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SLIT Tablets for Polysensitized Allergic Rhinitis

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Abstract Sublingual immunotherapy (SLIT) clinical trials demonstrate clinical efficacy and safety in patients with allergic rhinitis/rhinoconjunctivitis (AR). In 2014, the Unites States Food and Drug Administration approved two grass pollen SLIT tablets for the treatment of AR, as well as one short ragweed SLIT tablet. With the availability of single-allergen SLIT tablets for allergic individuals in the US, the question of how to treat the polysensitized AR patient has emerged among treating physicians. In fact, multiple efficacy studies have included polysensitized patients and generally report that patients demonstrate clinical improvement with SLIT tablet treatment. However, there are several factors that limit a thorough evidence-based approach to answering this clinically important question. Additional post-marketing effectiveness studies would be useful to bolster the current literature on SLIT tablets in the real world before thorough evidence-based conclusions are drawn regarding the role of SLIT tablets in treatment of the polysensitized patient.

Keywords Sublingual immunotherapy · Subcutaneous immunotherapy · Allergic rhinoconjunctivitis · Allergic rhinitis · Polysensitized · Grass tablets

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Introduction

Allergic rhinitis/rhinoconjunctivitis (AR) is one of the most common chronic medical problems for which patients are seen in the ambulatory care setting, affecting at least 500 million people worldwide and approximately 30 million people in the United States [1]. Allergies to grass pollen account for many of these cases [2]. Traditional symptoms include rhinorrhea, nasal congestion, sneezing, nasal and ocular pruritus, and watery eyes. These symptoms are not just an annoyance but can place a considerable burden on the patient, who will often have a reduced quality of life score when compared to individuals without AR. Patients with AR can suffer from sleep disturbances with subsequent cognitive impairment and altered performance at work and school [3]. Additionally, over one-third of patients with AR have asthma. AR has been found to frequently precede the diagnosis of asthma, and it is now considered to be an independent risk factor for its development [4••].

The United States Food and Drug Administration (US FDA) classifies allergic rhinitis as perennial or seasonal. Perennial (year round) allergies are usually associated with allergens found within the home, such as dust mite or pet dander. Seasonal allergies, on the other hand, are usually attributed to plant pollens, and the offending allergen can often be predicted by the pollination season during which symptoms occur. Other allergic rhinitis classification schemes, such as intermittent versus persistent, similar to asthma classification, also exist. Classically, treatment for AR has consisted of allergen avoidance and pharmacotherapy directed at controlling the symptoms of the allergen-induced inflammatory response. Currently, drugs used to treat allergy symptoms often include oral and intranasal antihistamines, nasal

corticosteroids, intranasal anticholinergics, oral leukotriene inhibitors, and oral and topical decongestants [5]. While many patients find some relief with these therapies, satisfactory control of symptoms is often not achieved due to poor medication adherence, unwanted side effects, or lack of effectiveness.

Allergen immunotherapy (AIT) is also an option for allergic patients, traditionally reserved for patients in whom treatment with pharmacotherapy is ineffective or poorly tolerated. In contrast to pharmacotherapy or allergen avoidance, AIT is a disease-modifying treatment. It involves repeated allergen exposure with the goal of ultimately stimulating the cellular and humoral immune system to generate allergen-specific immune tolerance. AIT has historically been given in many forms. Current AIT largely consists of subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT).

Several well-designed clinical trials have reported efficacy of SCIT versus placebo or SLIT versus placebo for seasonal allergic rhinitis to grass pollens [6]. A few indirect analyses comparing the efficacy and safety between SLIT and SCIT have been published [7•, 8•]. For many patients and practitioners, SLIT has become a favored AIT treatment for multiple reasons, including a higher safety profile versus SCIT, no need for needles and injections, and less frequent office visits. In 2014, the US FDA approved two SLIT tablets for those who suffer from AR due to grass pollen sensitization: a Timothy grass SLIT tablet (Grastek®, Timothy grass pollen allergen extract tablet for sublingual use 2800 BAU, Merck & Co.) and a 5-grass SLIT tablet (Oralair®, Greer Laboratories). The 5-grass tablet includes extracts from Timothy, perennial rye, sweet vernal, orchard, and Kentucky blue grasses. Also approved for use in the US in 2014 was a short ragweed tablet (Ragwitek®, short ragweed pollen allergen extract tablet for sublingual use 12 Amb a1-U, Merck & Co.).

Many AR patients are polysensitized, demonstrating sensitivities to more than one allergen on skin or specific IgE testing. Because of this, the question of how to treat the polysensitized AR patient in the setting of "single-allergen" SLIT tablets has arisen. This paper will provide a working definition of polysensitization and evaluate the available literature on SLIT in the polysensitized patient. This paper will largely focus on grass pollen allergy to discuss the concept of "single antigen" SLIT tablet treatment in the polysensitized patient, as the majority of rigorous clinical research has revolved around grass pollen SLIT tablets in recent years. The ultimate goal of this paper is to provide a framework for the practicing physician to consider the potential benefits and drawbacks involved in treating polysensitized patients with available single-allergen SLIT tablets recently approved in the US.

Immunotherapy

Inhalational allergies are type I hypersensitivity reactions that are elicited by the contact between causative allergens and their specific IgE antibodies. This process is driven by antigen presenting cells, T lymphocytes, cytokines (which determine the immunologic path that will be followed), B lymphocytes, epithelial cells, and various effector cells (mast cells, basophils, and eosinophils). The mainstay treatments of inhalational allergies are allergen avoidance and pharmacotherapy to obtain symptom relief [5, 9]. The avoidance of allergens, especially aeroallergens, can be quite difficult for many patients. In addition, a 2006 publication noted that despite modest relief of symptoms for some, 40 % of patients with AR describe their symptom management as being poorly controlled with available pharmacotherapy options [10]. AIT, however, involves titrated patient exposure to sensitized allergen to induce immune tolerance [11]. AIT has been shown to reduce the risk of subsequent asthma in allergic patients, especially when started earlier in the course of AR [12]. The benefits of AIT have been shown to persist for a number of years after completing therapy [4].

SCIT is a bi-phased strategy that consists of an induction phase of allergen extract injections in escalating doses, typically over the course of several of months. The maintenance phase is initiated when a final target dose is reached. In this phase, patients continue to receive therapy at the maintenance dose for 3–5 years [8]. SCIT has demonstrated efficacy in providing symptom control, but SCIT is not ideal for all patients. Many patients are not capable of the time commitment required for frequent office visits to receive injections, and this delivery system is not ideal for patients that have an aversion to needles. The possibility of life threatening side effects also exists, with a prevalence of anaphylaxis at approximately 0.13 % [4]. The safety concerns and inconvenience of frequent injections make SCIT undesirable for many patients [13].

SLIT may be given in aqueous drops of allergen extract, used off-label in the US, or via FDA-approved single-allergen tablets. Escalation and dosing methods for SLIT vary widely, but generally, SLIT protocols have much shorter escalation (or no escalation), and dose ranges are much higher.

Until recently, SCIT was the only FDA-approved option for grass or short ragweed pollen AIT in the US, but in 2014, three SLIT tablets were approved for use in this country. With each of these tablets, the first dose is given in the physician's office and patients are observed for 30 min following the dose. If no adverse effects are noted, the patient takes a once daily dose at home. The Timothy grass and short ragweed tablet are both initiated at the

maintenance dose, without any escalation period. The 5-grass tablet is initiated at the maintenance dose in adults, but has a short 3-day escalation period in children. All approved SLIT tablets are indicated for pollen-induced AR with specific IgE testing positive to the pollen contained in the tablet, or a cross-reactive pollen in the case of the Timothy grass tablet. SLIT tablets are typically dosed pre-seasonally (12–16 weeks) and co-seasonally, although the Timothy grass tablet can be given on a continuous basis. All tablets are approved up to age 65, with the grass tablets approved down to age 5 and 10 for the Timothy grass and 5-grass tablets, respectively. The short ragweed tablet is approved for adults 18–65. SLIT tablet contraindications include severe uncontrolled asthma, history of severe reaction to SLIT, eosinophilic esophagitis, or hypersensitivity to one of the inactive ingredients in the tablets. In general, the safety profile of SLIT is quite good. Most adverse events are mild to moderate in severity, with the most common being oral pruritus, throat irritation, mouth edema, tongue pruritus, cough, and oropharyngeal pain [14, 15]. Extensive reviews of the available Timothy grass and 5-grass SLIT tablet literature were published in 2014 by Nelson [16••] and Didier et al. [5], respectively. Each of these reviews addresses the pharmacodynamics and pharmacokinetics of the tablets, efficacy and safety data in Phase I–III trials, dose-finding studies, long-term efficacy, subgroup analyses, post-marketing surveillance, economics, and additional aspects of the grass SLIT tablets. A detailed description of these items is beyond the scope of this paper, but the reader is directed to these references for additional information.

Polysensitization

As SLIT tablets have been making their way to FDA approval in the US, and effectiveness and safety of these tablets have been demonstrated, practitioners and researchers have considered the polysensitized patient and the potential for use of SLIT tablets in this patient population. However, this is very little data available regarding SLIT efficacy in the polysensitized patient specifically. A few factors likely underlie this lack of information. First, the term polysensitization must be defined. A polysensitized patient demonstrates positive reactions to more than one tested allergen on skin or in vitro allergy testing. For patients with multiple allergen sensitivities, symptoms may or may not be present upon exposure to each of the allergens. A poly-allergic patient demonstrates sensitivities to more than one type of allergen and also suffers symptoms that correspond with exposure to the sensitized allergens. An example of a poly-allergic patient would be an individual who on allergy testing is sensitive to grass pollen, house dust mites, and tree pollens that has symptoms year round, with exacerbation during grass and tree pollination seasons. In an excellent 2014 review by Migueres et al., additional terms in this realm are also highlighted [17••]. Paucisensitization is noted as polysensitization to 2–4 allergens; co-sensitization is IgE reactivity in which multiple unrelated sensitizations are present against structurally different allergen groups; and cross-sensitization or cross-reactivity is present when IgE antibodies are originally raised to one allergen and subsequently bind to a similar protein in another allergen.

It has been documented that the majority (50–80 %) of patients seeking treatment for moderate to severe AR are polysensitized [18], and this has been supported in immunotherapy clinical trials by Malling et al. [14] and Emminger et al. [19]. Since the introduction of AIT for the treatment of AR and asthma, there has been a debate over how to treat the polysensitized patient. Physicians in the US and Europe have historically treated polysensitized patients somewhat differently. In the US, co-administration of multiple allergen extracts has been employed with the view that there is an advantage in treating as many of the patient's actual or potential sensitizations/allergies as possible [18]. AIT is notably allergen specific in its approach to the individual patient. Co-administration of numerous allergens in immunotherapy treatment regimens is an approach that has likely been influenced by various factors including data-supporting allergen specificity of AIT regimens, lengthy build-up time for SCIT, numerous visits to the provider, associated expenses incurred for this therapy, and patient satisfaction. In Europe, however, most patients are treated with fewer allergens in their AIT, with allergens selected based on what is deemed to be the most "problematic". In other words, it is commonly recognized in Europe that a "polysensitized" patient by skin or specific IgE testing is not necessarily "poly-allergic" or demonstrating significant symptoms upon a given allergen exposure. In fact, US studies have supported this concept as well, demonstrating that approximately 54 % of 10,508 people age 6–59 years old demonstrate positive skin test reactions (median = 3), but only a fraction of these exhibit true symptoms on allergen exposure [20].

Ultimately, the question to be answered is: do polysensitized, or poly-allergic, patients improve clinically with "single-allergen" immunotherapy, specifically SLIT tablets? An ideal clinical trial to answer this research question would involve a cohort of polysensitized (or poly-allergic) patients exhibiting the same allergen reactivity profiles on specific IgE testing and the same symptoms upon exposure to the offending allergen. This cohort of "identical" patients would then be randomized to three groups: active SLIT with multiple antigens, active SLIT with a single antigen, or placebo. Symptom and medication

scores would assess the clinical efficacy of each treatment arm, and the groups would be statistically compared to one another. One can easily surmise that this trial would be extraordinarily difficult to carry out because it is highly unlikely that such a cohort of identically polysensitized and identically symptomatic patients could be enrolled. Therefore, we look to alternative means of determining the efficacy of single-allergen therapy in polysensitized or poly-allergic patients.

In 2009, an ad hoc analysis by Malling et al. evaluated the efficacy of the 300 IR 5-grass pollen SLIT tablet in different subtypes of patients, including polysensitized patients [21]. The definition of polysensitization in this study included "patients sensitized to allergens other than grass pollens". However, only patients with polysensitization were included in the study if the other allergens did not cause symptoms during grass pollen season. This study reports similar efficacy of the 300 IR 5-grass pollen SLIT tablet between the monosensitized patients and the polysensitized patients when looking at the primary endpoint, rhinoconjunctivitis total symptom score (RTSS). This study was performed retrospectively with data collected during the original phase III efficacy trial. Including patients with perennial allergies or seasonal allergies that overlapped with grass pollen season would have had the potential to mask efficacy of this SLIT tablet, so it is understandable why certain polysensitized patients were excluded from this study. Furthermore, the primary outcomes of seasonal pollen allergen SLIT tablet studies are assessed during the active pollen season, which naturally limits the assessment of added benefit to poly-allergic patients during other potentially symptomatic times. Numerous other clinical trials have included polysensitized patients and demonstrated efficacy with "single-allergen" tablet SLIT, such as Malling et al. (51.5 % polysensitized) [14], Emminger et al. (35–37 % polysensitized) [19], Maloney et al. (85 % polysensitized) [15], and Nelson et al. (85 % polysensitized) [13].

Despite the apparent benefit of SLIT tablets in polysensitized patients, none of the trials listed were prospectively designed to specifically evaluate the efficacy of SLIT tablet "single-antigen" therapy or "monotherapy" in the polysensitized or poly-allergic patient. As noted, this type of study would be difficult to carry out in its purest form. Based upon the inclusion of polysensitized, poly-allergic patients in prior clinical efficacy studies, we believe SLIT tablets show benefit in this patient population and may temper overactive Th2-mediated immune mechanisms in these individuals. Additional post-marketing effectiveness studies would be helpful to assess the true benefit of SLIT tablets in the real world marketplace, allowing the inclusion of multiple different profiles of polysensitized patients.

Major Grass Allergens: Single or Multiple Allergens?

AR is a prevalent disease in the United States that is estimated to affect 18 % of the population over the age of 5 [22]. Grass pollen is a common inhalant allergen and in some regions of the United States, approximately 50–70 % of the atopic population is sensitized to grass allergens [13, 15]. Multiple species from the Pooideae subfamily of grass pollens exist in common geographic regions and pollinate at the same time. Therefore, many allergic patients are poly-exposed and likely polysensitized to allergens from the Pooideae subfamily. Thirteen allergen families are recognized within the Pooideae subfamily; however, group 1 and 5 allergens are the most clinically relevant with 95 % (group 1) and 65–85 % (group 5) of patients who are sensitized to these allergens. Group 1 and group 5 allergens demonstrate amino acid sequence homology within Pooideae grasses of approximately 90 and 55–80 %, respectively [23••, 24]. While detailed discussion of the molecular and cellular variabilities that exist within and between grass species is beyond the scope of this paper, there are certain aspects of grass pollen major allergen heterogeneity and homogeneity that may affect their allergenicity and cross-reactivity.

As noted previously, polysensitization in the AR patients is typically considered to be the sensitization to more than one allergen as determined by skin or specific IgE testing. Co-sensitization is polysensitization to structurally distinct allergens (e.g., Fel d1 cat allergen vs Phl p5 Timothy grass allergen). However, with two different SLIT tablets approved to treat grasspollen induced AR, we must consider the differences between the Timothy grass tablet and the 5-grass tablet allergens and the possibility that they may elicit different immune responses. Cross-reactivity across the three subfamilies of the Poaceae grasses has been studied via radioallergosorbent inhibition [25]. In this study, it was demonstrated that the Pooideae subfamily grasses June, rye, red top, and meadow fescue had complete inhibition by Timothy extract, whereas inhibition of sweet vernal was slightly less. Panicoideae grasses Johnson and Bahia had both shared and immunologically distinct reactivity compared to Pooideae, and Bermuda grass (Chloridoideae subfamily) was distinct from Pooideae.

Chabre et al. analyzed group 1 and 5 major allergens from the following Pooideae grasses: Timothy, Kentucky blue grass, cocksfoot or orchard, sweet vernal, and perennial rye [24]. These investigators found that each of the group 1 and 5 allergens contains both cross-reactive as well as species-restricted T- and B-cell epitopes. Further, in competitive experiments to investigate IgE binding conducted with sera from European and North American

allergic patients, 62 % had IgE's to group 1 antigens and 15 % had IgE to group 5 antigens which were completely inhibited by individual grasses and the 5-grass mix, demonstrating that these patients only have IgE's cross-reactive to all group 1 or 5 allergens (e.g., exhibiting shared epitopes). In the remaining patients, incomplete blocking was seen in 38 % (group 1 allergens) and 85 % (group 5 allergens) with individual extracts, whereas complete blocking was seen with the Pooideae 5-grass extract mix. Archila et al. evaluated cross-reactivity at the allergen-specific CD4+ T cell level in an in vitro model using blood mononuclear cells from grass pollen allergic subjects [23••]. In this study, certain sequence homologous, yet minimally cross-reactive, T cell epitopes were identified (i.e., Poa p1 $_{97–116}$, Lol p5a $_{199–218}$, etc.), and these particular epitopes were not cross-reactive with Phl p1 and Phl p5a. In addition, ex vivo tetramer staining assays showed that T cells from grass pollen allergic subjects will recognize these minimally cross-reactive T cell epitopes. Therefore it appears based upon laboratory evaluations, that certain T- and B-cell epitopes exhibited by the Pooideae subfamily grasses are species-specific and minimally cross-reactive, yet able to stimulate immune responses in vitro. Based upon these in vitro studies, the authors theorize that additional grass extracts in an immunotherapy treatment regimen would be of clinical benefit due to "real world poly-exposure", polysensitization to individual Pooideae grasses, and resulting distinct immune responses to these individual grasses.

As yet, controlled clinical trials have not been carried out to directly compare the response to grass SLIT tablet immunotherapy with the Timothy grass and 5-grass tablets that are currently available in the US. Therefore, we do not yet know if the minimally cross-reactive or non-cross-reactive T- and B-cell epitope reactivity seen in vitro are clinically important in allergic symptoms, and whether targeting these 5 combined Pooideae grass epitopes with SLIT provides symptomatic benefit over a single grass alone. The closest analogous study was published in 1983 by Frostad et al. [26], in which sixty Norwegian grass pollen allergic adults were treated for 3 years with a purified Timothy pollen extract, a crude Timothy extract, or a 4-grass mix (orchard, meadow fescue, rye, and June grasses). There was also a comparison control group that did not undergo treatment with any grass extracts. At study completion, patients receiving the purified Timothy extract were using less antihistamine medication than patients in the crude Timothy or 4-grass extract groups. In addition, the group treated with purified Timothy extract had higher tolerance on nasal challenge test than the crude Timothy extract group. These results, although performed quite some time ago, lends some historical support to the idea that clinically, single AIT performed with a properly selected allergen provides clinical benefit. Further studies, likely a triple-armed, blinded, randomized controlled head-to-head trial of available SLIT grass tablets would need to be performed to definitively answer the question of whether single grass or multiple grass tablets are clinically superior for allergy symptom control in the grass pollen allergic patient.

Conclusions

In 2014, the US had three tablets approved by the FDA for SLIT treatment of AR. This has changed the way AIT is contemplated by many providers, and has also raised numerous questions. In the classic immunotherapy environment of treating allergic patients with multiple allergen mixes, approaching the polysensitized patient with "single-allergen" immunotherapy seems contradictory to US AIT practice patterns held for decades. However, on close review of many published SLIT tablet clinical trials, polysensitized patients were included, and symptomatic benefit was achieved. Whether the practitioner chooses to continue classic US AIT practice and co-administer multiple allergen extracts, treat with a single allergen only, or consider SLIT tablet therapy supplemented by additional allergen extract sin injection or aqueous drop form will ultimately be the decision of the AIT provider and patient together.

Compliance with Ethics Guidelines

Conflict of Interest Rosa B. Lipin declares no conflict of interest. Sarah K. Wise reports that she is on the scientific advisory board of Greer Laboratories and that she has received research support from Genentech.

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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