G. Manzotti[1], A. Pappacoda[1], M. Dimatteo[2], C. Scolari[2],
G.G. Riario-Sforza[3], C. Incorvaia[3]

Ultra short pre-seasonal subcutaneous immunotherapy and pre-coseasonal sublingual immunotherapy for pollen allergy: an evaluation of patient's preference in real life

[1] Allergy Outpatients Service, General Hospital, Treviglio, Italy
[2] Pharmacy Unit, General Hospital, Treviglio, Italy
[3] Allergy/Pulmonary Rehabilitation, ICP Hospital, Milan, Italy - E-mail: cristoforo.incorvaia@gmail.com

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Corresponding author
Cristoforo Incorvaia
Allergy/Pulmonary Rehabilitation
ICP Hospital, via Bignami 1
20126 Milan, Italy
Tel +39 0257993289
Fax + 39 0257993315
E-mail: cristoforo.incorvaia@gmail.com

Summary

Background. *Specific immunotherapy (SIT) efficacy and safety by subcutaneous (SCIT) and sublingual (SLIT) route is supported by literature data. Pre-coseasonal treatment is currently the more accepted option for pollen immunotherapy in terms of costs and patient's compliance. This retrospective study evaluated the patient's preference concerning subcutaneous or sublingual route in pre-coseasonal treatment.* ***Materials and methods.*** *We evaluated 145 patients (79 males, 66 females, age ranging from 14 to 69 years), suffering from moderate-severe rhino-conjunctivitis or mild bronchial asthma and with homogeneous characteristic according to allergic disease severity. We proposed either SLIT, with extracts by different producers, or SCIT with Pollinex 4 (Allergy Therapeutics, Worthing, UK), a product designed for ultra-short administration in 4 injections, highlighting for each kind of SIT the major practical advantages or burdens.* ***Results.*** *Of 145 patients, 72 chose Pollinex 4 SCIT and 73 chose SLIT. SCIT-treated patients received a total of 90 vaccines (18 patients had double course of SCIT). SLIT-treated patients received a total of 87 vaccines (14 patients had double course of SLIT). In the SCIT group, there were 49 males and 23 females; in the SLIT group, there were 30 males and 43 females. Mean age was 36.5 years in SCIT group and 28.5 years in SLIT group. Males preferred SCIT (49 of 72 patients) and females preferred SLIT (43 of 73 patients). No severe reaction was observed either in SCIT or SLIT group.* ***Conclusion.*** *Patients are active subjects in decisional process. Trying to apply in real life the indications coming from guidelines about patient's preference is an important matter. In our patients SCIT with ultra short schedule and SLIT are similarly preferred.*

Introduction

Allergen-specific immunotherapy (SIT) has the capacity to change the natural course of the allergic disease and to prevent its exacerbations and the possible progression from rhino-conjunctivitis to asthma symptoms (1-3). SIT efficacy and safety is strongly supported from the literature reviewed and analyzed in consensus documents on the classical, subcutaneous immunotherapy (SCIT) (4), and the more recently introduced sublingual immunotherapy (SLIT) (5). Pre-coseasonal treatment is currently the most adequate method for pollen immunotherapy in terms of costs and it seems to fit better with patient's compliance (6,7). All the preparations to be used for SIT

should respond to precise requirements concerning standardization and quality (4,5).
SLIT generally consists in drops or tablets to be put under the tongue for about two minutes and then to be swallowed. Multiple pre-coseasonal administration schedules, according to different immunotherapy preparations are available. All of them must be taken regularly (every day or twice a week or three times a week) at least 8 weeks before the pollen season and during the pollen season itself to be effective (5).
Among SCIT preparations, Pollinex 4 (Allergy Therapeutics, Worthing, UK) is a preseasonal pollen immunotherapy product that contains allergen extracts of pollen (grasses, trees or weeds) to be used according to individual doctor's prescription. The allergen extracts are characterized and standardized in SU (Standardized Units) by biochemical methods to ensure that the allergoid content and immunogenic potency are consistent. The allergens are modified to allergoids by treatment with glutaraldehyde and are adsorbed onto L-tyrosine. Pollinex 4 should be administered as a course of four 1,0 ml injections, one 300 SU/ml injection, one 800 SU/ml injection and two 2000 SU/ml injections, injected subcutaneously prior to the pollen season. The first 3 injections must be administered in ascending order (vial 1 to vial 3) at 1 to 2 week intervals. The fourth injection (Vial 4) should be administered 1 to 4 weeks after the third injection. As for SCIT in general, the administration should be carried out by physicians with experience in immunotherapy, in the hospital or in a clinic where emergency treatment for systemic reactions is readily available (4).
Concerning SLIT, this treatment option is considered safe enough to be carried out and self administered by the patient in his/her own home after a correct training (7).
This retrospective study was aimed at evaluating the patient's preference concerning the use of SLIT or ultrashort SCIT in pre-coseasonal treatment with pollen extracts.

Patients and methods

During the pollen season 2010-2011 we included in this retrospective evaluation all patients, suffering from moderate-severe rhino-conjunctivitis (according to ARIA guidelines) (8), alone or associated with mild bronchial asthma (according to GINA guidelines) (9), who were prescribed SIT with pollen extracts. The population of patients could be considered homogeneous in terms of allergic disease severity and all of them were suitable for pre-seasonal SCIT or SLIT; no patient had received pollen immunotherapy in the past.
In our Hospital pollen SIT is free of charge and none of our patients was asked to pay any money to receive SCIT or SLIT if given with pre-coseasonal schedule or for SC route according to specific Italian Regional Regulatory Agency (10). As usual in real life, many patients were sensitized to different pollens and for some of the patients we suggested a double SIT treatment.
Because the patient is an active subject in decisional process to his/her own treatment, during the visit we explained the indications to pollen pre-coseasonal SIT and we discussed with the patients the options available to successfully carry it out, trying to apply in real life indications coming from the more recent guidelines where patient's preference is an important matter (11).
We proposed SLIT or SCIT with Pollinex 4 highlighting for each kind of SIT the major practical advantages or burdens. SLIT was based on preparations from 5 different producers: Allergopharma (Milan, Italy), ALK-Abellò (Horsholm, Denmark), Anallergo (Florence, Italy), Lofarma (Milan, Italy), and Stallergenes (Antony, France).
For SLIT we explained that: (1) administration is in drops or tablets to put under the tongue, (2) the timing is every day or almost every day at least 8 week before and during the pollens season for at least three years, (3) SLIT is safe enough to be taken at home but mild adverse events (mainly oral discomfort) or in rare cases also systemic adverse events were possible. The patient were informed that they must contact the doctor or a health care professional by a phone call immediately if any signs of adverse reactions occur at home in course of SLIT assumption at any time. All patients were required to sign an informed consent.
For Pollinex 4 SCIT we explained that: (1) administration is subcutaneous as a course of four 1,0 ml injections prior to the pollen season, administered in ascending dosage order at 1 to 2 week intervals, (2) SCIT can cause local reactions in the site of injection, sometimes with swelling or pain for some hours after the injections, that usually resolve spontaneously within 48 hours or more slowly with occurrence of local nodules; we remarked that systemic reactions or anaphylaxis are also possible, (3) SCIT should only be carried out in our outpatient clinic (in the hospital) in order to ensure a suitable equipped, emergency medical kit, with availability of epinephrine and oxygen in case of systemic adverse reactions, (4) after each injection it is needed to remain under medical observation

for at least 30 minutes. The period of observation can be extended if mild symptoms or signs of hypersensitivity develop and patients must remain under observation until these have completely resolved. A severe and prolonged adverse reaction may necessitate hospital admission. The patient must contact the doctor or a health care professional immediately if any signs of adverse reactions occur during the observation period or at any time following the injection. All patients were required to sign an informed consent.

When the patient was candidate to SIT for 2 allergens we proposed for SLIT either 2 treatments, one for each pollen, or a SLIT with a pollen mix (when feasible). For Pollinex 4 two treatments, one for each pollen or a pollen mix (when feasible) were proposed.

At the end of the visit we asked the patient to think about the options and to sign the SIT request form. Most patients took the decision quite soon but some of them asked to have a few days to choose the best option for themselves and than they came back to sign the SIT request form.

Results

One hundred forty-five patients (79 males, 66 females), with age ranging from 14 to 69 years were included in the evaluation. Of them, 72 chose Pollinex 4 SCIT and 73 chose SLIT. SCIT was preferred by males (49 of 72 patients, 68 %) and SLIT was preferred by females (43 of 73 patients, 59 %). Table 1 reports the demographic and history data from the two groups of patients. The 72 patients treated with Pollinex 4 received a total of 90 treatments because 18 patients had a double course of SCIT. The 73 patients treated with SLIT received a total of 87 treatments because 14 patients had a double course of SLIT. Table 2 shows the treatments received by patients, also including ongoing SIT with perennial allergens. One patient was treated with Pollinex 4 including both grass pollen and Parietaria pollen. Concerning SLIT, 18 patients received a pollen mix (4 grass + Parietaria, 10 grass + birch, 4 grass + ragweed).

In Pollinex 4 group 18 patients had double course of SIT: 15 patients had birch and grass pollen, 1 had grass and ragweed pollen, 1 had grass and Parietaria pollen, 1 had birch and grass + Parietaria pollen mix. In SLIT group 14 patients had double course of treatment: 9 patients had birch and grass pollen, 4 had birch and grass + Parietaria pollen mix, 1 had birch and grass + ragweed pollen mix. We administered 4 injections for each course of SCIT according to the Pollinex 4 schedule, for a total of 270 injections. All patients completed the treatment; no systemic reaction occurred. Mild local reactions were reported by 57 (69.5%) of patients, none so relevant to be men-

Table 1 - Demographic and history data of patients

Type of SIT	Males	Females	Mean age (range)	Kind of symptoms	Sensitization to perennial allergens
SCIT	49	23	36.5 years (15-69)	47 only rhinitis 25 rhinitis and asthma	21 dust mites 5 animal epithelia 7 moulds
SLIT	30	43	28.5 years (15-59)	45 only rhinitis 28 rhinitis and asthma	27 dust mites 11 animal epithelia 5 moulds

Table 2 - SIT treatments received by patients

Type of SIT	Grass pollens	Tree pollens	Parietaria pollen	Ragweed pollen	Other ongoing SIT
SCIT	56	28	3	3	9 dust mites (8 SCIT, 1 SLIT)
SLIT	53	27	3	4	7 dust mites (all SLIT)

tioned specifically into patients' records except for one case of large and long-lasting oedema in the site of injection. With SLIT, 34 (41%) of patients experienced oral discomfort and 3 patients also abdominal pain. None of the adverse effect was severe. Six patients asked SLIT interruption for persistent discomfort (3 patients for abdominal pain and 3 for oral mucosa symptoms). Three patients accepted to try the "spit schedule", that is, to spit the extract after 2 minutes instead to swallow it (12), instead of the "swallow schedule" but despite the change of schedule after few days they stopped SLIT. The overall rate of treatment withdrawal was 4.1%.

Discussion

In this retrospective analysis we considered patients with homogeneous characteristic according to allergic disease severity as obtained by clinical history. In our practice we started using Pollinex 4 as pre-seasonal immunotherapy from few years because of its characteristics of injective preparation designed for ultra-short SIT (13-15). This fits well with patients requiring SCIT but refusing a conventional slow treatment because of the difficulty to carry it on assiduously according to their life-style. At the end of the pollen season 2010-11 we realized that in our group of patients undergoing pollen SIT, about half of them had chosen SCIT and half had chosen SLIT.

In our group of patients, males (79 patients) more than females (66 patients) were suitable for SIT but, in terms of route of administration, SCIT has been preferred by males (68% of patients) and SLIT has been preferred by females (59% of patients). The mean age of Pollinex 4 group was 36.5 years while patients in SLIT group were younger (mean age 28.5 years). The mean age for males and females into the same group was not different.

The reason for younger females to prefer SLIT and for older males to prefer SCIT is not completely clear: maybe females feel to be able to regularly assume SLIT or males prefer to have planned visits to attend SCIT instead to self manage SLIT. We have no data about socio-economic factors (in particular the level of education of patients) that could have helped us to answer to some questions. Indeed, looking at patients' behaviours and choices could be a way to obtain information for better focusing immunotherapy in each patient. A factor influencing the choice seems to be the experience with the treatment: among patients treated with SIT for dust mites, all 7 SLIT-treated chose SLIT for pollen allergy, and 8 of 9 SCIT-treated chose SCIT for pollen allergy. Further studies on this issue are warranted.

It is worthy to note that the distribution of pollen sensitization in the two groups was almost the same but SLIT was preferred by patients with plurisensitization. In fact, 5 patients had 2 SLIT, 1 for single pollen and the other for a pollen mix, receiving in this way SLIT for 3 pollens. The same occurred to only 1 patient in the Pollinex 4 group.

In our patients no severe reaction either in Pollinex 4 group or in SLIT group was observed. Local reactions are fairly common during SCIT, ranging from 26 to 82% of patients and 0.7-16% of injections (16,17). They do not seem to be a major problem in terms of compliance, since only around 4% of patients withdraw the treatment because of them (18).

Formation of nodules (also persisting for a long time) is possible, sometimes related to incorrect intradermal administration (19,20). The possibility to develop a systemic reaction after large local reactions is still a matter of concern (21-24). Obviously, allergists must be very careful in real life but a previous local reaction is not a reason strong enough to withdraw administering SCIT. In our group of patient many of them reported local discomfort but none asked to stop the treatment. One male patient receiving ragweed SCIT had large and long lasting (about 72 hours) local oedema after the second injection; no systemic symptoms were reported. The history revealed that he underwent a local hot massage because of "tennis elbow" the same day of the injection in the same arm. Together with the patient we decided to administer the third injection without changing the dose after one week but in the other arm: just mild local reaction occurred. He completed the injective therapy without any other problem.

Oral-mucosal reactions occur with SLIT in up to 75% of patients (5) most frequently in the build-up phase, sometimes followed by gastrointestinal symptoms such as stomachache, abdominal pain or nausea. Usually they are considered mild in case-controlled studies and they do not determine patient's drop out in clinical trial. On the other side, they are an issue in clinical practice because patients may ask to stop SLIT due to such reactions. This happened in 6 of our patients in SLIT group.

Compliance and adherence are major issues in SIT and current literature data are not conclusive in recommending SCIT or SLIT to obtain a better outcome (25,26). We believe that patients must be active subjects in the decisional process to their own immunotherapy treatment and this could be, in our opinion, the first step to obtain a

better compliance and adherence to SIT. We did not measure adherence in this study, while compliance, as measured by the major criterion of treatment withdrawal, was 96%. In fact, it has been reported that an adequate education on SIT improves patients compliance (27).
SLIT has been proposed as a safer and less inconvenient treatment for patients with respiratory allergy in respect to the traditional long course of SCIT and it has met large application in paediatric age. Anyway, adult patients in our population seem do not mind the injection discomfort, but 50% of them preferred a short immunotherapy injective schedule they thought to better fit with their job or family business.
After a time when SCIT was declared "dead" (28) we now cannot subscribe with this point of view. Probably, traditional SCIT with prolonged induction phase may hardly be further proposed. In fact, classical schedules of SCIT are time consuming, with the updosing phase lasting 12-14 weeks. To shorten this period, cluster immunotherapy protocols have been proposed (29, 30) but also the use of allergoid vaccines or adjuvanted extracts, as the Pollinex 4 we used, is a possible strategy. A recent German market analysis, performed to evaluate the persistence of the use of different extracts for SCIT, demonstrated a significantly higher renewal of maintenance vials for shortened therapy regimen during the 2nd and 3rd year of therapy in comparison with extract administered according to the classical schedule, confirming a better adherence to short course of SCIT (31). Our data seem to add value to these observation at least in terms of patient's preference. Our group of patients treated with Pollinex 4 seemed to appreciate the short course of SCIT, although the patients were informed that the risk of systemic adverse reactions is not abolished with this product. Indeed, there were recent encouraging data about SCIT safety, mainly in Europe, where pollen mixes are less used than in North America (32,33) In particular, data on Pollinex 4 show that this kind of SCIT is even safer than traditional SCIT, with local reaction as the major discomfort (34).

Conclusions

SCIT and SLIT are both valid treatment options for allergic respiratory diseases, according to controlled trials and meta-analyses (4,5,35,36). We do not think that one route of administration is better than the other, but we highlight that the subcutaneous route is still essential. For both SLIT and SCIT, the use of new adjuvants to improve the immunogenicity as well as new strategies for administrations, such as the use of recombinant allergens, could offer better patient-tailored treatment in the future (35, 38). The introduction of more convenient and shorter schedules with adjuvanted extracts may also increase the adherence to this treatment and perhaps expand its use in daily practice as occurred in our population, where SCIT with ultra short schedule is as preferred as SLIT from the patients.
We acknowledge that our experience concerns a retrospective observation in real life but these data open the view to future well designed studies on patient' preference, as it is suggested in the more recent guidelines on medical treatments, where patient's preference is an important matter to obtain patient's compliance and adherence.

Disclosure of interest

Antonio Pappacoda is a scientific consultant for Allergy Therapeutics.
Cristoforo Incorvaia is a scientific consultant for Stallergenes Italy.
The other authors have no conflict of interest.

References

1. Durham SR, Leung DYM. One hundred years of allergen immunotherapy: time to ring the changes. J Allergy Clin Immunol 2011; 127: 3-7.
2. Durham SR, Walker SM, Varga EM, Jacobson MR, O'Brien F, Noble W, et al. Long-term clinical efficacy of grass-pollen immunotherapy. N Engl J Med 1999; 341:468-75.
3. Des Roches A, Paradis L, Menardo JL, Bouges S, Daures JP, Bousquet J. Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children. J Allergy Clin Immunol 1997;99:450-3.
4. Bousquet J, Lockey R, Malling HJ (eds). Allergen immunotherapy: therapeutic vaccines for allergic diseases. A WHO Position Paper. J Allergy Clin Immunol 1998; 102:558-62.
5. Canonica GW, Bousquet J, Casale T, Lockey RF, Baena-Cagani CE, Pawankar R, et al. Sub-lingual Immunotherapy World Allergy Organization Position Paper 2009. Allergy 2009; 64: Suppl 91:1-59
6. Lombardi C, Incorvaia C, Braga M, Senna G, Canonica GW, Passalacqua G. Administration regimens for sublingual immunotherapy to pollen allergens: What do we know? Allergy 2009; 64 : 849–85.
7. Incorvaia C, Masieri S, Berto P, Scurati S, Frati F. Specific immunotherapy by the sublingual route for respiratory allergy. Allergy Asthma Clin Immunol 2010;6:29-33.

8. Passalacqua G, Durham S. ARIA update: allergen immunotherapy J Allergy Clin Immunol 2007; 119: 881-91.
9. ginasthma.com (accessed February 6, 2010)
10. Giunta Regionale, Circolare n: 5/SAN 30/01/2004. Farmaci a somministrazione diretta a pazienti non ricoverati - File F; Indicazioni per il flusso Informativo a partire dal 01/01/2004 (Trasmissione Telematica).
11. Brozek JL, Akl EA, Alonso-Coello P, Lang D, Jaeschke R, Williams JW, et al. Grading quality of evidence and strength of recommendation in clinical pratice guidelines. Part 1 of 3. Am overview of the GRADE approach and grading quality of evidence about interventions. Allergy 2009;64:669-77.
12. Frati F, Sensi L, Di Rienzo V, Senna GE, Incorvaia C, Marcucci F. A model for management of sublingual immunotherapy. Eur Ann Allergy Clin Immunol 2003;35:56-60.
13. Drachenberg KJ, Wheeler AW, Stuebner P, Horak F. A well-tolerated grass pollen-specific allergy vaccine containing a novel adjuvant, monophosphoryl lipid A, reduces allergic symptoms after only four preseasonal injections. Allergy 2001;56:498-505.
14. Drachenberg KJ, Heinzkill M, Urban E, Woroniecki SR. Efficacy and tolerability of short-term specific immunotherapy with pollen allergoids adjuvanted by monophosphoryl lipid A (MPL) for children and adolescents. Allergol Immunopathol 2003;31: 270-7.
15. DuBuske LM, Frew A, Horak F, Keith PK, Corrigan CJ, Aberer W, et al. Ultrashort-specific immunotherapy successfully treats seasonal allergic rhinoconjuntivits to grass pollen. Allergy Asthma Proc 2011; 32: 239-47.
16. Calabria C, Coop C, Tanskersley M. The LOCAL study: Local reactions do not predict local reactions in allergen immunotherapy. J Allergy Clin Immunol 2009;124: 739-44
17. Coop C, Tanskersley M. Patient's perceptions regarding local reactions from allergen immunotherapy. Ann Allergy Asthma Immunol 2008:101:96-100
18. Coop C, Tanskersley M. Dose adjustment practices among allergists for local reactions to immunotherapy. Ann Allergy Asthma Immunol 2007;99:77-81.
19. Odzen MG, Kefeli M, Aydin F, Senturk N, Canturk T, Turanli AJ. Persistent subcutaneous nodules after immunotherapy injections for allergic asthma. J Cutan Pathol 2009; 36:212-4.
20. Netterlid E, Hindsen I, Bjork J, Eqvist S, Guner N, Henricson KA, et al. There is an association between contact allergy to aluminium and persistent subcutaneous nodules in children undergoing hyposensitization therapy. Contact Dermatitis 2009:60:41-9.
21. Kelso JM. The rate of systemic reactions to immunotherapy are the same whether or not the dose is reduced after a local reaction. Ann Allergy Asthma Immunol 2004; 92:225-7.
22. Roy SR, Sigmon JR, Olivier J, Moffitt JE, Brown DA, Marshall GD. Increased frequency of large local reactions among systemic reactors during subcutaneous immunotherapy. Ann Allergy Asthma Immunol 2007;99:82-6.
23. Bernstein DI, Epstey T, Murphy Berendts BS, Liss GM. Surveillance of systemic reactions to subcutaneous immunotherapy injections: year 1 outcomes of the ACAAI and AAAAI Collaborative study. Ann Allergy Asthma Immunol 2010;104: 530-5.
24. Calabria CW, Stolfi A, Tankersley M. The REPEAT study; recognizing and evaluating periodic local reactions in allergen immunotherapy and associated systemic reactions. Ann Allergy Asthma Immunol 2011;106:49-53.
25. Incorvaia C, Mauro M, Ridolo E, Puccinelli P, Liuzzo M, Scurati S, et al. Patient's compliance with allergen immunotherapy. Patient Prefer Adherence 2008;2:247-51.
26. Senna G, Ridolo E, Calderon M, Lombardi C, Canonica FW, Passalacqua G. Evidence of adherence to immunotherapy. Curr Opin Allergy Clin Immunol 2009;9:544-8.
27. Incorvaia C, Rapetti A, Scurati S, Puccinelli P, Capecce M, Frati F. Importance of patient's education in favouring compliance with sublingual immunotherapy. Allergy 2010;65:1341-2.
28. Mosges R. Is classical immunotherapy dead? Curr Opin Allergy Clin Immunol 2010;10:167.
29. Cox L. Advantages and disadvantages of accelerated immunotherapy schedules. J Allergy Clin Immunol 2008;122:432-4.
30. Pfaar O, Leitzbach S, Hormann K, Klimek L. Cluster protocols in SCIT: enough evidence for practical use? Curr Opin Allergy Clin Immunol 2010;10188-93.
31. Claes C, Mittendorf T, Graf von der Schulemburg JM. Persistence and frequency of of prescriptions of subcutaneous immunotherapy (SCIT) prescribed within the German statutory insurance. Med Klin 2009;15:536-42.
32. Windom HH, Lockey RF. An update on the safety of specific immunotherapy. Curr Opin Allergy Clin Immunol 2008;8:571-6.
33. Schiappoli M, Ridolo E, Senna G, et al. A prospective Italian survey of subcutaneous immunotherapy for respiratory allergy. Clin Exp Allergy 2009;39: 1569-74.
34. Crivellaro MA, Senna GE, Pappacoda A, Vanzelli N, Spacal B, Marchi G, et al Safety of ultrashort-term sit with pollen allergoids adjuvanted by monophosphoryl lipid A: a prospective italian survey Eur Ann Allergy Clin Immunol 2011;43:58-60.
35. Walker SM, Durham SR, Till SJ, Roberts G, Corrigan CJ, Leech SC, et al. Immunotherapy for allergic rhinitis. Clin Exp Allergy 2011;41:1177-200.
36. Calderon MA, Alves B, Jacobson M, Hurvitz B, Sheikh A, Durham S. Allergen injection immunotherapy for seasonal allergic rhinitis. Cochrane Database Syst Rev 2007 (1);CD001935.
37. Radulovic S, Wilson D, Calderon M, Durham S. Systematic reviews of sublingual immunotherapy (SLIT). Allergy 2011; 66:740-52.
38. Purohit A, Niederberger V, Kronqvist M, Horak F, Gronneberg R, Suck R, et al. Clinical effects of immunotherapy with genetically modified birch pollen Bet V 1 derivatives. Clin Exp Allergy 2008;38: 1514-25.