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Specific Immunotherapy (L Cox, Section Editor)

Oral and Sublingual Immunotherapy

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Opinion statement

Subcutaneous immunotherapy is the only disease-modifying treatment for allergic rhinitis and asthma. Unfortunately, it is not accessible or appropriate for all patients, for reasons such as the risks of treatment, time commitment and cost involved, poor access to subspecialty care, and even the fear of injections. In the case of food allergy, treatments are inaccessible simply because they do not exist. Oral and sublingual immunotherapies offer superior safety when compared to allergy shots. The ease of administration, in particular with sublingual immunotherapy, and the ability to dose at home make these modalities very attractive. Aeroallergen sublingual immunotherapy has been used extensively in Europe for more than 10 years, but is not approved in the United States, despite various studies demonstrating its safety and efficacy. Recent studies have focused on addressing continuing concerns, such as determining the ideal dose and protocol, the therapy's effect in polysensitized patients, its safety in more severe patients, and its long-term effects. As each of these concerns is addressed, it seems more likely that sublingual immunotherapy will be added to the arsenal of treatments available to US allergists. Both oral and sublingual immunotherapies have been studied for food allergy, with preliminary evidence suggesting the ability of these treatments to induce desensitization. Recent studies, including the Burks study reviewed in this manuscript, suggest the potential for tolerance induction. However, there has been ongoing debate on how tolerance should be defined and measured. In addition, questions remain about the short-term and long-term safety of the treatment. Until these questions can be addressed with larger controlled studies, these oral and sublingual immunotherapies should not be considered ready for clinical use for food allergy.

Introduction

Allergic diseases such as allergic rhinitis, asthma, and food allergy affect a large proportion of the population, and the prevalence of these diseases continues to increase for reasons that are not clear. In 2011, approximately 19 million American adults reported a current diagnosis of asthma, and about 17 million adults reported a diagnosis of allergic rhinitis [1]. Among American children less than the age of 18 years, 7 million children reported asthma, another 7 million children reported allergic rhinitis, and 4 million children reported food allergies [2]. Needless to say, the burden of these diseases is tremendous and continually growing.

For asthma and allergic rhinitis, medical management involving inhaled and intranasal steroids and oral antihistamines are able to control symptoms for a majority of patients. For patients whose symptoms are not adequately controlled or who are looking for a more definitive treatment, subcutaneous immunotherapy (SCIT) has been a mainstay of treatment for over 100 years. An alternative treatment modality, sublingual immunotherapy (SLIT) has continued to grow in popularity since 1991 when the World Health Organization (WHO) first endorsed the practice [3]. Numerous studies and meta-analyses have been published since this time, most of which have demonstrated the safety and efficacy of the SLIT, and it is estimated that currently up to half of patients on immunotherapy in Europe receive it by the sublingual route [4]. In the United States, however, there are no SLIT formulations that have been approved by the Food and Drug Administration (FDA), and its use has been off-label and unregulated. Some important concerns raised about SLIT have included a lack of adequate safety data on the most severe patients, a lack of adequate data on polysensitized patients whom are presumed to be more common in the United States, and a lack of consensus on the appropriate dose and protocol [5].

Although several options are available to patients with asthma and allergic rhinitis, unfortunately, there are no treatments available to those with food allergies. The standard of care involves 1) identifying the causative food allergen, 2) strictly avoiding the food, and 3) having ready access to self-injectable epinephrine and oral antihistamines to treat accidental ingestions [6]. Despite improvements in food labeling and patient awareness, accidental ingestions have remained very common, magnifying the need for an active treatment [7]. The use of SCIT for food allergy was abandoned years ago because of an unacceptable amount of risk with the therapy [8, 9]; however, a significant amount of progress has been made in the past 10 years on the use of immunotherapy by the oral route, and more recently, by the sublingual route.

The past year has brought some exciting advances in the use of oral immunotherapy (OIT) and SLIT for allergic diseases. Some highlights include a look at the long-term data from the first full 5-year sublingual grass tablet study, the results of a multi-grass tablet study in American adults, as well as the early results of a large multinational ragweed tablet study. Additionally, the results of a study of dual allergen SLIT in an American cohort, and the safety and efficacy of SLIT in several at-risk patient populations were presented.

With regards to food allergy, the results of two studies undertaken by the Consortium of Food Allergy Research (CoFAR), the first involving oral immunotherapy (OIT) for egg allergy and the second involving SLIT for peanut allergy, were published. The long-term results of a unique study comparing OIT and SLIT in a head-to-head manner were also presented in the last year. Finally, an immunological study of the use of OIT in combination with anti-IgE therapy suggested a possible novel mechanism for the effects of OIT.

Allergic rhinitis and asthma

Long-term effects of SLIT

Over the years, numerous studies have been published describing the safety, efficacy and convenience of SLIT for allergic rhinitis and asthma. However, many of these studies have focused on single pollen seasons, and there have

been far fewer papers describing the safety and efficacy of longer courses of treatment or the potential for long-lasting benefit. The safety and efficacy of the Grazax grass allergy sublingual immunotherapy tablet (*Phleum pratense* 75000 SQ-T/2800 BAU, ALK, Denmark) has been previously reported [10–16]. In 2012, Durham et al. reported the results of the first 5-year double blind, placebo controlled trial of a grass SLIT therapy [17••]. Adults with at least 2 years of grass pollen allergy and qualifying skin prick tests (SPT) and serum specific IgEs were recruited from 51 sites in eight European countries. Two hundred and thirty-eight patients (135 treatment, 103 placebo) completed 3 years of active treatment and 2 years of follow-up. The rhinitis combined score (RCS) was 27 to 41 % lower than placebo for each of the five pollen seasons. This result was statistically significant for each of the 5 years, including the 2 years off of treatment. The authors pointed out that the second year off of treatment coincided with the lowest grass pollen exposures of the study, which is noteworthy, because low pollen counts are known to reduce the observed benefit of allergy treatments. However, a statistically significant 27 % decrease in RCS compared to placebo was still detected. Significant decreases in the percentage of severe symptom days and improvement in quality of life surveys strengthened the clinical relevance of the group's findings. These results suggested that with appropriate dosing, the long-term expectations for SLIT might parallel SCIT with 3 to 5 years of treatment providing long-lasting clinical relief.

Efficacy and mechanisms of multi-allergen SLIT

Despite numerous positive studies such as the Durham et al. study, SLIT has yet to be approved for use in the United States. One reason given is that the existing SLIT literature has focused mostly on European populations that have a lower proportion of polysensitized patients than in the United States. To better mimic the exposure and sensitization patterns of American adults, Cox et al. studied the efficacy of a 300 index of reactivity (IR) five-grass pollen sublingual tablet [18]. This tablet incorporated equal proportions of orchard grass, Kentucky bluegrass, perennial rye, sweet vernal, and timothy grass. Four hundred and seventy-three adults from 51 American sites, with at least 2 years of grass pollen allergic rhinitis and a positive SPT, were treated for one season. The group detected a 28.2 % reduction in daily combined symptom and medication scores. Safety of the multi-allergen tablet was similar to other SLIT studies, with no episodes of anaphylaxis reported and with oral pruritus being by far the most commonly reported adverse effect. Despite a prior study that did not show a benefit using a ten-allergen SLIT formulation [19], this study suggested that a multi-allergen SLIT therapy could remain efficacious without increasing risk. It is worth noting, though, that the five grasses represented in the tablet were allergens that are commonly mixed together and readily available as a standardized mix from the major allergy companies.

In a recent small single-center phase I study, Swamy et al. looked at the use of multi-allergen SLIT using two unrelated allergens, timothy grass (*P. pratense*) and dust mite (*Dermatophagoides farinae*) [20•]. Patients were treated with sublingual drops beginning 4 months before the grass pollen season and continuing for 12 months. In addition to symptom scores and rescue medication usage, efficacy was objectively measured with a timothy grass nasal disc challenge (NDC). Patients were then observed off therapy for

6 months, and subsequently rechallenged. Improvements in the typical markers of efficacy, symptom score and medication usage did not reach significance. However, NDC-induced mucus production was significantly decreased in the treatment group. In addition, despite only 12 months of treatment, seven of the 16 patients demonstrated a persistent reduction of NDC-induced mucus production off of therapy, suggesting tolerance. Although the extent of clinical benefit from this study was unclear, further immunological analysis by the authors demonstrated some interesting findings.

Many SLIT studies, including the Durham and Cox studies described above, have shown allergen-specific changes in IgG4 and IgE with therapy. Swamy also showed increases in timothy grass and dust mite IgG4 and decreases in IgE, as well as a decrease in basophil reactivity. Beyond these basic immunologic markers, the group showed an increase in regulatory T cell (T_{Reg}) suppressive function and an increase in IL-10, PD-1 and Foxp3 transcription. Furthermore, evidence of reduced methylation of CpG islands within Foxp3 was also discovered, suggesting more stable and likely longer-term suppressive function. These immunologic findings shed further light on the mechanisms of SLIT, and lend further support for the efficacy of SLIT and its potential to induce long-term tolerance.

Additional large cohort studies of SLIT for ragweed allergy

With continually increasing evidence in support of grass pollen SLIT, two industry sponsored studies from the past year shifted the focus to another major aeroallergen, ragweed (*Ambrosia artemisiifolia*). Nolte et al. conducted a blinded study of a ragweed immunotherapy tablet (MK-3641) in North American adults with at least 2 years of ragweed allergic rhinitis symptoms and a positive SPT and ragweed specific IgE [21]. As is commonly found in North America, 85 % of patients in this cohort were polysensitized. After 52 weeks of treatment beginning 12 weeks prior to the ragweed season, significant improvements in total combined score (TCS) were found when compared to placebo, with the 12 Amb a 1 unit dose outperforming the 6 Amb a 1 unit dose (26 % reduction compared to 16 %, respectively, over the entire ragweed season).

Concurrently, a large multinational study of the same ragweed immunotherapy tablet (MK-3641) was conducted with patients from the United States, Canada, Hungary, Ukraine, and Russia [22]. As in the Nolte study, patients in this study were adults with at least 2 years of symptoms and qualifying skin and blood IgE tests. Also similar was a high proportion of polysensitized patients (76 – 79 %). Proposed as a dose-finding study, 1.5 Amb a 1 unit, 6 Amb a 1 unit, and 12 Amb a 1 unit doses were compared against placebo. Significant decreases in TCS were found in the 6 Amb a 1 and 12 Amb a 1 unit cohorts (18 % and 27 %, respectively). Neither the current study nor the Nolte study reported severe symptoms requiring epinephrine therapy, and as expected, the most common side effect reported was oropharyngeal itching. Together, these two large studies further demonstrated the efficacy and safety of SLIT therapy, and in particular its potential benefit in ragweed allergy.

Safety and efficacy of aeroallergen SLIT in at-risk populations

Children

Although the body of literature supporting the use of SLIT has grown rapidly, only a small minority has been dedicated to its use in at-risk populations. Children make up one of these important at-risk populations. Children's natural aversion to injections precludes many of them from receiving SCIT. SLIT seems ideally suited to this population, based on its painless administration, improved safety profile when compared to SCIT, and ability to dose at home. However, studies focused on this group are lacking. To address this need, Wahn et al. investigated the use of six-grass pollen SLIT in children aged 4 to 12 years [23]. Two hundred and seven children from 34 centers in Germany and Poland underwent baseline evaluations, and then were treated pre-seasonally and co-seasonally during the subsequent grass pollen season. Significant decreases in symptom-medication scores demonstrated the efficacy of treatment. Safety analysis showed side effects reported by 75.9 % of actively treated patients compared to 32.7 % of placebo treated patients. However, the vast majority of these were from oral pruritus, and no epinephrine was needed for any adverse effects. This relatively large pediatric study suggested that SLIT could be just as efficacious in children, while still remaining safe.

Elderly

Elderly patients are another population that has been rarely studied with regards to immunotherapy. Chronic unstable diseases, especially cardiovascular, often preclude elderly patients from immunotherapy because of the risks of anaphylaxis and epinephrine. Concerns have also been raised about the effectiveness of immunotherapy in the face of an aging immune system. With this background, Bozek et al. looked at the use of dual dust mite (*D. pteronyssinus* and *D. farinae*) SLIT in 111 patients aged 60 to 75 years [24]. Exclusion criteria that were particularly relevant in this age group were non-allergic rhinitis (including senile and vasomotor) and severe non-stable chronic diseases. However, patients with stable coronary disease, hypertension, and diabetes were included. Patients were treated with Staloral dust mite SLIT extract (Stallergenes, France) for 36 months, and reported significant decreases in nasal symptom score and medication scores when compared to placebo. The authors point out that this seems to debunk the idea that an aging immune system is not able to respond to immunotherapy. With regards to safety, only three out of the 47 patients on treatment reported any side effects (oral pruritus x2, flushing x1). This is dramatically less than reported in most SLIT studies, which often report oral pruritus in the range of 70 % of patients. The authors postulate that this may be a result of the aging oral and nasal mucosa. It is noteworthy, though, that there were no severe systemic side effects and no epinephrine required, a major concern in this age group. Although the study suggests that SLIT should be considered in the elderly, finding patients without non-allergic rhinitis who could truly experience a dramatic improvement, and without unstable diseases that could put them at higher risk, may be the rate-limiting step.

Pregnant women

Although guidelines exist for the use of SCIT in pregnant women, there have not been any studies on the use of SLIT in this patient group. Shaikh et al. investigated the safety of dust mite and multi-allergen SLIT in 155 pregnant women in India [25]. Patients were treated for 5 years and followed off of therapy for an additional year. There were no systemic adverse events and only 11 episodes of oral pruritus. In addition, the treatment group experienced fewer pregnancy complications than in either of the control groups, and even less than the reported rate in the Indian general population. However, it should be noted that the authors did not report any measures of efficacy. The maximum dose of SLIT administered was 750 AU/day of *D. farinae*. To put this in perspective, a recent study of dust mite SLIT used a high dose of 4,200 AU/day and found no clinical benefit [26]. Further studies are needed before generalizations can be made on the safety of SLIT in this patient population.

Optimal SLIT dosing protocol

Most of the current literature on SLIT is focused on specific allergens, allergen formulations, and specific populations. However, not as much attention is put on the actual SLIT administration protocol. One question that Stelmach et al. tried to address was whether a continuous course of treatment would be superior to simply treating pre-seasonally and co-seasonally [27]. A seasonal approach would perhaps provide improved compliance; however, it is unclear whether it would provide comparable efficacy and long-term immune changes to continuous therapy. Combined symptoms/medication score was significantly decreased with both protocols when compared to placebo, but no difference was detected between the two protocols. Findings were similar when symptom scores and medications scores were looked at individually. Unexpectedly, co-seasonal treatment resulted in significantly lower nasal symptom scores when compared to continuous treatment. Although both protocols demonstrated increases in Foxp3+ T_{Reg} cells, similar increases were also found in the placebo group. In their discussion, the authors disclosed that they assumed that continuous treatment would dramatically outperform co-seasonal therapy, and that perhaps as a result, the study was underpowered to detect a difference between the protocols. Based on this preliminary data, it seems that both protocols can potentially be efficacious, but further studies are needed to differentiate which of the protocols is superior.

Food allergy

Consortium of food allergy research (CoFAR)

There has been a growing body of literature supporting the use of oral immunotherapy for food allergies [28–30]. More recently, sublingual immunotherapy has also been investigated as an option [31]. Although the majority of studies have shown a benefit with therapy, critics point out that many of the studies are from single-centers and there is often heterogeneity in the protocols, making generalization of the results problematic. A joint venture of five large US teaching institutions, CoFAR has strived to produce high quality research in food allergy. Over the

past year, the long-term results of two CoFAR studies were presented. Burks et al. looked at the use of oral immunotherapy for the treatment of egg allergy in children [32••]. Fifty-five children with a history of mild to moderate reactions to egg and a qualifying egg specific IgE were randomized and treated with ingested egg-white powder or placebo (40 on treatment, 15 on placebo). After 10 months, 55 % of patients on egg OIT passed a 5-gram challenge compared to none on placebo. After 22 months, 75 % of the patients on egg OIT passed a 10-gram challenge, suggesting increasing benefit with prolonged dosing. Patients passing this latter challenge were then restricted from egg for 4–6 weeks. A subsequent identical 10-gram challenge was passed by 28 % of patients on egg OIT. Although it is tempting to declare these patients as tolerant, because of the lack of a consensus definition for clinical tolerance in food allergy, the authors used the term "sustained unresponsiveness" to describe this effect. These patients were instructed to introduce egg into their diets ad lib and were followed for an additional 12 months with no adverse events reported. This study further demonstrates the ability of OIT to induce desensitization while on therapy. It also goes on to suggest the ability of OIT to induce a more lasting effect, possibly tolerance, in a subset of treated patients. Several additional studies also investigating the long-term effects of OIT are ongoing, and it will be interesting to see if tolerance is truly possible and whether predictive factors can be identified.

Despite the recent successes of OIT, concerns about the safety of the treatment have remained [33, 34]. With its presumed superior safety profile and much simpler administration, SLIT provides an attractive alternative modality. The results of a blinded study of SLIT for the treatment peanut allergy conducted by the CoFAR group were recently published [35]. Teenagers and adults underwent an entry challenge and were then treated with low-dose (1,286 mg) peanut SLIT or placebo. After unblinding, patients on placebo were crossed over and received high-dose (3,696 mcg) peanut SLIT. Low-dose and high-dose peanut SLIT resulted in significantly higher reaction thresholds during peanut challenge after 44 weeks of treatment compared to baseline (371 vs. 21 mg and 603 vs. 71 mg, respectively). Patients on low dose SLIT who were continued on therapy for an additional 24 weeks experienced further increases in reaction threshold (996 mg). Despite the statistically significant findings in this study, the authors pointed out that the degree of desensitization reported in the current study was several-fold lower than the first blinded study of peanut SLIT [31]. Differences in population (adults vs. children) and single-center bias were postulated as possible reasons for the discrepancy. Although the safety of peanut SLIT has been established through these two studies, further evidence of efficacy is needed before it can truly be considered a potential therapy for food allergy.

OIT vs. SLIT for food allergy

Keet et al. sought to compare OIT and SLIT for the treatment of milk allergy in a unique head-to-head protocol [36]. Thirty children were

randomized to receive SLIT alone or SLIT followed by OIT for 60 weeks. Those on OIT were further randomized to receive low-dose (1,000 mg) or high-dose OIT (2,000 mg). OIT resulted in more robust desensitization, with 60 % and 80 % of OIT patients passing a food challenge compared to 10 % for SLIT patients. The authors then went on to look at the question of lasting clinical tolerance vs. transient desensitization by conducting food challenges 1 week and 6 weeks off of therapy for those passing the end of study challenge. Six out of 15 patients regained reactivity, suggesting a tolerance induction rate of 45 % with OIT. Interestingly, two of the six patients who regained reactivity did so after only 1 week. Overall, the authors concluded that while desensitization, in particular with OIT, seemed quite possible, the potential to induce long-lasting tolerance was unclear. Furthermore, the authors pointed out that with reactivity returning in some cases after 1 week, a strict adherence to dosing for an indefinite period of time would likely be needed for non-tolerant patients to ensure safety. These results add more considerations into the ongoing debate on the risks and benefits of immunotherapy for food allergy.

Mechanisms of OIT for food allergy

Previously, Nadeau et al. conducted a small study of OIT in conjunction with the anti-IgE monoclonal antibody, omalizumab, to try to improve the safety of OIT treatment for milk allergy [37]. After a 9-week pretreatment period on omalizumab, patients were started on an aggressive milk OIT protocol. After an additional 7 weeks, omalizumab was discontinued and maintenance OIT dosing (2,000 mg) was continued. After an additional 8 weeks of therapy, nine out of ten patients passed a 7,250 mg milk food challenge. During the last year, the group presented the immunological workup from this cohort [38•]. The authors found that within 1 week of initiating OIT, milk-specific CD4+ T cell proliferation was reduced. Surprisingly, this occurred without an increase in Foxp3+ regulatory T cells, leading the authors to suspect an anergic state rather than a suppressed state. After 4–6 months of treatment, they found that the CD4+ T cell response returned, but with increased secretion of IFN-gamma and milk-specific IgG4 and decreased secretion of milk-specific IgE, suggesting a shift to a T_H1 phenotype. The suggestion that regulatory T cells may not be essential to the early effects of OIT would be in contrast to previous findings in aeroallergen SCIT, and verification of these results would be eagerly anticipated.

Conclusion

The past year has brought about significant advances in the use of oral and sublingual immunotherapy for both allergic rhinitis and food allergies. These modalities continue to appear safe and relatively convenient. Newer aeroallergen SLIT therapies appear to be closing the gap when compared to SCIT for allergic rhinitis, and OIT and SLIT are offering hope for food allergies where no treatments currently exist. Continued research into these modalities is needed to further improve their short-term and long-term effects, to better understand their mechanisms, and to help to make these treatments available to all.

Compliance with Ethics Guidelines

Conflict of Interest

Edwin H Kim is on the medical advisory board for Triangle E Technologies and Kyruus.

Wesley Burks is the past President of AAAAI; is currently a consultant to GLG Research, Nutricia North America, and Regeneron Pharmaceuticals; received honoraria from Levine's Children's Hospital; received payment for development of educational presentations from Mylan Specialty; and has stock/stock options with Mastcell Pharmaceuticals.

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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