

EXPERT
REVIEWS

Sublingual allergen immunotherapy for respiratory allergies: what is new?

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Sublingual immunotherapy (SLIT) is a disease-modifying treatment for respiratory allergies that has been used for many years in Europe and has also recently been approved for use in North America. Its use is thus likely to increase. There is more evidence available regarding SLIT efficacy and its good safety profile, making it an appealing treatment option. The majority of studies have mostly focused on grass pollens; however, there are now data available regarding efficacy for other allergens. This review will summarize recent findings from SLIT clinical trials for respiratory allergies, including efficacy, safety, post-discontinuation effects and use in different age groups. Grass pollen, tree pollen, house dust mite and ragweed SLIT studies will be evaluated.

KEYWORDS: allergen immunotherapy • allergic rhinoconjunctivitis • grass pollen • house dust mite • ragweed • sublingual immunotherapy • tree pollen

Sublingual immunotherapy (SLIT) has been used in Europe for the treatment of allergic respiratory diseases for the last few decades. Its popularity has increased due to the ease of administration and good safety profile. Three SLIT tablet preparations have also recently been approved for use in North America [1,2].

Well-powered, double-blind, placebo-controlled randomized clinical trials (DBPC RCT) and meta-analyses have shown SLIT to be an effective treatment. Updated recommendations for its use have been published by the World Allergy Organization and American Academy of Allergy, Asthma & Immunology/European Academy of Allergy and Clinical Immunology [3,4]. Furthermore, more evidence is now becoming available regarding its long-term efficacy.

This review will discuss recent findings from SLIT clinical trials for the treatment of respiratory allergies. These will include new evidence regarding efficacy and safety as well as post-discontinuation effect of treatment. Furthermore, new information for the use of allergen immunotherapy (AIT) in different age groups including the elderly will be explored.

The review has been divided based on the type of SLIT allergen evaluated in the included studies: grass pollen, tree pollen, house dust mite (HDM) and ragweed pollen.

Grass pollens

Grass is the most well-studied allergen causing allergic rhinitis/conjunctivitis and seasonal asthma.

Sustained efficacy post-discontinuation of treatment is one of the advantages of SLIT compared with pharmacotherapy. A 5-year, double-blind, multinational, placebo-controlled trial in adults showed sustained clinical efficacy and disease modification 2 years after completion of 3 years of daily treatment with grass AIT (Grazax, *Phleum pratense* 75,000 SQ-T/2800 BAU, ALK, Denmark). The second follow-up and final year of this trial showed a statistically significant and clinically relevant sustained efficacy of 25% ($p = 0.004$) on the rhinoconjunctivitis symptom score in the active group relative to placebo. The significant reduction in symptoms was accompanied by less use of symptomatic medications. A significant reduction in rhinoconjunctivitis combined score

was obtained during the fifth season, with an average reduction of 33% (95% CI: 30–38%) in rhinoconjunctivitis combined score over the 5 years of the trial. No treatment-related serious adverse events (AEs) or events of severe systemic allergic reactions were reported during the 5 years of the trial [5].

Pre- and coseasonal treatment with 300 index of reactivity (IR) 5-grass pollen sublingual tablet (Stallergenes SA, Antony, France) administered discontinuously for three consecutive years has also been shown to be efficacious post-treatment, safe and well tolerated. In this randomized trial, adult participants received either placebo or a 300 IR tablet daily beginning either 4 or 2 months prior to each pollen season and continuing for its duration for three consecutive years. They were followed over the subsequent immunotherapy-free pollen season. In 435 patients included in the year 4 efficacy analyses, the least-squares mean differences in Average Adjusted Symptom Score (AAdSS) (adjusting the Rhinoconjunctivitis Total Symptom Score for rescue medication usage) between active treatment and placebo over the fourth pollen period were -1.14 (-2.03 ; -0.26) ($p = 0.0114$) and -1.43 (-2.32 ; -0.53) ($p = 0.0019$) in the 4 and 2 months groups, corresponding to -22.9 and -28.5% relative least-squares mean differences (vs placebo), respectively. The active groups also showed statistically significant differences compared with placebo in Average Rhinoconjunctivitis Total Symptom Score, Average Rescue Medication Score and overall Rhinoconjunctivitis Quality of Life Questionnaire Score [6].

Considering that in real-life clinical practice, the majority of patients are polysensitized, recent studies have carefully evaluated the sensitization profile of patients receiving SLIT. A large randomized controlled trial evaluated the grass sublingual immunotherapy tablet (MK-7243) (2800 BAU *P. pratense*) in 1501 adults and children with allergic rhinitis with or without conjunctivitis in North America. In this study, 85% of participants were polysensitized and 25% also had asthma. Participants received the treatment at least 12 weeks before and during the entire grass pollen season. MK-7243 yielded improvements versus placebo of 23% in the entire-season total combined score (TCS), 29% in the peak-season TCS, 20% in entire-season daily symptom score, 35% in entire-season daily medication score and 12% in peak-season Rhinoconjunctivitis Quality of Life Questionnaire. These results show that MK-7243 was effective in polysensitized grass-allergic individuals. In addition, the efficacy was similar in children and adults. Most AEs were transient local application-site reactions, with no serious treatment-related AEs or anaphylactic shock. Three subjects (one placebo, two MK-7243) had moderate systemic allergic reactions. There were no safety differences in participants with asthma [7].

Furthermore, a *post hoc* analysis of pooled data from six randomized, double-blind, placebo-controlled trials ($n = 1871$) comparing the efficacy and safety of the SQ-standardized grass allergy immunotherapy tablet, Grazax (*P. pratense* 75,000 SQ-T/2800 BAU, ALK, Denmark), in mono- and polysensitized subjects found reductions in the TCS to be similar between

mono- and polysensitized subjects, that is, 28 and 26%, respectively. The overall safety profile was also similar in mono- and polysensitized subjects [8].

SLIT is a good treatment alternative, especially in the case of children as it is painless compared with SCIT. A randomized, double-blind, placebo-controlled trial was carried out in 207 children aged 4–12 years with grass pollen-allergic rhinitis/rhinoconjunctivitis with/without bronchial asthma (Global Initiative for Asthma I/II). Participants received either high-dose grass pollen SLIT or placebo daily for one pre-/coseasonal period. This study showed significant reduction in symptoms and medication use in the first grass pollen season after the start of treatment. The number of well days and the percentage of responders were greater in the active group. Furthermore, the treatment was well tolerated with no serious treatment-related events reported [9].

A 2-year prospective, randomized, double-blind, placebo-controlled trial comparing the efficacy and the safety of SLIT given pre-coseasonally and continuously in children allergic to grass pollen found that both pre-coseasonal and continuous SLIT were associated with a substantial reduction in the combined symptoms/medication score when compared with placebo. There were no significant differences between the regimens (mean difference: 18.1 ± 12.4 , $p > 0.05$) with the exception of nasal symptoms that were lower in the pre-coseasonal group [10].

In routine medical practice, a prospective, open, non-controlled, non-interventional, multicenter study with 1482 patients (16.9 children and 13.7% adolescent) found that AIT with Oralair 5-grass pollen SLIT tablet (Stallergenes) was well tolerated by children and adolescents. All symptom scores and symptomatic medication use were reduced significantly after 1 and 2 years under Oralair treatment compared with the season preceding AIT. Polyallergic children and adolescents benefited as much from AIT as monoallergic individuals [11].

Tree pollens

Unfortunately, despite the high prevalence of tree pollen allergy, there are only limited studies on tree pollen SLIT. Recently, a prospective, randomized, open, blinded end point, controlled, single-center study in 74 birch allergic adults was performed to compare the clinical efficacy and safety of two sublingual birch pollen products. Patients with allergic rhinoconjunctivitis due to birch pollen with or without mild intermittent asthma were treated with SUBLIVAC FIX Birch (a liquid oral preparation) (SUB-B; HAL Allergy) or Staloral Birch (Stallergenes) once daily for 16–20 weeks. Treatment with both products was effective by means of reduction in allergic symptoms during a titrated nasal provocation test to birch pollen. The beneficial treatment effect was similar in both treatment groups, 33.3% for SUB-B versus 31.4% for Staloral Birch in the intention-to-treat population. The majority of the AEs recorded were of mild intensity. The same pattern of AEs was observed for both products [12].

In terms of SLIT and seasonal asthma, a 3-year open randomized study was recently carried out in 84 adults with asthma, which were uncontrolled during the previous birch pollen season, despite a treatment with budesonide 400 µg/day. Patients randomly received budesonide 800 µg/day, budesonide 1600 µg/day, budesonide 400 µg/day plus montelukast 10 µg/day and budesonide 400 µg/day plus carbamylated allergoid of *betulaceae* pre-coseasonally. All treatment options, except budesonide 800 µg/day, produced an improvement of mean monthly asthma control test ($p < 0.05$). Of note, patients undergoing low-dose budesonide plus immunotherapy achieved, after 3 years, an appreciable control (asthma control test mean score 24). Only budesonide together with immunotherapy reduced nasal eosinophils and nasal steroids usage [13].

House dust mite

There has been an increased interest in SLIT for HDM with randomized controlled trials being carried out in children, adults and the elderly. Different preparations and doses have been studied in patients with HDM-associated allergic rhinitis, or asthma or both.

Bergmann *et al.* [14] performed a randomized, double-blind, placebo-controlled, parallel group trial in seven European countries in 509 adults with HDM-associated allergic rhinitis. The efficacy and safety of two doses of HDM sublingual tablets (500 and 300 IR tablets) was assessed over one treatment year and the subsequent immunotherapy-free year. Over the year 1 primary period, the AAdSS was significantly lower in the active groups compared with the placebo group. The relative difference versus placebo was 20.2% for the 500 IR group and 17.9% for the 300 IR group. There was no significant difference between the active groups. The onset of action was at 4 months. Importantly, efficacy of both doses was maintained during the treatment-free follow-up year. The participants' global evaluation of treatment success was significantly higher in the 500 IR and 300 IR groups compared with the placebo group ($p = 0.0206$ and $p = 0.0001$, respectively). Presence of asthma and sensitization status did not affect the efficacy results. SLIT was well tolerated with no cases of anaphylaxis.

A recent trial investigated the efficacy and safety of a standardized quality HDM SLIT-tablet (ALK, Hørsholm, Denmark) in 604 subjects 14 years or older with HDM allergic rhinitis and mild-to-moderate asthma. Participants were randomized to daily treatment with one of three active doses (1, 3 or 6 SQ-HDM) or placebo. The primary end point was a reduction in inhaled corticosteroid (ICS) dose from the individual subject's baseline dose after 1 year of treatment. The mean difference between 6 SQ-HDM and placebo in the reduction in daily ICS dose was 81 µg ($p = 0.004$). Relative mean and median reductions were 42 and 50% for 6 SQ-HDM and 15 and 25% for placebo, respectively. The most common AEs were local reactions in the mouth. The rate and severity of AEs were higher for 3 and 6 SQ-HDM than for 1 SQ-HDM and placebo [15].

Following on from this study [15], ICS reduction, Asthma Quality of Life Questionnaire (AQLQ) and Asthma Control Questionnaire Score was analyzed *post hoc* in a subgroup with daily inhaled corticosteroid use of 400–800 µg and Asthma Control Questionnaire Score of 1–1.5, corresponding to partly controlled asthma ($n = 108$). The benefits of 1 year of treatment in this subgroup were significantly higher than the residual population. The difference between placebo and 6 SQ-HDM in change from baseline in daily ICS use was 327 µg ($p < 0.0001$), while it was 0.52 ($p = 0.010$) for AQLQ. The treatment effect on ICS reduction and AQLQ was increased for the subgroup versus the residual population (ICS reduction: $p < 0.001$; AQLQ: $p = 0.044$) [16].

Wang *et al.* [17] studied the efficacy and safety of 12-month daily SLIT (300 IR *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* extract) in 484 HDM-induced asthmatic adults in a DBPC RCT performed in China. The primary efficacy outcome was well-controlled asthma for at least 16 of the last 20 weeks of treatment. The proportions of patients achieving well controlled or totally controlled asthma by the study end were slightly but not significantly greater in the active treatment group than in the placebo group. *Post hoc* analysis by asthma severity revealed significant clinical benefits in actively treated subjects with moderate, persistent asthma ($n = 175$) at baseline, with greater achievement of well-controlled asthma ($p = 0.021$) and totally controlled asthma ($p = 0.008$), a higher percentage of patients with an Asthma Control Questionnaire score < 0.75 ($p = 0.039$) and a greater mean reduction in inhaled corticosteroid use (218.5 and 126.2 µg, respectively; $p = 0.004$). There was no significant difference for patients with mild asthma. There were no treatment-related serious AEs.

A DBPC RCT study aiming to investigate how quickly HDM induces allergic rhinitis symptoms in patients aged 4–60 years will improve with a *D. pteronyssinus* and *D. farinae* SLIT extract found that the total symptom and visual analog scores in the SLIT group decreased significantly when compared with the placebo controls ($p < 0.05$) after week 14. In the SLIT group, the nasal itching score was significantly lower than the placebo group after week 14 ($p < 0.05$), while nasal obstruction and sneezing scores showed a significant difference after week 22 ($p < 0.05$) [18].

A study investigating the efficacy of HDM SLIT (*D. farinae* extract) in monosensitized and polysensitized children with HDM-induced respiratory allergic diseases found that the global clinical parameters had significantly improved after 52 weeks treatment, with no significant difference between the monosensitized and polysensitized group throughout this period (all $p > 0.05$) [19].

The efficacy of AIT in the elderly patients is a neglected area with only very few studies carried out in this population. A double-blind, placebo-controlled study of 111 60- to 75-year-old patients with allergic rhinitis confirmed *D. pteronyssinus* and *D. farinae* allergy were randomized to receive HDM SLIT (Staloral 300R, Stallergenes) or placebo and were

monitored for 3 years. The total nasal symptom score decreased by 44% in the active group and 6% in the placebo group after 3 years of SLIT. This difference was only significant in the active group ($p < 0.05$). The total medication score of the active group decreased significantly by a maximum of 51% ($p < 0.05$), whereas the total medication score of the placebo control group showed an insignificant decrease ($p = 0.56$). The treatment was well tolerated with no systemic adverse reactions during the study [20].

Ragweed pollen

Short ragweed pollen is a significant cause of allergic rhinitis in North America and in some European countries. Recent studies have assessed the efficacy of AIT using a ragweed tablet or a liquid preparation.

North American adults ($n = 565$) with ragweed pollen-induced allergic rhinitis/conjunctivitis were treated with a daily ragweed AIT tablet (MK-3641) (6 or 12 *Ambrosia artemisiifolia* major allergen 1 [Amb a 1] units) or placebo before, throughout and after the ragweed season (~52 weeks). During peak season, the 6- and 12-Amb a 1 unit ragweed AIT doses showed 21 and 27% improvement in total combined score versus placebo ($p < 0.05$). The 6- and 12-Amb a 1 unit AIT doses significantly improved daily symptom score and daily medication score versus placebo ($p < 0.05$). Peak and entire season efficacy were comparable. Most treatment-related AEs were mild, oral reactions. No systemic allergic reactions were reported. One patient in the 6-Amb a 1 unit group received epinephrine for sensation of localized pharyngeal edema [21].

In another randomized controlled trial study, in this case including adults from North America and Europe ($n = 784$), participants were treated with a ragweed immunotherapy tablet containing 1.5, 6 or 12 units of Amb a 1-U or placebo for 52 weeks. AIT with 12 Amb a 1-U was found to be most effective with the total combined daily symptom/medication score reduced by 24% during peak ragweed season and 27% during the entire season compared with placebo. Furthermore, the tablet was well tolerated and no systemic allergic reactions occurred [22].

Overall, this ragweed sublingual tablet appears to be well tolerated as seen in these two trials as well as in two 28-day safety studies. Of the 1707 MK-3641-treated subjects, one systemic (anaphylactic) reaction was reported (0.06%) [23].

A DBPC RCT trial of a glycerinated short ragweed sublingual allergen immunotherapy liquid (RW-SAIL) was performed in adults with ragweed-related allergic rhinoconjunctivitis and with or without asthma treated approximately 8–16 weeks before and through the end of the ragweed pollen season. As reported by the investigators, during the entire season, there was a 43% decrease in total combined daily rhinoconjunctivitis symptom and medication scores (TCS) in subjects treated with RW-SAIL compared with placebo. Similar decreases were observed in TCS between the two groups during peak season (42%) and in daily symptom scores during the entire (42%) and peak (41%) seasons. The occurrence of AEs was similar between the treatment groups; most being mild in severity [24].

Expert review & five-year view

More evidence regarding the efficacy and safety of SLIT is now becoming available [25]. In addition, a recent meta-analysis of SLIT and pharmacotherapy in pollen-induced seasonal allergic rhinoconjunctivitis, in an indirect comparison found that grass pollen SLIT tablets had a greater mean relative clinical impact than second-generation antihistamines and montelukast and much the same mean relative clinical impact as nasal corticosteroids [26].

With the approval of two grass pollen and one ragweed preparation now in North America in addition to its already established use in Europe, it is likely that the use of SLIT is going to increase and more experience in its use will be acquired. More data are now also becoming available for perennial allergens such as HDM; however, there is still a need for well-designed SLIT studies to further assess this as well as identify the most appropriate preparation and dosing regime.

Overall, there has been an increased call for better designed SLIT studies. The European Academy of Allergy and Clinical Immunology has recently published recommendations regarding clinical outcomes in immunotherapy trials for allergic rhinoconjunctivitis [27]. These are likely to assist in standardizing outcome measures in order to enable better analysis of clinical efficacy and improve the comparability of results.

Cost-effectiveness of AIT is an important area that has recently attracted more attention. A systematic review of publications assessing health economics of AIT for a variety of perennial and seasonal allergic conditions, found that in 23 out of the 24 publications included AIT (SCIT or SLIT) led to cost savings compared with symptomatic drug treatment. When SCIT was compared with SLIT, four out of the six studies evaluating these two administration routes showed a favorable result for SLIT [28].

This area should be further explored in order to assess cost-effectiveness and identify in which groups of patients AIT is likely to bring the greatest benefits. Ruggeri *et al.* [29] conducted a *post hoc* analysis using the AAdSS to compare the effect of treatment of allergic rhinitis with 5-grass pollen tablets versus placebo. It was found that the 5-grass pollen tablet is a cost-effective treatment for adults with allergic rhinitis with a medium or high AAdSS.

Furthermore, it would be helpful to identify whether there are any difference in cost-effectiveness between different preparations and schedules. A systematic literature review of 20 double-blind, randomized, placebo-controlled trials compared four treatments from the Canadian healthcare perspective in order to identify the lowest first year cost of AIT for grass pollen allergic rhinitis among four treatments [30]. These included Oralair SLIT tablets (administered once-daily 4 months before and 1 month during the allergy season), Grazax SLIT tablets (administered daily throughout the year) and perennially administered and seasonally administered SCIT. Twenty trials were included. Investigators found that in the first year of treatment, Oralair was associated with significant cost savings compared with SCIT administered throughout the year, SCIT

administered seasonally and Grazax administered throughout the year. It was concluded that the seasonal administration of Oralair contributed to the product's favorable cost savings when compared with perennially administered Grazax and SCIT. However, the significant cost benefits reported for Oralair versus seasonally administered SCIT are notable.

Adherence is an area of possible concern regarding SLIT as this is self-administered and treatment for at least 3 years is currently recommended in order for it to have sustained long-term effects. Rates of adherence reported in various studies are highly variable. A systematic review of published research that assessed adherence or tested interventions to improve SLIT adherence found that across studies, 55–82% of patients abandoned SLIT before completing the recommended course of therapy [31]. However, adherence rates are difficult to evaluate as these can vary depending on the type of study, with controlled studies reporting better adherence rates compared with real-life studies [32]. Furthermore, length of follow-up of participants can affect rates as adherence may be better when initiating treatment but decline with time. It is important to focus research on identifying strategies such as educational or technological interventions that aim to improve and motivate better adherence [33].

In the next few years, it is likely that more SLIT studies will be performed with other allergens such as tree pollens. It is hoped that better standardized products will be developed and more data regarding the best treatment schedules, for example, pre-seasonal, pre-coseasonal will be identified for these allergens. The allergen exposure chamber developed as a

pharmacodynamic assessment tool to control the environmental allergens and to avoid problems associated with unpredictable pollen seasons has previously been used to evaluate the onset of action and efficacy of a grass pollen 300 IR SLIT tablet [34]. More recently, a sublingual HDM immunotherapy tablet (MK-8237 Merck/ALK-Abelló) was evaluated in a randomized, double-blind trial in 124 adults with allergic rhinitis/conjunctivitis with/without asthma that underwent exposure challenges in a chamber [35]. Allergen exposure chambers have also been used to assess silver birch SCIT [36], ragweed SCIT [37] and cat Fel d 1-derived peptide antigen desensitization [38]. As allergen exposure chambers have also been validated for other allergens such as Japanese cedar, it is likely these will be used in more immunotherapy clinical trials [39–41].

Overall, SLIT appears to be an efficacious disease-modifying treatment with a good safety profile. More evidence regarding its mechanism of action is becoming available [42,43]. This information is likely to further assist clinicians to decide whether SLIT is an appropriate treatment for their patients.

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Key issues

- Grass sublingual immunotherapy (SLIT) appears to be effective in polysensitized grass-allergic individuals as well as in grass monosensitized individuals.
- Treatment with grass SLIT leads to sustained efficacy post discontinuation of treatment.
- Presence of asthma and sensitization status does not appear to affect the efficacy results of house dust mite SLIT.
- SLIT is well tolerated with mild and local reactions being most frequent and only very low rates of systemic reactions.

References

Papers of special note have been highlighted as:

•• of considerable interest

1. Cox L. Sublingual immunotherapy for aeroallergens: status in the United States. *Allergy Asthma Proc* 2014;35(1):34–42
2. Approval Letter-RAGWITEK, Food and drug administration. 2014. Available from: www.fda.gov/BiologicsBloodVaccines/Allergens/ucm393806.htm [Last accessed 4 September 2014]
3. Canonica GW, Cox L, Pawankar R, et al. Sublingual immunotherapy: world allergy organization position paper 2013 update. *World Allergy Organ J* 2014;7(1):6
4. 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(5):1288–96
5. Durham SR, Emminger W, Kapp A, et al. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. *J Allergy Clin Immunol* 2012;129(3):717–25
6. Didier A, Malling HJ, Worm 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(5):568–77
7. Maloney J, Bernstein DI, Nelson H, et al. Efficacy and safety of grass sublingual immunotherapy tablet, MK-7243: a large

- randomized controlled trial. *Ann Allergy Asthma Immunol* 2014;112(2):146-53
8. Nelson H, Blaiss M, Nolte H, et al. Efficacy and safety of the SQ-standardized grass allergy immunotherapy tablet in mono- and polysensitized subjects. *Allergy* 2013;68(2):252-5
 9. Wahn U, Klimek L, Ploszczuk A, et al. High-dose sublingual immunotherapy with single-dose aqueous grass pollen extract in children is effective and safe: a double-blind, placebo-controlled study. *J Allergy Clin Immunol* 2012;130(4):886-93
 10. Stelmach I, Kaluzińska-Parzyszek I, Jerzynska J, et al. Comparative effect of pre-coseasonal and continuous grass sublingual immunotherapy in children. *Allergy* 2012;67(3):312-20
 11. Karagiannis E, Shah-Hosseini K, Hadler M, et al. Non-interventional 2-year study of sublingual immunotherapy in children and adolescents with allergic rhinoconjunctivitis caused by grass pollen. *Clin Transl Allergy* 2014;4(Suppl 1):P14
 12. Klimek L, Sperl A, van Twuijver E, et al. A prospective study comparing the efficacy and safety of two sublingual birch allergen preparations. *Clin Transl Allergy* 2014;4:23
 13. Marogna M, Braidì C, Bruno ME, et al. The contribution of sublingual immunotherapy to the achievement of control in birch-related mild persistent asthma: a real-life randomised trial. *Allergol Immunopathol (Madr)* 2013;41(4):216-24
 14. Bergmann KC, Demoly P, Worm M, et al. Efficacy and safety of sublingual tablets of house dust mite allergen extracts in adults with allergic rhinitis. *J Allergy Clin Immunol* 2014;133(6):1608-14
 15. Mosbech H, Deckelmann R, de Blay F, et al. Standardized quality (SQ) house dust mite sublingual immunotherapy tablet (ALK) reduces inhaled corticosteroid use while maintaining asthma control: a randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol* 2014;134:568-75
 16. de Blay F, Kuna P, Prieto L, et al. SQ HDM SLIT-tablet (ALK) in treatment of asthma - Post hoc results from a randomised trial. *Respir Med* 2014. [Epub ahead of print]
 17. Wang L, Yin J, Fadel R, et al. House dust mite sublingual immunotherapy is safe and appears to be effective in moderate, persistent asthma. *Allergy* 2014;69(9):1181-8
 18. Wang DH, Chen L, Cheng L, et al. Fast onset of action of sublingual immunotherapy in house dust mite-induced allergic rhinitis: a multicentre, randomized, double-blind, placebo-controlled trial. *Laryngoscope* 2013;123(6):1334-40
 19. Li P, Li Q, Huang Z, et al. Efficacy and safety of house dust mite sublingual immunotherapy in monosensitized and polysensitized children with respiratory allergic diseases. *Int Forum Allergy Rhinol* 2014. [Epub ahead of print]
 20. Bozek A, Ignasiak B, Filipowska B, et al. House dust mite sublingual immunotherapy: a double-blind, placebo-controlled study in elderly patients with allergic rhinitis. *Clin Exp Allergy* 2013;43(2):242-8
 21. Nolte H, Hébert J, Berman G, et al. Randomized controlled trial of ragweed allergy immunotherapy tablet efficacy and safety in North American adults. *Ann Allergy Asthma Immunol* 2013;110(6):450-6
 22. 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(5):1342-9
 23. Nolte H, Amar N, Bernstein DI, et al. Safety and tolerability of a short ragweed sublingual immunotherapy tablet. *Ann Allergy Asthma Immunol* 2014;113(1):93-100
 24. Creticos PS, Esch RE, Couroux P, et al. Randomized, double-blind, placebo-controlled trial of standardized ragweed sublingual-liquid immunotherapy for allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2014;133(3):751-8
 25. Lin SY, Ereksom N, Kim JM, et al. Sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review. *JAMA* 2013;309:1278-88
 26. Devillier P, Dreyfus JF, Demoly P, et al. A meta-analysis of sublingual allergen immunotherapy and pharmacotherapy in pollen-induced seasonal allergic rhinoconjunctivitis. *BMC Med* 2014;12:71
 27. Pfaar O, Demoly P, Gerth van Wijk R, et al. Recommendations for the standardization of clinical outcomes used in allergen immunotherapy trials for allergic rhinoconjunctivitis: an EAACI Position Paper. *Allergy* 2014;69(7):854-67
 28. Hankin CS, Cox L. Allergy immunotherapy: what is the evidence for cost saving? *Curr Opin Allergy Clin Immunol* 2014;14:363-70
- **A systematic review assessing the evidence for allergen immunotherapy cost savings.**
29. Ruggeri M, Oradei M, Frati F, et al. Economic evaluation of 5-grass pollen tablets versus placebo in the treatment of allergic rhinitis in adults. *Clin Drug Investig* 2013;33(5):343-9
 30. 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
 31. Bender BG, Oppenheimer J. The special challenge of nonadherence with sublingual immunotherapy. *J Allergy Clin Immunol Pract* 2014;2(2):152-5
 32. Kiel MA, Röder E, Gerth van Wijk R, et al. Real-life compliance and persistence among users of subcutaneous and sublingual allergen immunotherapy. *J Allergy Clin Immunol* 2013;132(2):353-60
 33. Antico A. Long-term-adherence to sublingual therapy: literature review and suggestions for management strategies based on patients' needs and preferences. *Clin Exp Allergy* 2014. [Epub ahead of print]
 34. Horak F, Ziegelmayer P, Ziegelmayer R, et al. Early onset of action of a 5-grass-pollen 300-IR sublingual immunotherapy tablet evaluated in an allergen challenge chamber. *J Allergy Clin Immunol* 2009;124(3):471-7
 35. Nolte H, Maloney J, Nelson HS, et al. Dose-finding efficacy and safety trial of the house dust mite sublingual immunotherapy tablet, mk-8237, using an environmental exposure chamber. *JACI* 2014; 133(2 Supplement):AB403
 36. Meyer W, Narkus A, Salapatek AM, et al. Double-blind, placebo-controlled, dose-ranging study of new recombinant hypoallergenic Bet v 1 in an environmental exposure chamber. *Allergy* 2013;68(6):724-31
 37. Patel P, Holdich T, Fischer von Weikersthal-Drachenberg KJ, et al. Efficacy of a short course of specific immunotherapy in patients with allergic rhinoconjunctivitis to ragweed pollen. *J Allergy Clin Immunol* 2014;133(1):121-9
 38. Patel D, Couroux P, Hickey P. Fel d 1-derived peptide antigen desensitization shows a persistent treatment effect 1 year after the start of dosing: a randomized, placebo-controlled study. *J Allergy Clin Immunol* 2013;131(1):103-9
 39. Hashiguchi K, Tang H, Fujita T, et al. Validation study of the OHIO Chamber in

- patients with Japanese cedar pollinosis. *Int Arch Allergy Immunol* 2009;149(2):141-9
40. Ziegelmayer PU. Are results of environmental exposure units transferable to real-life exposure? *Curr Opin Allergy Clin Immunol* 2013;13(3):244-8
41. Devillier P, Le Gall M, Horak F. The allergen challenge chamber: a valuable tool for optimizing the clinical development of pollen immunotherapy. *Allergy* 2011;66(2):163-9
42. Jay DC, Nadeau KC. Immune mechanisms of sublingual immunotherapy. *Curr Allergy Asthma Rep* 2014;14(11):473
43. Moingeon P. Update on immune mechanisms associated with sublingual immunotherapy: practical implications for the clinician. *J Allergy Clin Immunol Pract* 2013;1(3):228-41