Curr Treat Options Allergy (2016) 3:93–101
DOI 10.1007/s40521-016-0070-8

Specific Immunotherapy (L Cox, Section Editor)

Pre-Coseasonal vs Perennial Sublingual Immunotherapy for Seasonal Allergens Dosing Regimen: Long-Term Benefits, Adherence, and Cost-Effectiveness—Is There a Difference?

Stefania Arasi, MD
Giovanni B. Pajno, MD[*]

Address
[*]Department of Pediatrics- Allergy Unit, University of Messina, Via Consolare Valeria- Gazzi, Messina, Italy
Email: giovanni.pajno@unime.it

Published online: 29 January 2016

This article is part of the Topical Collection on *Specific Immunotherapy*

Keywords Allergic rhinitis · Allergic asthma · Pollen · Pre-seasonal immunotherapy · Co-seasonal immunotherapy · Perennial immunotherapy · Sublingual immunotherapy · Efficacy · Adherence to treatment · Health economics

Opinion statement

Allergen immunotherapy (AIT) is to date the only disease-modifying and etiological treatment for IgE-mediated respiratory allergies. In France and Italy, the main route of administration of AIT for respiratory allergies is currently constituted by sublingual allergen immunotherapy (SLIT). In other European countries, the marketing is growing. In the USA, SLIT is increasingly taking hold, too. Various SLIT regimens have been employed to date for respiratory allergies induced by pollen, which constitutes a major atopic sensitizer in Europe and North America: continuous (all year-round), pre-seasonal only, co-seasonal only, and pre-coseasonal. The best maintenance SLIT regimen is a pivotal issue to clinicians. In fact, a continuous regimen may pose problems of adherence, and patients could be reluctant to take a treatment when they are symptom-free, out of the pollen season. In addition, a continuous treatment carries on a relevant economic cost. Obviously, the economic aspect may not be primary on safety and efficacy. Data provided evidence of short-term, sustained, and post-treatment efficacy of pre-coseasonal

regimen. However, further head-to-head studies are required to establish whether discontinuous SLIT regimens are associated with better safety and/or major very long-lasting and preventative benefits than perennial SLIT regimens.

Introduction

Allergen immunotherapy (AIT) is currently the only guideline-approved, disease-modifying, and etiological treatment for IgE-mediated respiratory allergies. In the 1980s, sublingual allergen immunotherapy (SLIT) was proposed as an alternative to the traditional subcutaneous route of administration, in order to provide a more convenient and safer therapeutic intervention [1••]. Since then, the use of SLIT rapidly spread in Europe, where it currently constitutes the preferred route of administration of AIT for respiratory allergies [2]. Since 2014, when the Food and Drug Administration (FDA) approved the first sublingual allergen tablets for the treatment of respiratory allergies caused by grass pollen and ragweed [1••], SLIT has been progressively spreading in the US, too.

In Europe and North America, one of the major atopic sensitizers in the general population is the pollen released by wind-pollinated plants (grasses, weeds, and trees) for one or more periods per each year (start date and duration vary from year to year and for geographic and climatic area) [3, 4, 5••].

A large body of evidence attests to the safety and efficacy of SLIT for pollen-induced respiratory allergies both in adults and in children [1••, 5••].

The SLIT safety profile is overall favorable, although local adverse events, usually mild, are described [1••].

Most of the meta-analyses confirmed the efficacy of SLIT in reducing symptoms and medication intake, as compared with placebo in patients with allergic respiratory diseases [1••] with an enhanced efficacy during the peak pollen season [6]. Furthermore, AIT, as immune-modulating treatment, may modify the natural history of the allergic diseases: long-term clinical efficacy for up to 12 years [7, 8]; reduction of the risk of development of asthma [9–11] and bronchial hyper-reactivity in patients with allergic rhinitis [12]; and reduction of the onset of new sensitizations [13].

Notwithstanding, data attest to the short-term and long-term efficacy of SLIT, as well as a long clinical experience, there are several practical aspects of SLIT that still need to be better defined, including: the administration frequency, the treatment regimen, and the seasonality of AIT in pollen-induced allergic respiratory diseases [14, 15].

Pollen SLIT Administration Regimens

In order to assess long-term clinical advantages, AIT, once a clinical benefit is ascertained, should be continued for a period of at least 3 years (range 3–5 years) [1••]. However, a clinical improvement in symptoms and medication score can be reasonably expected already in the first year of therapy [1••], and the onset of action (in an allergen challenge chamber study) was found to occur already after 1 month of treatment [16].

Different multiyear administration regimens have been employed to date [17]. They can be divided into continuous (all-year-round, independently from pollen season) and discontinuous (i.e., with a treatment-free period each year). In turn, the latter, may be distinguished in pre-seasonal only, co-seasonal only, and pre-coseasonal. Overall, the regimen most commonly used is the pre-coseasonal one, followed by the perennial one [17].

Pollen SLIT preparations can be administered as drop or tablet formulations [1••]. Historically, pollen SLIT drops have been administered daily, every other day or three times a week. Tablets are usually administered daily [1••].

Table 1. Studies comparing efficacy of pre-coseasonal and perennial SLIT on allergic respiratory diseases

Study	Group	Population (*n*, disease, age)	Regimen	Timing	Dosing regimen	Magnitude of improvement
Sieber et al. [19]	#1	*n* = 451, AR ± A, age: 2–80 ys	Continuous	Nov 2000 → Mar 2002	- 1st day: 1 IR - up-dosing: up to 24th day - maintenance phase: 150 IR 1/day for 5 days a week	Similar SS, MS statistical improvement compared to baseline
	#2	*n* = 254, AR ± A, age: 9–72 ys	Co-seasonal	Jan 2003 → Oct 2003	Ultra-rush titration up to maintenance dose (240 IR 1/day) within 90 min (30–60–120–2-40 IR)	
	#3	*n* = 358, AR ± A, age 3–78 ys	Continuous or co-seasonal regimen	Sep 2000 → Dec 2003 continuously (P) or only in pollen seasons (C)	Build-up phase: 10 IR daily increased up to maintenance dose on day 11 Maintenance phase: 240 IR/day until the end of the season (C) or 240 IR on alternate days (P)	
Quercia et al. [20]	#1	*n* = 10, A, age 18–70 ys	Continuous regimen	Nov 2005→ July 2007	Build-up phase: for 16 days 25 AU, 100 AU, 300 AU and 1000 AU Maintenance phase: 1000 AU/week for 2 years	SS, MS, VAS: similar and significant improvement after the 1st and the 2nd pollen seasons vs baseline and also the SS vs a 3rd group taking symptomatic medications only (*n* = 11).
	#2	*n* = 11, A, age 18–70 ys	Pre-coseasonal	Nov 2005→ Feb 2006 + Nov2006→ Feb 2007	Build-up phase: for 16 days 25 AU, 100 AU, 300 AU and 1000 AU Maintenance dosage: 5000 AU 1/week (i.e., 1 tablet 5 times a week) for 10 weeks/year pre-seasonally for 2 years	

Table 1. (Continued)

Study	Group	Population (*n*, disease, age)	Regimen	Timing	Dosing regimen	Magnitude of improvement
	#3	*n* = 11, A, age 18–70 ys	Symptomatic medications only	Nov 2005→ July 2007	–	
Pajno et al. [21]	#1	*n* = 40, AR/A/-AR + A age 8–16 ys	Continuous	Oct 2005→ Jun 2008	Build-up phase: 6 days Maintenance phase: 300 IR/ml	In the 1st season significant improvement (SS and MS) vs baseline only in the P-SLIT group. In the 2nd and 3rd yearr similar significant improvement in both regimens
	#2	*n* = 40, AR/A/-AR + A age 8–16 ys	Co-seasonal	Mar → Jul (2006 → 2008)	Build-up phase: 6 days Maintenance phase: 300 IR/ml	
Stelmarch et al. [26]	#1	*n* = 20 AR ± A, age 6–18 ys	Pre-coseasonal	Oct → Jun 2005 → 2008	Build-up phase: 5 days Maintenance phase: 10 µg of major allergens	Similar significant decrease in SS and MS for both protocols vs placebo with the exception of nasal symptoms (lower in the pre-coseasonal group)
	#2	*n* = 20 AR ± A, age 6–18 ys	Continuous	Oct 2005→ Jun 2008	Build-up phase: 5 days Maintenance phase: 10 µg of major allergens	
	#3	*n* = 20 AR ± A, age 6–18 ys	Placebo	Oct 2005→ Jun 2008	–	

P perennial, *C* co-seasonal, *AR* allergic rhinitis, *A* asthma, *SS* symptoms score, *MS* medication score, *VAS* visual analogue scale

Most studies of pre-coseasonal SLIT regimens have dealt with grass and birch pollen formulations but not exclusively [18].

Pre-Coseasonal vs Perennial SLIT Regimens

Few studies have performed head-to-head comparisons between a pre-coseasonal and a perennial regimen, in allergic rhinitis and still less in allergic asthma induced by pollen.

Single- or double-blind trials are difficult to perform, as the durations of the compared treatment regimens are obviously different (unless patients in the pre- and co-seasonal-treated groups receive placebo after the end of the pollen season).

Comparison of Efficacy

There is ample evidence to support the short- and long- term efficacy of pre-coseasonal and perennial SLIT on allergic respiratory diseases. However, as expressed above, few data are about the comparison between the two different SLIT regimens (Table 1).

Sieber et al. analyzed data of three open, prospective, observational trials of standardized Pooideae family or Betulaceae family pollen SLIT preparations in a total of 1052 patients with pollen-induced allergic rhinitis [19]. They indirectly compared perennial treatments with co-seasonal treatments: overall, the different SLIT regimens were all associated with improvements in symptoms and medication scores (in comparison to baseline), without significant differences between the regimens. Authors suggested that the equivalent effectiveness of co-seasonal and perennial SLIT treatment might have an impact on the cost of treatment, although compliance was not assessed [19].

Quercia et al. performed a head-to-head study of a perennial regimen ($n = 10$; 1000 allergenic unit (AU) tablet taken once a week continuously from November 2005 to July 2007) with a solely pre-seasonal regimen ($n = 11$; 1000 AU tablet taken five times a week during each 10-week pre-seasonal period) in patients with grass pollen-induced allergic rhinitis [20]. Both SLIT regimens were associated to a similar and significant improvement on a visual analog scale of symptom severity after the first and the second pollen seasons, relative to the baseline symptoms and also the symptoms of a third group of patients taking symptomatic medications only ($n = 11$). Several limitations have vitiated the study: open design, small sample size, and different doses of allergen in the presumably crucial pre-seasonal period.

Pajno et al. [21] performed an open randomized clinical trial, comparing the clinical efficacy of a continuous and a co-seasonal SLIT regimen over 3 years in 80 children with rhinitis/asthma induced by grass pollen. In the first year of treatment, asthma and rhinitis symptoms and drug intake scores improved more in the continuous group vs baseline. Conversely, in the subsequent years, the two regimens are nearly equivalent. These results may be explained by the fact that the continuous group started the AIT before the other group; therefore, the first one actually received also a pre-seasonal AIT [22]. In this regard, trials of a five-grass pollen SLIT tablet formulation [23–25] and a trial of a single-grass pollen SLIT tablet formulation found that the magnitude of the reductions in rhino-conjunctivitis symptom, and medication scores increased with the duration of pre-seasonal treatment (4 months appeared to be optimal) [22].

A 2-year prospective, randomized, double blind, placebo-controlled trial by Stelmach and colleagues compared a pre-/co-seasonal vs a continuous SLIT regimen [26]. Sixty children affected with grass pollen-induced rhinitis, of which 20 with concomitant asthma, participated to the study. Cumulative doses of major allergens for continuous SLIT group and pre-coseasonal SLIT group were 7.3 and 3.6 mg, respectively. Both protocols were effective compared with placebo and showed similar decreases for combined symptoms/medication score, with the exception of nasal symptoms that were surprisingly lower in the pre- and co-seasonal group. The latter finding raises a question whether it is the seasonal rather than total cumulative SLIT allergens, as traditionally thought, that decide about the clinical efficacy of SLIT in the treatment of seasonal allergies.

No significant differences were observed in medication, ocular, and asthma

scores between the regimens [26]. However, the absence of a baseline evaluation does not allow to assess the effect of SLIT in the first season and compare the results to Pajno's study [19].

Overall, in the treatment of pollen-induced allergic respiratory diseases, pre-coseasonal SLIT regimens appear to be at least as effective as perennial SLIT regimens in short term.

Recently, Di Bona et al. conducted a meta-analysis on the efficacy of pre-coseasonal grass pollen SLIT tablets in patients (both children and adults) with moderate to severe seasonal allergic rhino-conjunctivitis [27]. In line with previous data, they attested clinical benefit of the treatment in reducing symptoms and rescue medication use, compared with placebo. However, the authors underlined that the magnitude of SLIT benefit was small and burdened by adverse events [27]. The 13 studies included in the meta- analysis, selected for their good methodological quality, were conducted for an average treatment duration of 23 weeks (range 18–33 weeks), that is much lower than the duration recommended in guidelines. The majority of adverse events were mild and self-resolving after few days of treatment [27]. Therefore, the short duration of treatment could have affected the evaluation on results of efficacy and safety.

An important issue concerns the sustained clinical effect (defined as the maintenance of significant and clinically relevant efficacy during two to three treatment years) and long-term efficacy (defined as sustained significant and clinically relevant efficacy in post-treatment years, i.e., a disease-modifying effect). They are both currently required by the European Medicines Agency to AIT preparations [28].

Unfortunately, in this regard, head-to-head comparisons between a pre-coseasonal and a perennial regimen are lacking.

Comparison of Safety

There are no head-to-head comparative studies of the safety of a pre-coseasonal regimen vs a year-round regimen. However, it is reasonable that there are no significant differences between the two regimens. Overall, although the majority of adult and pediatric patients taken SLIT experienced adverse events, the latter were generally local, mild-to moderate, and transient (first for frequency, oral pruritus) [1••]. So far, other reactions have been reported, such as asthma, urticaria, abdominal pain, and a few anecdotal cases of anaphylaxis [29, 30], of which one occurred at the first SLIT dose [29]. No fatality due to SLIT was reported in more than 30 years of clinical use. Other serious events such as eosinophilic esophagitis have been occasionally reported [31]. Adverse reactions occur more frequently during the beginning of treatment than in the maintenance phase [1••], but accelerated induction schedules or no-induction seem to be tolerated as well as slower inductions [1••].

Comparison of Adherence

Behavioral studies demonstrate that longer periods of medication are associated with poorer compliance and thus a lower likelihood of effectiveness [32, 33]. Moreover, in pollen-induced allergic respiratory diseases, continuous (or post-seasonal) SLIT administration is challenging as patients do not perceive the benefit of AIT after the pollen period has ended, that is when they were asymptomatic already before starting of SLIT [5••].

On the other hand, pre- and co-seasonal regimens are also burdened by

limitations. The length of pre-seasonal treatment (followed by co-seasonal treatment) has been shown to influence the effectiveness of SLIT, intended as magnitude of the reductions in rhino-conjunctivitis symptom and medication scores: 2 months is less effective than 4 months of pre-seasonal treatment [23, 24], and 4 months appeared to be optimal [14]. Hence, a patient with a pollen allergy following a pre- and co-seasonal regimen from 1 year to another has to remember to obtain E n medication and initiate treatment long enough ahead of the pollen season. The persistence of treatment is a problem avoided if a year-round regimen is strictly adhered to.

Health Economics Profile

Pre-coseasonal treatment regimens have economic and compliance benefits in comparison with perennial regimens [34, 35]. A shorter duration of treatment of discontinuous protocols implies that patients will receive less medication, thus leading to a lower acquisition cost of medication. Moreover, in the treatment of pollen-induced allergic diseases, pre-coseasonal SLIT regimens appear to be at least as effective and safe as perennial SLIT regimens; hence, costs for rescue therapies are at least the same, if not lower.

Conclusions

To identify the best maintenance SLIT regimen in pollen-induced allergic respiratory diseases is a crucial issue for clinicians. It is not clear if a continuous treatment is more effective than an intermittent one in producing immunological changes over long time, which are likely associated with preventative effects, too. However, to date, SLIT administered in pre-coseasonal regimens has provided evidence of short-term, sustained, and post-treatment efficacy [8, 24]. In addition, it is evident that, in comparison to perennial regimen, pre-coseasonal regimen is associated with lower costs (indifferently from the kind of health national system) and good compliance to the treatment [5••]. Good compliance constitutes a further factor in favor of SLIT efficacy.

On the basis of clinical trials and post-marketing, "real-life" trials, in birch or grass pollen-induced respiratory allergic diseases, pre-coseasonal SLIT regimens, administered daily, for at least 4 months of pre-seasonal treatment and at least three treatment seasons appear to be at least as effective and safe as perennial SLIT regimens and are associated with lower costs and good compliance.

However, overall, further head-to-head studies are required to establish whether discontinuous SLIT regimens are associated with better compliance and/or safety and/or major very long-term benefits than perennial SLIT regimens.

Pediatric Considerations

Immunotherapy guidelines do not specify a particular lower age for AIT initiation [36]. Some clinical trials have shown the efficacy and safety of SLIT in preschool age [37]. SLIT constitutes the modality of disease-modifying treatment more available and attractive for young children and their caregivers on

the basis of its favorable safety profile and at-home management. In younger children, compliance to the treatment is further crucial (they may have difficulty in assumption of oral doses). Another aspect, pivotal above all in pediatric population, is the preventive benefit of AIT: the latter is expected to be greater if initiated early in the course of the allergic disease, when the disease progression may be more effectively hampered [1••].

Compliance with Ethical Standards

Conflict of Interest
Dr. Stefania Arasi declares that she has no conflict of interest.
Dr. Giovanni B. Pajno declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
•• Of major importance

1.•• Canonica GW, Cox L, Pawankar R, et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. World Allergy Organ J. 2014;7:6.

The updated position paper of World Allergy Organization focused on sublingual immunotherapy.

2. Arasi S, Passalacqua G, Caminiti L, et al. Efficacy and safety of sublingual immunotherapy in children. Expert Rev Clin Immunol. 2016;12:49–56.
3. Arbes Jr SJ, Gergen PJ, Elliott L, Zeldin DC. Prevalences of positive skin test responses to 10 common allergens in the US population: results from the third National Health and Nutrition Examination Survey. J Allergy Clin Immunol. 2005;116:377–83.
4. Bousquet PJ, Castelli C, Daures JP, et al. Assessment of allergen sensitization in a general population-based survey (European Community Respiratory Health Survey I). Ann Epidemiol. 2010;20:797–803.
5.•• Demoly P, Calderon MA, Casale TB, Malling HJ, Wahn U. The value of pre- and co-seasonal sublingual immunotherapy in pollen-induced allergic rhinoconjunctivitis. Clin Transl Allergy. 2015;5:18.

Critical recent overview on the topic.

6. Halken S, Agertoft L, Seidenberg J, et al. Five-grass pollen 300IR SLIT tablets: efficacy and safety in children and adolescents. Pediatr Allergy Immunol. 2010;21:970–6.
7. Eng PA, Borer-Reinhold M, Heijnen IA, Gnehm HP. Twelve-year follow-up after discontinuation of preseasonal grass pollen immunotherapy in childhood. Allergy. 2006;61:198–201.
8. Burks AW, Calderon MA, Casale T, Cox L, Demoly P, Jutel M, 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;131:1288–96.
9. Novembre E, Galli E, Landi F, et al. Coseasonal sublingual immunotherapy reduces the development of asthma in children with Allergic rhino-conjunctivitis. J Allergy Clin Immunol. 2004;114:851–7.
10. Walker SM, Pajno GB, Lima MT, et al. Grass pollen immunotherapy for seasonal rhinitis and asthma: a randomized controlled trial. J Allergy Clin Immunol. 2001;107:87–93.
11. Mosges R, Klimek L. Today's allergic rhinitis patients are different: new factors that may play a role. Allergy. 2007;62:969–75.
12. Pajno GB, Passalacqua G, Vita D, et al. Sublingual immunotherapy abrogates seasonal bronchial hyperresponsiveness in children with Parietaria-induced respiratory allergy: a randomized controlled trial. Allergy. 2004;59:883–7.
13. Pajno GB, Barberio G, De Luca F, et al. Prevention of new sensitization in asthmatic children monosensitized to house dust mite by specific immunotherapy: a six-year follow-up study. Clin Exp Allergy. 2001;31:1392–7.

14. Calderon M, Mösges R, Hellmich M, Demoly P. Towards evidence-based medicine in specific grass pollen immunotherapy. Allergy. 2010;65:420–34.
15. Calderon MA, Casale TB, Nelson HS, Demoly P. An evidence-based analysis of house dust mite allergen immunotherapy: a call for more rigorous clinical studies. J Allergy Clin Immunol. 2013;132:1322–36.
16. Horak F, Zieglmayer P, Zieglmayer R, Lemell P, Devillier P, Montagut A, et al. Early onset of action of a 5-grass-pollen 300IRsublingual immunotherapy tablet evaluated in an allergen challenge chamber. J Allergy Clin Immunol. 2009;124:471–7.
17. Lombardi C, Incorvaia C, Braga M, Senna G, Canonica GW, Passalacqua G. Administration regimens for sublingual mmunotherapy: what do we know. Allergy. 2009;64:849–54.
18. Creticos PS, Esch RE, Couroux P, Gentile D, D'Angelo P, Whitlow B, et al. Randomized, double-blind, placebo-controlled trial of standardized ragweed sublingual-liquid immunotherapy for allergic rhinoconjunctivitis. J Allergy Clin Immunol. 2014;133:751–8.
19. Sieber J, Köberlein J, Mösges R. Sublingual immunotherapy in daily medical practice: effectiveness of different treatment schedules - IPD meta-analysis. Curr Med Res Opin. 2010;26:925–32.
20. Quercia O, Bruno ME, Compalati E, Falagiani P, Mistrello G, Stefanini GF. Efficacy and safety of sublingual immunotherapy with grass monomeric allergoid: comparison between two different treatment regimens. Eur Ann Allergy Clin Immunol. 2011;43:176–83.
21. Pajno GB, Caminiti L, Crisafulli G, et al. Direct comparison between continuous and coseasonal regimen for sublingual immunotherapy in children with grass allergy: a randomized controlled study. Pediatr Allergy Immunol. 2011;22:803–7.
22. Calderon MA, Birk AO, Andersen JS, Durham SR. Prolonged preseasonal treatment phase with Grazax sublingual immunotherapy increases clinical efficacy. Allergy. 2007;62:958–61.
23. Didier A, Worm M, Horak F, Sussman G, de Beaumont O, Le Gall M, et al. Sustained 3-year efficacy of pre- and coseasonal 5-grass-pollen sublingual immunotherapy tablets in patients with grass pollen-induced rhinoconjunctivitis. J Allergy Clin Immunol. 2011;128:559–66.
24. Didier A, Malling HJ, Worm M, Horak F, Sussman G, Melac M, et al. Post-treatment efficacy of discontinuous treatment with 300IR 5-grass pollen sublingual tablet in adults with grass pollen-induced allergic rhinoconjunctivitis. Clin Exp Allergy. 2013;43:568–77.
25. Di Bona D, Plaia A, Scafidi V, Leto-Barone MS, Di Lorenzo G. Efficacy of sublingual immunotherapy with grass allergens for seasonal allergic rhinitis: a systematic review and meta-analysis. J Allergy Clin Immunol. 2010;126:558–66.
26. Stelmach I, Kaluzi_nska-Parzyszek I, Jerzynska J, et al. Comparative effect of pre-coseasonal and continuous grass sublingual immunotherapy in children. Allergy. 2012;67:312e320.
27. Di Bona D, Plaia A, Leto-Barone MS, La Piana S, Di Lorenzo G. Efficacy of grass pollen allergen sublingual immunotherapy tablets for seasonal allergic rhinoconjunctivitis: a systematic review and meta-analysis [published online June 29, 2015]. JAMA Intern Med.
28. Committee for Medicinal Products for Human Use at the European Medicines Agency. Guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases, Draft CHMP/EWP/18504/2006. London: 2008.
29. de Groot H, Bijl A. Anaphylactic reaction after the first dose of sublingual immunotherapy with grass pollen tablet. Allergy. 2009;64:963–4.
30. Eifan AO, Keles S, Bahceciler NN, Barlan IB. Anaphylaxis to multiple pollen allergen sublingual immunotherapy. Allergy. 2007;62:567–8.
31. Antico A, Fante R. Esophageal hypereosinophilia induced by grass sublingual immunotherapy. J Allergy Clin Immunol. 2014;133(5):1482–4.
32. Sabate E: Adherence to long-term therapies: evidence for action. Available from: http://www.who.int/chp/knowledge/publications/adherence_report/en/.
33. Christensen AJ. Patient adherence to medical treatment regimens: bridging the gap between behavioral science and biomedicine. Current Perspectives In Psychology. New Haven: Yale University Press; 2004.
34. Westerhout KY, Verheggen BG, Schreder CH, Augustin M. Cost effectiveness analysis of immunotherapy in patients with grass pollen allergic rhinoconjunctivitis in Germany. J Med Econ. 2012;15:906–17.
35. Dranitsaris G, Ellis AK. Sublingual or subcutaneous immunotherapy for seasonal allergic rhinitis: an indirect analysis of efficacy, safety and cost. J Eval Clin Pract. 2014;20:225–38.
36. Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: a practice parameter third update. J Allergy Clin Immunol. 2011;127:S1–S55.
37. Fiocchi A, Pajno G, La Grutta S, et al. Safety of sublingual-swallow immunotherapy in children aged 3- to 7 years. Ann Allergy Asthma Immunol. 2005;95:254–8.