

Randomized controlled trial of high-dose sublingual immunotherapy to treat seasonal allergic rhinitis

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Background: Seasonal allergic rhinitis is common and troublesome. Sublingual immunotherapy (SLIT) has been proposed as an alternative to injection immunotherapy and might offer some advantages if it were effective and practical in a community setting.

Objectives: To assess the efficacy and side-effect profile of SLIT in patients with summer hay fever uncontrolled on current standard medication. To assess the feasibility of delivering SLIT in a United Kingdom general practice setting.

Methods: Double-blind, placebo-controlled study in 186 patients with severe summer hay fever identified from 16 United Kingdom general practices. After a baseline year to ensure balanced groups, subjects were randomized, and SLIT was given for 1 or 2 years and compared with placebo. The principal outcome measure was symptoms as recorded on diary cards. Secondary criteria were skin and conjunctival reactivity, allergen-specific IgE and IgG₄, and the frequency and severity of adverse effects.

Results: One hundred thirty-six subjects completed the study. After 1 year, no significant differences were found between actively treated subjects and the placebo group. After the second year of therapy, subjects who had received 2 years treatment were 6.8 times more likely to show a reduction in nose running ($P < .001$) and 2.4 times more likely to have reduced sneezing ($P < .05$) compared with subjects in the placebo group. Benefits for nasal blockage were found at the peak pollen season and were similar in both actively treated groups.

Conclusion: Sublingual immunotherapy can be given successfully and safely in the community. High-dose SLIT has beneficial effects on nasal symptoms during the peak pollen season in patients with severe seasonal allergic rhinitis. At least

2 years of treatment with SLIT is required to show a benefit. (*J Allergy Clin Immunol* 2004;114:831-7.)

Key words: Sublingual immunotherapy, immunotherapy, seasonal allergic rhinitis, grass pollen, hay fever

Seasonal allergic rhinitis is an increasingly common problem.^{1,2} Antiallergic drugs are effective for many patients,³ but significant numbers continue to have uncontrolled seasonal allergic rhinitis, despite regular and appropriate medication.⁴

Specific immunotherapy (SIT) consisting of 2 to 3 years of injections of allergen extracts is effective^{5,6} but has been out of favor in the United Kingdom (UK) since 1986, when stringent conditions were imposed on SIT after several fatal adverse reactions.⁷ Widespread adoption of SIT in the UK remains unlikely because SIT is restricted to the relatively few specialist clinics. Consequently, there is great interest in alternative forms of allergy care.

European studies suggest that sublingual immunotherapy (SLIT) may be effective in allergic rhinitis without the risks of conventional SIT.⁸⁻¹² This evidence cannot be directly extrapolated to the UK because SIT and SLIT are often given to European patients with relatively mild disease, whereas in the UK, SIT is reserved for more severe cases. Moreover, questions remain about the duration of efficacy of SLIT and the feasibility of delivering SLIT in nonspecialist settings. We therefore conducted a community-based, double-blind, placebo-controlled trial of high-dose SLIT in patients whose seasonal allergic rhinitis was not satisfactorily controlled by pharmacotherapy.

METHODS

A double-blind, randomized, placebo-controlled trial of 1 or 2 years of SLIT was conducted. Suitable subjects with seasonal rhinitis who were prescribed antihistamines and nasal corticosteroid sprays in 1997 were identified from diagnostic registers of 16 general practices in Wessex (Hampshire, Wiltshire, Dorset, and Isle of Wight).

Adults (18-60 years) were eligible if their seasonal rhinitis was not well controlled in previous years, despite prescription of nasal steroids and/or oral antihistamines, together with evidence of grass pollen sensitization (skin prick wheal diameter >4 mm and IgE-RAST $\geq$ class 2).

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Supported by Stallergenes SA, Antony, France.

Received for publication November 17, 2003; revised June 23, 2004; accepted for publication June 28, 2004.

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0091-6749/\$30.00

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doi:10.1016/j.jaci.2004.06.058

Abbreviations used

SIT: Specific immunotherapy
SLIT: Sublingual immunotherapy
UK: United Kingdom

Exclusion criteria were perennial rhinitis, asthma (except for peak seasonal wheezing), other significant medical illness, anticipation of difficulty attending follow-up, treatment with β -blockers or systemic corticosteroids, and pregnancy or planned pregnancy.

In 1998, subjects documented their hay fever symptoms while taking their usual pharmacotherapy. One hundred eighty-six patients with significant symptoms and adequate data sets were then randomized into 3 groups, which were checked for homogeneity regarding demographics, symptom scores, and relevant clinical parameters.

One group received active treatment for 2 years, 1 group received 1 year of active treatment and then placebo, and the third group received placebo in both years. Each year, treatment started in February with increasing daily doses of grass pollen extract (orchard, meadow, rye, sweet vernal, and timothy grasses; Stallergenes, Antony, France) followed by maintenance therapy until July 31. The extract was standardized in IR units: 100 IR/mL was defined as the concentration eliciting a mean skin prick wheal diameter of 7 mm in 30 sensitized subjects. The quantity 100 IR contained 24 μ g Lol p 1 and 14 μ g Dac g 5.

Patients received increasing doses starting with 1 drop of 1 IR/mL and increasing to 20 drops of 100 IR/mL by day 14. Patients then switched to tablets (100 IR), using 1 tablet/d for 1 week, 2 tablets/d for a week, and then 3 tablets/d for 4 weeks. Subsequent maintenance therapy was given as tablets (3 times/wk for 17 weeks). Subjects consistently unable to tolerate 300 IR were maintained with their maximum tolerated dose (4 at 200 IR; 1 at 100 IR). The cumulative annual dose was 26,100 IR (6264 μ g Lol p 1 and 3654 μ g Dac g 5). Placebo tablets and drops were physically identical to active medication.

All patients were carefully instructed in SLIT and reviewed by study nurses every 6 weeks. Compliance was assessed by diary cards and tablet counts. Subjects who returned >12% tablets were excluded. The study was approved by the South West Multicentre Research Ethics Committee.

Outcome measures

Symptom scores during the peak pollen season (defined in advance as June 1 to July 25) were the primary outcome measure. Secondary outcomes were conjunctival provocation thresholds, skin test responses, rescue medication usage, and frequency and severity of side effects.

Symptom scores

Patients completed daily diary cards from April 1 to July 31 each year, covering nasal symptoms (sneezing, blocked nose, running nose), ocular symptoms (itching, streaming, swelling), lung symptoms (cough, breathlessness, tightness) and oropharyngeal itching. Each symptom was graded 0 to 3, where 0 = no symptoms, 1 = symptoms present but mild, 2 = moderate, and 3 = severe. Intergroup comparisons were based on mean weekly scores for each symptom.

Concomitant medication

Subjects were provided with free aqueous beclomethasone and loratadine or cetirizine and were allowed antiallergic drugs as

required. Subjects were recommended not to take more than 1 antihistamine tablet or 200 μ g nasal corticosteroid daily. All drug use was recorded on diary cards.

Allergen-specific antibodies

Serum grass pollen-specific IgE + IgG₄ antibodies were measured each fall. Specific IgE was measured in kU/L. Specific IgG₄ was reported as a binding percentage compared with a reference standard serum.

Conjunctival provocation threshold

Allergen conjunctival challenges were performed each fall. Lyophilized allergen extracts were reconstituted with nonphenolated saline at 100, 33, 11, 3.7, and 1.2 IR/mL. Starting at the lowest concentration, at 10-minute intervals, 1 drop of extract was placed in the lower conjunctival fornix of the right eye, and saline diluent was placed in the left eye. Conjunctival itching and burning, conjunctival hyperemia, weeping, nasal blockage, and posterior rhinorrhea were assessed as 0 = absent, 1 = mild, 2 = moderate, and 3 = severe. When the total symptom score reached 5, the provocation dose was noted and the test discontinued.

Skin tests

Each fall, skin prick tests were performed on the forearm to cat, house dust mite, and grass pollen. Grass pollen was tested in duplicate at 30, 100, and 300 IR/mL, with the other tests single. Skin reactions were recorded after 15 minutes by outlining the wheal and transferring the outline to paper with adhesive tape. The mean of maximum and perpendicular diameters was recorded.

Side effects

Side effects were recorded on diary cards and at each study visit. Systemic reactions were graded according to the European Academy of Allergology and Clinical Immunology immunotherapy position paper: grade 1 = nonspecific, grade 2 = mild systemic reactions, grade 3 = non-life-threatening systemic reactions including urticaria, and grade 4 = anaphylactic shock.⁵

Pollen counts

Daily pollen counts were obtained from pollen monitoring stations in Bournemouth, Portsmouth, and Winchester and were averaged.

Statistical methods

Symptom scores were analyzed over the same 8-week period each year.

For each symptom, independent of treatment, subjects were categorized as having better or worse than average change in symptom score. Odds ratios were calculated comparing the number of subjects with better or worse than average symptoms according to the treatment received. Where symptoms showed significant intergroup differences, a 2-week analysis was performed to assess consistency across the pollen season.

Nasal symptoms were analyzed in greater detail by using a similar methodology. Ignoring treatment groups, subjects were split into quartiles according to their change in total symptom scores. By using Stata (version 7), associations between treatment groups were assessed by Fisher exact test, and side-effect frequencies were assessed by χ^2 analysis.

RESULTS

In the baseline year, most patients were symptomatic for nose running (96%), sneezing (98%), eye itching

TABLE I. Characteristics of patients included in study

Parameter	Active-placebo	Active-active	Placebo-placebo
Sex M:F	22:25	21:23	27:18
Age, median (range)	40 (19-58)	38 (20-58)	39 (18-56)
Baseline symptoms, weekly total, median			
Sneezing	31	53	38
Nose blocking	30	21	37
Nose running	24	44	42
Eye itching	40	51	36
Eye streaming	10	19	10
Eye swelling	2	8	5
Mouth and throat itching	13	18	8

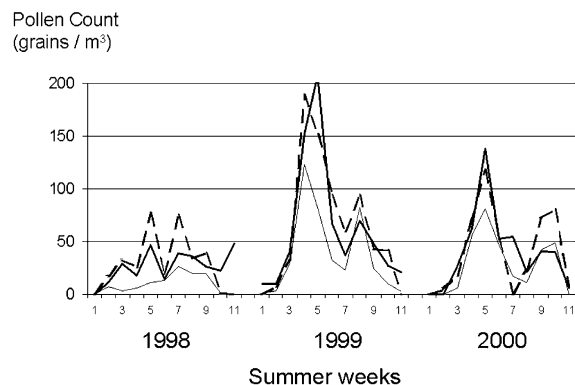


FIG 1. Pollen counts in Bournemouth (—), Portsmouth (—) and Winchester (---) during the baseline year (1998) and treatment years (1999 and 2000).

(98%), and nasal blockage (88%). Other symptoms were less prevalent: eye streaming (79%), eye swelling (68%), mouth and throat itching (79%), breathlessness (48%), coughing (62%), and lung tightness (55%). The groups were well matched for age, sex, and symptom severity (Table I), with the only significant baseline difference lower nose running score in the group that would receive 1 year of active treatment ($P < .05$).

Of 186 patients included in the study, 6 withdrew before the intervention commenced, 29 in the first year and 11 in the second year. Equal numbers withdrew themselves and were withdrawn by the investigators. Side effects caused 11 withdrawals, but most withdrew because of contraindications to therapy (pregnancy, newly prescribed drugs, comorbidity; 11), poor adherence (9), or relocation (7). Of those completing the trial, 49 received SLIT for 1 year, 45 received 2 years of SLIT, and 46 received placebo for 2 years. Four were excluded from analysis because of incomplete data sets. Compliance was excellent as judged by tablet counts and diary cards.

Pollen counts for 1998 were lower than in 1999 and 2000. The peak pollen season was similar in all 3 years (weeks 3-10; Fig 1).

Symptom scores

All groups showed year-on-year improvement in symptom scores (Fig 2; Table II). The active and placebo groups showed similar improvements in all symptoms in

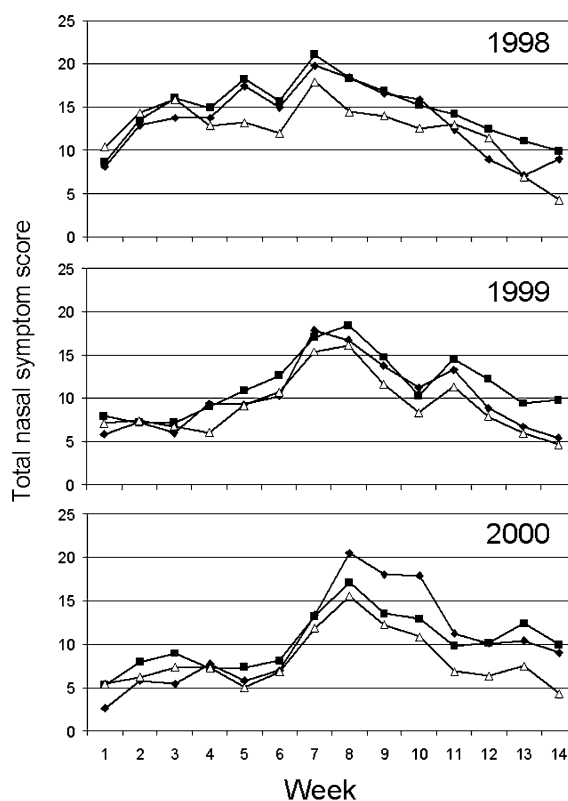


FIG 2. Weekly nasal symptom scores for each group at baseline (1998), after 1 year (1999), and after 2 years treatment (2000) with SLIT versus placebo. Active-active, Δ ; active-placebo, $\blacksquare$; placebo-placebo, $\blacklozenge$.

1999. This absence of effect was confirmed in the 2-weekly nasal symptom subanalysis. However, after 2 years active treatment, subjects were 6.8 times more likely to show reduced nose running ($P < .001$) and 2.4 times more likely to have reduced sneezing ($P < .05$) compared with the placebo group (Fig 3; Table II). Benefits for nasal blockage were identified only at the height of the season. Interestingly, a similar improvement in nasal blockage was seen in 2000 in subjects who had active therapy only in 1999 and subjects who had 2 years of active treatment.

Medication scores

Rescue medication use was reduced in all groups, with greater reductions in active groups than the placebo group

TABLE II. Relative likelihood of above-average improvement in hay fever symptoms after 1 or 2 years of SLIT

		Number*		% Improved	Odds ratio†	P value
		Better than average	Worse			
Sneezing						
1998 to 1999	Plac	21	24	47%	1.0	.36
	Act	50	41	55%	1.4	
1998 to 2000	Plac-Plac	17	28	38%	1.0	
	Act-Plac	25	22	53%	1.9	
	Act-Act	26	18	59%	2.4	
Nose running						
1998 to 1999	Plac	21	24	47%	1.0	.51
	Act	48	43	53%	1.3	
1998 to 2000	Plac-Plac	15	30	33%	1.0	
	Act-Plac	23	24	49%	1.9	
	Act-Act	34	10	77%	6.8	
Nose blocking						
1998 to 1999	Plac	23	22	51%	1.0	.59
	Act	51	40	56%	1.2	
1998 to 2000	Plac-Plac	18	27	40%	1.0	
	Act-Plac	27	20	57%	2.0	
	Act-Act	23	21	52%	1.6	

*Subjects were classified so that approximately half of all participants were categorized as improving better than average, and half as worse than average.

†Odds of better than average improvement on active treatment (compared with being on placebo for 1998-1999 comparison, or on placebo for both years for 1998-2000 comparisons). *Plac*, Placebo; *Act*, active.

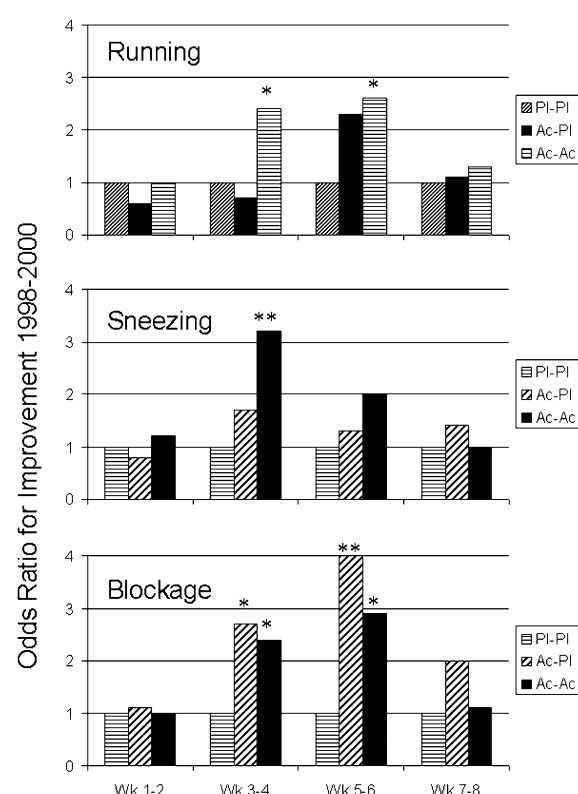


FIG 3. Odds ratio for above-average improvement in nasal symptoms in each group for nasal running, sneezing, and blockage after 1 or 2 years of treatment with SLIT versus placebo.

Tablet equivalents

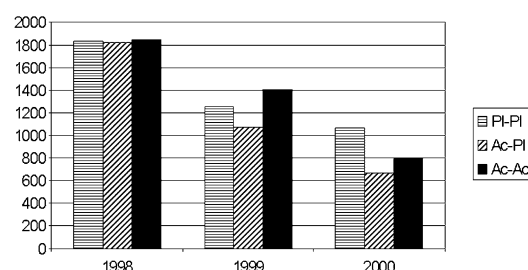


FIG 4. Effect of 1 or 2 years of SLIT on antihistamine usage during the pollen season. Tablet equivalent: 1 for each short-acting antihistamine tablet, 2 for each long-acting antihistamine tablet to a maximum daily score of 4). *PI-PI*, Two years placebo; *Ac-PI*, active treatment for first year, placebo in second; *Ac-Ac*, 2 years active treatment.

(Fig 4). Nasal corticosteroid use was similar in all 3 groups and remained unchanged throughout the study.

Laboratory tests

Allergen-specific IgE increased in actively treated subjects after 1 year of treatment, whereas the placebo-treated group showed no change. After 2 years, mean values dropped below baseline in all 3 groups, with no significant intergroup differences (Table III). Allergen-specific IgG₄ concentrations increased approximately 3-fold in the actively treated groups after 1 year of SLIT. This change was sustained after 2 years of treatment, but decreased toward baseline in the group who received only 1 year of SLIT (Table III).

TABLE III. Allergen-specific IgE and IgG₄ in serum of patients after 1 or 2 years of SLIT with high-dose grass pollen extract*

Specific IgE						
Group	1998		1999		2000	
	GM	SEM	GM	SEM	GM	SEM
Active-placebo	7.4	1.3	8.4	1.4	3.7	2.7
Active-active	7.7	1.3	13.5	1.5	10.7	1.3
Placebo-placebo	9.6	1.3	7.1	1.3	8.5	1.3

Specific IgG ₄						
Group	1998		1999		2000	
	Mean	SEM	Mean	SEM	Mean	SEM
Active-placebo	14.6	3.1	39.9	7.8	24.0	7.5
Active-active	8.3	1.7	28.3	4.9	26.3	5.5
Placebo-placebo	13.4	2.9	19.8	3.5	15.7	4.6

*IgE values are given as geometric means (GMs) because of skewed data. No statistical difference between groups for 1998 and 1999 or 1998 and 2000 for allergen-specific IgG or allergen specific IgG₄ (Kruskal-Wallis test; $P > .05$).

TABLE IV. Skin test responses and conjunctival provocation thresholds to grass pollen extract after 1 or 2 years of SLIT with high-dose grass pollen extract*

Skin test to 300 IR solution of grass pollen extract (mean diameter in mm)							
Group	Strength IR/mL	1998		1999		2000	
		Mean	SEM	Mean	SEM	Mean	SEM
Active-placebo	300	9.7	0.4	9.8	0.5	10.0	0.4
Active-active	300	9.9	0.6	9.6	0.4	9.6	0.5
Placebo-placebo	300	9.6	0.5	10.3	0.5	10.0	0.4

Number of subjects showing changes in conjunctival provocation threshold to grass pollen extract after 1 or 2 years of treatment with sublingual grass pollen immunotherapy							
Group	1998-1999			1998-2000			
	Improved	Same	Worse	Improved	Same	Worse	
Active-placebo	24	21	4	23	18	8	
Active-active	19	23	4	23	17	4	
Placebo-placebo	19	25	4	15	22	5	

*No statistical differences between groups for 1998-1999 or 1998-2000 (Kruskal-Wallis test; $P > .05$).

Conjunctival and skin test responses remained stable throughout the study, with no apparent effect of treatment (Table IV).

Safety assessment

Minor side effects were reported by 85 of 121 (70%) subjects receiving active SLIT and 26 of 59 (44%) placebo-treated subjects in year 1 (Table V). Buccal and nasal side effects were more frequent in SLIT-treated subjects ($P < .05$). In actively treated subjects, 86% of side effects occurred during dose escalation, mostly at 3 tablets/d, and only 14% of events occurred during maintenance. In year 2, fewer side effects occurred: 15 of 103 (15%) placebo-treated subjects and 17 of 48 (35%) actively treated subjects reported 1 or more side effects ($P < .05$), mainly in mouth or nose.

Most side effects were mild and well tolerated. However, in year 1, 7 patients withdrew because of side effects (all receiving active treatment), and 4 were withdrawn for systemic but non-life-threatening reactions. Three had transient breathlessness and throat tightness (grade 2 reactions; all on active therapy). One placebo subject had generalized urticaria (grade 3).

DISCUSSION

Many previous SLIT studies are difficult to interpret because the active and placebo groups were ill matched.¹³ This matters particularly when, as here, the placebo group shows a large improvement. We took particular care to balance the groups by making baseline measurements and

TABLE V. Side effects reported in double-blind, placebo-controlled trial of 1 or 2 years of SLIT for severe summer hay fever

Side effects, year 1	Active (n = 121)		Placebo (n = 59)	
	N	%	N	%
Oral itch/soreness	66	54.5	15	25.4
Lip swelling	12	9.9	2	3.4
Rhinitis	45	37.2	9	15.3
Itching ears	7	5.8	0	0
Conjunctivitis	23	19.0	7	11.9
Mild wheeze	10	8.3	1	1.7
Gastrointestinal upset	2	1.7	0	0
Other (including skin)	13	10.7	6	10.2
Any side effects	85	70.2	26	44.1

Side effects, year 2	Active (n = 48)		Placebo (n = 103)	
	N	%	N	%
Oral itch/soreness	14	29.2	7	6.8
Lip swelling	2	4.2	0	0
Rhinitis	6	12.5	6	5.8
Itching ears	1	2.1	0	0
Conjunctivitis	1	2.1	5	4.9
Mild wheeze	2	4.2	0	0
Gastrointestinal upset	0	0	0	0
Other (including skin)	2	4.2	4	3.9
Any side effects	17	35.4	15	14.6

checking comparability after randomization. The only significant baseline difference was for nose running, which was less in subjects who received 1 year of therapy. This may have contributed to their lesser response for this symptom, although they also responded less for sneezing, for which the groups were well matched.

Before this study, it was suggested that SLIT might be less effective in patients with more severe rhinitis. However, nasal symptoms improved, especially when pollen counts were highest. Pollen counts were higher in 2000 than in the baseline year and represent a good challenge to test responsiveness in this more severe group.

Some dropout is inevitable in any 3-year study. Our retention rate (75%) is good for a community-based study and compares favorably with those of other published 2-year SLIT studies.^{14,15} Side effects were reported by many subjects, even those receiving placebo. In part, this reflects the care we took to capture side effects. To assess the safety of SLIT for use in the community, we asked subjects to record all symptoms, however mild. The lower side-effect rates in 2000 may reflect greater familiarity with the study medication, or greater tolerance of local treatment-associated irritation. Informal discussions with other investigators suggest that some researchers regard local itching as trivial and not worth reporting. Because our patients had more severe rhinitis than in other SLIT studies, the higher side-effect rates may simply reflect their greater sensitivity to allergen.^{9-12,16} Moreover, we used a relatively high dose of allergen (300 times the SIT dose), whereas other studies used 29 to 70 times the SIT

dose.^{9,11} Few subjects had more significant side effects: most side effects were mild and well tolerated, indicating that SLIT is generally benign and safe in community settings.

It has been suggested that SLIT might induce asthma, although most studies report either improvement^{8,15} or unchanged lung function¹⁷; we found no increase in asthmatic symptoms in actively treated subjects.

Previous studies have not addressed long-term benefits of SLIT. This is critical in determining our view of SLIT as annual therapy or long-term immunomodulation, and has economic dimensions for patients and healthcare providers. Conventional SIT is usually given for 3 years, with symptom benefits for at least 4 to 5 years thereafter.¹⁸ One open study has suggested clinical benefit for 5 years after 4 to 5 years of SLIT, but the open study design limits interpretation of the data.¹⁹ Clinical use of SLIT has been favorably reviewed in several official position papers.^{6,8,20} However, none of these reviews addressed lasting benefit. Neither has SLIT been compared with SIT except for simple symptom control.²¹ Our study assessed the value of 1 year of SLIT, which had no effect on sneezing or nose running in the following year, although some benefit was identified for nasal blockage. Similarly, it seems premature to extrapolate from studies showing that SIT can reduce the rate of progression to asthma²² to conclude that SLIT will also do this.

It remains unclear how SLIT works; we are also unclear about the mechanisms of successful SIT injections. Our study was not designed to answer this, but the observed increases in allergen-specific IgE and IgG₄ confirm that SLIT represents a significant immunologic challenge. Induction of IgG₄ by SLIT has been reported in some^{23,24} but not all SLIT studies,^{10,21} perhaps reflecting variation in dose. SIT injections usually induce allergen-specific IgG₄ antibodies: it was once thought that SIT worked by inducing IgG antibodies, which prevented allergen binding to IgE. It now seems more probable that SIT induces IL-10-producing T-regulatory cells, which suppress the T-cell response and promote production of allergen-specific IgG₄ antibodies.²⁵ IgG₄ is thus a marker of T-cell responses rather than the mechanism of benefit. The serologic data from our study suggest that high-dose SLIT also induces this mechanism. How this translates into clinical efficacy, and why some symptoms improve more than others, remain unclear.

In conclusion, 2 years of high-dose grass pollen SLIT confers clinical benefit in patients whose hay fever was resistant to conventional drug treatment. One year of SLIT was ineffective. SLIT was practical and safe for use in community settings. Side effects were common but well tolerated. Further studies on the durability of benefit would help determine the potential of SLIT as a long-term treatment for seasonal allergic rhinoconjunctivitis.

The authors thank Lucy Wright and Fran Webley, who recruited the practices and coordinated the study. Raj Patel, Jonathon Goddard, and William Peace helped with data cleaning. We also acknowledge the support and hard work of the doctors and nurses of the Wessex

Primary Care Research Network: Dr M. Radcliffe, Hythe; Dr N. Waring, Basingstoke; Dr H. Bethell, Alton; Dr A. Fitzgerald-Baron, Winchester; Dr O'Sullivan, Twyford; Dr Taylor, Brook Lane Surgery; Dr R. Lorge, Overton; Dr R. Brown, Wilton; and Dr P. White, Nightingale Surgery, Romsey.

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