

Sublingual immunotherapy

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Purpose of review

Sublingual immunotherapy is an established treatment option for allergic rhinitis in many European countries, but it is not approved in the United States and is considered investigational. Sublingual immunotherapy has received increasing attention in the United States as an alternative to subcutaneous immunotherapy for the treatment of allergic rhinitis and possibly asthma.

Recent findings

Evidence for the safety and efficacy of sublingual immunotherapy is accumulating. The immunological effects of sublingual immunotherapy appear to be similar to those of subcutaneous immunotherapy, but their mechanisms may differ. The unique attributes of sublingual immunotherapy may offer advantages in selected patients. Controlled studies are being extended to evaluate sublingual immunotherapy for other indications, including allergic asthma, latex allergy, atopic dermatitis and food allergies.

Summary

Increasing data support the safety and efficacy of sublingual immunotherapy and its validity as a first-line treatment option for allergic rhinitis; however, acceptance in the United States is hindered by the lack of confirmatory evidence with United States-licensed products and the reluctance of allergists to accept evidence based on European studies and products. The future of sublingual immunotherapy in the United States will require addressing regulatory, economic and medical criteria.

Keywords

allergic rhinitis, efficacy and safety, sublingual immunotherapy

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Introduction

Allergen immunotherapy has been practiced for over a century to treat allergic patients. The basic approach, developed by Noon [1], aims to control IgE-mediated allergic symptoms by induction of active immunity toward the specific environmental allergens responsible for producing the symptoms. Initially, allergen immunotherapy was used to treat 'hay fever' or seasonal allergic rhinitis caused by pollen allergens, but its use has expanded to include treating allergies caused by hymenoptera stings, house dust mites, animal danders, fungi, and other allergen sources [2]. Extracts or vaccines derived from these allergen sources are administered in regular, safe, and progressive doses until an effective maintenance dose is achieved. Maintenance doses are continued for a period of 3–5 years to induce a long-lasting protective effect demonstrated by the reduction of clinical symptoms and medication use; inhibition of late-phase responses in the skin, nose, and lungs; increases in allergen-specific IgG and IgG4 antibody responses; and induction of various local and systemic cellular responses. In the United States, the administration by subcutaneous injection is the traditional,

standard, and only approved route. Alternative routes (intranasal, oral, and sublingual) have been proposed sporadically since the 1920s as an alternative to subcutaneous injections [3–5]. However, they have remained controversial because their results have been equivocal in terms of safety and efficacy. Owing to primarily safety concerns and an increase in inexpensive and effective antiallergy drugs, interest in noninjection routes of allergen immunotherapy has received increased attention in recent years [6].

Recent evidence-based studies

Initial clinical trials investigating the safety and efficacy of sublingual immunotherapy (SLIT) in the 1980s were fraught with methodological flaws and questions regarding allergen quality, dose, patient selection criteria, and clinical endpoints [7]. More recently, better designed clinical trials have been conducted, and there is an increasing body of evidence-based studies that support the safety and efficacy of SLIT. In 2005, a systematic review [8] of 22 double-blind, placebo-controlled trials involving 979 patients found a significant treatment effect in symptom reduction [standardized mean difference (SMD) –0.42, 95%

confidence level (CI) -0.69 – 0.15 , $P=0.002$] and medication use (SMD -0.43 , 95% CI -0.63 – 0.23 , $P=0.00003$). Similar effect sizes were observed with seasonal (pollen) and perennial (house dust mite) allergens, and no serious adverse events were reported in any of the studies. Most studies, however, reported oral mucosal itching or swelling. Reliable conclusions about the efficacy of SLIT in children could not be made because of the limited number of pediatric studies: Of the 22 trials, only five were limited to children involving 111 SLIT and 107 placebo participants. More recently, a meta-analysis of 10 pediatric trials [9] involving 484 participants found significant improvement in rhinitis symptoms caused by seasonal and perennial allergens (SMD -0.56 , 95% CI -1.01 – 0.10 , $P=0.02$). A subanalysis of house dust mite SLIT showed a significant difference in efficacy based on the duration of treatment. Efficacy for treatment of house dust mite allergy required treatment for more than 18 months (SMD -0.72 , 95% CI -1.35 – 0.12 , $P=0.02$), although treatment for less than 18 months was not significant (SMD -0.26 , 95% CI -0.95 – 0.44 , $P=0.47$). A meta-analysis of 25 controlled studies [10] involving 1706 patients with allergic asthma found a significant symptom reduction with SLIT as compared to placebo [risk difference (RD) -0.27 , 95% CI -0.33 – 0.21 ; $P<0.01$] when categorical or discrete outcomes were used but not with continuous measures (SMD -0.38 , 95% CI -0.79 – 0.03 , $P=0.07$). However, when continuous measures included symptom and asthma medication scores, a significant benefit of SLIT was shown (SMD -0.79 , 95% CI -1.34 – 0.24 , $P=0.005$). The analysis included trials with seasonal and perennial allergens as well as 10 trials with children only.

These meta-analyses of well controlled clinical trials have confirmed that SLIT is beneficial for the treatment of allergic rhinitis and, to some extent, of allergic asthma. Although individual clinical trials employed different allergens, dosing regimens, patient selection criteria, outcome measures, and scoring systems, an overall benefit in terms of reduction in allergy symptoms and medication use is convincing, especially in the treatment of allergic rhinitis. The most common reported side effect of SLIT was oral mucosal itching and swelling. These and other adverse events were usually mild and self-resolving or resolved after dose adjustment. Serious adverse events attributed to SLIT were not reported and the safety profile was such that doses could be self-administered at home.

Differences between subcutaneous immunotherapy and sublingual immunotherapy

One of the major differences between subcutaneous immunotherapy (SCIT) and SLIT other than the obvious difference in the route of administration is the dose that is

required to induce a beneficial therapeutic effect. In most trials showing the efficacy of SLIT, doses in the range of three to more than 100 times the target monthly cumulative SCIT maintenance dose were administered [11–13]. To achieve these cumulative doses, allergen preparations must be administered frequently (usually daily) and for long duration (usually year round). Possible explanations for this may be the inefficient delivery of allergen to the immune cells, such as the oral dendritic cells and their difficulty to ultimately induce a robust and protective T-cell response.

There is increasing evidence that the immunological changes induced by SLIT are similar to those associated with SCIT [14]: Both forms of allergen immunotherapy are allergen specific, increase allergen-specific serum IgG and IgG4 concentrations in a dose-dependent manner, inhibit allergen-induced recruitment of eosinophils to ocular and nasal mucosa, can change the pattern of allergen-specific T cells from a Th2-type to Th1-type response (immune deviation), and have been shown to be capable of inducing a regulatory T-cell response as evidenced by IL-10 production [15,16]. However, more precise studies on the mechanisms of SLIT should be conducted. A potential differentiating mechanism may involve the oral dendritic cells. Their constitutive FcεRI expression, increased expression of major histocompatibility complex (MHC) class I and II complexes, and accessory molecules [17,18] suggest that they play a pivotal role in the induction of mucosal tolerance. The identification of the specific molecular interactions between the allergens and the dendritic cell receptors may lead to new therapeutic strategies that are unique to SLIT [19–21].

The improved tolerability and safety profile as compared to SCIT is the hallmark of SLIT. This has allowed for self-administration and home administration of allergen immunotherapy, avoiding the frequent visits to the allergist's office. The increased tolerability of SLIT has also allowed for experimentation with various dosing regimens. For example, several studies have shown that the buildup phase can be accelerated and maintenance doses can be achieved rapidly without severe adverse events [22–24]. The reduced presence of effector cells, that is, mast cells, basophils, and eosinophils in the oral mucosa may in part explain this tolerability of SLIT. Biodistribution studies [25,26] suggest that the allergen is sequestered in the oral mucosa for an extended period, thus further reducing the risk of adverse allergic reactions while sustaining beneficial local immune responses. The limited absorptive capacity of the sublingual mucosa may also explain why multiple daily low-dose administration of allergen is more efficacious than once daily dosing at higher doses [27].

Only a limited number of studies have been conducted to compare the efficacy of SLIT with SCIT [28,29]. In one study [28] involving 36 adults with house dust mite asthma, significant improvement in rhinitis ($P < 0.05$) and asthma ($P < 0.01$) symptoms was observed with the SCIT group after 1 year. The SLIT group, treated with 80 times of cumulative SCIT treatment dose over 1 year, showed improvement in both rhinitis and asthma symptoms, but significant benefit was only present for rhinitis symptoms ($P < 0.01$). In another study [29], 71 birch pollen hay fever patients were treated with SLIT, SCIT, or placebo in a double-blind, double dummy manner for 2 years. The relative changes in symptom and medication scores were significant for both SCIT ($P < 0.001$ and $P < 0.02$, respectively) and SLIT ($P < 0.01$ and $P < 0.05$, respectively). Although there was no significant difference between the SCIT and SLIT groups, the magnitude of the effect of SLIT was about half that of SCIT.

Future of sublingual immunotherapy

In Europe, SLIT has gained wide acceptance as an alternative to SCIT for treating allergic diseases. Second-generation SLIT products based on fast dissolve tablets have been approved, and novel products including mucosal adjuvants and recombinant allergens are being evaluated [30,31]. The long-lasting and preventive effects of allergen immunotherapy were previously established only with SCIT [32,33]. Now, it has also been demonstrated that SLIT can prevent the onset of new sensitizations and reduce the onset of asthma when initiated early in childhood [34–36]. These studies conducted in Europe continue to support the validity of SLIT as a first-line treatment option for allergic rhinitis. More recently, a radical approach to reverse the progression of allergic disease has been proposed by inducing mucosal tolerance induction in children with a high genetic risk of asthma/atopy. In a study sponsored by the Immune Tolerance Network [37^{••}], young children between the ages of 18 and 30 months with a history of atopic dermatitis or food allergy but without sensitization to inhaled allergens and whose biological parent or one sibling has a well documented history of atopy will receive SLIT containing house dust mite, timothy grass, and cat allergens. After 1 year of daily treatment with SLIT or placebo, the development of allergen sensitization and asthma will be monitored for 3 years. If the trial is successful, the dream of prophylaxis immunotherapy for allergic disease may be finally realized.

The application of SLIT in treating diseases other than allergic rhinitis and asthma is also being evaluated. Preliminary results of SLIT in patients with latex-induced urticaria [38], children with atopic dermatitis and sensitization to house dust mites [39], and food allergies [40] all

have shown promise. Continued efforts toward extending SLIT for new indications and to reach more allergic patients are being made.

Acceptance of sublingual immunotherapy in the United States

Essentially all of the controlled trials evaluating the safety and efficacy, compliance, and cost-effectiveness of SLIT have been conducted in Europe. As early as 1997, a World Health Organization (WHO) position paper [41] concluded that SLIT was a viable alternative to SCIT and justified its use in adults with allergic rhinitis. In 2001, a second WHO position paper [42] extended the indication of SLIT to children. SLIT is now commercially available and widely used in many European countries. In the meantime, there have been no published reports on the safety and efficacy of SLIT using allergen products available in the United States, and there are no products approved by the Food and Drug Administration (FDA) for SLIT. The American Medical Association's Current Procedural Terminology (CPT) Manual includes only the parenteral administration of allergenic extracts for immunotherapy, which precludes the reimbursement for SLIT by most insurance carriers. A structured evidence-based assessment of SLIT in adults conducted by the Blue Cross Blue Shield Association's Technology Evaluation Center (TEC) in 2003 [43] concluded that regardless of whether sublingual immunotherapy improves health outcomes, it is uncertain whether FDA-licensed allergen preparations are suitable for sublingual administration. Thus, SLIT did not meet the TEC criteria and remains investigational. In 2006, a joint task force of the American College of Allergy, Asthma and Immunology and the American Academy of Allergy, Asthma and Immunology's Immunotherapy and Allergy Diagnostic Committees evaluated the evidence on the effectiveness of SLIT [12]. They concluded that despite clear evidence on the safety and efficacy of SLIT, there are still many unanswered questions including effective dosage and treatment schedules, cost/benefit ratio, and its safety in high-risk asthmatic patients. Another barrier to the Joint Task Force's endorsement of SLIT was the absence of an FDA-approved product for SLIT. In 2007, a similar critical review of the published evidence on the effectiveness of SLIT was conducted by members of the American Academy of Otolaryngology-Head and Neck Surgery Foundation and the American Academy of Otolaryngic Allergy [44^{••}]. The report emphasized the potential advantages of SLIT over SCIT including its improved safety profile and the possibility of increasing access to immunotherapy because of patient convenience, home administration, and more affordable allergy testing. The authors concluded that even though unanswered questions remain, SLIT may be a valuable

addition to the treatment choices that could be offered to patients, especially for those who wish to pay out of pocket for the convenience of SLIT.

There are several reasons why we in the United States must proceed with caution in adopting SLIT based on the European experience. First, most of the evidence for safety and efficacy is based on treatment with single relevant allergens in monosensitized patients. In the United States, immunotherapy is routinely administered using multiple noncrossreactive allergens in polysensitized patients. Only one controlled trial, an open-label, parallel-group, randomized study involving 58 adults sensitized to birch and grass pollen, has been published [45]. The clinical results achieved were promising for SLIT in polysensitized patients. However, without the knowledge of the required dose in terms of units used to label allergen products in the United States, it would be difficult to predict the clinical utility of SLIT. FDA-approved dosing trials with standardized allergenic extracts are in progress, and industry-sponsored clinical trials with the goal of obtaining license approvals have been initiated in the United States. Second, the formulation of patient-specific extract/vaccines in the United States is performed by the practicing physician instead of by the allergen manufacturers. This makes standardization, quality control, and regulation of SLIT extremely difficult. Finally, there is a fear that the introduction of SLIT in the United States will undermine the specialty of allergy practices and lead patients to seek a less effective treatment in exchange for convenience. For these reasons, it is doubtful that we will realize the full benefit of SLIT without establishing practice parameters to be followed by practicing allergists. Critical reviews of evidence-based studies can help define a place for both SCIT and SLIT in the treatment armamentarium.

Conclusion

In many ways, the development and application of SLIT parallels that of SCIT. In the past, SCIT was considered controversial in spite of the clinical documentation of efficacy. It was practiced for decades based on trial and error, recorded observations, and the transition from empirical trials to controlled clinical investigations. The information required to apply allergen immunotherapy to a wider range of allergic patients and to improve its effectiveness had to await a deeper understanding of the natural history of allergic disease and its underlying genetic and immunological mechanisms. As the practice of allergen immunotherapy evolved, it has become clear that SLIT offers advantages to those patients that refuse SCIT, but its acceptance in the United States must overcome regulatory, economic, and medical criteria.

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- of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 298).

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