

SQ-standardised Grass Tablet Sublingual Immunotherapy: Persistent Clinical Benefit and Progressive Immunological Changes During Three Years Treatment

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Background

Allergen immunotherapy involves the repeated administration of allergenic proteins in order to induce a state of clinical and immunologic tolerance [1]. The first published trial was that of Noon who in 1911 was able to demonstrate a reduction in immediate ocular symptoms following subcutaneous injection of grass pollen extracts [2]. The first randomised controlled trial was reported in 1958 and showed a decrease in seasonal symptoms in grass pollen sensitive patients [3]. Studies in the 1960's from Lowell and colleagues confirmed the efficacy of the subcutaneous approach in patients sensitive to ragweed pollen [4]. Since the 1980's, the availability of allergen extracts that are standardised in terms of their biologic potency (generally judged by skin testing and/or biochemical characterisation in terms of content of major allergenic proteins) has resulted in numerous randomised controlled trials that have confirmed the value of this approach in IgE-sensitised subjects with severe disease unresponsive to usual pharmacotherapy [1].

Recent studies using recombinant protein allergens have reproduced these findings in birch- and grass-sensitive subjects [5,6]. The subcutaneous approach is limited by the occasional incidence of systemic side effects that restrict its use to trained individuals in specialist centres with access to resuscitative measures and the requirement to attend generally weekly for 8–16 weeks followed by monthly visits for supervised injections with an observation period of 30–60 minutes [7].

Sublingual immunotherapy

In the past 20 years sublingual allergen immunotherapy has emerged as a viable and well-tolerated alternative compared to the subcutaneous route [8,9]. Whereas local itching and swelling under the tongue occur commonly during early daily administration, these symptoms are in general not bothersome and resolve within

2–14 days in the majority of subjects and are regarded as comparable to the large local skin responses that occur following subcutaneous treatment, only rarely requiring treatment or dose adjustment and only occasionally resulting in treatment withdrawal (in approximately 5% of subjects treated).

Systematic reviews and meta-analyses [9,10] have supported the use of sublingual immunotherapy as an effective and well-tolerated alternative whereas the widely differing indications, age groups, different allergen preparations, dosing schedules and durations of therapy make generalisations difficult. Wilson *et al.* [9] supported moderate efficacy in adults in both seasonal and perennial rhinitis 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 [10] 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. Whereas the overall effect size documented for the sublingual route was lower than the subcutaneous route, the level of heterogeneity in these studies in terms of patient selection, age group, dose and formulation of allergen and varied outcome measures make formal comparisons unreliable and emphasised the need for large ‘definitive’ adequately powered trials in targeted groups with both clear-cut symptoms on exposure and confirmation of IgE sensitivity to the relevant allergens.

The ‘Big trials’

There are now two such trials in adults published. One employed a rapidly dissolving grass allergen tablet (Grazax, ALK Abello, Hørsholm, Denmark) that included a single species – *Phleum pratense*. 634 adults with moderate-severe hay fever of at least 2-year duration received four months preseasonal followed by continued treatment throughout the season, with daily tablets containing 15 µg *Phl p 5* major allergen [11]. Treatment was associated with a 30% reduction in mean rhinoconjunctivitis symptoms ($p < 0.0001$) and a 38% decrease in seasonal use of anti-allergic drug ($p < 0.00001$). The tablets were effective against all individual nasal symptoms [12], and improved rhinitis-specific quality of life scores (26%, $p < 0.0001$) [13]. 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 treatment was well-tolerated. Local side effects after taking the tablets, such as itching and swelling in the mouth, were common (affecting 65% of patients compared to 35% of placebo-treated patients) although not bothersome, resolving within a median of 6 days and rarely requiring discontinuation (in less than 5% of cases).

Similarly, the efficacy and safety of a five-grass allergen mix tablet for sublingual use (Oralair Grasses, Stallergènes SA, Antony, France) including orchard, meadow, ryegrass, sweet vernal and timothy species has recently been evaluated [14]. Daily dosing in a total population of 640 patients with tablets containing 8.3, 25 and 41 µg, respectively, of group-5 major grass allergens or matched placebo tablets were given for 4 months prior to and throughout the grass pollen season. The 25 µg dose

was found to have the most favourable benefit/local side-effect profile and significantly reduced mean symptoms by 27% ($p=0.0001$) compared with placebo treatment. Medication use expressed as median ‘percent days with rescue medication’ was reduced 46% ($p<0.02$). There was also an improvement in quality of life score ($p<0.0001$ peak and $p<0.003$ end season).

These results from two independent trials of SLIT using a 4-month preseasonal treatment by Didier *et al.* and Dahl *et al.* were highly consistent. Median effect sizes were comparable to those reported following a large controlled trial of subcutaneous grass allergen immunotherapy that employed an alum-based vaccine in a comparable group of 410 adults with severe hay fever [15]. A cluster regimen was followed by monthly injections for a total of 4 months preseasonally and throughout the pollen season. Median results for the 3 trials are represented in Fig. 1.

Three years perennial treatment with ‘Grazax’ for severe hay fever

Subcutaneous allergen immunotherapy, in contrast to treatment with anti-allergic drugs, induces long term antigen-specific tolerance for years following discontinuation [16]. This is evident as long term remission for at least three years [17], reduction of the onset of new allergen sensitisations [18] and a reduced progression of disease from rhinitis to asthma in children [19]. Although preliminary data for sublingual immunotherapy is encouraging, this requires confirmation in long term studies in large numbers of patients. The study reported by Dahl *et al.* [11,20] was planned along these lines. Thus of 640 patients randomised in year one to Grazax or placebo, 340 patients agreed to continue to take once daily tablets containing 15 µg major grass allergen *Phleum pratense* continuously for three years followed by a planned period of two years withdrawal from immunotherapy with continued double blinding for the original 3-year treatments.

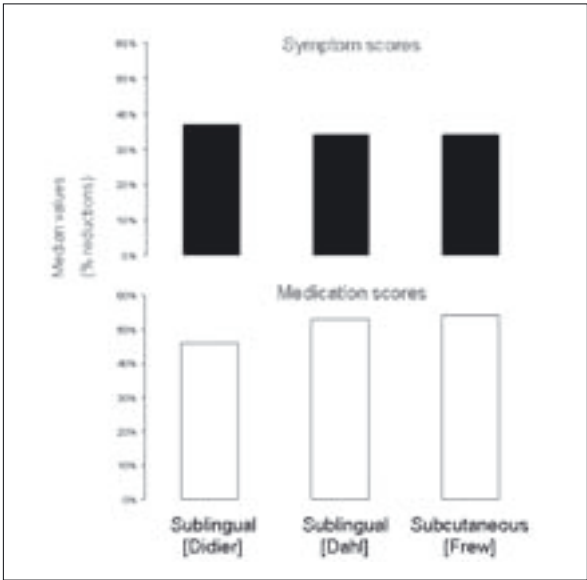


Fig. 1. Comparison of sublingual and subcutaneous grass pollen immunotherapy trials

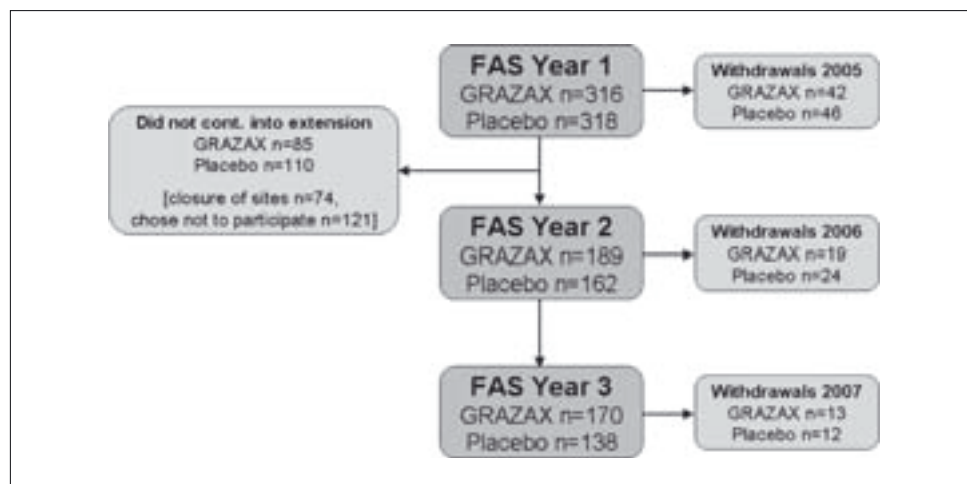


Fig. 2. Subject disposition 2005–2007 Full Analysis Sets (FAS)

Efficacy

The results for the three years continuous treatment are now available. The subject numbers and reasons for drop out are given in Fig 2. The major reasons for a reduction in numbers in year 2 was a decline by the Spanish regulatory authorities to permit a trial extension from one to five years whereas a proportion of individual subjects also declined to give informed consent as indicated (Fig. 2). One limitation may have been that the large ‘drop out’ after year one may have resulted in a ‘survivor effect’ by which those with good efficacy in year one would be more likely to continue in the trial. However, when the level of efficacy in year one was compared for those who did and those who did not continue for three years, there was no difference in their level of either efficacy or side effects in year one which makes such an effect most unlikely. Another possible limitation is that patients who received active treatment may have been ‘unblinded’ by the presence of itching and local swelling in the mouth after taking the tablets. This is also unlikely since when symptoms and use of rescue medication were compared in year one for those who did or did not experience local side effects, there was no difference in the level of efficacy between the two groups.

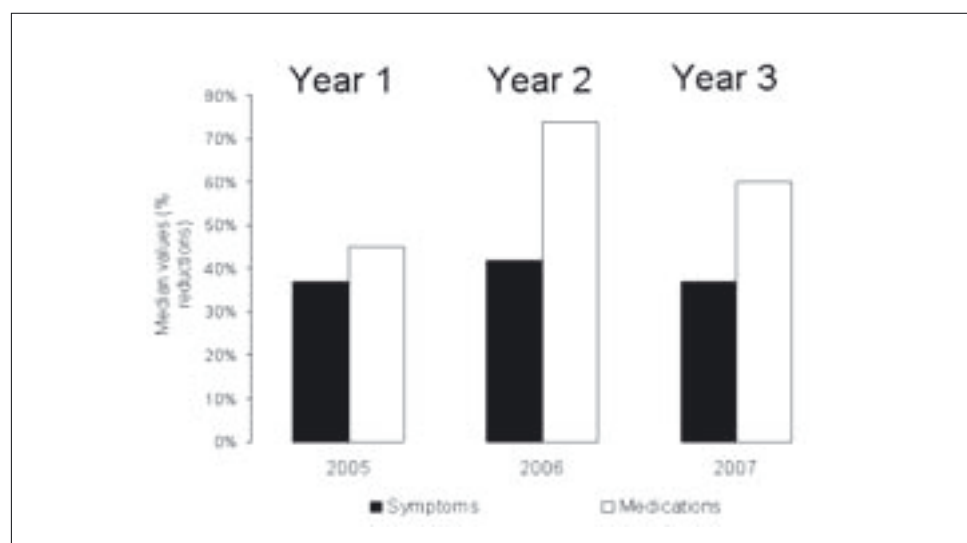
Results for seasonal symptoms and overall use of rescue medication during three years perennial treatment with grass allergen tablets are represented in Table 1. The overall scores were low. This is almost universal in immunotherapy trials, reflecting the prophylactic nature of the treatment which is given over months that include days with low or absent pollen counts and counts that may vary from year to year. Despite the low average counts there was a consistent reduction in both mean symptom scores (varying 29–33%, $p < 0.0001$) and mean medication scores (varying 35–46%, $p < 0.01$ – $p < 0.0001$) that was sustained throughout the three years. The data is represented as changes in median values in Fig. 3. These reductions were observed in patients with severe disease who had free access to best available pharmacotherapy during the season and in the face of high pollen counts throughout

Table 1. Rhinoconjunctivitis symptom and medication scores. Comparing year 2005–2007

Year	Symptoms (Mean)		Medication (Mean)	
	Placebo	Grazax	Diff mean (%)	
1 st : 2005	4.20	1.37***	2.85*	1.01
	2.82	(33%)	1.84	(35%)
2 nd : 2006	3.81	1.36***	3.18***	4.7
	2.45	(36%)	1.73	(46%)
3 rd : 2007	3.59	1.04***	2.99**	1.19
	2.56	(29%)	1.80	(40%)

* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$

the study. An alternative approach to the data is to measure the number of ‘hell days’ in which patients suffered severe symptoms and to compare the numbers for active- and placebo-treated groups. For example if the number of days with severe symptoms with a threshold of greater than 13/18 is considered, 540 days with a score above this level were observed for placebo-treated patients compared to 144 days in the Grazax-treated group (odds ratio, 3.2 in favour of Grazax). These consistent reductions in symptoms and rescue medication were accompanied by progressive increases in serum allergen-specific IgG4 antibodies to grass pollen and an increase in serum IgG-associated inhibitory activity as measured by inhibitory activity for IgE-facilitated allergen-IgE binding to B cells, a surrogate for impaired IgE-facilitated allergen presentation (data not shown).

**Fig. 3.** Three years perennial treatment with SQ-standardised grass allergen sublingual tablets

Adverse events

Adverse events for the original population (N=634) was published by Dahl *et al.* The total number of adverse events during the first three years for the 'extension' population (N=351) was 706 in the placebo group versus 1017 in the grass tablet group. The overall percentages of participants having any adverse events during the three years of treatment were 84% in the placebo group and 96% in the active group. 36% of all adverse events in the active group were considered to be investigational medicinal product (IMP)-related by the investigators. In the placebo group, 14% of all adverse events were considered to be IMP-related. The differences between the treatment groups were most pronounced during the first year where 60% of all events in the active group but only 23% in the placebo group were considered possible or probable related to the IMP. The number of IMP-related adverse events in the active group decreased considerably after the first year of treatment and subsequently approached the level of placebo. Thus within the third year, 15% of the adverse events in the active group and 8% in the placebo group were considered to be IMP-related. The onset of half of all the IMP-related adverse events was found to be within the first two days of treatment.

Most of the IMP-related adverse events were assessed as mild in severity and comprised oral pruritus (51% of the participants), mouth oedema (21%), ear pruritus (12%) and throat irritation (12%). Overall, withdrawals due to adverse events were registered for 24 participants during the first year (16 active, 8 placebo), 3 participants during the second year (1 active, 2 placebo), and 2 participants during the third year (1 active, 1 placebo). During the first year 22 adverse event withdrawals were assessed as IMP-related (primarily local reactions), during the second year 2 adverse event withdrawals were assessed as IMP-related (headache and mild arthritis) and during the third year 1 adverse event withdrawal was assessed as IMP-related (moderate asthma). Thus in total, 25 of the 29 adverse event-withdrawals were assessed as IMP-related. Less than 1% of the IMP-related adverse events were assessed as being severe; these included 3 events in the active group and 1 event in the placebo group over the three years of treatment. The 4 events were 2 events of mouth oedema, 1 event of bronchitis and 1 event of eczema (treatment groups blinded). None of these severe adverse events led to withdrawal from the study.

In summary SQ-standardised grass allergen tablet sublingual immunotherapy resulted in sustained reductions in rhinoconjunctivitis symptoms and need for rescue medication during three years. Clinical improvement was accompanied by progressive increases in IgG4 antibody responses. The treatment was well-tolerated with minor local side effects and no serious treatment-related adverse events.

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Discussion

Valenta: You reported about the antibody developments and I was wondering whether you had any observations regarding the IgE antibody levels in the Grazax group? Was there an induction? Secondly can you define for me the relative unit in the IgG increase?

Durham: In relation to IgE, I did not show the data but there is a mild increase in allergen-specific IgE antibodies in relation to sublingual immunotherapy. And this has been observed in – to my knowledge – all the trials of sublingual immunotherapy. We also see it in relation to subcutaneous immunotherapy. It could be Th2 priming, we do not know what the effects are. One thing is clear – it is not associated

with an exacerbation of disease. And as far as I am aware it is not associated with an increase in side effects when the IgE titers rise. So, whether this is high-affinity antibody or whether it is junk antibody, whether it is necessary or has a relevance at all, the ongoing effect of immunotherapy is not known. But you are quite right – it is well-known with subcutaneous immunotherapy and will associate with sublingual immunotherapy. It does not seem to have clinical implications.

Valenta: Can you comment on the magnitude of the rises in IgE titers under sublingual versus subcutaneous therapy?

Durham: It would only be an impression because I have not looked at that specifically and I think it varies between different sublingual immunotherapy trials. In general, I would say that via the mucosa route that we see a higher increase in the IgE levels than what we see via the subcutaneous route. Although I think that there is no evidence that that is in any way deleterious to patients either in terms of local side effects with the treatment or the emergence of side effects or worsening of disease in the patients that have been studied. In relation to IgG, as you say, they are relative units. It is actually extremely difficult to try and compare these to international units of IgG. We tried and we were unsuccessful. So I cannot really answer your question specifically in relation to what the units are for IgG. What we are looking at there is actually an internal change in magnitude.

Van Wijk: Stephen, going back to our first discussion about quality of life and symptom scores we know that there is a weak correlation between symptom scores and quality of life. But if you take those hell days, perhaps if you try to compare or try to correlate the number of hell days with quality of life, you get a better correlation...

Durham: I think that is a very good point, Roy, and this is something that we really need to be exploring in the future. I think we have to correlate quality of life and these global assessments and certainly the severe days on what patients really complain about and impair their quality of life – we have not done that yet. What I can tell you is that the changes of quality of life in percentages for the three studies that I showed you is round about 25–30 percent for the Didier and the Dahl studies. It is round about 40 percent for the Frew study, although they are not strictly comparable. The latter did use the RQLQ (Rhinoconjunctivitis Quality-of-Life Questionnaire), but the studies were done at different times of the seasons, which might affect their results. But there were substantial changes in quality of life with both treatments. Numerically, it was higher for subcutaneous treatment, but again I think that just highlights the importance of the need to do the head-to-head trial.

Rak: I have a question about clinical trials to you. Because I noticed that none of the study you mentioned had a baseline year. What is your opinion about the baseline year – it is just losing valuable time?

Durham: No, I think you are right. There are pros and cons of having a baseline year. The advantage of having a baseline year is that you can compare each patient with their own control. And that is particularly important, e.g., when you try to develop

biomarkers where you can look within patients and changes. And I think we have to sort of relying on that type of study for that. But of course, there are also problems. There is variation in pollen counts from one year to the next and it is also a fact that you get a substantial dropout rate. Because in order to have a baseline comparison you have two unique values rather than just one value. In other words you are doing a delta analysis which depends on the presence of two values. So, if in two years you got a 50 percent failure to record symptoms, e.g., and they are different patients, then you got a 30 percent loss of data. So I think that the variation in pollen counts from year to year and an increased dropout rate actually would argue against using a baseline year in these very large trials. And actually, the statisticians have looked at data by going back to trials where we do have a baseline year and have looked at what can you gain statistically by having a baseline year and what you lose and you actually do not gain very much. You do gain a little, but of course what you do lose is time in the sense that it takes you another year to do the trial. I think the dropout rate is a real issue in these big trials having a baseline year. But you are quite right: to be correct it is much better to have a baseline year.

Rak: But if you applied these statistics you showed and corrected it for the amount of pollen, then you can avoid at least this problem.

Durham: Yes, I agree.

Robinson: Can I just focus on the last slide you showed looking at adverse events, because I think I am right in saying that the full study had a focus on relative grade 3 reactions which were not seen at all in the sublingual study. And I think your comment on the need for a head-to-head comparison very apt. Clearly, we have no idea what the relative systemic dose is for sublingual versus subcutaneous therapy and I think that is what Rudi's question was alluding to – the relative changes in IgE and IgG are generally less for sublingual compared to subcutaneous.

Durham: Well, Rudi is right. It is paradox that the IgE increases more, if anything, whereas, you are quite right, the IgG actually tends to increase less. But that does not relate to the efficacy in any way as far as we can see looking at immunoreactive antibody levels. And I think that is the point: It is not the immunoreactive antibody levels, what those antibodies do is important.

Kleine-Tebbe: How do you feel about not having an observation year that you cannot really estimate the placebo effect? In other words – if you have an observation year then you have an estimate on the placebo effect.

Durham: Now, that is a fair comment. What you are saying is, if you got a pure natural observation year then you can actually work out what the real effect is. I do not know if any of these large trials would have been done with the baseline year, to be able to do that sort of comparison. It is very nice to have a large trial with 400 patients where you got a baseline year and you could look at the dropout rates, and you could look at what is to be gained by having that year and being able to estimate placebo effects and then to compare that with just the single-dose active *versus* placebo. I am not saying it is not a good idea to have a baseline year – I think it is. But I think that there are practical problems in terms of moving to registration, the time that it takes is a major dropout rate. And the fact that you lose paired data which can compromise your analysis as well. So it is not a straightforward answer, but I agree with you that, if time was not a factor, a baseline year is a very good thing.

Van Wijk: But in the business of large trials you have to be practical and sometimes what you really want to do is impossible.

Valenta: As you said, this IgE that was induced was doing nothing here. It is nice that you say this. But have you had the chance to check whether these people had a decreased or increased skin reactivity to the allergen or whether it remained the same? So in other words did you perform a simple skin test and look at its results? Because, obviously, with the increased IgE levels you would also get a higher skin sensitivity.

Durham: That is sure – that is a good point. I have not got a detailed time course during the immediate period of sublingual immunotherapy to specifically address the questions you are asking. But I do have that data in relation to subcutaneous immunotherapy where we get similar increases in IgE and we do not see any increases in skin test reactivity to the antigen. So I would think that it is unlikely, but you need to do the time course in order to specifically look at that. The problem with doing a time course of skin reactivity is, as we heard earlier from Dr. Kleine-Tebbe, giving intradermal antigens is actually also a good way of inducing an immune response. You know, the test itself can actually alter the IgE antibody tests. In subcutaneous immunotherapy there is an increase in IgE and I would suggest that most of that IgE is not biologically relevant. We need to look at that. We do not have a time course of the immediate skin prick test response.

Leibold: You have this beautiful curve comparing the three years where the reduction rate increases from the second to the third year. First of all, did you look if the patients who responded the second year were the same ones who responded the third year? In other words, do you have a kind of responder and non-responder group?

Durham: That is a good question and I do not have the data. I certainly feed that back. It would be a good thing to do.

Leibold: The other question is, how do you explain that during the season the reduction goes down?

Durham: That is very clear. The reason for that is that the pollen count goes down. The whole point of this is that you have got a very high pollen count at the beginning of the season in the second year of the trial. And, whereas the overall effects were very similar, if you relate it to the pollen count it does suggest that with that *post-hoc* analysis that I showed you that you are getting a progressive and bigger effect as one year goes to the next. But that needs to be tested prospectively.

Jacobsen: I just have a remark on the placebo effect. Actually, I would not be so worried about the placebo effect, because you have a comparative study. You see the beneficial outcome of treatment and we discussed it in Bangkok and Tony said at a certain time that maybe the placebo effect should be regarded as an integrated part of the full effect because it will always be there. I think that we should not be too hard against ourselves on that issue.

