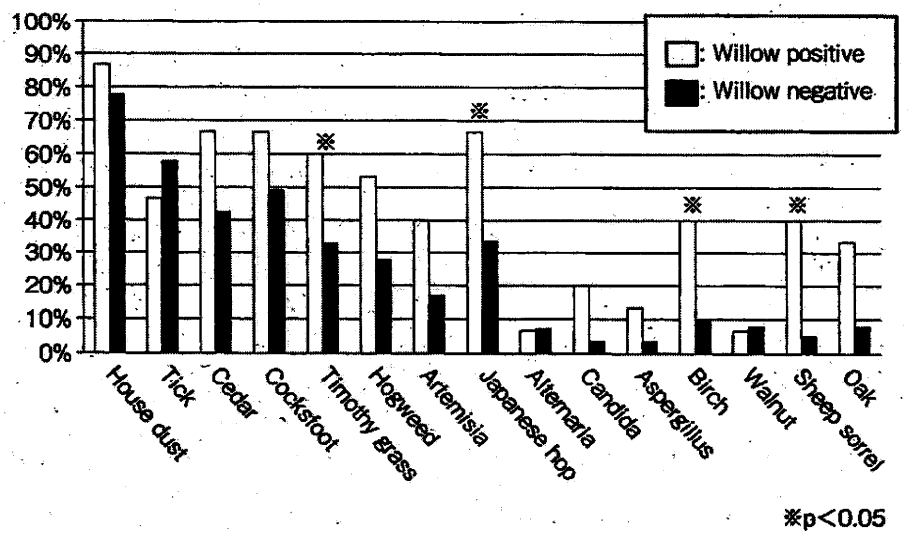

Fig. 8. Overlapping positive ratio with Willow.

カンバ森林蓄積やシラカンバ花粉RAST陽性率などの報告は数多くされており，現在では札幌市における花粉症抗原の約50%を占める重要な抗原であると考えられている[7][8]．シラカンバ花粉の飛散時期は北海道では4月から6月[9]，山形県では4月から5月中旬である．

クルミ花粉症は，栽培が盛んな長野県を中心に発生しており1976年に加藤らによってはじめて報告された．これは長野県の症例であるが近年は特に地域特性についての報告はない．花粉飛散時期は山形県では4月下旬から5月下旬である[10]．

ヒメスイバ花粉症の初報告は1974年に我妻らが行っており，北海道では6月下旬をピークにかなり飛散している[11]．北海道以外での地域特性についての報告はない．山形県では5月から6月である．

コナラ花粉症は1970年に降矢らが相模地方での報告を行っている[12]が，その他は特に地域特性についての報告はない．花粉飛散時期は北部で5月から6月，中央部以南は4月から6月[13]，山形県では4月下旬から5月下旬である．

ヤナギ花粉症の初報告は1980年に宇佐神が行っている．日本全土に分布しよく見かける植物であるが，地域特性についての報告はない．3月から5月に開花し花粉を飛散する[14]．山形県の花粉飛散時期は4月上旬から5月上旬である．

山形市の2002，2003年の各種花粉総飛散数(個/cm²)は以下の通りである．カバノキ属(248，531)，クルミ属(205，305)，コナラ属(2795，2094)と，スギ(3358，5798)と比べると少ないもののイネ科(352，192)と同等かそれ以上の総飛散数を認める[15][16]．シラカンバ・クルミ・ヒメスイバ・コナラ・ヤナギの花粉飛散状況や抗原陽性率，他の抗原との重複の状態，さらに地域特性についての報告は稀少であり，今回の検討の結果これらの花粉アレルゲンは臨床の場においても重要と考えられた．

年齢別では，ハウスダスト・ダニは若年層で抗原陽性率が高い傾向があり，これは曝露される機会が多いためと考えられる．また，カモガヤ・ブタクサ・カナムグラ・ヤナギでは31歳以降で抗原陽性率が高い．これはハウスダスト・ダニに比べると曝露される機会が少ないためと予想されるがその他の花粉抗原との差異については単純に曝露機会の問題だけでは説明しきれず，他の要因も関連してくる可能性がある．

スクラッチテスト施行時期別では，シラカンバ・ヒメスイバ・コナラ・ヤナギでは2~4月に

陽性率が高い傾向があり，なかでもヒメスイバは有意差を認めた．ヤナギはこれらの中でも比較的早期に花粉が飛散するので飛散時期と一部合致している傾向はあるが，その他は花粉飛散時期とは一致しなかった．2～4月はスギ花粉の飛散時期と重なるがスギ花粉陽性者は11～1月に多い傾向があり，花粉飛散時期と陽性者の多い時期は一致しなかった．イネ科も7～10月で陽性率が高く，こちらも花粉飛散時期とは一致していなかった．

シラカンバ陽性者ではクルミ・ヒメスイバ・コナラ・ヤナギ花粉との重複陽性率が高かった．シラカンバ花粉症患者は，リンゴ・サクランボなどを摂取した時に口腔・咽頭粘膜や口唇にかゆみ・腫脹などをきたし，時には蕁麻疹・呼吸困難，稀にショックを起こす口腔アレルギー症候群（oral allergy syndrome）の合併が多いとされる．合併率は報告によって31％から61％までと差が認められる．今回の調査では21％（19例中9例）であった．口腔アレルギー症候群は花粉と食物の交差抗原性が原因で起こるⅠ型アレルギー反応である．各花粉との重複陽性率の高さも交差反応性が原因である可能性が考えられる．

クルミ陽性者ではシラカンバ・コナラ花粉への重複陽性率が高く，ヒメスイバ陽性者ではシラカンバ・コナラ・ヤナギ花粉への重複陽性率が高く，ヤナギ陽性者ではシラカンバ・ヒメスイバ花粉への重複陽性率が高かった．これらは植物学的にもまったく異なったもの同士であり明らかな原因は不明である．

コナラ陽性者ではシラカンバ・クルミ・ヒメスイバ花粉への重複陽性率が高かった．シラカンバとコナラは科・属は異なるが同じブナ目同士であり植物分類学的には近い関係である．花粉アレルゲン間の交差反応性の程度は，植物分類学上の近縁関係の程度とほぼ一致しており，近縁度の高い関係にあるものほど強い交差反応性を示す[17]．同じ属のブタクサとクワモドキ（ブタクサ属），同じ科のシラカンバとハンノキ（カバノキ科）が花粉アレルゲン間の交差反応性を示すのと同様に同じ目のシラカンバとコナラにも交差反応性があるものと考えられる．

また，シラカンバ花粉とクルミ・ヒメスイバ・コナラ・ヤナギ花粉，クルミ花粉とコナラ花粉，ヒメスイバ花粉とコナラ・ヤナギ花粉では各々の陽性者にて重複陽性率が有意差をもって高く，何らかの共通抗原性を持つ可能性がある．今回の調査における重複陽性率の高さは何らかの交差反応性に起因する可能性があり，今後RAST inhibition test等を用いこれら花粉間の共通抗原性の有無を検索する必要と考えられた．

5. おわりに

今回の調査ではスギ花粉よりもイネ科花粉のほうが陽性率が高い傾向が認められた．イネ科花粉の飛散時期は5月から6月とスギ花粉飛散時期に続いており，スギ花粉飛散終了後も症状が遷延するイネ科花粉症患者の割合も高いと考えられる．また，花粉飛散時期がイネ科花粉に一致するシラカンバ・クルミ・ヒメスイバ・コナラ・ヤナギ花粉の陽性率も高い傾向がありイネ科花粉に対し陰性であってもこれらの花粉に反応し症状が悪化する患者も多数いるものと考えられる．臨床の現場においてはこれらが原因花粉である可能性も考え検査を進めていく必要があると考えられた．

この報告を持って山形市全体の花粉アレルギーの傾向を提言するには症例数が不十分であり今後も症例数を重ねることが必要と思われる．しかしシラカンバ・クルミ・ヒメスイバ・コナラ・ヤナギといった従来検討されていなかった花粉については臨床の場において無視できないものである可能性は示された．また，各々の花粉に重複して陽性を示す症例も多数存在し，何らかの共通抗原性が存在する可能性も示唆された．今後RAST inhibition test等を用いた抗原間の交差反応性の検索が必要と考えられた．

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（総合）研究報告書

アレルギー性鼻炎と下気道病変の連関性に関する研究

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研究要旨

花粉症における舌下ペプチド・アジュバンド療法開発の初期段階として、まずアレルゲン免疫療法を一般化させる必要がある。免疫療法の意義のひとつとして、鼻炎のみならず合併しえる下気道病変をもふくんだいわゆる one airway one disease に対する包括的治療としての期待がある。我々は、鼻疾患と喘息を合併する症例を対象に、鼻症状と喘息症状の連関の頻度及び特徴を調査する目的でのアンケート調査を行った。その結果、喘息コントロールのよくない患者では、鼻症状の悪化に伴い喘息症状が悪化しやすく、鼻治療により喘息症状が改善しやすいと自覚していることがわかった。また喘息は未発症でスギ花粉症のみの患者に、スギ花粉飛散前と飛散時期に喘息における下気道の炎症マーカーである呼気 NO 濃度を測定したところ、呼気 NO 濃度は飛散期においては有意に上昇していた。One airway one disease に対する包括的治療は喘息がある患者で特に重要であり、また喘息発症阻止に有益な可能性があり、アレルゲン免疫療法を主軸とした包括的なアレルギー診療が重要と考えられた。

A.　研究目的

わが国ではアレルゲン免疫療法の普及は著しく遅れている。特に舌下療法については先進国でこれが臨床に供されていない数少ない国のひとつとなってしまっており、まず、免疫療法の意義を広く再認識し、これを普及せしめることの重要性を、臨床医に広く認識してもらうことが急務である。

アレルゲン免疫療法の重要な特性として、花粉症・アレルギー性鼻炎に高率に合併する喘息症状に対しても効果が期待できる。すなわち、いわゆる one airway one disease に対する包括的治療としての意義がある。

アレルギー性鼻炎と気管支喘息が合併する割合は高く、アレルギー性鼻炎の 30-40%に気管支喘息が、気管支喘息の 50-80%にアレルギー性鼻炎が合併するとされている。またアレルギー性鼻炎患者では、気管支喘息を発症していなくても、気道過敏性亢進や好酸球の気管支への集積などの、喘息と同様の病態がサブクリニカルには観察されている。また鼻粘膜へのアレルゲン曝露が、下気道の平滑筋収縮、好酸球浸潤、気道過敏性亢進を誘導することも報告されている。さらに、鼻炎の治療を行うことで、喘息症状や気道過敏性を改善させ、急性増悪頻度を減少させうることも報告されている。このように上気道と下気道は、共通の進行する炎症性反応の影響を受け、連動するメカニズム(one airway one disease)により持続・増幅すると考えられている。

しかしながら、鼻炎と喘息の合併例における上気道症状と下気道症状の連関は、日常臨床において、すべての患者で観察されるものではない。また、両者の連関がどのような患者で観察されやすいかについては、今まであまり検討されてこなかった。今回我々は、鼻炎症状と喘息症状の連関についてアンケート調査を行い、その連関の頻度および特徴について検討した。

また鼻炎症例における潜在的喘息病変の早期発見の目的において、臨床的な気管支喘息の合併がないスギ花粉症症例を対象に、携帯用 NO 測定機器 NIOX MINO（Aerocrine 社）を用い、気管支喘息における下気道のアレルギー性炎症を評価する新規バイオマーカー検査である呼気 NO 濃度についての検討を行った。

B.　研究方法

1．鼻炎症状と喘息症状の連関についてのアンケート調査

埼玉医科大学病院アレルギーセンターに通院中の鼻炎症状と喘息症状を合併した患者 126 人を対象に、両者の連関についてアンケート調査を行った。性別は、男性 49 名、女性 75 名、記載なし 2 名であり、平均年齢は 48.1 歳であった。基礎疾患の内訳は、アレルギー性鼻炎 82 名、花粉症 74 名、

慢性副鼻腔炎 28 名、気管支喘息 113 名、咳喘息 16 名であった。アンケート調査により、①鼻症状と喘息症状の連関の頻度②どのような患者で、鼻症状の変化によって、喘息症状が影響されるか、について検討した。統計学的解析として、異なる 2 群における検討には $\chi 2$ 乗検定を用いた。

2．スギ花粉症症例における下気道のアレルギー性炎症の検討

通年症状がなく、純粋に２～４月のスギ花粉飛散時期のみに鼻炎症状を呈する、スギ花粉症症例 7 例を対象とした。全例が非喘息症例であり、非喫煙者であった。慢性閉塞性肺疾患(COPD)、気管支拡張症、びまん性汎細気管支炎などの慢性の気道性呼吸器疾患、心不全、脳血管障害など重症の基礎疾患を有する症例、妊娠している症例、鼻副鼻腔手術既往症例、う歯、歯科治療中の症例は除外した。

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。呼吸機能検査は、オートスパイロ 307(MINATO 社製)を使用して行った。呼気 NO 濃度は、携帯用 NO 測定機器 NIOX MINO（Aerocrine 社）で測定した。

C. 研究結果

1．鼻炎症状と喘息症状の連関についてアンケート調査

鼻症状と喘息症状を合併した患者 126 名のうち、38 名(30%)で、鼻症状の悪化に伴って喘息症状が悪化することを自覚し、28 名(22%)で、鼻治療により喘息症状が改善することを自覚していた。一方、28 名(22%)で、喘息症状の悪化に伴って鼻症状が悪化すると自覚し、24 名(19%)で、喘息治療により鼻症状が改善することを自覚していた。

どのような患者で、鼻症状の変化によって、喘息症状が影響されるか、についての解析は、アンケートの回答が得られた 99 名を対象とした。鼻症状の変化が喘息症状に与える影響は、喘息コントロールが良くない患者で有意に強かった。すなわち、通年的に喘息症状がある群では、通年的には症状がない群と比較し、鼻炎症状の悪化により、喘息症状が悪化するとより自覚していることがわかった(通年喘息症状あり 53%(31/58); 喘息症状なし 17%(7/41); p=0.0002)。さらに、通年的に喘息症状のある群では、鼻症状の治療により喘息症状がより改善すると自覚していた(喘息症状あり 36%(21/58); 喘息症状なし 17%(7/41); p=0.03)。鼻炎症状の悪化に伴う喘息症状の悪化を自覚する頻度及び鼻炎治療に伴う喘息症状の改善を自覚する頻度は、喘息の重症度別で有意差はなかったが、最重症持続型（ステップ 4 でコントロール不良）に相当する 5 名においては、5 名全員が、鼻炎症状が悪化すると喘息症状が悪化すると回答し、重症度が高くなると両者の連関を認識しやすくなる可能性が示唆された。また、副鼻腔炎のある患者で両者の連関はより強い傾向にあった。

2．スギ花粉症症例における下気道のアレルギー性炎症の検討

スギ花粉症症例において、スギ花粉飛散前期にあらかじめ呼気 NO が 40ppb 以上（喘息と診断しえるレベルの異常高値）であった症例が 1 症例存在した。これを除外した、6 症例について主に季節性のアレルゲン暴露に伴う変化の追跡を行った。これらの 6 症例において、各症状、鼻内所見は、鼻腔容積変化を除くすべてにおいて、スギ花粉飛散期に症状は悪化し、鼻内所見でも有意な変化を示した($p < 0.05$)。

呼気 NO 濃度については、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 との相関性では、花粉症症例、非花粉症症例ともに有意な相関性は認められなかった。

呼吸機能検査では、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。なおこれらの 6 症例においては、スギ花粉飛散時期においても、明らかな気管支喘息症状を呈した症例はみられなかった。

D. 考察：

アレルギー性鼻炎に伴って喘息症状が悪化する機序としては、①アレルゲンが直接下気道に到達し喘息症状を誘発する②鼻閉塞によってアレルゲンが下気道に侵入しやすくなる③鼻局所でロイコトリエンなどの化学伝達物質が産生・放出され、一部が下気道に下降する④アレルゲン曝露に伴い IL-5 などの Th2 サイトカインの産生が亢進し、骨髄に作用し好酸球を増加または活性化させ、気道への好酸球浸潤が増加する、などが想定されている。実際には、これらが複合的に病態形成に関与していると考えられるが、それぞれの関与の割合は不明である。今回、鼻疾患と喘息を合併する患者においては、約 30%で両者の連関を自覚していた。鼻に対する治療は、通年的に喘息症状がある患者で特に、喘息コントロールに重要と考えられた。自覚症状から見た場合、普段から喘息コントロールを良くすることが、鼻炎症状と喘息症状を合併している患者の管理において特に重要と考えられた。

アレルギー性鼻炎患者では、気管支喘息を発症していなくても、気道過敏性亢進や好酸球の気管支への集積などの喘息と同様の病態の存在がこれまでにも観察されている。今回検討したスギ花粉症症例においては、喘息性気道炎症のバイオマーカーである呼気NOが、飛散期と非飛散期とで有意差が認められ、飛散時期における明らかな上昇が認められた。このことから、スギ花粉症症例では、喘息に代表される下気道のアレルギー症状を臨床的に明らかに呈していない症例においても、潜在的には下気道にアレルギー性炎症が発現することが示された。これらの症例では喘息症状自体の発現、あるいは呼吸機能検査での気流制限、閉塞性換気障害の発現などはみられておらず、純粋なスギ花粉症患者においてのみみると、かかる下気道での炎症病態は臨床的な喘息を発症する前段階的なものである可能性が推察された。症例数が少ないため、スギ花粉症による呼吸機能への影響の頻度、大きさまでは言及できないが、呼気NOは、呼吸機能とは相間性を認めず、しかしながらスギ花粉飛散により有意な上昇が認められたことから、呼吸機能検査よりも早期に下気道の病態の変化を察知している可能性があるとも考えられた。

E. 結論

アレルゲン免疫療法には、花粉症・アレルギー性鼻炎に合併する喘息症状に対しても効果を期待しての、いわゆるone airway one diseaseに対する包括的治療としての意義が期待される。
本研究において鼻疾患と喘息を合併する患者では、約30%で両者の連関を自覚していることを確認した。通年的に喘息症状がある患者では、鼻治療により喘息症状が改善すると自覚しており、鼻治療は喘息コントロールに重要と考えられた。スギ花粉症の症例では喘息症状に代表される下気道の症状を訴えていない段階で、スギ花粉飛散時期において気管支喘息様のアレルギー性炎症が下気道に発現することが示された。
これらの成績が示唆するものは、鼻のみに対する例えば点鼻ステロイド療法であるとか、あるいはレーザー治療などといった局所的治療介入のみでは、スギ花粉症の包括的な治療アプローチとしては不十分である可能性である。舌下ペプチド・アジュバンド療法を含むアレルゲン免疫療法を主軸とした、上下気道にわたる包括的なアレルギー診療が必要と考えられる。
平行した研究において我々はアレルギー性喘息患者においては、低用量の吸入ステロイド療法によって長期的に寛解状態にある症例においても、吸入ステロイドを中止すれば下気道の炎症は再発し、喘息が再燃することを見出している(論文発表3)。アレルギー病態に対して包括的に機能するとともにその自然経過におよぼす効果が期待しえるアレルゲン免疫療法の意義は極めて重要であり、今後はわが国でも充分に普及されていく必要があると考える。

F. 研究発表

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G. 知的財産権の出願・登録状況(予定を含む)

1．特許取得
なし

2．実用新案登録
なし

3．その他
なし

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Changes in Airway Inflammation and Hyperresponsiveness after Inhaled Corticosteroid Cessation in Allergic Asthma

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Key Words

Airway hyperresponsiveness · Asthma, relapse · *Dermatophagoides farinae* · Eosinophils · House dust mites · Inhaled corticosteroids · Interleukin-4 · Remission, asthma

Abstract

Background: Most patients with asthma are currently controlled by pharmacotherapeutic means such as inhaled corticosteroid (ICS). However, whether ICS actually induces remission of asthma remains unknown. The present study evaluates changes in airway inflammation and hyperresponsiveness in adult patients with asthma after stopping ICS. ***Methods:*** We enrolled 11 patients with allergic asthma (7 males and 4 females; mean age, 52.3 years) who had been asymptomatic and had no exacerbation by low-dose ICS. Airway hyperresponsiveness (AHR) was assessed using methacholine challenge, and induced sputum was evaluated before and every 3 months after ICS cessation during the 1-year follow-up. ***Results:*** Among the 11 asthmatics, AHR increased in 10 (90.9%) and asthma clinically relapsed in 4 (36.4%) within 1 year of ICS cessation. AHR increased in all 7 asthmatics that were sensitized to *Dermatophagoides farinae* and asthma clinically relapsed in 4 (57.1%) of them. Furthermore, eosinophil numbers and IL-4 concentrations in the sputum significantly increased after ICS cessation. ***Conclusions:*** Remission with normal airway response to methacholine (no AHR) might be rare in adult patients with allergic asthma, and sensitization to house dust mites appears to play an important role in relapse. Therefore, ICS cessation should be carefully considered in patients sensitive to house dust mites. Serial determination of eosinophil counts or IL-4 concentrations in sputum might be appropriate for monitoring and preventing asthma relapse in adults.

Introduction

The prevalence of asthma is increasing, and effective pharmacological therapies such as inhaled corticosteroid (ICS) and other management strategies have been developed that have rendered asthma manageable. However, whether ICS could actually induce asthma remission (defined as the absence of asthma symptoms without asthma treatment [1]) was uncertain.

Asthma remission rates are considerably higher in childhood than in adults [2–12]. For example, Vonk et al. [2] reported that 22% of asthmatic children achieved complete remission [defined as the absence of asthma symptoms, no ICS use, normal lung function and no airway hyperresponsiveness (AHR)] and a further 30% achieved clinical remission (no symptoms and no ICS; total 52%) by the age of 32–42 years. In a study by Seker-

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el et al. [3], 27% and a further 26% of asthmatic children achieved complete remission (no symptoms, no medications, normal lung function and no AHR) and clinical remission (no symptoms and no medications), respectively, by the age of 17 years. Age at onset [4], disease duration [4], response to initial treatment [2, 5], forced expiratory volume in 1 s (FEV_1) at onset [2, 5–9], AHR at onset [6–9], total IgE [5–11], female gender [3, 6] or sensitization to house dust mites [8, 10] were predictive factors for remission or relapse of childhood asthma.

In contrast, little information is available regarding remission or relapse of adult asthma. Therefore, the prognosis of adult asthma is not understood in detail, and how treatment could be reduced or stopped has not been fully clarified. The Global Initiative for Asthma guidelines recommend that therapies for asthma control, e.g. ICS, can be stopped if asthma remains controlled in patients on the lowest dose and symptoms do not recur for 1 year [12]. However, the guidelines also indicate that little experimental data support the optimal timing, sequence and magnitude of reductions or cessation of treatment for asthmatic adults [12].

The present study investigates whether ICS administration could be stopped in adult asthmatics without relapse or AHR induction. We also evaluated changes in airway inflammation and AHR after ICS cessation.

Patients and Methods

Patients and Study Protocol

This observational study was conducted in the Allergy and Asthma Center of the Saitama Medical University Hospital after receiving approval from the Institutional Review Board of the Hospital and written informed consent from all patients who participated. Adult asthmatics that had been asymptomatic by low-dose ICS (fluticasone propionate 100 μg b.i.d. or equivalent) were evaluated for 12 months after ICS cessation. Asthma was diagnosed based on a history of recurrent wheezing, dyspnea, chest tightness and either reversible airflow limitation (FEV_1 <70% of predicted or a previous best value that increased by >15% after the inhalation of 200 μg salbutamol) or methacholine (MCh)-induced AHR. Before enrolment, we confirmed that the patients had been regularly treated with ICS for at least 6 months without regular long-acting bronchodilators, and that they had been asymptomatic and stable on low-dose ICS over the past 3 months. Eleven adult patients (7 males and 4 females, mean age 52.3 years, range: 30–71 years) participated in the study. All were atopic according to positive skin prick tests or had specific IgE antibody in response to common inhalant allergens such as house dust mites *(Dermatophagoides farinae, Df)*. None of the patients had any other respiratory or systemic disease.

At the start of the run-in period, all of the patients recorded symptom scores and peak expiratory flow rates (PEFR) using a diary. At the end of the run-in period, all of them underwent baseline spirometry, the MCh challenge test and sputum evaluation for inflammation. To proceed to ICS cessation, asthma had to be 'controlled'. We defined 'controlled' asthma based on the definition of 'totally controlled' asthma in the Gaining Optimal Asthma ControL (GOAL) study [13] except for the evaluation of 'morning PEF'. (We used 'over 80% personal best' criteria, but not 'over 80% predicted' criteria [13].) After treatment cessation, all patients underwent the MCh challenge test and sputum evaluation every 3 months, and PEFR was monitored and symptoms were managed for 12 months. Relapse was defined as insufficient asthma control according to the GOAL study [13].

Monitoring PEFR and Asthmatic Symptoms

All of the patients monitored PEFR using a mini-Wright Peak Flow Meter twice daily (early morning and at bedtime before drug inhalation) for 3 consecutive months at the start of the study (run-in period) and then for up to 12 months. The weekly mean of the highest value of three exhalations into the meter (mean PEFR) was recorded in their diaries and evaluated. All patients also recorded asthmatic symptoms (cough, dyspnea and wheezing) in their diaries.

Pulmonary Function and MCh Challenge Tests

Pulmonary function tests were performed according to the American Thoracic Society guidelines [14] using an AS307 spirometer (Minato Medical Science, Osaka, Japan) and the MCh challenge proceeded as described previously [15, 16]. Briefly, baseline FEV_1 was recorded and then, after confirming that FEV_1 did not fall with an inhalation of saline, increasing concentrations of MCh (39–20,000 μg) were delivered using a DeVilbiss 646 jet nebulizer every 2 min, and FEV_1 was measured immediately after each inhalation. The concentration of MCh that induced a 20% fall in FEV_1 was calculated from the semi-log scale dose-response curve and is expressed as PD_{20} FEV_1 (cumulative dose producing a 20% fall in FEV_1).

Sputum Induction and Processing

Sputum was induced as described previously [17–19]. Salbutamol was delivered using a metered dose inhaler. Fifteen minutes later, sterile hypertonic saline (4.5%) was inhaled using an ultrasonic nebulizer at room temperature. Sputum was collected at 5-min intervals for up to 30 min. Rinsing with mouthwash before each expectoration was encouraged to minimize salivary contamination. All initial samples were discarded. Induced sputum samples collected into 50-ml polypropylene tubes were stored at 4°C for processing. Hanks' balanced salt solution (HBSS; 1 ml) containing 1% dithiothreitol (Sigma, St. Louis, Mo., USA) was added to sputum samples, which were then vortex mixed and repeatedly aspirated at ambient temperature until the mixture was homogeneous. Samples were diluted with HBSS to 5 ml, and separated by centrifugation at 400 *g* for 10 min. Cytokine concentrations were measured in supernatants, and cytospin slides of resuspended pellets were stained with May-Giemsa for differential cell counts. At least 500 inflammatory cells were counted for each sample. Cytospin slides were judged as adequate when <50% of squamous epithelial cells were present. Concentrations of IFN-γ and IL-4 in sputum supernatants were measured using Bio-Plex assay kits (Bio-Rad, Mississauga, Ont., Canada).

Table 1. Clinical characteristics of the patients

Patients			Disease duration years	FEV_1 % of predicted	Total IgE IU/ml	Specific IgE Ab to mite	Pets	Pediatric asthma	Smoking
No.	sex	age years							
1	F	67	7	105	33	–	dog	–	–
2	M	60	14	91	73	–	–	–	–
3	M	71	15	66	985	–	cat	–	–
4	F	64	17	89	188	+	cat	–	–
5	M	34	31	66	364	+	–	+	–
6	M	59	14	72	639	+	–	–	+
7	F	44	6	98	396	+	cat	–	–
8	M	30	1	112	524	+	–	–	–
9	M	63	23	72	67	–	cat	–	–
10	M	53	27	85	32	+	–	+	–
11	F	30	10	94	1,443	+	–	–	–

Table 2. Outcome after ICS cessation

Patient No.	PD_{20}, μg/ml		Recurrence
	before	after	
1	>20,000	312	–
2	>20,000	<78	–
3	154	78	–
4	3,375	ND	+ (10)
5	624	ND	+ (4)
6	1,812	ND	+ (16)
7	>20,000	4,750	–
8	>20,000	18,500	–
9	1,125	468	–
10	2,375	ND	+ (12)
11	2,812	1,875	–

ND = Not done. Mean duration of asthma recurrence after ICS is shown in parentheses (in weeks).

Statistical Analysis

Statistical significance was determined using the Kruskal-Wallis test. $p < 0.05$ was considered to indicate a statistically significant difference. Values are shown as means ± SEM.

Results

Treatment with ICS was discontinued in 11 patients with asthma that was 'controlled' by a minimal dose of ICS (fluticasone propionate 100 μg b.i.d. or equivalent) for >3 months. All of them had allergic asthma, 9 had adult-onset and 2 had a history of pediatric asthma. Ten were nonsmokers, 1 currently smoked, and 1 had used a short-acting β_2-agonist within the past year. In 8 patients, the duration of asthma was >10 years and FEV_1 was <70% of predicted in 2 of them (table 1).

Within 1 year of stopping ICS, AHR worsened in 10 (90.9%) of the 11 patients and asthma recurred in 4 (36.4%) of them (table 2). Asthma symptoms recurred in some patients immediately after ICS cessation and in all of them within 4 months. All of those with clinical asthma relapse were sensitized to *Df*, and the 1 current smoker as well as the patient who had used the short-acting β_2-agonist within the past year also relapsed. Of the 7 patients with specific IgE antibody against *Df*, AHR aggravated in all of them and asthma recurred in 4 (57.1%). AHR worsened in all 5 patients with a pet (dog or cat). Four patients without AHR during the run-in period have remained asymptomatic for 1 year (tables 1, 2).

Sputum was obtained from 9 patients. After ICS cessation, AHR worsened in 8 of them and 3 relapsed. The ratio of eosinophils in sputum obtained immediately before asthma relapse or AHR induction was significantly increased compared with that obtained during the run-in period (2.1 ± 0.6 vs. 1.1 ± 0.3%, $p < 0.05$; fig. 1). Macrophages, neutrophils, lymphocytes and total cell counts in sputum did not significantly differ (data not shown).

We measured cytokine concentrations in the sputum from 6 patients. After ICS cessation, AHR worsened in all patients and 2 relapsed. The IFN-γ concentration did not significantly change after ICS cessation (before vs. after cessation: 46.1 ± 10.6 vs. 34.6 ± 6.1 pg/ml; fig. 2). In contrast, the IL-4 concentration in sputum obtained just before asthma relapse or AHR induction was significantly increased compared with that during the run-in period (2.8 ± 0.8 vs. 1.5 ± 0.5 pg/ml, $p < 0.05$; fig. 2).

Among other potential predictors of asthma recurrence, the influence of disease duration, ICS treatment duration, lung function (e.g. FEV_1 and PEFR) or eosinophils in peripheral blood were also investigated, but none was associated with clinical relapse.

Discussion

We demonstrated that among 11 adult patients with allergic asthma 'controlled' by low-dose ICS alone, ICS cessation induced an increase in AHR in 10 (90.9%) of them and asthma relapse in 4 (36.4%). The discontinua-

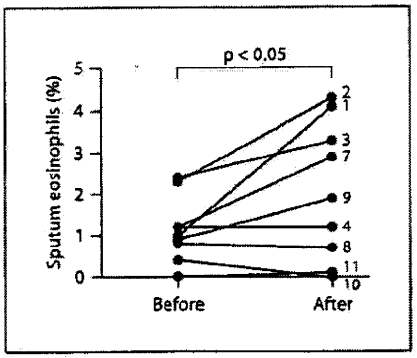

Fig. 1. Changes in sputum eosinophil ratios (%) after ICS cessation. Sputum was obtained from adult asthmatics (n = 9) during the run-in period (before cessation of ICS) or at the end of the study (after ICS cessation). Eosinophils were identified by May-Giemsa staining and morphologically. Patient numbers are shown on the right.

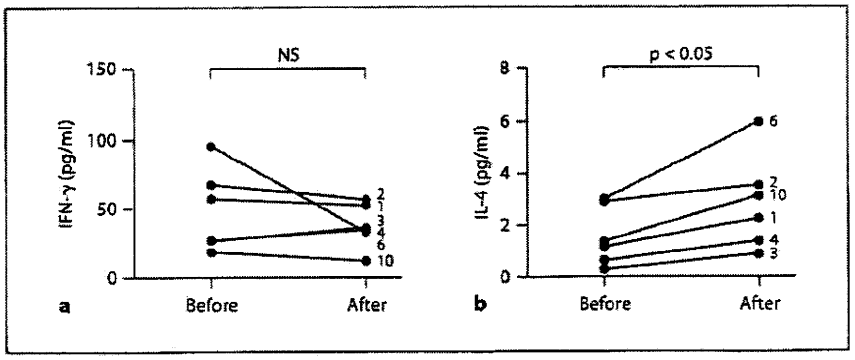

Fig. 2. Changes in IFN-γ (**a**) and IL-4 concentrations (**b**) in sputum after ICS cessation. Sputum was obtained from adult asthmatics (n = 6) during the run-in period (before cessation of ICS) or at the end of the study (after ICS cessation). Concentrations of IFN-γ or IL-4 in sputum supernatant are shown. Patient numbers are shown on the right. NS = Nonsignificant.

tion of ICS resulted in an increase in AHR in all 7 *Df*-sensitized adult asthmatics and asthma relapse in 4 (57.1%). The 4 who clinically relapsed were all sensitized to *Df*. Eosinophil numbers and IL-4 concentrations increased in sputum immediately before asthma relapse or AHR induction. These results indicate that remission in adult patients with allergic asthma, especially among those who are sensitized to house dust mites, is rare. The results also suggest that the eosinophil count or IL-4 concentration in sputum after ICS cessation could be an important predictive factor for relapse in adult asthma.

There is no standardized definition about complete remission or clinical remission in adult asthma. In this study, we used the term 'remission', but not 'complete remission' or 'clinical remission', according to the definition by the Japanese Pediatric Guidelines for the Treatment and Management of Asthma [1], as we evaluated patients only 1 year after ICS cessation. Our results demonstrated that only 1 patient (9.1%) achieved remission with normal airway response to MCh (no AHR) even 1 year after ICS cessation (table 2). Six patients had AHR without asthma symptoms for 1 year (54.5%), and asthma relapsed in 4 (36.4%) patients, all of whom relapsed within 4 months (table 2). Panhuysen et al. [20] studied 181 asthma patients aged 13–44 years at enrolment and found that only 11% remained in remission with no AHR and normal lung function after 25 years. Moreover, recent reports suggest that about 50% of adult asthmatics relapse within 1 year after ICS cessation [21–23], and that most clinical relapses occur within 3 months [21, 24]. Therefore, our results were consistent with these previous studies and confirmed that remission with no AHR in adult asthma would be more difficult to achieve. As increasing evidence indicates that airway inflammation is present during the remission of allergic asthma [25], our results might support the significance of an anti-inflammatory strategy, such as ICS therapy for asymptomatic adult asthmatics, but further studies are required.

AHR worsened in 10 (90.9%) of the 11 patients with allergic asthma after ICS cessation, and asthma recurred in 4 (36.4%) of them (table 2). Of the 7 *Df*-sensitized adult asthmatics, AHR was aggravated in all of them and asthma recurred in 4 (57.1%). Therefore, the atopic status, especially sensitization to house dust mites, may play an important role in the pathogenesis of asthma relapse, leading to the hypothesis that relapse in allergic asthma might be inevitable unless allergen avoidance is completely achieved. In childhood asthma, Bjerg-Bäcklund et al. [26] reported that the frequency of remission was significantly higher in non-allergic asthmatics than in allergic asthmatics. Limb et al. [11] reported that lower IgE levels and fewer positive allergy skin tests in addition to milder symptoms were factors predictive of remission of moderate-severe asthma. Sears et al. [27] reported that factors predictive of relapse were childhood sensitization to house dust mites as well as AHR and early age at onset. Our results in adult asthma were consistent with these findings in childhood asthma. Moreover, sensitization to

inhalant allergens, e.g. house dust mites, increases the risk of developing asthma [28, 29]. Toelle et al. [6] demonstrated that in addition to a low FEV_1 and AHR, atopy in childhood is a predictive factor for having asthma in adulthood. In a study by Visser et al. [7] the increase in AHR after ICS withdrawal was associated with more atopic features (positive RAST and high IgE) as well as lower FEV_1 levels, indicating that continued sensitization to house dust mites could trigger the development of asthma or the increase in AHR.

Eosinophils and IL-4 concentrations in sputum increased immediately before asthma relapse or AHR induction (fig. 1, 2), suggesting that the Th2-mediated immune response played an important role in these processes. Eosinophils release various lipid mediators, cytokines and growth factors involved in the pathogenesis of asthma [30]. IL-4 drives B-cell isotype switching from IgM to IgE [31] and augments eosinophil adhesion to and transmigration of eosinophils through the endothelium by enhancing the expression of adhesion molecules on endothelial cells [32], thus initiating eosinophil infiltration into the airways. In a report by Masuyama et al. [33], intranasal corticosteroid inhibited eosinophilic nasal inflammation and mRNA expression of IL-4 in the nasal mucosa, suggesting that IL-4 would mediate the development of eosinophilic inflammation in the airways. In a mouse model of allergic airway inflammation, To et al. [34] reported that antigen systemic sensitization could induce AHR and increase IL-4 concentration in bronchoalveolar lavage fluid before or at the early phase of eosinophilic airway inflammation. Therefore, IL-4 played an essential role in the increase in AHR at the early phase of eosinophilic airway inflammation, which was consistent with our results.

The effect of eosinophil counts in sputum on the prevention of asthma exacerbation has recently been highlighted [35], and Deykin et al. reported that asthma relapse in children is associated with an increased number of eosinophils in sputum [36]. Furthermore, Giannini et al. [23] reported that sputum eosinophil ratios significantly increase during symptom recurrence in adult asthmatics after ICS cessation. Therefore, evaluation of eosinophils in sputum would be a reasonable strategy for monitoring and preventing asthma relapse. Serial measurements of Th2 cytokines such as IL-4 in sputum might also be useful for monitoring.

However, limitations of this study were the small study cohort (only 11 patients participated in this study) and the allergic type of their asthma. Therefore, caution should be applied when extrapolating the findings of this study to all asthmatics. Further studies are required to clarify changes in eosinophil ratios and IL-4 concentrations in sputum after ICS cessation in all types of asthma, including non-allergic asthma.

In conclusion, we demonstrated that remission in adult patients with allergic asthma, especially those who are allergic to house dust mites, is difficult to achieve. Eosinophil ratios and IL-4 concentrations in sputum increased immediately before asthma relapse or AHR induction. Therefore, ICS cessation should be carefully considered in *Df*-sensitized adult asthmatics. Serial examination of eosinophil counts or IL-4 concentrations in sputum might provides a reasonable and useful strategy for monitoring and preventing asthma relapse.

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Disclosure Statement

The authors declare that no financial or other conflict of interest exists in relation to the content of this article.

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REVIEW ARTICLE

Allergen Immunotherapy in Asthma: Current Status and Future Perspectives

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ABSTRACT

Allergen immunotherapy targets Th2 cells activated by specific allergens, which constitutes the basis of allergic disease. Therefore, this approach has therapeutic potential for a variety of allergic diseases, including asthma, and may modify their natural course. Immunotherapy results in systemic immunological changes to allergens, thereby providing clinical benefits in allergic asthma. For example, immunotherapy attenuates T-cell-mediated airway inflammation by down-modulating Th2 and inducing Th1 differentiation. In addition, immunotherapy induces regulatory T cells, which produce IL-10. Meta-analysis has demonstrated that allergen immunotherapy improves clinical symptoms and non-specific airway hyperresponsiveness in asthma, and decreases drug requirements. Clinical studies have supported the usefulness if immunotherapy in mild to moderate asthma cases, particularly in patients with concomitant rhinitis. Several promising novel approaches have emerged as future immunotherapeutic strategies for the treatment of asthma. Current pharmacotherapy, including inhalational corticosteroids, provides powerful anti-symptomatic benefits in asthma; however, pharmacotherapy cannot cure or modify the natural course of asthma. As immunotherapy targets the background immunological state in asthma, it is expected to lead to long-term amelioration or cure. It is hoped that the positioning of allergen immunotherapy as a treatment option will allow the comprehensive management of symptoms in allergic individuals, and the modification of disease course.

KEY WORDS

allergic asthma, allergic conjunctivitis, allergic rhinitis, immunotherapy, Th2 responses

INTRODUCTION

Allergen immunotherapy constitutes a treatment method that modifies immunoreactive responses to specific allergens by administrating allergens that cause allergic diseases such as asthma. According to the WHO position paper,[1] immunotherapy is effective for diseases that are associated with type I allergic reactions, such as allergic rhinitis and allergic bronchial asthma. As a result of anti-symptomatic therapies, including the use of inhalational corticosteroids (ICS), management of asthma has markedly improved. Consequently, the use of allergen immunotherapy has been reduced. However, there is increasing evidence that ICS does not affect the natural course of asthma.[2-4] Furthermore, ICS does not provide therapeutic benefits for symptoms caused by rhinoconjunctivitis, which is commonly observed in asthmatic patients. In contrast to ICS, allergen immunotherapy targets the Th2 cells pathophysiologically activated by specific allergens, thus providing therapeutic potency for the variety of allergic diseases observed simultaneously in allergic individuals, and possibly modifying the natural course of allergic diseases.[1] In this article, the authors review the current understanding of the role of allergen immunotherapy in asthma and discuss future perspectives of this treatment modality in this field.

MECHANISMS OF ALLERGEN IMMUNOTHERAPY

Airway inflammation is a key feature of asthma. For example, infiltration of activated eosinophils is an important factor and is known to be associated with disease severity. In successful cases of immunotherapy in asthma, indexes of airway inflammation, including

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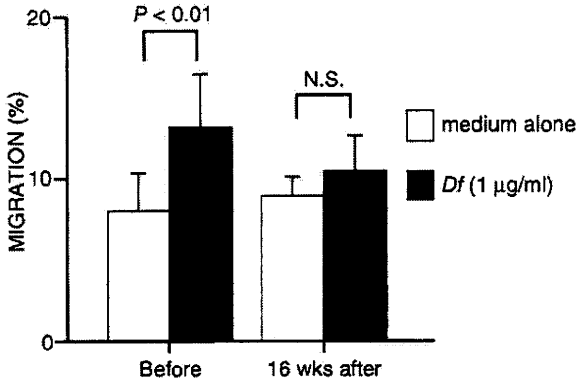

Fig. 1 Eosinophil transendothelial migration induced by culture supernatants of peripheral blood mononuclear cells (PBMC) obtained from *Dermatophagoides farinae* (*Df*)-sensitive atopic asthmatics treated by rush immunotherapy (n = 5). *Df* (-); eosinophil migration in response to supernatants of PBMC cultured with medium alone. *Df* (+); eosinophil migration in response to supernatants of PBMC cultured with *Df*-antigen. Data are expressed as mean ± SEM.

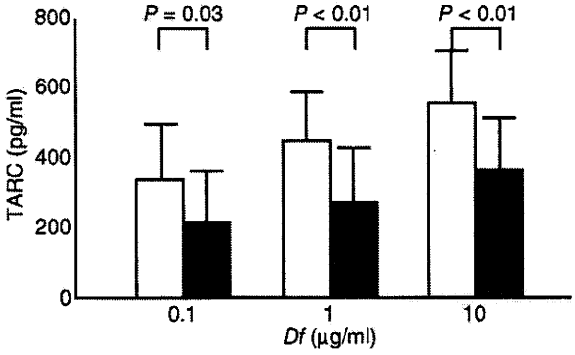

Fig. 2 Effects of rush immunotherapy on production of TARC by peripheral blood mononuclear cells obtained from house dust mite-sensitive asthmatics. Open bars represent data before immunotherapy, and closed bars represent data at 16 weeks following induction of allergen immunotherapy. Data are expressed as mean ± SEM from 8 donors.

the number of infiltrated eosinophils and/or concentrations of eosinophil specific-granule proteins, are reduced.[5-7] For circulating eosinophils to accumulate in asthmatic airways, they must adhere to and then migrate across vascular endothelial cells. These processes are largely regulated by cytokines/chemokines produced by various cells, including Th2 cells. During the allergen exposure period in birch pollen asthma, increased adhesiveness of peripheral blood eosinophils and increased chemotactic activity for eosinophils in bronchoalveolar lavage fluid are observed, and these actions are blocked by immunotherapy.[5,8]

The authors previously confirmed that stimulation of mononuclear leukocytes from house dust mite-sensitive allergic asthmatics with mite-allergen results in productions of eosinophil adhesion-inducing activity, eosinophil chemotactic activity, and eosinophil transendothelial migration-inducing activity and the increases of those parameters were attenuated in patients treated with allergen immunotherapy (Fig. 1).[9-11] These findings suggest that modification of the responsiveness of T cells, particularly Th2 cells, to specific allergens by immunotherapy results in the suppression of eosinophil accumulation in the airways. These effects are likely to involve down-regulation of Th2 cells.

It has been demonstrated that the production of Th2 cytokines, such as IL-4 and IL-5, is decreased by immunotherapy.[8,12] We recently found that immunotherapy attenuates the house dust mite allergen-specific production of TARC, a potent chemokine activator of Th2 cells, from peripheral blood mononuclear cells obtained from patients with house dust mite-sensitive allergic asthma, thus suggesting that immunotherapy can reduce accumulation of Th2 cells during allergen exposure (Fig. 2). Therefore, immunotherapy results in systemic immunological changes in response to allergens, and provides some clinical benefits in allergic asthma. In addition to modulating effects on the Th2 cascade, immunotherapy induced differentiation to the Th1, rather than the Th2, phenotype in Th0 cells.[13]

It has been reported[13] that allergen-challenge-induced expression of IL-12 mRNA in the skin was augmented by immunotherapy. These findings support the notion that immunotherapy attenuates T-cell-mediated airway inflammation via down-modulation of Th2 and induction of Th1 differentiation. There is also increasing evidence that immunotherapy induces regulatory T cells (Treg), which produce IL-10 and down-modulate allergic inflammation.[14-16] For example, in bee venom allergy, immunotherapy increases the production of IL-10, which is associated with inhibitory effects in response to specific allergens. However, recent investigations using immunotherapy with Th1 adjuvants, such as CpG-motif, have shown some clinical benefits without production of IL-10, thus indicating the need for further research to elucidate the significance of Treg/IL-10. Involvement of Treg/IL-10 in immunotherapy for Th2 suppression may be regulated by multiple factors, including allergen, adjuvant and time of assessment.

CURRENT STATUS OF ALLERGEN IMMUNOTHERAPY IN ASTHMA

The clinical indications for immunotherapy in asthma are not fully established; however, this therapy should be considered for allergic asthma patients who have identified environmental aero allergens that

Table Clinical effects in terms of step-down rate after rush immunotherapy in house dust mite-sensitive asthmatics

	FEV_1%		Duration	
	≧70%	<70%	≧10 y	<10 y
Unchanged:	15 (39.5%)	8 (66.7%)	18 (54.5%)	5 (29.4%)
Improved:	23 (60.5%)	4 (33.3%)	15 (45.5%)	12 (70.6%)
	$P = 0.009$		$P = 0.043$	

are difficult to avoid or for cases that are not severe and present normal pulmonary function. This approach was outlined in the recent US asthma guideline Expert Panel 3.[17] In asthma, meta-analysis has demonstrated that allergen immunotherapy improves clinical symptoms and non-specific airway hyperresponsiveness, and decreases drug requirements.[18] For immunotherapy to be successful, the maintenance allergen dose to be administered should be sufficiently high. In rush immunotherapy, patients are hospitalized and repeatedly injected under clinically controlled conditions, and the target concentration is easily achieved in several days, with clinical effects being seen rapidly[19]; improvement in symptom medication scores and allergen-specific bronchial hyperresponsiveness typically appears within several weeks. Using this method, we observed that clinical effects, based on the rate of obtaining step-down of asthma severity, is significantly less in patients with more than 10 years of disease or FEV1% of less than 70% (Table). Therefore, it is conceivable that immunotherapy would be beneficial for asthmatics with early-stage allergic asthma, without development of airway remodeling.

What happens if immunotherapy is prescribed in addition to ICS? Current pharmacotherapy, including ICS, recommended by the latest guidelines tends to rapidly improve symptoms in mild to moderate asthma. Maestrelli *et al.*[20] investigated the additional effects of immunotherapy when it was combined with pharmacotherapy according to the Global Initiative for Asthma (GINA) guidelines in mild to moderate disease in mite-sensitive asthmatic patients. The immunotherapy group showed partial suppression in mite-induced immediate skin reactions, decreased frequency of rescue use of short-acting β2-agonist, and improved peak expiratory flow rate, thus suggesting immunotherapy provides additive effects in patients treated with ICS. More recently, Garcia-Robaina *et al.*[21] investigated the effects of a depigmented polymerized allergen vaccine containing a 50% mixture of *Dermatophagoides pteronyssinus* and *Dermatophagoides farina* on mild to moderate asthma, and found that the median improvement in total symptom and medication scores in the active versus placebo group was 53.8% and 58.1%, respectively. This study also demonstrated that this immunotherapy improves symptoms of rhinoconjunctivitis, thereby confirming that immunotherapy acts as an active systemic therapy for allergic individuals. In this context, Marogna *et al.*[22] compared the effects of sublingual immunotherapy (SLIT) and ICS in patients with mild asthma and concomitant rhinitis due to grass pollen allergy. After a run-in season, patients were randomized to either 800 μg/day budesonide, an ICS, during the pollen season or continuous grass SLIT for 5 years. Asthma symptoms decreased significantly in both groups; however, improvements were greater in the SLIT patients at 3 and 5 years. Furthermore, a decrease in both nasal symptoms and nasal eosinophils was observed only in the SLIT group. These results indicate that SLIT is equally effective as ICS in treating seasonal asthma and provides benefits in treating rhinitis symptoms.

Taken together, these clinical studies confirmed the rationale of current US guideline EPR3, and support the usefulness of immunotherapy in mild to moderate asthma, particularly in those with rhinoconjunctivitis.

MODIFICATION OF NATURAL HISTORY BY IMMUNOTHERAPY

What about the significance of immunotherapy in its original role of modification of the natural history of allergic diseases such as asthma? The approaches described in the following section provide promising data. As noted above, it is speculated that immunotherapy would be less effective in asthmatic patients with longer disease period because of development of airway remodeling. Moller *et al.*[23] investigated the effects of immunotherapy on onset of asthma in pollen allergy rhinitis patients. Non-specific airway hyperresponsiveness during the pollen season improved only in the active treatment group. After three years of follow up, the ratio of asthma development was significantly lower in the immunotherapy treatment group (21%) than in the control group (44%). These results suggest that immunotherapy is more effective when introduced at early stages.

Thus, Di Rienzo *et al.*[24] investigated whether mite-allergen immunotherapy using SLIT can improve the natural course of children suffering from mite allergy. At the end of a 4- to 5-year course of SLIT treatment and a further 4 to 5 years after SLIT discontinuation, there was a significant reduction in the presence of asthma in the treated patients, as compared with baseline. On the other hand, in the control group, no clinical changes were observed after 5 and 10 years of follow-up. There was a highly significant difference between the two groups, at both the end of SLIT and after 5 years. This study demonstrates that SLIT improves the prognosis of children with mite allergy, and that clinical efficacy is maintained for 4 to 5 years after discontinuation.

NEW APPROACHES FOR ALLERGEN IMMUNOTHERAPY

The following novel approaches constitute promising future immunotherapy modalities for asthma. It has been demonstrated that Th1 adjuvants, such as liposome, monophosphoryl lipid A (MPL) or the immunostimulatory DNA sequence CpG motif, may facilitate the action of allergen immunotherapy. For example, Basomba *et al.*[25] conducted a double blinded comparative study of immunotherapy using liposomal mite allergen on mild to moderate asthma. Approximately half (46%) of the immunotherapy group showed a decrease in symptom-medication scores of more than 60%, while fewer patients (only 12%) in the placebo group showed such improvement. In the active treatment group, mite-specific IgG4 was increased, while allergen-specific bronchial responsiveness was improved. It was meaningful to demonstrate that liposome, which is known to be a Th1 adjuvant, can be used for allergen immunotherapy in asthma; however, it is unclear whether this modification can overcome current treads in conventional immunotherapy.

Drachenberg *et al.*[26] examined whether a grass pollen-specific vaccine containing MPL, a potent Th1 adjuvant and a ligand for toll-like receptor 4, would modify allergic symptoms in grass pollen-sensitive subjects. Tyrosine-absorbed glutaraldehyde-modified grass pollen extract containing MPL adjuvant was used. After only four preseasonal injections, the vaccine containing MPL reduced nasal symptoms, ocular symptoms, and combined symptom and medication scores.

Tulik *et al.*[27] investigated whether a conjugate of the major ragweed allergen Amb a 1 and CpG motif (A1C) would modify asthma and rhinitis due to ragweed hay fever. No severe side effects were observed, and the active treatment was well tolerated. In the active group, nasally administered allergen induced IL-4 producing cells were blocked while IFN-γ was increased, confirming an immunological shift from the Th2 to Th1 system. During the pollen season, the AIC group showed significantly fewer asthma and rhinitis symptoms as compared with the control group. Creticos *et al.*[28] also reported that a 6-week regimen of the AIC vaccine appeared to offer long-term clinical efficacy in the treatment of ragweed allergic rhinitis: During the first ragweed season, the AIC group had better peak-season rhinitis scores than the placebo group and a clinical benefits were again observed in the subsequent ragweed season. These studies are important for demonstrating that induction of Th1 and reduction of Th2 response act as mechanisms of immunotherapy, thus raising the future possibility of additional Th1 adjuvants.

There is increasing evidence that recombinant DNA technology has the potential to produce allergen-specific immunotherapy vaccines.[29,30] Pauli *et al.*[29] evaluated the effectiveness of a recombinant birch pollen allergen vaccine in patients with birch pollen allergy. A randomized, double-blind, placebo-controlled trial was undertaken in order to compare the following three vaccines in 134 adults with birch pollen allergy: recombinant birch pollen allergen vaccine (rBet v 1a), licensed birch pollen extract, natural purified birch pollen allergen (nBet v 1), and placebo. Significant reductions (about 50%) in rhinoconjunctivitis symptoms, rescue medication, and skin sensitivities were observed in the three actively treated groups, as compared with the placebo. No severe systemic adverse events were observed in the rBet v 1-treated group. These results indicate that the rBet v 1-based vaccine is safe and effective in treating birch pollen allergy.

FUTURE PERSPECTIVES

Application of immunotherapy upon onset of asthma is clinically feasible in Japan with the aim of prevention. Patients with Japanese cedar pollinosis, for example, may be candidates for immunotherapy in terms of preventing development of asthma. The present study also suggests the usefulness of early intervention in producing improvements. The study on mite allergy using SLIT strongly suggests that immunotherapy can improve the natural course of allergic diseases, including asthma, in children. However, it remains to be elucidated whether such effects can also be achieved in adult asthmatics.

Among recent progress and newly developed approaches regarding allergen immunotherapy, liposomal allergen vaccination is promising; however, it should be clarified whether this method is better than conventional allergen immunotherapy. On the other hand, selective Th1 adjuvants, such as CpG motif or MPL, have the potential to become useful therapies for allergic asthma, such as in mite allergy. In any case, the application of Th1 system adjuvant may be useful as a modified vaccine approach in immunotherapy. Immunotherapy using recombinant allergen would provide a further possibility to improve this form of therapy. The results of a study by Pauli *et al.*[29] are extremely promising, and suggest the possible use of this approach in dust mite allergy.

Current pharmacotherapy, such as ICS, provides powerful anti-symptomatic benefits in asthma; however, it does not cure or modify the natural disease course. As immunotherapy targets the immunological background in asthma, including pathological activation of Th2 cells, it is expected to lead to long-term amelioration of asthma. It is hoped that the novel approaches described in this article will become more sophisticated and provide better efficacy, and that the positioning of allergen immunotherapy as a treatment option for comprehensive management of allergy symptoms and for modification of disease course.

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原　著

鼻炎症状と喘息症状の連関についてのアンケート調査

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【背景】アレルギー性鼻炎などの鼻疾患と気管支喘息は，互いに影響することがよく知られている．しかし特に我が国で，鼻疾患と喘息の連関に関する疫学的データは少ない．今回我々は，鼻症状と喘息症状の連関の頻度及び特徴を調査する目的で，アンケートを行った．

【方法】鼻疾患（アレルギー性鼻炎・花粉症・慢性副鼻腔炎）と喘息を合併する126名を対象に，アンケート調査により，鼻症状と喘息症状の連関の頻度を検討した．またどのような患者で，鼻症状の変化によって，喘息症状が影響されるかについても，同時に検討した．

【結果】38名（30%）で，鼻疾患の悪化に伴って喘息が悪化することを自覚していた．一方，28名（22%）で，鼻治療により喘息が改善した．鼻症状の変化が喘息症状に与える影響は，喘息コントロールが良くない患者で有意に強かった．また，副鼻腔炎のある患者で両者の連関はより強い傾向にあった．

【結語】鼻疾患と喘息を合併する患者において，約30%で両者の連関を自覚していた．鼻に対する治療は，通年的に喘息症状がある患者で特に，喘息コントロールに重要と考えられた．上下気道にわたる包括的なアレルギー診療の重要性が示唆された．

Key words: allergic rhinitis —— bronchial asthma —— one airway one disease

緒　言

アレルギー性鼻炎と気管支喘息が合併する割合は高く，アレルギー性鼻炎の30-40%に気管支喘息が，気管支喘息の50-80%にアレルギー性鼻炎が合併するとされている[1]．アレルギー性鼻炎患者は，健常者と比較し，約3倍喘息に移行しやすいことが報告され[2]，気管支喘息発症の独立した危険因子と認識されている．アレルギー性鼻炎患者では，気管支喘息の有無と無関係に，気道過敏性亢進[3]や好酸球の気管支への集積[4]が見られる．また鼻粘膜へのアレルゲン曝露が，下気道の平滑筋収縮，好酸球浸潤，気道過敏性亢進を誘導することも報告されている[5]．さらに，アレルギー性鼻炎の治療を行うことで，喘息症状や気道過敏性を改善させ[6]-[9]，急性増悪頻度を減少させうることも報告されている[10]．一方で，気管支喘息患者においても，アレルギー性鼻炎の有無と無関係に，好

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Abbreviations: ICS "inhalational corticosteroid", H1RA "histamine 1 receptor antagonist", LABA "long acting beta2-agoist", LTRA "leukotriene receptor antagonist"
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Table 1 Clinical characteristics of patients

Number of the subjects	
1. Sex: Male	49
Female	75
Not described	2
2. Age: < 20 yr	1
20-29 yr	16
30-39 yr	26
40-49 yr	23
50-59 yr	21
60-69 yr	29
70-79 yr	8
80 < yr	1
Not described	1
3. Atopy: Atopic	106
House-dust-mite	53
Japanese cedar	83
Non-atopic	7
Unknown	13
4. Treatment: ICS	113
LABA	60
SABA	22
Theophylline	40
LTRA	75
Nasal conticosteroid	34
H1RA	44
Immunotherapy	22
5. Step: Step1	7
Step2	24
Step3	46
Step4	41
Unknown	8

Table 2 Pre-existing nasal disease

Number of the subjects	
Allergic rhinitis (AR)	28
Japanese cedar pollinosis (JCP)	26
Chronic sinusitis	5
AR + JCP	32
AR + chronic sinusitis	7
JCP + chronic sinusitis	2
AR + JCP + chronic sinusitis	14
Unknown	12

酸球の上気道への集積が見られる[11]．また経気管支鏡的気管内アレルゲン投与が，鼻炎症状と鼻粘膜組織への好酸球浸潤を誘導することも報告されている[12]．このように上気道と下気道は，共通の進行する炎症性反応の影響を受け，連動するメカニズムにより持続・増幅すると考えられている[13]．

また副鼻腔炎も，喘息の増悪因子の一つであることがよく知られている[14]．近年では，従来のマクロライド治療が有効な慢性副鼻腔炎に加え，アレルギー性副鼻腔炎や好酸球性副鼻腔炎などが提唱され，病態の多様性が認識されるようになった[15][16]．その中でも，好酸球性副鼻腔炎では，ポリープがロイコトリエンなどの化学伝達物質の産生源とされており，ポリープ切除により喘息コントロールが改善することがしばしば経験される[17]．

しかしながら，鼻疾患と喘息の合併例における上気道症状と下気道症状の連関は，日常臨床において，すべての患者で観察されるものではない．また，両者の連関がどのような患者で観察されやすいかについては，今まであまり検討されてこなかった．今回我々は，鼻疾患(アレルギー性鼻炎・花粉症・慢性副鼻腔炎）と気管支喘息・咳喘息を合併する患者において，鼻炎症状と喘息症状の連関についてアンケート調査を行い，その連関の頻度および特徴について検討したので，ここに報告する．

研究対象と方法

2007年11月から12月にかけて，埼玉医科大学病院アレルギー・喘息センター，あるいは耳鼻咽喉科に通院中の，鼻疾患（アレルギー性鼻炎・花粉症・慢性副鼻腔炎）と喘息を持ち，鼻炎症状と喘息症状を合併した患者を対象に，両者の連関についてアンケート調査を行った．本試験の公表について同意を得られた，126人を対象とした(Table 1)．性別は，男性49名，女性75名，記載なし2名であり，平均年齢は48.1歳であった．基礎疾患の内訳は，アレルギー性鼻炎81名，花粉症74名，慢性副鼻腔炎28名，気管支喘息113名，咳喘息16名であった(Table 2；重複有り)．アンケート質問内容は，①鼻炎症状からみた喘息症状との連関に

Table 3　Questionnaire for determining relationship between nasal and asthma symptoms

1-1　以下と診断されたことはありますか？ 診断されたものに○をつけてください.
　　アレルギー性鼻炎（1年中不定期に続く，原因　カビやダニ，ホコリ）
　　花粉症（春や秋などの花粉で鼻症状がある）
　　蓄膿や鼻茸（慢性副鼻腔炎）
　　喘息
　　咳喘息（ゼイゼイはしないけれど，咳が出る）
1-2　鼻の症状と，喘息症状に対して日常，連続して使用している薬に○をつけてください.
　　飲み薬　オノン，シングレア
　　セレスタミン，プレドニゾロン，プレドニン，リンデロン
　　テオドール，テオロング，ユニフィル，スピロペント
　　アレジオン，クラリチン，アレグラ，アレロック，ジルテック，ニポラジン，
　　タリオン，ザジテン，アゼプチン，セルテクト，エバステル
　　クラリス，クラリシッド，ルリッド，その他（　　）
　　貼付薬　ホクナリンテープ
　　点鼻薬　フルナーゼ，アルデシン，スカイロン，リノコート，インタール点鼻薬，ザジテン点鼻薬，
　　その他（　　）
　　吸入薬　フルタイド，キュバール，パルミコート，セレベント，アドエア，
　　オルベスコ，メプチン，サルタノール，スピリーバ，その他（　　）
　　免疫（減感作）療法　スギ，ダニ，ハウスダスト
　　手術　下鼻甲介切除，下鼻甲介焼灼（レーザーなど）その他（　　）
2-1　かぜをひいているときでなくとも，喘息に関連する症状（息苦しさ，咳，ゼイゼイ，胸の違和感）がありますか
　　しばしばある，ときどきある，ほとんどない
2-2　かぜをひいている時でなくとも，鼻の症状（鼻水，鼻汁，くしゃみ，鼻つまり）がありますか？
　　しばしばある，ときどきある，ほとんどない
3-1　鼻症状が悪くなると喘息症状はどうなりますか？
　　悪くなる，変化しない，良くなる
3-2　喘息症状が悪くなると鼻症状はどうなりますか？
　　悪くなる，変化しない，良くなる
4-1　鼻症状を薬で治療すると，喘息症状はどうなりますか？
　　良くなる，変化しない，悪化する
4-2　喘息症状を薬で治療すると，鼻症状はどうなりますか？
　　良くなる，変化しない，悪化する

ついて（鼻症状が悪化すると喘息症状は悪化するか？鼻症状を治療すると喘息症状は改善するか？）②喘息症状からみた鼻炎症状との連関について（喘息症状が悪化すると鼻症状は悪化するか？喘息症状を治療すると鼻症状は改善するか？）③鼻炎症状と喘息症状の程度（頻度）について（しばしばある，ときどきある，ほとんどない）④普段の治療内容について，などである（Table 3）．統計学的解析として，異なる2群における検討には$\chi 2$乗検定を用いた．

結　果

①全症例（126例）における鼻炎症状と喘息症状の連関の検討

（1）鼻炎症状の変化に伴う喘息症状の変化

初めに，鼻疾患と喘息を合併し，鼻炎症状と喘息症状を呈する126症例における，鼻炎症状の変化に伴う喘息症状の変化について，検討した．全症例のうち30%（38/126）で，鼻炎症状が悪化すると，喘息症状が悪化すると自覚していることがわかった（Table 4）．一方で，鼻を治療すると，22%