厚生労働科学研究費補助金

免疫アレルギー疾患等予防・治療研究事業

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

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

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

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研究要旨
スギ花粉症の問題点はこれまでの検討から有病率が高く、QOL が阻害されることが明らかになった。このためセルフケアと根治的治療法の開発の研究を行った。セルフケアに重要なリアルタイムモニターであるが、補正値によりより精度を増すこと、近い部位での測定は非常に相関性が良いことが示された。またスギ花粉症時期では呼吸機能は減弱し、呼気中 NO は増加した。スギ花粉症の責任遺伝子の検討では ORMDL3 において rs7216389 のアレルで花粉症患者に相関を示した。根治的治療法のアレルゲン免疫療法は皮下注射と舌下投与で行われ、スギ花粉アレルゲンでの免疫療法ではヒノキに対する効果が弱いことが、治療後の PBMC のヒノキアレルゲン Chao1 での反応で明らかになった。小児での舌下免疫療法は高い効果を示したが、少量飛散年では薬物療法と差が小さかった。また継年的な舌下免疫療法は単年の効果を増強させた。ペプチド免疫療法はその効果が認められたが、細かい検討は残された。このペプチドを舌下で入れた場合にはその効果は血液学的に証明されたが、症状の抑制は認められなかった。このペプチド免疫療法ではさらにアジュバントの効果とも相乗効果を検討しなければならない。

A.　研究目的：
スギ花粉症の問題点はこれまでの検討から、ＱＯＬの悪化する事、小児での発症が多くなってきたことであり、いずれも医療費の増加につながる。しかし正確なリアルタイムでの花粉飛散がセルフケアを向上させ、医療費の低下につながることが期待される。リアルタイムモニターでの問題点を解決し、今後患者が使用しやすい情報発信の方法

が望まれる。また東京以外でのこれらの検討は少なく、地方都市での精度などの確認も必要である。花粉症患者の特徴や喘息との関連性の問題などは実際の QOL などとも直接関連する事項であり、花粉症の臨床研究においては重要なものである。さらに新しい治療法の検討では免疫療法におけるメカニズムの解明から生まれるものもあり、サイトカイン、制御性T細胞、スギ特異的T細胞クローンなどより詳細な検討が必要である。舌下免疫療法では成人、小児での検討や、抗原をペプチドに置き換えた検討など今後の新しい治療法の開発の礎となるよう検討を行いたい。

B. 方法：

① リアルタイムモニターの精度改善の研究（岡本、太田）

花粉誤認率から補正マトリックスを作成し、この補正式を利用して自動花粉測定器による花粉数とダーラム式花粉測定結果について検討した。山形市、福井市、甲府市にてリアルタイムモニター(KH300)およびダーラム型花粉捕集器を用い測定したスギ花粉飛散数の相関を検討した。

② 重症スギ花粉症患者の鼻粘膜組織検討(太田)

また、重症スギ花粉症患者の鼻粘膜におけるステロイド受容体（αおよびβ受容体)、ペリオスチンおよびペンドリンの発現を免疫組織学的に検討した。

③ スギ花粉症患者の呼気中 NO 濃度の検討（永田）

スギ花粉症症例 7 例で、全例、非喘息症例、非喫煙者とした。スギ花粉飛散前と飛散時期に、症状を評価し、呼気 NO ならびに呼吸機能検査を施行した。鼻症状の重症度評価は、鼻アレルギー診療ガイドラインに準拠しておこなった呼気NO濃度は、携帯用 NO 測定機器 NIOX MINO で測定した。

④ 花粉症患者の候補遺伝子の検討（藤枝）

ORMDL3 遺伝子に関して、スギ花粉症患者、非アレルギー症例によって SNP 解析を行いリスクアレルを同定した。①同定したリスクアレルを B 細胞に遺伝子導入後 ORMDL3 の蛋白発現、②ORMDL3 の発現細胞の同定、③ORMDL3 の発現増強の刺激、④アレル別細胞でのサイトカイン産生の違い、⑤アレル別細胞でのスフィンゴシン 1 リン酸の産生。鼻粘膜で発現する遺伝子の網羅的解析を検討した。遺伝子の鼻粘膜での産生細胞を免疫組織化学で検討した。

⑤ 免疫療法の効果発現機序の研究（岡野、湯田）

免疫療法施行および非施行のスギ・ヒノキ花粉症患者より PBMC を採取し、Cry j 2 あるいは Cha o 2 にて 72 時間培養後、上清中の IL-5 を測定した。小児舌下免疫例の末梢血から PBMC を精製し、Cryj1 and Cryj2 で 12 時間培養し、IL-10 産生 CD4T 細胞と IL-10 産生 CD14 陽性単球の割合を測定した。また、血清 IgG4,IL-17A, IL-31, IL-33 を ELISA で測定した。

⑥ 舌下免疫療法の方法論の研究（湯田）

初期療法(薬物療法)・舌下免疫療法・皮下免疫療法の３群を設定し、少量飛散年(2010 年)・中等度飛散年(2008 年)と大量飛散年(2009 年)で症状スコアと QOL を検討した。また 60 例の小児舌下免疫群と 23 例の薬物療法群で、臨床症状と薬物使用量の比較を行った。

⑦ 舌下ペプチド免疫療法の実際（後藤、大久保）

スギ花粉症患者に、スギ花粉ペプチド CS-712 1 回 10 mg を 1 週間隔又は 2 週間隔にて 24 週間舌下保持後嚥下投与するプラセボ対照無作為化二重盲検試験を実施した。また、翌年のスギ花粉飛散期に追跡調査を行い、効果の持続性を検討した。

⑧ スギ花粉ペプチドに関する T 細胞の反応性（岡本）

スギ花粉の主要抗原の合成ペプチド、またダニ主要抗原の合成ペプチドでスギ花粉症患者、ダニ通年性アレルギー性鼻炎患者末梢血中の抗原特異的T細胞のクローンサイズを1月と5月で比較した。

⑨ 制御性 T 細胞の検討（増山）

スギ花粉症患者および健常者の末梢血よりリンパ球から CD4+T 細胞（nTreg 含有群）と CD4+CD25-T 細胞（nTreg 除去群）に分けた。これらをスギ花粉抗原 Cry j 1 および HLA-DP5 拘束性 Cry j 1 関連ペプチド（p61-75）で刺激し培養した。抗原特異的増殖能とサイトカイン産生を測定し、比較検討した。また、Cry j 1 特異的 IL-10 産生 Treg の検出を行った。

C. 結果：

①成田市でのダーラム法による花粉測定数（1 ㎠/day）は 3137 個であったが、神栄リアルタイムモニター（S-RM）の測定値（1 ㎥/day）と日別相関係数は 0.90、補正値は 0.92 であった。一方、千葉市での 2 月 18 日から 3 月 30 日のダーラム法による積算値は 2132 で S-RM との相関は 0.77, 補正値では 0.84 であった。山形市、福井市、甲府市のスギ花粉飛散数飛散状況は同一市内の複数の測定施設の値は、KH-3000 とらーラムの値はほぼ連動しており一致していた。

②グルココルチコイドβ受容体の発現が増強しており、ステロイド耐性状態であることが示唆された。ペンドリンおよびペリオスチンの発現も増加しており、粘液分泌過多とリモデリングの変化が生じていると考えられた。

③各症状、鼻内所見はスギ花粉飛散期に症状は悪

化した($p < 0.05$)。呼気 NO 濃度は、飛散期、非飛散期で有意差を認め、飛散期で上昇していた($p < 0.05$)。各症状、鼻内所見と NO との相関は認められなかった。スギ花粉飛散時期の前後において、VC，%VC，FEV1%，及びピークフロー（PEF）は有意な変動は認められなかった。

④ORMDL3 における 13SNP 解析にて 9 SNP において有意な相関を認めた。SNP（rs7216389）においても高い有意な相関を示した。リスクアレルは TT であり、EB ウイルスにより不活化した B 細胞株に遺伝子導入するとリスクアレルで ORMDL3 発現が有意に上昇した。ORMDL3 発現は、鼻粘膜上皮、線維芽細胞で認め、それぞれ poly-IC 刺激で発現が亢進した。リスクアレル TT で IL-10, IL-17 の産生が有意に高かった。スフィンゴシン 1 リン酸もリスクアレル TT で高値であった。鼻粘膜で Intelectin-1 とその他 17 の遺伝子が有意に変動した。Intelection-1 は鼻粘膜上皮で産生されることが同定でき、スギ花粉発症直前に関与する可能性が示唆された。Intelection-1 は、IL-4、IL-13 刺激によって発現が亢進した。

⑤免疫療法施行群における Cry j 2 に対する IL-5 産生は有意に抑制されていた。Cha o 2 に対する IL-5 産生は 2 群間で有意な差を認めなかった。免疫療法施行群では Cry j 2 と Cha o 2 に対する IL-5 産生量は有意な相関を示さなかった。舌下免疫療法で IL-10 産生 T 細胞と CD14 陽性単球の経時的増加があった。IgG4 は経時的な増加に乏しかったが、効果良好群で IgG4 の増加傾向があった。小児の IL-31 は高かった。

⑥日の症状スコアおよび QOL ともに皮下免疫療法の効果が最も良く、次いで舌下免疫療法、初期療法の順であった 2010 年は少量飛散年であったため小児ではどの治療法も効果的で、舌下免疫療法と薬物療法で臨床症状に差はなかった。しかし、舌下免疫療法の薬物スコアは有意に小さく、舌下免疫療法の効果がうかがわれた。

⑦Symptom-Medication Score（以下 SMS）は CS-712 各群のいずれもプラセボ群と比較してスギ花粉症症状を抑制させる傾向は認められず、2007 年の SMS の推移も同様だった。本格飛散時の SMS 1 日平均スコアは、プラセボ群、CS-712 2 週間隔群及び 1 週間隔群でそれぞれ 4.30、5.91 及び 3.89 であり、2 週間隔群はプラセボ群に比較して有意に高値であった。翌年も 2 週間隔群はプラセボ群より有意に高値であった。

⑧合成ペプチドを用いた ELISPOT 法によるスギ花粉症患者末梢血リンパ球のスギ花粉特異的 Th2 メモリークローンサイズは 1 月に比較して 5 月には平均 1.7 倍の増加がみられ、スギ花粉特異的 IgE 値と相関がみられた。ダニアレルギー性鼻炎患者では全例に Der f 特異的 Th2 細胞クローンが確認されたが、1 月と 5 月でそのサイズに変化は見られなかった。

⑨細胞増殖能には差は認めなかった。IFN-・産生に関しては Cry j 1 刺激において、nTreg 除去によりその産生は有意に増加した。一方、IL-5 産生に関しては、nTreg 除去の影響は認めなかった。さらに、IL-10 の産生は、Cry j 1、ペプチド刺激において nTreg の除去により有意に低下した。スギ花粉症患者において IL-10 産生細胞のスポットを確認できた。

D. 考察：

現在のスギ花粉症における問題点として、その有病率の高さがあげられる。このため、セルフケアと治癒を望める治療法の確立が医療費の問題点からも重要な国家課題となる。国民への正しい情報がセルフケアを高める上でも重要であることを述べてきたが、現状で報告されるリアルタイムモニターでは十分な情報が発信されていない。これは補正しないとダーラムで報告される花粉飛散実数値との差が生じるからであり、今後の問題点と考えられる。

実際のスギ花粉症患者では下気道の症状を発現する可能性がその呼気中ＮＯからも考えられ、喘息との関連性が組織中の特徴からも考えられた。この様な花粉症を治癒させるには免疫療法は重要であり、舌下免疫療法の効果が成人でも小児でも検証され、その効果がサイトカインや制御性Ｔ細胞から分かるような結果が得られた。実際のペプチド免疫療法は現状での方法論では臨床応用にはやはりアジュバントなど、さらなる工夫が必要であると考えられる。基礎的な研究からは制御性Ｔ細胞や抗原特異的Ｔ細胞クローンサイズがスギ花粉症の治療バイオマーカーになる可能性が示唆され、スギ花粉症の治癒に向けた検討が明らかになったものと考えられる。

E. 結論

タイムモニターの精度には限界があるが、これをうまく生かしてセルフケアにつなげることが患者の下気道症状への影響や喘息のような慢性変化への移行を防ぐことになると考えられる。また免疫療法では舌下、皮下とも高い効果を示し、そのメカニズムが抗原特異的Ｔ細胞のサイトカイン産生の変化、制御性Ｔ細胞の増加などによる事が示された。しかしペプチドは現状のままでは舌下では十分な効果は検証できなかった。バイオマーカーの検討では制御性Ｔ細胞や抗原特異的Ｔ細胞クローンサイズがスギ花粉症の治療バイオマーカーになる可能性が明らかになった。今後、新しい免疫

療法の検討にはこれら基礎と臨床の検討を元に行ってゆきたい。

F. 健康危険情報

特になし

G. 研究発表

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2．学会発表

H. 知的財産権の出願・登録状況

1．特許申請

該当項目なし

2．実用新案登録

該当項目なし

3．その他

該当項目なし

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REVIEW

Prevalence of Japanese cedar pollinosis in Tokyo: a survey conducted by the Tokyo Metropolitan Government

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Conflicts of interest: The authors have declared no conflicts of interest.

Summary

In 2006, a survey was conducted to estimate the prevalence of Japanese cedar pollinosis in three target areas in Tokyo, namely Akiruno-shi, Chofu-shi, and Ota-ku; this survey was similar to two surveys conducted previously, in 1983–1987 (first survey) and 1996 (second survey). In the most recent survey, the overall prevalence of Japanese cedar pollinosis in Tokyo, except the islands of Tokyo, was estimated as 28.2%. This prevalence rate exceeds that estimated by the first and second surveys by 18.2 and 8.8 percentage points, respectively. The prevalence of Japanese cedar pollinosis in the three survey target areas increased by 2.3–10.8 percentage points vs. the rates obtained in the second survey. Furthermore, differences among the prevalence rates in the three areas decreased. Compared with the results obtained in the second survey, increases in the prevalence rate were noted in all age groups other than in people aged 30–44 years. In particular, the prevalence rate in children aged 0–14 years increased markedly, showing a threefold increase. The prevalence rate exceeded 30% in all age groups between 15 and 59 years.

Keywords epidemiological survey, Japanese cedar pollinosis, prevalence, Tokyo Metropolitan Government

Introduction

The Tokyo Metropolitan Government has conducted two previous surveys designed to investigate the epidemiology of pollinosis among its citizens. In the first survey conducted during the period 1983–1987, the proportion of Tokyo residents with Japanese cedar pollinosis was found to be approximately 1 in 10 [1, 2], whereas in the second survey conducted in 1996 the proportion was about 1 in 5 [3, 4]. Thus, these surveys revealed that the prevalence of Japanese cedar pollinosis increased twofold over the 10-year interim.

Ten years after the second survey, with airborne pollen counts tending to increase, the Tokyo Metropolitan Government conducted a third survey of people affected by pollinosis. This study, conducted in 2006, attempted to identify the disease prevalence and circumstances of pollinosis patients by age and area and compared the survey results with those of the previous two surveys.

In this article, we present an outline of the latest survey results [5] and discuss our findings in the context of the related literature.

Survey populations and methods

The survey populations and methods were similar to those of the previous two surveys [1, 3]. As in the previous two surveys, the present survey was conducted in residents of three Tokyo areas, namely Akiruno-shi, Chofu-shi, and Ota-ku, as shown in Fig. 1. A questionnaire was sent to the residents selected by a systematic sampling from the residents' register of each area. As in the previous two surveys, this survey was conducted principally by a self-administered data collection method; participants were given the option of returning their completed questionnaire by mail.

The questionnaire survey period was from October to November 2006.

Fig. 1. Areas surveyed for the prevalence rate of pollinosis in Tokyo. The Tokyo Metropolitan Prefecture comprises three administrative subdivisions as follows: districts (yellow); cities (red); and 23 wards (blue). For the present survey, one representative area was selected from each of these three entities (Akiruno-shi, Chofu-shi, and Ota-ku, respectively). Tokyo outlying islands were not included in this survey.

Table 1. Requirements for 'suspected pollinosis' in questionnaire respondents*

Question	Response
Q1: Months when you experience pollinosis symptoms	Include February–May and July–October
Q2: No. sneezing fits daily	Either 5–9 or > 10
Q3: No. nose-blowing episodes daily	Either 5–9 or > 10
Q4: Nasal obstruction/hours of mouth breathing each day	Either very severe/many hours or severe/intermittent
Q5: Do you experience itchy eyes?	Yes

*Respondents providing answers shown to question 1 in addition to any of questions 2–5 were suspected of having pollinosis and invited to undergo physical examination.

Of valid respondents to the questionnaire, those who fulfilled the requirements set out in Table 1 during the pollen dispersal seasons of Japanese cedar, cypress, orchard grass, and ragweed (February to May, July to October) were assessed as having 'suspected pollinosis' and invited to undergo physical examinations by specialists (otorhinolaryngologists and ophthalmologists) and a serum-specific IgE antibody test (for Japanese cedar, cypress, orchard grass, and ragweed pollens and *Dermatophagoides pteronyssinus*) at three medical centres in the Tokyo area.

Based on the physical examination results, a diagnosis of Japanese cedar pollinosis was confirmed in people who tested positive for a specific IgE antibody (class ≥ 2 in capRAST) to Japanese cedar pollen accompanied by pollinosis symptoms or the status of being on drugs for pollinosis on the day of physical examinations. The prevalence rate in each survey target area was standardized using the 'population by age' as recorded in the residents' register. The results were then extrapolated in order to estimate the prevalence rate for the entire Tokyo Metropolis.

Results of the questionnaire survey

The questionnaire survey was performed in 1200 residents of each survey target area, making a total sample population of 3600 people. The sampling rate in the three areas combined was 2.3% of residents.

Valid responses for the questionnaire were obtained from 2012 people, with a mean recovery rate of 58.0%.

Of the 2012 responders, 792 people satisfied the criteria for being suspected of having pollinosis. Accordingly, the proportion of people invited to undergo physical examinations in Akiruno-shi, Chofu-shi, and Ota-ku was 40.9%, 40.0%, and 37.1%, respectively (overall mean, 39.5%).

Physical examination in people with suspected pollinosis

In all, 281 of the 792 people invited to undergo physical examination underwent the examination. The proportion of invited subjects who underwent physical examinations in Akiruno-shi, Chofu-shi, and Ota-ku was 39.4%, 34.5%, and 30.8%, respectively (overall, 35.4%). Among the subjects examined, the proportion receiving a positive diagnosis of Japanese cedar pollinosis in the three target areas were 65.6%, 67.5%, and 76.7% (overall, 69.0%).

Prevalence of Japanese cedar pollinosis by age and area

The standardized estimated prevalence rate for all age groups in Akiruno-shi, Chofu-shi, and Ota-ku was 28.0%, 27.1%, and 28.5%, respectively.

Standardized estimated prevalence rates in all age groups in each survey target area are shown along with the findings of the previous two surveys in Fig. 2. Average pollen count (Durham type) at each site during the survey

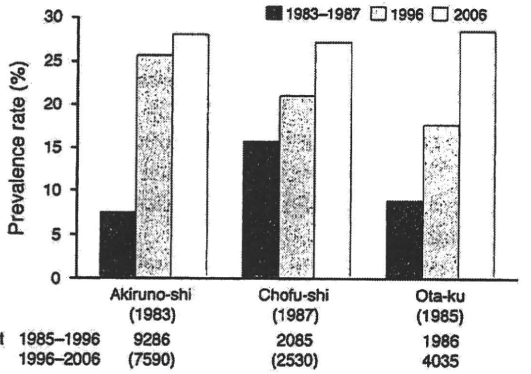

Fig. 2. Standardized estimated prevalence rate of Japanese cedar pollinosis by target area in three surveys conducted in 1983–1987, 1996, and 2006.

years is indicated at the bottom of the figure; numbers in parentheses are believed to be 10–20% lower than actual values due to missing historical data. Not only did the prevalence rate increase in all three areas according to each successive survey but also differences in the prevalence rate among the three survey areas declined over time. In Ota-ku, in particular, the average pollen count increased twofold from 1986 grains/cm^2 in the second survey to 4035 grains/cm^2 in the third survey, and this area showed a marked increase in the proportion of inhabitants with pollinosis in the interim.

Figure 3 displays the estimated prevalence rate of pollinosis in people stratified by age in the three target areas in each successive survey. In the second survey compared with the first survey, the prevalence rate increased in all age groups, and in both these surveys the distribution of the prevalence rate showed a peak in people aged 30–44 years. The third survey on the other hand revealed increased prevalence rates vs. the second survey in all age groups except in those aged 30–44 years. In particular, the prevalence in children aged 0–14 years increased markedly, showing a threefold increase.

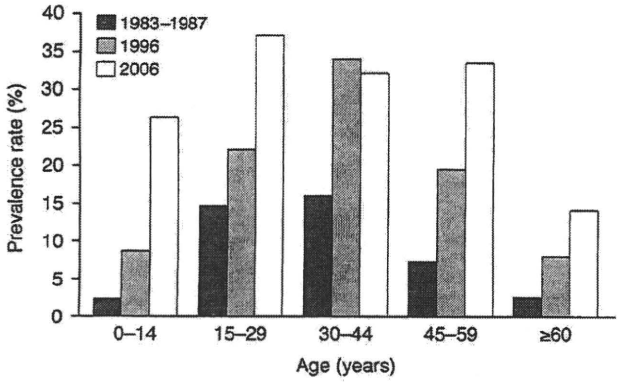

Fig. 3. Estimated prevalence rate of Japanese cedar pollinosis by age in three target areas in 1983–1987, 1996, and 2006.

Estimated prevalence of Japanese cedar pollinosis in Tokyo

Changes in prevalence rate of pollinosis in the three surveys and average Japanese cedar and cypress pollen counts in Tokyo during the survey periods are shown in Fig. 4. These values are similar to and thereby confirm results obtained from nationwide questionnaire surveys [6–9].

Discussion

The present survey suggests that approximately one in every 3.5 residents of Tokyo has Japanese cedar pollinosis. Over the past 20 years, the prevalence rate has increased by about 1 percentage point/year on average, with increasing trends of pollen counts over the time period. A nationwide survey conducted by Baba and colleagues [8, 9] similarly showed an increase of about 10% in the prevalence of Japanese cedar pollinosis during the 10-year period from 1998 to 2008. This increase is more marked than that of allergic rhinitis due to other allergens than Japanese cedar pollen. The average pollen count during the 10-year period from the second to the third survey was 5114 grains/cm^2, which is approximately twofold higher than that (2282 grains/cm^2) obtained during the interim between the first and second surveys. In particular, the second survey showed a marked increase in the prevalence rate in Akiruno-shi, where pollen counts were extremely high after the first survey. In addition, a high percent increase in prevalence was also observed in Ota-ku, where pollen counts increased twofold from the second to the third survey. These findings suggest that the increased prevalence rates are directly due to the increasing pollen counts in Tokyo.

These three survey results do not indicate how long the trend of increasing prevalence rates will last. Comparison between the second and third surveys by area shows a slow down of the increase in prevalence in Akiruno-shi, where pollen counts have been high. In addition, comparison of the three surveys by age group shows no increase in

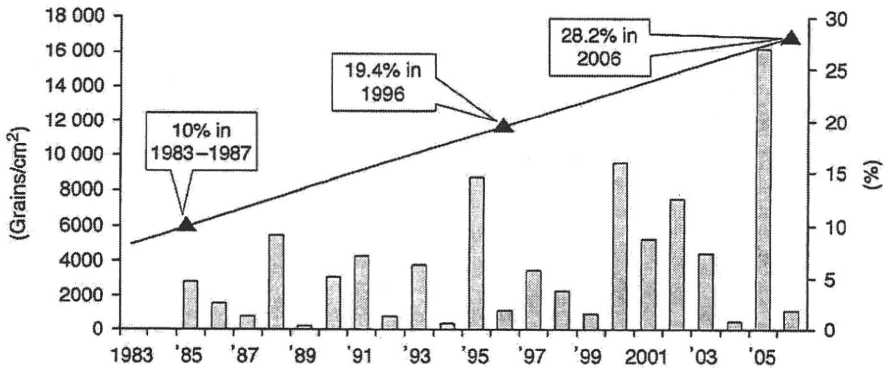

Fig. 4. Time-course of prevalence rate of pollinosis according to three successive surveys and average Japanese cedar and cypress pollen counts in Tokyo during the survey periods.

prevalence in people aged 30–44 years – the highest affected age group in the first and second surveys. These findings suggest the possibility that the trend of increase in prevalence may slow down in future. On the other hand, however, with rising pollen counts reported in many areas and prevalence rates of pollinosis noted as >40% in one nationwide survey [8, 9] it appears necessary to remain vigilant and continue conducting regular surveys to identify trends in the prevalence of this disease in future.

Of particular concern is the finding of markedly increased prevalence of pollinosis in young people aged ≤ 15 years, in concert with some reports [8–11] that are pointing to a lower age shift of Japanese cedar pollinosis. This finding should be monitored carefully.

Acknowledgements

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Original article

Olopatadine hydrochloride in children: efficacy and safety for perennial allergic rhinitis

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Key words:
Antihistamine – Children – Double-blind study – Olopatadine – Perennial allergic rhinitis – Placebo

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Abstract

Objective:
The efficacy of antihistamines in perennial allergic rhinitis in children has been evaluated in studies using active comparators, whereas placebo-controlled studies are very few. A randomized, multicenter, double-blind, parallel-group clinical study was carried out to evaluate the dose–response relationship and superiority of olopatadine hydrochloride over placebo in children aged 7 to 16 years with perennial allergic rhinitis.

Methods:
Subjects received twice daily treatment for two weeks with either olopatadine 2.5 mg, 5 mg or placebo after a one-week observation period. Efficacy was assessed based on the diary card score the subject (or guardian) recorded.

Results:
Of the 302 subjects randomized, two were excluded from analysis: one did not receive treatment; the other was not monitored for efficacy parameters. The remaining 300 subjects (97 in the placebo group, 103 in the olopatadine 2.5-mg group and 100 in the olopatadine 5-mg group) constituted the full analysis set (FAS) for the efficacy analysis. As a primary endpoint, the total three nasal symptom score (for sneezing, rhinorrhea and nasal congestion) at final assessment was compared with baseline or the score obtained in the observation period. The change from baseline was then tested using analysis of covariance (ANCOVA) with the baseline score as covariate. Williams' test was applied to the least squares means estimated from this ANCOVA model for each treatment group, resulting in showing the monotonicity Williams' test assumed. The total three nasal symptom score significantly improved in the 5-mg group compared with the placebo group ($p = 0.019$). In contrast, the 2.5-mg group did not differ statistically from the placebo group. Adverse events occurred in 33.7% (33/98 subjects) in the placebo group, 35.9% (37/103 subjects) in the 2.5-mg group and 35.0% (35/100 subjects) in the 5-mg group. There were no serious or severe adverse events.

Conclusions:
Olopatadine hydrochloride 5 mg twice daily is an effective and safe treatment for perennial allergic rhinitis in children.

Introduction

Allergic rhinitis, the prevalence of which is increasing worldwide, is known to affect school performance and work productivity and sometimes to impair sleep[1]. It is a common pediatric disease that induces or aggravates asthma, sinusitis, otitis media and other diseases[2]. Treating children with allergic rhinitis is all the more difficult because they may not accurately describe their symptoms[2,3].

Most cases of allergic rhinitis in Japanese children are perennial. Diagnosis and medical treatment of pediatric allergic rhinitis are made according to the guideline provided for adults. Histamine plays an important role in producing nasal symptoms including sneezing and rhinorrhea, and second-generation

antihistamines are commonly used for the relief of these symptoms. The need for antihistamines is growing in children as well as in adults.

Olopatadine hydrochloride, synthesized by Kyowa Hakko Kogyo Co., Ltd (currently Kyowa Hakko Kirin Co., Ltd), is an antiallergic that acts primarily against the histamine H_1 receptor, inhibits release of mediators such as thromboxanes and leukotrienes and exhibits inhibitory effect on the release of tachykinins known to contribute to exacerbation of allergic inflammation[4]. Its oral preparation has been approved for adult allergic rhinitis, urticaria and pruritic skin diseases first in Japan, while ophthalmic and nasal preparations have been developed mainly in the USA. The efficacy and safety of olopatadine are now acknowledged worldwide[5–9].

With an aim to obtain approval for pediatric use of olopatadine hydrochloride in Japan, a randomized, multicenter, double-blind, parallel-group clinical study was carried out to evaluate the superiority over placebo and safety of oral olopatadine in children aged 7 to 16 years with perennial allergic rhinitis. Subjects received twice daily treatment for two weeks with either olopatadine 2.5 mg, 5 mg or placebo. Assessment was based on the diary card score the subject (or guardian) recorded concerning his/her nasal allergy symptoms.

The study was conducted at 31 sites in Japan between July 2005 and March 2006 in accordance with the principles described in the Declaration of Helsinki, Good Clinical Practice (GCP) and the protocol that had been approved by each institutional review board.

Methods

Study design

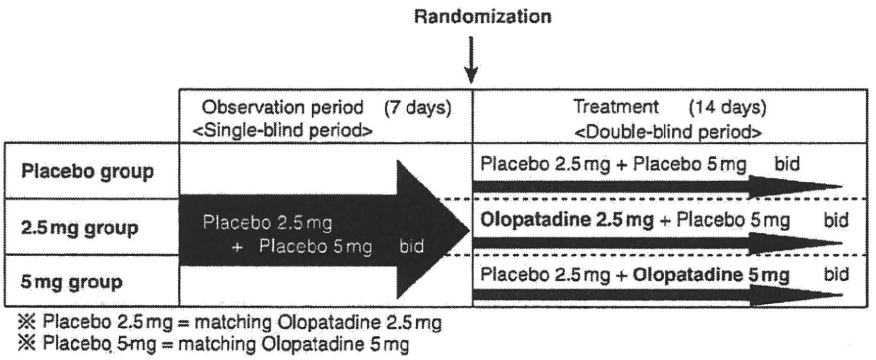
The study period was three weeks, consisting of a one-week observation period (single-blind period) and a two-week double-blind period as shown in Table 1.

Subjects and methods

Children aged 7 to 16 years with perennial allergic rhinitis were recruited if they were allergic to house dust or mites on the skin test (intradermal or scratch test) or test for serum specific IgE antibodies and if they showed a positive nasal challenge test or a positive eosinophil count in nasal discharge in accordance with the criteria shown in Tables 2 and 3. Children who had concurrent severe bronchial asthma or atopic dermatitis or in whom requirement for antihistamines, leukotriene antagonists, steroids or any other drug that acted on nasal symptoms was anticipated were excluded from the study. When the observation and the double-blind period were in the pollen season (pollen from cocksfoot, timothy grass, ragweed, artemisia, cedar, cypress, Alnus japonica and white birch) children who were positive to any of the pollen antigens were also excluded from the study. All subjects received placebo in a single-blind fashion in the observation period to identify subjects who showed nasal symptoms suitable for evaluation and who could keep a diary as instructed. Subjects were randomized to double-blind treatment if they had a mean rhinorrhea score of 2 or more and a mean total three nasal symptom score of 4 or more for the last four days prior to randomization as determined using Table 2 and unless their diary card data were missing for two days or more.

The following medications were prohibited after laboratory tests prior to the observation period through the end of the double-blind period (or until discontinuation): chemical mediator release inhibitors, antihistamines, thromboxane A_2 inhibitors, thromboxane A_2 antagonists, leukotriene antagonists, Th2 cytokine inhibitors, corticosteroids, α-sympathetic stimulants, anti-cholinergics, drugs for nonspecific modulation therapy, biological preparations, glycyrrhizine products, herbal medications, drugs for bronchial asthma (inhaled corticosteroids), vasodilators (β_2-stimulants, theophylline products), expectorants (stimulants of airway secretion, airway mucolytics, airway

Table 1. Study design.



mucus adjusters), centrally acting non-narcotic antitussives (approved for use in bronchial asthma), antitussive–expectorant combinations (approved for use in bronchial asthma) and immunosuppressants for oral, injection, nasal, inhalation, external or suppository use. The use of external or ocular corticosteroids was also prohibited.

Voluntary written informed consent to participate in the study was obtained from all guardians. All subjects provided voluntary assent to study participation.

After written consent was obtained from guardians, baseline characteristics and eligibility of subjects were recorded and hematology, blood chemistry and urinalysis performed. On the first day of the observation period, eligibility was assessed on the basis of diagnosis, body weight and laboratory findings. Once eligibility was confirmed, subjects/guardians were supplied with nasal allergy diary cards and the study drug to be taken during the observation period. They were fully instructed how to record and manage the diary. On the first day of the double-blind period, diary records and compliance with study medication during the observation period were assessed; subjects/guardians were asked whether the subject had experienced cold symptoms during the observation period. Subjects who fulfilled all of the inclusion/exclusion criteria were considered eligible and supplied with a double-blind medication designated as drug number. Rhinoscopic findings and diary records were checked on the first day of the double-blind period and at the week-1 and week-2 visits. Diary cards were collected and hematology, blood chemistry and urinalysis performed at the week-2 visit.

Criteria for evaluation

Efficacy

The severity of nasal symptoms (sneezing, rhinorrhea, nasal congestion and disturbance of daily life) was scored as shown in Table 4 and recorded on diary cards. Mean total three symptom score and mean individual symptom scores were calculated using diary cards on which all of the three main nasal symptoms were rated. Diary scores on the last four days prior to each assessment time point were used to calculate daily mean score. Mean scores obtained in the observation period were considered as baseline and the change from baseline over the double-blind period was calculated at each assessment.

The primary analysis was carried out at final assessment at the end of the two-week treatment (or at the end of the one-week treatment if data at the end of the two-week treatment were missing).

The primary efficacy endpoint was the change from baseline in total three nasal symptom score (for sneezing, rhinorrhea and nasal congestion) and secondary endpoints included changes in individual symptom scores (sneezing, rhinorrhea, nasal congestion and disturbance of daily life), individual nasal local finding scores and severity score. Nasal local findings at each assessment time point were scored according to the criteria given in Table 5. Mean individual symptom scores (for sneezing, rhinorrhea and nasal congestion) in the observation, week-1 treatment and week-2 treatment periods calculated from diary records were used to classify and score the severity of allergic rhinitis as shown in Table 6.

Safety

Safety was assessed on the basis of adverse events and reactions newly developing or aggravated in the double-blind period. The sponsor coded reported adverse events using the ICH Medical Dictionary for Regulatory Activities/Japanese Edition (MedDRA/J version 9.0). Laboratory data were assessed for abnormalities suggestive of adverse event and for changes over time.

Table 3. Evaluation criteria of the test for serum specific IgE antibodies.

Test \ Evaluation criteria	Positive	False positive/negative
RAST, CAP-RAST, LUMIWARD, SIST, AlaSTAT	Class 2 or higher	Class 1 or Class 0
MAST	Class 1 or higher	Class 0

Table 2. Diagnostic criteria for allergic rhinitis.

Test \ Severity	+++	++	+	±	−
	Positive			Negative	
Intradermal test*	Erythema: ≥ 41 mm Wheal: ≥16 mm	Erythema: 40–20 mm Wheal: 15–10 mm	Erythema: 40–20 mm Wheal: ≤9 mm		Erythema: ≤19 mm Wheal: ≤9 mm
Nasal challenge test**	Three symptoms, particularly more than 6 sneezes	Three symptoms	Two symptoms	One symptom	0
Eosinophil count in nasal discharge	Present in groups	Between (+++) and (+)	Found by weak magnification		0

*A scratch (prick) test is considered positive when a wheal or erythema is more than twice that of control in diameter or an erythema is greater than 10 mm or a wheal greater than 5 mm in diameter after 15 to 30 minutes.
**Three symptoms: (1) Sneezing, nasal itching, (2) Swelling and pallor of the lower nasal turbinate membrane, (3) Watery secretion.

Table 4. Severity of nasal symptoms[10].

Symptom \ Severity	++++ (Score: 4)	+++ (Score: 3)	++ (Score: 2)	+ (Score: 1)	− (Score: 0)
Sneezing (Mean episodes/day)	21 or more	20 to 11	10 to 6	5 to 1	0
Rhinorrhea (Mean episodes/day)	21 or more	20 to 11	10 to 6	5 to 1	0
Nasal congestion	Complete congestion, all day	Very severe nasal congestion with frequent oral breathing	Severe nasal congestion with occasional oral breathing	No oral breathing but nasal congestion (+)	None
Disturbance of daily life	Unable to eat, play, study or sleep	Eating, playing or studying difficult	Eating, playing or studying a little difficult	Eating, playing or studying not difficult but efforts required	No difficulty with eating, playing or studying

Statistical analysis

For the efficacy analysis, the full analysis set (FAS) was defined as all randomized subjects who received at least one dose of study medication in the double-blind period and who were monitored for efficacy parameters at least once in each of the observation and double-blind periods. The safety population consisted of all randomized subjects who received at least one dose of study medication in the double-blind period and from whom post-dose safety data were available.

It was anticipated that baseline scores obtained in the observation period would influence the primary and secondary endpoints, which were assessed based on the mean change in symptom scores from baseline to each assessment time point. The primary analysis was therefore performed using an analysis of covariance (ANCOVA) with the baseline score as covariate. For the primary endpoint, alternative hypotheses 'mean for the placebo group $\leq$ mean for the olopatadine 2.5-mg group $\leq$ mean for the olopatadine 5-mg group (wherein at least one $\leq$ was $<$)' and 'mean for the placebo group $<$ mean for the olopatadine 2.5-mg group' were tested using Williams' test at a one-sided significance level of 2.5% to assess dose–response relationship.

The level of significance was 5% for two-sided exploratory analysis of efficacy and safety. Whether there was demographic bias or interaction was tested with a two-sided significance level of 15%.

Results

Demographics

Of the 413 subjects who were screened in the observation period, 111 did not meet the inclusion/exclusion criteria and were withdrawn from the study, while 302 were randomized to treatment. Failure to meet the criterion: 'a mean rhinorrhea score of 2 or more and a mean total three nasal symptom score of 4 or more for the last four days prior to randomization' was the most common reason for withdrawal (96 subjects). Of the randomized subjects, 93 in the placebo group, 98 in the 2.5-mg group and 93 in the 5-mg group completed the study, while six in the placebo group, five in the 2.5-mg group and seven in the 5-mg group discontinued treatment (Table 7).

Two subjects randomized to placebo were excluded from efficacy analysis because one did not receive double-blind treatment and the other was not monitored for efficacy parameters. The FAS for the efficacy analysis included 300 subjects (97 on placebo, 103 on 2.5 mg and 100 on 5 mg). The one subject randomized but not treated was also excluded from safety evaluation and the safety

Table 5. Severity of local findings.

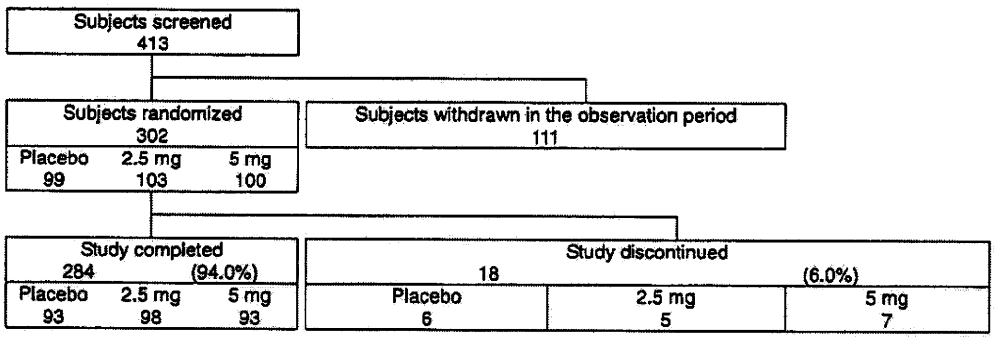
Findings \ Severity	+++ (Score: 3)	++ (Score: 2)	+ (Score: 1)	− (Score: 0)
Swelling of the inferior turbinate mucosa	Middle turbinate not visible	Intermediate between +++ and +	Visible up to the center of the middle turbinate	No swelling
Watery secretion	Filling the nasal meatus	Intermediate between +++ and +	Seen adhering to the mucosa in small quantities	None

Table 6. Severity.

Severity		Sneezing or rhinorrhea (whichever is more severe)				
		++++	+++	++	+	−
Nasal congestion	++++	Most severe	Most severe	Most severe	Most severe	Most severe
	+++	Most severe	Severe	Severe	Severe	Severe
	++	Most severe	Severe	Moderate	Moderate	Moderate
	+	Most severe	Severe	Moderate	Mild	Mild
	−	Most severe	Severe	Moderate	Mild	No symptom

Score: Most severe, 4; Severe, 3; Moderate, 2; Mild, 1; No symptom, 0.

Table 7. Subject participation.



population consisted of 301 subjects (98 on placebo, 103 on 2.5 mg and 100 on 5 mg).

Demographic and other baseline characteristics of the FAS are summarized in Table 8. A two-sided test at the 15% significance level revealed no bias in the distribution of sex, age and body weight among three groups.

Efficacy

Primary efficacy endpoint (changes from baseline in total three nasal symptom scores – sneezing, rhinorrhea and nasal congestion) were compared using ANCOVA with the baseline score as covariate. The least squares mean estimated for each treatment group from this ANCOVA model was evaluated using Williams' test. The results are shown in Tables 9 and 10.

The least squares mean for the changes from baseline to final assessment in total three symptom score was −0.88, −0.95 and −1.38 for the placebo, 2.5-mg and 5-mg groups, respectively, showing the monotonicity of dose response Williams test assumed. The difference in least squares mean between the 5-mg and placebo groups (placebo group – 5-mg group) was 0.51 (95% confidence interval: 0.04 to 0.98) with a p value of 0.019 by Williams' test, demonstrating that olopatadine 5 mg significantly reduced total three symptom score compared with placebo. In contrast, there was no significant difference between the 2.5-mg and placebo groups since the difference in least squares mean between the groups (placebo group - 2.5-mg group) was 0.08 (95% confidence interval: −0.39 to 0.54) with a p value of 0.375.

The ANCOVA with the total three symptoms score at baseline as covariate yielded least squares

Table 8. Subject characteristics.

	Treatment	Placebo	2.5 mg	5 mg	p
	Number of subjects	97	103	100	
Sex	Male	65 (67.0%)	67 (65.0%)	63 (63.0%)	[a]0.835
	Female	32 (33.0%)	36 (35.0%)	37 (37.0%)	
Age (years)	Mean ± SD	10.6 ± 2.5	10.9 ± 2.7	10.9 ± 2.8	[b]0.707
	Median	11.0	10.0	11.0	[c]0.827
	Min–max	7–16	7–16	7–16	
Body weight (kg)	Mean ± SD	38.27 ± 12.10	38.57 ± 13.95	39.43 ± 13.45	[b]0.814
	Median	37.50	35.50	36.30	[c]0.835
	Min–max	20.0–79.0	20.0–96.0	21.0–74.4	

[a]Fisher's exact test.
[b]One-way analysis of variance.
[c]Kruskal–Wallis test.
SD: Standard deviation.

Table 9. Analysis of covariance for changes from baseline to final assessment in total three nasal symptom score (sneezing, rhinorrhea and nasal congestion).

			Placebo ($n=97$)	2.5 mg ($n=103$)	5 mg ($n=100$)
Observation period (baseline)	Descriptive statistics	Number of subjects	97	103	100
		Mean ± SD	5.99 ± 1.17	6.09 ± 1.20	6.14 ± 1.44
		Median	6.00	6.00	6.00
		Min ~ max	4.0 ~ 10.8	4.0 ~ 9.5	4.0 ~ 10.8
Final assessment score – baseline score	Descriptive statistics	Number of subjects	97	103	100
		Mean ± SD	−0.84 ± 1.58	−0.96 ± 1.70	−1.41 ± 1.99
		Median	−0.80	−0.70	−1.50
		Min ~ max	−5.5 ~ 3.0	−5.5 ~ 4.3	−5.0 ~ 6.7
	ANCOVA	Least squares mean	−0.88	−0.95	−1.38
		95% CI	[−1.21, −0.54]	[−1.27, −0.63]	[−1.71, −1.05]
		p^a	<0.001*	<0.001*	<0.001*
	ANCOVA (placebo -olopatadine)	Least squares mean	–	0.08	0.51
		95% CI	–	[−0.39, 0.54]	[0.04, 0.98]
		p^b	–	0.750	0.034*

[a]p value by the two-sided t-test evaluating the null hypothesis that final assessment-baseline = 0.
[b]p value by the two-sided t-test evaluating the null hypothesis that the score for the placebo group the-olopatadine 2.5-mg (5-mg) group = 0.
*$p < 0.05$.

Table 10. Williams' test for changes from baseline to final assessment in total three nasal symptom score (sneezing, rhinorrhea and nasal congestion).

Final assessment-baseline		Placebo $n=97$	2.5 mg $n=103$	5 mg $n=100$
Least squares mean[a]		−0.88	−0.95	−1.38
Difference from the placebo group	Least squares mean		0.08	0.51
	95% CI		[−0.39, 0.54]	[0.04, 0.98]
	p^b		0.375	0.019*

[a]Estimated from a model with treatment arm (placebo/2.5 mg/5 mg) as factor and the total three symptom score at baseline as covariate.
[b]p value by Williams' test (one-sided).
5-mg group: p value by the one-sided test evaluating the alternative hypothesis that mean for the placebo group ≤ mean for the olopatadine 2.5-mg group ≤ mean for the olopatadine 5-mg group (at least one ≤ is <).
2.5-mg group: p value by the one-sided test evaluating the alternative hypothesis that mean for the placebo group < mean for the olopatadine 2.5-mg group.
*$p < 0.025$.

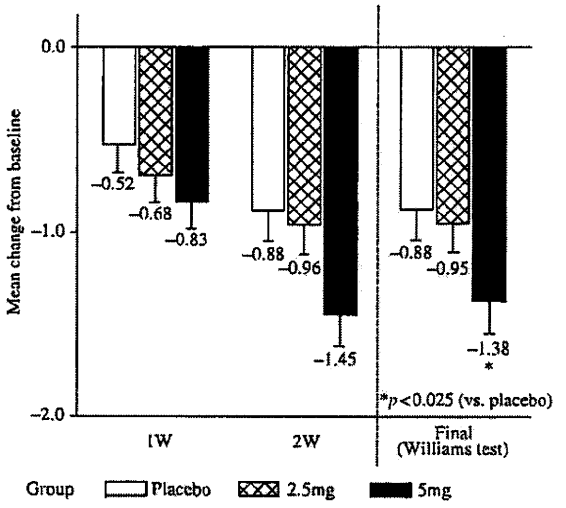


Figure 1. Transition of mean change from baseline in total nasal symptom scores.

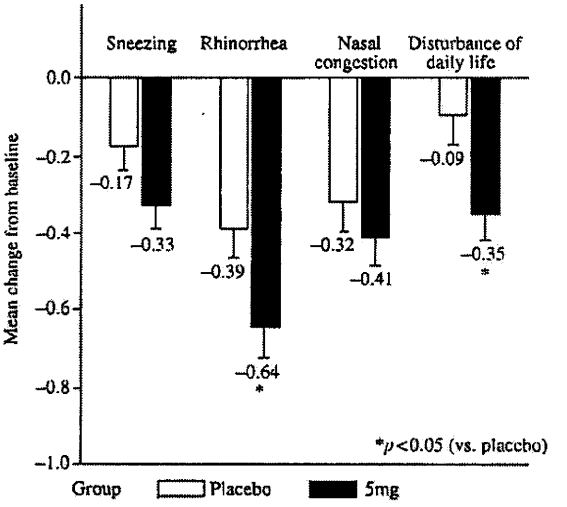


Figure 2. Mean change from baseline in individual nasal symptom scores at final assessment.

means ± standard error, which are presented in Figure 1 by assessment time point. The total score was lower after the two-week treatment than after the one-week treatment in all three groups.

Secondary efficacy endpoints

Least squares means for the changes from baseline to final assessment in individual symptom scores (for sneezing, rhinorrhea, nasal congestion and disturbance of daily life) indicated that the scores for sneezing, rhinorrhea and nasal congestion at final assessment were reduced compared with those at baseline in all three groups. The difference in least squares mean at final assessment between the 5-mg and placebo groups was 0.16 (95% confidence interval: −0.02 to 0.33) for sneezing, 0.25 (95% confidence interval: 0.04 to 0.47) for rhinorrhea, 0.09 (95% confidence interval: −0.12 to 0.31) for nasal congestion and 0.26 (95% confidence interval: 0.05 to 0.46) for disturbance of daily life. Olopatadine 5 mg significantly improved rhinorrhea and disturbance of daily life at final assessment compared with placebo ($p=0.022$ for rhinorrhea; $p=0.013$ for disturbance of daily life) (Figure 2).

The ANCOVA for the changes from baseline in individual scores for local findings (swelling and color of the inferior turbinate mucosa, watery secretion and appearance of nasal discharge) performed in the same fashion as for the primary endpoint showed that the scores at final assessment were reduced compared with those at baseline for all findings and in all groups. No differences were observed among the three groups.

The ANCOVA for the changes from baseline in severity scores showed that olopatadine 5 mg improved allergic rhinitis compared with placebo ($p=0.006$).

Safety

Adverse events occurred at similar rates across three groups: 33.7% (33/98 subjects) in the placebo group, 35.9% (37/103) in the olopatadine 2.5-mg group and 35.0% (35/100) in the olopatadine 5-mg group (Table 11). There were no serious or severe adverse events. The most frequent adverse event was nasopharyngitis, which occurred in 8.2% (8/98) on placebo, 6.8% (7/103) on 2.5 mg and 6.0% (6/100) on 5 mg, followed by alanine aminotransferase increasing, which occurred in 3.1% (3/98) on placebo, 3.9% (4/103) on 2.5 mg and 7.0% (7/100) on 5 mg. White blood cell count increased in 2.9% (3/103) on 2.5 mg and 4.0% (4/100) on 5 mg. The incidence of the adverse event somnolence was 1.0% (1/98) in the placebo group, 2.9% (3/103) in the 2.5-mg group and 1.0% (1/100) in the 5-mg group. Somnolence was mild in severity in all of these subjects.

Discussion

Olopatadine hydrochloride alleviates allergic reactions through its histamine H_1 receptor antagonist activity. Its oral preparation has been approved for adult allergic rhinitis, urticaria and pruritic skin diseases first in Japan. Since then ophthalmic and nasal preparations have been developed mainly in the USA and are now used worldwide. Oral olopatadine was demonstrated to be a histamine H_1 receptor antagonist more potent than other drugs in the same therapeutic class[11] and to be effective in the treatment of the most common seasonal allergic rhinitis in Japan, Japanese cedar pollinosis[12].

This is a placebo-controlled study to evaluate the efficacy and safety of olopatadine in children with perennial

Table 11. Frequency of adverse event occurrence (occurring in two or more subjects).

AEs (Preferred Term)	Placebo (n=98)		2.5 mg (n=103)		5 mg (n=100)	
Total	Number	%	Number	%	Number	%
	33	33.7	37	35.9	35	35.0
Abdominal pain	2	2.0	2	1.9	0	0.0
Diarrhea	2	2.0	3	2.9	2	2.0
Acute tonsillitis	1	1.0	2	1.9	0	0.0
Gastroenteritis	3	3.1	1	1.0	1	1.0
Influenza	3	3.1	1	1.0	1	1.0
Nasopharyngitis	8	8.2	7	6.8	6	6.0
Pharyngitis	1	1.0	1	1.0	3	3.0
Rhinitis	0	0.0	0	0.0	2	2.0
Laryngopharyngitis	0	0.0	3	2.9	1	1.0
Alanine aminotransferase increased	3	3.1	4	3.9	7	7.0
Aspartate aminotransferase increased	3	3.1	2	1.9	1	1.0
Blood urea increased	2	2.0	0	0.0	1	1.0
Blood urine present	0	0.0	2	1.9	0	0.0
White blood cell count increased	0	0.0	3	2.9	4	4.0
Protein urine present	2	2.0	0	0.0	1	1.0
Headache	2	2.0	3	2.9	1	1.0
Somnolence	1	1.0	3	2.9	1	1.0
Cough	0	0.0	2	1.9	1	1.0
Upper respiratory tract inflammation	0	0.0	2	1.9	2	2.0

allergic rhinitis. Approximately 70 to 80% of Japanese children are likely to develop mite allergy and most clinical studies in children aim at the more prevalent category, perennial allergic rhinitis[13,14]. In conducting the study, the authors tried to eliminate seasonal factors that might affect study results by excluding patients who showed a positive reaction to the pollens that were thought to be dispersing during the study period. The severity of allergic rhinitis was determined on the basis of the three main symptoms, sneezing, rhinorrhea and nasal congestion. They are commonly used as a comprehensive indicator of the severity of allergic rhinitis in clinical settings in Japan and especially helpful in therapeutic decision making for children. In this study, they served as one of the criteria on which to assess subject eligibility and efficacy. Subjects or guardians were instructed to record the number of sneezes, frequency of nose blow and degree of nasal congestion on diary cards each day, which were scored to represent the severity of nasal symptoms. Evident nasal symptoms and accurate diary data were considered requirements for the subject to progress from the seven-day observation period to the double-blind phase. Subjects were therefore randomized to double-blind treatment if they had a mean rhinorrhea score of 2 or more and a mean total three symptom score of 4 or more for the last four days prior to the double-blind phase, unless their diary card data were missing for two days or more.

Oral olopatadine 5 mg administered for 14 days was superior to placebo in reducing total three nasal symptom score. The International Conference on Harmonization Notes for Guidance on Good Clinical Practice (E4: Dose–Response Information to Support Drug Registration) providing that including a placebo group is desirable in dose–response studies is applied to this study. Though some authors have reported placebo-controlled studies in children with seasonal allergic rhinitis[15–17], few placebo-controlled studies have been published concerning pediatric perennial allergic rhinitis. Levocetirizine significantly improved Total 4 Symptoms Score (the sum of scores for sneezing, rhinorrhea, nasal pruritus and ocular pruritus), 50% response rate and other efficacy variables compared with placebo in a study with approximately 150 subjects per group[18]. Neither placebo-controlled studies of oral olopatadine nor studies similar to this study of other drugs in the same therapeutic class have been reported. This study seems to be of particular interest as it is the only study that shows the superiority of olopatadine over placebo in three main nasal symptoms in children and as it demonstrates the histamine H_1 receptor antagonist activity of olopatadine.

No serious adverse events occurred during the study. There were no large differences in the incidence of adverse events between olopatadine (2.5 and 5 mg) treated and placebo-treated groups. The most frequent adverse event was nasopharyngitis and its high incidence was possibly attributable to the facts that the subjects were children and that they participated in the study in winter. Somnolence, an adverse event commonly reported with histamine H_1 receptor antagonists, was seen only in a limited number of subjects in this study; the incidence was similar between olopatadine and placebo groups and the severity was mild.

These results demonstrate that olopatadine hydrochloride 5 mg twice daily is an effective and safe treatment for perennial allergic rhinitis in children.