

Sublingual immunotherapy: what have we learnt from the 'big trials'?

Stephen R. Durham

Section of Allergy and Clinical Immunology, National Heart and Lung Institute, Imperial College and Royal Brompton Hospital, London, UK

Correspondence to Professor Stephen R. Durham, Hriad, Section of Allergy and Clinical Immunology, National Heart and Lung Institute, Imperial College London, Dovehouse Street, London SW3 6LY, UK. Tel: +44 207 351 8024, e-mail: s.durham@imperial.ac.uk

Current Opinion in Allergy and Clinical Immunology 2008, 8:577-584

Purpose of review

Recent systematic reviews support the use of sublingual immunotherapy for allergic rhinoconjunctivitis in adults, whereas data in children have been less convincing. The present review evaluates three recent 'definitive' trials in adults and one in children.

Recent findings

Two large independent randomized controlled trials of grass allergen tablets have confirmed the efficacy of sublingual immunotherapy in adults with seasonal allergic rhinoconjunctivitis. Effects were both allergen dose-dependent and time-dependent. Tablets were well tolerated and equally effective in immunosensitized compared with polysensitized patients and in patients with peak seasonal asthma (patients with perennial asthma were specifically excluded). Local side effects were common but largely self-limiting and not bothersome. There were no serious treatment-related adverse events. Results were similar in magnitude to those observed in a comparable study of subcutaneous immunotherapy using an alum-based vaccine. A trial of sublingual drops in children with hayfever in a primary care setting was negative, although these results could not be generalized.

Summary

Sublingual immunotherapy represents an effective and well tolerated treatment for seasonal allergic rhinoconjunctivitis in adults. Current ongoing paediatric trials and evaluation of long-term effects in adults will further define its role in therapy.

Keywords

efficacy, rhinoconjunctivitis, safety, sublingual immunotherapy

Curr Opin Allergy Clin Immunol 8:577-584
© 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins
1528-4050

Introduction

International guidelines [1-3] and systematic reviews [4,5] support the use of sublingual immunotherapy as an effective and well tolerated alternative to the subcutaneous route in adults with seasonal and perennial allergic rhinoconjunctivitis, whereas evidence for its potential long-term benefits and its use in children is less convincing. The present review evaluates recent 'definitive' phase III trials of sublingual grass pollen immunotherapy in adults with hayfever and one in children.

Background

Allergen immunotherapy involves the repeated administration of an allergen product to IgE-sensitized allergic individuals in order to induce a state of clinical and immunological tolerance on natural reexposure to the relevant allergen [1]. The subcutaneous route is effective for allergic rhinitis and asthma and is indicated in individuals who fail to respond to avoidance measures and usual antiallergic drugs [6,7]. Subcutaneous immu-

notherapy is also highly effective for life-threatening wasp and bee venom anaphylaxis. An advantage of immunotherapy over drug therapy is its ability to induce tolerance as shown by long-term disease remission for up to 3-5 years after discontinuation of therapy [8]. Immunotherapy has also been shown to prevent the onset of new sensitizations [9] and, in a 10-year randomized controlled trial on children, to prevent the progression from rhinitis to asthma [10]. The benefit-risk ratio is reduced in asthma in view of the increased risk of systemic side effects. Although effective, the discomfort of injections, increased risks and the inconvenience of regular visits to a specialist clinic have tended to restrict the wider use of the subcutaneous route.

Sublingual immunotherapy

Current international guidelines, based on systematic reviews of evidence and meta-analyses, support sublingual immunotherapy as an effective and well tolerated alternative route in adults [4,5]. However, the widely differing indications, age groups, different allergen preparations, dosing schedules and durations of therapy make

generalizations difficult [11,12]. Problems are compounded by the varied size and quality of immunotherapy studies and the many different outcomes used. For example, the meta-analysis by Wilson *et al.* [4] supported moderate efficacy in adults in both seasonal and perennial rhinitis with an acceptable level of heterogeneity, whereas subgroup analyses had insufficient power to comment on the dose dependency or duration dependency or possible benefits in children. A recent update of this analysis reported in abstract form [5] confirmed the same level of efficacy in adults, with the suggestion that a longer duration of therapy (more than 12 months) may be more effective than shorter courses. Nonetheless, it was not possible from the published literature to comment on optimal doses, and evidence for efficacy in children remained unconvincing.

Open questions

There is a need for more definitive evidence based on adequately powered randomized controlled trials that target defined populations using well characterized allergen extracts and with robust outcome measures. A recent publication from the World Allergy Organization highlights these issues and provides guidance on appropriate standardized endpoints [13]. Individuals who respond best are those with both IgE sensitivity and symptoms on exposure to the relevant allergen. Studies that adequately define both the optimal dose (best effect size with acceptable level of side effects) and duration of therapy are needed. More detailed and proactive documentation of side effects is required. Three such 'big trials' of sublingual immunotherapy for seasonal grass pollen-induced rhinoconjunctivitis (comprising more than 100 individuals per treatment arm) have been reported in the past 1–2 years [14,15,17]. The results are evaluated here, together with those of a large trial of subcutaneous immunotherapy [18] using very similar outcome measures and targeting a comparable population of hayfever sufferers (Table 1).

The 'big trials'

Grazax (ALK Abello, Horsholm, Denmark) is a rapidly dissolving single grass allergen (*Phleum pratense*) tablet for sublingual use in adults with grass pollen-induced seasonal allergic rhinoconjunctivitis. Preliminary tolerability studies revealed no serious adverse events in adults with doses up to 1 000 000 standardized quality tablet units (SQ-T) (containing the equivalent of 200 mcg of the major grass allergen, *Pil p5*) [19]. Local side effects were common and comprised short-lived oral itching and swelling that were well tolerated and self-limiting with resolution within a mean of 6.3 days for the 75 000 SQ-T tablet, the top dose selected for evaluation of efficacy.

Table 1 Grass pollen immunotherapy for hayfever: the recent 'big trials'

Reference	Diagnosis	Immunotherapy/ placebo*	Age (mean)	Allergen	Units	Presentation	Preseasonal IT duration/ cumulative dose	Season duration/ cumulative dose	Total cumulative dose	Dropout rate (%)
Sublingual										
Didier <i>et al.</i> [17**]	R, C, A	155/156	29.1	Five-grass mix ^b	300 IR	Tablets	>16 weeks/3.25 mg	30 days/0.75 mg	~4.0 mg	11
Durheim <i>et al.</i> [14]	R, C, A	153/150	37	<i>Phleum pratense</i>	75000 SQ-T	Tablets	8 weeks/0.84 mg	10 weeks/1.05 mg	~1.9 mg	8
Carl <i>et al.</i> [15**]	R, C, A	315/318	34.5	<i>Phleum pratense</i>	75000 SQ-T	Tablets	>16 weeks/1.6 mg	8–10 weeks/0.8 mg	~2.5 mg	14
Subcutaneous										
Frew <i>et al.</i> [16]	R, C, A	203/103	38.3	<i>Phleum pratense</i>	100000 SQ	s.c. injections	>16 weeks/~110 µg	10 weeks/40 µg	~150 µg	15

R, seasonal rhinitis; C, seasonal conjunctivitis; s.c., subcutaneous.

*Intention to treat.

^bFive-grass mix included orchard, meadow, ryegrass, sweet vernal and timothy.

Table 2 Grass pollen immunotherapy for hayfever: seasonal symptoms

Reference	Symptom score (immunotherapy)	Symptom score (placebo)	Reduction in symptoms compared with placebo (%)	Difference mean (95% CI)	<i>P</i>
Sublingual					
Didier <i>et al.</i> [17**]	3.58 ± 3.0	4.93 ± 3.2	-27	-1.39 (-2.09 to -0.69)	0.0001
Durham <i>et al.</i> [14]	2.47 ± 2.0	2.93 ± 2.0	-16	0.46 (-0.96 to 0.04)	0.07
Dahl <i>et al.</i> [15**,16**]	2.4 ± 1.6	3.4 ± 2.2	-30	-0.52 (-0.69 to -0.35)	<0.0001
Subcutaneous					
Frew <i>et al.</i> [18]	3.13 ± 3.4	4.39 ± 3.0	-29	-1.26 (-1.89 to -0.62)	0.001

Values are mean ± SD. CI, confidence interval.

An initial dose-ranging study compared daily 2500 SQ-T, 25 000 SQ-T and 75 000 SQ-T tablets that contained 0.5, 5.0 and 15 µg *Phl p5*, respectively. Tablets were taken for a mean of 8 weeks prior to the onset of the pollen season and continued throughout the season [14]. Treatment with 75 000 SQ-T resulted in a reduction in seasonal symptoms (16% compared with placebo, $P=0.07$) and in the use of antiallergic drugs (29%, $P=0.047$). Although the overall effect on symptoms was modest, the study established a clear dose-response relationship and the need for high doses of sublingual allergen for efficacy. Patients who received therapy for at least 8 weeks before the start of the pollen season appeared to do better than those receiving for less than 8 weeks, and a recent review [20] indicated that a minimum of 4 months of preseasonal therapy might be optimal for efficacy.

On the basis of these data, a second randomized controlled trial was performed using the optimized daily dose (75 000 SQ-T) for a minimum of 4 months prior to and during the grass pollen season. Six hundred and thirty-four adults with moderate-severe hayfever of at least 2-year duration were included [15**,16**]. This more prolonged preseasonal treatment was associated with a greater reduction in mean rhinoconjunctivitis symptoms (30%, $P<0.0001$) (Table 2) and seasonal use of antiallergic drug (38%, $P<0.00001$) (Table 3). The tablets were effective against all individual nasal symptoms, compared with placebo treatment (including nasal obstruction and eye symptoms [21]), and improved rhinitis-specific quality of life scores (26%, $P<0.0001$) [22]. A global evaluation by patients revealed that 82% improved on active therapy compared with 55% on

placebo, an overall response rate of 49% ($P<0.001$). The observed high placebo response could be explained in part by the provision of usual antiallergic drugs (antihistamine and intranasal corticosteroid) for all patients.

A second grass allergen tablet for sublingual use is a five-grass mix of orchard, meadow, ryegrass, sweet vernal and timothy species (Olaair Grasses, Stallergenes SA, Antony, France) [17**]. Preliminary studies on 30 patients demonstrated the safety of once daily 300-index of reactivity (IR) and 500-IR tablets with self-limiting side effects confined mainly to the site of administration and resolving within days [23]. A randomized controlled trial was performed on 640 adults with moderate-severe grass allergen-related rhinitis of at least 2-year duration. Daily dosing with 300-IR, 300-IR and 500-IR grass tablets containing 8.3, 25 and 41 mcg, respectively, of group five major grass allergens or matched placebo tablets were given for 4 months prior to and throughout the grass pollen season. The 300-IR and 500-IR doses were associated with comparable clinical efficacy, whereas patients on the 300-IR dose reported fewer side effects. The 300-IR dose significantly reduced mean symptoms (27%, $P=0.0001$) compared with placebo treatment (Table 2). Medication scores were not given, although medication use expressed as median 'percent days with rescue medication' was reduced in the 300-IR group (46%, $P<0.02$) (Table 3). There was also an improvement in quality of life score ($P<0.0001$ peak and $P<0.003$ end season), although the magnitude of the effect was not reported in the paper.

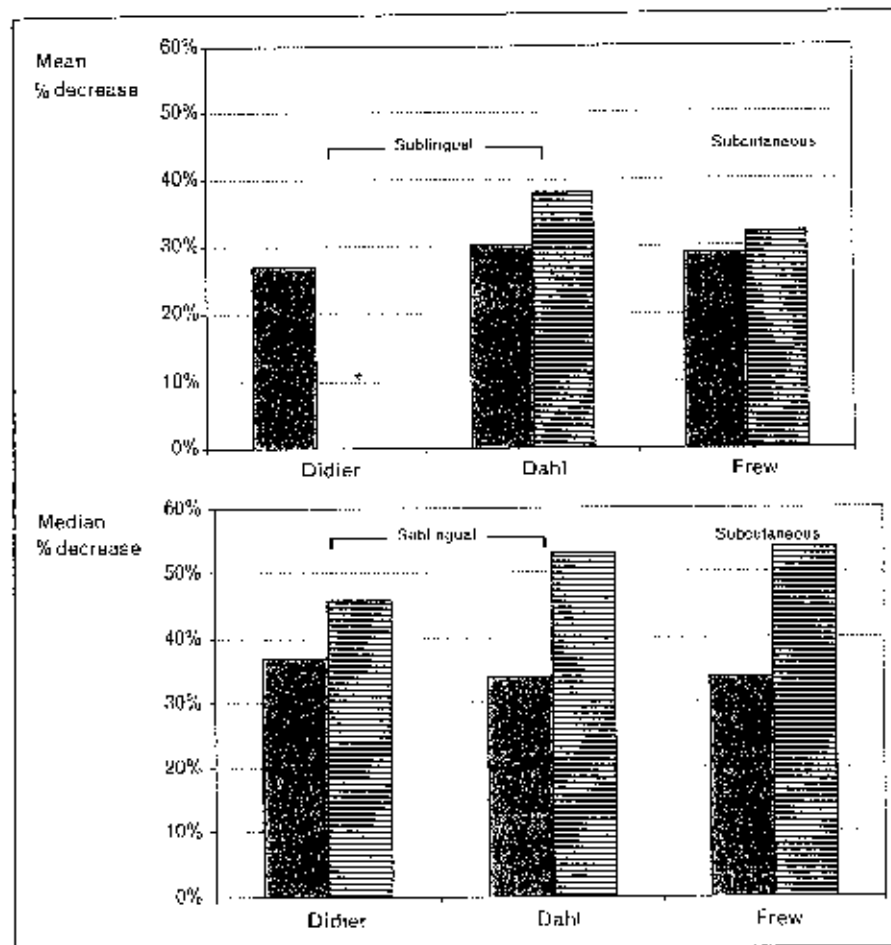
A recent randomized controlled trial of subcutaneous grass pollen immunotherapy using an alum-based vaccine

Table 3 Grass pollen immunotherapy for hayfever: seasonal medication use

Reference	Medication use (immunotherapy)	Medication use (placebo)	Reduction in medication use compared with placebo (%)	Difference mean (95% CI)	<i>P</i>
Sublingual					
Didier <i>et al.</i> [17**]	10.62 (median)	19.72 (median)	-46	ND	0.019
Durham <i>et al.</i> [14]	1.46 ± 2.4	2.05 ± 2.4	-28	-0.58 (-1.16 to -0.008)	0.047
Dahl <i>et al.</i> [15**,16**]	1.5 ± 1.9	2.4 ± 2.5	-38	0.40 (-0.57 to 0.24)	<0.0001
Subcutaneous					
Frew <i>et al.</i> [16]	2.85 ± 4.2	4.21 ± 3.7	-32	-1.36 (-2.14 to -0.58)	0.0007

Values are mean ± SD. CI, confidence intervals. ND, not done.

Figure 1 Reductions in seasonal symptoms and use of anti-allergic medication in two independent trials of sublingual immunotherapy using grass pollen tablets



Results are compared with those using an alum-based vaccine in a comparable target population in the study by Frew *et al.* [18]. In the top panel, results are expressed as percentage reduction in mean values compared with placebo and in the bottom panel as percentage reduction in median values [15**, 17**]. *The study by Didier *et al.* [17**] did not include mean values for medication use, [▨] symptoms; [▨] anti-allergic drugs.

(Alutard SQ *Phleum pratense*, ALK Abello, Hørsholm, Denmark) is included for comparison (Table 1). The study comprised 410 adults with moderate-severe hayfever selected according to very similar criteria [18,24]. Following a rapid-cluster build-up phase of 8 weeks, participants received 100 000 SQ U, or 10 000 SQ-U containing 20 meg and 2 meg or matched placebo injections 6 weekly for 4–6 months prior to and during the grass pollen season. The study confirmed dose-dependent efficacy with a reduction in mean symptoms (29%, $P < 0.001$) and anti-allergic drugs (32%, $P < 0.0007$) and in mean rhinitis quality of life scores (40%, $P < 0.0001$).

What have we learnt?

Data from the four trials are presented in Table 1, and summary data for the three trials that included greater or

equal to 4-month preseasonal treatment is summarized as mean and median values in Fig. 1.

Efficacy

There is a remarkable consistency in results between the two independent trials of sublingual immunotherapy by Didier *et al.* [17**] and Dahl *et al.* [15**, 16**] that involved 4-month preseasonal therapy, with an approximate 30% mean (35% median) reduction in symptom scores and a 35% mean (50% median) decrease in the use of anti-allergic drugs. Neither the presence of polysensitization nor seasonal asthma was observed to reduce the efficacy of immunotherapy (data not shown). Reductions in symptoms and rescue medication (Fig. 1) for sublingual immunotherapy were virtually identical to those observed for subcutaneous immunotherapy in a comparable group of patients, whereas the percentage improvement in overall

Table 4 Grass pollen immunotherapy for hayfever adverse events

Reference	Intervention	Patients, N	Mild, n (%)	Moderate, n (%)	Severe, n (%)	AE withdrawn, n (%)	
Sublingual	Didier <i>et al.</i> ^a [17**]	Active	74 (49)	52 (34)	8 (5)	8 (5)	
		Placebo	156	55 (35)	40 (26)	3 (2)	0
	Durham <i>et al.</i> ^a [14]	Active	153	123 (80)	81 (53)	13 (9)	7 (5)
		Placebo	150	98 (65)	58 (39)	13 (9)	2 (1)
Dahl <i>et al.</i> ^a [15**,16**]	Active	316	243 (77)	118 (37)	18 (5)	18 (5)	
	Placebo	318	177 (56)	75 (24)	21 (7)	8 (3)	
Subcutaneous	Frew <i>et al.</i> ^b [18]	Active	203	57 ^c (28)	9 (4)	0	16 (8)
		Placebo	103	17 ^c (17)	0	0	1 (1)

Adverse events patient numbers (%). AE, adverse event.

^aAE coded using MedDRA 7.1 or a severity score.

^bFAACI adverse events classification (grade 0 is lack of AEs; grade 1, nonspecific mild symptoms; grade 2, mild systemic reactions; grade 3, nonlife threatening systemic reactions; and grade 4, anaphylactic shock).

^cIncludes nonspecific symptoms (active $n = 22$, placebo $n = 9$). Adapted from [26].

rhinitis-specific quality-of-life scores was numerically higher for subcutaneous immunotherapy (40 vs. 26%).

Effect sizes reported here for sublingual immunotherapy compare favourably with those reported in a recent Cochrane review and meta-analysis of antiallergic drugs that included antileukotrienes, antihistamines and intranasal corticosteroids [25], although only direct comparisons would confirm or refute this.

Safety

An overall high prevalence of treatment-unrelated mild–moderate adverse events is to be expected in such prolonged trials (Table 4). Data confirm an excess of mild–moderate events for actively treated patients in all three sublingual trials, largely accounted by local itching and swelling in the mouth (Table 4). Severe adverse events were rare and unrelated to the sublingual treatment. The withdrawal rate for adverse events was acceptable at 5% in all three sublingual trials. Data for side effects for the subcutaneous immunotherapy trial is reported according to the criteria of the European Academy of Allergy and Clinical Immunology [26] and is not strictly comparable. Nonetheless, there was an excess of mild and moderate side effects of subcutaneous treatment as compared with placebo, and the 8% drop out for subcutaneous treatment was numerically higher than that observed for sublingual treatment (5%). No anaphylactic (grade 4) reactions or use of adrenaline was observed in any of these trials.

Limitations

There are also limitations to the interpretation of the results. The reported weekly average symptom scores for the entire season for placebo-treated groups were low for all four studies (with total symptom scores varying between three to five out of a possible 18 points), which might indicate that the overall level of disease severity was milder than anticipated. However, modest average

weekly symptom scores are commonly observed in trials of immunotherapy because, unlike trials of pharmacotherapy, immunotherapy is given prophylactically and scores reflect average values obtained in the face of low pollen counts at the beginning and the end of the season and fluctuations in counts throughout the season, as well as variability in pollen counts from year to year. It is also likely that the overall low symptom scores may have been due, in part, to free access to 'best available' antiallergic medication (antihistamines and topical intranasal corticosteroids).

The marked placebo response with up to half of placebo-treated patients reporting clinical benefit is also common in immunotherapy trials. This is likely because of a combination of factors that include 'clinical trial effect' secondary to more intensive medical care in a therapeutic environment, 'regression to the mean' in the face of random disease variability, patients tend to enter clinical trials when they are 'sick' such that there is a tendency to improve spontaneously with time. Increased compliance in a trial setting and the availability of 'standard of care' rescue medication would also favour the placebo group. It is not clear whether compliance with sublingual immunotherapy will be as good in routine practice, although it is encouraging that drop-out rates of less than 15% were consistently observed in these prolonged trials.

Long-term tolerance

An important question is whether sublingual immunotherapy may induce long-term tolerance as observed for the subcutaneous route. Preliminary data [27–29] suggest that this may be the case, although more evidence is required. The report by Dahl *et al.* [15**,16**] is an interim analysis of the results for the first year of a randomized controlled 5-year study (2004–2009), which includes a 3 year treatment and a 2-year withdrawal phase. The report of the second year of the trial [16**]

demonstrated sustained clinical benefit during the second year, with a 36% mean (median 42%) reduction in symptoms and a 46% (median 74%) decrease in medication use and progressive increases in IgG4 antibodies and serum IgG-associated inhibitory activities.

Sublingual immunotherapy in children

In contrast to the data available on adults, evidence favouring the use of sublingual immunotherapy in children is inconclusive [30]. Two recent systematic reviews and meta-analyses evaluated the evidence for sublingual immunotherapy in allergic rhinitis and asthma in children [31,32]. Although the overall effect was positive, the limited number and small size of randomized controlled trials and the observed very marked heterogeneity (85–95%) imply that it is not possible to make definitive recommendations for the routine use of sublingual immunotherapy in children.

A large randomized controlled trial of a five-grass mix in 6–18-year olds (median age 13 years) with seasonal rhinitis was performed in a primary care setting in the Netherlands [33]. The sublingual vaccine was administered as drops during a 20-day uposing phase followed by twice-weekly drops (containing 21 mcg Lol p5) for 2 years (cumulative dose, 4.5 mg). The major inclusion criterion was a score of more than five on a retrospective five symptom score based on symptoms experienced during the previous pollen season, the maximum score possible being 15. The 208 patients were matched at entry for moderately severe retrospective recall of symptoms (mean 8.7 and 9.0 for active-treated and placebo-treated groups, respectively). Mean daily scores observed after 2 years of active and placebo treatment during a substantial pollen season were 3.1 and 3.4, respectively (not significantly different). It is of interest that seasonal scores in placebo-treated patients were comparable to those recorded in adult trials (above), indicating that low average symptom scores are 'generic' to immunotherapy trials even in patients with a history of severe disease.

Although the clinical trial was well performed, there are major limitations to the interpretation and generalization of these results. Firstly, the trial involved a novel vaccine using an untested twice-weekly regimen. Although the cumulative dosage over 2 years was substantial, the allergen content of the weekly maintenance dose was 3–4 fold less than in adult trials [15**,17**] and at a level that was similarly ineffective in adults. Secondly, patients were recruited in primary care, whereas in line with current international guidelines [3], in the adult studies reported above, patients were recruited and selected by specialists. The observed 25% drop-out rate is a further limitation to the interpretation of results. Confidence in

the authors' generalization that 'sublingual immunotherapy is not effective in symptomatic youngsters in primary care' [33] would require the use of a well validated vaccine in adequate dosage and of proven efficacy in a specialist setting in adults and children before considering embarking on a more speculative trial using the same vaccine and dose in children in a primary care setting. Large definitive trials in children recruited in a specialist setting and using well validated extracts are currently in progress.

Other developments in sublingual immunotherapy

Recent developments beyond the scope of the present review include the publication of phase II trials of sublingual immunotherapy for potential novel indications: Japanese cedar [34], cat [35] and latex allergy [36] and evaluation of a house dust mite extract in mite-allergic adults [37] and children [38] with atopic dermatitis. A successful trial of sublingual bee venom extract in the treatment of IgE-associated large local reactions provided 'proof of principle' for a possible therapeutic application in venom sting anaphylaxis, [39**].

Following the widespread use of sublingual immunotherapy in Europe, there have been two reports of nonfatal anaphylaxis. One occurred in an 11-year-old girl during the use of a high-dose mix of multiple pollens during the peak pollen season [40]. The second involved a 16-year-old girl with intermittent asthma who was on house dust mite maintenance sublingual therapy. The reaction occurred after an inexplicable 3-week gap in therapy followed by self-administration of a dose six fold her previous well tolerated maintenance dose [41]. These isolated episodes occurred during 'off-label' use in children and in association with risk factors that could have been avoided. The reports highlight the need for specialist prescribing in appropriate cases and for continual surveillance of the treatment.

Current concepts on the mode of action of sublingual immunotherapy are covered in two recent reviews [42,43]. There is evidence that increased IL-10 production [44,45*] and elevations in 'protective' IgG4 antibodies [14,15**] may be involved as for the subcutaneous route, although local factors involving dendritic cell–T cell interactions in the sublingual mucosa and regional lymph nodes are likely to be equally important [46*,47].

Conclusion

Sublingual immunotherapy is effective and well tolerated for seasonal allergic rhinoconjunctivitis in adults. Current ongoing paediatric trials and evaluation of long-term effects in adults will further define its role in therapy.

Direct comparisons with the subcutaneous route would also be of value.

Acknowledgement

The author is grateful for the assistance of Dr Martin Penagos with the tables and figures and Dr Moises Calderon and Dr Penagos for their helpful comments.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 595–596)

- 1 Bousquet J, Lockey R, Malling HJ, et al. Allergen immunotherapy: therapeutic vaccines for allergic diseases. WHO position paper. *Allergy* 1998; 53 (Suppl 44):1–42.
- 2 Passalacqua G, Durham SR. Allergic rhinitis and its impact on asthma: immunotherapy update. *J Allergy Clin Immunol* 2007; 119:881–891.
- 3 Alvarez-Cuesta E, Bousquet J, Canonica GW, et al. EAACI Immunotherapy Task Force. Standards for practical allergen specific immunotherapy. *Allergy* 2006; 61 (Suppl 82):1–20.
- 4 Wilson DR, Lima MT, Durham SR. Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. *Allergy* 2005; 60:4–12.
- 5 Radulovic S, Calderon M, Wilson S, Durham SR. Sublingual immunotherapy for allergic rhinitis: an updated Cochrane systematic review and meta-analysis. *Allergy* 2007; 62 (883):187–551.
- 6 Calderon MA, Alves B, Jacobson M, et al. Allergen injection immunotherapy for seasonal allergic rhinitis. *Cochrane Database Syst Rev* 2007; CD004996.
- 7 Abramson MJ, Puy RM, Weiner JM. Allergen immunotherapy for asthma. *Cochrane Database Syst Rev* 2003; CD000126.
- 8 Durham SR, Walker SM, Varga EM, et al. Long term clinical efficacy of grass pollen immunotherapy. *N Engl J Med* 1999; 341:460–475.
- 9 Pajno GB, Barberio G, De Luca FR, et al. Prevention of new sensitisations in asthmatic children mono-sensitized to house dust mites by specific immunotherapy. A six-year follow-up study. *Clin Exp Allergy* 2001; 31:1382–1397.
- 10 Jacobsen L, Niggeman B, Dreborg S, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy* 2007; 62:943–948.
- 11 Cox LS, Larenas Linneman D, Kohe H, et al. Sublingual immunotherapy: a comprehensive review. *J Allergy Clin Immunol* 2005; 117:10021–10036.
- 12 Calamita Z, Sacconato H, Pitha AB, Alallah AN. Efficacy of sublingual immunotherapy in asthma: systematic review of randomized clinical trials using the Cochrane Collaboration method. *Allergy* 2006; 61:1162–1172.
- 13 Canonica GW, Beeghs Cagnani CE, Bousquet J, et al. Recommendations for standardization of clinical trials with allergen specific immunotherapy for respiratory allergy. A statement of a World Allergy Organization (WAO) taskforce. *Allergy* 2007; 62:17–24.
- 14 Durham SR, Yang WJ, Anderson MR, et al. Sublingual immunotherapy with once-daily grass allergen tablets: a randomized controlled trial in seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006; 117:802–809.
- 15 Dahl R, Kapp A, Colombo G, et al. Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006; 118:434–440.
- A large randomized controlled trial of grass allergen tablets for comparison with Diner et al. [17]. Results are very similar.
- 16 Dahl R, Kapp A, Colombo G, et al. Sublingual grass allergen tablet immunotherapy provides sustained clinical benefit with progressive immunologic changes over 2 years. *J Allergy Clin Immunol* 2006; 117:519–526.
- A large randomized controlled trial of grass allergen tablets for comparison with Diner et al. [17].
- 17 Didier A, Malling HJ, Worm M, et al. Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis. *J Allergy Clin Immunol* 2007; 120:1238–1245.
- Reports results of a large randomized controlled trial of grass allergen tablets for comparison with Dahl et al. [15,16]. Results are very similar.
- 18 Frew AJ, Powell RJ, Corrigan CJ, Durham SR, UK Immunotherapy Study group. Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006; 117:318–325.
- 19 Klimek-Tebbe J, Rihl M, Harold DA. Safety of a SQ-standardised grass allergen tablet for sublingual immunotherapy: a randomized, placebo-controlled trial. *Allergy* 2006; 61:181–184.
- 20 Cuddeback MA, Birk AO, Anderson JS, Durham SR. Prolonged pre-seasonal treatment phase with Grazax sublingual immunotherapy increases clinical efficacy. *Allergy* 2007; 62:958–961.
- 21 Durham SR, Riis D. Grass allergen tablet immunotherapy relieves individual seasonal eye and nasal symptoms, including nasal blockage. *Allergy* 2007; 62:954–957.
- 22 Rex S, Yang WJ, Anderson MR, Durham SR. Once-daily sublingual allergen-specific immunotherapy improves quality of life in patients with grass pollen induced allergic rhinoconjunctivitis: a double-blind, randomised study. *Qual Life Res* 2007; 16:191–201.
- 23 Laiser T, Poulsen L, Misic M, et al. Safety and tolerability of grass tablets in sublingual immunotherapy (SIT): a phase I study. *Allergy* 2006; 61:1173–1176.
- 24 Powell RJ, Frew AJ, Corrigan CJ, Durham SR. Effect of grass pollen immunotherapy with Alutard SQ on quality of life in seasonal allergic rhinoconjunctivitis. *Allergy* 2007; 62:1335–1338.
- 25 Wilson A, O'Byrne P, Parameswaran K. Leukotriene receptor antagonists for allergic rhinitis: a systematic review and meta-analysis. *Am J Med* 2004; 116:338–344.
- 26 Malling H, Weeks B. Immunotherapy: position paper of the European Academy of Allergy and Clinical Immunology. *Allergy* 1997; 48:S8–S35.
- 27 D. Kienzo V, Marotta F, Piccinelli F, et al. Longlasting effect of sublingual immunotherapy in children with asthma due to house dust mite allergy: a 10-year prospective study. *Clin Exp Allergy* 2003; 33:206–210.
- 28 Novembre F, Galli E, Landi F, et al. Cross-seasonal sublingual immunotherapy reduces the development of asthma in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2004; 114:R51–R57.
- 29 Merogian M, Tomassetti D, Uornasconi A, et al. Preventive effects of sublingual immunotherapy in childhood: an open randomised controlled study. *Ann Allergy Asthma Immunol* 2008; 101:200–211.
- 30 Röder E, Berger MY, de Groot H, van Wijck RG. Immunotherapy in children and adolescents with allergic rhinoconjunctivitis: systematic review. *Pediatr Allergy Immunol* 2008; 19:197–207.
- 31 Penagos M, Compalati E, Tarantini F, et al. Efficacy of sublingual immunotherapy in the treatment of allergic rhinitis in pediatric patients 3 to 18 years of age: a meta-analysis of randomized, placebo-controlled, double-blind trials. *Ann Allergy Asthma Immunol* 2006; 97:141–148.
- 32 Penagos M, Passalacqua G, Compalati E, et al. Meta-analysis of the efficacy of sublingual immunotherapy in the treatment of allergic asthma in pediatric patients, 3 to 18 years of age. *Chest* 2008; 133:595–609.
- 33 Röder E, Berger MY, Hup WC, et al. Sublingual immunotherapy with grass pollen is not effective in symptomatically youngsters in primary care. *J Allergy Clin Immunol* 2007; 119:892–898.
- 34 Horiguchi S, Okamoto Y, Yoshida S, et al. A randomized controlled trial of sublingual immunotherapy in Japanese cedar pollinosis. *Int Arch Allergy Immunol* 2007; 148:75–84.
- 35 Alvarez-Cuesta E, Borges-Gimeno P, González-Mancebo E, et al. Sublingual immunotherapy with a standardized cat dander extract: evaluation of efficacy in a double-blind placebo-controlled study. *Allergy* 2007; 62:810–817.
- 36 Nohs T, Onizumi MC, Succo AL, et al. Double-blind, placebo-controlled study of sublingual immunotherapy in patients with latex-induced urticaria: a 12-month study. *Br J Dermatol* 2007; 56:674–681.
- 37 Werfel T, Breuer K, Rueff F, et al. Usefulness of specific immunotherapy in patients with atopic dermatitis and allergic sensitization to house dust mites: a multicentre, randomised dose response study. *Allergy* 2006; 61:202–205.
- 38 Pajno GB, Caminiti L, Vita D, et al. Sublingual immunotherapy in mite sensitized children with atopic dermatitis: a randomized double-blind placebo controlled study. *J Allergy Clin Immunol* 2007; 120:164–170.
- 39 Severino MG, Cortellini G, Bonadonna P, et al. Sublingual immunotherapy for large oral reactions caused by honey bee sting: a double-blind placebo-controlled trial. *J Allergy Clin Immunol* 2008; 122:44–48.
- Sublingual immunotherapy with bee venom extract reduced IgE associated large local reactions. It provides further of principle for studies of the sublingual route for venom sting anaphylaxis.

- 40 Eifan AO, Keles S, Bahoncilir NN, Barlas IB. Anaphylaxis to multiple pollen allergen sublingual immunotherapy. *Allergy* 2007; 62:567-568.
- 41 Blazewski L. Anaphylactic shock because of sublingual immunotherapy overdose during third year of maintenance dose. *Allergy* 2008; 63:374.
- 42 Moringeot M, Bizard T, Fadel R *et al*. Immune mechanisms of allergen specific sublingual immunotherapy. *Allergy* 2006; 61:51-65.
- 43 Novak N, Haberstick J, Bieber T, Atan JP. The immune privilege of the oral mucosa. *Trends Mol Med* 2008; 14:191-198.
- 44 Savolainen J, Nieminen K, Laaksonen K *et al*. Allergen-induced *in vitro* expression of IL-18, SLAMF7 and GATA-3 mRNA in PBMC during sublingual immunotherapy. *Allergy* 2007; 62:949-953.
- 45 Bohle B, Kinoshita T, Gerstmayr M *et al*. Sublingual immunotherapy induces IL-10-producing T regulatory cells, allergen-specific Tbet^{hi} tolerance, and immune deviation. *J Allergy Clin Immunol* 2007; 120:707-713.
- This study supports the role of regulatory T cells in the mechanism of sublingual immunotherapy, as previously observed for subcutaneous route.
- 46 Allam JP, Peng WM, Appel T *et al*. Toll-like receptor 4 ligation enhances tolerogenic properties of oral mucosal Langerhans cells. *J Allergy Clin Immunol* 2008; 121:968-974.
- Novel functional study of Langerhans cells purified from human oral mucosa. The study emphasizes the importance of local immune regulation, which may be relevant to the mechanism of sublingual immunotherapy.
- 47 Mascarello I, Lombardi V, Louise A *et al*. Oral dendritic cells mediate antigen-specific tolerance by stimulating TH1 and regulatory CD4⁺ T cells. *J Allergy Clin Immunol* 2008; 122:608-609.