

Letter to the Editor

Sublingual immunotherapy in children: more optimism today

Dear Editor,

Following our recent reviews (1, 2) we read with interest your just published systematic review of immunotherapy in children and adolescents with allergic rhinoconjunctivitis (3). We were surprised by the authors' negative conclusion concerning sublingual immunotherapy (SLIT) in the paediatric age group. The review is well structured and the quality of the studies was assessed with acceptable tools (Delphi list), as well as inter-reviewers' variability (Cohen's κ). Even so we would like to make the following remarks (see Table 1).

1. Dose: The most recent SLIT studies in adults (4, 5) and children (6) demonstrate a clear dose-response relationship. In half of the studies reviewed by Röder very low doses were used and not surprisingly there was poor efficacy.

2. Dosing frequency: Daily dosing tends to be more effective than dosing with lower frequency (4, 5, 7). Only in two of the reported studies doses were given daily.
3. Pre-seasonal dosing: Commencing SLIT at least 4 months before the start of the pollen season augments its efficacy (8). This was not the case in three of the seven seasonal studies cited.
4. Patient selection, asthma: Two of the studies focused on asthma and in these studies symptoms of rhinitis were secondary (or exploratory) endpoints, with likely insufficient power to detect a difference if one existed.
5. Duration of treatment: 4/11 studies had interrupted treatment. In the latest Cochrane review on SLIT the best effect was seen in studies with at least 1 yr of continuous treatment.

Table 1. Details of studies included in the systematic review by Röder et al.(3)

Study outcome	Q	Author (yr)*	N SLIT/pl	Allergen	Relative dose/month	Duration	Doses/wk	Start of SLIT preseason (months)	Remarks
Pos		L La Rose (1999)	16/17	Parietaria	273	24 month	3	0–2	
Neg		H Vourdas (1998)	34/32	Olive	100	6 month/yr × 2 yr	7	4	Polisensitized patients included. Significance increase symptoms during pollen season placebo group, not in SLIT.
Neg		H Bufer (2004)	63/63	Grass	38	12 month	7	5	Clinical index = symptoms and medication score, improved only in severe AR group after 3 yr SLIT.
Pos		L Yuksel (1999)	10/10	Grass	21	12 month	2	0	
Neg		H Bahceciler (2001)	8/7	HDM	20	6 month/yr × 2 yr	2		Asthma study
Neg		H Hirsch (1997)	12/10	HDM	5	12 month	3		
Neg		H Pajno (2003)	14/13	Parietaria	4	13 month	3	6	Asthma, fluticasone, Nose Sx SLIT vs. placebo: 0.059
Pos		L Tari (1990)	30/28	HDM	1.5	18 month	3		History of AR: maximum 1 previous season
Pos		H Novembre (2004)	54/59	Grass	1	4 month/yr × 3 yr	5	0–1	Asthma study
Insuf. data		H Ippoliti (2003)	18/15	HDM	1	6 month/yr × 2 yr	3		
Neg		L Rolinck-Werninghaus (2004)	49/48	Grass	0.6	32 month	3	4	

Relative dose/month, dose in microgram given in SLIT treatment per month, relative to the monthly recommended maintenance dose in SCIT; AR, allergic rhinitis; SLIT, sublingual immunotherapy; Pos/neg, study showing/not showing statistically significant effect of SLIT on rhinitis/rhinoconjunctivitis; HDM, house dust mite. Q, quality of the study, as determined by the Delphi list; N, patients with allergic rhinitis in SLIT group and in placebo group.

*See references in original article (Röder et al., 2008).

6. Patient selection, polysensitization: In the study done by Voudras et al. polysensitized children were included. In the SLIT group 30/34 were polysensitized and 23 of them to grass. The olive pollen season starts in may, showing important overlap with the grass pollen season that starts just 1 month earlier in Greece. Of the placebo patients, only 15/32 were sensitized to grass. Taking a closer look at the figures on symptom scores, it becomes clear that during the first year the SLIT group showed higher symptoms than the placebo group, while during the second year this relationship was reversed with more symptoms in the placebo-group. Although statistics did not show difference between groups, with these reservations, a beneficial treatment effect seems likely.
7. Number of patients with allergic rhinitis included: Almost half the studies were underpowered, with < 20 allergic rhinitis subjects in the actively treated groups.
8. Possible confounding by drug effects: In one study, all patients received maintenance inhaled fluticasone during the pollen season, in addition to SLIT/placebo, which may have resulted in marked improvement in both SLIT and placebo-groups thereby reducing inter-group differences for symptoms. ($p = 0.059$ for nasal symptoms).

Whereas the authors reasonably question the efficacy of SLIT in rhinoconjunctivitis in children on the evidence reviewed, there are major limitations to their conclusions and the evidence base has moved on since 2006, the end date of the review. A consistent more recent finding, confirmed in two independent studies in adults and one in children has been the dose-dependency of SLIT for achieving efficacy (4–6).

Röder et al. state that a strong level of evidence for a certain recommendation can be reached when at least two high-quality randomized controlled trials show consistent findings. Review of studies in children published since June 2006 till May 2008 provides the real 'at present' state of the art. One randomized, double-blind, placebo-controlled dose-response SLIT trial in children (6) (Delphi-list score of 10/11) in tree pollen-allergic children confirmed a dose-response, with statistically significant improvement in symptom and medication scores. A second high-quality SLIT study in children (9) confirmed efficacy to be comparative to that found in adults and the results of a third presented in June 2008 also show statistically

significant improvement (10). These studies confirm efficacy in both adults and children. However, still more information on clinical effect size and comparative studies with other medications for allergic rhinitis are needed. Critically, before firm recommendations for routine use can be made, we need to know whether long-term benefits with SLIT can be achieved as for the subcutaneous route. None the less, we believe that the current position for the value of SLIT for paediatric allergy suffers is far more cheerful than that depicted by Röder and colleagues.

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