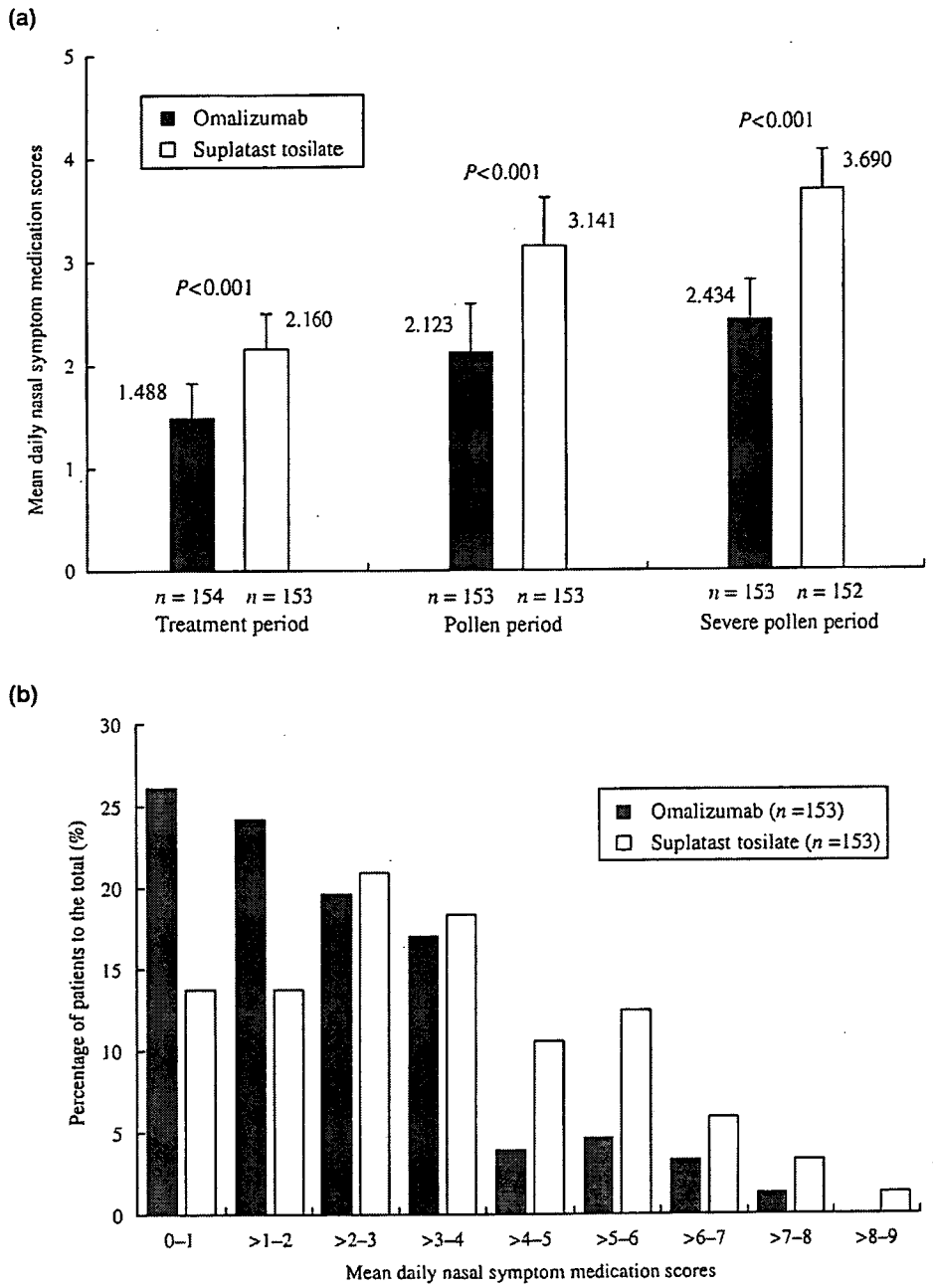

Fig. 2. (a) Mean daily nasal symptom medication scores [full analysis set (FAS)] during the treatment period, the pollen period, and the severe pollen period. (b) Percentages to the total of patients with the mean daily nasal symptom medication scores FAS during the pollen period.

Daily ocular symptom medication score

The omalizumab group had significantly lower mean daily ocular symptom medication scores compared with the suplatast tosilate group during the treatment period (0.734 ± 0.110 and 0.991 ± 0.110, respectively; $P = 0.008$; Fig. 3). Statistical analyses revealed similar results with respect to the relevant scores during the pollen and the severe pollen period.

Daily nasal and ocular symptom severity scores

The omalizumab group had significantly lower mean daily nasal symptom severity scores compared with the suplatast tosilate group during the three evaluation periods (e.g. 1.458 ± 0.333 and 2.103 ± 0.333, respectively; $P < 0.001$, the treatment period). Each of the mean daily nasal and ocular symptom severity scores during the three evaluation periods (sneezing, runny nose, stuffy nose,

itchy nose, itchy eyes, watery eyes, and red eyes) was significantly lower in the omalizumab group (*P*-values ranging from <0.001 to 0.025; Fig. 4).

Use of rescue medications

The mean daily nasal rescue medication scores were significantly lower in the omalizumab group than in the suplatast tosilate group during the pollen period (0.048 ± 0.016 and 0.090 ± 0.016, respectively; $P = 0.039$), and the mean ocular rescue medication scores tended to show a significant difference.

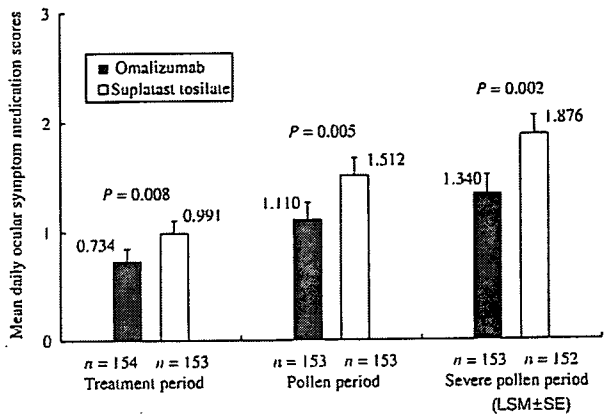

Fig. 3. Mean daily ocular symptom medication scores [full analysis set (FAS)] during the treatment period, the pollen period, and the severe pollen period. LSM, Least-square mean.

The mean consumption per day of each of two rescue medications [clemastine fumarate (tablet), sodium cromoglycate (eye drop)] was significantly lower in the omalizumab group than in the suplatast tosilate group during the pollen period ($P = 0.009$ and 0.001, respectively), and sodium cromoglycate (nose drop) tended to show a significant difference in consumptions. Naphazoline nitrate (nose drop) was hardly used.

The proportions of days in which any rescue medication was taken were higher in the suplatast tosilate group than in the omalizumab group (e.g. 13.5% and 7.9%, respectively; $P<0.001$, the pollen period).

Serum-free immunoglobulin E levels

In the omalizumab group, serum-free IgE levels decreased markedly, compared with the baseline levels, to below 50 ng/mL at 12 weeks of the treatment period in all patients (range from 6.39 to 46.83 ng/mL). In contrast, there were only two patients whose concentration of serum-free IgE was under 50 ng/mL at 12 weeks of the treatment period in the suplatast tosilate group.

Safety

Treatment with omalizumab was generally well tolerated. The adverse reaction profiles were similar between the study groups (Table 2). Although the overall incidences of injection site reactions were higher in the omalizumab

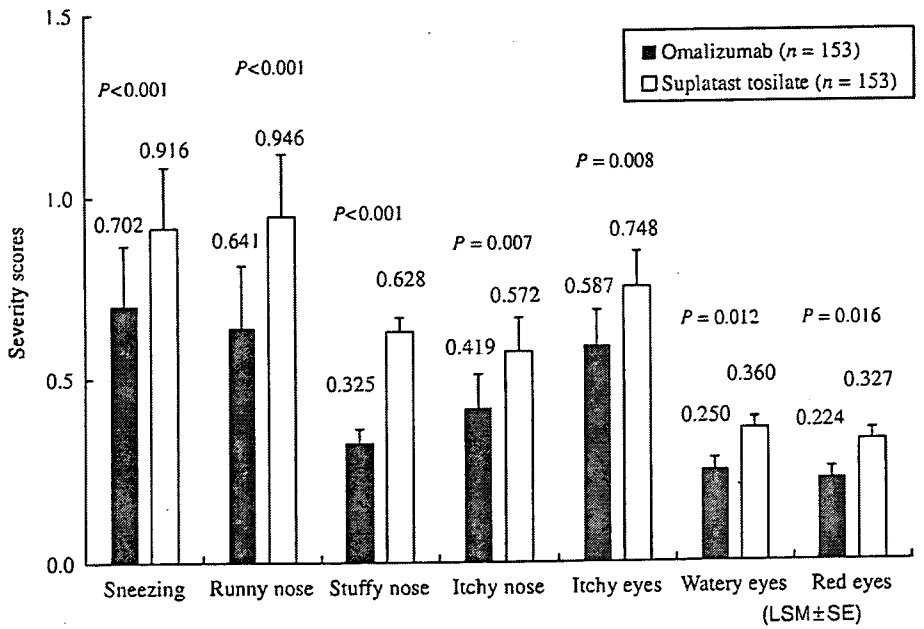

Fig. 4. Effects of omalizumab on each of the mean daily nasal and ocular symptom severity scores [full analysis set (FAS)] during the pollen period. Statistically significant differences were also noted during the treatment and severe pollen periods. LSM, Least-square mean.

Table 2. Drug-related adverse events (≥ 1% in either group)

	Omalizumab ($n = 154$), n (%)	Suplatast tosilate ($n = 153$), n (%)
Total number of patients with drug-related adverse event	45 (29.2)	40 (26.1)
Gastrointestinal disorders	3 (1.9)	7 (4.6)
General disorders and administration site conditions	34 (22.1)	16 (10.5)
Injection site reactions*	32 (20.8)	15 (9.8)
Erythema	12 (7.8)	6 (3.9)
Haemorrhage	13 (8.4)	7 (4.6)
Induration	2 (1.3)	1 (0.7)
Pain	6 (3.9)	4 (2.6)
Pruritus	8 (5.2)	0
Swelling	13 (8.4)	2 (1.3)
Malaise	2 (1.3)	0
Nervous system disorders	2 (1.3)	4 (2.6)
Headache	1 (0.6)	2 (1.3)
Somnolence	1 (0.6)	2 (1.3)
Skin and subcutaneous tissue disorders	3 (1.9)	1 (0.7)
Investigations	9 (5.8)†	13 (8.5)‡

*Injection site reactions in the suplatast tosilate group were caused by administration of placebo of omalizumab.

†ALT↑2 (1.3), ALP↑2 (1.3), glucose urine present 2 (1.3), red blood cells urine positive 2 (1.3).

‡ALT↑3 (2.0), AST↑3 (2.0), γ-GTP↑3 (2.0), white blood cell↑2 (1.3), eosinophil↑2 (1.3), neutrophil↑2 (1.3); ↑, increased; ↓, decreased.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GTP, guanosine triphosphate.

group than in the suplatast tosilate group, all these events were of a mild degree and disappeared without any additional treatment.

One patient in the suplatast tosilate group discontinued treatment because of severe adverse events (otitis media serous and nasopharyngitis) that were not drug related, while none discontinued treatment in the omalizumab group. During the follow-up period, one serious adverse event (ureteric calculus) was reported in one patient in the omalizumab group. However, the investigator considered its causality with the drug to be unrelated. There were no anaphylactic reactions, and no evidence of immune complex disease or clinically important abnormalities in vital signs and laboratory tests were found. No anti-omalizumab antibodies were detected.

Discussion

This is the first study directly comparing the effect of omalizumab on SAR patients with an anti-allergy drug, not placebo. This study revealed that omalizumab was more effective than suplatast tosilate in preventing and controlling rhinoconjunctival symptoms associated with Japanese cedar pollen-induced SAR and in reducing rescue medication use for rhinoconjunctival symptoms. In addition, our results suggest that monotherapy with omalizumab at a 2- or 4-week interval can control both nasal and ocular symptoms, thus simplifying SAR therapy.

Suplatast tosilate is a selective Th2 cytokine inhibitor *in vitro* [18] and is shown to decrease symptoms of AR and bronchial asthma. It decreased symptom scores for puffy nose, rhinorrhoea, and sneezing in patients with perennial nasal allergies [15]. Furthermore, it inhibited the infiltration of $CD4^+$ T cell and eosinophil infiltration, and also decreased the levels of Th2 cytokines (IL-4, IL-5, and IL-13) in human nasal mucosa obtained by nasal brushing [15]. Treatment with suplatast tosilate in steroid-dependent asthma improved lung function and symptoms, and allowed a decrease in the amount of inhaled corticosteroids [14].

In this study, the amount of Japanese cedar pollens in Tokyo was larger than that of Osaka; however, the mean daily nasal symptom medication scores were consistently lower in the omalizumab group than in the suplatast tosilate group in Tokyo and Osaka, respectively. Regardless of the amount of Japanese cedar pollens, omalizumab would be effective against SAR.

The adverse reaction profiles were similar between the study groups. In the omalizumab group, all adverse events, except for one (ureteric calculus), which was not drug related, were mild to moderate in severity. The most frequently reported drug-related adverse events in the omalizumab group were injection site reactions, with a higher incidence than in the suplatast tosilate group; however, all these events were of a mild degree and disappeared without an additional treatment. No clinically important abnormal values in laboratory tests or vital signs were reported; no anti-omalizumab antibodies were detected. Furthermore, no cases of anaphylaxis were reported. Therefore, the safety profile of omalizumab in the treatment of SAR appears to be favourable.

In the omalizumab group, serum-free IgE levels decreased markedly to below 50 ng/mL at 12 weeks of the treatment period in all patients and it was associated with clinical effectiveness. In contrast, there were only two patients whose concentration of serum-free IgE was under 50 ng/mL in the suplatast tosilate group.

Omalizumab has been reported not only to inhibit basophils and mast cells responses but to also have a profound effect on the numbers of inflammatory cells [29], such as eosinophils, T lymphocytes, B lymphocytes, and dendritic cells (DCs) [30].

Suplatast tosilate also has widespread anti-inflammatory effects. This drug selectively inhibits the Th2 cytokine production from T cells and this causes suppression of eosinophlic inflammation and IgE production and also inhibits the differentiation and function of monocyte-derived DCs [31]. In addition, inhibition of thymus- and

activation-regulated chemokine production from human Th2 cells [32], chemical mediator release from mast cells [19], and inhibition of murine mast cell differentiation [33] by suplatast tosilate have been demonstrated.

Although these two drugs have similar effects on inflammatory cells, the direct acting point of each drug is different, IgE for omalizumab and Th2 cytokine for suplatast tosilate, and suppression of free IgE was much stronger in the omalizumab group than the suplatast tosilate group. The result of this study that omalizumab was more effective than suplatast tosilate in the treatment of SAR suggests that IgE is likely more potent than Th2 cytokines whose generation is blocked by IPD as a therapeutic target of SAR.

For moderate to severe SAR, antihistamine drugs or nasal steroids are usually used, but in some cases, it is not sufficient and patient's QOL is impaired. The patients sometimes have to take oral steroids for several weeks. As shown in this study, when we used omalizumab, almost no rescue medication was needed. Although omalizumab is expensive, from the viewpoint of patients' QOL or adherence, there is an advantage to using omalizumab for moderate to severe SAR.

Other studies have shown the efficacy of omalizumab for both SAR and perennial allergic rhinitis (PAR) [34, 35]. Combination therapy with omalizumab and SIT not only reduced acute allergic reactions compared with SIT alone [36] but also enhanced the efficacy of SIT [36, 37]. Furthermore, as The World Health Organization-sponsored AR and its Impact on Asthma workshop report recommended that strategies that combine the treatment of upper and lower airways be used where possible [38], omalizumab has been shown to be effective against patients with moderate-to-severe asthma and concomitant moderate-to-severe PAR [39].

In conclusion, omalizumab was superior over suplatast tosilate in preventing and controlling symptoms and in reducing rescue medication use and was well tolerated in patients with moderate-to-severe Japanese cedar pollen-induced SAR. Therefore, omalizumab represents a new promising treatment for patients with SAR induced by Japanese cedar pollens.

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ORIGINAL ARTICLE

Preliminary Study on Japanese Cedar Pollinosis in an Artificial Exposure Chamber (OHIO Chamber)

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ABSTRACT

Background: A pollen exposure chamber (OHIO Chamber) was built in central Tokyo, Japan, in order to study seasonal allergic rhinitis (SAR). Since satisfactory outcomes were obtained from the controlled pollen exposure at the chamber, we conducted preliminary studies in volunteers with SAR.

Methods: Ten volunteers with SAR sensitive to Japanese cedar (JC) pollen were enrolled in this study. In order to investigate the intranasal and intraocular pollen number, volunteers were initially exposed to a low concentration of JC (2500 grains/m^3) for at most 1 hour in this chamber. Before and after the exposure, nasal cavities and eyes were washed with 100 ml and 25 ml of saline, respectively. Nasal and eye washing solutions were collected and the number of JC pollen was counted.

After 3 hours the volunteers were subsequently exposed to a moderate concentration of JC (4500 grains/m3) for 2 hours. Subjective nasal and ocular symptoms were recorded and the amount of nasal secretion was measured during the allergen exposure periods.

Results: During the initial exposure, all volunteers except one stayed in the chamber for 1 hour without any nasal or ocular symptoms. The number of pollen in the nose and eyes was 249.2 ± 120.9 and 13.6 ± 13.6 grains, respectively.

During the subsequent 2-hour exposure to JC pollen, nasal and ocular symptoms developed gradually in a time dependent manner in all the volunteers except one.

Conclusions: This is the first clinical study using Japanese cedar pollen under well-controlled conditions in the OHIO chamber in which the induction of allergic symptoms was observed. The OHIO chamber will be useful for studying allergic rhinitis in Japan.

KEY WORDS

allergen exposure, allergy symptoms, artificial exposure chamber, intranasal and intraocular pollen count, Japanese cedar pollen

INTRODUCTION

Japanese cedar (JC) pollinosis is a seasonal allergy, which is unique to Japan, and the causative allergen (JC pollen) is dispersed usually between February and April although the pollen count varies every year. Over 16% of the Japanese population suffer from the allergy during this season[1] and an incredible amount of anti-allergy agent is used, resulting in an undermined QOL[2] and decline in labor productivity.[3] This fact indicates that JC pollinosis is a social and economical problem which cannot be ignored.

Allergen exposure tests in natural environments have been conducted as fundamental research on this kind of allergy and also to examine the effectiveness of anti-allergy agents.[4,5] Studies of this sort, however, are greatly influenced by natural factors such as the amount of pollen, the weather, the temperature, or

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the wind velocity. The biggest problem is that the tests can be done only during the pollen season.

Several allergen exposure units have been built in Europe and the US to evaluate the efficacy of drugs and they are operating safely and effectively.[6-8] A predefined amount of pollen can be dispersed under stable conditions in these chambers.

Despite the fact that so many Japanese are allergic to JC pollen, this kind of chamber was not available in Japan before 2004. To meet the increased needs for such facilities, the first pollen exposure units in Japan were developed in Wakayama[9] in the first half of 2005. We built the third allergen exposure chamber, an artificial exposure chamber (AEC; OHIO Chamber), in the center of Tokyo in September, 2005. This chamber not only keeps the temperature and humidity constant, but also automatically cleans and dries the inside of the chamber.

Due to the lack of AECs in Japan, little fundamental data concerning Japanese cedar pollinosis were available up to this point. Since satisfactory outcomes were obtained from the controlled exposure at the OHIO Chamber, we were able to conduct preliminary studies on mildly symptomatic patients, in which we examined the amount of intranasal and intraocular pollen grains and the development of symptoms.

METHODS

SUBJECTS

The subjects of our study were mildly symptomatic adult patients. The inclusion criteria were as follows:

- Subjects must have at least a 2-year history of allergic symptoms during the pollen season, such as sneezing, nasal discharge, nasal obstruction, and itchy eyes.
- Subjects must also have had blood tests within 1.5 years showing positive RAST scores (≥Class 2) for JC pollen and negative RAST scores (≤Class 1) for house dust mite.

The exclusion criteria were as follows:

- Subjects with nasal obstruction attributable to a polyp or deformity of the nose.
- Subjects with acute upper respiratory infection(s) such as acute sinusitis, acute pharyngitis, and acute upper respiratory inflammation.
- Subjects with uncontrolled asthma, diabetes, high blood pressure, or eye diseases (glaucoma/cataract).
- Subjects who used anti-allergy agent(s) within a week before the start of this study.
- Pregnant women or women who trying to become pregnant.

The study was conducted in accordance with GCP Guidelines and the Declaration of Helsinki. The study was conducted on December 23 (2 months ahead of the start of the pollen season) after having been reviewed and approved by the ethics committee of Shinanozaka Clinic. Informed consent was obtained from all the subjects prior to study entry.

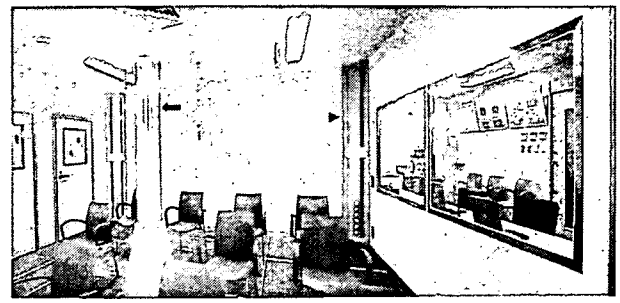
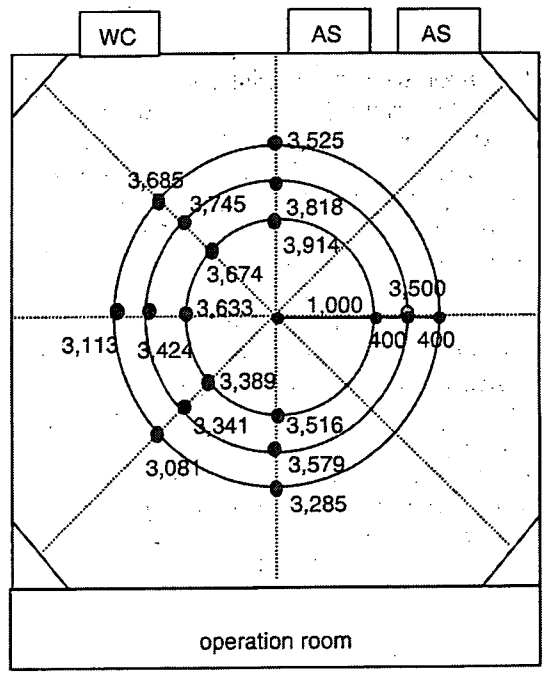


Fig. 1 Appearance of the artificial exposure chamber (OHIO Chamber). Pollen-diffuser in the center (arrow). Blower module in the corner of the room (arrow head)



Target concentration: 3500 grains/m³

WC: toilet AS: air shower

Fig. 2 Spatial concentration distributions of pollen in the OHIO Chamber at a height of 1.15 m at the target concentration of 3500 grains/m³. The average concentration of pollen was 3500 ± 419 grains/m³.

OHIO CHAMBER

The OHIO Chamber was installed in Samoncho Clinic in Yotsuya, the center of Tokyo. Its square measure is 25 m², the height 2.5 m, and the capacity 10 subjects (Fig. 1).

Compressed air transfers pollen grains from an outside dust feeder into the operation room where it is mixed with conditioned air inside the pollen diffuser after which the mixed air jets out upward from the diffuser. The diffuser and the blower modules in

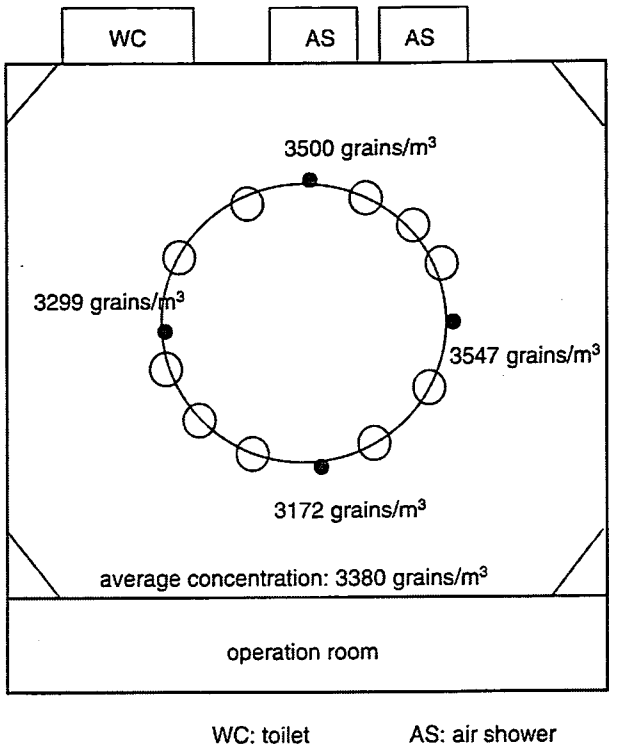


Fig. 3 The pollen concentration at a height of 1.15 m at the four points (●) when the ten volunteers (○) were present in the OHIO chamber. The average concentration was 3380 grains/m³ and uniform distribution of pollen was achieved.

four corners help the pollen grains get distributed evenly. The concentration of pollen grains in the room is measured by a particle counter equipped with a semiconductor laser (KC-20; Rion Co, Tokyo, Japan). This counter can absorb up to 30 L of air per minute and detects particles sized 10–100 μm.

Spatial distributions of pollen in the unmanned and manned chamber at a height of 1.15 m were measured. The pollen concentration distribution was within a range of ± 12% of the target value of 3500 grains/m³ in the unmanned chamber (Fig. 2). The pollen number at each of four points and the average pollen concentration are shown in Figure 3 when 10 subjects were present in the chamber.

The pollen count in this room is stable between 2500 and 120000 grains/m³ (data not shown). Also, the temperature inside the chamber was set at 22 ± 0.2℃ and the humidity was set about 20–55%. The pollen count, temperature, and humidity were monitored every 3 minutes and recorded accordingly.

Before entering the room, subjects were instructed to wear protection gowns so that the pollen grains were not attached to their hair or clothes. When entering or exiting, they also went through an air shower so as to avoid pollen grain contamination outside of the room. During the test, subjects were assigned to sit on chairs in designated areas of the chamber and in order to ensure the subjects' safety, their behavior was observed closely by staff and physicians situated in the operating room.

Table 1 Backgrounds of the subjects.

Subject No.	Sex	Age	RAST score
1	female	37	3
2	female	35	5
3	male	34	4
4	male	45	3
5	male	36	2
6	female	34	4
7	male	41	2
8	female	32	2
9	female	43	3
10	male	48	2

Five men and five women with mild symptoms were enrolled in this study.

This table shows their age and antibody titers (RAST scores) against cedar pollen.

STUDY DESIGN

This study consisted of two parts. In the first part, subjects were exposed to low-concentrated JC pollen (2500 grains/m³) in the chamber for up to an hour. They were allowed to exit the room if allergic symptoms developed (either in the nose or in the eyes). Immediately after exiting the room, all the subjects went through an intranasal and intraocular irrigation process using a syringe (Nasaline®; Entpro, Sweden), washing the nasal cavities with 100 ml of saline and the eyes with 25 ml of saline. Then the washing solution from each subject was collected to investigate the number of pollen grains in it.

The subjects were subsequently exposed to moderate-concentrated JC pollen (4500 grains/m³) for 2 hours. Each subject recorded their symptoms (such as sneezing, nasal discharge, nasal obstruction, itchy nose, itchy eyes, and tears) into computers at certain points (after 15, 30, 60, 90, and 120 minutes from the start of exposure).

The symptoms were classified as follows: 1. none, 2. mild, 3. moderate, 4. severe, and 5. very severe. We collected tissue papers with which subjects had blown their noses and measured them by weight. The weight difference between tissue papers before and after use was considered to be the weight of nasal secretion.

The amount of intranasal and intraocular pollen was determined by the following methods. We added 1.25 *g* of Safranine-O (Wako Jyunnyaku Kogyo Inc. Tokyo) to 50 ml of saline and 50 ml of ethanol to create stain solutions, and 5 ml of this stain solution was added to the nasal or ocular lavage fluid. Furthermore, we added 20 drops of Proteinase K (Dako Cy-

Table 2 The number of intraocular and intranasal pollen grains in the first part of the study.

Subject No.#	1	2	3 *	4	5	6	7	8	9	10	Mean ± SD
Intraocular pollen	2	13	3	6	15	20	12	6	49	10	13.6 ± 13.6 (grains)
Intranasal pollen	175	175	303	160	198	522	90	260	281	328	249.2 ± 120.9 (grains)

One subject (*) exited the chamber 10 min earlier since she was about to sneeze.
The remaining subjects were able to stay for an hour without developing symptoms.
As to the subject numbers, see Table 1

Table 3 The number of subjects who showed nose or eye symptoms during 2-hour allergen exposure.

	15	30	60	90	120	(min)
Rhinorrhea	1	3	3	6	8	
Sneezing	0	1	1	4	4	
Nasal obstruction	1	4	6	6	7	
Nasal itching	2	4	4	7	8	
Eye itching	2	5	6	7	6	
Watery eyes	0	2	3	3	3	
Nasal secretion (g/hr)	←	0.23 ± 0.39	→ ←	0.73 ± 0.83	→	

There were increases in the number of subjects who developed nasal and ocular symptoms in a time dependent manner. Six subjects developed nasal obstruction after 60 minutes of exposure, of which 3 subjects marked their symptoms as moderate while 1 subject marked them as severe. Although 8 subjects developed rhinorrhea and nasal itching after 2 hours of exposure to the allergen, only 4 subjects developed sneezing and their symptoms were mild. We measured the amount of nasal secretion from 3 subjects in the first half of the study and from 7 in the latter half of the study. Ocular symptoms also developed as time went by. During the study period, 1 subject showed neither nasal nor ocular symptoms.

tomation Inc, Tokyo, Japan) to nasal lavage fluid in order to reduce its viscosity. After shaking the nasal or ocular lavage fluid for 5 minutes at room temperature, it was put into a suction filtration device using 0.5 μm filter papers (Advantee Cellulose Nitrate, Toyo Roshi Inc, Tokyo, Japan). Hereafter, the leftover solution was washed once more with saline and the solution was put into a suction filtration device to keep any single grain from being left behind. In this way, all the filter papers were examined under a light microscope (×100) and the pollen count was recorded.

RESULTS

The subjects consisted of 5 men and 5 women with mild symptoms. Their ages ranged from 32 to 48 years (the average age was 38.5 ± 5.4). Background factors of the subjects are shown in Table 1.

In the first part of this study, the temperature, the humidity, and the concentration of pollen grains in the room were kept within the targeted values. That is, the average number of pollen grains was 2572.8 ± 264.5 grains /m^3, the average temperature 22.1 ± 0.14℃, and the average humidity 44.7 ± 0.48% (Fig. 4). Intranasal pollen counts in the subjects ranged from 90 to 522 and intraocular grains ranged from 2 to 49. No relation was seen between the positions of the subjects within the chamber and the numbers of pollen detected in the nose and eyes. Even though 1 subject had to leave the chamber 10 minutes earlier than the scheduled time because of symptom development, the rest of the subjects were able to stay in the room for an hour without developing symptoms. The average number of intranasal pollen grains and intraocular grains was 249.2 ± 120.9 and 13.6 ± 13.6, respectively (Table 2).

In the second part of this study, the temperature, the humidity, and the concentration of pollen grains inside the chamber were within targeted values: the average number of pollen grains was 4367 ± 207 grains/m^3, the temperature 22.2 ± 0.35℃, and the humidity 44.8 ± 0.65% (Fig. 5). As time went by, more and more subjects started developing nasal symptoms such as nasal discharge, sneezing, nasal obstruction, and itchy nose. Only 3 subjects showed nasal discharge 60 minutes after the start of exposure, but 6 subjects after 90 minutes and 8 subjects after 120 minutes. Likewise, the number of subjects who developed nasal obstruction increased after 60 minutes of exposure, of which 3 subjects marked their symptoms as moderate while 1 subject marked severe. Although 8 subjects showed nasal itching after 120 minutes, only 4 subjects developed sneezing during exposure and their symptoms were mild. Three subjects blew their nose within 1 hour of the first half of the study, and 7 in the latter half. The amount of nasal secretion in the first half and the latter half of the study was 0.23 ± 0.39 g/hour and 0.73 ± 0.83 g/