というのがわかったわけで，そこまで医師が注意してやらなければ多分わからないだろうと思います．

**岡本**　確かに副作用はなかなか判断が難しいですね．下条先生はいかがでしょうか．

**下条**　小児の副作用に関しては，保護者からのお答えで副作用があると答えられた方は10%ほどで，それも目に見える肌ということになります．ただ，成人と小児で使っている期間がどのくらいなのか私はよくわかりませんが，小児の場合は先ほどお話ししたとおり，かなり短い期間で副作用が出る前にその代替医療自体が変わっている可能性があります．副作用には早く出る副作用や長期にわたって使っているうちに出る副作用など，いろいろな出方があります．そういうことで，小児の場合少なかったという可能性はあるかもしれません．いずれにしろ副作用は先ほどお話しされたとおり，思っていたほどはないだろうと思います．

**岡本**　判断が難しいということが理由の１つにあるかもしれないということですね．代替医療の効果はプラセボ効果がかなりを占めている．それから費用も決して安くはない．副作用も詳細はなかなか明らかにはなってこないにせよ，やはり隠れているだろう．代替医療を受ける理由というのは先ほどお話が出てきたとおり，病気そのものの根治性が難しい，それから患者さんの不安などいくつもあると考えられ，なかなか複雑です．患者さんが受けているこのような代替医療に対して，医師はどのように対応すれば良いのか．半分くらいの人は医師にも話をしているということを，先ほど下条先生も調査からおっしゃっていましたけれど，そういう代替医療を使っている患者さんにどう対応したら良いか．あるいは代替医療について相談を受けたときにどう対応するか．これが一番大きな重要な点だと思いますが，塩原先生はどうお考えですか．

**塩原**　私は根本的には代替医療はしなくて良いと言っています．少し話がそれますが，先日，医学生に「いろんな治療法がある場合，あなたはどのように患者さんに説明をするか」と聞いたときに，６人いたグループのうち，男性４人は「『こういう治療法があります』と治療法を並べて説明して患者さんに選ばせる」と言い，女性２人は「自分が良いと思っている治療法を選ばせるように誘導する」と言いました．私自身はひどいアトピー性皮膚炎ならやはりステロイドを使わせるように，つまりオーソドックスな治療をする方向へ持っていくように「これはこういう点があり，悪い点もあります」とかなりバイアスをつけて話をします．「これも良い，あれも良い」という言い方をすると，ある意味では医者としての責任を放棄していることになりますので，私は自分の信念を持って「これが良いと思います」ということを患者さんに言っています．ですから「私はこう思う」ということで「私は代替医療に関しては経験がないから何とも言えないけれど，こうい

う点がわからないので，わからないから良いと思われているところがあって，副作用も非常に多いだろうと思う」と話しています．代替医療も先ほどの温泉のような一部のものに関しては止めはしませんけれど，水やサプリメントなどの無駄なものは「やめなさい」とはっきりと言っています．

**岡本**　下条先生はいかがですか．

**下条**　乳児のアトピー性皮膚炎で代替医療にはまりやすいのは，やはりお母さんですね．実際に民間療法で亡くなった方もいらっしゃいますし，それから極めて重症になっているのも最近報告が出ています．やはり塩原先生がお話しされたとおり，のんびりやって良いものと，非常に早めにきちんとアラートしなければいけないものがあると思います．

**岡本**　今年，花粉症でもスギ花粉を多量に含むカプセルを摂取後にテニスをして，ショックになった人の報告が和歌山でありましたね．全国の新聞にも取り上げられました．下条先生のおっしゃるのはどんな方ですか．

**下条**　私が経験したのは食物アレルギーを合併しているアトピー性皮膚炎の乳児です．食べ物が悪いのではないかと食べ物を過度に制限して発達も遅れていましたし，非常に成長も遅れているような赤ちゃんでした．代替医療には副作用がないと思われていますが，とんでもないことです．お母さん方には特に気をつけていただきたいと思います．

患者さんが代替医療の情報をどこから手に入れるかということを考えたときに，私は最初，雑誌とかインターネットではないかと思っていたのですが，実は半数は非常に近いところ，ご家族や友人からだそうです．最近読んだ海外の文献によりますと，彼らが相談するようなごく近くの友人や親戚，そういう方たちの中に代替医療の経験がある方がいるかいないかが非常に大きいようです．われわれはすべての代替医療に精通することはできませんが，一応知識として知っておかないといけないと思います．アンケート調査では，医師の反応としては，患者さんが代替医療について話した場合に，半分くらいは「やめなさい」とも「続けなさい」とも言わないで「あ，そう」と答えているという話だったわけです．つまりわれわれは代替医療のことをよく知らないわけです．患者さんに「儲けようとしている可能性のあるものがあるから，非常に高価なものはやめなさい」とお話ししますけれど，実は先ほどの塩原先生のお話のように，高くなくても副作用があるものはあるわけですから，われわれ自身がもっと代替医療の，少なくともある程度のカテゴリーをちゃんと知識として知っておかないと答えられないかなと思います．「代替医療はどうでしょうか」と聞かれたときに，その代替医療を「よく知りません」としか言えなければ代替医療について話はできないわけです．「西洋医学はこういうことがで

きます」ということしか言えないのと，あとは大きな問題がなければ「いいでしょう」くらいでお茶を濁しているのが実情なので，やはり患者さんのニーズというのは大きいから，それをもっと知らないといけないな，というのはあります．

**塩原**　その点に関して，私はちょっと先生に提案したいのです．つまり民間療法を否定するばかりでなく，実際に検証してみるという態度も必要ですね．アメリカのルーシーショーか何かで紹介された民間療法の話で，アレルギー性鼻炎の治療として足浴療法というのがありますね．その治験をしてみたらよく効いた，というのがJACIか何かに載っていました．ですからそういう俗説も，実際に試してみるということも必要だと思います．

**下条**　先ほど少しお話ししましたが，代替医療に行ってしまうパスウェイはいくつかあるそうです．たとえば西洋医学に満足しているけれど，もう少し良くできないか，という考え方もあります．また，西洋医学の治療自体に不安が大きくて代替療法に走ってしまう道筋もあります．少なくとも後者の方たちに関しては，西洋医学に関してもっときちんとお話をすることで，代替医療に行く患者さんの数を減らすことは可能だと思います．

**岡本**　確かに患者さんの中には薬とか，医療に対する不安感を持っている方はいらっしゃいますね．

**下条**　小児の場合でも，ときにはかなりの数の薬を用いることがあります．そういうことを，子供たちに毎日しなければいけないというのは，親にとって大きなストレスです．「今は落ち着いているとしても，あと何年したらどうか」という親の質問に，「一般的に多くの人たちを診ている限りは問題はありませんでした」と答えられますが，それが100%正しいかということはわかりません．もっと母親のことを考えないといけません．母親というのは非常に注意深い観察者なので，やはり自分のパートナーとして話すような形で，親御さんに納得してもらうような形をとるとアドヒアランスも良くなると思います．理知的なお母さんほどわけのわからない代替医療に走らないという報告もありますので，そういうことをきちっとやるということは小児では特に重要だと思います．

**岡本**　すべての疾患に標準治療というのがあること，一方で代替医療の副作用ははっきり評価できていない，効果そのものも評価されていないということをきちっと患者さんに説明をしなくてはいけないということですね．さらに標準治療の安全性について，医師の説明も重要だし，評価されているものについてはもっと積極的に説明をしなくてはいけないということに尽きるでしょう．標準治療を行いながら，もし患者さんがそのうえで代替医療の使用を希望していらっしゃるのであれば，費用や副作用の配慮も必要ですが，もしかしたら良いのかもしれませんね．

**塩原**　私も決してそれをとめるわけではありません．ただし，いかにも金もうけ主義のところに走って，引っかかっているなと思うときにはそれは完全に否定します．しかしもし効果が本当にあると私自身が判断できた場合には，逆にどうして効果があったのだろうと考えて，これを検証しようと思います．先ほどの足浴ではありませんが，ひとつ検証してみようかなという気になりますね．

**岡本**　薬も考えてみると植物の葉から抽出されて有効性が明らかになっている薬もたくさんあるわけですし，代替医療も期待できないわけではないと思います．たとえば下条先生は，いまプロバイオティクスをいろいろ検討されていらっしゃると思いますが，今後の見通しはいかがですか．

**下条**　その前に先ほどちょっとカテゴリーのお話をしましたが，代替医療のカテゴリーにいくつか分け方があるようで，たとえばヨガも代替医療になっていますし，ハーブもあります．それから鍼灸，アロマセラピー，カイロプラクティック，日本では一般的にはまだやられていないと思いますが，ホメオパシーなどもあります．そういうことをもう少し整理して考えなければいけないと思います．

**岡本**　最初に定義をどうするかという話が欠けていたのですが，一般的に多くの医師が医療機関で施行したり指導する医療以外の医療，その多くは作用機序が検証されていないもの，あるいはもっと広い意味ではたとえば保険診療で認められていない医療というとらえ方もできますし，さらには先ほど下条先生が触れた空気清浄器とか，そういうものも入ってくる可能性もありますね．

**下条**　先ほどどこから代替医療に関する情報を手に入れたか，ということで，家族や友人から「ちょっとこれがいいよ」というインフォメーションを聞いたというのが多いと申しましたが，今は街にたくさんのドラッグストアがあって，そこには基本的に１人ずつちゃんとした薬剤師さんもいらっしゃるわけです．そういう街の大きなドラッグストアに行くと，いつもセルフメディケーションが謳われています．ですから代替医療を増やしている大きな理由の１つは，街のドラッグストアである可能性も非常に大きい．ちょっと話が飛んでしまいますが，代替医療を考える場合に，そういうところの薬剤師さんたちと一緒にやらなければいけないのではないかと思っていますので，次の調査のときに聞いてみたいところです．薬局なので，ヨガや鍼灸，カイロプラクティックなどの話はしなくて，おもにハーブやアロマやヨーグルトだったりするわけです．必然的に日本ではそういうものが多いということは，そういうところから情報が入ってきている可能性は大きいかもしれないとも思います．それをきちっと検証してやらないといけません．薬剤師さんの影響はかなり大きいと思います．

われわれがステロイドの外用薬を出すと「こんなに使っていいの？大丈夫なの？」と言う薬剤師さんもいまだにいらっしゃると聞きます．

医師が患者さんに直接薬を渡すわけではないので，そこに介在する薬剤師さんとかなりしっかり連携をとっておかないと代替医療は非常に心配です．

**岡本**　それと関連しますが，マスコミの影響もありますね．特にテレビの司会者の発言の影響は大きいようです．

**下条**　それはあります．

**岡本**　「これが効きますよ」と言うと反響は大きいようです．

**下条**　マスコミで取り上げたら，街のドラッグストアというドラッグストアから途端に売り切れたというのは聞いたことがあります．

**岡本**　そういう影響が大きいというのは，調査を担当した医師が言っていました．マスコミにも問題があるのかもしれませんね．

## ■代替医療への期待

**下条**　やはり患者さんに投与するには安全性ということもあります．仮にプロバイオティクス[*1]としても生菌を投与した場合に，translocationして敗血症になるということもあり得ますので，いま，慎重にやっています．まず私たちが行おうとしているのはプレバイオティクス[*2]で，対象は赤ちゃんや妊婦さんです．やはり医師が行うとなるとかなり安全性を考えなければなりません．きちんとした情報やエビデンスを得るのはかなり難しいところもありますが，やらないといけないのではないかと思います．誰がやるかというシステムとしては，それを「医療」と考えると医師が指導しなくてはいけませんが，そうではない宣伝がたくさん出てきてしまうので，そのあたりをどのようにエビデンスに基づいて行うかというのは難しいです．食品なども，今，非常に難しいのではないかと思います．

**岡本**　今はアレルギー疾患では食品についても特定保健用食品のようなものはまだ認められていません．評価が難しいということもあると思います．アトピー性皮膚炎もいろいろなもので効果があるといった報告がありますね．先ほどのお話にも出ましたけれど，妊婦さんに投与すると鼻炎の発症抑制はないが，アトピー性皮膚炎の抑制には効果があったといったものも見られます．代替医療の効果のエビデンスについて，塩原先生はどのようにお考えでしょうか．

**塩原**　私がアトピー性皮膚炎に関して最近注目しているのは汗です．汗の中に抗菌ペプチドがいろいろ入っていますし，アトピー性皮膚炎の患者さんではそれが量的に低下している．汗の絶対量が少ないことを考えると，中に入っている抗菌ペプチドのdermcidin[*3]なども非常に少なくなっているということになります．ですからそれを代替するとか増やしていくような代替医療であればかまわないと思います．患者さんと話をしていると，さきほどのヨガやアロマセラピー，ハーブなど「こういうものをやっている，ああいうものをやっている」と教えてくれるのですが，私は全然知らないのです．しかしそばにいる

＊1）プロバイオティクス：腸内細菌のバランスを変えることで宿主に有効な機能をもたらす生きた微生物のこと．

＊2）プレバイオティクス：摂取後そのまま大腸に到達して腸内の有用菌を増やす食物繊維やオリゴ糖などの物質．

＊3）dermcidin：汗の中に含まれる抗菌ペプチドで，炎症の原因となる大腸菌，黄色葡萄球菌などの表皮常在菌に対して抗菌活性を示す．

若い女医さんは全部知っているようです．たまたまきょうは男性だけですけれど，若い女性が見ている世界というのは，おそらくわれわれとはまったく違うのでしょう．われわれはまったく知らないし，わからないのでそういうところに理解がありませんが，代替医療に対して目を開く女医さんが出てきて，実際にその有効性を検証して何か理論づけをしてもらえれば良いかな，と思っていますので，次回こういう機会があった場合には，ぜひ女性の先生を呼んでいただいて，意見を聞かれると良いかもしれません．われわれ男性脳で考えてしまうと，どうしても代替医療というものに対してかなりネガティブな方向で見がちですが，実際若い女医さんは自分でもヨガをやったりしますし，そういう意味での変な先入観がないかもしれません．

**下条**　代替医療を選ぶ基本には，やはり健康観というか，健康志向が女性は非常に強くありますが，男性はあまりないですね．それに女性は特に老化したくないということもあります．食品だけではなく健康ブームですね．世代の差もそうですが，塩原先生がおっしゃったように性別による違いが非常に大きくて，代替医療の底辺にあるのではないかとも思っています．

**岡本**　きょうは代替医療ということでお話を聞かせていただきました．確かに代替医療の内容は非常に多彩で，疾患を治すためとか，症状コントロールで使うという患者さんもいらっしゃいますが，塩原先生がお話しになったように，身近なまわりの医師や事務の方でもアロマ療法などを行っている方も少なくはなく，その人たちはアレルギーの症状を抑えようというわけではなくて，一種の精神的な健康を求める，といったようなことでも用いています．ですから代替医療と言っても底辺はなかなか広いし，確かに乳酸菌を飲んでいる人も必ずしも本当に喘息を抑えよう，鼻炎を抑えようという人だけではなく，漠然と健康のためと思っている方も少なくないでしょう．ただ，一方で，さまざまな代替医療があり，かつ症状の緩和を目的にかなりのアレルギー疾患の患者さんが使っているのも事実です．多くの代替医療の効果については決して高いものではありませんし，評価も十分に行われていないのが実態です．それに副作用についてもまだまだ明らかになっていないものもあります．費用も必ずしも安いものではなく，塩原先生のお話では１千万円といった金額をかけている方もいらっしゃる．そういったことからもやはり，医師からはまず標準的な治療や疾患に対する正しい知識を説明する必要があります．そういう標準医療を推奨していくことが，今のところはこの代替医療に対する私たちの対応である，と言えます．今後，代替医療については科学的な評価をして，その結果もきちっと公表していく必要があるのではないかとも感じました．

きょうはお忙しいところをお集まりいただき，貴重なお話をどうもありがとうございました．

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# Cedar and Cypress Pollinosis and Allergic Rhinitis: Quality of Life Effects of Early Intervention with Leukotriene Receptor Antagonists

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**Key Words**
Pollinosis · Cedar pollen · Cypress pollen · Leukotriene receptor antagonist

**Abstract**
***Background:*** Allergic rhinitis involves inflammation of the nasal passages. The use of nasal steroids is generally very effective in providing significant symptom relief. However, compliance for their use is sometimes poor. ***Methods:*** To examine the efficacy of early intervention (before pollen dispersal) with oral cysteinyl leukotriene receptor antagonists (LTRA) on pollinosis in patients with allergy to cedar and Japanese cypress pollens, groups of subjects were treated with LTRA or a placebo for 4 weeks at the beginning of the cedar pollen dispersal season. Subsequently, all patients received nasal steroid therapy concomitantly with LTRA throughout the remaining period of the pollen dispersal season. The effects of such early treatment with LTRA on pollinosis were investigated using symptom scores from an allergy diary and quality of life (QOL) scores. ***Results:*** Sneezing and nasal congestion scores were significantly lower in the LTRA-pretreated subjects than observed in the placebo-pretreated patients between weeks 4 and 6 and weeks 3 and 5, respectively. QOL scores improved significantly in all domains after concomitant therapy with nasal steroids. The percent improvement in the nasal congestion score after the concomitant therapy was significantly higher in the LTRA group (69%) than in the placebo group (41%). ***Conclusion:*** Significant differences observed in symptoms and in QOL effects between LTRA- and placebo-pretreated patients and the absence of major adverse effects noted in these studies suggest that early intervention with LTRA is beneficial and safe and should be considered in the management of pollinosis-associated allergic rhinitis.


## Introduction

Allergic rhinitis is a type I allergic disease mediated by specific IgE antibody responses. The disease develops as inflammation associated with early infiltration with eosinophils and other pro-inflammatory cells into the nasal mucosa. The pathogenesis of later phases of allergic rhinitis exhibits many characteristics similar to bronchial asthma [1, 2]. Dust mite allergens are responsible for at least 90% of cases of perennial allergic rhinitis. Arboreal pollens, including that of cedar and Japanese cypress, are also important causes of rhinitis, especially in Japan [3–

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5]. Cedar forests cover nearly 18% of the total land area of Japan, while Japanese cypress is concentrated in the Kanto region and the western part of the country. Both cedar and Japanese cypress produce enormous amounts of pollen which is dispersed over many kilometers and reaches major cities, including Tokyo and Osaka, causing widespread pollinosis. Cedar pollen dispersal precedes Japanese cypress pollen dispersal, and approximately 70% of patients with cedar pollinosis are also allergic to Japanese cypress pollen. Cedar pollen dispersal starts in early February and reaches a peak between late February and early March, and this is followed by the dispersal of Japanese cypress pollen, which reaches a peak from late March to early April, with some variation due to changes in the climate each year [6]. The pollen dispersal season lasts for more than 10 weeks in and around the area of Chiba.

Outside the pollen dispersal season, patients with cedar and Japanese cypress pollinosis who do not have rhinitis caused by other allergens in general exhibit normal nasal mucosa with few or no symptoms. Repeated exposure to pollen induces allergic inflammation and increases hypersensitivity of the nasal mucosa, and early intervention against mild pollinosis just after the start of the pollen dispersal season may have a significant effect on the severity of symptoms when pollen dispersal is at its peak. In Japan, the Ministry of the Environment makes a detailed prediction of the date around which cedar pollen dispersal is likely to start, making it easy to assess the effects of early intervention in patients with pollinosis due to cedar and Japanese cypress.

Leukotriene receptor antagonists (LTRA) have been shown to be effective in controlling nasal inflammation [7, 8] by their ability to inhibit eosinophil secretion in the airway [9, 10]. Recent studies have shown that LTRA are as effective as antihistamines but less effective than nasal steroids [11–13]. Nasal steroids reduce sneezing, nasal secretion as well as nasal obstruction. However, the compliance for use of nasal steroids is sometimes poor [14] and their market share is much smaller than that for other oral anti-allergic medications in Japan, because patients seem to prefer such non-sensory attribute, painless route of administration [15, 16].

LTRA do not exert any central nervous system depression or adrenal suppressive effects and may be more suitable for early interventional use especially in patients with milder symptoms. In order to determine the effects of early intervention with LTRA on cedar and Japanese cypress pollinosis, we conducted a double-blind, placebo-controlled trial in subjects allergic to both pollens. Either LTRA or placebo was administered to subjects immediately before the start of the pollen dispersal season and continued throughout the pollen season. All subjects received nasal steroids after the initial treatment with LTRA. Symptom and quality of life (QOL) scores were monitored during the pollen and before the dispersal season and after concomitant therapy with nasal steroids and LTRA.

## Subjects and Methods

*Subjects*

The study population comprised 60 subjects (30 males and 30 females), ranging in age from 20 to 65 years, who were otherwise healthy, but who had a clinical history of moderate/severe Japanese cedar and cypress pollinosis for at least 3 consecutive cedar and cypress pollen seasons. The subjects lived in and around Chiba City where the pollen spread would be expected to be consistent. The diagnosis of cedar and cypress pollinosis was based on clinical history, positive allergen-specific skin tests (wheal diameter $\geq$10 mm) to a standardized cedar pollen extract (Torii Pharmaceutical Co., Tokyo, Japan), and a serum cedar and cypress pollen-specific IgE level score $\geq$2 by a CAP radioallergosorbent test (SRL Inc., Tokyo, Japan). Exclusion criteria were complication of moderate/severe perennial allergic rhinitis with a need for treatment, a history of severe asthma, use of anti-allergic drugs within 4 weeks, and a prior history of any allergen-specific immunotherapy, including for cedar pollen. Pregnant women or those at risk of pregnancy were also excluded. The study was conducted at Chiba University Hospital in compliance with the Ethical Guidelines for Clinical Studies and Good Clinical Practice and the Declaration of Helsinki (2000 revision). The Ethics Committee of Chiba University approved the protocol, and written informed consent was obtained from each subject prior to his or her participation in the study.

*Methods*

Capsules containing 112.5 mg of pranlukast hydrate or placebo were used in the study. The study schedule is shown in figure 1. Prior to the study, patients were interviewed regarding their medical history and underwent the skin test for cedar pollen extract and a CAP radioallergosorbent test in late January 2007 to measure specific serum antibodies against cedar and Japanese cypress pollen. Administration of LTRA or placebo was initiated before the start of the cedar pollen dispersal season, which had been forecast to be in early February. Two capsules were administered orally twice a day after breakfast and dinner for 4 weeks (hereafter referred to as 'pretreatment' period). During the latter 2 weeks of this period, subjects were allowed to use an antihistamine (loratadine, 1 capsule per day), other nasal vasoconstriction drops (tetrahydrozoline hydrochloride, maximum 2 drops to each nasal cavity per day and less than 7 days successively), or disodium cromoglycate eye drops (maximum 4 drops to each eye) at their own discretion, based on the severity of symptoms. Subsequently, all subjects took nasal steroids (fluticasone propionate) and LTRA for 4 weeks (main dispersal treatment period) in accordance with ARIA [2] and the Practical Guidelines for the Management of Allergic Rhinitis in Japan [4], again based on the severity of symptoms.

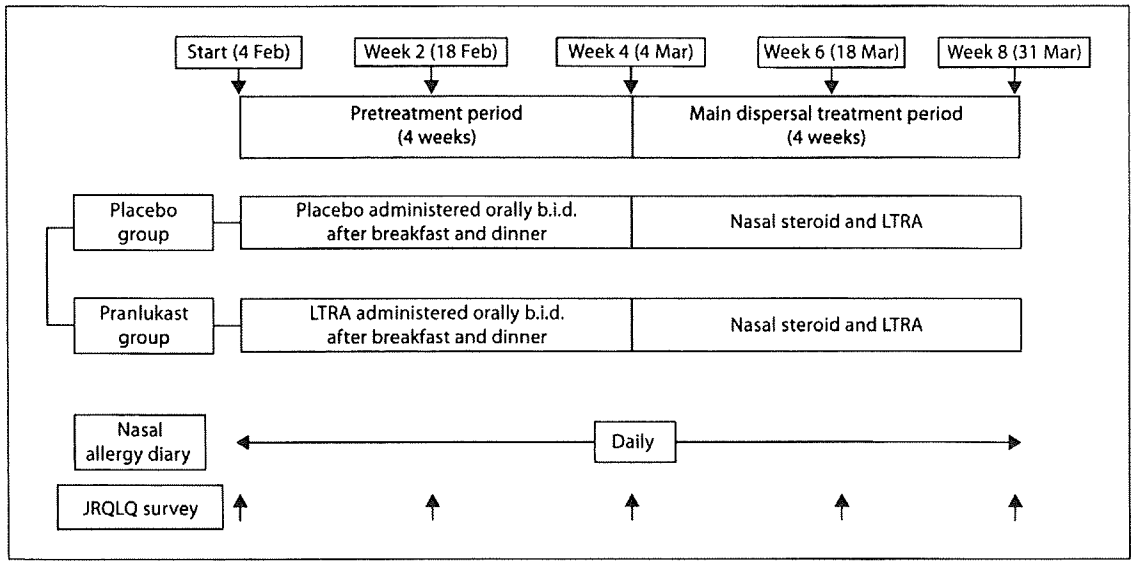


**Fig. 1.** Study schedule. b.i.d. = Twice daily.

**Table 1.** Severity of nasal symptoms

| Parameter | Severity | | | | |
|---|---|---|---|---|---|
| | ++++ | +++ | ++ | + | - |
| Paroxysmal sneezing, times/day | ≥21 | 11–21 | 6–10 | 1–5 | 0 |
| Runny nose (nose blowing frequency) times/day | ≥21 | 11–21 | 6–10 | 1–5 | 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 |

Adapted from the Practical Guideline for the Management of Allergic Rhinitis in Japan, 2005 [5].

Some subjects (n = 30) received LTRA throughout the study period (LTRA group). However, a group of other subjects (n = 30) received placebo during the pretreatment period and LTRA during the main treatment period (placebo group). The sample size was determined based on previous studies of LTRA on the change and variance of clinical symptoms [17]. A nasal allergy diary was written daily, and Japan Rhinoconjunctivitis Quality of Life Questionnaire (JRQLQ) survey sheets [18, 19] were completed every 2 weeks until completion of the study. For assignment of subjects to groups, limited randomization was performed in subgroups of 6 age- and sex-matched subjects each, of whom 3 were assigned to the LTRA group and 3 were assigned to the placebo group. A controller who was not directly involved in the study was responsible for group allocation. A group allocation number was given to each subject. This information was closely guarded by the controller and by 1 member of the ethical committee not directly involved in the study.

During the study period, all study subjects recorded their use (dose and frequency) of permitted concomitant medications (listed above) in a nasal allergy diary. Use of other drugs considered unlikely to affect the study was also allowed.

Cedar and Japanese cypress pollen dispersal was measured with a Durham sampler installed on the roof top of one of the buildings in the School of Medicine, Chiba University.

Nasal symptoms, eye symptoms, symptom scores, medication scores and symptom-medication scores were evaluated from the nasal allergy diary using the following criteria. For nasal symptoms, the severity of paroxysmal sneezing (number of sneezes per day), runny nose (number of times of blowing the nose per day), nasal congestion, and the degree of interference with daily life were evaluated on a 5-point scale (0–4) using a modified Okuda classification [4, 20] (table 1). Symptom scores for classification of the severity of nasal symptoms were calculated using the same classification. The daily total nasal symptom score was expressed

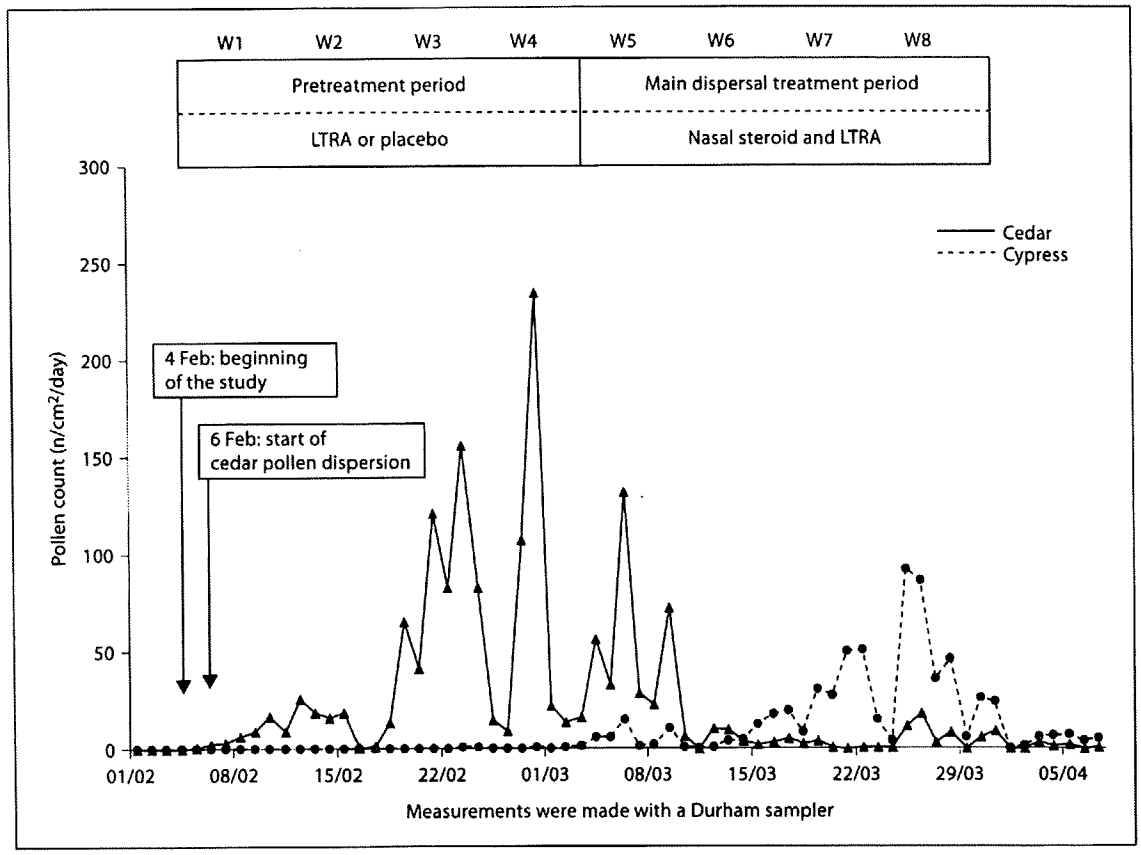


**Fig. 2.** Dispersal of cedar and Japanese cypress pollen in 2007 and study schedule.

as the highest sore of nasal symptoms. For eye symptoms, itching and watering were evaluated using a 4-point scale. The use of other medications was also scored and recorded according to the characteristics of the drug and the duration of usage, based on the following guidelines: anti-histamines, mast cell stabilizers and vasoconstrictors scored as 1, topical nasal steroids scored as 2, and the symptom-medication score was determined by adding the symptom score and the medication score. The score for each QOL item was also evaluated on a 5-point scale (0–4). In addition, the percent improvement in nasal symptoms was analyzed and expressed as the ratio of the patients who had improved nasal symptoms ≥1 in week 8 at the end of the study compared with week 4 before the concomitant therapy with nasal steroids. The symptom-medication score was used as the primary outcome parameter and other items were used as secondary parameters.

*Statistical Analysis*

After completion of the study (clinical and laboratory), a biostatistician who had not been involved in carrying out the clinical trial, analyzed the data. After completing the analysis, the allocation identification numbers for the active and placebo groups were accessed. Data comparisons were performed using 2-tailed tests at a significance level of 5%, using a $\chi^2$ test, the Fisher exact test, the Mann-Whitney U test, a 2-sample t test, a paired t test, and the Wilcoxon test in SAS version 8.02 (SAS Inc., Cary, N.C., USA).

## Results

*Dispersal of Cedar and Japanese Cypress Pollen*

Measurements with a Durham sampler (fig. 2) indicated that 6 February was the start of the cedar pollen dispersal season, based on a pollen count of ≥1/cm²/day. After 19 February, a pollen count ≥20/cm²/day was obtained on most days, which dropped to <10/cm²/day after 10 March, marking the end of the dispersal season. Japanese cypress pollen was observed in the middle of March and reached a count of >20/cm²/day on most days after 19 March until dispersal ended in early April.

*Subjects*

Four subjects withdrew from the study for personal reasons, and not because of any adverse effects. All other subjects exhibited full compliance with the study protocol. Thus, a total of 56 subjects were included for complete evaluation. The LTRA group comprised 29 subjects (mean age 36.1 years and cedar pollen RAST score 3.9). The placebo group comprised 27 subjects (mean age 33

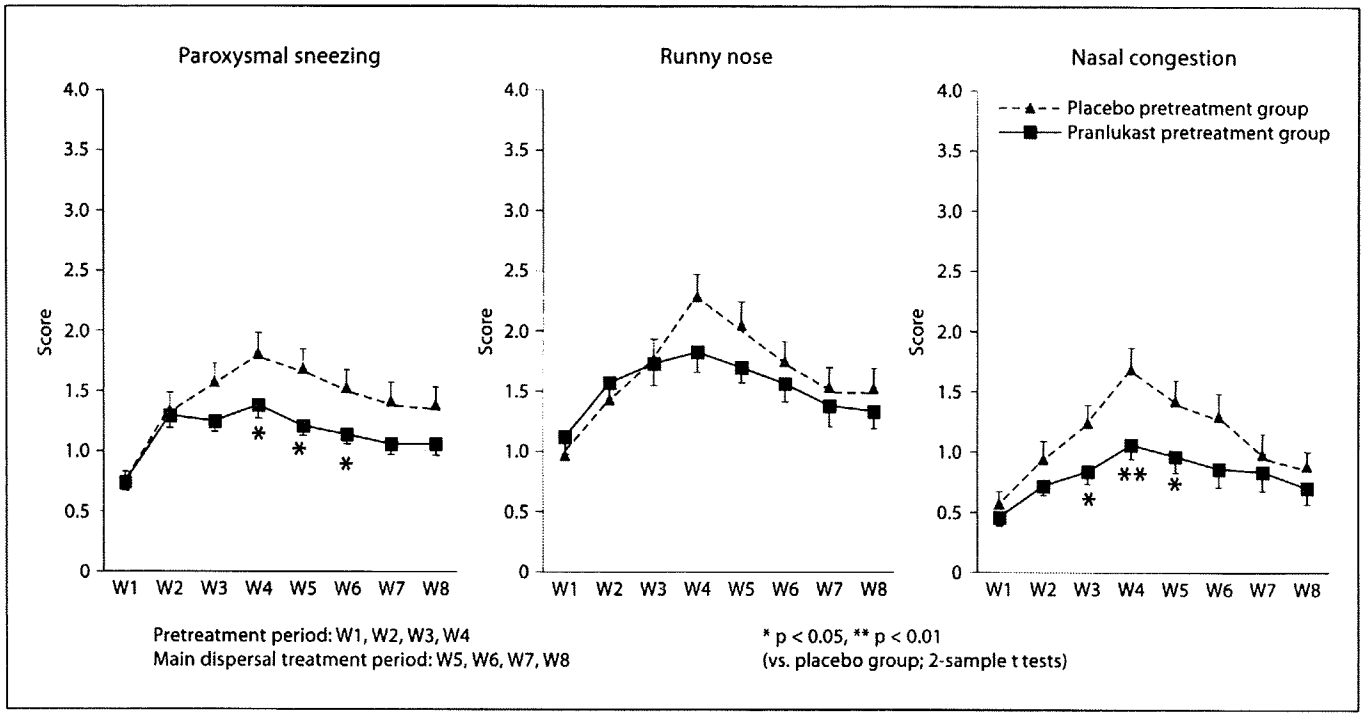


**Fig. 3.** Mean weekly score for each nasal symptom.

years and cedar pollen RAST score 3.5). There were no significant differences between the 2 study groups for age at disease onset, disease duration, or any subsequent complications.

*Treatment Effects*

The mean nasal symptom scores for each week of the pollen season are shown in figure 3. In both groups, symptoms worsened as cedar pollen dispersal increased and then improved after week 5, after the start of nasal steroid drops. In the LTRA group, nasal symptoms were mild from week 3 until the end of the study, and sneezing and nasal congestion scores were significantly lower in the LTRA group than in the placebo group between weeks 4 and 6 and weeks 3 and 5, respectively.

The total nasal symptom score increased in both groups from the start of the cedar pollen dispersal season and decreased in week 5, after the use of nasal steroids at the peak of the cedar dispersal season (fig. 4). Mean symptom scores were significantly lower in the LTRA group than in the placebo group in weeks 4 and 5 (fig. 4). Medication and symptom-medication scores also increased following the start of cedar pollen dispersal and decreased in week 5, after the start of nasal steroid therapy. These scores were lower in the LTRA group than in the placebo group during the pretreatment period, although the differences were not significant (data not shown). There were no significant differences in eye itching or watering scores between the groups (data not shown).

The degree of interference with daily life increased in both groups following the onset of cedar pollen dispersal and decreased in week 5 following the start of nasal steroid therapy. The score in the LTRA group was significantly lower than that in the placebo group in week 4 (fig. 4).

A comparative analysis of the improvement in nasal symptom score in week 8 (at the end of the study) and in week 4 (before the concomitant therapy with nasal steroids) is shown in table 2. The percent improvement in nasal congestion was significantly higher in LTRA-pretreated patients (69.0%) than in placebo-pretreated patients (40.7%).

*JRQLQ Scores*

For 17 QOL items, each mean QOL score generally increased by ≥0.5 points after pollen dispersal (data not shown) and improved for all items after the start of concomitant therapy at week 5 with nasal steroid drops (fig. 5). Although scores for all items in the LTRA group

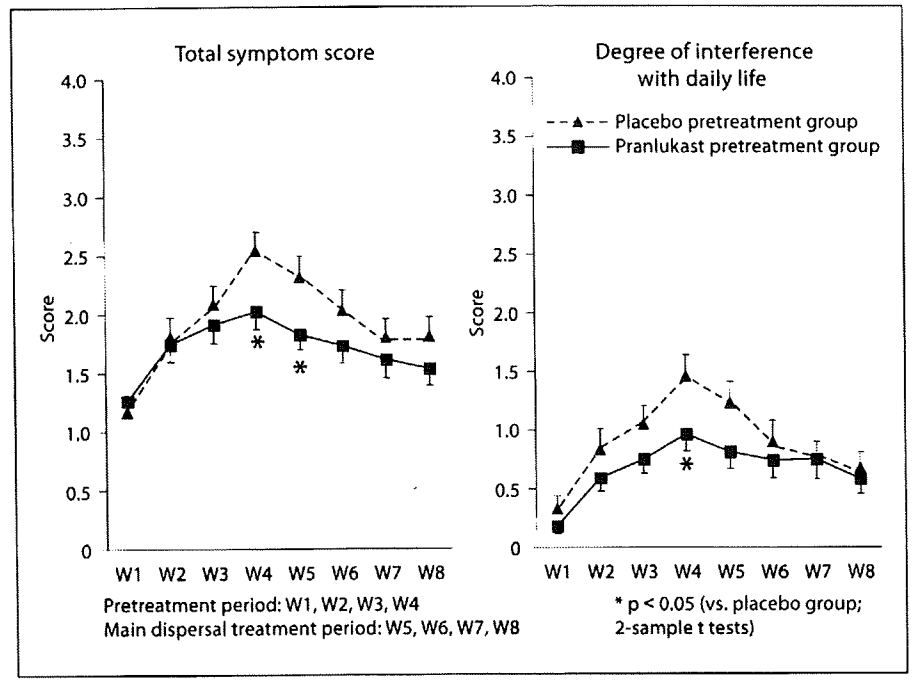


**Fig. 4.** Symptom scores and the degree of interference with daily life.

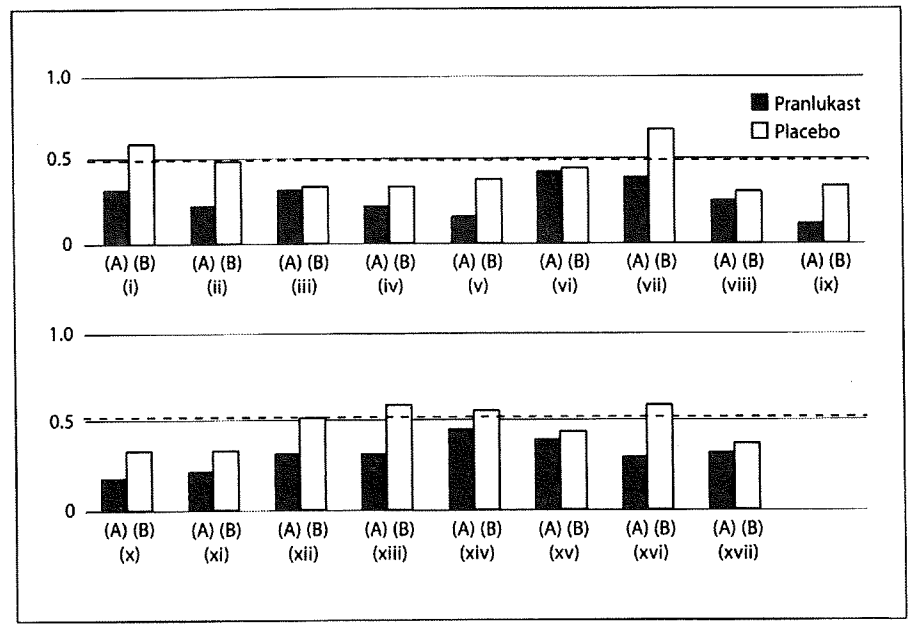


**Fig. 5.** QOL items at week 8 versus week 0. (i) = Reduced productivity at work/home/school; (ii) = poor mental concentration; (iii) = reduced thinking power; (iv) = impaired reading book/paper; (v) = reduced memory loss; (vi) = limitation of outdoor life (e.g., sports, picnic); (vii) = limitation of going out; (viii) = hesitation visiting friends or relatives; (ix) = reduced contact with friends or others by telephone or conversation; (x) = not an easy person to be around; (xi) = impaired sleeping; (xii) = tiredness; (xiii) = fatigue; (xiv) = frustration; (xv) = irritability; (xvi) = depression; (xvii) = unhappiness.

did not increase by 0.5 points at week 8 compared with week 0 (before pollen dispersal), scores for 7 items (interference with study, work and housework; poor concentration; interference with going out; malaise; fatigue; frustration; depressed feeling) in the placebo group still increased by ≥0.5 points at week 8.

These 17 QOL items were categorized into 6 domains (daily life; outdoor activities; social life; physical exercise; mental life; sleep) and scores were compared among domains (table 3). Mean QOL scores generally increased with cedar pollen dispersal when compared between week 4 and week 0, and scores increased by ≥0.5 points

**Table 2.** Improvement in nasal symptom score at week 8 compared with week 4

| | Improved ≥1 point | Improved <1 point | $\chi^2$ test[1] |
|---|---|---|---|
| Runny nose | | | |
| Pranlukast | 16 (55.2) | 13 (44.8) | 0.977 |
| Placebo | 15 (55.6) | 12 (44.4) | |
| Sneezing | | | |
| Pranlukast | 16 (55.2) | 13 (44.8) | 0.803 |
| Placebo | 14 (51.9) | 13 (48.1) | |
| Nasal congestion | | | |
| Pranlukast | 20 (69.0) | 9 (31.0) | 0.034 |
| Placebo | 11 (40.7) | 16 (59.3) | |

Data are number of patients, with percentages in parentheses.

[1] The number of the patients who had an improved score of ≥1 point in the pranlukast-pretreated group was compared with that in the placebo-pretreated group.

**Table 3.** QOL score by JRQLQ (domains)

| | Week | Pranlukast mean ± SE | Placebo mean ± SE |
|---|---|---|---|
| **Versus week 0** | | | |
| Usual daily activities | 0 | 0.25 ± 0.08 | 0.13 ± 0.06 |
| | 4 | 0.97 ± 0.15*** | 0.87 ± 0.14*** |
| | 8 | 0.48 ± 0.10* | 0.56 ± 0.14* |
| Outdoor activities | 0 | 0.14 ± 0.05 | 0.19 ± 0.07 |
| | 4 | 1.02 ± 0.19*** | 1.20 ± 0.19*** |
| | 8 | 0.53 ± 0.14** | 0.74 ± 0.18** |
| Social functioning | 0 | 0.10 ± 0.04 | 0.06 ± 0.03 |
| | 4 | 0.69 ± 0.14*** | 0.53 ± 0.13*** |
| | 8 | 0.28 ± 0.09 | 0.38 ± 0.11** |
| Sleep problem | 0 | 0.17 ± 0.07 | 0.19 ± 0.09 |
| | 4 | 0.59 ± 0.14** | 0.81 ± 0.15*** |
| | 8 | 0.38 ± 0.10 | 0.52 ± 0.13* |
| General physical function | 0 | 0.21 ± 0.08 | 0.13 ± 0.07 |
| | 4 | 1.00 ± 0.16*** | 0.96 ± 0.20*** |
| | 8 | 0.52 ± 0.12* | 0.69 ± 0.18** |
| Emotional function | 0 | 0.14 ± 0.05 | 0.06 ± 0.04 |
| | 4 | 0.78 ± 0.16*** | 0.74 ± 0.15*** |
| | 8 | 0.05 ± 0.14* | 0.55 ± 0.15** |
| Overall QOL condition | 0 | 1.07 ± 0.19 | 0.81 ± 0.13 |
| | 4 | 2.48 ± 0.15*** | 2.26 ± 0.19*** |
| | 8 | 1.45 ± 0.17 | 1.41 ± 0.16* |
| **Versus week 4** | | | |
| Usual daily activities | 4 | 0.97 ± 0.15 | 0.87 ± 0.14 |
| | 8 | 0.48 ± 0.10*** | 0.56 ± 0.14* |
| Outdoor activities | 4 | 1.02 ± 0.19 | 1.20 ± 0.19 |
| | 8 | 0.53 ± 0.14** | 0.74 ± 0.18** |
| Social functioning | 4 | 0.69 ± 0.14 | 0.53 ± 0.13 |
| | 8 | 0.28 ± 0.09*** | 0.38 ± 0.11 |
| Sleep problem | 4 | 0.59 ± 0.14 | 0.81 ± 0.15 |
| | 8 | 0.38 ± 0.10 | 0.52 ± 0.13 |
| General physical function | 4 | 1.00 ± 0.16 | 0.96 ± 0.20 |
| | 8 | 0.52 ± 0.12*** | 0.69 ± 0.18 |
| Emotional function | 4 | 0.78 ± 0.16 | 0.74 ± 0.15 |
| | 8 | 0.05 ± 0.14* | 0.55 ± 0.15 |

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ (2-sample t test).

for 5 of the 6 domains excluding sleeping problem in the LTRA group and for 5 domains excluding social functioning in the placebo group. After the start of nasal steroid therapy at week 5, scores in all 5 domains which had increased by ≥0.5 points at week 4 exhibited significant improvement at week 8 in the LTRA-treated group. The sleep problem and social functioning domains were not significantly aggravated at week 8 under Japanese cypress pollen dispersal when compared with week 0.

In contrast, in the placebo group, scores for 4 domains (social functioning; sleep problem; physical problems; emotional function) did not manifest significant improvement when evaluated during week 8 when compared with the scores observed at week 4 (before nasal steroid therapy). All domains exhibited a still significant increase at week 8 when compared with the scores observed at the beginning of the study (week 0).

Overall QOL condition scores also increased after pollen dispersal in both LTRA- and placebo-treated groups. After the use of nasal steroids, significant improvement was observed at week 8 in the LTRA-treated group but not in the placebo group compared with the scores at week 4.

*Use of Concomitant Medications and Safety*

Antihistamines and nasal vasoconstrictor drugs were used less frequently by the subjects in the LTRA group in the latter 2 weeks of the pretreatment period than in the placebo group; however, the differences were not significant (data not shown). The compliance for the use of LTRA and nasal steroids during the whole study period did not differ between the groups. However, an adverse event was reported by 1 patient in the LTRA group who experienced abdominal pain on day 16, but this resolved 2 days later and did not prevent continuation of study drug administration.

## Discussion

In the present studies, the symptoms of allergic rhinitis increased predictably in the placebo group of subjects. However, many JRQLQ scores also worsened even in the LTRA group at the height of the pollen dispersal season. Therefore, pretreatment with LTRA alone did not appear to result in significant relief of nasal symptoms, and additional nasal steroid therapy in accordance with the standard guidelines was required to induce significant symptom relief [2, 4]. During the later phases of the cedar pollen dispersal season, symptoms and QOL scores exhibited improvement following the initiation of nasal steroid therapy in both LTRA and placebo-pretreated groups. However, differences between the groups in scores for sneezing and nasal congestion were still statistically significant. Subsequently, the symptoms in both groups improved and there were no significant differences in scores between the 2 groups. These findings are considered to reflect the effects of nasal steroid therapy. However, the degree of improvement in nasal congestion scores in week 8 at the end of the study compared with week 4 just before the concomitant therapy with nasal steroids was significantly higher in the LTRA-pretreated group than in the placebo-pretreated group.

QOL scores are considered to be more sensitive markers of clinical improvement than symptom scores derived from an allergy diary [21–23]. All QOL scores improved significantly in the LTRA group after the initiation of concomitant therapy with nasal steroids. The QOL items were categorized into 6 domains (daily life; outdoor activities; social life; physical exercise; mental life; sleep). Scores for the first 5 domains and the overall condition were significantly improved in the LTRA group after the initiation of concomitant nasal steroid therapy. Sleep was not significantly affected in the Japanese cypress pollen dispersal season. In contrast, in the placebo group, domain scores for social life, physical exercise, mental life and sleep (which was disturbed in the Japanese cypress pollen dispersal season in the placebo group) did not improve even after concomitant therapy with nasal steroid, and daily life and overall condition scores demonstrated delayed improvement compared with the LTRA group.

In Japan, pollen counts are typically measured using the gravimetric method with a Durham sampler, in contrast to Western countries in which a Burkard sampler is typically used. In a study in Chiba Prefecture in 2005, the amount of air-borne pollen counted with a Burkard sampler was about 12 times greater than that counted with a Durham sampler [24]. For Durham sampler measurements, a count of 1–10/cm$^2$/day is defined as low dispersal and >20/cm$^2$/day is considered high dispersal. In this study (2007), cedar pollen dispersal was detected by a Durham sampler at the beginning of February. The count was >20/cm$^2$/day on many days after 19 February and then returned to <10/cm$^2$/day after 10 March, after which dispersal ended. Japanese cypress pollen was detected at the end of February, had a count of >20/cm$^2$/day on many days after 19 March, with dispersal ending in early April.

Symptoms of allergic rhinitis are generally mild immediately after the start of the pollen dispersal season, but hypersensitivity-induced inflammation of the nasal mucosa is produced by repeated exposure to pollen. Such exposure results in enhanced expression of adhesion molecules, increased infiltration of the nasal mucosa by inflammatory cells, hyperpermeability of epithelial cells, and an increased neural sensory response [1, 2, 25]. Even in the LTRA group, many JRQLQ scores increased by ≥0.5 points at the height of the pollen dispersal season. With standard therapy using nasal steroids for severely affected patients, the QOL scores in the LTRA group were still lower than those in the placebo group. In the placebo group, nasal steroid therapy produced a smaller improvement in QOL scores.

The observations reported here and other earlier studies have suggested that LTRA are extremely safe and do not result in any major adverse effects, such as anticholinergic activity, local irritation or adrenal suppression. In this study, mild abdominal pain was reported by 1 patient, but no causal relationship with LTRA was detected.

Nasal steroids are generally very effective and provide a significant resolution of symptoms. Nasal steroids might be advantageous for early intervention; however, the compliance is sometimes poor, since many patients prefer to use oral medication, particularly in Japan [14, 15].

Although the number of patients enrolled in the study was limited and a comparative study with LTRA and steroids in a large scale will be needed to evaluate the effectiveness, based on the information summarized here, it is proposed that the use of LTRA is safe and might be appropriate for pretreatment before the appearance and establishment of clinical symptoms early in the course of the cedar pollen season.

## Acknowledgements

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## *CD14* and *IL4R* gene polymorphisms modify the effect of day care attendance on serum IgE levels

*To the Editor:*

The cause of atopy is generally traced to the interplay of genetic and environmental factors.[1] Day care appears to be one of the most frequently investigated environmental factors. Although the results of studies investigating the association between day care attendance and atopy, as assessed by skin prick test responses, were inconsistent, all studies[2-4] measuring serum IgE levels have thus far shown a constant decreasing effect on serum IgE levels.

Among the genes that show a gene-environment interaction for the development of atopy or allergic diseases, the most frequently investigated is the *CD14* gene.[1] However, there is no report that investigates interaction of this gene and day care attendance. CD14 is a pattern-recognition receptor involved in the clearance of bacterial endotoxin and is also known as a receptor of respiratory syncytial virus. We investigated *CD14*−159C/T (rs2569190) and *CD14*−550C/T (rs5744455) polymorphisms in Japanese patients with severe respiratory syncytial virus–induced bronchiolitis and found that *CD14*−550C/T but not *CD14*−159C/T was significantly associated with the condition.[5]

The IL-4 receptor α gene *(IL4R)* is also one of the most frequently investigated genes and has been shown to be associated with atopy and atopic diseases.[6] The Ile50Val polymorphism (rs1805010) of the *IL4R* gene is a functional polymorphism and has been reported to be strongly associated with atopy and atopic asthma in the Japanese population. To date, only one study has reported the interaction of the *IL4R* Ile50Val polymorphism and day care attendance in the first year of life.[7] The result showed a

**TABLE I.** Characteristics of the subjects

| | |
|---|---|
| Total no. of participants | 473 |
| Age (mo) | |
| Mean ± SD | 111.1 ± 19.9 |
| Range | 76-147 |
| Sex ratio (male:female) | 1.00:1.01 |
| Day care attendance before age 2 y (%) | 14.5 |
| Total IgE (IU/mL), mean ± SD | |
| Male | 254 ± 340 |
| Female | 241 ± 469 |
| Prevalence of atopy (%) | |
| Male | 76.9 |
| Female | 68.0 |
| Prevalence of allergic disorders (%) | |
| Asthma | |
| Male | 14.1 |
| Female | 6.6 |
| Atopic dermatitis | |
| Male | 11.5 |
| Female | 9.7 |
| Allergic rhinitis | |
| Male | 42.1 |
| Female | 31.2 |
| Food allergy | |
| Male | 3.0 |
| Female | 3.4 |

significant gene-environment interaction for IFN-γ production at 1 year of age. However, it is not known whether this modified cytokine response affects the chance of having atopy or allergic diseases in the later period of life.

Here we report a relationship between serum total and specific IgE levels in Japanese elementary school children and day care attendance during earlier life. Our results suggest that day care attendance is associated with serum IgE levels, and this effect is modified by *CD14*−550C/T and *IL4R* Ile50Val polymorphisms. This is the first report that suggests an interaction between early-life day care attendance and genetic variations on IgE levels in later life.

Children attending an elementary school located in the central area of Chiba city (population of approximately 930,000) were recruited for this study. We first asked all (n = 843) children for participate in the survey. We then sent a detailed questionnaire to those who had a positive response (n = 582). Children with congenital heart diseases and lung diseases caused by immature birth were excluded. A total of 473 school children aged 6 to 12 years were enrolled. Blood samples were collected from 411 children on 2 separate days (July 3 and 12, 2006) for serum and DNA preparation. A complete set of information on total and 8 specific IgE levels, genotypes, and environmental factors was obtained from 375 children. All parents provided written informed consent. The study protocol was approved by the Ethics Committee of Chiba University Graduate School of Medicine.

The status of allergic diseases was evaluated by using questions based on the International Study of Asthma and Allergies in Childhood. We asked whether the child regularly attends a day care center where time is spent with other children at or before 2 years of age. For parents who responded yes to this question, the age of entry of their child to the day care center was obtained. The questionnaire also included the following items to assess possible confounding factors: number of siblings; number of older siblings; allergic diseases of parents and siblings (family history: scored as positive if parents, siblings, or both had any of 4 allergic diseases [asthma, allergic rhinitis, atopic eczema, and food allergy]); residential area (6 categories), type of house structure (5 categories), and floor type of bedroom (5 categories); yogurt/fermented food consumption; pet ownership; and smoking among family members.

Genotyping of the *CD14*−550C/T polymorphism was performed as described previously,[5] whereas that of the *IL4R* Ile50Val (rs1805010) polymorphism was carried out with the TaqMan allele-specific PCR method.[8] Primer sequences were as shown in this article's Online Repository at www.jacionline.org.

Table I shows the characteristics of the investigated population. The percentage of children who had regularly attended day care before 2 years of age was 14.5%. Atopy was defined as the presence of positive (≥0.35 IU/mL) specific IgE level against at least 1 of the 8 allergens. Although the prevalences of asthma, atopic dermatitis, and food allergy were compatible with those in a recent large study,[9] prevalences of allergic rhinitis and atopy were about 10 to 20 points higher, suggesting that children who had allergic rhinitis were more likely to attend this study.

Table II shows the association between day care attendance and serum IgE levels or atopy after being stratified with the *CD14*−550C/T genotype. Day care significantly decreased total IgE levels ($P = 9.7 \times 10^{-5}$), mite-specific IgE levels ($P = .0016$), and rate of atopy ($P = .00041$) in individuals with the C/T or T/T genotype, whereas the effect of day care was not observed in those with the C/C genotype. Numbers of children with the C/T+T/T genotype and those with the C/C genotype were similar, suggesting that the difference is not likely due to the statistical power for detecting association. Multivariate analyses with confounding factors were performed to evaluate the significance of this gene-environment interaction. The interaction between the *CD14*−550C/T polymorphism and day care was significant for $\log_{10}$(total IgE) ($P = .0046$), mite-specific IgE classes ($P = .00047$), and atopy ($P = .0097$) after adjusting for age, sex, family history, and number of siblings.

Table III shows the association between day care attendance and serum IgE levels or atopy after being stratified with the *IL4R* Val50Ile genotype. The effects of day care on total and some specific IgE levels were significant in Val/Ile heterozygotes but not in Val/Val or Ile/Ile homozygotes. In Val/Ile individuals day care significantly decreased total IgE levels ($P = .0012$), mite-specific ($P = .011$) and cedar pollen–specific ($P = .034$) IgE levels, and rate of atopy ($P = .018$). No such trend was observed in Val/Val or Ile/Ile individuals. The numbers of Val/Val and Val/Ile individuals were similar. It is therefore unlikely that the lack of significant association in Val/Val individuals was due to smaller statistical power for detecting association. When the significance of gene-environment interaction was assessed with the confounding factors, the interaction term between *IL4R* and day care attendance was significant for $\log_{10}$(total IgE) ($P = .019$) and mite-specific ($P = .0025$) and cedar pollen–specific ($P = .040$) IgE classes but not for atopy.

Total IgE levels in 4 genotype groups (group 1: *CD14* C/C, *IL4R* Ile/Ile+Val/Val; group 2: *CD14* C/C, *IL4R* Val/Ile; group 3: *CD14* C/T+T/T, *IL4R* Ile/Ile+Val/Val; and group 4: *CD14* C/T+T/T, *IL4R* Val/Ile) were compared to evaluate the combined effect of 2 polymorphisms on total IgE levels. Fig 1 shows the box

**TABLE II.** Effects of day care attendance on IgE levels when stratified by *CD14*–550C/T genotype

| | C/C | | | | C/T + T/T | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Day care attendance | | Effect size or odds ratio (95% CI) | *P* value | Day care attendance | | Effect size or odds ratio (95% CI) | *P* value | Gene-environment interaction *P* value* |
| | No | Yes | | | No | Yes | | | |
| No. of subjects | 169 | 22 | | | 157 | 28 | | | |
| $Log_{10}$(total IgE) | | | | | | | | | |
| Mean | 1.88 | 1.98 | 0.094 (−0.21 to 0.39)¶ | 0.54† | 2.09 | 1.58 | −0.50 (−0.26 to −0.76)¶ | $9.7 \times 10^{-5}$† | .0046** |
| SD | 0.77 | 0.76 | | | 0.63 | 0.51 | | | |
| Specific IgE (positive‡ rate) | | | | | | | | | |
| Mite | 0.49 | 0.59 | 1.50 (0.61 to 3.69)# | .51§ | 0.61 | 0.32 | 0.30 (0.13 to 0.71)# | .0016§ | .00047†† |
| Cedar pollen | 0.45 | 0.46 | 1.02 (0.42 to 2.45)# | .92§ | 0.57 | 0.32 | 0.35 (0.15 to 0.83)# | .032§ | .116†† |
| Atopy (rate) | 0.77 | 0.68 | 1.60 (0.56 to 4.55)# | .38‖ | 0.81 | 0.50 | 0.24 (0.10 to 0.55)# | .00041‖ | .0097‡‡ |

Boldface indicates statistically significant values.
*Adjusted for age, sex, number of siblings, and family history.
†Analysis of variance for $log_{10}$(total IgE [in international units per milliliter]).
‡Class ≥1 (≥0.35 IU/mL).
§Kruskal-Wallis test for IgE value (in international units per milliliter).
‖$\chi^2$ Test of independence.
¶Effect size.
#Odds ratio.
**General liner model.
††Generalized linear model (Poisson distribution, log link function).
‡‡Logistic regression.

**TABLE III.** Effects of day care attendance on IgE levels when stratified by *IL4R* Val50Ile genotype

| | Val/Val | | | | Val/Ile | | | | Ile/Ile | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day care attendance | | Effect size or odds ratio (95% CI) | *P* value | Day care attendance | | Effect size or odds ratio (95% CI) | *P* value | Day care attendance | | Effect size of odds ratio (95% CI) | *P* value | Gene-environment interaction *P* value* |
| | No | Yes | | | No | Yes | | | No | Yes | | | |
| No. of subjects | 125 | 18 | | | 152 | 27 | | | 49 | 5 | | | |
| $Log_{10}$(total IgE) | | | | | | | | | | | | | |
| Mean | 1.94 | 1.91 | −0.058 (−0.38 to 0.27)¶ | .72† | 1.88 | 1.55 | −0.44 (−0.71 to −0.18)¶ | .0012† | 1.99 | 2.32 | 0.33 (−0.31 to 0.97)¶ | .12† | .019** |
| SD | 0.64 | 0.72 | | | 0.57 | 0.56 | | | 0.69 | 0.52 | | | |
| Specific IgE (positive‡ rate) | | | | | | | | | | | | | |
| Mite | 0.57 | 0.56 | 0.95 (0.35 to 2.57)# | .51§ | 0.52 | 0.30 | 0.39 (0.16 to 0.94)# | .011§ | 0.59 | 0.80 | 2.76 (0.29 to 26.5)# | .36§ | .0025†† |
| Cedar pollen | 0.50 | 0.50 | 1.01 (0.38 to 2.73)# | .93§ | 0.51 | 0.30 | 0.41 (0.17 to 0.99)# | .034§ | 0.55 | 0.40 | 0.54 (0.083 to 3.54)# | .91§ | .040†† |
| Atopy (rate) | 0.74 | 0.72 | 0.93 (0.31 to 2.82)# | .90‖ | 0.74 | 0.52 | 0.37 (0.16 to 0.86)# | .018‖ | 0.76 | 0.80 | 1.30 (0.13 to 12.8)# | .82‖ | .118‡‡ |

Boldface indicates statistically significant values.
*Adjusted for age, sex, number of siblings, and family history.
†Analysis of variance for $log_{10}$(total IgE [in international units per milliliter]).
‡Class ≥1 (≥0.35 IU/mL).
§Kruskal-Wallis test for IgE value (in international units per milliliter).
‖$\chi^2$ Test of independence.
¶Effect size.
#Odds ratio.
**General liner model.
††Generalized linear model (Poisson distribution, log link function).
‡‡Logistic regression.

plot of $log_{10}$(total IgE) in 4 genotype groups. Among children who attended day care compared with group 1, the mean $log_{10}$ (total IgE) values of groups 2, 3, and 4 decreased by 0.41, 0.35, and 0.69, respectively. This magnitude of change suggests that the effects of *CD14* and *IL4R* were additive. The children in group 4 showed significantly ($P$ = .0046) lower total IgE levels than those in group 1. On the other hand, among children who did not attend day care, the $log_{10}$(total IgE) levels of children in groups 3 ($P$ = .031) and 4 ($P$ = .036) were significantly higher than those of children in group 1. The *CD14* C/T and T/T genotypes appeared to show the opposite effect on the serum total IgE level in children who did not attend day care compared

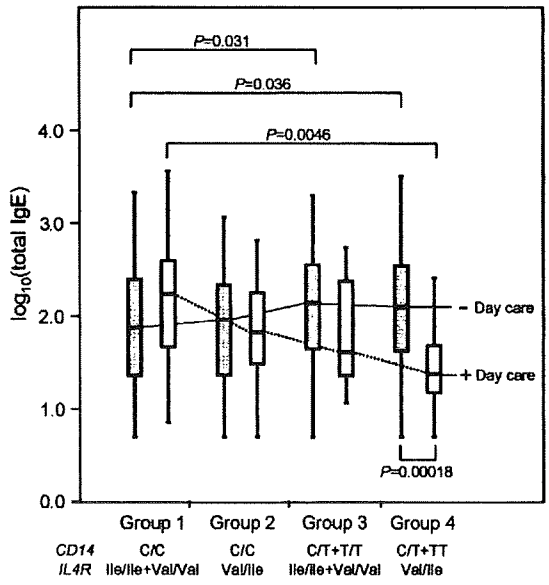


**FIG 1.** Total IgE levels in 4 groups of children classified based on a combination of *IL4R* and *CD14* genotypes. Box plot of $\log_{10}$(total IgE) values is shown for children who attended day care *(+Day care)* and for those who did not *(−Day care)*. Results are presented as medians and interquartile ranges. Only significant *P* values (<.05) are shown.

with those who did attend day care. When we examined the effect of day care in each genotype group, the effect was not sufficiently large to show a significant change in IgE level in groups 2 and 3, in which individuals had only 1 IgE level–decreasing genotype. However, in group 4, in which individuals had 2 IgE level–decreasing genotypes, the effect was sufficiently large to show a significant difference ($P$ = .00018). Significance of interaction between the *CD14* and *IL4R* genotypes was also evaluated by using general linear models in which age, sex, family history, number of siblings, and day care were included as variables. The interaction term of the 2 genes was not significant, suggesting an independent effect of the *CD14* and *IL4R* genes.

The interaction of the *CD14* gene with day care attendance suggests that the mechanism of the effect of day care involves at least in part a response to infection, environmental endotoxin exposure, or both. The interaction of the *IL4R* gene with day care attendance suggests that the mechanism also involves those related to $T_H2$ cell proliferation and IgE production. These results suggest that the complex nature of mechanisms underlies the effect of day care attendance on serum IgE levels.

Environmental factors investigated in the present study were determined based on a questionnaire on past day care attendance, and therefore recall bias can be a potential problem. The number of subjects investigated in this study was not so large and might be the acceptable minimum for investigating gene-environment interactions. The subjects evaluated were children who attended a single school and lived in a medium-populated city, thus representing those living in rather small regional environments in Japan. Nevertheless, these characteristics of the present sample might have contributed to minimizing the variances of background and outcome parameters and might have resulted in the positive findings obtained from a relatively small number of subjects. It is necessary to perform a cohort study to follow children with or without day care attendance until they reach school age to validate the current observations.

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# A Randomized Controlled Trial of Sublingual Immunotherapy for Japanese Cedar Pollinosis

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**Key Words**
Specific Immunotherapy · Allergic rhinitis · Clinical trial · Th2 · T cell clone

**Abstract**
***Background:*** Japanese cedar pollen represents an important and unique allergen. Sublingual immunotherapy (SLIT) has been suggested to be a highly effective route of desensitization against a variety of allergens. However, little information is available about its use in cedar pollen allergy. ***Methods:*** A blinded randomized, placebo-controlled trial employing SLIT for cedar pollinosis was conducted over a period of 6 months. Sixty-seven subjects were enrolled and the symptom scores during the pollen season were evaluated by a symptom diary, measurement of cedar-specific IgE and IgG4, and determination of Cry j-specific Th2 clones before SLIT and before and after the pollen season. ***Results:*** No major adverse effects were observed in either group. The serum-specific IgG4 activity increased significantly after SLIT in the active group. The active group also exhibited significantly lower symptom scores compared to the placebo. The specific Th2 clone sizes were not significantly different between the groups before the pollen season. However, an increase in the clone size was observed after the pollen season in the placebo group, but not in the active group. ***Conclusion:*** Use of SLIT for Japanese cedar pollinosis was found to be safe and associated with an increase in cedar-specific IgG4 levels. Such therapy inhibited the increase in Cry j-specific Th2 clone size induced by pollen exposure. Finally, use of SLIT resulted in significant improvement of the clinical symptoms of cedar pollinosis in this patient population. These observations suggest that SLIT may offer another safe approach to the management of cedar pollinosis.



## Introduction

In recent years, many countries have experienced an increase in the prevalence of allergic rhinitis as well as other allergic disorders [1, 2]. The most important pollen allergens in Japan are tree pollens, such as the Japanese cedar and Japanese cypress [3, 4]. With the exception of the Hokkaido and Okinawa regions, the Japanese cedar is widely distributed and occupies more than 18% of Japan's land surface area. The Japanese cypress is distributed predominantly to the west of the Kanto region. However, the planting of Japanese cedar trees is increasing. Cedar and cypress pollens share a common antigen

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