

Sublingual immunotherapy: Dosing in relation to clinical and immunological efficacy

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ABSTRACT

An increasing number of clinical immunotherapy trials have been published in the United States and Europe. In the allergy community on both sides of the Atlantic, there is a growing interest in obtaining a better understanding of the allergen doses used in these studies. The question of effective allergen dose is particularly important in sublingual immunotherapy, but the effective dose range still is to be determined.

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Key words: Allergen, allergen extract, bronchial provocation, desensitization, dosing, immunoglobulin E, immunoglobulin G₄, immunotherapy, rhinitis, sublingual

There is no universal way of measuring the potency of an allergen extract. An allergen extract, *e.g.*, cat, is a mix of many different molecules, among which the proteins are of importance in the field of allergy. However, protein nitrogen units are not an adequate way of expressing potency, because just some of the proteins will produce an allergic reaction and are allergens. To study the potency of an allergic extract, *in vivo* and *in vitro* techniques can be used. For commercial batches the *in vitro* tests are most suitable. With these latter qualitative and quantitative characteristics of the extract must be studied. Examples of *in vitro* quality techniques are protein separation methods (iso-electric focusing, SDS-PAGE, and two-dimensional electrophoresis) and allergen detection methods (immunoblotting) that spot the allergens among the proteins in the mixture, determining the qualitative characteristics. Allergen quantification methods are RAST inhibition and various types of ELISAs.¹

Of these *in vitro* methods, the allergen quantification methods will be most suitable for potency expression as they measure how much active ingredients behold the extract. Roughly, two different approaches exist. First, micrograms of major allergen (MMA) can be calculated. This method will reflect only the amount of one allergen present in a mixture, *e.g.*, Fel d 1. The expression "major allergen" refers to an allergenic mol-

ecule to which >50% of all the patients, allergic to this substance, react with the production of specific immunoglobulin E (IgE).² The second approach is the measurement of total IgE binding capacity. This technique gives a more global idea of the total allergenic potency of the extract, because also minor allergens in the mixture will add to the total IgE binding capacity, *e.g.*, Fel d 2, 3, 4, etc. A drawback of this technique is that the result is very much dependent on the pooled serum used. The *in vivo* methods are all based on tests in allergic patients, either skin-prick tests or intradermal tests.

ALLERGEN EXTRACT POTENCY EXPRESSION IN THE UNITED STATES AND EUROPE

Although in the United States of America the Food and Drug Administration, Center for Biologics Evaluation and Research, establishes for each allergen a standard *in vitro* potency test with which all allergen manufacturers have to compare their allergen extracts,³ the situation in Europe is completely different. In 1989 the Nordic Guidelines gave recommendations for the standardization of allergen extracts,^{4,5} but there is no uniform established method or reference extract. In Europe, each allergen manufacturer has its own In House Reference Standard extract (IHRS).⁶ The potency of this IHRS is tested *in vivo* on allergic patients and each company has its own method to do so. Details can be found in a recent publication.⁷ The commercial batches are just tested with *in vitro* methods against this IHRS.⁸ Between the European manufacturers there is variation in the techniques used for testing the commercial extracts against this IHRS.

There is another difference between potency measurement of European and IHRS extracts. Although in Europe the *in vivo* tests are mostly skin-prick tests,⁹ in the United States intradermal skin tests are used.² As

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such, it is impossible to compare potency reviewing skin tests results, performed by the manufacturers during in-house standardization. Therefore, it would be best if the actual situation changed. However, the details of the production of the allergen extracts often is part of the allergen manufacturer's intellectual property, which makes change in this practice in the near future not very probable.

On the other hand, many European manufacturers test the MMA in their standardized extracts and, most recently, published articles on immunotherapy refer to this measure. Although the outcome of this quantification also is method dependent, it might be the measure most closely related to the real biological potency we have today and as such the most suitable to compare allergen extract potency in published literature.^{10,11}

SUBLINGUAL IMMUNOTHERAPY (SLIT) AND ALLERGEN DOSING

One of the reasons why SLIT efficacy is doubted has been the great variety of dosing used in different clinical trials published since the 1980s.^{11,12} Because most SLIT literature comes from European research, the diversity of allergen extract potency expressions (as mentioned previously) makes interpretation even more difficult, as concluded in an in-depth review on SLIT literature until October 2005.¹² In the course of 2006 and 2007 more double-blind placebo-controlled SLIT assays have been published,¹³⁻²¹ as well as some large dose searching studies on SLIT,^{22,23} which together more than triple the total number of patients in all studies up until 2005, and as such make the dosing issue for some extracts clearer. The results of dosing in relation to clinical efficacy in this publication will be shown for the studies of the SLIT literature review until October 2005¹² and in the same figure the results for the dosing-efficacy relationship including also the newer studies up until October 2007 will be shown. Some additional details will be discussed in the final section of this publication.

Extract Potency Expressions in SLIT

Because most SLIT literature is published in Europe, where each manufacturer has its own "units," potency expressions vary from biologic units, standard treatment units, histamine equivalent in prick, and index of reactivity, all based on skin-prick tests, to biologic allergen units of HAL (Haarlems Allergen Laboratorium) allergy that adopted the intradermal United States method to test for the potency of their extracts.

SLIT Dosing Schedules

Apart from the allergen quantities, the dosing schedules in SLIT vary considerably. Dosing frequency runs

from once a week²⁴ to daily during maintenance and even twice daily during the build-up phase.²⁵

SLIT Build-Up Phase

The duration of the build-up phase is variable, from 2 months in the first clinical trials²⁶ to no build-up at all in the latest ALK grass studies.^{16,22} Most build-up phases are between 15 and 30 days, with daily or twice-daily dosing.

Dosing in Subcutaneous Immunotherapy (SCIT)

In SCIT the optimal dosing, expressed as MMA, is somewhat better known. Dosing studies have shown the optimal maintenance dose for some standardized extracts and in official guidelines this is between 5 and 20 μ g of major allergen per month.²⁷ The Practice Parameters on Immunotherapy² and its update²⁸ provide more detailed recommendations for optimal doses of some of the allergen extracts, which we will use in this publication. Nevertheless, these recommended doses can be disputed, because most are based on European studies with physically modified extracts.^{6,10,28}

OBJECTIVE

This study had three goals. The first objective was to get some idea of the allergen extract doses used for SLIT relative to SCIT recommended maintenance dose, translating vaccine administered into MMA per month.

Second, the results of dosing in relation to clinical efficacy in this publication will be shown for the studies of the SLIT literature review until October 2005 and in the same figure the results of a second dose-response analysis will be shown, adding double-blind placebo-controlled studies published until October 2007. A relationship will be sought between relative dose and clinical efficacy, immunologic changes, and improvement in provocation tests.

METHODS

Publications Reviewed

A systematic review was undertaken of all clinical trials with SLIT published until October 2005 by a Joint Task Force on Sublingual Immunotherapy of the American College and Academy of Allergy, Asthma and Immunology and published elsewhere.¹² All studies included in the aforementioned review with clear dosing schedules were taken into account and the total number of patients treated per protocol was used for the calculations of the data "until October 2005" (left columns in Fig. 1). For the second data set the newer studies published until October 2007¹³⁻²³ were added, making for the data "until October 2007" (right col-

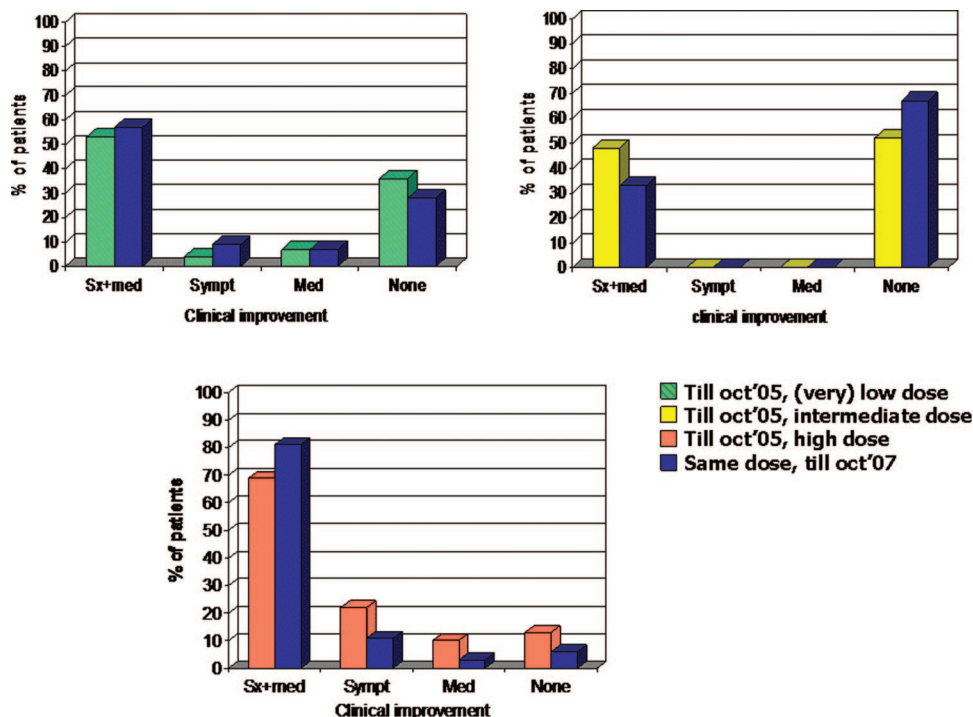


Figure 1. SLIT dosing and clinical efficacy. Statistically significant improvement in symptom score, medication score, both or none, according to SLIT relative dosing groups. Studies until October 2005 in dosing color codes. Adding all studies until 2007 in blue. Color coding according to monthly SLIT dose used, relative to the recommended monthly SCIT dose: Very low and low dose ($<5 \times$ SCIT), intermediate dose ($5\text{--}50 \times$ SCIT), and high dose ($>50 \times$ SCIT).

umns in Fig. 1). Double-blind, randomized, placebo-controlled studies were included, but also open randomized controlled studies and postmarketing studies were included, as long as clear dosing and symptom and medication scores were reported. Only the studies that provide specific information for each parameter in question were incorporated in each separate analysis of this article.

MMA per Month

To get some idea of the doses of allergenic extract used in studies with SLIT we decided to use the measure adapted by the World Health Organization for its recommendations on SCIT immunotherapy: MMA. The MMA doses, as reported in the SLIT literature reviewed, were converted in monthly MMA to compensate for the various dosing schedules applied with SLIT. For the analysis of this article, only SLIT studies with unmodified allergen extracts were included, because it is not possible to quantify major allergen in allergoids.

Allergen Dosing in SLIT Studies Relative to SCIT Recommended Monthly Maintenance Dosing

Thus, to compare more directly the SLIT doses to the established SCIT doses, MMA per month is then divided by the recommended SCIT monthly maintenance

dose, as given by the practice parameters.^{2,28} For example, in an SLIT study 2 MMA of *Dermatophagoides pteronyssinus* is given daily, and then the monthly dose is $2 \text{ MMA} \times 30 \text{ days} = 60 \text{ MMA/month}$. The recommended SCIT maintenance dose for this allergen is 10 MMA/month; thus, the relative SLIT dose is $60/10 = 6 \times$ the SCIT dose. This leads to the classification of SLIT studies into “relative” dosing categories, see Table 1.

Efficacy Parameters Relative to Dosing Categories

The second objective of this study was to tabulate the reduction in symptoms and medication use according to the dosing categories. To reach this objective, we did an analysis per dosing category of all studies with statistically significant improvement in medication and symptoms, improvement in just symptoms or medication, or no statistically significant improvement at all. Finally, the total number of patients in the active group taken into account for the “per protocol” analysis of each study was summed up to give in each analysis the percentage of patients with/without improvement. A similar scrutiny was performed for the relation between dosing category and changes in immediate hypersensitivity (titrated skin-prick test) and bronchial provocation test threshold, as well as changes in immunologic parameters. Given the fact that the studies

Table 1 Relative dosing categories according to MMA administered monthly in SLIT studies, compared with recommended SCIT monthly maintenance dose for studies published before October 2005 and from October 2005–2007

Dosing Category	Relative to Recommended Monthly Maintenance SCIT Dose (2)	Studies in Dosing Category (%)	
		Until October 2005	October 2005–2007
Very low dose	<2 times	56	21
Low dose	2–5 times	13	5
Intermediate dose	6–50 times	18	26
High dose	>50 times	14	47

included were of great variety, no specific statistical calculations have been done to compare between dosing categories, because this would give a false sense of statistical power.

RESULTS

SLIT Dosing Used in Clinical Trials

Table 1 shows the amount of studies using very low, low, intermediate, and high doses until October 2005 and from October 2005 to the present. It is clear that only a minority of the studies until October 2005 used the high dosing. The more recent studies, however, show a tendency to administer higher doses.^{14–17,19,21–23}

SLIT Dosing and Efficacy

In Fig. 1, A–C, the relationship between relative SLIT dosing and clinical efficacy is given for the studies until 2005 and for the studies until 2007. Some studies report partial improvement, only during the peak season or only in the subgroup of most severe patients. These reports have not been taken into account, and only total statistically significant improvement in the primary efficacy outcome has been considered for the calculations on “patients improved.” With higher dose there is a rising percentage of patients with statistically significant improvement in both symptoms and medication scores and a lower percentage of patients without improvement. This becomes clearer in the analysis that includes the recent publications. However, also with low and very low relative SLIT doses one-half of the patients were in studies that indicated statistically significant improvement.

SLIT Dosing and Skin-Prick Test Changes

On reviewing the SLIT articles in the 2005 review (for exact references of all articles see Ref.10) in which quantitative skin-prick tests have been performed and classifying the patients again by monthly MMA dose received relative to SCIT recommended dose, according to the dosing groups defined previously in Table 1,

no good correlation can be found between dose and skin-prick test improvement or between duration of SLIT and skin-prick test improvement.

There seems to be a trend to a higher percentage of patients with improvement at a higher dose: of all patients receiving very low dose only 27% were in studies that showed reduction in skin test sensitivity versus 85% of patients in studies receiving a high dose. The same holds true for a longer duration of SLIT: 20% of all patients receiving <6 months of SLIT were in studies that showed quantitative skin-prick test improvement against 64% in studies of at least 24 months of SLIT. There are three studies in this analysis in which skin-prick tests have been done at different time points; they all showed only improvement at the later time point.^{26,29,30}

Antibody Changes and Dosing

The changes in specific serum IgE in relation to SLIT dosing category are depicted in Fig. 2, A–D, whereas Fig. 3, A–D, gives the relation between SLIT duration and specific serum IgE changes. It seems that a higher dose tends to give a temporary rise in IgE at ~6–12 months of treatment. Then, in studies with regular IgE measurements, after 12 months of treatment IgE can be shown to come down again, following the pattern seen with SCIT.

For specific serum IgG₄ the relationship between dosing and rise in serum titers is much clearer, as can be seen in Fig. 4. Specific serum IgG₄ increased in 89% of the patients in studies in the highest dosing category. This rise is already present from 6 months on, as Fig. 5 shows.

Changes in Challenge Tests and Dosing

In total, 13 studies reported the results of bronchial challenge tests, 3 of these were with the specific allergen in question.^{26,31,32} All of these showed a statistically significant rise in threshold. Of the 10 nonspecific bronchial challenge tests, done with metacholine, only 3 failed to show a statistically significant rise in thresh-

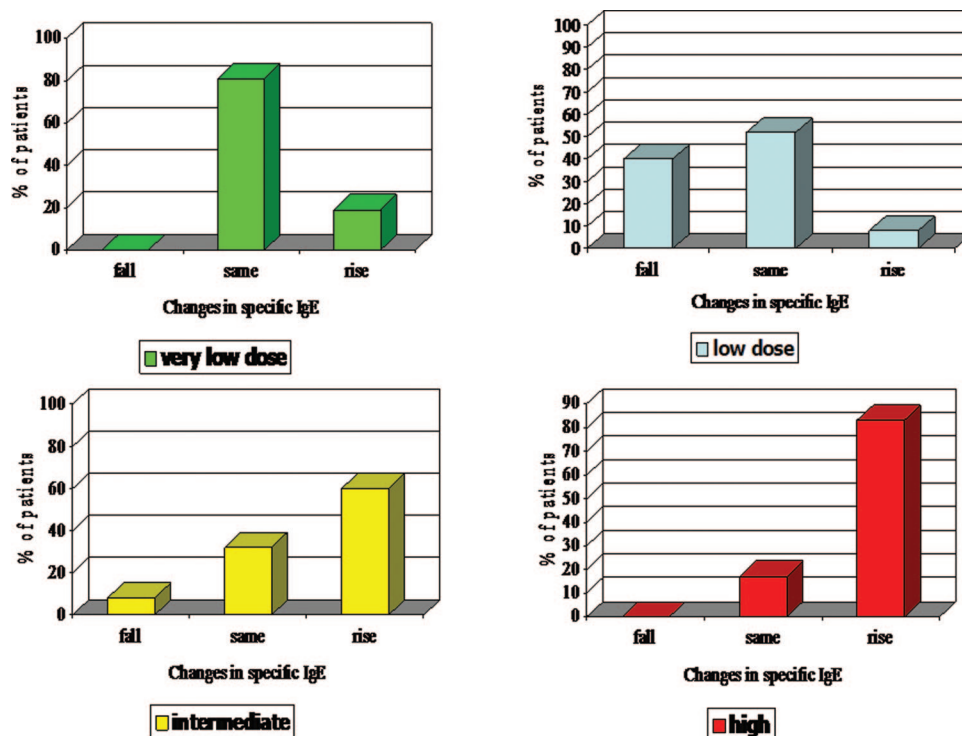


Figure 2. SLIT dosing and changes in serum-specific IgE. Statistically significant decrease, rise, or no change in serum-specific IgE, according to relative SLIT dosing group. Very low dose ($<2\times$ SCIT), low dose ($2-5\times$ SCIT), intermediate dose ($5-50\times$ SCIT), and high dose ($>50\times$ SCIT).

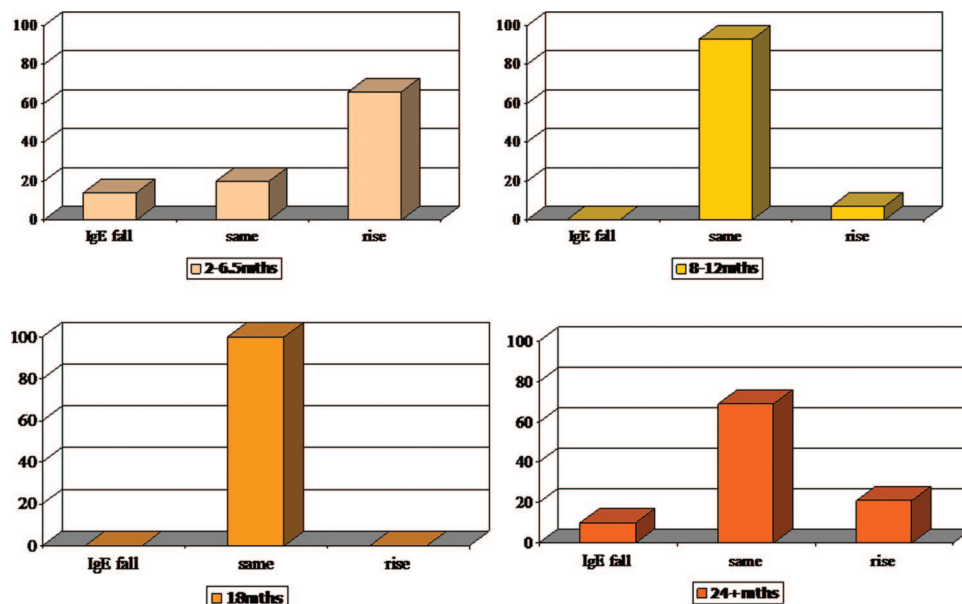


Figure 3. Duration of SLIT and changes in serum-specific IgE. Statistically significant decrease, rise, or no change in serum-specific IgE, according to duration of SLIT.

old, 2 with low dose and 1 with intermediate relative monthly dose. Paradoxically, of the studies with improved threshold five were with low dose and one was with very low dose. Therefore, no relationship could be found between dose and bronchial challenge test improvement (Table 2, studies referenced can be found in

Ref.12) The results of nasal and conjunctival challenge tests also are depicted in Table 2.

DISCUSSION

It is striking that the relative SLIT doses used in the literature mostly have been quite low doses, although

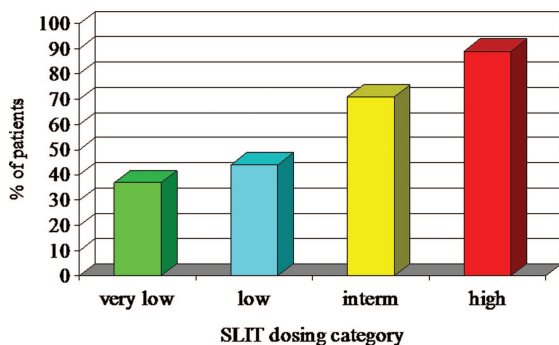


Figure 4. SLIT dosing and changes in serum-specific IgG₄. Percent of patients in studies with statistically significant rise in serum-specific IgG₄, according to relative SLIT dosing group. Very low dose (<2× SCIT), low dose (2–5× SCIT), intermediate dose (5–50× SCIT), and high dose (>50× SCIT).

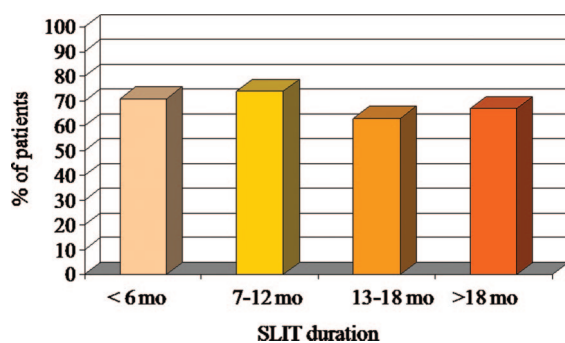


Figure 5. Duration of SLIT and changes in serum-specific IgG₄. Percent of patients in studies with statistically significant rise in serum-specific IgG₄, according to duration of SLIT.

internationally it had been recommended to use 50–100 times the SCIT dose.²⁷ More recent studies show a tendency to administer these higher doses.^{14–17,19,21–23} Although the studies in our review were quite heterogeneous, Fig. 1 shows clearly that the chance of clinical improvement increases with higher dose. However, interestingly, some studies with very low and low doses did show clinical statistically significant improvement and a rise in threshold of provocation tests. Particularly, two studies deserve mentioning. First, the study by Bordignon *et al.*, a very low-dose SLIT study was not included in the analysis, because no symptom score was measured and patients were not randomly assigned to active or control groups.³³ However, the design grabs attention. The aim of the study was to show that SLIT efficacy increases with multiple daily application. For that purpose, 1/25 of the normal SLIT dose was applied one to three times per day in the 1st year and three times daily in all groups during the 2nd year. Expressed in MMA, the relative monthly SLIT dose given was 0.4–1.1 times the monthly recommended SCIT dose. Nevertheless, low-dose skin-prick test reactivity and medication use reduced significantly in all groups from the moment patients started to

receive SLIT three times daily (group C the 1st year and groups A and B the 2nd year).

The second very low-dose study was performed in Spain with cat allergens (1.5 µg of Fel d 1 per month).³⁴ Even with this very low dose statistically significant improvement in peak flow measurements of patients exposed to the cat room were reported. Because no medication scores were registered here, again, this study was not included in the aforementioned analyses.

These phenomena could be explained by the local immunologic changes provoked by SLIT, very specific for this route of administration as discussed in excellent review articles^{35–38} and briefly in this study. Interestingly, the latest ARIA document on immunotherapy no longer provides specific dosing recommendation.³⁹

The third study not included in the efficacy analysis was a negative SLIT study performed at the primary health care level. The children included were possibly not well selected by nonspecialists and positive skin-prick test was not one of the inclusion criteria.⁴⁰

Until now, only a few dose-efficacy studies with SLIT have been published and there are two blinded, randomized controlled trials with three different doses and an adequate number of patients.^{22,23} The first study uses a grass tablet (*Phleum pratense*) in 855 patients. A dose-response in clinical efficacy and medication reduction is shown. There is no improvement in the placebo group or in the low-dose group. There is a mild improvement in the group receiving 5 µg of Phl p 5, but only the highest dosing group, receiving 15 µg daily (75,000 SQ-T) shows a statistically significant improvement. The reduction in symptoms and medication score with this treatment has been higher starting SLIT at least 4 months before the beginning of the season.⁴¹ The latest (2007) Cochrane analysis of SLIT efficacy in allergic rhinitis based on 39 studies, did not address the dosing issue but showed there was a significant reduction in symptoms (standard mean difference, -0.42 [-0.56, -0.28]; *p* < 0.00001) and medication requirements (standard mean difference, -0.41 [-0.55, -0.28], *p* < 0.00001).⁴² A subgroup analysis was performed for duration of SLIT, with statistically significant reduction of symptoms already present in studies of <6 months duration.

The second dosing study was performed with 5 grass tablets of 100, 300, and 500 index for reactivity, which corresponds to ~7, 21, and 35 µg of group 5 major grass allergen daily. It is the first study that shows a plateau on the dose-response curve, because the highest group did not have any extra improvement. High-dose patients did, however, show adverse reactions more often.²³

Changes in IgG₄-specific antibodies are clearly doserelated in our review, with a rise in this parameter in 89% of the patients in high-dose studies, already

Table 2 Changes in provocation tests in relation to allergen dose and duration of sublingual immunotherapy

No Change			Rise in Threshold		
Author (no. of SLIT patients)	Dose allergen*	Duration (mo)	Author (no. of SLIT patients)	Dose allergen*	Duration (mo)
Specific and nonspecific bronchial challenge tests					
Bahceciler 2001 (8); ⁴⁹ met	20 Dpt/f	6	Arikan (32) allergen ³²	20 Dpt/f	6
			Bahceciler 2005 (17); met ⁵²	20 Dpt/f	6
			Cirla (18) allergen ³¹	2.3 Bet-coryl	2 × 3.5
Hirsch (13) ⁵⁰ histamine	5 Dpt/f	12	Bahceciler 2005 (14); met ⁵²	20 Dpt/f	12
Mungan (15); ⁵¹ met	4 Dpt/f	12	Tari 1990 (30) allergen ²⁶	2.4 Dpt/f	12
			Tari 1990 (30); met ²⁶	2.4 Dpt/f	12
			Pajno 2004 (14); met ⁵³	4 pletory	18
			Lombardi 2001–2002 (26); met ⁵⁴	Allergoid	3xpre/coseason
			Silvestri (10); met ⁵⁵	5.2 Der p/f	24
			Margona 2005 (29); met ⁵⁶	0.5 Birch	6, 18, 30#
Specific nasal challenge tests with allergen					
			Horak (21) ⁵⁷	3.6 Birch	4
			Passalacqua 99 (14) ^{25¶}	(0.36) Pletory	6
			Passalacqua 99 (14) ²⁵	(0.36) Pletory	6
			Cirla (18) ³¹	2.3 Bet-coryl	2 × 3.5
			Ariano (10) ⁵⁸	5 cupress	8
Voltolini (2 yr:10) ⁵⁹	4,2 Betula	2 × 5.5	Troise (15) ⁶²	(0.06) pletory	10
Marcucci 2003 (13) ⁶⁰	0.9 Dpt	12	Sanchez P. (20) ⁶³	0.017 cat	12
Hirsch (13) ⁵⁰	5 Dpt/f	12	Tari 1990 (30) ²⁶	2.4 Dpt/f	12
			Valle (15) ⁶⁴	0.4? Ragweed	18
			Tonnel (1 yr:15, 2 yr:10) ^{29¶}	11.4 Dpt/f	12, 24
Rolinck-W 04 (39) ⁶¹	0.6 5 grasses	32	Bernardis (12) ⁶⁵	3.6 <i>Alternaria</i>	24
Specific conjunctival challenge tests with allergen					
			Horak (21) ⁵⁷	3.6 Birch	4
			Gozalo (35) ⁶⁶	(1–3) lolium	2 Seasons
Torres Lima (26) ⁶⁷	128 Phleum	18	Mortemosque (26) ⁶⁹	33 Dpt/Df	6, 12, 18, 24 steady rise TH
Smith (1 yr:94.2 yr:45) ⁶⁸	55 grass	2 × 6	La Rose (16) ³⁰	273 pletory	12, 24
Rolinck-W (39) ^{61§}	0.6 5-grass	12, 24, 32	Passalacqua 98 ⁷⁰	Allergoid	12, 24
Glove use test and latex rubbing test					
			Cisteró (26) ⁷¹	? Latex	2

*Allergen dose is expressed in monthly SLIT dose, relative to monthly SCIT dose in MMA (number is the factor, times SCIT dose). After the relative dose the allergen studied is mentioned.

#Steady rise in methacholine challenge: after 6 mo $p < 0.03$, after 18 and 30 mo, $p < 0.001$.

§Step-wise rise in tolerated dose, although difference is not significant.

¶Rise in threshold is NS, due to small number of patients.

Results of provocation tests in the SLIT studies reviewed (for references of the studies see Ref. 10). Left part, no statistically significant change; right part, statistically significant rise in threshold. Studies are put in order by study duration. Number of patients in the active group in ITT analysis are marked between brackets.

met = Methacholine

from 6 months on. The same has been shown in the first dose–response grass study discussed previously.⁴³

Changes in specific IgE are more variable, because the time of measurement is crucial. Figure 3 shows that specific IgE tends to augment in the 1st months of treatment, before coming down to (almost) pretreatment levels. Figure 2 shows that a rise in specific IgE any time during the treatment course is more frequent

in the studies using high-dose SLIT. This correlates nicely with findings in the large SLIT grass dosing study⁴³ and with findings in SCIT.⁴⁴

Surface IgA might be a crucial immunoglobulin in the action of SLIT, especially in the lower doses of this variant. Recent studies in grass-sensitized mice showed that SLIT caused a dose- and time-related rise in bronchial and nasal lavage fluid IgA, up to 30-fold of

the values found in the placebo group.⁴⁵ Moreover, the levels of secretory IgA were correlated to the serum IgA concentration. No change in serum-specific IgG or IgE were reported in this particular study, so probably relative SLIT doses in this mice study were quite low. Nevertheless, the rise in specific secretory IgA was marked. The large grass SLIT study in humans, discussed previously, showed a serum IgA rise, which was statistically significant when compared with placebo in the intermediate and high-dose groups.⁴³ In conclusion, the data suggest an increase in specific surface IgA is seen with lower doses than those that appear to cause systemic IgE and IgG changes. An excellent article on the mechanisms of SLIT has been published earlier this year in this same journal.³⁵

Our review could not show any clear relationship between dosing and a reduction in skin-prick test sensitivity. With SCIT, recent clinical trials have shown a dose- and time-response relationship for changes in early and late skin reactions, in correlation with immunologic changes. The first weeks of up-dosing the late-phase skin reaction is markedly reduced, correlating with a rise in serum IL-10. However, it takes more than 3 months before the early phase skin-prick reactions are reduced; this is in correlation with a rise in specific IgG₄ "blocking" antibodies in serum.⁴⁴ Thus, it seems skin-prick test sensitivity reduction is related to changes in systemic immunoglobulins. One of the crucial cytokines related to this shift in immunoglobulins is IL-10, produced by regulatory T cells.⁴⁶ It stimulates the B cells to a class switch from IgE to IgG₄. The importance of this IL for immunoregulation during the 1st months of immunotherapy, but not at 1 year of SCIT, was elegantly shown by Bohle *et al.*⁴⁷

In contrast to these systemic changes, the reduction in sensitivity of the end-organ, as expressed by bronchial and nasal provocation tests, probably are more related to local immunologic changes,^{37,38} as, *e.g.*, a rise in local secretory IgA and speculative local regulatory T-cell activity. These changes possibly could occur at much lower SLIT doses. This might be an explanation for the data presented that show a rise in provocation test threshold in almost all studies, irrespective of SLIT dose used. The study of Alvarez-Cuesta with very low-dose cat SLIT,³⁴ discussed previously, goes in line with this theory.

In conclusion, SLIT seems an interesting variant of immunotherapy application. With time the dosing puzzle seems to get closer and closer to resolution, teaching us that probably a straight dose-effect relationship does not exist. So many other variables have to be taken into account: quality of the extract, quantity of extract per dose, tablet or drop, volume of dose, mixing of extracts, dosing frequency in a week and per day, total duration of treatment and the addition of adjuvants, etc. Although there are still many loose ends,

it seems that SLIT is a procedure for which its time has come,⁴⁸ because in the end it might give us the opportunity to broaden our indications for the only causative treatment of allergies, immunotherapy that is still too much underused at the present time.

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