www.medscape.com

Safety and Tolerability of Sublingual Immunotherapy in Clinical Trials and Real Life

Gianenrico Senna, Marco Caminati, Giorgio Walter Canonica

Curr Opin Allergy Clin Immunol. 2013;13(6):656-662.

Abstract and Introduction

Abstract

Purpose of review Sublingual immunotherapy (SLIT) is effective in allergic rhinitis and asthma. Apart from its efficacy, safety is crucial as this treatment is usually self-administered at home. Tolerability also plays a pivotal role, as mild local reactions, although not life-threatening, may represent a risk for treatment withdrawal and can therefore negatively affect clinical outcomes. The present study addresses this issue by reviewing double-blind, placebo-controlled, randomized trials and real-life studies.

Recent findings The number of life-threatening SLIT-related reactions is negligible. SLIT-related adverse events are not always consistently reported nor uniformly classified in published studies. However, systemic reactions are rare and side effects mostly consist of mild, self-limiting local reactions. No treatment-related risk factors for adverse events have been clearly defined, as far as type of allergen, dose or schedule.

Summary SLIT provides an optimal safety profile both in children and in adults. Apart from life-threatening reactions, the lack of standardization of adverse events reporting may account for the wide variability of the prevalence of side effects in clinical trials and in real-life setting. It can lead to a possible underestimation of adverse events, concerning, in particular, local reactions. Since poor tolerability may affect adherence and cause treatment discontinuation, adopting shared strategies in order to recognize, grade and manage adverse events is mandatory.

Introduction

Allergen-specific immunotherapy (SIT) has been used for over a century. It is the only causal treatment currently available for allergic respiratory disease. However, the risk of systemic side effects has been the main drawback of subcutaneous immunotherapy (SCIT) and has led to the development of new routes of allergen administration. More recently, nasal and oral immunotherapies had been proposed, but dismissed as possible options, firstly because nasal effects were bothersome, and secondly for lack of efficacy. Sublingual immunotherapy (SLIT) has been found to be effective in allergic rhinitis and asthma,[1,2] and its use is growing in Europe as well as in United States, even without US Food and Drug Administration (FDA) official approval.[3] Apart from its efficacy, safety of SLIT is a crucial parameter as this treatment is usually self-administered at home. In this study, we address this issue by reviewing the double-blind, placebo-controlled, randomized clinical trials (DB-PC-RCTs), as well as postmarketing surveillances published up to now. Moreover, we also investigate the tolerability of SLIT, as mild reactions, although local and not life-threatening, may represent a risk for treatment withdrawal and therefore can negatively affect clinical outcomes.

Safety in Clinical Trials

The definition of safety refers to SLIT-related reactions that occur far from the site of administration and include both life-threatening and nonlife-threatening systemic adverse events.[4] Looking at DB-PC-RCTs for allergic asthma, allergic rhinitis or allergic rhino-conjunctivitis published up to 30 June 2013, SLIT appears to provide an optimal safety profile.[1,5–11] Epinephrine has been used in three trials, in the context of reactions that have not always been considered SLIT-related by the investigators. In total, six patients received epinephrine.[9,12,13] Of note, there were two patients in the placebo group: one patient administered self-injectable epinephrine after a nontreatment-related anxiety attack and was discontinued from the trial.[13] The second one was given epinephrine at the investigational site because of wheezing, probably related to previous exposure to a grassy field according to the investigators.[12] The other four individuals were in the active group. Two of them presented with non-SLIT-related systemic reactions. In one case, an inappropriate epinephrine administration occurred in the emergency department where the patient was later diagnosed with viral pharyngitis.[12] The second was a case of food-induced allergic reaction in a patient with a known history of food hypersensitivity. He continued in the trial.[9] Only the remaining two patients experienced SLIT-related nonlife-threatening systemic adverse events in two different trials.[12,13] In both cases, no hypotension, respiratory distress, wheezing and vital sign alteration were reported. Both patients were discontinued from the trials, but it can be argued that epinephrine administration by the investigators was perhaps not appropriate. In conclusion, no episodes of certain anaphylaxis, life-threatening reactions or death were reported in any treated patient across the reviewed studies.

Nonlife-threatening systemic adverse events account for a minority of SLIT-related side effects. According to the World Allergy

Organization (WAO) subcutaneous immunotherapy systemic reaction grading system,[4] asthma, urticaria, angioedema, rhinitis and ocular symptoms should be classified as systemic adverse events. As the administration of any allergen, irrespective of the administration route, can lead to systemic reactions, the WAO statement mentioned above can also be applied to SLIT.

International recommendations for SLIT clinical trials include evaluation of both local and systemic reactions as a secondary outcome.[14,15] Nevertheless, data concerning safety are not always consistently reported nor extensively discussed in published studies. A clear grading system of severity is not systematically provided. In addition, adverse events are not uniformly classified as local or systemic reactions. This mainly concerns gastrointestinal manifestations. According to the Medical Dictionary for Regulatory Activities (MedDRA),[16] they should be rated as local adverse events unless they occur together with other systemic manifestations, as remarked by the recently published WAO statement on grading local side effects of SLIT.[17] Nevertheless, some clinical trials, a recent systematic review and many postmarketing surveys report symptoms involving upper and lower gastrointestinal tract as systemic adverse events.[1,18–22] It is, therefore, quite difficult to deeply analyze the data concerning safety. However, in the evaluation of adverse events due to SLIT we referred to the aforementioned WAO statements about systemic and local reactions. We considered cough as a systemic effect, as it was not included in the previous documents.

Data on the exact number of patients experiencing systemic adverse events and on the severity of reactions are more or less clearly reported in approximately 70% of the DB-PC-RCTs published up to 30 June 2013.[1,5–11] On the basis of available information, the prevalence of systemic adverse events (overall number of patients who reported systemic adverse events) is 19.31% (SD 22.92), which is consistent with previous estimations.[2,23] Severe reactions are rated between 1 and 2% of total reported events, but most of them are unspecified. It is worth pointing out that the overall occurrence of systemic adverse events does not significantly differ between active (18.05%, SD 21.96) and placebo (21.21%, SD 24.44) group (P = 0.48). The lack of standardization of adverse event reporting may account for the wide variability of the prevalence of adverse events in the reviewed trials. The small sample size and the heterogeneity of allergen extracts and treatment schedules in many of the published trials do not allow further considerations on the potential relationship between type of allergen, dose and systemic adverse events. No patient-related risk factors for systemic reactions have been clearly defined, even if uncontrolled asthma, oral lesions or infections and previous severe SCIT-related adverse events can be considered specific risk factors.[23,24] In general, cardiovascular disease and long-term therapy with noncardio-selective beta-blockers may represent a nonspecific risk factor,[23] even if they are not usually considered as an absolute contra-indication to SLIT treatment.

Tolerability in Clinical Trials

The definition of tolerability refers to local adverse events, which account for the majority of SLIT-related reactions.[25] The WAO statement on grading local side effects of SLIT,[17] according to MedDRA,[16] provides an extensive list of adverse events that should be classified as local. It includes signs and symptoms involving the oropharyngeal tract, ear, and upper and lower gastrointestinal tract. On the basis of data reported in reviewed DB-PC-RCTs,[1,5–11] the prevalence of local adverse events (overall number of patients who reported local adverse events) is 22.79% (SD 22.34). The grading is often unspecified. Differently from systemic reactions, the overall occurrence of local adverse events significantly differs between active (28.56%, SD 24.38) and placebo group (15.24%, SD 16.82) (P = 0.002). In some cases, however, it was not possible to estimate or calculate the exact number of patients experiencing these kinds of side effects. Moreover, local adverse events are not always considered in the safety analysis, or they are not properly discussed, since most of the reviewed trials are not specifically designed to evaluate treatment tolerability. This may account for the wide variability of the prevalence of adverse events in the reviewed trials and, of note, it can lead to a possible underestimation. It should be noted that local reactions do not imply alterations of objective parameters, such as changes in forced expiratory volume in 1 second or in blood pressure, so that their identification and the grading of their severity may be quite difficult.

Local adverse events generally arise within the first doses of treatment with a rapid onset, they are self-limiting and resolve without pharmacological intervention as treatment is continued.[2] A dose–response relationship is still controversial, given the small number of available data together with the wide variability of extracts administered.[1,26,27] Local adverse events seem to be independent of treatment schedule and type of allergen.[23] Previous severe local reactions to SLIT and SCIT, oral infections or lesions may represent potential patient-related risk factors for local adverse events. Suboptimal administration procedures (use of nonstandardized extracts, mixtures of many allergens, over-dosing) may also increase the risk of local adverse events.[23,28]

The Real-life Setting

The safety and tolerability of SLIT in daily practice was evaluated in several postmarketing surveys published up to 30 June 2013[18–22,29–34] ( ). Overall, a population of 1795 patients, mostly children, was assessed. In fact 7 out of the 11 surveys considered only a pediatric population,[18,20,21,29–31,34] and in two surveys children below 5 years were included.[29,30] A total of 72 systemic reactions and 291 local reactions were registered. However, if we focus only on the use of epinephrine as a

marker of life-threatening reactions, this was utilized only in two cases (0.1%). Most of the systemic reactions reported were mild and resolved spontaneously without treatment. On the contrary, a higher number of local reactions were registered. Most of them were limited to the oral mucosa (itching of the mouth or the tongue, swelling of lips), but several cases of abdominal pain were also reported. According to two well designed studies,[19,21] polysensitization is not a risk factor for higher frequency of systemic or local reactions in children as well as in adults. Moreover, local or systemic side effects were not significantly linked to a particular allergen. Of note, the lack of uniform classification and grading systems affects adverse events reporting in real-life studies, as in clinical trials; therefore no stringent conclusions can be derived. However, these data, collected in a real-life setting, suggest that SLIT can be safely self-administered at home in both adults and children. Apart from these surveys, we have to remember that millions of doses have been and are being administered every day all over the world. It is, therefore, noteworthy that looking at the reports published up to 30 June 2013, merely 12 cases of anaphylaxis due to SLIT have been observed[33,35–41] ( ). However, in seven of these reports, epinephrine was used,[33,38–41] whereas in the remaining it was not required or its use was not mentioned. Furthermore, no serum tryptase level measurements have been performed in any of these cases. Even if according to published available data the diagnosis of anaphylaxis is not always certain, the reported cases give us some advice. In fact, an over-dosage of allergen, the use of non standardized extracts such as latex or multiple allergen extracts could partially account for these reactions. Moreover, it is also interesting that SLIT tablet-induced anaphylaxis was reported in patients with previous systemic reactions to SCIT. Therefore, on clinical grounds, switching from SCIT to SLIT in patients with systemic reactions to SCIT is not advisable. Furthermore, the use of only standardized extracts is recommended in daily practice.

Table 1. Summary of adverse events reported in postmarketing surveys

Reference	Study population	Number of patients	Follow-up (months)	Local reactions	Systemic reactions	Use of epinephrine
Di Rienzo *et al.*, 1999 [18]	Pediatric	268	3–84	1	7	0
Lombardi *et al.*, 2001 [19]	Adult	198	36	6	11	0
Pajno *et al.*, 2003 [20]	Pediatric	354	37	15	19	0
Drachenberg *et al.*, 2004 [22]	Adult and pediatric	43	12	8	4	0
Agostinis *et al.*, 2005 [29]	Pediatric	36	12–36	2	0	0
Di Rienzo *et al.*, 2005 [30]	Pediatric	126	24	9	0	0
Fiocchi *et al.*, 2005 [21]	Pediatric	65	12	7	6	0
Agostinis *et al.*, 2008 [31]	Pediatric	433	6–24	161	17	0
Lombardi *et al.*, 2008 [32]	Adult	159	12	76	20	0
Rodriguez-Perez *et al.*, 2008 [33]	Adult and pediatric	43	12	21	7	2
De Castro *et al.*, 2013 [34]	Pediatric	70	12	6	2	0

Table 2. Summary of published cases of SLIT-related systemic reactions described as anaphylaxis

Reference	Patient sex (age)	Allergen (manufacturer if stated)	Phase	Onset timing	Clinical presentation	Use of epinephrine
Antico *et al.*, 2006 [35]	F (36)	Latex	End of rush build-up	10 min	Asthma, generalized urticaria	Not specified
Dunsky *et al.*, 2006 [36]	F (31)	Alternaria, cat, dog, grass ragweed (Greer)	2nd day of up-dosing	5 min	Angioedema, dizziness, dyspnea, generalized itching	No
Eifan *et al.*,	F (11)	HDM, grass pollen	Maintenance	3 min	Abdominal pain, chest pain, fever,	Not specified

2008 [37]		mix (Stallergenes)			nausea	
Blazowski, 2008 [38]	F (16)	HDM (Stallergenes)	Maintenance (overdose)	10 min	Hypotension collapse, flushing, urticaria	Yes
Rodriguez-Perez *et al.*, 2008 [33]	F (27)	HDM, *Periplanetaamericana,* mold mix	Maintenance	20 min	Wheezing, dyspnea, anxiety, flushing, dizziness	Yes
	F (7)	HDM, pecar tree	Maintenance	30 min	Wheezing, dyspnea, anxiety, flushing, dizziness	Yes
	M (11)	HDM	Maintenance	20 min	Urticaria, angioedema, dyspnea, wheezing	No
De Groot and Bijl, 2009 [39]	M (13)	Grass (Grazax, ALK-Abellò)	First dose	15 min	Generalized urticaria, swelling of tongue	No
	F (27)	Grass (Grazax, ALK-Abellò)	First dose	5 min	Abdominal cramps, asthma, generalized itching, hypotension	Yes
Buyukozturk *et al.*, 2010 [40]	Adult patient	Latex	2nd day of up-dosing	Not stated	Flushing, itching, rhinitis, conjunctivitis, wheezing, dyspnea, chest tightness, hypotension	Yes
	Adult patient	Latex	3rd day of up-dosing	Not stated	Flushing, itching, rhinitis, conjunctivitis, wheezing, dyspnea, chest tightness, hypotension	Yes
Vovolis *et al.*, 2012 [41]	F (35)	HDM, *Olea europea* (HAL)	Maintenance (repeated episodes)	10 min	Flushing, hoarseness, dyspnea, dizziness, mild hypotension	Yes

HDM, house dust mites.

Safety and Tolerability: Practical Implications

According to the published data from controlled trials as well as real-life experience, SLIT can be safely self-administered at home in adults as well as in children. In fact, the number of life-threatening reactions is negligible, compared with the number of administrations performed in the world every day. As a consequence, the use of SLIT is currently widespread and it has led to a great availability of different commercial extracts, administered with different formulations and schedules.[1,42] Even if the overall safety of SLIT is well accepted and proved, it has to be outlined that safety as well as efficacy has to be demonstrated for the single extract of each brand.[43]

A higher prevalence of adverse events was observed in controlled trials in comparison with postmarketing surveillances, in which, mild and not risky reactions may be under-reported. Conversely, severe systemic adverse events are generally reported both in controlled and retrospective studies. Moreover, the wide range of the frequency of adverse events described in the controlled studies as well as in postmarketing surveillances may be related to the different and not regular assessment methodology. As postmarketing surveillances include a lower number of patients compared with clinical trials in the present scenario, further real-life studies are needed.

As far as local adverse events are concerned, the evaluation of SLIT tolerability can be regarded as an unmet need, because of its great impact on clinical outcomes.[2,44–46] Actually, tolerability does not threaten either the patient's safety or his health. This provides a possible explanation for the lack of information on local reactions in DB-PC-RCTs and it can lead to an underestimation both in clinical trials and in real-life setting. It should be noted that the extensive patient assessment and the regular follow-up in RCTs may increase adherence to treatment despite slight tolerability concerns.[44,46,47] In daily clinical practice, time for clinical evaluation and education of patients is often short and a regular follow-up may be difficult for many reasons. In this setting, severity, persistence or simply poor awareness of local reactions may even increase the risk of treatment discontinuation, despite its efficacy. An analysis of drop-outs in DB-PC-RCTs for allergic asthma, allergic rhinitis or allergic rhino-conjunctivitis published up to 30 June 2013[1,5–11] confirms that adverse events play a pivotal role in causing patient withdrawal. The reviewed trials comprise 10 903 patients, 4590 allocated to a placebo arm and 6313 allocated to active treatment arms. For each study, the drop-out percentage was calculated. The overall drop-out rate was quite low (13.05%, SD 12.20), and it did not significantly differ between active (12.38%, SD 11.00) and placebo groups (13.73%, SD 13.35) (P = 0.47) (Fig. 1a). Of note, if we consider the number of drop-outs due to adverse events, it accounts for at least one-fourth of all drop-outs (23.64%, SD 28.86). Moreover, the drop-out rate in the active group (32.80%, SD 32.21) is significantly higher than in the

comparator group (14.65%, SD 21.94) (*P* = 0.0004) (Fig. 1b).

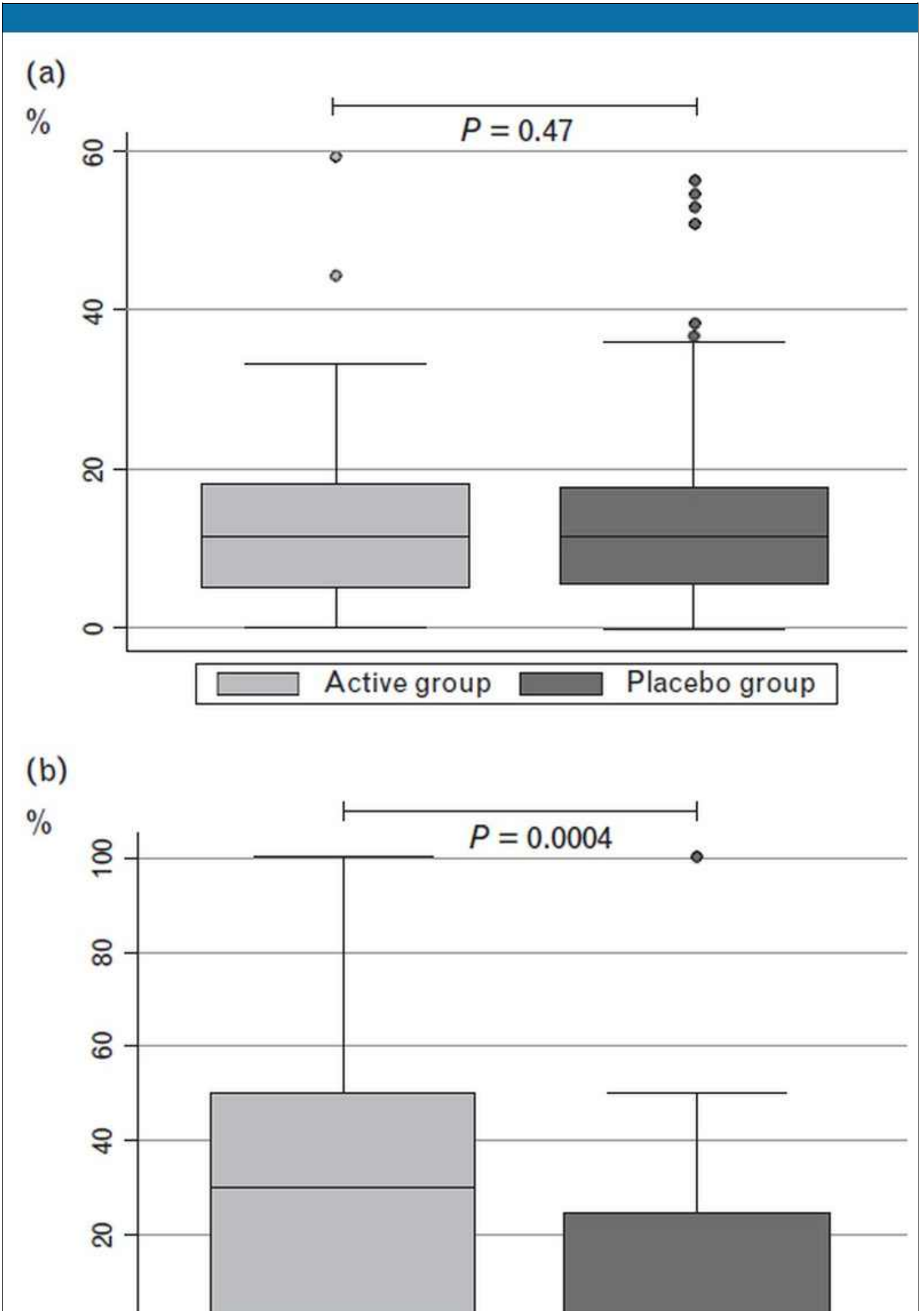

Figure 1.

Analysis of drop-outs in reviewed DB-PC-RCTs. (a) Overall drop-out rate in active and placebo groups. (b) Proportion of drop-outs due to AEs in active and placebo groups. The analysis was performed using STATA, version 12.0 (StataCorp, College Station, Texas, USA). Results are expressed as mean and SD for continuous data, as percentage for categorical data. Shapiro-Wilk test was used to test the normality in distribution for continuous data. Two-sample mean comparison test (*t*-test), with Welch's approximation, was used to compare the mean of two independent variables. A *P*-value less than 0.05 was to be considered statistically significant. AEs, adverse events; DB-PC-RCT, double-blind, placebo-controlled, randomized clinical trial.

Looking at postmarketing surveys published so far, only one study[34] reported 13 drop-outs. Seven (10%) were in the control group and dropped out because of intolerable worsening of symptoms. For the same reason, four treated patients discontinued SLIT. Two more patients in the SLIT group stopped treatment for economic reasons and lack of compliance. The drop-out rate in treated patients was 8.6%.

Both systemic and local adverse events may affect adherence to treatment.[44–46,48] Of note, local reactions are more frequent and the risk of underestimation in clinical trials and even more in real-life setting is higher in respect to systemic reactions. Therefore, local adverse events in particular may lead to poor adherence or treatment discontinuation, finally affecting treatment effectiveness despite its efficacy.[44–47] According to published data regarding the Italian market, where SLIT is predominant compared with SCIT, the adherence to SLIT is very poor, as only 3 out of 10 patients complete a 3-year course of immunotherapy, thus reducing the clinical benefit of the treatment.[48] Lack of tolerability, together with costs and inefficacy, are the main factors that negatively affect the adherence to treatment. Thus, it is crucial that doctors are able to recognize and grade local reactions and that patients know that they may occur without any risk for their safety and health. The proposed WAO grading system for SLIT-induced local adverse events[17] will certainly help in achieving the goal. Shared strategies are currently missing with regard to prevention, treatment and management of local reactions. No international guidelines on the role of premedication, dose adjustment, discontinuation and re-administration are available, nor are shared operative protocols currently adopted, according to the severity of local adverse events.

Conclusion

The safety of SLIT is definitely proved and therefore its routine use at home is allowed. Nevertheless, the first dose should be administered under medical observation, an up-dosing schedule should be adopted and every patient treated with SLIT should be provided with an action plan for systemic and local reactions. The assessment of SLIT tolerability deserves more attention and has to be properly assessed in clinical trials and real-life studies. Further research is needed in order to evaluate the role of new strategies, such as different techniques for oral administration, in improving treatment tolerability.

Sidebar

Key Points

- SLIT provides an optimal safety profile both in children and in adults.
- Systemic reactions are rare and side effects mostly consist of mild, self-limiting local reactions.
- Adverse events are not always consistently reported nor uniformly classified in published studies. It can lead to a possible underestimation of adverse events, concerning, in particular, local reactions.
- Since poor tolerability may affect adherence and cause treatment discontinuation, adopting shared strategies in order to recognize, grade and manage adverse events is mandatory.

References

1. Lin SY, Erekosima N, Kim JM, *et al.* Sublingual immunotherapy for the treatment of allergic rhinoconjuntivits and asthma. J Am Med Assoc 2013; 309:1278–1288.

** To our knowledge, the last published comprehensive review providing an overview into efficacy, safety and tolerability of sublingual immunotherapy for allergic respiratory diseases in children and adults.

2. Canonica GW, Bousquet J, Casale T, *et al.* Sub-lingual immunotherapy: World Allergy Organization Position Paper 2009. Allergy 2009; 64:1–59.

3. Sikora JM, Takersley MS, ACAAI Immunotherapy and Diagnostic Committee. Perception and practice of sublingual immunotherapy among practicing allergists in the United States. Ann Allergy Asthma Immunol 2013; 110:194–197.

4. Cox L, Larenas-Linnemann D, Lockey RF, Passalacqua G. Speaking the same language: the World Allergy Organization subcutaneous immunotherapy systemic reaction grading system. J Allergy Clin Immunol 2010; 125:569–574.

5. Yukselen A, Kendirli SG, Yilmaz M, *et al.* Effect of one-year subcutaneous and sublingual immunotherapy on clinical and laboratory parameters in children with rhinitis and asthma: a randomized, placebo-controlled, double-blind, double-dummy study. Int Arch Allergy Immunol 2012; 157:288–298.

6. Nayak AS, Atiee GJ, Dige E, *et al.* Safety of ragweed sublingual allergy immunotherapy tablets in adults with allergic rhinoconjunctivitis. Allergy Asthma Proc 2012; 33:404–410.

7. Cox LS, Casale TB, Nayak AS, *et al.* Clinical efficacy of 300IR 5-grass pollen sublingual tablet in a US study: the importance of allergen-specific serum IgE. J Allergy Clin Immunol 2012; 130:1327–1334.

8. Bozek A, Ignasiak B, Filipowska B, Jarzab J. House dust mite sublingual immunotherapy: a double-blind, placebo-controlled study in elderly patients with allergic rhinitis. Clin Exp Allergy 2013; 43:242–248.

9. Creticos PS, Maloney J, Bernstein DI, *et al.* Randomized controlled trial of a ragweed allergy immunotherapy tablet in North American and European adults. J Allergy Clin Immunol 2013; 131:1342–1349.

10. Wang DH, Chen L, Cheng L, *et al.* Fast onset of action of sublingual immunotherapy in house dust mite-induced allergic rhinitis: a multicenter, randomized, double-blind, placebo-controlled trial. Laryngoscope 2013; 123:1334–1340.

11. Aydogan M, Eifan AO, Keles S, *et al.* Sublingual immunotherapy in children with allergic rhinoconjunctivitis mono-sensitized to house-dust-mites: a double-blind-placebo-controlled randomised trial. Respir Med 2013; 107:1322–1329.

12. Blaiss M, Maloney J, Nolte H. Efficacy and safety of timothy grass allergy immunotherapy tablets in North American children and adolescents. J Allergy Clin Immunol 2011; 127:64–71.

13. Nelson HS, Nolte H, Creticos P, *et al.* Efficacy and safety of timothy grass allergy immunotherapy tablet treatment in North American adults. J Allergy Clin Immunol 2011; 127:72–80.

14. Bousquet PJ, Brozek J, Bachert C, *et al.* The CONSORT statement checklist in allergen-specific immunotherapy: a GA2LEN paper. Allergy 2009; 64:1737–1745.

15. Casale TB, Canonica GW, Bousquet J, *et al.* Recommendations for appropriate sublingual immunotherapy clinical trials. J Allergy Clin Immunol 2009; 124:666–670.

16. Medical Dictionary for Regulatory Activities (MedDRA). Maintenance support services and organization. http://www.meddramsso.com/. [Accessed May 2013]

17. Passalacqua G, Baena-Cagnani CE, Bousquet J, *et al.* Grading local side effects of sublingual immunotherapy for respiratory allergy: speaking the same language. J Allergy Clin Immunol 2013; 132:93–98.
** A WAO Task Force proposes here the first grading system of SLIT-related local side effects, on the basis of the available literature and the postmarketing surveillance data.

18. Di Rienzo V, Pagani A, Parmiani S, *et al.* Postmarketing surveillance study on the safety of sublingual immunotherapy in children. Allergy 1999; 54:1110–1113.

19. Lombardi C, Gargioni S, Melchiorre A, Passalacqua G. Safety of sublingual immunotherapy in adults: a post marketing surveillance study. Allergy 2001; 56:889–892.

20. Pajno GB, Peroni DG, Vita D, *et al.* Safety of Sublingual immunotherapy in children with asthma. Paediatr Drugs 2003; 5:777–781.

21. Fiocchi A, Pajno G, La Grutta S, *et al.* Safety of SLIT in children aged 3 to 7 years. Ann Allergy Asthma Immunol 2005; 95:254–258.

22. Drachenberg KJ, Urban E, Proll S, Woroniecki SR. Sublingual specific immunotherapy for adults and children: a post marketing survey. Allergol Immunopathol 2004; 32:76–81.

23. Calderon MA, Simons FER, Malling H-J, *et al.* Sublingual allergen immunotherapy: mode of action and its relationship with the safety profile. Allergy 2012; 67:302–311.
* This recent review discusses and provides an interesting insight into local and systemic adverse effects of allergen immunotherapy and focuses on their management. It also highlights potential risk factors associated with SLIT and SCIT-related anaphylaxis.

24. Passalacqua G, Canonica GW. Specific immunotherapy in asthma: efficacy and safety. Clin Exp Allergy 2011; 41:1247–1255.

25. Calderón MA, Casale TB, Togias A, *et al.* Allergen-specific immunotherapy for respiratory allergies: from meta-analysis to registration and beyond. J Allergy Cin Immunol 2011; 127:30–38.

26. Calderon MA, Larenas D, Kleine-Tebbe J, *et al.* European Academy of Allergy and Clinical Immunology task force on 'dose-response relationship in allergen-specific immunotherapy'. Allergy 2011; 66:1345–1359.

27. Gidaro GB, Frati F, Sensi L, *et al.* The safety of sublingual-swallow immunotherapy: an analysis of published studies. Clin Exp Allergy 2005; 35:565–571.

28. Calderon MA, Cox L, Casale TB, *et al.* Multiple-allergen and single-allergen immunotherapy strategies in polysensitized patients: looking at the published evidence. J Allergy Clin Immunol 2012; 129:929–934.

29. Agostinis F, Tellarini R, Canonica GW, *et al.* Safety of sublingual immunotherapy with a monomeric allergoid in very young children. Allergy 2005; 60:133.

30. Di Rienzo V, Minelli M, Musarra A, *et al.* Post marketing survey on the safety of sublingual immunotherapy in children below the age of 5 years. Clin Exp Allergy 2005; 35:560–564.

31. Agostinis F, Foglia C, Landi M, *et al.* The safety of sublingual immunotherapy with one or multiple pollen allergens in children. Allergy 2008; 63:1637–1639.

32. Lombardi C, Gargioni S, Cottini M, *et al.* The safety of sublingual immunotherapy with one or more allergens in adults. Allergy 2008; 63:675–676.

33. Rodriguez-Perez N, Ambriz-Moreno AJ, Canonica GW, Penagos M. Frequency of acute systemic reactions in patients with allergic rhinitis and asthma treated with sublingual immunotherapy. Ann Allergy Asthma Immunol 2008; 101:304–310.

34. De Castro G, Zicai AM, Indinnimeo L, *et al.* Efficacy of sublilngual immunotherapy on allergic asthma in children's real life. Eur Rev Med Pharmacol Sci 2013; 17:2225–2231.

35. Antico A, Pagani M, Crema A. Anaphylaxis by latex sublingual immunotherapy. Allergy 2006; 61:1236–1237.

36. Dunsky EH, Goldstein MF, Dvorin DJ, Belecanech GA. Anaphylaxis to sublingual immunotherapy. Allergy 2006; 61:1235.

37. Eifan AO, Keles S, Bahceciler NN, Barlan IB. Anaphylaxis to multiple pollen allergen sublingual immunotherapy. Allergy 2008; 62:567–568.

38. Blazowski L. Anaphylactic shock because of sublingual immunotherapy overdose during third year of maintenance dose. Allergy 2008; 63:374.

39. de Groot H, Bijl A. Anaphylactic reaction after the first dose of sublingual immuno-therapy with grass pollen tablet. Allergy 2009; 64:963–964.

40. Buyukozturk S, Gelincik A, Ozşeker F, *et al.* Latex sublingual immunotherapy: can its safety be predicted? Ann Allergy Asthma Immunol 2010; 104:339–342.

41. Vovolis V, Kalogiros L, Mitsias D, Sifnaios E. Severe repeated anaphylactic reactions to sublingual immunotherapy.

Allergol Immunopathol Madr 2012; 17:263–267.

42. Burks AW, Calderon MA, Casale T, *et al.* Update on allergy immunotherapy: American Academy of Allergy, Asthma & Immunology/European Academy of Allergy and Clinical Immunology/PRACTALL consensus report. J Allergy Clin Immunol 2013; 131:1288–1296.

43. Bachert C, Canonica GW, Bufe A. SIT: efficacy depends on product, not on route of application. Pediatr Allergy Immunol 2012; 23:401.

44. Senna G, Ridolo E, Calderon M, *et al.* Evidence of adherence to immunotherapy. Curr Opin Allergy Clin Immunol 2009; 9:544–548.

45. Pajno GB, Caminiti L, Crisafulli G, *et al.* Adherence to sublingual immunotherapy in preschool children. Pediatr Allergy Immunol 2012; 23:688–689.

46. Savi E, Peveri S, Senna G, Passalacqua G. Causes of SLIT discontinuation and strategies to improve the adherence: a pragmatic approach. Allergy 2013. [Epub ahead of print]

47. Passalacqua G, Baiardini I, Senna G, Canonica GW. Adherence to pharmacological treatment and specific immunotherapy in allergic rhinitis. Clin Exp Allergy 2013; 43:22–28.

48. Senna G, Lombardi C, Passalacqua G, Canonica GW. How adherent to sublingual immunotherapy prescriptions are patients? The manufacturer's point of view. J Allergy Clin Immunol 2010; 126:668–669.

Papers of particular interest, published within the annual period of review, have been highlighted as:
* of special interest
** of outstanding interest

Acknowledgements We are grateful to Massimo Guerriero for statistical support and Melina Makatsori for linguistic revision.

Curr Opin Allergy Clin Immunol. 2013;13(6):656-662.