表4　花粉症治療薬の副作用

ケミカルメディエーター遊離抑制薬	肝障害，黄疸，膀胱炎，白血球減少，血小板減少 アナフィラキシー
第1世代抗ヒスタミン薬	1）脳内H1受容体遮断　鎮静，倦怠感，傾眠 2）抗コリン作用　口渇，便秘，眼圧亢進 3）α受容体遮断　めまい，起立性低血圧 4）Kチャンネル阻害　QT延長，心室性不整脈 5）過量　小児けいれん，多動症，乳幼児無呼吸，突然死
第2世代抗ヒスタミン薬	肝障害，味覚異常，錐体外路症状，皮膚粘膜眼症候群　血小板減少
抗ロイコトリエン薬	肝障害，下痢，腹痛，白血球減少，血小板減少，肺炎， 横紋筋融解症，Churg-Strauss症候群
鼻噴霧用ステロイド薬	鼻出血，眼圧亢進，無臭覚，アナフィラキシー
点鼻用血管収縮薬	習慣性，耐性，リバウンド鼻閉悪化，過量　昇圧，頻脈，傾眠，振戦

患者のQOL改善に役立つ治療法に切り替える必要がある。アレルギー性鼻炎の治療薬の中心を占める抗ヒスタミン薬は，副作用の少ない第2世代のものが推奨されているが[3]，頻用されているOTCには第1世代の抗ヒスタミン薬が多く含まれていることを念頭に置き患者指導をする必要がある。第1世代の抗ヒスタミン薬は受容体選択性が低く，血液脳関門通過性が高いため，中枢抑制作用や消化器，循環器障害が現れやすいと一般的に認識されている[4]。車を運転や危険な作業に従事する場合は注意して投与する必要がある。また，抗コリン作用の強い第1世代の抗ヒスタミン剤は緑内障，前立腺肥大症，喘息には禁忌である。しかし小児では，抗ヒスタミン剤による中枢神経抑制性副作用は成人に比較すると少なく，逆に興奮の状態，痙攣や不穏，不眠，振戦を誘発することもあるため注意を必要とする。第2世代の抗ヒスタミン薬は，第1世代と比較して副作用は少ないが肝障害，錐体外路症状，味覚異常などが生じることがある。抗ロイコトリエン薬では肝障害，下痢，腹痛，白血球減少，血小板減少に注意を要する。また，鼻噴霧用ステロイド薬は，成人では全身的な副作用は報告されていないが，小児の場合は成長抑制の問題があり慎重に投与する必要がある[3,4]。フルチカゾンは喘息投与量で1年間使用した小児症例でも成長抑制が認められないと報告されており安全性が高いと考えられるが，基本的にはステロイド薬であること認識して使用すべきである[3]。また，気管支喘息の合併で吸入ステロイドを施用されている場合は，鼻噴霧ステロイド薬の併用によって総投与量が増えるため配慮が必要である。点鼻用血管収縮薬は，小児では傾眠，振戦，心悸を起こすことがあるため倍量希釈して用いることでそのリスクを回避することができる。小児のステロイドの内服は発達抑制と頭蓋内圧亢進症状のリスクがあり基本的に避けることが望ましい。

c)点眼薬

花粉症では眼症状を呈することが多い。ケ

ミカルメディエーター遊離抑制薬，第2世代抗ヒスタミン剤の点眼薬を用いるが，効果が不十分な場合はステロイド薬の点眼を使用せざるを得ない場合も多い。この場合，緑内障や感染に注意する必要がある。

おわりに

花粉症では薬物療法の進歩により，早期に治療を開始し，症状や重症度に応じて複数の作用機序の異なる薬物を組み合わせて治療することにより，花粉大量飛散期においても大きな苦痛なく，日常生活を送ることが可能となった。しかし，薬物療法の効果と副作用は，個人差が大きいため，患者とのコミュニケーションを重視し医師と患者の共同作業によって可及的速やかに個々の患者にとって最適の治療パターンを確立する努力が求められる。

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特集●鼻副鼻腔手術を極める●

内視鏡下鼻副鼻腔手術のための支援機器
レーザー

太田伸男*
Nobuo OHTA

● Key Words ●内視鏡下鼻副鼻腔手術，CO_2レーザー，半導体レーザー，KTP レーザー●

はじめに

1985 年に Kennedy，Stammberger らが内視鏡を用いた鼻内経由の副鼻腔手術を“endoscopic sinus surgery（ESS）”として発表して以来，この鼻科手術の革命の発端となる ESS は全世界に普及し，慢性副鼻腔炎の手術方法のスタンダードとして確立した。この背景として，種々の副鼻腔疾患への応用を可能にさせた大きな原動力がさまざまな手術の支援機器や手術器具の開発である。新しい支援機器の開発により手術術式そのものも変貌してきた。レーザーもその 1 つである。

レーザーが鼻科手術に導入されて以来，20 数年が経過し，多くのレーザー機器の登場とその臨床応用の変遷が繰り返された。現在では，鼻科手術への適応となるレーザーの機種，疾患と病態についてはほぼ定まったと考えられる。最近登場した切開蒸散を目的とした機器を含めて，日常一般診療の観点からその用途を概説する。

Ⅰ．レーザーの種類と特徴（表 1）

1．CO_2レーザー

CO_2レーザー光の最大の特徴は非接触型の照射でもエネルギーのほとんどが粘膜表層で吸収されることで，組織への深達度は最大で 0.05 mm と極めて浅く，深部組織を損傷する危険性がほとんどない。この特性を利用して，アレルギー性鼻炎に対する下鼻甲介粘膜焼灼術に使用される機器の中で最も安全なレーザー光である。しかし，CO_2レーザー光は石英ファイバー中を通過させることができず，一般的に多関節マニュピュレーターを介し，ハンドピースを通して照射されるため鼻腔深部の焼灼に問題があったが，最近 CO_2レーザーを通す特殊なファイバーが開発され，鼻腔後方の操作が容易になった。

また，水に吸収される特性を生かして，照射し

表 1　各種レーザー手術装置の比較

	CO_2レーザー	diode レーザー	KTP レーザー	Ho：YAG レーザー
媒　体	炭酸ガス	半導体素子	ネオジウム	ホルミウム
波　長	10,600 nm	632～980 nm	1064 nm	2100 nm
モード	非接触	接触・非接触	接触・非接触	非接触
吸　収	組織中の水	暗赤色	暗赤色	組織中の水
出　力	連続照射	連続照射	連続照射	パルス照射
適　応	切開・蒸散	切開・凝固	切開・凝固	切開・凝固・蒸散
熱深達度	浅い（最大 0.05 mm）	深い（最大 4 mm）	深い（最大 4 mm）	浅い（最大 0.5 mm）
組織の熱変性	少ない	比較的多い	比較的多い	少ない
操作性	直射，斜側射	直射	直射	斜側射
価　格	300 万台	200 万円	2100 万円	2000 万円

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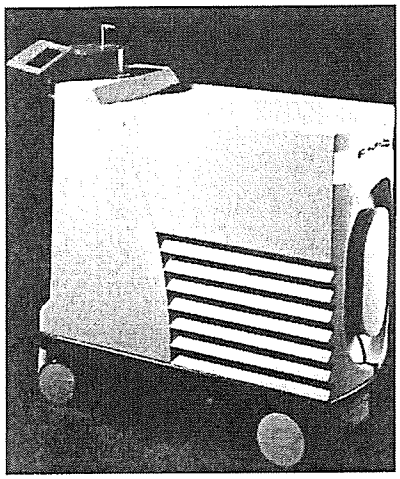

図 1　Ho：YAG レーザーの本体

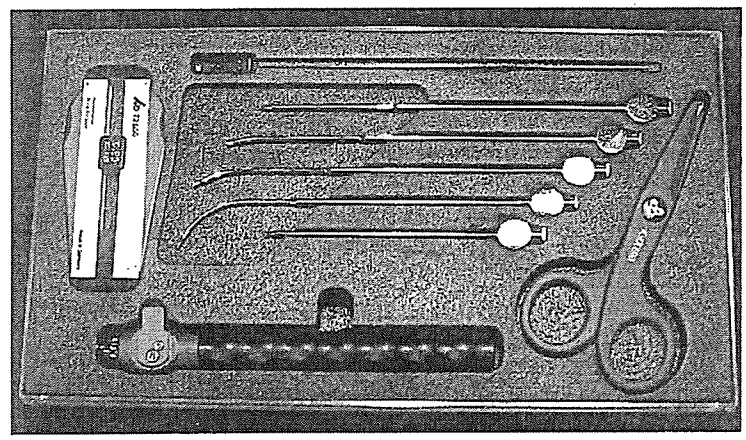

図 2　Ho：YAG のハンドピース

たくない部分に生理食塩水で十分に湿らせたガーゼなどを当てることによって，その部位を照射から保護することができる。適応はアレルギー性鼻炎，鼻出血，鼻茸切除術などである[1,2]。

2．diode レーザー

diode レーザーは小型軽量で安価，切開・止血・除痛に適している。632～980 nm という波長特性はヘモグロビン，オキシヘモグロビン，メラニンなど暗赤色などの暗赤色に吸収される[1~3]。組織へのエネルギー吸収効率が高く，切開凝固能が高い反面，組織への熱深達度が最大で 4 mm と深く，周辺組織への熱変性も大きいため，熱障害に起因する反応性腫脹や術後の出血，長期間の clot の付着や術後疼痛が続く場合が多い。適応は鼻出血，アレルギー性鼻炎，鼻ポリープ切除などである。

3．KTP レーザー（Nd：YAG レーザー）

KTP レーザーは，カリウムとチタンとリンよりなる合材の結晶に，ネオジウム・イットニウムアルミウムガーネット（Nd-YAG）を媒体として得られる波長 1064 nm の緑色可視光である。ヘモグロビン，オキシヘモグロビン，メラニンなどの暗赤色によく吸収され，このため切開蒸散と凝固のバランスに優れている[1~4]。

また，石英ファイバー中を通過できるため鼻腔内での操作性に優れている。ハンドピースとファイバーを組み合わせ接触照射として使用される。組織への熱深達度は最大で 4 mm と深く，周囲組織への熱変性も強いため組織の治癒が遅延する傾向があり，過剰に照射すると下鼻甲介が壊死に陥る危険性もある。適応はアレルギー性鼻炎，鼻ポリープ，鼻腔乳頭腫，副鼻腔嚢胞，血管性病変などである。

4．Ho：YAG レーザー（図 1，2）

Ho：YAG レーザーは YAG 母材の中に 3 価イオンであるホロミウム（Ho）を注入した固体レーザーで 2100 nm の発振波長を持つ赤外光である[5]。発振波形は多数のスパイク状波形が集合した幅 200～250msec のパルスで，深達度は 0.5 mm 以下である。Ho：YAG レーザーの特徴的な生体作用は，パルス幅を変えることによって軟部組織の切開・凝固・蒸散だけでなく硬組織の破砕や切開も可能な点である。これは骨などの硬組織にも数％含まれる水分が水蒸気となり硬組織の内圧が上昇し破壊に至るためである。

他のレーザーに比べて強い凝固能を有するが，組織の色調に関係なく均一に切開・蒸散することができるため熱侵襲が少ない点が利点である。柔軟な石英ファイバーを伝送路に使用できるので操作性に優れ，内視鏡下，細い穿刺針や軟性ファイバーの送気口を通しての治療も可能である。適応はアレルギー性鼻炎，副鼻腔嚢胞，下鼻甲介切除術，涙嚢鼻腔吻合術などである。

表 2　下鼻甲介粘膜手術の術後成績

	ハーモニック	CO_2		CO_2，KTP 混合	Nd：YAG
手術回数	1 回	5 回	1 回	1 回	1 回
症例数	35 例	45 例	27 例	50 例	100 例
観察期間	43 カ月	12 カ月	15～58 カ月	26～52 カ月	12 カ月
改善率					
くしゃみ	56%	70%	33%	81%	67%
鼻　漏	66%	67%	41%	78%	60%
鼻　閉	71%	72%	56%	76%	74%
報告者	宇田川	川村	菊地	中之坊	渡邉

その主な作用機序は鼻粘膜の扁平上皮化生と固有層表層の瘢痕形成による抗原性物質の侵入と炎症性細胞の浸潤抑制，鼻分泌線や毛細血管の減少などによるアレルギー反応の抑制である。

II．アレルギー性鼻炎における下鼻甲介粘膜焼灼術

レーザーの鼻科手術への応用はアレルギー性鼻炎の手術方法の確立とその普及に大きく貢献した。当科にて施行している Ho：YAG レーザーを用いた下鼻甲介粘膜焼灼術の実際について概説する。

具体的な方法であるが，外来で局所麻酔下に施行可能である。まず，下鼻甲介を 4%キロカインと 1000 倍エピネフリンを添加したガーゼで約 30 分間表面麻酔を行う。浸潤麻酔は通常必要ないが疼痛の強い場合は適宜追加している。この後，鼻科手術用ハンドピースの中に外径 0.6 mm の導光石英ファイバーを通し，Ho：YAG レザーのパワー 10 ワットに設定し下鼻甲介全体を処置する。全例，内視鏡下に手術を施行している。術中にハンドピースの先端に炭化した組織片や凝血塊が付着すると出力が低下するため，適宜先端を清拭する。手術の所要時間は両側で約 10～15 分である。原則として鼻内タンポンは不要である。

術後の鼻粘膜には炭化したような出血性の痂皮形成を認めることが多い。術後に鼻粘膜に凝血塊を認めることがあるが，これを吸引除去しても出血することは少ない。日帰り手術の目安は処置に伴う出血の有無であるが，レーザー手術は組織を凝固するため術中術後ともほとんど出血が認められず，入院が必要となった症例は経験しておらず日帰り手術の良い適応と考えられる。処置後 1～2 週間はフィブリンが鼻内に付着し，下鼻甲介粘膜は中等度の腫脹が認められる。術後 2～3 週目頃から粘膜の腫脹は徐々に軽快，術後 4～6 週後頃に腫脹が消失し鼻閉も改善した。

III．手術成績と長期予後

各種レーザーによる下鼻甲介粘膜手術の成績と比較すると，有効率の定義が各報告間で異なり単純な比較は困難であるがレーザー手術はハーモニックスカルペル®とほぼ同等の成績が得られている（表 2）[6~9]。下鼻甲介粘膜焼灼術では，術後 2 年間で約 20～40%の症例で鼻漏，くしゃみが再発すると報告されている[6~9]。再燃時期は平均約 32 週で，特にくしゃみの鼻漏の症状再燃が多い。くしゃみは三叉神経知覚線維を求心路として中枢経路で迷走神経を刺激することによって生じるが，重症例では粘膜浮腫による腫脹が高度であるため焼灼が粘膜表層にとどまり，三叉神経神経終末および鼻腺の十分な焼灼が行われなかったために効果が低かった可能性が示唆されている[6~9]。

このような難治例の取り扱いであるが，手術施行時に，

1）出力をより高くして深部を焼灼する
2）焼灼の回数を複数回に増やす
3）鼻漏の多い場合は鼻内後鼻神経切断術などの他の外科的治療を追加する

などの対策も考慮すべきである。

また，鼻閉の特に強いアレルギー性鼻炎症例では鼻中隔彎曲症，肥厚性鼻炎，鼻茸などの鼻腔形態異常を合併している場合がある。鼻腔通気抵抗は鼻腔断面積の 2 乗に逆比例して増加するために，

鼻腔形態異常を合併しているアレルギー性鼻炎症例ではアレルギー反応による鼻粘膜腫脹がたとえ軽度でも鼻腔通気抵抗は大きく増加し鼻閉を惹起することとなる。これらの鼻腔形態異常は外科的治療によって改善することが可能で，積極的に外科的治療を施行する必要がある。

Ⅳ．レーザー手術の合併症とその予防と対策

1．視器障害

レーザーを使用した手術を行うには術者や周囲の人への目に対する誤照射に注意することはもっとも基本的な点であるが，防護用メガネの装用にて防止できる。また，レーザー照射中の手術室へのスタッフの入退室は極力避けるように努める。

2．呼吸器障害

レーザー手術による下鼻甲介手術は安全かつ簡便に行えるが，レーザー光で蒸散された炭化層粒子の飛散による焼煙よる呼吸器障害の可能性も指摘されている。局所麻酔下の気道手術のため患者は多少なりとも炭化層粒子を吸入してしまう。これを避けるために，術中患者には口で息を吸い鼻から吐くように十分に指導するとともに鼻腔内の焼煙の十分な吸引を行い，炭化層粒子が下気道に吸引されないように最大限の注意を払う必要がある。また，術者および看護スタッフは手術用マスクを装着する。

3．粘膜癒着

術後合併症として，鼻中隔と下鼻甲介の粘膜癒着が生じることがある。粘膜癒着部位は，鼻中隔の骨棘部に生ずることが多く，この部にレーザーを誤照射しないように留意することが肝要である。粘膜癒着が生じた場合には，癒着を下鼻甲介剪刀にて切離した後にテラマイシン軟膏を塗布したベスキチンＦをスペーサーとして留置する。また，鼻腔内の分泌物をなるべく粘膜を損傷しないように十分吸引除去することが必要である。

4．腐　骨

腐骨形成は下鼻甲介前端に生じる例が多く，この部への過剰なレーザー照射に起因する。鼻粘膜が再生上皮化する術後２カ月を経過しても腐骨の表面には痂皮が付着する。腐骨は下鼻甲介剪刀で容易に切除でき，切除後は短期間にこの部も上皮化される。

まとめ

レーザー機器は進歩し，鼻科手術における有用性も確立している。しかし，レーザー機器から発生するレーザー光は固有の物理特性，生態作用を持つため安全性を高めるためにレーザー手術を行うにあたっては，その適応と特徴を十分に理解し，使用するレーザーの特性に合わせた照射法を選択することが重要である。

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リアルタイムモニター花粉症の情報のあり方の研究と舌下ペプチド・アジュバンド療法の臨床研究
スギ花粉症患者における薬物療法の効果検証-花粉暴露室を用いて-

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研究要旨

鼻アレルギー診療ガイドラインでは初期治療あるいは中等症以上の鼻閉の症例に対して抗ロイコトリエン薬が推奨されている。現在薬剤の効果を検証する方法として抗原暴露室が使用されている。この暴露室を用いて抗ロイコトリエン薬の効果を検証した。抗ロイコトリエン薬プランルカストはやはり鼻閉に対する効果が高く、1 ㎥中 8000 個の花粉飛散においても鼻症状を抑制した。今後このような暴露室を用いて花粉症治療薬の効果の検証を行っていかなければならない。

A. 研究目的

アレルギー性鼻炎に対する治療法は現状では薬物療法が最も花粉症に広く行われている治療法である。しかし薬物療法の効果の検証については発売以降の二重盲険比較試験などのエビデンスレベルの高い研究はごくわずかである。これは研究にかかる費用の問題と一般臨床と話した形での試験が難しいためである。厚生労働省では 2009 年から臨床試験の指針を発表し、今以上に花粉症などの common disease では臨床試験が難しくなると思われる。この点を鑑みて、我々は花粉暴露室を用いた検討を以前より行っている。今回は今までに国外で 1 報の報告しかない抗ロイコトリエン薬の効果をスギ花粉症患者ボランティアに対して花粉暴露室 OHIO チェンバーを用いて検証した。

B. 研究方法

中等症以上のスギ花粉症患者 39 症例に対してプラセボ対照クロスオーバー試験を行った。試験薬剤はプランルカストカプセルと同一のカプセルに入ったプラセボである。花粉暴露前日夜 2 日カプセル、当日朝 2 カプセル、花粉暴露後当日夜 2 カプセル、翌朝 2 カプセルの服用である。実際の花粉暴露は OHIO チェンバーで 1 m3 中 8000 個の花粉を 3 時間暴露した。15 分ごとの鼻のかゆみ、くしゃみ、鼻水、鼻閉、目のかゆみ、涙目、咳の症状をスコアで記入させ、暴露後 3 日までの症状を遅発相の反応として検証した。

C. 研究結果

中等症以上のスギ花粉症患者では OHIO チェンバーで 1 m3 中 8000 個の花粉暴露でおよそ 90 分以内に全症例に症状が出現した。しかしプランルカスト群はプラセボ群に比較し「鼻閉スコア」「総合鼻症状スコア」を有意に減少させた。スギ花粉暴露後ではプランルカスト群は「鼻閉スコア」「鼻のかゆみスコア」「目のかゆみスコア」及び「総合鼻症状スコア」でプラセボを対照として有意に改善させた。

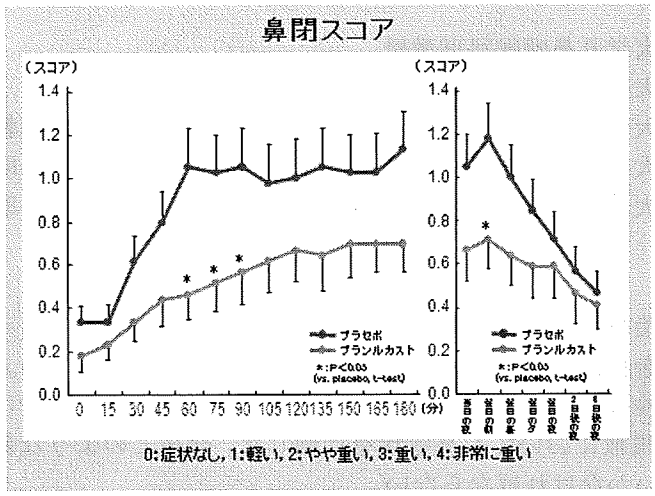
D. 考察

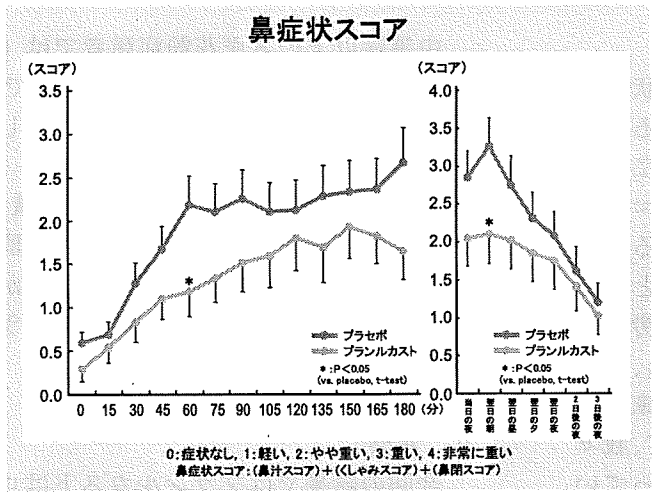
今回の結果ではプランルカストはロイコトリエンの拮抗薬であるため、鼻閉を中心に症状をコントロールした。もちろんヒスタミンの関与が強い暴露中の鼻のかゆみ、目のかゆみ、くしゃみはもちろん抑制しなかった。しかし一方で暴露終了後の遅発相の反応で生じるこれらの症状を抑制したことは抗原特異的ではない過敏性の亢進を減少させることが証明された。このメカニズムは好酸球浸潤阻止あるいは神経ペプチド系に与える影響なのかは判明しないが、今後注目する作用メカニズムになりうる効果である。

E. 結論

花粉暴露室においてプランルカストが高濃度の花粉暴露で生じうる鼻閉を抑制することを証明した。薬剤の服用は 1 日であり、即効性を示すものである。今後、このような暴露室でどの薬剤はどの症状をどのように抑制するかを検証することが、バリエーションの豊富なそれぞれの花粉症症状に合わせた個人個人のレディメイ

ド治療を構築できるものと考える。





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G. 知的財産権の出願・登録状況

1. 特許取得

藤枝重治、高橋　昇、大澤　陽子、窪　誠太、有波 忠雄、野口　恵美子、牧野　友香、内田　和彦、大久保　公裕　アレルギー疾患の治療薬且つ治療効果マーカー（特願2008－053768　平成20年3月4日提出）

2. 実用新案登録

なし

3. その他

なし

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ORIGINAL ARTICLE

A Randomized Double-Blind Comparative Study of Sublingual Immunotherapy for Cedar Pollinosis

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ABSTRACT

Background: Seasonal allergic rhinitis (SAR) induced by Japanese cedar pollen is a substantial problem in Japan. Sublingual immuno-therapy (SLIT) is safer than conventional antigen-specific immunotherapy, the only treatment modality by which complete cure of the disease can be expected. We investigated the safety and efficacy of SLIT in the treatment of cedar pollinosis patients compared to placebo.

Methods: A randomized, placebo-controlled, double-blind study was conducted in 61 cedar pollinosis patients. Increasing doses of standardized Japanese cedar extract or placebo were administered sublingually in intervals ranging from daily to once a week after six weeks. The primary efficacy variable was the mean of the daily total symptom scores (TSS) during the pollen dispersing period. Secondary efficacy variables included the QOL scores and related variables.

Results: Primary efficacy variable scores were significantly lower for some days in the SLIT group than in the placebo group ($P < .01$ or $P < .05$). Secondary efficacy for the QOL score in SLIT group was almost of half of placebo group. There was no significant difference in the overall incidence of side effects between the SLIT group and the placebo group.

Conclusions: SLIT was effective and safe in the treatment of cedar pollinosis.

KEY WORDS

Japanese cedar, placebo-controlled study, QOL, seasonal allergic rhinitis

INTRODUCTION

In agreement with the results of worldwide epidemiological assessments, the number of patients with allergic rhinitis such as Japanese cedar (JC) pollinosis in Japan is increasing.[1] Okuda considers that the current prevalence of allergic rhinitis is 16%, but many researchers predict that the rate will still increase.[2] Pollinosis is a typical type I allergy in which allergic conjunctivitis and allergic rhinitis develop. In spite of its refractory nature, pollinosis deteriorates patient QOL only in severe cases; however, it greatly affects the patient's life in general in that they must keep working even if the condition is severe.[3] Many of the patients with cedar pollinosis have also been sensitized to cypress pollen which disperses after cedar pollen. Consequently, symptoms of cedar pollinosis are followed by those of cypress pollinosis; patient symptoms last, though they are seasonal, for as long as 4 months (from February to May).

Pharmacological therapy prescribed by general practitioners is common for the treatment of the disease. Both oral medications and topical medication, however, are symptomatic treatment; they do not cure the disease or remain effective until the following year.[4] Antigen-specific subcutaneous immuno-

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therapy (SCIT) is the only treatment modality by which complete cure of the disease can be expected.[5] WHO position paper stipulates the use of standardized antigen and the concentration of the antigen to be maintained.[6] The efficacy of the therapy has been proven in placebo-controlled, double-blind comparative studies using pollen, house dust mite, and animal protein.[6,7] In Japan, it is customary to start the administration of causative antigen extract by subcutaneous injection at the threshold of skin reaction or its 10-fold diluted concentration, and to increase the dose gradually.[4] Treatment with SCIT requires special attention because it may cause, as a side effect, anaphylactic shock, which prevents the therapy from becoming popular in Japan.[8] In order to reduce the possibility of this side effect, immunotherapy is administered by other routes (sublingual, intranasal, oral, and transbronchial) in Europe and the United States, and has achieved desired outcomes.[9-11] Especially, sublingual immunotherapy (SLIT) has become popular in Europe considerably, and there are many reports supporting the effectiveness of the therapy.[11-13] As for side effects due to SLIT, there are no reports of anaphylactic shock, but oral itching, skin reaction (such as urticaria), and mild asthma-like attacks have been reported.[13] Since cedar pollinosis greatly deteriorates patient QOL, many physicians and patients will opt for immunotherapy if it is proven to be safe. We conducted a randomized, placebo-controlled double-blind comparative study to investigate whether SLIT reported in Europe and the United States is effective for the treatment of JC pollinosis and whether it can be performed safely.

STUDY DESIGN

This multi-centre, double-blind, randomized, placebo-controlled, parallel-group study was conducted in six centers across Japan between October 2004 and April 2005. The study protocol was approved by the appropriate local ethics committees, and the study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent prior to participation.

SUBJECTS

Patients with JC pollinosis were enrolled in this study if they had a RAST score of 2 against JC or above and pollinosis symptoms during the cedar pollen dispersal period at least in the past 2 years and if they had visited any of the following medical institutions: Department of Otorhinolaryngology, Nippon Medical School; Department of Otorhinolaryngology, University of Fukui; Department of Otorhinolaryngology, Head and Neck Surgery, Okayama University; Department of Otorhinolaryngology, Dokkyo University School of Medicine; Department of Otorhinolaryngology, University of Yamanashi; and Department of Otorhinolaryngology, Head and Neck Surgery, Chiba University. Patients who had nose diseases (perennial allergic rhinitis, nasal septum deviation, or sinusitis) which may interfere with accurate symptom assessment were excluded from the study. Patients receiving treatment for conditions such as severe cardiac disease and malignant tumor were also excluded. As a result, a total of 61 patients were blindly randomized either to the active group or the placebo group in the ratio of 2 active to 1 placebo.

METHODS

The study was initiated in October, 2004. Patients were assigned and randomized to either the active group or the placebo group. Cedar antigen extract (active group) at concentrations of 2 to 2000 JAU/ml diluted with diluent (made by Torii Pharmaceutical Co., Ltd.) and diluent alone (placebo group) were used in eye drop containers (made by Hirakata Plastic).

Administration of the antigen extract was started at 2 JAU/ml, which is considered a sufficiently safe level, and was increased to the final maintenance concentration of 2000 JAU/ml. Active drug was administered as follows: 1 drop (about 50 μl) to 20 drops (about 1 ml) of prepared extract was dropped onto bits of bread (about 1.5 cm × 1.5 cm × 1.5 cm), which were held sublingually for 2 minutes and then expectorated. The treatment schedule was as follows: antigen extract was administered sublingually daily from Week 1 to Week 4; 20 drops of the antigen extract 2000 JAU/ml were administered two days per week in Week 5, once per week in Week 6 and thereafter throughout the season (Table 1).

Patients experiencing pollinosis symptoms in cedar and cypress pollen dispersal periods received symptomatic treatment with medications such as antihistamines on an as needed basis; such patients were asked to record the date of treatment in their allergy diary.

ENDPOINTS

The patients were instructed to fill in their allergy diary from February 22, 2005 to April 6, 2005, the period when cedar and cypress pollen dispersed in 2005, and they were also asked to fill in QOL questionnaire once a month during the same period. Symptoms recorded in the allergy diary (sneezing, runny nose, nasal congestion, and interference with daily life), the total nasal symptom scores calculated based on each symptom, sneezing, runny nose, nasal congestion (none; 0, mild; 1, moderate; 2, severe; 3), and symptom medication scores (antihistamine; 1, topical steroid; 2, general steroid; 3) were calculated. The Japanese Allergic Rhinitis QOL Standard Questionnaire No.1 (JRQLQ No1) was used for the assessment of the QOL of patients with allergic rhinitis (Fig. 1). Nasal and Ocular symptom scores, QOL-

Table 1 Allergen administration schedule (Increasing dosing)

	Week 1 (2 JAU/ml)	Week 2 (20 JAU/ml)	Week 3 (200 JAU/ml)	Week 4 (2000 JAU/ml)	Week 5 (2000 JAU/ml)
Day 1	1 drop	1 drop	1 drop	1 drop	20 drops
Day 2	2 drops	2 drops	2 drops	2 drops	
Day 3	3 drops	3 drops	3 drops	4 drops	
Day 4	4 drops	4 drops	4 drops	8 drops	
Day 5	6 drops	6 drops	6 drops	12 drops	20 drops
Day 6	8 drops	8 drops	8 drops	18 drops	
Day 7	10 drops	10 drops	10 drops	20 drops	

Initial dose of SLIT for JC pollinosis was 1 drop of 2 JAU/ml of standardized JC allergen, and the administrating dose is increased up to 20 drops of 2000 JAU/ml at 4th week, the maintenance dose.

Japanese Rhino-conjunctivitis Quality of Life Questionnaire (JRQLQ No.1)

To patients with allergic rhinitis (including pollinosis)

These days, the aim of medical treatment is not just to cure disease but also to give patients a better quality of life. The purpose of this survey is to determine to what extent your rhinitis interferes with your life and whether it would be improved by treatment. As with all medical treatment, the information you provide in this survey will remain strictly confidential.

You may find some of the following questions difficult to answer, but just answer to the best of your ability.

/ Tick the box that best describes the severity of the worst nasal and eye symptoms you have experienced in the past 1–2weeks.

Nasal and eye symptoms	0. No	1. Mild	2. Moderate	3. Severe	4.Very severe
Runny nose	☐	☐	☐	☐	☐
Sneezing	☐	☐	☐	☐	☐
Blocked nose (nasal congestion)	☐	☐	☐	☐	☐
Itchy nose	☐	☐	☐	☐	☐
Itchy eyes	☐	☐	☐	☐	☐
Watery eyes	☐	☐	☐	☐	☐

// Tick the box that best describes the worst extent to which the symptoms in / above have interfered with your quality of life in the past 1–2 weeks. If any of the items listed under Quality of life below definitely do not relate to the symptoms in / (nose, eyes), then there is no need to tick a box for that particular item.

Quality of life	0. No	1.Yes, slightly	2.Yes, moderately	3.Yes, severe	4.Yes, very severe
1. Reduced at work/home	☐	☐	☐	☐	☐
2. Poor moral concentration	☐	☐	☐	☐	☐
3. Reduced thinking power	☐	☐	☐	☐	☐
4. Impaired reading book/newspaper	☐	☐	☐	☐	☐
5. Reduced memory loss	☐	☐	☐	☐	☐
6. Limitation of out of life (e.g. sport, picnics)	☐	☐	☐	☐	☐
7. Limitation going out	☐	☐	☐	☐	☐
8. Hesitation friends or relatives	☐	☐	☐	☐	☐
9. Reduced contact with friends or others by telephone or conversation	☐	☐	☐	☐	☐
10. Not an easy to be around	☐	☐	☐	☐	☐
11. Impaired sleeping	☐	☐	☐	☐	☐
12. Tiredness	☐	☐	☐	☐	☐
13. Fatigue	☐	☐	☐	☐	☐
14. Frustration	☐	☐	☐	☐	☐
15. Irritability	☐	☐	☐	☐	☐
16. Depression	☐	☐	☐	☐	☐
17. Unhappiness	☐	☐	☐	☐	☐

/// Please circle the number of the face that best describes your general state (including your symptoms, life and emotion) in the past 1–2 weeks.

Do not fill out the following

To be completed by physician

Patient's name: Medical record to: Age: yr Sex: M F

Name of medical institution: Physician's name: Date:

Diagnosis:
SAR (Antigen) Treatment [prevention,drug,immunology,therapy,operation]
PAR (Antigen) Treatment [prevention,drug,immunology,therapy,operation]
Non-Allergy: Disease: ( ) Treatment: ( )

QOL score: None 0 , Mild 1 , Moderate 2 , Severe 3 , Very severe 4
Total QOL score
Score by QOL category 1–5 points daily life 6–7 points out-door
8–10 points social 11 points sleep
12–13 points body 14–17 points psyco-life

Please write the names of drugs used it possible

Score: None: 0 points Mild: 1 point Moderate: 2 points
Severe: 3 points Very Severe: 4 points

Fig. 1 Japanese Allergic Rhinitis QOL Standard Questionnaire No.1 (JRQLQ No1).

related questionnaire scores, and the overall face scale were calculated and statistically analyzed. In other words, the QOL deterioration score was calculated by subtracting QOL-related questionnaire scores recorded in February (i.e. at baseline) from the scores recorded in the middle of March to April, when the largest amount of pollen dispersal was observed.

STATISTICAL ANALYSIS

Symptom scores, total symptom scores, and symptom medication scores calculated from the allergy diary in the placebo group and the active group were analyzed by non-paired t-test and the Chi-squared test

Table 2 The background of the subjects

Items	Placebo $n = 22$	Active $n = 37$	p value (*)
Age	40.14±15.30	40.65±15.14	0.901
Sex			
Male	7 (31.8%)	18 (48.6%)	
Female	15 (68.2%)	19 (51.4%)	
Nasal and eye symptoms	0.62±0.54	0.43±0.35	0.169
QOL-related questionnaire	0.25±0.29	0.21±0.25	0.568
Usual daily activities	0.13±0.25	0.11±0.32	0.762
Outdoor activities	0.14±0.48	0.21±0.46	0.630
Social functioning	0.05±0.22	0.08±0.23	0.648
Sleep disturbance	0.14±0.36	0.09±0.29	0.537
Physical problems	0.17±0.33	0.24±0.46	0.510
Emotional function	0.12±0.23	0.11±0.32	0.953
Overall face scale	1.14±0.73	1.09±0.74	0.780

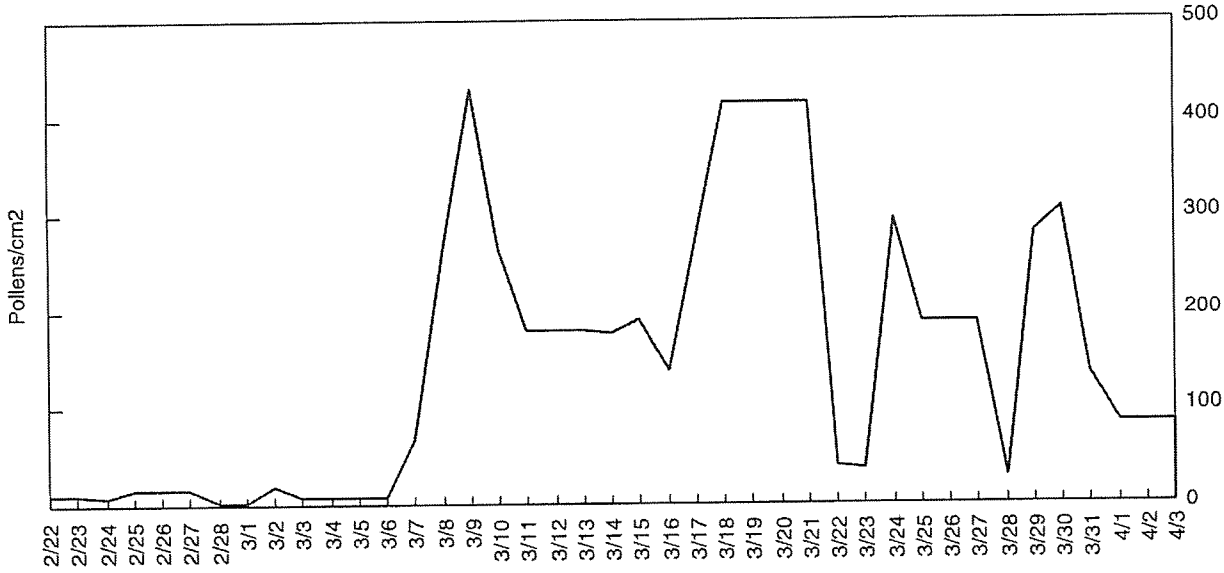


Fig. 2 The changing the number of cedar and cypress pollen dispersals in 2005.

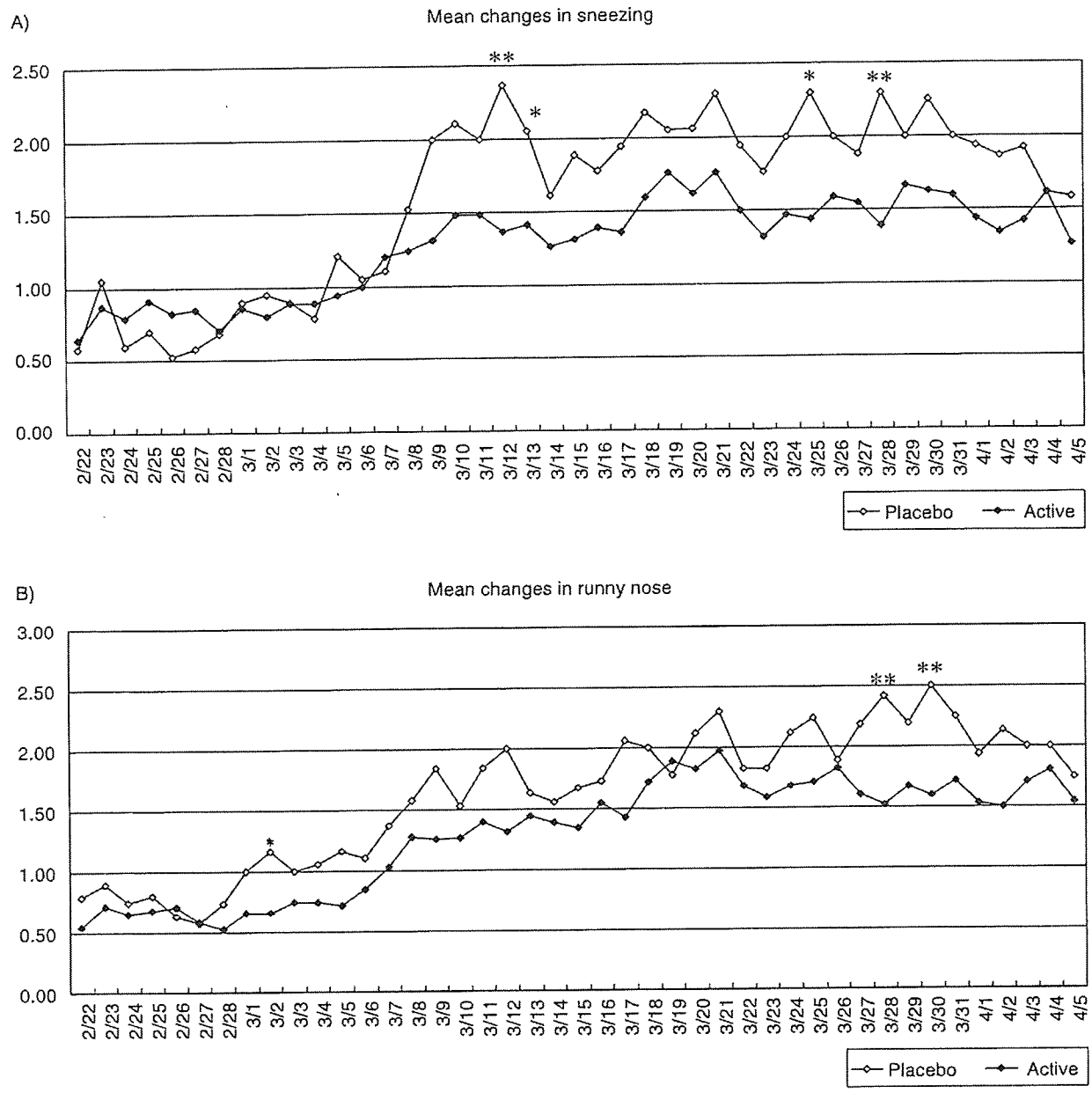
using SPSS 11.0J. QOL-related questionnaire score of the 2 groups were compared using analysis of covariance (ANCOVA).

RESULTS

Of the 61 randomized patients, there were 2 dropouts for those whose treatment was unknown; there were 37 patients in the active group and 22 patients in the placebo group. In the analysis of allergic symptoms, 2 patients whose outcome was available only in the form of a diary were excluded, and the results of 36 patients in the active group and 21 patients in the placebo group were analyzed. In the analysis of QOL, 3 patients were excluded because baseline assessment was unavailable, and the results of 35 patients in the active group and 21 patients in the placebo group were analyzed.

As shown in Table 2, no difference was observed between the two groups in terms of patient characteristics (sex was analyzed by the Chi-squared test, and other items were analyzed by t-test).

In 2005, the number of cedar and cypress pollen dispersals observed was the largest during the 10-year period since 1995. According to the data of the Chiyoda ward—the area nearest to the Nippon Medical School—announced by the Tokyo Metropolitan Government, the first pollen dispersal was observed on February 22, which was about the same time as in the past years, and an average of 10,625 pollens per square centimeter by the Durham method were ob-

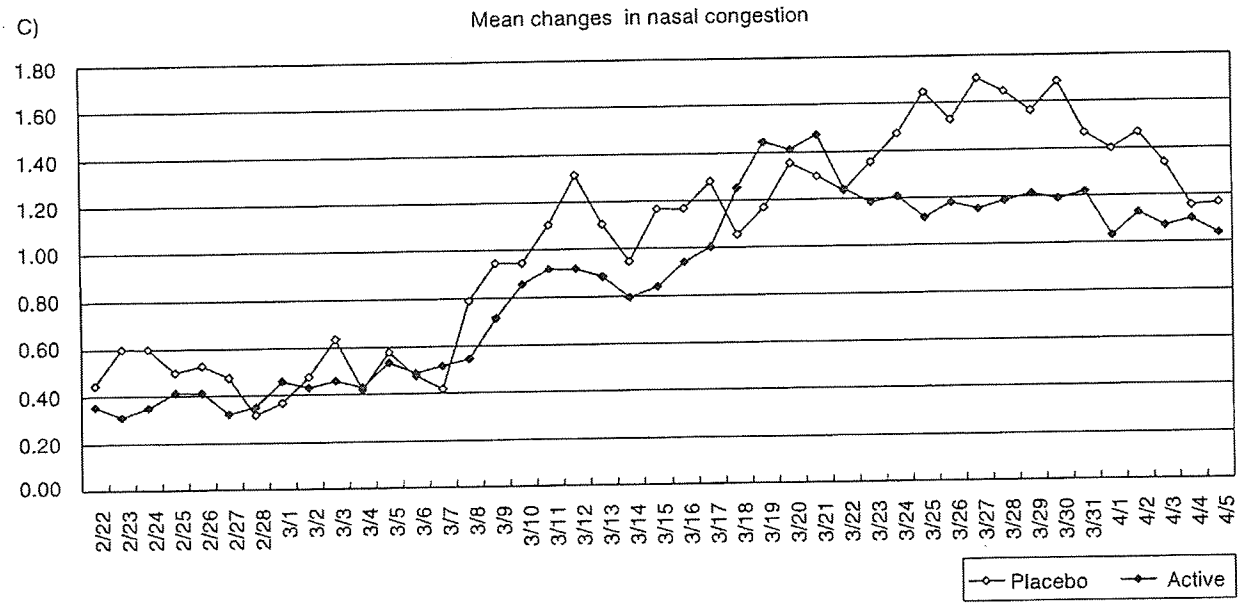


served during the season (Fig. 2). The number of the cedar and cypress pollens by the same method observed in each institution was 3424, 2383, 16002, 5859 and 7752 for University of Fukui, Okayama University, Dokkyo University, University of Yamanashi and Chiba University respectively, and these pollen numbers were also largest dispersing during the last ten years at any place.

Symptom scores for sneezing (Fig. 3A) and runny nose (Fig. 3B) in the active group were significantly better than those in the placebo group on 4 days and 2 days, respectively, but no difference was observed between the active group and the placebo group in terms of nasal congestion (Fig. 3C). Between the 2 groups, there was no difference in the number of medications used during the season (Fig. 3D).

The active group had a significantly lower total symptom score (Fig. 4A) and symptom medication score (Fig. 4B) on 4 days during the season. Overall, better outcomes were observed in the active group during the latter half of the season (i.e. from the end of March to the beginning of April), which roughly overlaps the period when the largest amount of cedar and cypress pollen was dispersed.

In the placebo group, the nasal and ocular symptom score was 1.15, the QOL-related questionnaire score was 1.10, and the overall face scale score was 1.24; in the active group, the nasal and ocular symptom score was 0.92, the QOL-related questionnaire score was 0.58, and the overall face scale score was 1.03: the deterioration score in the QOL-related questionnaire in the active group was only about half the score in the placebo group (Fig. 5A). In each domain of QOL question items, deterioration in usual daily activities, outdoor activities, social functioning, sleep problems, general physical problems, and emotional function in the active group was only about half the score in the placebo group as well. The p-values for the above domains were 0.089, 0.086, 0.067, 0.060, 0.083 and 0.046; a significant difference was observed



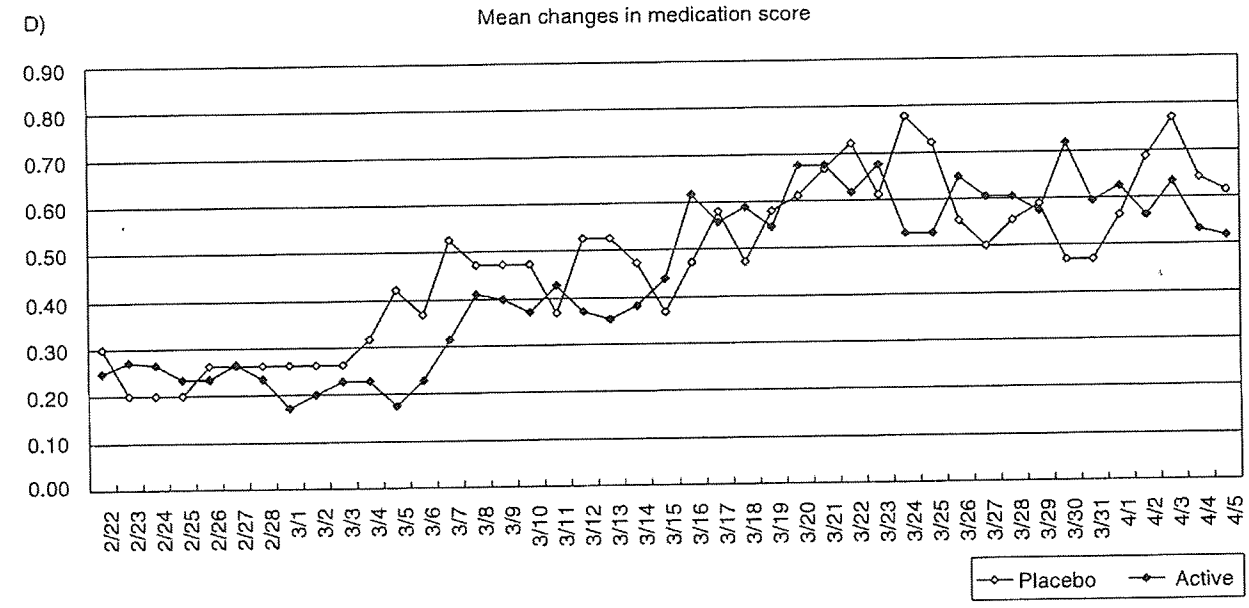


Fig. 3 The mean changes in each symptom in the season of 2005. **A)** Mean changes in sneezing. **B)** Mean changes in runny nose. **C)** Mean changes in nasal congestion. **D)** Mean changes in medication score. The open square indicates the placebo group, the filled square indicates the active group. Significant difference was evaluated as * $p < 0.05$; ** $p < 0.01$.

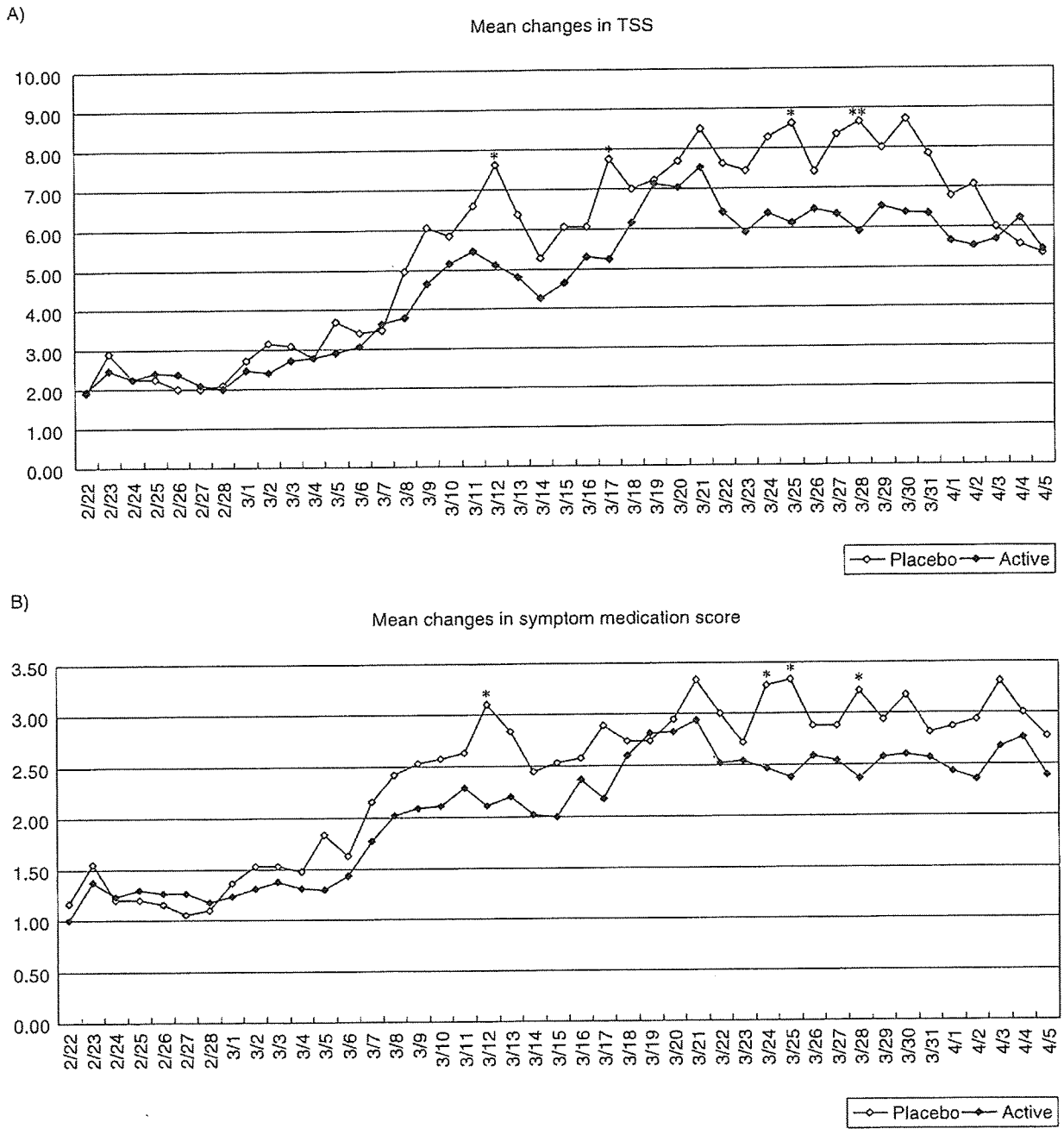


Fig. 4 The mean changes in **A)** the total symptom score (TSS) and **B)** symptom medication score in the season of 2005. Significant difference was evaluated as * $p < 0.05$; ** $p < 0.01$.

only in emotional function (Fig. 5B).

SIDE EFFECTS

No systemic side effect occurred during SLIT. Local side effects occurred in six volunteers in the active group. Mild mouth itching was exhibited in all six volunteers in increasing dose up to 2000 JAU 1 ml, however this itching was diminished for two or three times just after allergen administration. All six volunteers finished this study totally without any change of this protocol.

DISCUSSION

Approximately 16% of the Japanese population are af-

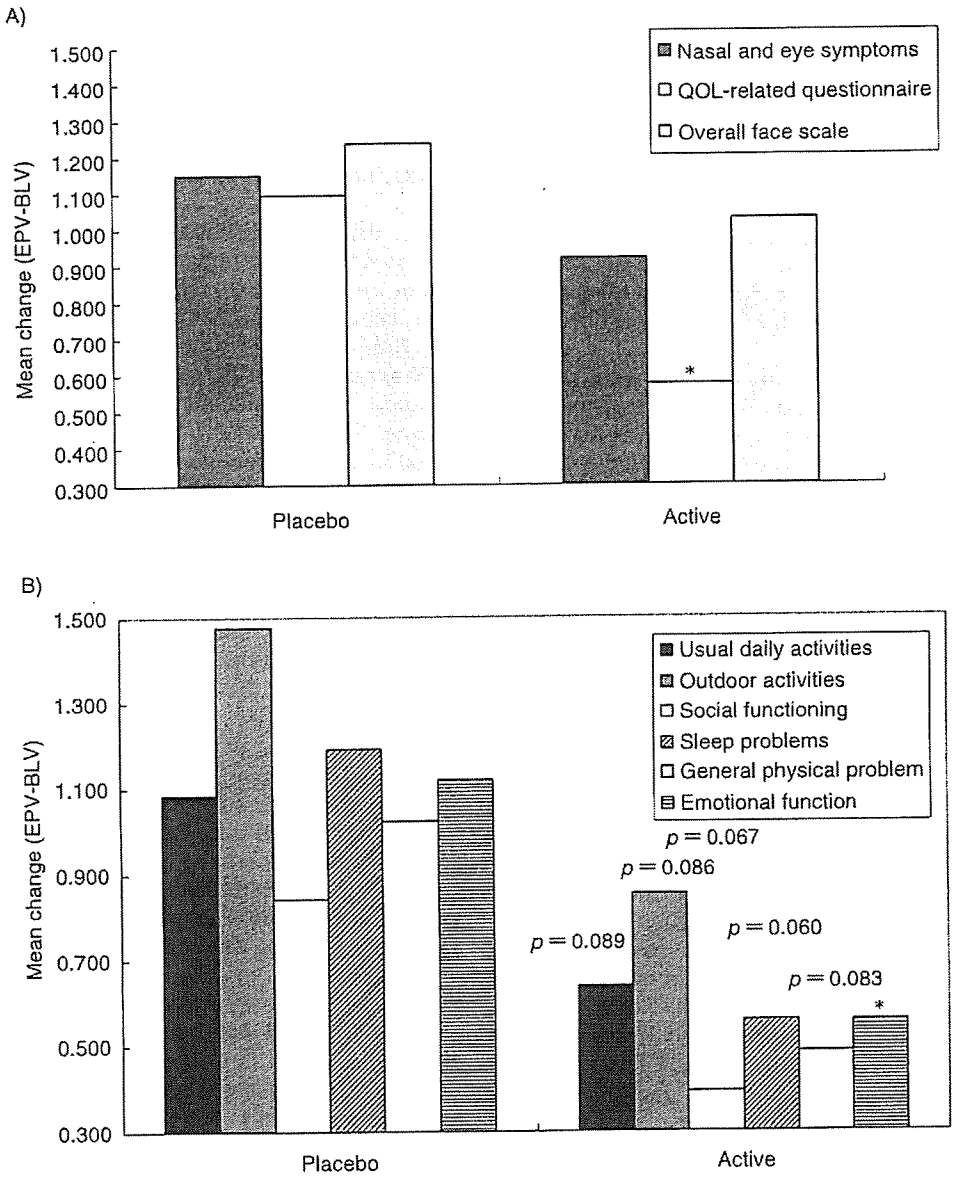


Fig. 5 The mean changes of **A)** QOL scores (nasal and eye symptoms, QOL related questionnaire, overall face scale) and **B)** each domain of QOL question items deterioration (in usual daily activities, outdoor activities, social functioning, sleep problems, general physical problems, and emotional function) from baseline data of February to peak data of peak pollen scattering period. Difference between placebo and active indicates * $p < 0.05$ (analysis of covariance, ANCOVA). Placebo: $n = 21$, Active: $n = 35$.

fected by Japanese cedar pollinosis[2] and the proportion of severe status patients is higher than with grass or ragweed pollinosis, which are the representative conditions in other countries, and the symptoms 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 (late season) 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 SCIT 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.

As shown in the WHO position paper, the effects of immunotherapy in the treatment of pollinosis have been substantiated in many double-blind comparative studies.[6] However, the therapy tends to be avoided in Japan because of factors such as the current high cost, the complicated procedure involved, and possible side effects. In Japan, owing to these disadvantages and the fact that the department of allergy has not been widely established in medical institutions, pharmacological therapy is the mainstream modality for the treatment of pollinosis. Still, immunotherapy is an important modality for the complete cure of allergic diseases.

The efficacy of our SLIT was not demonstrated based on patient allergy diaries. However, the quality of life (QOL) score was approximately 1/2 of that in the placebo group, with a significant difference. In addition, a *P*-value corresponding to a significant difference was obtained in each QOL domain. In the mental health domain, there was a significant difference. Assessment using the Japanese guidelines differs from that in other countries; even a single sneeze is regarded as (+). In other countries, 4 grades (none, mild, moderate, and severe) are employed for assessment, and the presence or absence of symptoms is not evaluated. For this reason, the usefulness of SLIT may not have been demonstrated based on diaries. However, the QOL is evaluated via self-assessment, which is consistent with the system for the self-reporting of symptoms in other countries (none to severe). Therefore, QOL assessment of SLIT was favorable, and was consistent with the reduction rates in other countries. According to the JRQLQ criteria, the reduction rate for nasal/ocular symptoms was 22%, consistent with the evaluation of SLIT in other countries. In the future, the JRQLQ criteria, which were designed in reference to overseas self-assessment, may be essential for evaluating drug efficacy and such a novel treatment. This finding is suggestive of the fact that the QOL questionnaire developed in Japan is of good quality,[14] and that SLIT is effective for preventing QOL deterioration in patients with pollinosis rather than for lowering their symptom score. Placebo effects of SLIT may be present. However, it was evaluated in 2005, when the amount of scattered pollen was highest over the past 10 years. In addition, considering that the study involved a placebo-controlled design, we can conclude that SLIT was effective for cedar pollinosis in Japan. In evaluating the treatment response, we cannot rule out the influence of Japanese cypress pollen scattering. However, in a study excluding Japanese cypress pollen-positive reacting patients, the efficacy of SLIT and reduction rate for symptoms were also similar (unpublished data). This maybe caused by the combination of a large amount of JC and a small amount of cypress that was dispersed in 2005. These types of pollinosis should be regarded as JC/Japanese cypress pollinosis, as their seasons are sequential in the near future. In addition, a Japanese cypress pollen antigen for immunotherapy must be prepared. It should be considered that symptoms of cedar/Japanese cypress pollinosis in April are associated with cedar pollen scattering-related nasal mucosal/conjunctival inflammation, not with Japanese cypress pollen scattering alone.

Less side effects including problematic anaphylaxis are noted in SLIT although the side effects observed cannot be theoretically complete anaphylactic shock when comparing the therapy administered via injection with sublingual route.[15] Similar to the oral allergy syndrome (OAS), which is the focus of public attention, the development of symptoms such as strange feelings, oral itching, and swelling were feared because the antigen remains in the oral cavity; however, itching was the only reaction observed so far. The results obtained from the study of tentative SLIT, which was performed exclusively in the Department of Otorhinolaryngology, Nippon Medical School, were roughly consistent with the results of similar studies conducted every year thereafter, including the results of the study in 2005,[16] In our study of SLIT for the treatment of cedar pollinosis, symptom medication score was consistently lower than that of the pharmacological therapy group throughout the pollen dispersal season. The finding indicates that patients receiving SLIT tend to use fewer drugs, which is consistent with the results of a double-blind comparative study using a placebo,[17] SLIT, which is as effective as pharmacological therapy and decreases the amount of drug use, is considered advantageous also in the current medical economy in Japan.

The mechanism of action for SLIT, or for conventional SCIT, is still unclear, but for SCIT, reduction of effector cells[18,19] and blocking antibody[20-23] have been the conventional theories. Recently, however, it has become widely accepted that immunotherapy may modify the T cell response to natural allergen because of T cell anergy and/or immune deviation.[24-27] For SLIT in particular, allergen administered to the oral mucosa accumulates in the submandibular lymph node, in which the immune response occurs[28] and peaks at approximately 2 hours after administration.[29] In our investigation, an increase in the Stimulatory Index in PBMC during the early phase of SLIT conducted in 1999 shows at least that systemic immune induction was caused by sublingually administered antigen.[30] In SLIT, it is intended to cause fewer side effects than SCIT injection by decreasing systemic effects. However, it has become clear that the therapy also leads to systemic immune induction, which is greatly different from conventional topical immunotherapy administered intranasally or orally.

In the present study, 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. This study may contribute to the methodology for the future immunotherapy in Japan.

The development of this SLIT in Japan is in progress as a multi-center study conducted as part of the research project on the prevention and treatment of immunological and allergic diseases (H17-immunology-common-001) entitled "Evaluation research of the relationship between the number of dispersed pollen observed by real-time monitoring and QOL achieved by the current treatment modalities, and the development of definitive treatment for pollinosis", which is supported by Health and Labour Sciences Research Grants from the Ministry of Health, Labour and Welfare.

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