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Evidence and Practicalities of Aqueous Sublingual Immunotherapy, Tablet Sublingual Immunotherapy, and Oral Mucosal Immunotherapy for Allergic Rhinitis and Allergic Asthma

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Abstract

Purpose of Review Allergen immunotherapy (AIT) is the only disease-modifying treatment for allergic rhinitis (AR). Multiple modalities of AIT dosed via sublingual or oral routes are becoming available. This review discusses current evidence and practicalities of aqueous and tablet sublingual immunotherapy (SLIT) and oral mucosal immunotherapy (OMIT) in the treatment of AR and allergic asthma.

Recent Findings Several large-scale studies demonstrate the efficacy and safety of SLIT. These studies have led to the United States Food and Drug Administration (USFDA) approval of tablet SLIT against grass, ragweed, and house dust mites (HDM). However, off-label use of aqueous SLIT is still practiced as a safe and effective alternative in polysensitized patients. Growing evidence suggests a role for SLIT in patients with allergic asthma.

Summary The literature supports the efficacy and safety of aqueous and tablet SLIT for AR, while some controversy remains over the utility of SLIT for allergic asthma. OMIT is currently in the early stages of development.

Keywords Allergic rhinitis · Allergic asthma · Allergen immunotherapy · Sublingual immunotherapy · Oral mucosal immunotherapy

Introduction

Treatment of allergic rhinitis (AR) ranges from avoidance measures, to pharmacotherapy, to allergen immunotherapy (AIT). AIT is the only modality that has the ability to modify the disease process and lead to clinical improvement after cessation of therapy [1–3]. The gold standard for AIT has traditionally been subcutaneous immunotherapy (SCIT), which was first described by Noon in 1911 [4, 5]. However, long treatment courses with multiple injections and several reports of fatalities due to anaphylaxis have led allergists and otolaryngologists to seek additional AIT options [6].

Over the past several decades, sublingual immunotherapy (SLIT) has arisen as a safe and efficacious alternative treatment option for AR and allergic asthma [1, 7•, 8–10]. The two main forms of SLIT that have been used in the United States (US) and European Union (EU) include the tablet form and aqueous drops. A third modality, oral mucosal immunotherapy (OMIT), is currently under development as an alternative to drops and tablets. The goal of this review is to discuss the safety, efficacy, and practical logistics of administration of tablet SLIT, aqueous SLIT, and OMIT in the treatment of AR and allergic asthma. An overview of these comparisons is shown in Table 1.

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Aqueous Sublingual Immunotherapy

Patient Dosing and Standardization Considerations

Aqueous SLIT is commonly administered by utilizing aqueous SCIT antigens in "off-label" fashion [11]. Patients are

Table 1 Comparison of sublingual immunotherapy modalities

Modality	Dosage considerations	Standardization of therapy	Efficacy in allergic rhinitis	Efficacy in allergic asthma	Safety considerations
Tablet	Most formulations once daily dosing. Short escalation period (3 days) required in patients 5–17 years old undergoing treatment with Oralair.	2 standardized tablets to grass, 1 to ragweed, 1 to HDM** available in the US.	Double-blind RCTs*** showed efficacy.	Double-blind RCTs showed efficacy for HDM tablets only.	Systemic adverse events are rare, but patients should be prescribed an epinephrine autoinjector. Local reactions (GI upset, oral cavity swelling, pruritus) common.
Aqueous	Drops held under tongue for 2 min then swallowed or expelled. Daily dosing most common, although weekly dosing has been reported. Dose escalation variable.	Extracts often not standardized.	Double-blind RCTs showed efficacy.	Moderate evidence supporting the use of aqueous birch, grass, and HDM formulations.	Considered "off-label" in US. Studies reveal rare systemic adverse events. Local reaction rates similar to tablets.
OMIT*	Patients brush teeth for 2 min daily using glycerin-based fluoride toothpaste. No escalation required.	No formal standardization at this time.	Small pilot study showed similar improvements over placebo compared to aqueous sublingual immunotherapy.	No studies to date assessing efficacy in allergic asthma.	In experimental phases at this time. No systemic adverse events reported in small pilot study. Local adverse event rates similar to aqueous sublingual immunotherapy.

**OMIT* oral mucosal immunotherapy

***HDM* house dust mites

****RCTs* randomized controlled trials

typically instructed to place the drops under their tongue for approximately 2 min, then either spit out the drops or swallow them. Large-scale randomized controlled trials (RCTs) of SLIT reveal that daily dosing is most commonly used [12, 13]. Dose escalation is variable, from no dose escalation to a short escalation phase [12].

In the US, there are currently 4 licensed manufacturers of aqueous AIT products that market hundreds of different allergen extracts, 19 of which have been standardized for SCIT [14, 15]. However, most glycerinated aqueous allergen extracts used "off-label" for SLIT are not standardized in the US due to regulations being placed on extraction methods, rather than methods used to produce allergen source materials [15]. In the EU, extracts for AIT are produced in multiple countries and production practices vary widely, making it impossible to compare strength and efficacy of extracts until reference standards are established [15, 16]. Regulatory legislation in the EU is complex and beyond the scope of this review, but has been recently described in publications by the European Academy of Allergy and Clinical Immunology [17, 18]. An additional consideration in the US is that the "off-label" use of these extracts often leads to out-of-pocket expenses as most insurance companies will not reimburse for these services [15].

Efficacy in Allergic Rhinitis

Several large systematic reviews have been performed to assess the efficacy of SLIT both in aqueous and tablet forms. A 2010 Cochrane review of 22 blinded RCTs included 20 that used aqueous SLIT. This analysis revealed a reduction in symptoms and medication requirements following SLIT, with longer treatment regimens (> 12 months) providing the most benefit [19]. A 2013 systematic review included 63 RCTs and 5131 participants. Among these studies, grass mix and HDM were most commonly studied and the majority of the trials used aqueous SLIT. Overall, moderate evidence suggested improved rhinoconjunctivitis symptoms, decreased medication usage, and improved disease-specific quality of life [13]. Given the current evidence, the International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis (ICAR:AR) recommended aqueous SLIT (as well as tablet SLIT) for patients with seasonal or perennial AR who wish to reduce their symptoms or their medication usage [7•].

Efficacy in Allergic Asthma

Uncontrolled asthma is a contraindication to the use of all forms of AIT [20]. However, the 2008 Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines gave SLIT a conditional recommendation for use in controlled allergic asthma [21]. As HDM is the most important indoor allergen implicated in development of asthma [8, 22–24], the majority of evidence has focused on HDM SLIT and its role in allergic asthma. A recent systematic review of RCTs identified 14 studies assessing the efficacy of aqueous or tablet SLIT for asthma

and included studies using HDM, birch, or grass allergen [25•]. Studies using aqueous SLIT for HDM and birch revealed statistically significant improvements in asthma symptoms [26•, 27]. In terms of quick-relief medication use, studies assessing aqueous birch and grass SLIT reported significant decreases in short-acting beta agonist use [27, 28]. Meanwhile, results for aqueous HDM studies with respect to quick-relief medications were mixed [29, 30]. Results for reduction in long-term inhaled corticosteroid use were mixed, as one study reported a statistically significant decrease over placebo [26•] while another did not [29].

Safety

Systemic adverse events have been exceedingly rare, with a previous study by Calderon et al. reporting 9 cases of systemic allergic reactions to aqueous SLIT in the literature, all of which were non-fatal [31]. A recent systematic review found only 3 studies with 3 reported cases of anaphylaxis, 1 of which was not previously reported in the study by Calderon et al. [25•, 32] Local adverse reactions are common with SLIT and have previously been classified by the World Allergy Organization based on severity [33]. A 2006 systematic review identified 66 studies with available safety data, which revealed 823 local reactions or a rate of 0.68 per 1000 doses [34]. There were 3 studies using tablet SLIT included in this analysis [35–37]. Given that the majority of SLIT doses occur at home, it is important to note that rates of adverse events may be under reported.

Tablet Sublingual Immunotherapy

Patient Dosing and Standardization Considerations

The USFDA has approved and standardized 2 sublingual grass tablets (Oralair® and Grastek®), 1 ragweed tablet (Ragwitek®) and 1 HDM tablet (ODACTRA®). Oralair® is a mixture of sweet vernal, orchard, perennial rye, and Timothy and Kentucky bluegrass pollen extracts. Grastek® is a Timothy grass tablet. Ragwitek® is short ragweed pollen allergen extract and Odactra® is a combination of *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* HDM antigens. All tablets are administered through standard dosing. None has an escalation phase except for Oralair®, in which patients 5–17 years old undergo a 3-day escalation period. All patients undergoing treatment with SLIT tablets must have their first dose of therapy in the physician's office and should also be prescribed and instructed on the use of an epinephrine autoinjector in the event of a systemic reaction at home. An overview of FDA-approved tablet SLIT products is shown in Table 2.

Table 2 Overview of United States Food and Drug Administration–approved sublingual immunotherapy tablets*

Trade name	Generic name (antigen mixture)	Dosing	Dosing escalation
Oralair	Sweet vernal, orchard, perennial rye, and Timothy and Kentucky bluegrass mixed pollen extracts	Age 10–17 years: 100 IR** on day 1, 200 IR on day 2, 300 IR thereafter; age 18–65 years: 300 IR daily	For patients 10–-17 years old
Grastek	Timothy grass pollen extract	1 tablet (2800 BAU°) daily	No
Odactra	*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* house dust mite extract	1 tablet (12 SQ-HDM°°) daily	No
Ragwitek	Short ragweed pollen extract (*Ambrosia artemisiifolia*)	1 tablet (12 Amb at 1 unit) daily	No

*Trade names are used in this manuscript due to length of generic names

***IR* index of reactivity

°*BAU* bioequivalent allergy units

°°*SQ-HDM* standardized quality-house dust mite

Efficacy in Allergic Rhinitis

Several large RCTs have been performed with grass tablet SLIT. A 2008 study of 351 participants found grass tablet SLIT treatment for an average of 22 months to significantly improve rhinoconjunctivitis symptom scores, medication scores, and quality of life [38]. Another RCT of 855 participants also showed improvements in quality of life and symptom scores over placebo [39]. Two additional large RCTs showed benefit of grass tablets up to 2 years after cessation of therapy [40, 41]. Similarly, large RCTs have confirmed efficacy for HDM SLIT. A recent large RCT of 991 participants performed in 12 European countries showed significant improvements in rhinitis symptoms, medication scores, and disease-specific quality of life [42]. Another RCT of 509 participants showed improvement in symptoms and a sustained benefit 1 year after completion of AIT [43]. Finally, while there is a smaller body of literature for ragweed tablet SLIT, a large US RCT of 565 patients assessing the ragweed SLIT tablet found a dose-dependent treatment response, with a higher dose (12 μg versus 6 μg) showing a larger improvement over placebo in total combined scores (TCS) and medication usage [44].

Given a preponderance of evidence supporting the efficacy of tablet SLIT, the ICAR:AR document strongly recommends grass, ragweed, and HDM SLIT in tablet form [7•]. The 2018 European Academy of Allergy and Clinical Immunology (EAACI) guidelines also strongly recommend grass tablets

for short- and long-term benefits in AR, strongly recommend HDM tablets for short-term benefit in AR, and provide a moderate recommendation for HDM long-term benefit [9].

Efficacy in Allergic Asthma

As discussed above, the majority of studies assessing SLIT tablets for asthma evaluate HDM therapy. There is moderate evidence to support the use of HDM SLIT tablets for patients with HDM-induced AR and allergic asthma not well controlled by inhaled corticosteroids [45••]. This evidence is derived from 3 large double-blind randomized controlled trials [46–48], each of which assess different clinical endpoints. The largest study to date by Virchow et al. assessed time to moderate-severe asthma exacerbation after withdrawal of inhaled corticosteroids and found that there was a significant risk reduction in the SLIT group [48]. Another large double-blind RCT by Mosbech et al. assessed inhaled corticosteroid dose and found a significant decrease in inhaled corticosteroid dose in patients being treated with high-dose HDM tablets [46]. Finally, a study by Nolte and colleagues assessing symptom scores in 83 patients treated with HDM compared with 41 with placebo found statistical improvements above placebo [47]. There is little evidence to date regarding the efficacy of ragweed and grass tablets in allergic asthma.

Safety

As with aqueous SLIT, tablet SLIT has been shown to have a favorable safety profile. Systemic adverse events have been rare, with 2 non-fatal cases noted in tablet patients in the previously mentioned 2012 Calderon study [31]. Of note, both of these patients had prior discontinuation of SCIT due to systemic reactions. More recently, no serious treatment-related adverse events were reported in any of the large RCTs of grass tablet SLIT [38–41]. Local adverse events were more frequent and most commonly consisted of oral cavity pruritus (44–52%) [38, 39, 41], oral cavity swelling (19%), or throat pruritus (13%) [41]. In the HDM tablet studies, there was one RCT reporting 2 treatment-emergent adverse events in the HDM group, neither of which required epinephrine (1 respiratory distress due to sublingual edema, 1 pharyngeal edema) [43]. Another RCT reported 1 patient receiving epinephrine for mild laryngeal edema, who later completed the trial without further systemic adverse events [42]. Local adverse event rates with HDM tablets were similar to those reported above for grass tablet SLIT and aqueous SLIT, with rates of oral pruritus of 25–30%, oral cavity edema 2–16%, and throat irritation 21–24% [43]. In the ragweed trial, 1 patient had pharyngeal edema requiring epinephrine, and there were throat irritation rates of 25–28%, local oral pruritus rates of 18–19%, and tongue swelling rates of 11–19% [44].

Oral Mucosal Immunotherapy

Patient Dosing and Standardization Considerations

Previous work has suggested that oral Langerhans cells (oLC), the antigen-presenting cells most active in expressing the high affinity receptor for immunoglobulin E (IgE), are found in the highest density in the oral vestibule and buccal mucosal regions [49]. Therefore, oral mucosal immunotherapy (OMIT), a glycerin-based toothpaste vehicle, has been developed with the hypothesis of better efficacy of AIT or similar efficacy at lower doses due to increased presentation of the allergens to oLCs in the vestibular and buccal mucosa [50].

In OMIT, allergen extracts are mixed with a glycerin-based fluoride toothpaste. Patients are instructed to place 0.9 mL of toothpaste on their toothbrush and brush in standard fashion for 2 min without expelling the foam. The foam is then expelled after 2 min of brushing [51•]. Just as in other forms of SLIT, the first dose is given in the office followed by at-home dosing. Unlike aqueous SLIT, no dosing escalation is used. Proponents of OMIT suggest that this form of therapy may increase adherence to therapy due to linking the therapy to a universal daily activity [51•]. However, a recent prospective study assessing AIT modality preferences in 228 AR patients did not show a statistically significant difference in preference among tablet SLIT, aqueous SLIT, or OMIT [52].

Efficacy and Safety

To date, only one pilot study has been performed to assess the safety and efficacy of OMIT in humans [51•]. This study included 12 patients who underwent OMIT and a control group of 12 who underwent aqueous SLIT for 12 months. There were 2 patients (16.7%) who dropped out in the OMIT group (1 unknown reasons, 1 for financial difficulties) and 4 (33.3%) in the SLIT group. The study found no serious adverse events and no significant difference in adverse event rates between the OMIT and SLIT groups. Patients receiving OMIT were noted to have similar improvements to the SLIT group in symptom and medication scores (mean weekly total combined score decrease 15.6% versus 22.3%), rhinoconjunctivitis quality of life questionnaire scores (2.23 ± 1.09 to 1.38 ± 1.06 versus 2.57 ± 1.36 to 1.47 ± 0.68), skin reactivity (43.2% with decrease in skin wheal diameter versus 42.4%), and antibody levels (increased specific IgG4 levels in 57% versus 86%) [51•]. There are currently no studies assessing OMIT in the treatment of allergic asthma nor

has there been any standardization of this therapy given its early stages of development.

Conclusions

SLIT has become a widely practiced modality of AIT in the US and EU. A large body of literature has shown SLIT to be safe and efficacious in the management of AR, and growing evidence suggests utility of aqueous and tablet SLIT in the treatment of allergic asthma. While superior ability to standardize tablets has led to USFDA approval, aqueous SLIT is still widely utilized. Further studies are required to determine if OMIT is a viable alternative dosage form of SLIT for patients with AR and allergic asthma.

Compliance with Ethical Standards

Conflict of Interest Christopher R. Roxbury declares that he has no conflict of interest.

Sandra Y. Lin reports personal fees from Gowanus Technologies, personal fees from Aerin Medical, and other from Resdesign Health.

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.

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- •• Of major importance

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