Invited Review Article

The global development and clinical efficacy of sublingual tablet immunotherapy for allergic diseases

Hendrik Nolte*, Jennifer Maloney

ALK, Hørsholm, Denmark

A R T I C L E   I N F O

Article info
Article history:
Received 26 February 2018
Available online 16 May 2018

Keywords:
Allergic rhinitis
Asthma
Rhinocconjunctivitis
Sublingual immunotherapy
SLIT

A B S T R A C T

Allergy immunotherapy (AIT) is a treatment option for respiratory allergy that is complementary to pharmacotherapy, with a distinct mechanism of action. Alternative methods to subcutaneous administration of AIT that enable patients to safely self-administer AIT is considered an unmet clinical need. The sublingual immunotherapy tablet (SLIT-tablet) is an orally disintegrating pharmaceutical formulation (oral lyophilisate) containing standardized allergens. SLIT-tablets have been developed for sublingual immunotherapy (SLIT) of cedar-pollen, grass-pollen, ragweed-pollen, tree-pollen, and house dust mite allergies. It is a once-daily tablet treatment to be self-administered after the first dose has been provided under the supervision of a physician with experience in the diagnosis and treatment of allergic diseases. Once the first dose is adequately tolerated, subsequent doses may be self-administered. SLIT-tablets have proven efficacy for allergic rhinitis (AR) and asthma (AA) in adults, children, and poly-sensitized allergic patients. Meta-analyses indicate that SLIT-tablets have superior or similar efficacy compared with anti-allergic pharmacotherapies for seasonal AR and superior efficacy for perennial AR. SLIT-tablets have also demonstrated clinically relevant improvements of asthma, with significant reductions in the following: daily inhaled corticosteroid use, risk of asthma exacerbations, and asthma symptoms. SLIT-tablets are generally well tolerated, with a low risk of systemic allergic reactions. The most common treatment-related adverse events are mild-moderate oral reactions. Current evidence supports SLIT-tablets to be considered as an alternative or add-on treatment to pharmacotherapy for AR/C and asthma. Future SLIT developments may include early intervention to prevent the development or progression of allergic disease in children.

* Corresponding author. ALK, US Highway 135 Route 202/206, Bedminster, NJ 07921, USA.
E-mail address: Hendrik.nolte@alk.net (H. Nolte).
Peer review under responsibility of Japanese Society of Allergology.

Introduction

Allergy immunotherapy (AIT) is a treatment option for respiratory allergy that is complementary to pharmacotherapy, with a distinct mechanism of action on the immune system. AIT is performed by repeated sublingual or subcutaneous doses of allergens to an allergic person in order to gradually induce immunological tolerance towards the allergens. AIT modulates the basic immunologic mechanism of the allergic disease and is the only known treatment option with the potential to provide long-term, post-treatment benefits and alter the natural course of allergic disease.1 Sublingual immunotherapy (SLIT)-tablets are an alternative to subcutaneous immunotherapy that provide the benefits of AIT without the cost and inconvenience of frequent office visits or the discomfort of injections. The original idea supporting sublingual administration was to achieve a prompt systemic absorption of the allergen through the sublingual mucosa. However, biodistribution studies with radio-labeled allergens in humans have shown that the systemic absorption of the allergen through the oral mucosa was absent or negligible. Therefore, the clinical effect should be ascribed to the local interaction of the allergen with the mucosal immune system.2,3 Although not fully understood, a possible mechanism of sublingual immunotherapy is that the oromucosal contact with allergen results in tolerance development through the interaction of dendritic cells, Langerhans cells, and T-cells within the mucosa or in the regional lymph nodes.4

Sublingual immunotherapy tablet (SLIT-tablet) is an orally disintegrating pharmaceutical formulation (oral lyophilisate) containing standardized allergen extracts that been developed as sublingual immunotherapy (SLIT) for allergic rhinitis with and without conjunctivitis (AR/C) and allergic asthma (AA). SLIT-tablets have been developed for treatment of AR/C for cedar-pollen, grass-
pollen, ragweed-pollen, tree-pollen (in development), and for AR/C AA of house dust mite (D.pteronyssinus, D farinae) allergies. It is a once-daily tablet treatment to be self-administered after the first dose has been provided under the supervision of a physician with experience in the diagnosis and treatment of allergic diseases. Once the first dose is adequately tolerated, subsequent doses may be administered without medical supervision. Professional society AR/C guidelines recommend AIT for patients with seasonal or perennial AR/C and the recent 2017 GINA asthma guideline update recommends SLIT-tablet for patients for whom there is a clear relationship between asthma symptoms and exposure to HDM. Despite these recommendations, AIT is underutilized, with only about 20% of patients with AR/C and even less patients with asthma, having ever received AIT. The purpose of this review is to describe the current development and evidence of SLIT-tablets as an add-on or alternative treatment option to pharmacotherapy for AR/C and allergic asthma.

### Treatment options for allergic asthma and rhinoconjunctivitis (AR/C)

Currently, the treatments for allergic diseases are based on allergen avoidance, allergy pharmacotherapy, and AIT.

The purpose of allergen avoidance is to decrease exposure to allergens. For patients allergic to widespread inhalant allergens such as grass and tree pollen, allergen avoidance which creates a low-exposure allergen environment (such as, the patient’s home) is not a practical treatment option. For perennial allergens, such as house dust mite, this implies extensive sanitation and environmental control measures, e.g., mattress/pillow covers, frequent washing of bedding, focus on ventilation and decreasing humidity, increased frequency of vacuuming. Even if allergen levels are reduced in the home, other locations such as schools and day cares, are important sources for continuous exposure. Evidence suggests that mite allergen avoidance is not sufficient to relieve patients’ symptoms; therefore, international treatment guidelines question whether the effect justifies the cost and effort.

Pharmacotherapy for respiratory allergy most commonly includes antihistamines (oral or topical), local corticosteroids (nasal and/or inhaled), leukotriene antagonists, and inhaled β2-agonists, depending on the clinical manifestation and severity. Despite availability of these medications, rhinitis patients note that they are dissatisfied with treatments due to incomplete relief, slow onset of action, relief that lasts for <24 h, and decreased effects with continued use. In addition, asthma exacerbations remain a significant problem in many patients despite conventional treatment (e.g., inhaled corticosteroids [ICS] or ICS/long-acting beta agonists [LABA] combination). Newer biologic therapies, such as anti-IgE, have demonstrated efficacy with respect to reduction in asthma exacerbations, but are generally reserved for the most severe patients, and are associated with significant costs. Common to all approved forms of allergy pharmacotherapy treatments is that they do not provide long-term, post-treatment benefits or alter the natural course of the allergic disease.

AIT is another treatment option for respiratory allergies and is delivered either subcutaneously (SCIT) or sublingually (SLIT). SCIT is generally administered weekly or biweekly under medical supervision in a physician’s office, whereas SLIT is generally administered daily at home via drop or tablet formulations. In some parts of the world, SLIT drops are an off-label use of extracts intended for SCIT. Such off-label use is concerning, as there is little evidence to support the efficacy of such practice, the allergen extracts are not adequately standardized, and a safe and effective dose has not been established through rigorous clinical trials. Additionally, when utilizing SLIT drops, multiple allergens may be mixed together which augments the dosing variability of this treatment. In contrast, SLIT-tablets are well-characterized, standardized oral formulations that have been evaluated in large clinical trials and have been recently approved by regulatory agencies in the marketed countries. Furthermore, the Timothy SLIT-tablet has been shown to provide preventive and long-term benefits, including sustained improvement and persistent efficacy beyond the treatment period both in adults and children.

### Key development goals of sublingual immunotherapy tablets for AR/C and asthma

The three key development goals for SLIT-tablets include: (1) Prevention of allergic symptoms: Efficacy in the first pollen season after start of specific immunotherapy and some months of treatment; (2) Sustained clinical effect: Maintenance of significant and clinically relevant efficacy during 2—3 treatment years of continuing daily treatment; and (3) Disease-modifying effect: Sustained significant and clinically relevant efficacy in post-treatment years. Table 1 provides an overview of the different SLIT-tablets and their current development stage in adults and children.

Many pivotal clinical trials conducted in countries worldwide have demonstrated efficacy of SLIT-tablets for AR/C, for asthma and for the prevention of disease progression. Two SLIT-tablets are currently approved in Australia, Europe, the United States, and Canada for grass AR/C. These tablets are the timothy grass SLIT-tablet (GRASTEK®/GRAZAX®, ALK, Hørsholm, Denmark) for patients aged 5 + years, and the 5-grass (sweet vernal, orchard, perennial rye, timothy, and Kentucky blue grass) SLIT-tablet (ORALAIR®, Stallergenes, Antony, France/Greer Laboratories, Lenoir, NC, USA) for patients aged 10 + years in the US and 5 years and older in other countries. One SLIT-tablet is approved in the United States, Canada and Europe for ragweed AR/C (RAGWITEK®, RAGWIZAX®, ALK, Hørsholm) for patients aged 18 + years. Two SLIT-tablets for HDM (ODACTRA®,ACARIZAX®,MITICURE®, USA/ALK/Torii Pharmaceutical, Tokyo, Japan and ACTAIR® (Stallergens/Greer) are approved in Europe (not ACTAIR®), Australia, and Japan for treatment of AR, and also for allergic asthma (ACARIZAX® only) in Europe and Australia. The HDM (ODACTRA®,ACARIZAX®,MITICURE®) SLIT-tablet is approved for patients 18 + years in North America, 12 + years in Europe and Australia, and recently for 5 + years in Japan. Two tablets (Torii Pharmaceutical, Tokyo, Japan and Stallergens/Greer) are approved for Cedar pollen AR in Japan. A tree tablet (ALK-Abello) containing birch pollen extract is in Phase III development.

The key learnings from multiple SLIT-tablet trials are that the magnitude of efficacy is dose-dependent. Dose dependent efficacy may be most notable in an EEC design (chamber trial), where the variability of allergen exposure, which is inherent in any in-field trial, is removed. The onset of effect on allergic symptoms occurs approximately 4—8 weeks (earliest assessment in EEC) after treatment initiation. Onset of effect occurs slightly later in field trials (12—16 weeks) with a treatment effect that was maintained throughout the year/season with continued treatment. The overall treatment effect is consistent regardless of age group, gender, race, asthma status, or allergen sensitization profile (monosensitized/poly sensitized). Other key findings from numerous SLIT-tablet trials are that the magnitude of the observed treatment effects range from approximately 16%—40% in relative reduction in symptom and medication scores. The variation is related to allergen exposure during the season and year of the trial. When allergen exposure during the trial year is high the greatest treatment effects are observed. In lower pollen exposure years, the treatment effect is less pronounced. The treatment effect appears to be similar in patients.
with milder and moderate/severe AR/C. However, the treatment effect may be more easily detected in moderate/severe patients as the symptoms scores will be higher and subjects can better discern an improvement.

A particular focus has been to develop an effective and safe HDM SLIT-tablet. Although, HDM allergens (D. farinae and D. pteronyssinus allergens) products for subcutaneous use are commercially available in many parts of the world, only a small number of clinical trials have been conducted to demonstrate their efficacy. In an evidenced-based analysis of HDM trials conducted with commercially available SCIT extracts (maintenance dose ranged from 7 to 70 mcg of Der p1 or Der f1), only 3 out of 7 studies reported a significant effect on AR/C symptoms and 9 out of 19 studies reported a significant effect on asthma symptoms. The lack of efficacy in many of these trials may have been due to inadequate or non-standardized HDM extract formulations, inadequate numbers of subjects, use of subtherapeutic doses, or ill-defined efficacy endpoints and inclusion/exclusion criteria. The premise for designing and conducting more rigorous clinical HDM AIT trials was the need for consistency among the broadest possible range of HDM allergens to which patients are sensitized across geographic regions. The new ACARIZAX® tablet. Although, HDM allergen (D. farinae and D. pteronyssinus) products for subcutaneous use are commercially available, SCIT doses, mostly due to lack of extract standardization and characterization. Furthermore, onset of action studies have not been conducted. Thus, most SCIT therapy dosing is variable and based on individual and empirical knowledge rather than being evidence based.

Immunotherapy acts on the immune system and allergens are not metabolized or excreted. Thus, sublingual or subcutaneous routes of administration are not expected to result in differences in efficacy as long as adequate therapeutic dosing has been established for each treatment modality. However, the comparative efficacy of SLIT vs SCIT is inconclusive. There are no head-to-head trials of SLIT tablets and SCIT products. A robust head-to-head trial of SLIT versus SCIT would require a double-dummy design in order to maintain blinding between treatment groups due to the use of patient-reported outcomes. This study would require thousands of patients per arm to be appropriately powered due to a higher dropout rate in double-dummy trials and due to the onerous administration of both injections and tablets. As a result of these reasons, the relative efficacy of SLIT versus SCIT is most appropriately assessed using meta-analyses and indirect comparisons. Efficacy of SLIT vs SCIT has been indirectly compared in several meta-analyses of double-blind, placebo-controlled trials. The most recent meta-analysis, which includes the recent large grass SLIT-tablet trials, was published in 2015 and focused on commercially available SCIT, SLIT-tablets, and SLIT-drops for grass AR/C. Improvements in AR symptoms vs placebo based on standardized mean difference (SMD) were grass SLIT-tablet equal to SCIT and larger than SLIT-drops, with no significant differences between treatments. There are no current systematic reviews or meta-analyses including the new large HDM trials. Durham et al. reviewed the available PAR (predominantly HDM) SLIT and SCIT trials published up to 2015. In a comparison of Cochrane meta-analyses for SLIT and SCIT versus placebo for perennial allergens (predominantly HDM), the mean effect size for improvement in symptom scores for SCIT and SLIT compared to placebo were similar (−0.93 [95% CI: −1.69 to −0.17] versus −0.86 [−1.48 to −0.23]), while the mean effect size for improvement in medication scores was numerically greater with SLIT compared to SCIT (−0.34 [95% CI: −0.97 to 0.27] versus 0.46 [95% CI: −2.20 to 2.2]). However, these analyses were based on between 4 and 10 studies that had considerable heterogeneity, with I² statistic values ranging from 26% to 92%, highlighting the limitations of performing meta-analyses across allergic rhinitis trials. Data from the Cochrane meta-analyses suggest that both SCIT and SLIT are effective for perennial allergic rhinitis, with no statistically significant differences in symptom and mediation scores.

The need for alternatives to pharmacotherapy for AR is underscored by results of a survey of healthcare practitioners, in which the primary reason for prescribing AIT was identified as “other therapies don’t work.” However, there is no direct comparison of the efficacy of pharmacotherapy vs SLIT for AR as no head-to-head trials have been conducted. Indirect comparisons between pharmacotherapies and SLIT are hindered by substantial differences in trial designs. However, an observed treatment effect size of approximately 20% or more with SLIT is fairly impressive and considering meta-analyses of pharmacotherapy trials have reported an estimated treatment effect vs placebo of 5% for leukotriene antagonists, 7%–9% for antihistamines, and 17%–26% for intranasal corticosteroids (INCS). Although heterogeneity in trial designs exists, attempts have been made to indirectly compare the effect of pharmacotherapy vs SLIT-tablets for AR using meta-analyses.

### Table 1

<table>
<thead>
<tr>
<th>SLIT-tablet</th>
<th>AR/C Symptom Improvement</th>
<th>AA Symptom Improvement</th>
<th>Sustained Treatment Effect</th>
<th>Disease-modifying Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adults</td>
<td>Children</td>
<td>Adults</td>
<td>Children</td>
</tr>
<tr>
<td>Timothy grass (GRAZAX®, GRASTEK)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>5-grass (ORALAIR)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Ragweed (RAGWITEK)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Cedar (CEDARCURE)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>House-dust mites (ACARIZAX®)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>House-dust mites (ACTAIR)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

AR/C, allergic rhinoconjunctivitis; AA, allergic asthma.

1 Only SLIT-tablets that have been evaluated in trials of more than 1 year.
Devillier et al. compared treatments for grass AR and found the symptom effect size vs placebo was 29.6% with a 5-grass SLIT-tablet, 23.5% with INCS, 19.2% with a timothy grass SLIT-tablet, 15.0% with oral antihistamines, and 6.5% with a leukotriene receptor antagonist.54 Recently, Durham et al.55 compared treatments for seasonal and perennial AR (to reduce heterogeneity conjunctivitis symptoms were excluded from the analyses) and found the effect size vs placebo for seasonal AR was 22.2% with an INCS, 17.1% with a ragweed SLIT-tablet, 16.3% with a timothy grass SLIT-tablet, 8.5% with an oral antihistamine, and 5.4% with a leukotriene receptor antagonist (Table 2). For perennial AR, the effect size vs placebo was 16.1% with a HDM SLIT-tablet, 11.2% with an INCS, 4.8% with an oral antihistamine, and 3.7% with a leukotriene receptor antagonist (Table 2). These data indicate that SLIT-tablets are comparable to INCS and more effective than antihistamines and leukotriene receptor antagonists in reducing seasonal AR symptoms. SLIT-tablets also appear to be more effective than pharmacotherapies for perennial AR.

No head-to-head trials have been performed to evaluate the efficacy of pharmacotherapy vs SLIT-tablets for treatment of asthma. Several clinically-relevant benefits for asthma have been demonstrated with HDM SLIT-tablets. In a trial of subjects with mild-to-moderate asthma controlled by ICS, 1 year of treatment with HDM SLIT-tablet resulted in an 81 mcg/day greater ICS reduction compared with placebo65 ICS use was reduced even more in the subgroup of patients with partially controlled asthma, with a 327 mcg/day greater ICS reduction compared with placebo.65 A trial of up to 18 months of HDM SLIT-tablet treatment in asthma subjects inadequately controlled by ICS demonstrated a 34% relative reduction in the risk of moderate or severe asthma exacerbation vs placebo (hazard ratio = 0.66 [95% CI, 0.47–0.93]; P = 0.02).65 Furthermore, in a trial of HDM SLIT-tablet in subjects with AR with or without asthma, up to 1 year of treatment improved asthma symptom scores by 19% vs placebo in the overall trial population, and by 25% in the subjects with a history of asthma.64 Thus, there is compelling evidence that HDM SLIT-tablet decrease ICS use, asthma exacerbations, and improve asthma symptoms.

Three long-term trials with SLIT-tablets have been conducted to evaluate the disease-modifying effects of AIT. The first study, a 5-year study in adults with daily timothy grass SLIT-tablet demonstrated a significant beneficial effect on AR/C symptom scores up to 2 years after ending a 3-year treatment period.12 This study led to an indication of timothy grass SLIT-tablet as a disease-modifying treatment in Europe and led to recognition by the FDA as having a sustained effect. The second study, a 5-year study with a 5-grass SLIT-tablet administered pre-and co-seasonally demonstrated a significant combined symptom/medication score compared with placebo up to 2 years after a 3-year treatment period.66 The third long-term SLIT-tablet trial (GAP) was a 1:1, randomized, parallel-group, double-blind, placebo-controlled trial, including 812 children (5–12 years at study entry) with a clinically relevant history of grass pollen allergic rhinoconjunctivitis (AR/C) and no medical history of asthma. The primary objective was to investigate whether 3 consecutive years of daily treatment with timothy grass SLIT-tablet (GRAZAX (2800 BAU/75,000 SQ-T) compared with placebo reduces the risk of developing asthma based on the time to onset of asthma. Asthma was defined by a composite endpoint of asthma symptoms, medication use, and reversible impairment of lung function (forced expiratory volume after 1 min [FEV1] ≥ 12% after beta-2-agonist administration.13 Subjects were followed in a blinded fashion for an additional 2 years after cessation of treatment. The trial did not meet the primary endpoint and a notable number of subjects did not reveal lung function reversibility despite reporting asthma symptoms and medication use. Although the trial did not show a significant effect in terms of time to first diagnosis of asthma, defined by the composite endpoint of
symptoms, asthma medication use, and reversible lung function, the trial demonstrated that timothy grass SLIT treatment significantly reduced the proportion of children reporting asthma symptoms and/or asthma medication use. This effect was observed after two years of treatment and was sustained for the rest of the study including two years (Year 4 and Year 5) without daily treatment. The odds ratio (OR) for experiencing asthma symptoms or using asthma medication in the GAZAX group versus placebo was in favor of GAZAX each year, with statistical significance (p-value < 0.05) from Year 2 and onwards; the corresponding relative risk reductions ranged from 36.2% to 50.7% (odds ratio = 0.66, P < 0.036). Also, grass allergic rhinoconjunctivitis symptoms were 22%–30% reduced (P < 0.005 for all 5 years). At the end of the trial, the use of allergic rhinoconjunctivitis pharmacotherapy was significantly less (27% relative difference to placebo, P < 0.001).

These data provide further support to the concept that a lung function criterion may not be adequately sensitive (although specific) for the purpose of diagnosing asthma in children. Conversely, asthma as determined by symptoms and/or medication use, but not lung function, may be appropriately sensitive and specific for the purpose of early intervention trials. In summary, the GAP trial is important because it replicates adult data and show a disease-modifying effect of early intervention trials. In summary, the GAP trial is important because it replicates adult data and show a disease-modifying effect of early intervention trials. In summary, the GAP trial is important because it replicates adult data and show a disease-modifying effect of early intervention trials. In summary, the GAP trial is important because it replicates adult data and show a disease-modifying effect of early intervention trials. In summary, the GAP trial is important because it replicates adult data and show a disease-modifying effect of early intervention trials.

Safety of AIT

The majority of adverse events with SCIT are injection site reactions, and the majority of adverse events with SLIT are local oral reactions (e.g., oral pruritus, throat irritation). In general, SLIT-tablets offer a favorable safety profile suitable for home treatment and requires no up-titration. Both therapies carry the risk of systemic allergic reactions and anaphylaxis. Cases of anaphylaxis are estimated to be 1 per 33,300 injections of SCIT, and 1 per 100 million administrations of SLIT.31 SCIT has been associated with fatal and near-fatal systemic allergic reactions,35,36 whereas no fatal reactions have been reported with SLIT.37

The four most common side effects for SLIT-tablets are mild to moderate oral site reactions (ie, oral pruritus, throat irritation, ear pruritus, mucosa swelling37, Table 3a, b). The oral site reactions generally have an onset with the first dose of the SLIT-tablet and recur for less than 14 days.38 The duration of the reactions is approximately 30–60 min. Oral site reactions typically do not require any treatment and are more of a tolerability issue than a serious safety concern.

Table 2
Symptom treatment effect size for SLIT-tablets and pharmacotherapies for SAR and PAR.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of trial subjects, N</th>
<th>Difference in Mean: Active Treatment from Placebo (95% CI)</th>
<th>Relative Difference From Placebo, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timothy grass SLIT-tablet</td>
<td>6, 3094</td>
<td>-0.46 (-0.60, -0.32)</td>
<td>-16.3</td>
</tr>
<tr>
<td>Ragweed SLIT-tablet</td>
<td>2, 658</td>
<td>-0.57 (-0.87, -0.26)</td>
<td>-17.1</td>
</tr>
<tr>
<td>HDM SLIT-tablet</td>
<td>2, 1768</td>
<td>-0.57 (-0.83, -0.31)</td>
<td>-16.1</td>
</tr>
<tr>
<td>Cedar SLIT-tablet</td>
<td>Not done</td>
<td>Not done</td>
<td>Not done</td>
</tr>
<tr>
<td>Leukotriene receptor antagonist</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAR</td>
<td>5, 3584</td>
<td>-0.40 (-0.54, -0.25)</td>
<td>-5.4</td>
</tr>
<tr>
<td>PAR</td>
<td>2, 3215</td>
<td>-0.25 (-0.39, -0.12)</td>
<td>-3.7</td>
</tr>
<tr>
<td>Oral antihistamine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAR</td>
<td>6, 1916</td>
<td>-0.59 (-0.79, -0.40)</td>
<td>-8.5</td>
</tr>
<tr>
<td>PAR</td>
<td>3, 2539</td>
<td>-0.31 (-0.49, -0.13)</td>
<td>-4.8</td>
</tr>
<tr>
<td>Intranasal corticosteroid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAR</td>
<td>4, 958</td>
<td>-1.44 (-1.74, -1.15)</td>
<td>-22.2</td>
</tr>
<tr>
<td>PAR</td>
<td>4, 1182</td>
<td>-0.58 (-0.77, -0.39)</td>
<td>-11.2</td>
</tr>
</tbody>
</table>

HDM, house dust mite; PAR, perennial allergic rhinitis; SAR, seasonal allergic rhinitis; SLIT, sublingual immunotherapy. This table is modified from34.

1 = Calculated as (active treatment−placebo)/placebo x 100% for rhinitis symptoms only.

2 = Relative % improvement in rhinoconjunctivitis daily rescue medication score ranged from 27% to 38% in the trials.

3 = Relative % improvement in rhinoconjunctivitis daily rescue medication score was 38% and 46% in the two trials.

4 = Relative % improvement in rhinitis daily rescue medication score in the 2 trials was 18% and 21%.

Table 3a
Common side-effects for Timothy SLIT-tablets. Treatment-related AEs in ≥3% of subjects.

<table>
<thead>
<tr>
<th>Treatment-related AEs, % of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
</tr>
<tr>
<td>Timothy grass SLIT-Tablet N = 1669</td>
</tr>
<tr>
<td>Placebo N = 1645</td>
</tr>
<tr>
<td>Adults</td>
</tr>
<tr>
<td>Timothy grass SLIT-Tablet N = 1669</td>
</tr>
<tr>
<td>Placebo N = 1645</td>
</tr>
<tr>
<td>Oral pruritus</td>
</tr>
<tr>
<td>Throat irritation</td>
</tr>
<tr>
<td>Ear pruritus</td>
</tr>
<tr>
<td>Mouth edema</td>
</tr>
<tr>
<td>Oral parasthesia</td>
</tr>
<tr>
<td>Tongue pruritus</td>
</tr>
<tr>
<td>Lip swelling</td>
</tr>
<tr>
<td>Pharyngeal edema</td>
</tr>
<tr>
<td>Eye pruritus</td>
</tr>
</tbody>
</table>

AE, adverse event; SLIT, sublingual immunotherapy.

Table 3b
Common side-effects for HDM SLIT-tablets (ODACTRA®/ACARIZAX®). Treatment-related AEs in ≥3% of adult subjects.

<table>
<thead>
<tr>
<th>Treatment-related AEs, % of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
</tr>
<tr>
<td>HDM SLIT-tablet N = 1383</td>
</tr>
<tr>
<td>Placebo N = 1540</td>
</tr>
<tr>
<td>Oral pruritus</td>
</tr>
<tr>
<td>Ear pruritus</td>
</tr>
<tr>
<td>Lip swelling</td>
</tr>
<tr>
<td>Swollen tongue</td>
</tr>
<tr>
<td>Glossodynia</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Paraesthesia oral</td>
</tr>
<tr>
<td>Tongue ulceration</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
</tr>
<tr>
<td>Mouth swelling</td>
</tr>
<tr>
<td>Palatal swelling</td>
</tr>
<tr>
<td>Mouth ulceration</td>
</tr>
<tr>
<td>Dysgeusia</td>
</tr>
<tr>
<td>Tongue pruritus</td>
</tr>
<tr>
<td>Mouth edema</td>
</tr>
</tbody>
</table>

AE, adverse event; SLIT, sublingual immunotherapy.
Systemic allergic reactions are possible with SLIT-tablets. To date, none of the reported systemic allergic reactions from the clinical development programs associated with SLIT-tablets have been life-threatening or reported as serious. Across the clinical development program of the ALK timothy grass, ragweed, and HDM SLIT-tablets, representing 8152 treated patients, there have been 11 (0.1%) reported systemic allergic reactions. Epinephrine was administered for SLIT-tablet-related events at a rate of 1.80 administrations per 100,000 SLIT-tablets. It is generally recommended that SLIT-tablets should not be prescribed to patients with a history of severe, uncontrolled asthma, severe systemic allergic reaction or prior severe local reaction to SLIT.

Therefore, with regards to safety, the assumption of therapeutic equivalence of SCIT and SLIT, the analysis favors SLIT leaving the patient in clinical equipoise. Thus, it appears at this point, the decision to administer either SCIT or SLIT should be determined on the grounds of availability of standardized extracts, safety considerations, patient preference, convenience, cost, and readiness of clinic resources. Regardless, the availability of SLIT as an alternative treatment option for AIT should result in more patients choosing and completing AIT.

When to prescribe SLIT-tablets

HDM SLIT-tablets can initiated at any time of the year. For pollen SLIT-tablets, it is recommended to initiate treatment 2—4 months before the start of the respective pollen season. Thus, patients need to be evaluated for potential SLIT-tablet treatment months before regional pollen, which may be challenging as patients often do not seek treatment until symptoms appear. Some physicians may be reluctant to start AIT during the pollen season due to concerns about an increased risk of severe or serious systemic allergic reactions. However, a recent systematic review has demonstrated that there does not appear to be an increase in systemic allergic reactions or significant local reactions when AIT is initiated during the pollen season. If SLIT-tablets are initiated during pollen season, patients should be advised that improvement in symptoms may not be readily apparent during the initiating season.

Given the risk of severe or serious local or systemic allergic reactions, the first dose of SLIT-tablet should be administered under the supervision of a physician experienced in the diagnosis and treatment of allergic diseases, followed by at least a 30 min observation period. Patients should be educated on how to recognize the symptoms of a systemic allergic reaction and should be told to seek immediate medical care if they experience a severe allergic reaction. The current immunotherapy guidelines recommend continued treatment for at least 3 years for all allergen immunotherapy before discontinuing treatment to allow for the development of the disease-modifying effect.

Whom to prescribe SLIT-tablets

Although traditionally AIT was reserved for patients with severe allergies, according to guidelines, AIT should be considered for patients who have positive allergenspecific IgE against clinically relevant allergens and who have corresponding allergic rhinoconjunctivitis symptoms. In some countries, AIT is reserved for patients who are symptomatic despite pharmacotherapy. In the US, there are no such restrictions. Patients who have troublesome side effects with pharmacotherapy and patients who need to improve health-related quality of life (ie, sleep quality, work/school productivity) are groups for whom SLIT-tablets should be considered as useful treatment options. Also, SLIT-tablets may be particularly beneficial for children who fear injections and needles. SLIT-tablets provide the benefits of AIT without the inconvenience of time-consuming frequent office visits for children and caregivers and without the need of injections, which may deter children and their caregivers from traditional SCIT. Not only are SLIT-tablets effective in allergic children, but the ability of AIT to potentially reduce the risk of developing asthma symptoms and need for asthma medication, as recently shown with the Timothy grass tablet, is appealing.

As with any long-term treatment, adherence and persistence is key to AIT efficacy. The ability of a patient to be compliant to daily SLIT-tablet treatment should be determined before prescribing. Furthermore, the presence and severity of asthma needs to be evaluated before prescribing SLIT-tablets. If asthma is present, it should be stable and well-controlled. The safety of SLIT-tablets has not been evaluated in patients with severe, unstable, uncontrolled asthma, and the presence of such a condition is a contraindication. Reasons for patients choosing not to opt for AIT is reluctance to initiate therapy because of the need for long-term commitment, regular office visits, or symptom burden is considered acceptable by the patient and does not justify the cost and inconvenience of 3 years of treatment. In fact, only a minority (2—9%) of US AR patients initiate SCIT and studies indicate a preponderance of patients who initiate treatment discontinue therapy prematurely (~53% completed less than 1 year of treatment and 84% completed less than 3 years of treatment). However, multiple studies have shown that over the course of several years, AIT is more cost-effective than pharmacotherapy (reviewed in Hankin and Cox, 2014). The cost-savings with AIT appear to be due to decreased AR pharmacotherapy use, decreased asthma medication use, and decreased asthma-related healthcare. A potential disadvantage is the relatively slow onset of action (4—8 weeks) and the potential nuisance of oral reactions at tablet intake during the first weeks of treatment. Although, side effects are mild to moderate in intensity, approximately 5% of subjects will discontinue due to local adverse events. In some countries, cost to patients due to inadequate or no AIT insurance coverage may be a deterrent to initiating AIT or result in discontinuing treatment early. Further adding to cost is that in the United States patients receiving SLIT-tablets are required to be prescribed an epinephrine auto-injector. Epinephrine auto-injectors are not mandated outside of the US, as the risk of anaphylaxis is very low. Thus, adherence to AIT is variable and not just related to patient motivation but also very much related to product specific (i.e. year round treatment vs pre-and co-seasonal treatment) and country specific factors. Therefore, adherence rates may range from rates as low as 25%—84%.

Conclusions/future directions of SLIT

SLIT-tablets have similar or superior efficacy when compared to pharmacotherapies for AR and can provide clinically relevant benefits for asthma patients. The safety of SLIT-tablets is favorable; the self-administration of oral administration AIT provides a safe and convenient alternative to traditional SCIT. As such, SLIT-tablets should be considered as an alternative or add-on treatment to pharmacotherapy for AR with or without conjunctivitis, and with or without asthma.

There is now significant progress in the development of SLIT for treatment of several respiratory allergies. The recent GAP trial has demonstrated that early SLIT treatment may also prevent asthma development. It, therefore, seems reasonable to consider even earlier intervention with immunotherapy, e.g. in infancy. The rationale is based on studies indicating that weakly primed fetal Th2 responses are subjected to a variety of immunoregulatory processes driven by direct contact with allergen from the outside environment. The outcomes of which can include effective
suppression of allergen specific reactivity by T cell deletion/anergy, further boosting of Th2 responses, or immune deviation towards the Th1 cytokine pattern characteristic of adult non-atopic sub-
jects. Recent clinical trial data (LEAP, MAPS) are consistent with a
general model for postnatal control of allergen-specific T cell re-
sponses in which (as for the animal models) the nature of the
regulatory mechanisms employed is dictated by the respective oral
allergen exposure levels. High tolerance to food or inhalant anti-
gens which are encountered at high concentrations, may lead to
silencing of reactive T cells via anergy/deletion, versus immune
development of asthma and other allergic disease.

References

rhinitis and its impact on asthma (ARIA) 2008 update (in collaboration with the
World health organization, GA(2)LEN and AllerGen).

2. Schmitt J, Stadler E, Kuster D, Wüstenberg EG. Medical care and treatment of
rhinitis and its impact on asthma (ARIA) 2008 update (in collaboration with the
World health organization, GA(2)LEN and AllerGen).


Sublingual immunotherapy. A focused allergen immunotherapy practice
point of view.

5. Maloney J, Bernstein DI, Nelson HS, Kleine-Tebbe J, et al. Sequential treatment initia-
tion with SQ house dust mite sublingual immunotherapy tablets followed by simul-

efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen

7. Durham SR, Yang WH, Pedersen MR, Johansen N, Raks S. Sublingual immuno-

cacy and safety of sublingual immunotherapy with grass allergens for sea-

9. Dahl R, Stender A, Rals S. Specific immunotherapy with SQ standardized grass
allergen tablets in asthmatics with rhinoconjunctivitis. Allergy 2006;61:185–90.

Sublingual immunotherapy. A focused allergen immunotherapy practice
point of view.


safety of timothy grass allergy immunotherapy tablet treatment in North

double-blind, placebo-controlled trial of a ragweed allergy immunotherapy tablet in

14. Nolte H, Hebert J, Creticos P, Maloney J, Wu J, Bernstein DI. Efficacy and
safety of timothy grass allergy immunotherapy tablet treatment in North

15. Nelson HS, Nolte H, Creticos P, Maloney J, Wu J, Bernstein DI. Efficacy and
safety of timothy grass allergy immunotherapy tablet treatment in North

Conflict of interest

HN and JM are employees of ALK-Abello.

307


cy and safety of sublingual tablets of house dust mite allergen extracts in adults with allergic rhinitis with or without intermittent asthma. J Allergy Clin Immunol 2011;127:57–61.

Blais M, Maloney J, Nolte H, Gawkchik S, Yao R, Skoner DP. Efficacy and safety of
safety of timothy grass allergy immunotherapy tablets in North American children and

and efficacy in children of an SQ-standardized grass allergen tablet for sub-


cacy and safety of sublingual immunotherapy with grass allergens for sea-

Dahl R, Stender A, Rals S. Specific immunotherapy with SQ standardized grass
allergen tablets in asthmatics with rhinoconjunctivitis. Allergy 2006;61:185–90.

efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen


Durham SR, Yang WH, Pedersen MR, Johansen N, Raks S. Sublingual immuno-


Mosbeck H, Deckelmann R, de Blay F, Pastorell E, Trebas-Pietras E, Andre LS, et al. Standardized quality (SQ) house dust mite sublingual

Allergy 2001;31:54–60.


Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and


Blais MS, Dykewicz MS, Skoner DP, Smith N, Leatherman B, Craig TJ, et al. Diagnosis and treatment of nasal and ocular allergies: the allergists, immu-

REFERENCES