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A Bright Future for Sublingual Immunotherapy – Contra

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Abstract

Defining the role of sublingual immunotherapy (SLIT) for the treatment of allergic rhinoconjunctivitis and allergic asthma is hampered for various reasons: Heterogeneity in study designs, different allergen extracts and dosages, imperfect assessment strategies and partially inconclusive results. A number of questions need to be addressed before replacing subcutaneous immunotherapy (SCIT) by the sublingual route: Ideal dose, treatment duration, magnitude of improvement, modification of the immune response, long-term and preventive effects. At present, SLIT might be used in adults with pollen related rhinoconjunctivitis, particularly if SCIT is not suitable for the patient (i. e. systemic effects). Only few data support SLIT for house dust mite allergy or bronchial asthma. Due to a lack of convincing results SLIT for children should only be applied in controlled studies and not in the daily routine. A more substantiated and conclusive judgment of SLIT is possibly warranted in a few years, when more studies with larger patient groups have addressed open questions concerning SLIT.

Introduction

Sublingual immunotherapy with allergens (SLIT) has been introduced in many European countries promoting an alternative route of application of allergen extracts for the treatment of allergic diseases. An increasing number of clinical studies have addressed efficacy and safety of SLIT in children and adults with rhinoconjunctivitis and allergic asthma (reviewed in [1-4]). Final conclusions on the clinical value of SLIT, particularly in comparison to subcutaneously applied specific immunotherapy (SCIT), are hampered by large heterogeneity in study design, different allergen extracts and varying doses used, assessment methods and partially inconclusive results. Some of the contributing factors and scientific flaws will be highlighted explaining the present difficulty of judging SLIT on a solid scientific basis. A considerably high number of clinical studies from France and Italy have led

to strong support of SLIT in Southern Europe. Subsequently, international recommendations have highlighted the clinical utility of SLIT (ARIA) [5].

Clinical studies with sublingual immunotherapy (SLIT): potentials and pitfalls

Modern clinical research is based on randomized studies, usually performed double blinded for at least one year with specific immunotherapy (SIT) [6]. Such studies should use clearly-defined interventions and endpoints. Blinded assessment of validated important outcomes and a rigorous analysis of all results are further important requirements. Unfortunately, many of the published studies on SLIT are far from perfect and demonstrate experimental flaws, more specifically biases in selection, performance and assessment (Lit TechReport).

A large number of studies have no run-in-period, which is important for successful randomization of study subjects, particularly if outcome analyses are based on subjective measures (symptom score, rescue medication) [7-21]. Many studies on SLIT demonstrate excessive drop-outs with subsequent loss of follow-up [7,12,14,20,22-31]. Such observations impose a risk, that prior randomization will be skewed to one of the treatment arms (verum or placebo). Careful description of the reason for drop-outs is therefore important and unfortunately often lacking in publications on clinical studies with SLIT.

A common bias of a number of SLIT studies is a lack of intend-to-treat analyses for efficacy outcomes [7,8,13,14,19,21-23,32-35]. Calculations based only on per-protocol-treated subjects impose a high risk of assessment biases. This becomes important when large differences occur between the intend-to-treat and the per-protocol-treated subjects. Further issues include incomplete reporting or analysis of symptoms or medication scores over the entire study duration [7,8,14,16-19,23,32,34,35]. More specifically, differences should not only be evaluated within the groups before and after therapy but also between the groups. Ideally, predefined assessment plans should be part of a study plan, forming the basis of the entire analysis. A number of SLIT studies have to be criticized for documenting and publishing only statistically significant results or selected variables. This practice, becoming a “fishing expedition” for desired results, should not longer be accepted by the scientific community and editors of scientific journals.

Meta-analysis of SLIT in allergic rhinoconjunctivitis: evidence in favor for SLIT

A meta-analysis on SLIT has been published by the Cochrane Library, bundling 22 studies; 17 in adults and 5 in children [4]. Despite considerable heterogeneity of these studies, analysis of standardized mean differences (SMD) of symptom and medication scores revealed effect sizes of -0.42 and -0.43, considered as a slight (<0.2) to moderate (0.2 - 0.5) effect size in favor for SLIT compared to placebo. Further subgroup analysis revealed statistical significant SMDs in adults, but not in children. Seasonal allergens (grass pollen, *Parietaria*) also showed favorable results for

SLIT, which was not the case for perennial allergens (house dust mite). Only short study durations (< 6 months) were associated with a significant positive outcome of SLIT but not the studies exceeding 6 months (Table 1). These results might represent random effects, since a higher cumulative dose as a consequence of an extended study duration should usually be associated with stronger clinical efficacy. Slight effects through SLIT together with strong placebo effects might be another explanation for this unexpected finding. The authors of the meta-analysis have addressed a number of open questions, which are at present still valid for a general conclusion on SLIT (see open questions).

Table 1. *SLIT meta-analysis: Subgroup analysis with heterogenous results*

	Variables	SLIT [n] sympt (medic)	Placebo [n] sympt (medic)	symptom score [SMD]	rescue medic [SMD]
Season	seasonal	346	344	-0.30	-0.36
	perennial	138 (59)	131 (54)	n.s.	n.s.
Age	adults	373 (343)	368 (338)	-0.40	-0.51
	children	111 (62)	107 (60)	n.s.	n.s.
Duration	< 6 months	183 (163)	175 (154)	-0.36	-0.63
	6–12 mon.	193 (178)	195 (180)	n.s.	n.s.
	> 12 mon.	108 (64)	105 (64)	n.s.	n.s.
Allergens	grasses	144	143	-0.37	-0.41
	Parietaria	79	83	n.s.	-0.39
	HDM	118 (59)	110 (54)	n.s.	n.s.

(from Wilson DR, Torres Lima M, Durham SR. Sublingual immunotherapy for allergic rhinitis (Cochrane Review). In: *The Cochrane Library*, Issue 2 2003. Oxford: Update Software [4])

Abbreviations: sympt: symptoms; medic: medication; HDM: house dust mite; ns statistically not significant; SMD: Standardized Mean Differences.

Controversies about the allergen dose for SLIT: unresolved issues

The dosage of applied allergens might play not only an important role in SCIT, but also in SLIT. Confusion arises from different definitions, i.e. single, monthly or total cumulative dosage (Figure 1). Furthermore, SLIT studies have been reported with different allergen products, representing different allergen compositions, different potencies and different units, depending on the allergen manufacturer. It should be emphasized, that huge differences for example in major allergen content have been reported between different SLIT extracts. In the future, a collaborative European project (CREATE 1) might provide candidates and reference materials of major allergens, suitable for further characterization of in-house standards of allergen manufacturers. Another important step is the establishment of solid and comparable immunoassays for the determination of single allergens (CREATE 2). Agree-

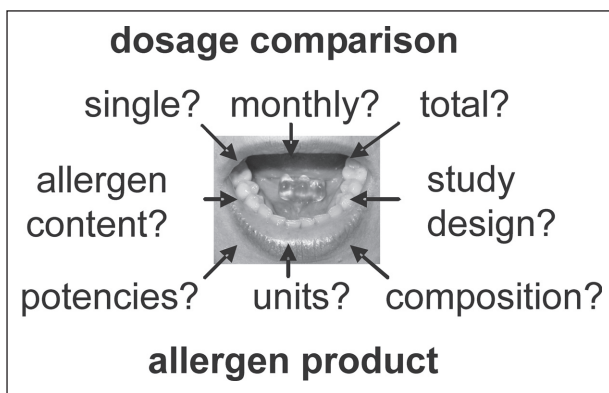


Fig. 1. *SLIT dosage discussion. Comparisons of SLIT and SCIT dosages remain meaningless, as long as important variables have not been defined.*

ment on and accessibility of appropriate assay systems would allow the quantification of the molar allergen content in the future. Being introduced in allergen characterization and standardization, these tools will facilitate improved assessment and interpretation of studies using allergen extracts relating the dose to the clinical effects.

An often-cited recommendation suggests that 50 - 100 times more allergen should be used for SLIT than for SCIT to initiate a significant clinical effect [5]. However, since this relation depends also on the potency of the SCIT extract, it remains meaningless, as long as these extracts lack also a clear definition in their allergen content.

Comparison between subcutaneous and sublingual application and preventive effects: limited experience

An important question is the effect size of SLIT in comparison to SCIT. So far, three studies [25,36,37] have addressed this issue and have been carefully discussed [38]. Only one study allows valid conclusions due to its double-dummy-placebo controlled design [25]. After one year of immunotherapy, birch pollen allergic subjects demonstrated greater improvement after SLIT and SCIT (30% and 50% improvement of a combined symptom and medication score) compared to placebo. No statistical differences occurred between SLIT and SCIT. The authors pointed out that this lack of significant difference does not mean equal effectiveness, but that larger patient groups might have resulted in statistically significant differences. Further studies are needed comparing the effect size of SLIT and SCIT. The same is true for potentially preventive effects in terms of new sensitizations and the development of asthma [31]. Studies on the long term outcome are hampered by poor controlled design and a lack of randomization [23,39].

Clinical utility of SLIT in children: lack of evidence for sound efficacy

Great interest exists in the potential benefit of SLIT in children. However, a smaller number of studies has addressed young subjects (Table 2) - unfortunately demonstrating inconsistent or negative results using SLIT [7,8,19,21,23,35,40,41].

Table 2. *SLIT in children: Studies with inconsistent results*

	author	n	nose	lung	medication	IgG	IgE
1.	Tari	58	(+)	(+)	(+)	↑	↓
2.	Hirsch	29	-	+/-	-	-	↑
3.	Vourdas	66	-	+	-	-	-
4.	La Rosa	41	- (1 y) + (2 y)		-	↑	-
5.	Caffarelli	48	-	+	-		
6.	Pajno	21		+	+	-	-
7.	Bahceciler	15	-	-	(+)		-
8.	Ippoliti	86	(+)	(+)			
9.	Pajno	34	-	-	-		
10.	Bufe	132	- (clin. index)	-	-	(↑)	(↑)
11.	Rolinck-W.	75	-	-	- (2 y) + (3 y)		-

(with permission of Dr. Thomas Hirsch, MD; Klinik für Kinderheilkunde Bergen/Rügen, Germany)
 Comparison verum versus placebo: + verum improved; (+) no verum/placebo comparison, but improvement during therapy; – verum not significantly improved.

Newer studies with larger patient groups and better study designs [24,27,42] were not able to fuel the enthusiasm: negative results or inconsistencies in the reported outcomes make a final conclusion impossible. Therefore, the use of SLIT should not be considered as a routine treatment in children, since further studies are clearly needed to demonstrate clinical efficacy.

Safety remarks: the “home use” issue

An important driving force in the development of SLIT is the decreased risk of severe systemic adverse events [43] compared to SCIT [44]. Depending on the allergen dosage, local symptoms summarized as oral allergy syndrome can occur quite frequently, usually declining over time [45]. In a few subjects, local symptoms of unacceptable severity or systemic adverse events have been reported after SLIT. The latter ones have been of mild to moderate nature, including gastro-intestinal, urticarial and asthmatic symptoms. Despite the lower risk of adverse events after SLIT in comparison to SCIT, the application of allergen products at home displays a residual risk, since no professional help can be provided in case of immediate type allergic symptoms. Proper information of patients undergoing SLIT should therefore include the use of rescue medication and an appropriate emergency plan.

Open questions regarding SLIT: answers needed for clinicians

A constant stream of published clinical studies is contrasted by a number of questions, related to various aspects of SLIT for the treatment of allergic diseases:

Open questions with regard to SLIT (from Wilson DR *et al.* [4])

1. What is the ideal dose and treatment duration and is this the same for all allergens, seasonal or perennial?
2. What is the magnitude of symptomatic improvement when SLIT is compared directly with injection immunotherapy?
3. Does SLIT result in modification of the immune response and is the effect of treatment long-lasting, persisting after withdrawal of active treatment?
4. Will compliance with daily home treatment for up to two years be as good outside the confines of a controlled trial?
5. The attractive nature of SLIT as a treatment for children with allergic rhinitis, and also asthma, means that further study is warranted in this area despite current lack of evidence regarding efficacy.

These issues have been put forward by the authors of the meta-analysis on SLIT studies [4]. The remarks and unanswered topics should be addressed in future studies to better define the value of SLIT for the practicing allergologist treating patients with allergic diseases.

SLIT perspectives: future between facts and fiction

At present it is hardly possible, to reach a final conclusion on the role of SLIT for the treatment of allergic diseases. Variable study designs and inconsistent data are responsible for the persisting skepticisms in terms of SLIT [46]. Ongoing studies with better defined allergenic products, improved designs and larger patient groups might lead to a stronger scientific basis, thereby allowing future conclusions about SLIT with more confidence. At present, SLIT might be considered in adults with pollen allergies, particularly if SCIT is not an option (previous systemic side effects, not willing to accept the injections, no time for regular injections). With regard to house dust mite allergy, but also in asthmatic patients, medical doctors should be aware, that fewer data exist and that SCIT is more indicated due to its better scientific documentation compared to SLIT. The sublingual route, being an interesting option for children, should not be used routinely in this age group due to a lack of documented clinical efficacy. The future will tell how we can place SLIT in comparison to SCIT for the treatment of allergic individuals. Our conclusions should exclusively be based on solid scientific evidence and not on strategic marketing efforts which can hamper a critical and objective evaluation of novel therapies.

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Discussion

Bousquet: There are differences between Germany and France. First of all, our trains are much more reliable than yours and secondly, I do not drink beer. So I cannot see a glass half full or half empty. I am used to give immunotherapy pro and con-discussions not only for sublingual but also for subcutaneous immunotherapy. And frankly speaking, when someone is giving a lecture against subcutaneous immunotherapy it has exactly all your comments. So, do you do immunotherapy at all?

Kleine-Tebbe: Yes.

Bousquet: You should not, because when someone is saying something against immunotherapy he uses exactly the same data. Because when you say publication bias, there are not too many publications bias by the way, because all the studies I know have been published, whether or not they have been positive. When you say run-in period, I am strongly against any run-in period in immunotherapy. Well, we can discuss this later, but one year does not reflect the other. So, everytime you have a run-in period - and this is particularly true in the Khinchi study - the first year very high pollen counts, second year medium pollen counts, the third year it was not possible to analyze the patients because even those in the placebo group did not get symptoms. I think immunotherapy is effective within a day when it is given at a proper dose and I have published an editorial on that last year. I think that, frankly speaking, either you are against immunotherapy, or you are in favour of immunotherapy and the criticisms you gave are the same for both.

Fernández-Caldas: I would like to congratulate both speakers and the moderator on this enlightening session, but I think that both speakers are wrong. I want to explain that. I think that, maybe, we are comparing two completely different things. Can a

person, who has been on maintenance subcutaneous immunotherapy, be moved to maintenance sublingual therapy without any build-up phase? Or can somebody who has been on sublingual immunotherapy for a year get a shot of subcutaneous immunotherapy and nothing happens? Are both mechanisms the same? We have these questions, maybe we should not compare? Are the two mechanisms the same?

Kleine-Tebbe: From my point of view you cannot tell, and it is pretty unlikely.

Bousquet: Well, we will see.

Valenta: I have more or less the concern of a scientist who likes to watch immunological changes. I like things that I can measure. What amazes me is when I read that there are many thousands of patients treated by SLIT, but there is no change of antibody levels during this treatment. I am not aware of any study that shows a convincing change in skin prick reactivity which, Jean Bousquet knows best, is a parameter that shows that subcutaneous immunotherapy works. And this is all lacking for sublingual immunotherapy and I wonder why.

Bousquet: Well, in fact there are studies measuring antibodies and skin tests. The problem is that we still do not know how corticosteroids work, but no one in the room will say that they are not effective. I am a clinician, and sometimes I am also a scientist. When I see a patient my problem is not to decide the mechanism of the treatment, but is to decide which treatment is going to work or not. First of all, we need large clinical trials, to demonstrate that subcutaneous and sublingual immunotherapy work. And after that we will go to the mechanisms. I think we can agree on that.

Kleine-Tebbe: But I will ask for an appropriate design, we have discussed all these points. I think that is very important even if there were studies on subcutaneous immunotherapy which lack the same thing. I agree on that.

Bousquet: There is not a single one that does not lack the same thing.

Jacobsen: Can I ask both of you a general question? We have discussed here for several days whether it is actually possible at all to make this overview of different studies and compare them. Shouldn't we be careful? Do you not think it will be more beneficial that each of the products that are intended for use should individually show efficacy in clinical trials?

Bousquet: I told you before that I would like to open two bottles of champagne at the end of the year. Because there are two big studies which should answer all the questions. I would like to ask you to read the paper of Ronald Dahl. This study clearly shows on 95 patients that at least nasal symptoms are significantly improved. This is one of the best studies available today.

Dreborg: Is it not so that Ronald Dahl's study is with one preparation and as Lars Jacobsen said, every preparation should stand for itself. So you must document different ways of administration. Ronald Dahl used the tablets in sublingual low-dose

studies over six months or one year. They are not comparable to long-term studies with subcutaneous immunotherapy. You are not correct when you say they are the same as subcutaneous.

Bousquet: The problem is the same as for subcutaneous immunotherapy. I think we reviewed all the papers of subcutaneous as well and I have had a pro and con on subcutaneous immunotherapy in asthma three times this year. And exactly the same questions as we got here arose. But when you go to inhaled steroids, except for the studies performed after 1995, you do not get better results. And we all know that these products were very good. I think that we can always say that there are problems everywhere, but either you have a product which gives similar results in most studies. This is the case for sublingual immunotherapy and you say there is good reason to do a large double-blind placebo-controlled study, two of them are being done this year. Or there is no data at all and then the Cochrane analysis, which is a very good system in which only studies which can be compared are used, then we will have a definite proof, although perhaps not yet today. You can always say there is a problem, but you should see the glass of wine half full or half empty - not the glass of beer.

Kleine-Tebbe: A consensus conference of different German allergologists just offered a different point of view, saying that it might be okay to treat adult patients with SLIT, especially if they are not suitable for subcutaneous immunotherapy. But with perennial allergens and also for asthmatic patients I do not see any reason to switch from subcutaneous immunotherapy, because it had been repeatedly demonstrated that it is an effective procedure. And for children SLIT is not recommended at all in Germany by this new consensus conference, but only in clinical studies.

Bousquet: But I totally agree, that is what I said. I showed you rhinitis and conjunctivitis in children "NO" and in adults "YES" - so I do not see why we are arguing, because it is exactly what I have said.

Kleine-Tebbe: I would say there are subtle differences, e.g. with the perennials.

Jacobsen: Okay, gentlemen, gentlemen, I think that we stop the debate at this point for now. This is a debate that will go on for the next couple of years, because we do actually know that we will get much further information and knowledge about this kind of treatment in the coming years. And we look forward to that. Thank you to both of you.