Grading local side effects of sublingual immunotherapy for respiratory allergy: Speaking the same language

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Sublingual immunotherapy (SLIT) is increasingly used worldwide. Despite its safety being well ascertained, there is no universally accepted system to grade and classify its adverse events (AEs). According to the literature, it seems reasonable to classify and grade systemic side effects by using the previously published World Allergy Organization recommendations. On the other hand, local side effects are the most frequent with SLIT, sometimes leading to its discontinuation. Therefore grading of the severity of local side effects was perceived as necessary for the purpose of uniform reporting, classification, and quantification of this aspect. A World Allergy Organization Taskforce, after examining the available literature and the postmarketing surveillance data, proposed a clinically based grading of the severity of local AEs caused by SLIT. The use of the Medical Dictionary for Regulatory Activities nomenclature for AEs was also included in this context. The proposed grading system for SLIT-induced local reactions is expected to improve and harmonize surveillance and reporting of the safety of SLIT. (J Allergy Clin Immunol 2013;132:93-8.)

Key words: *Sublingual immunotherapy, safety, local side effects, grading*

Sublingual immunotherapy (SLIT) was first described in a double-blind randomized trial in 1986,[1] with the primary rationale of making immunotherapy safer and more convenient for the patient based on the observation that severe and even fatal adverse events (AEs) can occur with subcutaneous immunotherapy (SCIT).[2] SLIT has gradually been accepted in clinical practice as a viable alternative to SCIT,[3,4] especially in Europe, Latin America, and other parts of the world. It is not US Food and Drug Administration approved for use in the United States.[5]

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Abbreviations used
AE: Adverse event
MedDRA: Medical Dictionary for Regulatory Activities
RCT: Randomized controlled trial
SCIT: Subcutaneous immunotherapy
SLIT: Sublingual immunotherapy
WAO: World Allergy Organization

There are more than 60 randomized double-blind, placebo-controlled trials, several systematic reviews of such trials,[6-13] and a World Allergy Organization (WAO) position paper[14] about SLIT. The safety profile of SLIT is superior to that of SCIT[15]; no fatalities have been reported, and severe systemic reactions are rare. The rate of AEs after SLIT is variable in the reported studies, but local AEs are predominant. More importantly, the report and description of such reactions are less than ideal, making it difficult to compare adverse reactions among studies, to identify risk factors, and to recommend appropriate action to take when a reaction occurs. Therefore a uniform grading system of AEs associated with SLIT, especially of local reactions, is necessary. This is appropriate because the WAO and other regional organizations recently approved a grading system for systemic adverse reactions to SCIT.[16] The main advantages of using a widely agreed upon grading system in SLIT are (1) uniformity in reporting and comparing the safety of extracts, doses, and regimens; (2) improved epidemiologic knowledge on the safety of SLIT; (3) increased value of the postmarketing surveillance studies; (4) the possibility of identifying risk factors for AEs; and (5) provision of guidelines to doctors and patients on how to respond to a particular AE (ie, to continue, adjust, or stop treatment).

This document was based on randomized double-blind, placebo-controlled trials published in English and mentioned in the WAO position paper,[14] studies with the same characteristics, postmarketing surveys, and case reports published up to December 2011.

ADVERSE REACTIONS ASSOCIATED WITH SLIT

To date, the safety profile of SLIT has been overall favorable. Systemic side effects (rhinitis, asthma, urticaria, angioedema, and hypotension) make up a minority of the adverse reactions because local reactions (oropharyngeal or gastrointestinal) are most frequently reported. Table I reports local AEs, as described in the literature, plus their coding according to the Medical Dictionary for Regulatory Activities (MedDRA)[17] for reporting AEs. In this system AEs are hierarchically classified in 5 levels of detail, starting from the more general (system organ class) to the more specific (lowest level term). Each level better details the AEs and terminology of the previous levels. For example, Table I shows the 2 more detailed classification levels with the associated codes.

The current knowledge of adverse reactions caused by SLIT is based on randomized controlled trials (RCTs), postmarketing surveys, and case reports.

Randomized controlled studies

The safety of SLIT in RCTs is reviewed in the 2009 WAO position paper[14] and in other reviews.[15,18,19] André et al[18] examined 8 trials performed with vaccines from a single manufacturer involving 690 subjects (347 receiving active treatment plus 343 receiving placebo), of whom 218 were children aged 5 to 16 years (103 receiving active treatment plus 115 receiving placebo). Systemic reactions were mild, and the incidence did not differ in the active versus placebo groups. The oral and gastrointestinal side effects were more frequent with SLIT, with a similar rate in adults and children. Another review[15] examined the safety of SLIT in the studies available up to October 2005. There were 1,047 adverse reactions from a total of 386,149 doses, which is 2.7 per 1,000 doses in 41 studies with sufficient information to analyze. The occurrence of severe reactions was 0.096 per 1,000 doses in studies that specified the severity of the reactions. Overall, 14 serious AEs were considered most likely treatment related (0.033/1,000 doses). In another review the occurrence of AEs was evaluated according to the SLIT dose, which was expressed as the ratio of SLIT and the equivalent SCIT.[19] This review concluded that oral side effects were more frequent with low doses of allergen (<50 times the corresponding SCIT dose) than with higher doses. On the contrary, gastrointestinal complaints (nausea, upper abdominal pain, and vomiting) occurred more frequently with higher doses. However, this study is of limited value because the dichotomous distinction between high and low doses is totally arbitrary and has no experimental basis. More detailed information on local side effects has been reported in recent large trials (>200 patients) performed with grass extracts (Table II).[20-27] The overall occurrence of systemic side effects is similar between the placebo and active groups in most studies. Oral side effects are quite frequent and invariably occur in more than 50% of patients receiving active SLIT, but their duration generally does not exceed 10 days, and discontinuation because of side effects is almost always less than 5%. Also, serious AEs reported in these trials are rare and usually not related to treatment. Of note, the occurrence and severity of AEs gradually decrease in the subsequent years of treatment, as reported in some follow-up assessment of previous trials.[28-30]

Postmarketing surveys and case reports

There are numerous SLIT postmarketing surveys[31-40] for both adult and pediatric subjects, some involving children younger than 5 years. These surveys are summarized in Table III, and show that the overall occurrence of AEs is lower in postmarketing surveys than in RCTs; this holds true especially for local AEs. This is probably the result of many events being judged as minimal by patients and not being reported.[32,35,40] Where a more rigorous recording methodology is used (as happens in RCTs), the occurrence of AEs in patients approximates 50%. The majority of AEs in postmarketing studies are reported as oral, mild, and self-limiting, and the rate is less than 10 per 1,000 doses.

There have been, until December 2011, 6 case reports[41-45] of SLIT-induced systemic reactions that have been of a severity to be categorized as anaphylaxis.[46] Five occurred with standardized extracts and 1 with a mixture of 4 standardized and 2 nonstandardized extracts. One case was associated with the inadvertent administration of an overdose. An additional case of severe asthma after SLIT has been described.[47] Numbers were too small to permit firm conclusions with regard to risk factors for severe systemic reactions. Five of 6 patients were female, all were adolescents or young adults, 5 of 6 had a history of asthma, and 2 had a previous history of severe reactions to SCIT.

One potential approach as a result of these reports is to consider administering the first dose or doses of SLIT under medical