厚生労働科学研究費補助金

免疫アレルギー疾患等予防・治療研究事業

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

平成20～22年度 総合研究報告書

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Ⅰ．総合研究報告

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

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

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研究要旨

花粉症のセルフケアに対して花粉飛散数を表示するリアルタイムモニターは、花粉見落とし率、花粉誤認率を考慮した新たな補正を加えることで、花粉測定の精度の向上が期待された。また近隣する地点でのこれらの観測は近似し、機器そのものの信頼性は得られた。花粉症と下気道疾患の関連性では喘息のコントロールに対して鼻、つまり花粉症のアレルゲン免疫療法（SCIT）を含む治療が有用であることが示唆された。スギ花粉症の症状を抑制し，薬物の使用量を減少させられる舌下免疫療法（SLIT）は医療経済上でも有用な方法であった。またヒノキ花粉症への効果は限定的であることが皮下注射による免疫療法で分かった。経年的な効果増強が示され、今後はより効果的な長期的治療スケジュールの確立をしなければならない。今回の最終目的であったペプチド SCIT によるものではその高い効果が認められたが、SLIT では効果は限定的であり、やはり基礎研究で行ったアジュバントの併用の必要性が感じられた。

バイオマーカーの検討ではヒノキ粗抗原特異的 IL-31 産生はヒノキ花粉飛散期の症状および QOL を反映し、その可能性が示唆された。重症花粉症の鼻粘膜では、グルココルチコイドβ受容体などの発現が亢進し、重症化の一因と考えられた。スギ花粉症の遺伝子では *IFN・R 1* プロモーター領域（rs2234711）、*IL-33*（rs1929992）、DAF（rs10746463）が同定できた。またアポ A4 は、舌下免疫療法で効果を示した症例で上昇していた。スギ抗原特異的制御性 T 細胞（nTreg）の存在を確認し、Th1 優位に抑制している可能性が示唆された。また誘導性制御性 T 細胞（Tr1）が免疫療法の効果機序に大きく係っていることが考えられた。

A. 研究目的：

スギ花粉症は有病率も高く、QOL が障害される国民病であり、さらに小児での発症が多くなってきたことが問題である。リアルタイムモニターでの問題点を解決し、今後患者が使用しやすい情報発信の方法が望まれる。また東京以外でのこれらの検討は少なく、地方都市での精度などの確認も必要である。花粉症患者の特徴や喘息との関連性の問題などは実際の QOL などとも直接関連する事項であり、花粉症の臨床研究においては重要なものである。さらに新しい治療法の検討では免疫療法におけるメカニズムの解明から生まれるものもあり、サイトカイン、制御性T細胞、スギ特異的T細胞クローンなどより詳細な検討が必要である。舌下免疫療法では成人、小児での検討や、抗原をペプチドに置き換えた検討など今後の新しい治療法の開発の礎となるべきである。以上のように花粉症の患者の QOL 向上、医療政策上の問題点として、セルフケアと根治的治療法という2つのキイワードがある。このため、我々の研究班ではセルフケア向上と根治的治療法の開発を二つの柱としてリアルタイムモニターの問題点克服、QOL 悪化につながる要因の解明、根治的治療につながる舌下ペプチドアジュバント免疫療法、そして遺伝子やサイトカインなどのバイオマーカーの検討を軸に研究を行った。

B. 方法：

① リアルタイムモニターの精度改善の研究（岡本、太田）

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

② 花粉症の睡眠・QOL への影響重症（太田）

今まで都市部でしか検討されていなかった QOL ならびに睡眠障害の実態を JRQLQ No1、No2 およびピッツバーグ睡眠問診票を用いて検討した。

③ 花粉症における下気道への影響の検討(永田)

鼻炎症状を持つ喘息患者へのアンケートからその関連性の調査を行った。またスギ花粉症患者の下気道の状況を呼気 NO ならびに呼吸機能検査から検討した。

④ 花粉症患者の候補遺伝子、バイオマーカーの検討（藤枝）

スギ花粉症患者と陰性コントロールで候補遺伝子アプローチと全ゲノム解析を行った。また SLIT 治療効果の判定のバイオマーカーの検索として網羅的タンパク解析を行い、その機能解析を行った。

⑤ スギ花粉症患者の鼻粘膜組織検討（太田）

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

⑥ 免疫療法の効果発現機序の研究(岡野、永田、藤枝)

SCIT 施行および非施行のスギ・ヒノキ花粉症患者より PBMC を採取し、Cry j 2 あるいは Cha o 2 にて 72 時間培養後、上清中の IL-5 を測定した。小児 SLIT 例の末梢血から PBMC を精製し、Cryj1 and Cryj2 で 12 時間培養し、IL-10 産生 CD4T 細胞と IL-10 産生 CD14 陽性単球の割合を測定した。また、血清 IgG4,IL-17A, IL-31, IL-33 を ELISA で測定した。SLIT 患者血清で網羅的タンパク解析を行った。成人のスギ花粉症患者でクラスター免疫療法を実施し、その安全性を評価した。

⑦ SLIT の方法論の研究（大久保、湯田、後藤）

初期療法・SLIT・SLIT の3群を設定し、少量飛散年(2010 年)・中等度飛散年(2008 年)と大量飛散年(2009 年)で症状スコアと QOL を検討した。また 60 例の小児 SLIT の比較を行った。経年的な SLIT の効果を 2009 年に検討した。

⑧ ペプチド免疫療法の実際（後藤、大久保）

スギ花粉症患者にスギ花粉ペプチド TAK-201、2.5 mgを週 1 回で 4 回 SCIT ランダム化比較試験を行い、その効果を検証した。また同じペプチドである CS-712 1 回 10 mg を 1 週間隔又は 2 週間隔にて 24 週間、SLIT プラセボ対照無作為化二重盲検試験を実施した。

⑨ 免疫療法におけるアジュバントの研究(後藤、大久保)

BALB-c マウスにスギ花粉抗原で感作し、スギ花粉により腹腔内の好酸球浸潤を増多するモデルを開発し、丸山ワクチンの市販版であるアンサ 20 を投与し、抑制効果を検討した。

⑩ スギ花粉ペプチドに関する T 細胞の反応性の研究（岡本）

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

⑪ T 細胞のスギ花粉ペプチド反応性と制御性 T 細胞の検討（増山、湯田）

既知のスギ花粉ペプチド以外の分子の検出を行った。またペプチドの反応性の個々の違いについて検討を行った。またリンパ球から CD4+T 細胞（nTreg 含有群）と CD4+CD25-T 細胞（nTreg 除去群）に分け、これらをスギ花粉抗原 Cry j 1 および HLA-DP5 拘束性 Cry j 1 関連ペプチド(p61-75)

で刺激し培養した。抗原特異的増殖能とサイトカイン産生を測定し、比較検討した。また、Cry j 1 特異的 IL-10 産生 Treg の検出を行った。

C. 結果：

①2008 年 1 月の花粉非飛散期の検討から花粉誤認率は、千葉市、成田市ともに 0.111 で、ダーラム法による花粉数の相関は、千葉市で 0.80、成田市で 0.78、補正式を用いた補正では 0.76、0.87 であったこの相関は 2009 年では、0.81、0.77 であった。花粉の少ない季節では新たな補正式で相関値が改善することが判明した。山形市、福井市、甲府市の 3 地域での複数の施設でのスギ花粉飛散数は、花粉開始時期、最大飛散数、日々の飛散数の変化はほぼ一致していたが、部分的に異なる傾向もあった。

②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。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。呼気 NO 調査では飛散期、非飛散期で有意差を認め、飛散期で上昇していた($p < 0.05$)。

③スギ花粉飛散ピーク時には眼鼻の症状が増悪するだけでなく、気道、のど、口耳皮膚、全身に影響が及ぶことが確認された。また花粉飛散ピーク時期ではスギ花粉症患者では有意な睡眠スコアの有上昇が認められ、睡眠が障害されていた。

④候補遺伝子は IFN-γ 受容体であり、プロモーター領域（rs2234711）であった。リスクアレルは、C であった。また IL-33 の rs1929992 において相関していた。血清中 IL-33 は、スギ花粉症において有意に高値を示した。全ゲノム解析では *DAF* に注目し解析を行ったところ、rs10746463 においてリスクアレル A がスギ花粉症と有意な相関を認めた。DAF のプロモーター領域 rs10746463 が A/ A になっていると血清中 IgE の高値を認めた。rs10746463 が A/ A になっていると DAF 蛋白の発現が低かった。*ORMDL3* における（rs7216389）においても高く有意な相関を示した。リスクアレルは TT であり、ORMDL3 発現は鼻粘膜上皮が最も高かった。鼻粘膜の解析では、スギ花粉症で Intelectin-1 とその他 17 の遺伝子が有意に変動し、スギ花粉飛散期に発現が亢進する遺伝子も存在した。

⑤アレルギー炎症の重症化の機序には糖質コルチコイド受容体、ペリオスチン、ペンドリンなどの分子が関与している可能性が示唆された。特に、グルココルチコイドのαβ受容体の発現のバランスが重要であり、ステロイドに抵抗する症例の局所ではβ受容体の発現が高い傾向が認められた。

⑥スギ花粉症患者の PBMC は、スギ、ヒノキ抗原いずれに対しても IL-5、IL-13 を有意に産生した。IL-31 産生に関しては、スギ粗抗原で有意に亢進した。ヒノキ飛散期においては症状スコアとヒノキ粗抗原特的 IL-31 産生との間に相関傾向を認め、さらに QOL スコアとヒノキ粗抗原特的 IL-31 産生との間に有意な正の相関がみられた。SCIT の Cry j 1-および Cha o 1 に対する IL-5 産生量は有意に低かった。スギ粗抗原、Cry j 2 に対する IL-5 産生量に関しては、SCIT 群は有意に低かった。SLIT の血清中網羅的蛋白解析では、Apolipoprotein A IV（アポ A4）が臨床効果と有意に相関し、症状が改善した者に高い誘導が認められた。リコンビナントアポ A4 は、CryJ1 刺激によるヒト好塩基球のヒスタミン遊離率を抑制した。クラスターSCIT は成人スギ花粉症患者 11 例中 10 例で、5 週以内で目標維持量に到達でき、速やかに維持療法に移行できた。 局所の腫脹は全例でみられた。3 例でアナフィラキシーなどの全身的副作用を生じた。

⑦症状スコア、QOL ともに SCIT の効果が最も良く、次いで SLIT、初期療法の順であった。症状スコアは中等度飛散に 3 群で差が開いていたが、少量飛散ではどの治療も効果的で差が小さかった。QOL は大量飛散年に差が出ていた。小児では 2010 年は少量飛散年であったためどの治療法も効果的で、SLIT と薬物療法で臨床症状に差はなかった。しかし、SLIT の薬物スコアは有意に小さかった。2 月初めから 3 月上旬まではプラセボ群、初回 SLIT 群、追加 SLIT 群共に総鼻症状スコア(TSS)に明らかな差を認めなかった。しかし、スギ花粉飛散が多くなる 3 月中旬以降には、プラセボがもっとも症状が強く、次に初回 SLIT 群、最も軽症だったのは追加 SLIT 群だった。この傾向は 4 月下旬まで継続した。経過中、局所および全身性の副作用は発生しなかった。

⑧ペプチド免疫療法では TAK-201 皮下注射によるものではその高い効果が認められたが、CS-712 の SLIT では効果は限定的であったが、特異的 IgE の季節中の上昇を抑え、今後引き続いての検討が必要と考えられた。

⑨マウス腹腔内好酸球はスギ花粉刺激で増加し、その増加をアンサ 20 単独では増強する効果を示し、抗原と共に口腔投与したには軽度抑制することが示され、アジュバントとしての丸山ワクチンの可能性が示された。

⑩ELISPOT 法によるリンパ球のスギ花粉特異的 Th2 メモリークローンサイズは,CD4 細胞特異的変化であること、また患者自己樹状細胞を抗原処理して反応させた場合と高い相関がみられ簡便に測定が可能であった。クローンサイズは 1 月に比較して 5 月には 1.7-2 倍の増加がみられ、スギ花粉

特異的 IgE 値と相関がみられた。
⑪Cry j 1 特異的 T 細胞株はペプチド p61-80、p115-132、p206-225、p337-353 にて増殖反応を誘導された。2 例は Th2 優位、3 例は Th1 優位、4 例は Th0 パターを示した。ペプチド特異的 IL-4・IL-5 産生細胞と Cry J 1,2 特異的 IL-4・IL-5 産生細胞との間には高い正の相関が見られた。ペプチドへの反応性は個々の株で異なっていた。IFN-・産生に関しては Cry j 1 刺激で nTreg 除去によりその産生は有意に増加したが、IL-5 産生に関しては、nTreg 除去の影響は認めなかった。また、IL-10 の産生は Cry j 1 刺激において nTreg の除去により有意に低下した。Cry j 1 特異的 CD4+CD25+ (nTreg) IL-10 産生細胞を ELISPOT にて確認できた。一方、SLIT 施行中の小児では nTreg は未治療群と変化ないが、誘導性 Tr1 は正常人と同じでスギ抗原刺激で増加することが示された。

D. 考察：
現在のスギ花粉症における問題点として、その有病率の高さがあげられる。このため、セルフケアと治癒を望める治療法の確立が医療費の問題点からも重要な国家課題となる。国民への正しい情報がセルフケアを高める上でも重要であることを述べてきたが、現状で報告されるリアルタイムモニターでは十分な情報が発信されていない。これは補正しないとダーラムで報告される花粉飛散実数値との差が生じるからであり、今後の問題点と考えられる。
実際のスギ花粉症患者では喘息の悪化や下気道の症状を発現する可能性がその呼気中ＮＯからも考えられ、喘息との関連性が組織中の特徴からも考えられた。この様な花粉症を治癒させるには免疫療法は重要であり、舌下免疫療法の効果が成人でも小児でも検証され、その効果がサイトカインや制御性Ｔ細胞から分かるような結果が得られた。実際のペプチド免疫療法は現状での方法論では臨床応用にはやはりアジュバントなど、さらなる工夫が必要であると考えられる。基礎的な研究からは花粉症特異的な疾患遺伝子の同定が進み、また制御性Ｔ細胞や抗原特異的Ｔ細胞クローンサイズあるいはアポ AIVなどのプロテオームなどがスギ花粉症の早期診断や治療バイオマーカーになる可能性が示唆され、スギ花粉症の治癒に向けた検討が明らかになったものと考えられる。

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

F. 健康危険情報
研究における重篤な症例なしし

G. 研究発表
1．論文発表

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分担研究者の論文発表は分担研究者の報告書に詳細を記す。

2．学会発表

多数

H. 知的財産権の出願・登録状況

1．特許申請

① 「アレルギー疾患の治療薬かつ治療効果のマーカー」特願 2008-053768 出願日 2008 年

② 「減感作療法における治療効果を予測するバイオマーカー」特願 2009-241435　出願日：2009 年 10 月 20 日　特許出願人：財団法人東京都医学研究機構、学校法人日本医科大学　発明者：廣井隆親、大久保公裕

③ 「減感作療法における治療効果を予測するバイオマーカー」特願 2009-244965 出願日：2009 年 10 月 23 日　特許出願人：財団法人東京都医学研究機構、学校法人日本医科大学　発明者：廣井隆親、大久保公裕

2．実用新案登録

該当項目なし

3．その他

該当項目なし

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REVIEW ARTICLE

Sublingual Immunotherapy for Japanese Cedar Pollinosis

Kimihiro Okubo[1] and Minoru Gotoh[1]

ABSTRACT
The prevalence of pollinosis caused by cedar pollen has increased by 10% these ten years of 26.5% in the investigation of 2008 in Japan. The pharmacotherapy is a main treatment tool for pollinosis, and the surgical treatment is not acknowledged to the treatment of pollinosis internationally. Moreover, allergen immunotherapy enters a special treatment method, and is an important therapeutic procedure. The allergen immunotherapy is unique for having possibility of curing allergen specific allergic diseases. However the side effect of allergen subcutaneous immunotherapy (SCIT), such as anaphylaxis is kept at a distance in a medical situation in Japan. Then, a sublingual immunotherapy (SLIT) that was safer than it, developed in Europe for pollinosis induced by grass or ragweed, but not in Japan. As a result, the effect of SLIT was proven in the cedar pollinosis in Japan as high level evidence. A whole body immunity induction is thought in the appearance of the effect, and, in addition, it is necessary to be going to be cleared the accurate mechanism of the effect in the future. Moreover, the development of a special SLIT and the import of an overseas product are needed in Japan.

KEY WORDS
Pollinosis, QOL, SCIT, Sublingual immunotherapy (SLIT)

INTRODUCTION

After Dr Noon begins to appear the conventional allergen specific subcutaneous immunotherapy (SCIT) in 1911, and is continuing treatment method.[1] The effect of SCIT on pollinosis caused by cedar pollen is low though the high therapeutic gain is admitted for the perennial allergic rhinitis in Japan. It is because the effect of SCIT has decreased relatively because this depends on the amount of pollen to which the symptoms of pollinosis and the amount of dispersion increases in recent years or the administering allergen of SCIT is a little. The problem of anaphylaxis in cause that SCIT has not become general treatment though effectiveness is confirmed.[2] An alternative immunotherapy to change the allergen administering route in Europe and United States to decrease the number of side effects of SCIT is done considerably than before. There are alternative route via the nose, sublingual, and the oral in the method development is not done respectively in Japan as for the double blind test comparison examination though effectiveness has been proven either. Therefore, it explains around sublingual immunotherapy (SLIT) that we are doing without the relation of the pharmaceutical company in Japan.

DEVELOPMENT IN JAPAN

In SLIT, high effectiveness is shown in Europe, and the few reports of the anaphylaxis have shown in randomized double blind placebo controlled (RCT) comparison examination evaluation.[3-5] It was one asthma case, and it was one diarrhea case in the SLIT 115 cases in three theses. It is recorded that it is not an anaphylaxis though the asthmatic attack is not described detailed. Moreover, that has not arrived importantly though the reaction of one case's near anaphylaxis externals less than ten times of allergen dose administration was observed by a recent report.[6]

To receive a lot of these reports, and to make SLIT adjust to pollinosis caused by cedar pollen from which the amount of the dispersion pollen was thought most, the research was started. We did the ex vivo culture experiment of the first human mouth mucous membrane incised by the time of surgery for analysis of allergen aspiration to the mucosal membrane. The double of the amount of the allergen dose

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Table 1 Allergen administration schedule (increasing dosing)

	1st week (2 JAU)	2nd week (20 JAU)	3rd week (200 JAU)	4th week (2000 JAU)	5th week (2000 JAU)
1st day	1 drop	1 drop	1 drop	1 drop	20 drops
2nd day	2 drops	2 drops	2 drops	2 drops	
3rd day	3 drops	3 drops	3 drops	4 drops	
4th day	4 drops	4 drops	4 drops	8 drops	
5th day	6 drops	6 drops	6 drops	12 drops	20 drops
6th day	8 drops	8 drops	8 drops	18 drops	
7th day	10 drops	10 drops	10 drops	20 drops	

[After sixth week to pollen dispersed season, 20 drops of allergen extract was administered once a week sublingually. After pollen dispersed season, same dose was administered once in two weeks.]

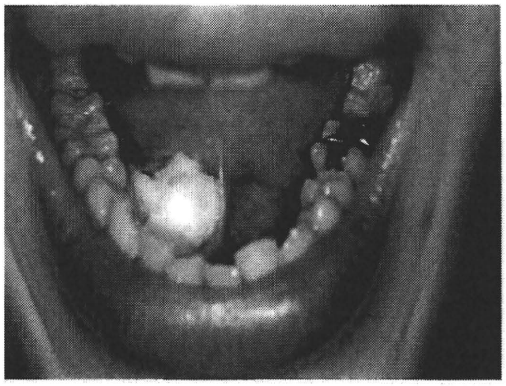

Fig. 1 How to be adapted the allergen extract and bit of bread.

in SCIT is almost the same dose aspirated by SLIT. So SLIT may act as the case of the SCIT is achieved is guessed by over the double dose of allergen at SCIT.[7]

HOW TO DO

The approval of the Nippon Medical School ethics committee was received to the pollinosis caused by cedar pollen patient and it went from some examinations including this basic experiment in SLIT. The allergen for SLIT, standardized Japanese cedar pollen allergen (2000 JAU [Japanese Allergology Unit]/ml, Torii Pharmaceutical, Tokyo, Japan), especially for SCIT products, was used for our SLIT trial. The allergen was able to be put on sublingual by using the bit of bread for the allergen to flow in actual sublingual and so as not to go out, then the allergen was kept to maintain at least for two minutes, and to present the antigen enough to the lymphatic tissue in the mouth.

The allergen administration was every day according the administration schedule from beginning to the forth week. On the first week, 2 JAU of allergen was administered from 1 drop to 10 drops, on the second week, 20 JAU of allergen was administered from 1 drop to 10 drops, on the third week, 200 JAU of allergen was administered from 1 drop to 10 drops, and then on forth week 2000 JAU of allergen was administered from 1 drop to 20 drops, as the final dose. On the fifth week twice a week after the sixth week, 2000 JAU/ml was administered to sublingual 20 drops as the final highest dose by once a week (Table 1, Fig. 1). There is tablet allergen for SLIT against grass pollinosis in Europe. There are some different allergen characters between Japanese cedar and grass. We cannot make the tablet allergen for SLIT of Japanese cedar pollinosis caused by its sticky character now.

THE EFFECT AND THE SIDE EFFECTS IN JAPANESE CEDAR POLLINOSIS

The Japanese cedar and cypress pollen dispersion was about 12000 grains, a large amount of dispersion in 2005 for these ten years. The RCT comparison by 60 cases was examined for making the first evidence in Japan. The SLIT group was intentionally low total symptom score (TSS) compared with the placebo (Fig. 2). This RCT of SLIT has shown to have lowered the symptom score more intentionally than the placebo in late pollen season.[8] SLIT had no significant difference with the drug therapy in the symptom score in the comparison research with the current drug therapy. However, the quality of life (QOL) score evaluated standardized Japanese Rhinitis Quality of Life Questionnaire (JRQLQ), is significantly decreased by SLIT group than placebo group, up to half level of score. QOL deterioration is significantly inhibited by SLIT (Fig. 3).

Moreover, it was confirmed though the side effect was completely fewer. Itchy of the tongue and the mouth when the antigen was administered, the feeling of numbness, nasal secretion increases, itchy of the skin, and hives were admitted at total of frequency of about 10% through the experiment, there were neither an anaphylaxis nor an asthmatic attack.

HOW TO ACT

The mechanism of the effect manifestation is known few up to the present time though the immunity induction of the limited part have some role on most of the effect of SLIT.[4] The mechanism of action for SCIT have been reported by the reduction of the effecter cells[9,10] and the increase of blocking antibody[11-14] in

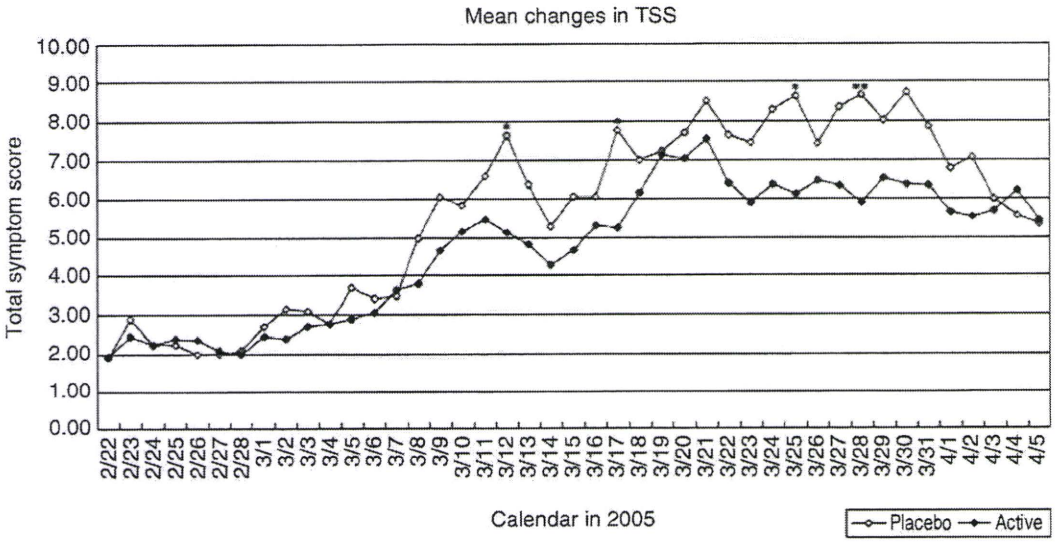

Fig. 2 Mean change of total nasal symptom score by SLIT and placebo group.

the conventional theories ten years ago. Recently, however, it has become widely accepted that SCIT may modify the T cell response to natural allergen because of T cell anergy and/or immune deviation[15-18] and regulatory T cell enhancement.[19]

For SLIT in particular, allergen administered to the oral mucosa accumulates in the sub-mandible lymph node, in which the immune response occurs[20] and peaks at approximately 2 h after administration.[21] An increase in stimulation index (SI) of PBMC at the early stage of the SLIT shows that the immunity induction of a sublingual allergen was at least caused in the general reaction.[22] It tried to reduce the side effect by reducing the effect throughout the body compared with past SCIT in SLIT. However, it has been understood that this result causes a general immunity induction. One more study of SLIT for Japanese cedar pollinosis was published by Chiba group also expressed the SLIT controlled the general Cry j-specific Th2 clone size.[23] The regulatory T cell enhancement in general by SLIT has reported in some papers recently.[24-26] So SLIT may act on generally, not just locally. It is necessary to clarify the exact effect mechanism of SLIT from the examination of the regional lymph node etc. by a similar examination that increased the number of cases or a detailed basic examination on animals in near future.

FOR THE FUTURE IN JAPAN

Approximately 15% of the Japanese population is affected by Japanese cedar pollinosis in 2002[27] and increase up to 26.5% in 2008.[28] The proportion of severe status patients is higher than with grass or ragweed pollinosis, which is the representative condition in other countries. The symptoms of Japanese cedar pollinosis persist for about 3 months, becoming a social issue. When the amount of pollen increases, patients show more severe symptoms, and the number of severe status patients is greatest in mid-March when the pollen count reaches its peak. Substantial antigen exposure enhances the antigen-antibody reaction in the airways (airway hypersensitivity), which is the mechanism involved in severe pollinosis, and immunotherapy with antigen-specific effects may control the exacerbation of the symptoms in the latter half of the cedar pollen season by inhibiting antigen-related enhancement of nasal mucosal hypersensitivity.

In SCIT for pollinosis treatment, the comments and responses of WHO are that the effect is verified from a lot of RCT comparison examinations.[29] However, it is a treatment method to which the medical treatment of Japan is kept at a distance because of the complexity, the possibility of the side effects, the cost and the enforcement under the present situation. The drug therapy is a main current in Japan where the allergy clinic has not been established from these problems for pollinosis. However, the immunotherapy that is fundamental treatment is an important method in the allergy management. The new SLIT shows the effect in pollinosis by cedar pollen was clarified in our examination in Japan. Any QOL fields and items became half QOL deterioration by the placebo in the evaluation using JRQLQ No1. This QOL questionnaire developed in Japan in the symptom score though the difference with the placebo was small in pharmacological treatment.[30] SLIT strongly controls the QOL deterioration in pollinosis rather than the symptom score to do effect is thought. Of the local immunotherapy modalities and SLIT is the most effective with a lower incidence of side effects, which complies with the WHO position paper on allergen

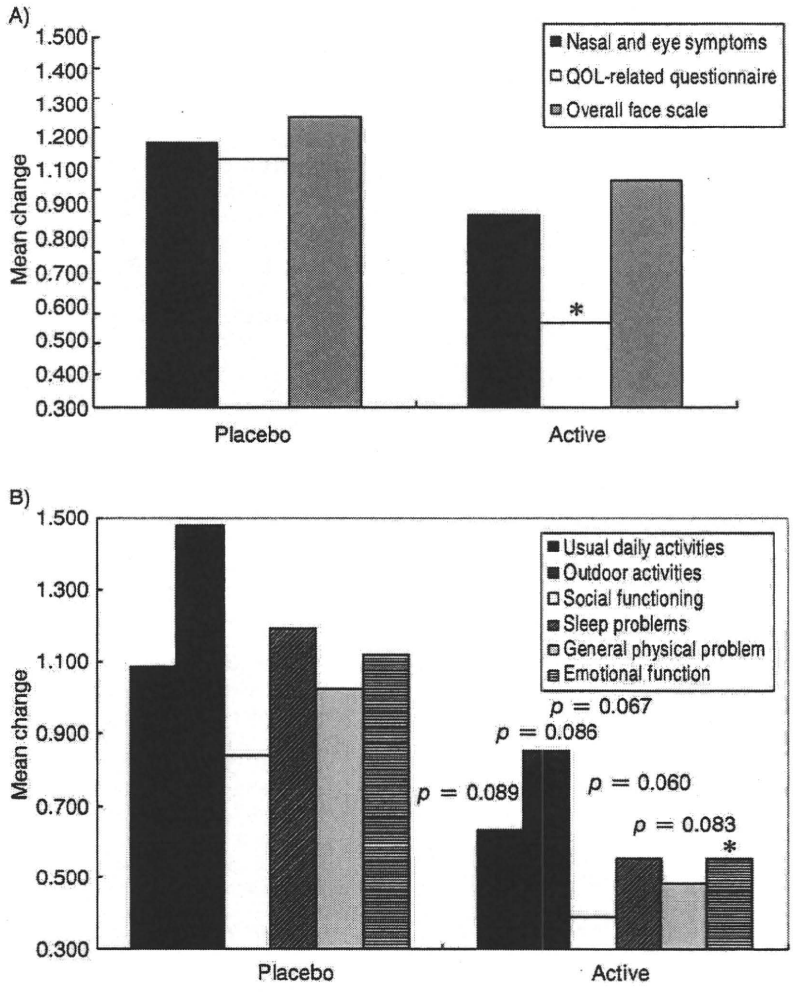

Fig. 3 The mean change of QOL score. **A)**, total QOL scores; **B)**, health related QOL fields.

immunotherapy requiring a new route of administration, such as local immunotherapy, and treatment that does not cause anaphylaxis, such as peptide therapy.[31]

In the comparison of double blinds RCT of the immunotherapy by a SLIT and the SCIT examination, the report is still few.[32] As for the level of the side effect frequency and the effect, it is uncertain. The score of the symptom medicine passes low through the pollen dispersion all seasons. This shows that the drug use decreases in SLIT and corresponding to the result of the RCT examination that uses the placebo.[33] It is thought that the effect equal with the drug use is shown, and a SLIT from which the use of the medicine is decreased is useful in economy. In SLIT studies in Japan, SLIT both inhibited the exacerbation of symptoms in the latter half of the season and reduced their severity throughout the season. Furthermore, there were neither local nor systemic side effects, as reported elsewhere for other antigens.

SLIT for cedar pollinosis is a new therapy and in the future SLIT may by indicated for patients with nasal allergy caused by other allergens such as house dust mites or animal dander through improvement of the administration schedule and establishing the dose at which the most potent effects are achieved.

It is the Ministry of Health, Labour and Welfare science research expense subsidy immunity and an allergy prevention treatment research grant (H14-immunity-001), (H17-immunity-general-001), as for development in this SLIT Japan. It is now progressing as a multicenter study in "Research of the ideal way of information on the real-time monitor pollen count and clinical research on sublingual peptide and the adjuvant therapy (H20-immunity-general-003)".

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REVIEW ARTICLE

Anti-IgE Antibody Therapy for Japanese Cedar Pollinosis: Omalizumab Update

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ABSTRACT
Seasonal allergic rhinitis (SAR) induced by Japanese cedar pollens is a substantial problem in Japan. Omalizumab, a novel humanized monoclonal anti-immunoglobulin E (IgE) antibody, has already been proven to reduce symptoms associated with SAR. To investigate the safety and efficacy of omalizumab in the treatment of patients with Japanese cedar pollen-induced SAR compared to placebo or anti-allergic drug, two randomized, double-blind studies were conducted in Japan. Omalizumab (150, 225, 300, or 375 mg) or placebo was administered subcutaneously every 2 or 4 weeks based on serum total IgE and body weight at baseline. IPD was administered 300 mg per day through the season. Primary and all secondary efficacy variable scores were significantly lower in the omalizumab group than in the placebo group ($P < .01$) and IPD, Th2 cytokine inhibitor group ($P < .01$). Omalizumab was effective and safe in the treatment of SAR induced by Japanese cedar pollens. And the methods of increasing effects by combining omalizumab with antibody-specific immunotherapy are being considered. These strategy is more effective than immune-therapy alone.

KEY WORDS
anti-IgE therapy, asthma, immunotherapy, omalizumab, seasonal allergic rhinitis

INTRODUCTION

Allergic rhinitis including hay fever is a disorder in which sensitization occurs through the inhalation of antigens (induction phase), and a local immune reaction then takes place between the antigen-specific IgE thereby produced and the antigens which have invaded the nasal mucosa (effecter phase). Treatment for allergic rhinitis depends on suppressing the flow of this allergic reaction at some point. Antigen-specific immunotherapy has its point of effect earlier than midway between the induction phase and effecter phase of allergic reaction, unlike general allergy medications (antihistamines, chemical mediator release inhibitors, leukotriene receptor antagonists, etc.). The anti-IgE antibody omalizumab is also such a drug whose point of action differs from previous allergy medications.

THE KNOWLEDGE OF ANTI-IgE ANTIBODY THERAPY

The anti-IgE antibody (omalizumab) produces its effect by binding to IgE which is not bound to mast cells, inhibiting it from binding to mast cells. Since omalizumab does not affect T cells, unlike conventional immunotherapy it is not a curative therapy, but it is a groundbreaking drug in its application of an immunological concept.[1]

This drug is under application in Japan as indicated for severe asthma. There is certainly much evidence for asthma and this is good news for inadequately controlled asthma. In the field of asthma the concept of response to omalizumab has already been published.[2] Currently research is focused on cost-effectiveness. Medical expenses for asthma in America in 2002 (direct and indirect expenses) totaled 14 billion dollar (direct medical expenses: 3.1 billion dollar for hospitalization, 4.6 billion dollar for drugs). The cost of omalizumab to improve QOL is 821,000 dollars, and at present cost-effectiveness is not good. If it could be reduced to 200 dollars or less, it is calculated that cost-effectiveness would increase.[3] However, in correspondence, D. Revicki argues that the purely medical cost-effectiveness which is not based

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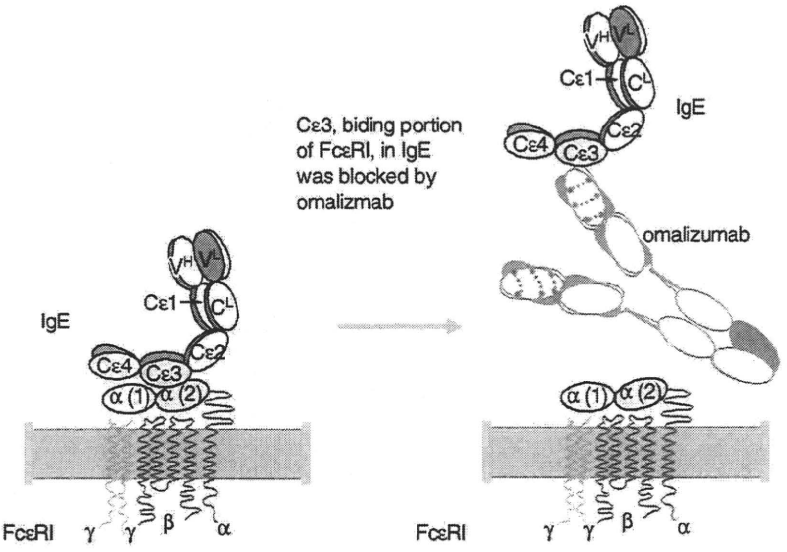

Fig. 1 The inhibition mechanism of allergic disease by omalizumab. Omalizumab was humanized monoclonal antibody against C epsilon 3 portion of Fc epsilon receptor I. Omalizumab blocks the binding between IgE and Fc epsilon receptor I, so allergic symptom must be reduced by this mechanism.

on the Asthma Policy Model is better.[4] The cost-effectiveness will be a large issue in using omalizumab for all allergic disorders in the future.

ANTI-IgE ANTIBODY

In 1991, the American company Genentech produced an antibody specific to Cε3 that binds to Fcε receptors, in the constant region of human IgE. Omalizumab is a humanized monoclonal antibody using mouse monoclonal antibody as a base, retaining the antigen-specific region and replacing the other fragments with human IgG1κ.

When this antibody binds to free IgE in blood by an antigen-antibody reaction between the Fcε receptor and the Cε3 binding site, an IgE–anti-IgE complex is formed, and as a result, free IgE is decreased (Fig. 1). Therefore, IgE that binds to mast cells is decreased, so that even if antigens invade, binding to mast cells to form cross-linking is inhibited and allergic reaction is controlled. Another effect is to inhibit the differentiation of B cells into IgE-producing cells. This is thought to be because it reacts with membrane-binding IgE on B cells, inhibiting mRNA expression of the ε chain. In actual animal experiments, IgE-producing B cells are virtually eliminated.[5]

EFFECTS OF ANTI-IgE ANTIBODY THERAPY IN THE US AND EUROPE

In the West, clinical trials of anti-IgE antibody therapy using omalizumab have been conducted for several years by subcutaneous injection. The target disorders are allergic rhinitis and atopic asthma, and clinical trials are being conducted in Japan for the same targets. In the West, the trials for hay fever differ from asthma, being conducted at single doses of 150 mg or 300 mg. Casale *et al.* have reported on a double-blind comparative trial of those dose levels plus a placebo and 50 mg for a total of 4 groups, using American patients with ragweed pollinosis.[6] The condition of 300 mg group was better than the placebo group throughout the pollen dispersal season and at the peak of pollen dispersal. Lower dose levels also showed effects, and dose relationship was observed. Omalizumab also showed significant improvement by the RQLQ (Juniper's QOL questionnaire). Similar results have been obtained for birch pollinosis in the West, and reduction in drugs for emergency use is being evaluated (Fig. 2).[7]

EFFECTS ON JAPANESE CEDAR POLLINOSIS IN JAPAN

Clinical trials were conducted on Japanese cedar pollinosis in Japan in 2002 and 2003. The trials of 2002 and 2003 were placebo-controlled comparative study and comparative study with an anti-allergy drug, respectively.

The placebo-controlled study used a dose concept of considering the level of omalizumab which can eliminate IgE systemically, as with asthma in Japan, in contrast to the overseas studies which have a set dosage of 300 mg. The amount of omalizumab was set from body weight and IgE level immediately before administration in December as 0.0016 mg/kg/

IgE (IU/mL) and revised every 4 weeks. Therefore, IgE was uniformly reduced to the detection limit (50 ng/mL) in the administration group. Results of the study showed omalizumab significantly reduced the nasal symptom medication score by about 40% for e, and significantly reduced ocular symptoms by 50% (Fig. 3). Individual symptoms of Japanese cedar pollinosis (itchy nose, sneezing, runny nose, stuffy nose, itchy eyes, watery eyes, red eyes) were all significantly alleviated (Fig. 4). Both nasal and ocular symptoms were decreased significantly more than in the placebo group. The major adverse event was pain at the injection site. And one case of ulcerative colitis was reported, but the colitis manifestation is not thought to be responsible omalizumab application.[8]

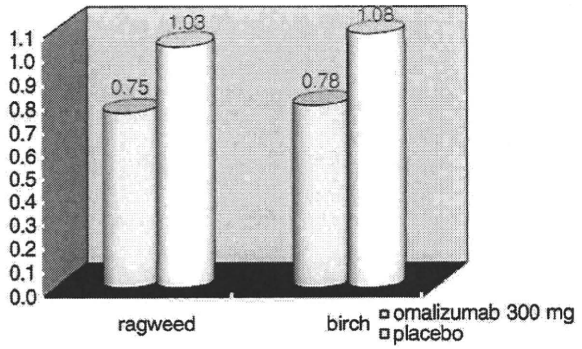

Fig. 2 Overseas study of omalizumab for ragweed or birch pollinosis. Daily nasal severity score in the placebo controlled study of the patients with ragweed pollinosis (reference 6), and birch pollinosis (reference 7). Significant reduction of daily nasal severity score in omalizumab group (yellow bar) compared to that in placebo (purple bar) at both studies.

In 2003, an active control study was conducted with IPD, Th2 cytokine inhibitor. Because the results of the placebo-controlled study were satisfactory, the first active control study, double dummy comparative controlled trial, of omalizumab in the worldwide was conducted. Dose levels were set to compare omalizumab and IPD using the dose concept. 300 mg per day of IPD was administered initial treatment from beginning of February, and through the season. The nasal symptom medication score during the pollen dispersal season was 30% lower than IPD (Fig. 5). In individual symptoms, omalizumab was more effective than IPD for sneezing, runny nose and stuffy nose, although there were no significant differences in itchy nose or ocular symptoms. Omalizumab was more effective to the same degree through the pollinating season including the high pollen dispersal season, and there were no adverse reactions.[9]

Omalizumab is currently under application at the Ministry of Health, Labour and Welfare for severe asthma, but application for hay fever has not been made. This may be because it is not a life-threatening illness, and since there are many patients, recogni-

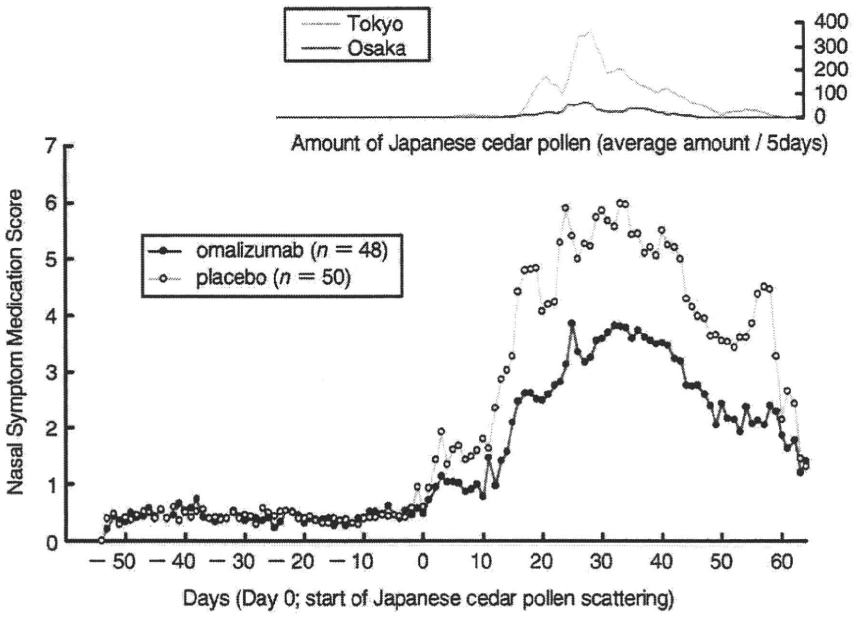

Fig. 3 The change in daily nasal symptom medication score in patients with Japanese cedar pollinosis in 2002. The nasal symptom medication score was significantly reduced in omalizumab group (filled square) in Japanese cedar pollen dispersing season in Tokyo and Osaka compared to the score in placebo (open square).

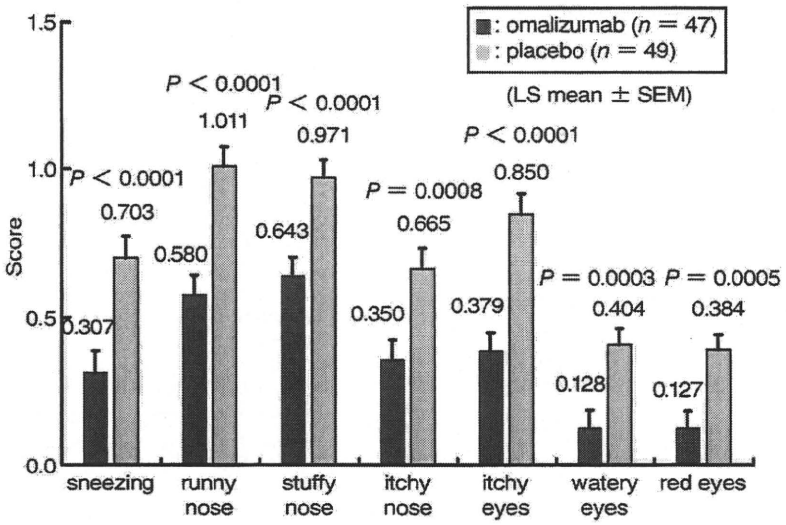

Fig. 4 The change in daily nasal and ocular symptom score in patients with Japanese cedar pollinosis in 2002. All symptoms score, sneezing, runny nose, stuffy nose, itchy nose, itchy eyes, watery eyes, and red eyes, were significant reduced in omalizumab group (purple bar) compared with the score in placebo (yellow bar), especially in eye symptoms.

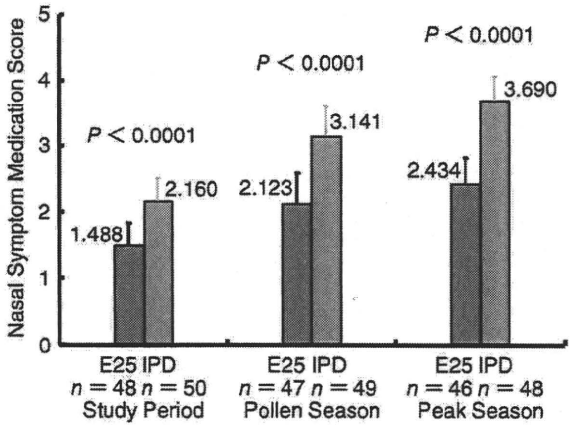

Fig. 5 The daily nasal symptom medication score in comparative study between omalizumab (E25) and IPD for patients with Japanese cedar pollinosis in 2003. Nasal symptom medication score was evaluated in three periods such as study period, pollen dispersing period (pollen season), peak pollen dispersing period (peak season). In all three period, nasal symptom medication score with omalizumab (E25) group (grey bar) was reduced compared to the score with the placebo (orange bar).

tion of the indication could lead to improper use. At any rate, application for allergic rhinitis, including Japanese cedar pollinosis has not been made in any country, but if with advances in technology lower costs for antibody manufacturing and means of reduction to safer numbers can be attained, the treatment for hay fever will become broader in Japan in the future.

OTHER USES FOR ANTI-IgE THERAPY

Overseas, methods of increasing effects by combining omalizumab with antibody-specific immunotherapy are being considered. Wahn *et al.* conducted an RCT in children with sensitization to birch and grass pollen using immunotherapy for either in combination with omalizumab, and the symptom scores for each immunotherapy were further reduced by half.[10] In a study of the same group, leukotriene release by antigen stimulation after the pollen dispersal season that was not reduced by immunotherapy alone was suppressed. However, this suppression reverts back one month after treatment.[11] Klunker *et al.* described combination with rush immunotherapy against ragweed pollinosis. In this study omalizumab administration was begun 9 weeks before the start of rush immunotherapy, with improved effects. This idea is in accordance with the idea of administering omalizumab before the advent of symptoms in the Japanese clinical study. There were no differences in the symptom scores of omalizumab alone and rush immunotherapy combined with omalizumab, but the ability of B cells to bind with allergen-IgE complexes was inhibited more than by rush immunotherapy alone. That is, omalizumab was shown to inhibit CD23 expression in B cells for 30 weeks after completion of immunotherapy at week 42.[12]

A study on nasal polyps was also conducted. Penn

et al. performed endoscopic surgery on nasal polyps complicated by allergic asthma and allergic rhinosinusitis, and observed the course of omalizumab administration thereafter. Recurrence was 25% with and without omalizumab (1/4), but the number of cases was small, and the effects have not been completely verified.[13,14]

THE FUTURE

In the field of allergies there are few illnesses in which IgE does not play a role, and the time may be coming when the use of omalizumab will be considered for all disorders whose pathology has some involvement of IgE. There are many problems that need to be overcome, including that of cost. However, as it is, reduction of IgE can improve the clinical condition in almost all allergic disorders, and we must demonstrate in Japan as well that the current application of omalizumab can be expanded to other indications.

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