

Certainties and doubts about sublingual and oral immunotherapy in children

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Purpose of review

Sublingual (SLIT) and oral immunotherapy (OIT) are two variants of immunotherapy that might be especially of interest for children. After adult studies, lately many trials in children are published. However, the quality of published material varies. In the present review we analyze paediatric SLIT publications from the past 2 years in the light of a new system of evaluation of quality of evidence, the grading of recommendations assessment, development and evaluation system.

Recent findings

High quality evidence in children: high-dose daily grass SLIT reduces symptoms and medication use; low-dose pollen SLIT reduces the development of new sensitizations. Low-dose SLIT reduces symptoms and medication in mild-moderate atopic dermatitis. Latex SLIT for 3 years results in a negative glove test. The evidence for the effectiveness of SLIT for seasonal and perennial asthma is still of moderate–low quality, as is the evidence for asthma prevention. Too high dose of mite SLIT seems ineffective for asthma. Oral allergen immunotherapy is promising for some food allergies. Some definite immunological changes are seen with SLIT; facilitated antibody presentation and IL-17 might correlate with efficacy.

Summary

Even after a hundred years of immunotherapy, it is still an ever changing field with SLIT and OIT making fast progress.

Keywords

allergens, children, desensitization, oral immunotherapy, sublingual immunotherapy

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Introduction

A growing number of studies on immunotherapy in children is being conducted lately, especially in the field of sublingual immunotherapy (SLIT) and oral immunotherapy (OIT), the latter mostly in the area of food allergy. There are some double-blind placebo-controlled (DBPC) trials, but most are randomized, controlled or open, observational trials. The quality of the studies varies and as such their strength of evidence, leaving open-space for discussion. Meta-analyses seemed to be the solution to get to more definite answers, but pitfalls can be detected [1•,2] and recently possible flaws in this kind of analysis have been discussed [3•], making the reader once again question previously drawn ‘evidence based’ conclusions on treatment usefulness.

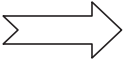
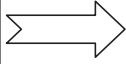
Lately, a new system has been proposed and is being applied for guideline development worldwide, in which clinical evidence is evaluated in a more complete way, not only based on the clinical trial design. In the present

article, we will assign quality of evidence to the trials, according to the grading of recommendations assessment, development and evaluation (GRADE) system [4•].

Certainties and doubts: grading of recommendations assessment, development and evaluation of quality of evidence

To comply with the title of this writing ‘certainties and doubts of immunotherapy in children’, the GRADE system [5] will be applied to classify the scientific evidence. The issues supported by high quality of evidence (Table 1) [6,7,8•] can be interpreted as ‘certainties’ and issues for which only moderate, low or very low quality studies could be found as support are still ‘doubts’ (see conclusion). This system has been chosen, because the author feels it is a more complete evaluation system that takes into account other factors apart from the study design to assign quality. Interestingly, in the GRADE evaluation process the opinion of the expert is crucial again.

Table 1 Assessment of clinical trials by the grading of recommendations assessment, development and evaluation approach: grading depends on study design and factors that can augment or decrease the quality of evidence

Study design	Add or subtract points depending on certain characteristics	Reduce quality if...	Augment quality if...	Calculate final quality of evidence	Quality of evidence
Randomized (4)		Study limitations* - 1 Serious - 2 Very serious Inconsistency - 1 Serious - 2 Very serious Indirectness	Large effect*** + 1 Large + 2 Very large Dose-response + 1 Evidence of a gradient		High (4)
Observational (2)		- 1 Serious - 2 Very serious Imprecision** - 1 Serious - 2 Very serious Publication bias - 1 Likely - 2 Very likely	All plausible confounding + 1 Would reduce a demonstrated effect, or + 1 Would suggest a spurious effect when results show no effect		Moderate (3)
					Low (2)
					Very low (1)

Improving the use of research evidence in guideline development. Adapted from reference [7,9[•]]. *Adequate sequence generation, allocation concealment, blinding, large percentage of drop-outs, early stopping. **Small sample size, rare events, large confidence intervals. ***Large effect, relative risk <0.5 or more than one standard deviation differences; very large effect, relative risk <0.2. Modified from [6].

Allergens and dosing

When analyzing all aspects of immunotherapy, apart from the quality of the studies, two more variables have to be taken into account: the allergen used and the dosing and application schedule. In two recently completed in-depth reviews on the dosing of subcutaneous (SCIT) and SLIT in children by the same author [8[•],9[•]] dosing and efficacy have been discussed thoroughly. In the present article, dosing of SLIT will be divided in low-dose versus intermediate-high dose on the basis of micrograms of major allergen that are administered monthly, relative to the recommended subcutaneous monthly dose. As in previous publications, SLIT with a monthly dose of less than five times the recommended SCIT monthly dose is called low-dose SLIT [10].

Literature search and included articles

A *PubMed* search was conducted using the keywords immunotherapy next allergen, hyposensiti*, child*, pediatri* to identify clinical trials published on immunotherapy in children. The time-limit from July 2007 to July 2009 was added. Although many more trials have been conducted on this subject, this article is mainly restricted to the most recent ones and only a few crucial trials from earlier dates will be included. All articles 2008–2009 were qualified, using the GRADE system (Table 2) [11–22]. The most interesting findings, as

judged by the author, will be discussed, including OIT and mechanisms of action of immunotherapy in paediatric trials.

Sublingual immunotherapy for rhinitis

SLIT for rhinitis has been investigated mainly for seasonal allergic rhinitis (SAR), with or without mild asthma. SLIT studies on perennial rhinitis are primarily those in which asthma is the primary inclusion criterion, with or without rhinitis.

Sublingual immunotherapy for rhinitis: pollen

Precoseasonal SLIT with daily high-dose grass pollen tablets is effective for SAR in children, as has been shown by two DBPC studies with high quality of evidence, of more than 200 patients each [12^{••},13^{••}]. Both studies showed a statistically significant reduction in symptoms and medication use during the pollen season, with an even higher effect during the peak pollen season. However, SLIT with twice a week high-dose grass drops continuously for 2 years is not effective, as was revealed by another DBPC high quality of evidence trial [23]. High-dose precoseasonal 3-grass SLIT thrice weekly for 10 months in adolescents and adults seemed not to be effective either in a DBPC multicentre study in France, but there were statistically significant differences between the active

Table 2 Quality of evidence of paediatric sublingual immunotherapy studies published in 2008–2009, according to the grading of recommendations assessment, development and evaluation approach

Author, year Some study details	Design (starting score)	Large effect	Confound* annulated	Dose-response gradient	TOTAL (+)	Limitations in design/execution	Inconsistency of results	Indirectness of evidence	Imprecision of results	Publ bias	Total (–)	Quality of evidence
Rhinitis studies												
Acquistapace <i>et al.</i> 2009 [11]; SAR/PAR; 90 SLIT, 81 control; 7–16 years; Low-dose SLIT daily for 2 years	OCT (2) Symptom reduction New asthma	Symptom reduction 50% x	x x	X X	+2 0	No blinding investigator, no blinding patient	x x	No diary data, point evaluation Asthma = reply 'yes' to wheezing question	x x	x x	–2 –2	Low Very low
Wahn <i>et al.</i> 2009 [12**] SAR (21% mild asthma); 131 SLIT, 135 placebo; 4–17 years; preseason, 25 µg group five grass tablet/day	New sensitizations DBPC (4)	6% vs. 36% $P < 0.001$ X	x x	x X	+1 0	SPT of study compared w/historical data x	x x		x x	x x	–2 0	Very low High
Tahamir <i>et al.</i> 2008 [14*] PAR, no asthma; 12–51 years; 97 SLIT, 96 SCIT; 3 years and observation 3 years; HDM; low-dose SLIT 3/week	Random two treatments (4) symptoms Long-term	x	x	X	0	No control group No blinding of patients nor investigators	x	x	x	x	–2	Low
Marogna <i>et al.</i> 2008 [15**] SAR and PAR (59% mild asthma); SLIT 130, placebo 66; 5–17 years; SLIT for 3 years; pollen or HDM; median-low dose, 3/week	RCT (4) Development persistent asthma RCT (4) New sensitizations	RR* mild persistent asthma 0.5; MCH positive 0.38 RR** new sensi- tizations 0.08	x x	X X	+1	No blinding of investigator; no blinding patients; symptoms baseline active group higher $P < 0.001$	x x	x	x	x	–2 –2	Low Moderate
Asthma												
Steinmach <i>et al.</i> 2009 [16*] Asthma mild-moderate persistent; SLIT 20, placebo 15; 6–17 years preseason for 2 years; 10 µg group five grass drops daily	DBPC (4)	+1	X	X	+1	40% drop-out in placebo group; symptoms/med adjusted for pollen count	x	x	No pollen count reported	x	–3	Low
Rodriguez-Santos 2008 [17] Asthma and/or rhinitis; SLIT HDM 69, placebo 69; 2–5 years; intermediate dose daily for 2 years	RCT (4)	RR** emergency visit 0.39; CS use 0.37	x	X	+1	No concealment of allocation, no blinding	x	x	No symptoms analyzed	No report other med	–3	Low
Safety												
Agostinis <i>et al.</i> 2008 [18] Safety, mono- pollen vs. multiple pollen SLIT; 179 single pollen SLIT, 254 multiple; 3–18 year, SLIT for 6–24 months; various manufacturers, dosing varied	Post-market (2)	X	x	X	0	No blinding of outcome	x	x	x	x	–1	Very low
Rodriguez Perez <i>et al.</i> 2008 [19*] Asthma and/or rhinitis; 8–25 years; low-dose daily SLIT, varying allergens	Observational (2)	x	x	X	0	No controls; evaluation not blinded	x	x	x	x	–1	Very low
Seidenberg <i>et al.</i> 2009 [20*] Rhinitis (58% mild-moderate asthma); high-dose daily coseasonal SLIT; build-up in 90 min, 4 months, 5–17 years; varying allergens	Observational (2)	x	x	X	0	28% did not finish study	x	x	x	x	–1	Very low
Other indications												
Bernardini <i>et al.</i> 2008 [21**] Latex allergy (w/oral allergy syndrome); SLIT 26, placebo 8, control 6	DBPC (4)	At end: no active pt reacts to glove test	x	Longer SLIT → better result	+3	x	x	x	Small placebo group	x	–1	High

(continued overleaf)

Table 2 (continued)

Author, year Some study details	Design (starting score)	Large effect	Confound* annulated	Dose-response gradient	TOTAL (+)	Limitations in design/execution	Inconsistency of results	Indirectness of evidence	Imprecision of results	Publ bias	Total (-)	Quality of evidence
Pajno <i>et al.</i> 2007 [22] Atopic dermatitis, 5–16 years; SLIT 23, placebo 23; SLIT low-dose 3/week, 18 months	DBPC (4)	x	x	+1	+1	x	x	x	Relatively small groups	x	-1	High

CS, corticosteroids; DBPC, double blind placebo controlled; HDM, house dust mite; MCH, metacholine challenge; MS, medication scores; OCT, open controlled trial; OR, odds ratio; PAR, perennial allergic rhinitis; pt, patient; RCT, randomized controlled trial; RR, relative risk; SAR, seasonal allergic rhinitis; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SPT, skin prick test.
* All plausible confounding may be working to reduce the demonstrated effect or increase the effect if no effect was observed.
** Large effect RR, <0.5; very large effect, RR<0.2. RR has been calculated from the data given in the articles.

and placebo group, reducing the quality of this trial to low [24].

Intermediate dose SLIT drops five times a week for tree pollen allergy is effective as a high quality DBPC dose-effect study confirmed [25].

An observational case–control trial of low-dose SLIT drops daily reported a large effect in symptoms and medication reduction (50 and 31%, respectively), but serious limitations in the design together with indirectness of the evidence make it a study with very low quality of evidence [11].

Sublingual immunotherapy for rhinitis: perennial allergens

The past 10 years, no high quality studies have been done with house dust mite (HDM) SLIT for perennial allergic rhinitis as main pathology in children. One low quality trial administered randomized HDM SLIT or SCIT to adolescents and adults (12–51 years) for 3 years and evaluated patients 3 years after discontinuation of nasal symptom score and skin prick test. The low-dose SLIT used in this trial three times a week resulted in a significant improvement in the symptom score at the end of the treatment period. However, no medication score could be evaluated, as the patients were only allowed to take antihistamines [14*].

Sublingual immunotherapy for asthma

The efficacy of SLIT in asthma has been documented in asthma trials, or as secondary outcome in rhinitis trials.

Sublingual immunotherapy for asthma and allergy to pollen

The evidence is of low quality for the efficacy of grass pollen tablet SLIT for seasonal asthma in children as only improvement in symptoms was shown whereas no statistically significant reduction in medication scores was seen. This was a rhinitis study, not designed to evaluate all aspects of asthma [13**].

Intermediate dose daily pollen drops (120IR=10 µg group five daily) in a coseasonal schedule on top of budesonida 400 µg daily during the pollen season improved symptoms, medication and forced expiratory volume in one second (FEV₁) significantly in the active group in comparison with placebo. However, this DBPC study was of low quality, because of the high drop-out rate in the placebo group (25 recruited, 15 finished). Also, symptom and medication scores were adjusted to 1000 pollen/m³, without any clear explanation in the

method section and the pollen count was not reported [16[•]].

Sublingual immunotherapy for asthma and allergy to perennial allergens

Ozdemir *et al.* [26] showed a strong reduction of the use of inhaled corticosteroids in children with HDM asthma with high-dose twice a week 3-year SLIT. The study design was observational, with an open control group and a high drop-out rate in the active group during the third year due to costs. Interestingly, large effect with a dose-response could be seen in the active group with regard to a year by year reduction of the corticosteroid dose in contrast to no reduction at all in the control group. As such the study is rated moderate quality.

The efficacy of HDM SLIT in children with asthma was investigated in another 3-year study. A major reduction in the number of asthmatic crisis was reported. Nevertheless, by the lack of a control group, the study has to be qualified as a very low quality study [27].

Pham-Thi [28] conducted a moderate quality DBPC study with daily high-dose SLIT tablets for 18 months in HDM asthmatic children. No improvement of symptoms, medication nor lung function test could be detected; a possible explanation might be that the dose used was too high.

Sublingual immunotherapy: long-term effects and prevention

One of the important issues in the comparison of SLIT with SCIT is the long-term effects. Although those of us, who use SLIT see long-term effects in our paediatric patients, clear scientific evidence is still lacking on this point.

Long-term efficacy after termination of treatment

In adults, high quality evidence is on the way of continued effect at 1 year after 3 years of high-dose daily grass tablet SLIT for SAR [29].

High quality evidence for long-term improvement from SLIT in children has been lacking until now. Three years after discontinuation of a 3-year treatment with HDM SLIT or SCIT for persistent allergic rhinitis, a nasal provocation test and symptoms were evaluated in 193 patients. The statistically significant improvement both groups had reached at the end of treatment was partly lost in the SLIT group, significantly different from the SCIT group in which the benefit persisted. A possible expla-

nation might be the low dosing, as low-dose SLIT was given just three times a week. Although elegant in design, this study had quite some major details that oblige the author to qualify it as low quality evidence [14[•]].

For asthma the long-term efficacy of SLIT was documented by Di Rienzo *et al.* [5] in an open controlled study, showing a large effect, but shortcomings in the design and presentation of results reduce the quality to very low.

Reduction of new sensitizations

A randomized controlled trial brought high quality evidence that new sensitizations are reduced with low-dose pollen or HDM SLIT three times a week for 3 years in children with SAR [15^{••}], as a large effect size was reported. However, a shortcoming in this trial is that pollen and HDM patients were analyzed together. Acquistapace [11] showed in an observational case-control trial with various allergens that low-dose daily SLIT drops might reduce new sensitizations. The quality of evidence is however low, as a skin prick test was only done during the observation period and compared with historical data, without stating if the same skin prick test extracts were used.

Development of asthma in children with rhinitis

Historically one study has been cited as the evidence that SLIT can prevent development of asthma in children with rhinitis [30]. Preseasonal SLIT for 3 years was shown by Novembre *et al.* [30] to reduce significantly asthma development in children with rhinitis. But the GRADE team found serious limitations in design and execution and qualified the study as low quality [4^{••}].

An observational case-control trial reported a large effect on symptoms and medication reduction (50 and 31%, respectively), but serious limitations in the design and indirectness of the evidence makes it a study with very low quality of evidence for the evaluation of the reduction of asthma development [11].

The best quality evidence (moderate) for a reduction of asthma development in children with SAR by 3 years of SLIT comes from the already cited Marogna study [15^{••}]. Although the design has some shortcomings, the very large effect size of SLIT reducing the development of the diagnosis of 'persistent asthma' and reducing the frequency of a positive metacholine challenge improves the quality of evidence of both these effects to 'moderate'.

Safety

Safety is a very important issue, especially in the treatment of children and in the treatment of normally non-fatal conditions, such as allergic rhinitis. As such, quite some safety analyses have been done for SLIT. As it is very hard to compare products of different companies with respect to potency [8[•]], earlier writings have not been able to find a relationship between SLIT dose and SLIT related adverse events. However, exact pronunciations can only be made comparing products from one and the same company with different doses. As such, two high quality safety studies in adults showed a clear dose-adverse event relationship [31,32]. Together with the efficacy dose-response analysis [33,34] these eventually led to the establishment of the ideal dose for the grass tablet in adults.

In a DBPC high quality safety analysis of the same grass tablet dose in children (5–12 years) 78% had local adverse events, 71% of them mild. Tongue pruritus, sore throat and swollen mouth were the most frequent adverse events, which resolved within 30 min in most patients. Two children dropped out because of adverse events, one with severe local and mild systemic symptoms and another one because of an asthmatic crisis [35]. These data are in line with the adverse events reported in the big paediatric grass tablet trials and in other studies cited in this article, in which about half of the patients have local oral events and some serious events do happen [19[•],35]. In a Mexican study of HDM SLIT drops 11 of 43 children presented systemic adverse events and two were treated with epinephrine [19[•]]. According to the manufacturer, however, the HDM dose was very low, stressing again the difficulty of comparing extract potency given by the manufacturers. There exists very low quality evidence from a postmarketing study that the rate of adverse events is the same in mono-pollen SLIT as in multipollen SLIT [18].

Ultra-short or no build-up phase, long-term study safety

A decade ago SLIT was typically given with a build-up phase of 30–60 days and generally lower doses were given than at present. Although some manufacturers have shown that ultra-short [10] or even no build-up can be well tolerated for grass tablet SLIT, in stable paediatric patients outside the pollen season [11,35], most still recommend a 15–30 days build-up phase for their product; the author's experience has made her in favour of such more conservative approach, especially in children. Adverse events are more frequent during the build-up phase or the first days after ultra-rush build-up, as very low [18], low [20[•]] and high quality studies have demonstrated [32]. Just as in adults, in moderate and high quality long-term studies, the adverse events were less frequent year by year [16[•]].

Sublingual immunotherapy for atopic dermatitis

One DBPC study was done in children with atopic dermatitis and HDM allergy [22]. SLIT resulted in a statistically significant improvement in scoring atopic dermatitis (SCORAD)-score and visual analogue scale assessments and in a reduction of drug-intake in the patients with mild-moderate atopic dermatitis (high quality evidence).

Sublingual immunotherapy for adverse reactions to hymenoptera venom

SLIT for adverse reactions to hymenoptera venom has not been studied in children till now.

Food allergy

Immunotherapy for food allergy has lately been studied in some centres worldwide, both via the oral and via the sublingual route.

In peanut allergy a landmark study in the 1990s showed peanut SCIT in adults gave too many systemic adverse reactions. Lately, moderate quality evidence comes from a group of US investigators who are showing very promising results with oral peanut immunotherapy in small children (1–9 years). After documenting the improved safety profile with this administration route [36^{••}], they went on to show clinical efficacy, 39 children were enrolled and 29 continued in the protocol after the initial dose escalation day at the clinic. Twenty-seven of these 29 treated children passed the oral peanut challenge at 4.7 months successfully [37^{••}]. Immunological changes were also investigated (see below).

The same group of investigators had also conducted a pilot study of egg OIT with the same schedule and reported good results of a double-blind oral egg challenge after 2 years in all of the seven children recruited [38].

The question always remains whether the protocols used cause desensitization or real tolerance. As of today there are no immunological markers for tolerance and only the evolution over the years will show the difference. In this context, a small pilot study of 21 milk allergic children investigated the outcome 5 years after discontinuation of a 6-month oral desensitization schedule [39^{••}]. Eighteen of 21 children reached complete or partial tolerance and after almost 5 years still 14 of 20 were partially or completely tolerant. At the same time skin prick tests and specific IgE were reduced in the tolerant children. However, the 'tolerance' was still accompanied by daily intake of dairy products. In one child who suspended milk for 1 month because of viral diarrhoea, urticaria and asthma developed on re-introduction of the previously tolerated 100 ml of milk, just as was described in another desensitized child as well [40].

There is a limited number of studies on SLIT for food allergy. Enrique *et al.* [41,42[•]] was the first to do a DBPC study with SLIT in patients with hazelnut allergy and to document improvement in an initial and follow-up communication. SLIT with prune extract augmented the quantity of prune tolerated in a DBPC food challenge after 6 months of SLIT treatment in a high quality study of 56 Spanish patients, randomized to SLIT with prune extract or placebo [43^{••}].

Immunological changes: in the search of biomarkers of efficacy

During immunotherapy many immunological changes have been reported, which suggest that immunotherapy induces early immune regulation with a rise in T regulator cytokines as IL-10 and transforming growth factor- β (TGF- β), and later on immune deviation from Th2 to a more Th1 pattern [44^{••},45]. This was also recently shown with peanut OIT in children [36^{••}]. However, it has been difficult to find molecular changes that predict success or failure of immunotherapy. In the sub-group of children with improved symptoms after 1 year of SLIT there were no changes in allergen-induced cytokine production by allergen-specific lymphocytes, nor did allergen specific immunoglobulin levels in plasma change [46]. In this paragraph we would like to mention only the few immunological changes that might be used as biomarkers of efficacy.

Functional assay of the activity of specific non-IgE antibodies, the facilitated allergen binding-assay

During immunotherapy a rise in specific serum IgG₄ has been documented by many investigators. The magnitude of the rise in specific IgG₄ is directly related to the degree of exposure, as it is highest in SCIT, less in high-dose SLIT and hardly detectable in low-dose SLIT [47,48]. However, IgG₄ changes correlate very poorly with immunotherapy outcome. It has been proposed that not so much the quantity, but more the functional quality of these immunotherapy induced non-IgE 'blocking antibodies' might be of importance, as can be tested with the IgE-facilitated allergen binding (FAB) assay [49]. Using this FAB assay in adults treated with a grass pollen tablet SLIT these IgE-blocking antibodies indeed were shown to account for around 40% of the observed treatment effect [50^{••}] and in children under the same treatment a very similar response was detected [51[•]].

During subcutaneous venom immunotherapy (VIT) in children and following 2 years of VIT withdrawal, the time course of serum inhibitory activity for IgE-facilitated antigen binding was investigated, again with the FAB assay. IgE-FAB was reduced after 2 years of VIT,

but not after withdrawal. In contrast with the results found in adult grass SLIT, the reduction in serum specific IgE, more than a reduction in IgE-facilitated antigen binding, was related to prolonged VIT efficacy [52^{••}].

In another paediatric study, OIT with peanut induced serum factors that inhibit IgE-peanut complex formation, as could be detected in an IgE-FAB assay. Yet, as 27 of the 29 children improved no sub-group analysis was done of responders and nonresponders [37^{••}].

IL-17 and IL-23

IL-17 and IL-23 are pro-inflammatory cytokines and a raise in their respective mRNA's during immunotherapy might be a marker of poor outcome or of progression of the allergic disease.

In one DBPC paediatric study [53^{••}], investigators looked for a relationship between immunological and clinical outcomes, after 2 years of SLIT with low-dose and high-dose of a tree pollen mix. Both, the symptom medication score (SMS) during the 2-year trial and asthma symptoms 5 years after discontinuation of the SLIT treatment were analyzed. During the study a positive correlation was found between high SMS and a raise in allergen induced IL-17A mRNA in peripheral blood mononuclear cells (PBMC). The Th17 subset of T helper cells and their IL-17 production have also previously been shown to be related to allergic inflammation [54] and recently a highly significant correlation between serum IL-17 and allergic rhinitis symptoms and drug use was found ($P=0.0001$ for both) [55[•]].

The presence of asthma symptoms 5 years after the completion of the SLIT study were also related to some immunological markers in the same paediatric study [53^{••}]. Here, only the children who did not present asthma 5 years later had had a progressive decrease in the allergen-induced IL-23p19 mRNA expression in the PBMC during their SLIT ($P=0.034$ after 1 year and $P=0.044$ after 2 years, Wilcoxon signed-rank test). On the contrast, an IL-23p19 mRNA expression rise during SLIT was related to later development of asthma symptoms, again with statistical significance.

Conclusion

Applying the GRADE approach to recent SLIT and OIT trials in the search for evidence for various aspects of immunotherapy efficacy and safety shines new light on the interpretation of studies (see Table 3). Not all DBPC studies deliver strong evidence; on the contrary some well designed and executed observational studies can give high quality support. It is mandatory to make this

Table 3 Certainties and doubts (see text for references to support the statements of outcome and quality of the evidence)

Allergic disease	Details	Outcome and quality of evidence for		Certainty?
		High/mid dose* 5–7 days/week	Low-dose or less frequent	
Seasonal allergic rhinitis	Reduction symptoms	Yes, ●●●● [12 ^{**} , 13 ^{**}]	No, ●●●● [23]	✓
	Reduction medication	Yes, ●●●● [12 ^{**} , 13 ^{**}]	No, ●●●● [23]	✓
	Long-term effect after treatment discontinuation	Yes, ●●●● [29]		
	Prevention of development of new sensitizations		Yes ^{**} , ●●●● [15 ^{**}]	✓
Perennial allergic rhinitis	Prevention of development of asthma		Yes ^{**} , ●●●○ [15 ^{**} , 29]	
	Reduction symptoms		Yes, ●●○○ [14 [*]]	
	Reduction medication			
	Long-term effect after treatment discontinuation		Yes, less than SCIT, ●●○○ [14 [*]]	
Seasonal asthma	Prevention of development of new sensitizations		Yes ^{**} , ●●●● [15 ^{**}]	✓
	Prevention of development of asthma		Yes ^{**} , ●●●○ [15 ^{**}]	
	Reduction of symptoms	Yes, ●●○○ [13 ^{**} , 16 [*]]		
	Reduction of medication	Yes, ●●○○ [16 [*]]		
Perennial asthma	Long-term effect after treatment discontinuation			
	Reduction of symptoms	No, ●●●○ [28]		
	Reduction of medication	No, ●●●○ [28]	Yes, ●●●○ [26]	
	Long-term effect after treatment discontinuation		Yes, ●○○○ [5]	
Atopic dermatitis	Mild-moderate: reduced SCORAD, VAS and medication		Yes, ●●●● [22]	✓
	Severe: reduced SCORAD, VAS and medication		No, ●●●● [22]	✓
Latex allergy		Yes, ●●●● [21 ^{**}]		✓
Hazelnut allergy (SLIT)	Tolerate limited daily hazelnut intake	Yes, ●●●○ [41]		
Prune allergy (SLIT)	Tolerate limited daily prune intake	Yes, ●●●● [42 [*]]		✓
Peanut allergy (OIT)	Tolerate limited daily peanut intake	Yes, ●●●○ [36 ^{**}]		
Milk allergy (OIT)	Tolerate limited daily milk intake;	Yes, ●●●○ [38]		
	Long-term tolerance	No, ●○○○ [39 ^{**}]		

OIT, oral immunotherapy; SCORAD, scoring atopic dermatitis; SLIT, sublingual immunotherapy; VAS, visual analogue scale to measure atopic dermatitis symptoms.

* High/mid dose = the SLIT dose, expressed in micrograms of major allergen a month, is more than five times the monthly recommended dose for SCIT (=10 µg Der p 1/2, 15 µg Phl p 5, 15 µg Fel d 1, all others 10 µg).

** As both, perennial and seasonal allergens SLIT was tested, and no sub-group analysis was reported in the Marogna 2008 study, it is not clear whether asthma was prevented with SAR or with PAR or with both. This reduces quality.

kind of analysis with all published articles on SLIT and extend the research to articles on SCIT in children and adults. Analysis in this article was performed by just one person, which may be questionable and can be improved augmenting the number of reviewers.

In the field of oral desensitization, excellent improvement is being made with clinical application of the findings coming closer every day.

Finally, the guideline for the future direction of immunotherapy ultimately will have to come from the investigators of the mechanistic studies who are moving fast forward in showing us biological markers for immunotherapy efficacy that ultimately will lead to improvement in evaluation of efficacy and safety of immunotherapy.

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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. 000–000).

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