

CLINICAL THERAPEUTICS

Sublingual Immunotherapy

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This Journal feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the author's clinical recommendations.

A busy 28-year-old professional consults his physician for advice on long-standing hay fever. He reports having itchy eyes and an itchy nose, lacrimation, sneezing, rhinorrhea, and nasal congestion during the summer months. In previous years, he tried various antihistamines and nasal sprays, but these treatments only had limited benefit. A friend has suggested a corticosteroid injection or allergy injections, but he is hesitant to receive corticosteroids and unable to give up the time from work to receive injections. He is evaluated by an allergist. Skin testing confirms that he is strongly sensitized to grass pollen, with modest reactions to cat dander and house-dust mites. A trial of sublingual immunotherapy is recommended.

THE CLINICAL PROBLEM

Allergic rhinitis is a common condition affecting about one quarter of adults in the developed world. Many patients have mild symptoms that are either ignored or managed with the occasional use of antihistamine tablets. More significant symptoms are treated with the addition of topical corticosteroid sprays. Nonetheless, a significant minority of patients with allergic rhinitis continue to have troublesome symptoms despite the regular and appropriate use of antihistamines and topical corticosteroids.¹

Although allergic rhinitis is not associated with a risk of death, the disorder can have a considerable effect on the patient's quality of life. Coexisting conditions include asthma, chronic sinusitis, otitis media, nasal polyposis, and upper respiratory tract infection.² It has been estimated that allergic rhinitis results in 3.5 million lost workdays and 2 million lost school days annually in the United States.² Estimates of the annual cost of this disorder in the United States, including indirect costs due to loss of productivity, range from \$2 billion to \$6 billion per year.^{3,4} Studies suggest that the effect of allergic rhinitis on the patient is often underestimated by the physician; this may result in undertreatment.⁵

PATHOPHYSIOLOGY AND EFFECT OF THERAPY

Allergic rhinitis is caused by a type I hypersensitivity response to inhaled allergenic particles such as pollen grains, animal dander, and the feces of house-dust mites. Allergen-specific IgE antibodies bind to high-affinity Fc receptors (FcεRI) on the surface of mast cells and basophils. On reexposure, the FcεRIs are cross-linked, activating the mast cells in the nasal mucosa with the subsequent release of histamine, leukotrienes, and various cytokines and chemokines. The soluble mediators cause vascular dilation, the leak of endothelial fluid, and irritation of the sensory nerves. Mucus and watery secretions appear in the nose, causing sneezing and rhinorrhea; vascular sinusoids in the nasal mucosa fill with blood, causing nasal congestion. For a few hours, inflammatory cells such as neutrophils, eosinophils, and T cells are recruited into the inflammatory site, causing a more prolonged inflammatory response. This delayed or late-phase response is dependent on the initial IgE-mediated response, but it is more prolonged

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and responds differently to medication than the initial response. In particular, glucocorticoids suppress the late-phase response but do not affect the immediate allergic response.⁶

Specific immunotherapy, also called allergen immunotherapy, is a method of reducing sensitivity to a given allergen by repeated administration of a dose of that allergen. The benefit of specific immunotherapy is dependent on both the dose and the route of administration. Although the mechanism by which this benefit occurs is not fully understood, the current consensus is that specific immunotherapy works by inducing allergen-specific T regulatory cells that reduce the late-phase response to the allergen (Fig. 1).⁷ During a period of years, specific immunotherapy also reduces the specific IgE-antibody response, but that is not thought to be the basis of clinical efficacy. In parallel, specific immunotherapy typically induces an allergen-specific IgG response. In the past, this type of antibody has been called blocking antibody, although there is no evidence that it actually blocks the allergic response or has any physiologic role. The IgG response is probably driven by interleukin-10 generated as part of the regulatory T-cell response.

Traditionally, specific immunotherapy has been administered as a course of subcutaneous injections. However, limitations of this form of therapy (see the discussion of clinical use below) have led to considerable interest in possible alternative approaches. If an allergen is given in a high dose by the sublingual route, a small proportion of the administered dose is absorbed through the buccal mucosa and taken up by local dendritic cells. These cells then pass to the regional lymph nodes, where they can interact with antigen-specific lymphocytes. The precise mechanism of the efficacy of sublingual immunotherapy is not known, but some of the immunologic features of injection immunotherapy are also seen with sublingual immunotherapy. For example, allergen-specific IgG antibody and interleukin-10 responses are seen with high-dose sublingual regimens.⁸

CLINICAL EVIDENCE

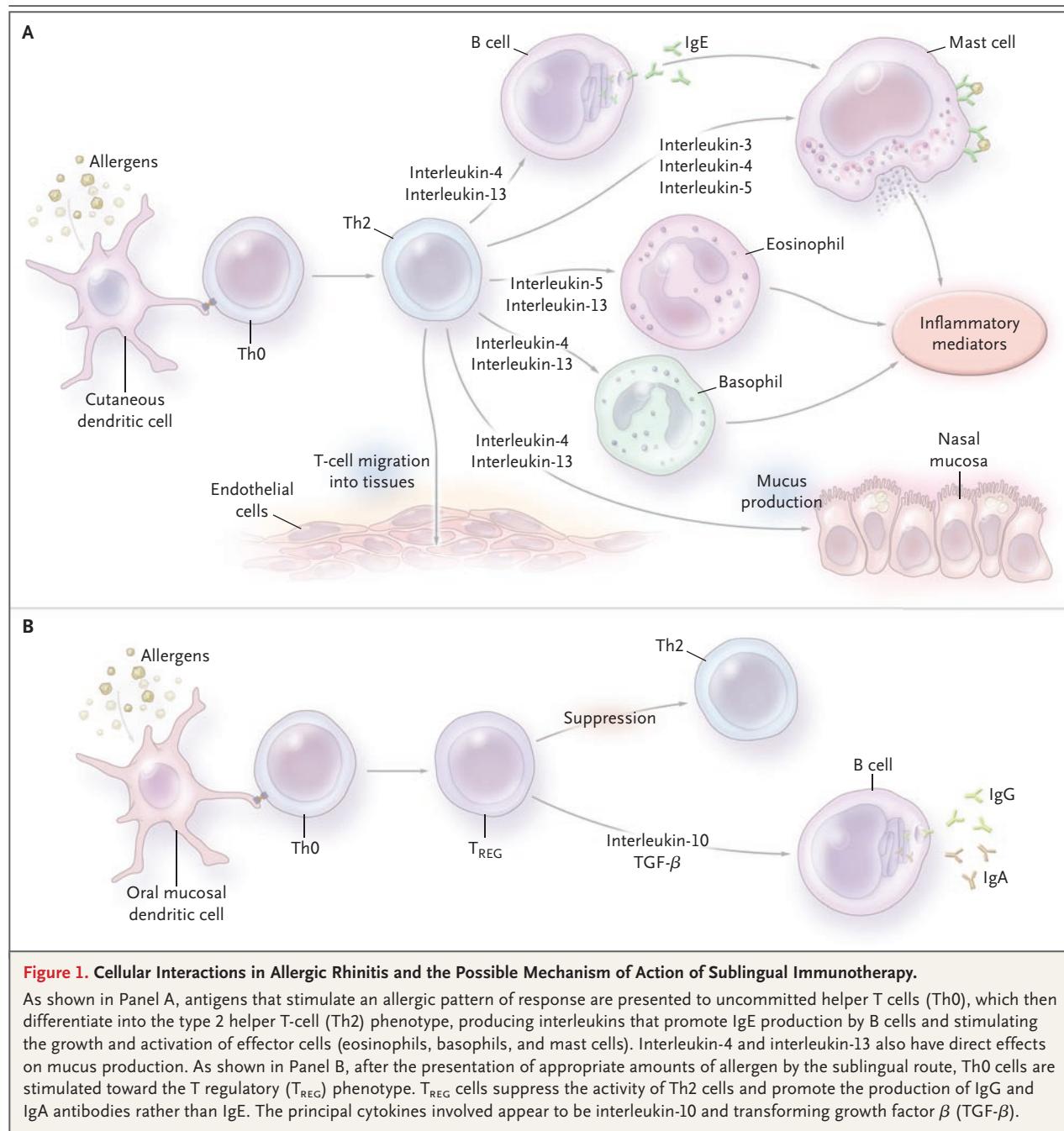
Sublingual immunotherapy was introduced into clinical practice in Europe without formal evidence of efficacy. A series of small uncontrolled or open studies were reported, but even as recently as 2000, only seven studies could be found with an adequate design to permit meta-analysis. Despite calls for large-scale trials,⁹ most studies remained small-

scale. By 2005, 21 trials of sublingual immunotherapy involving 959 subjects were available for meta-analysis. The results of these trials indicated that there was efficacy against allergic symptoms, although only cautious conclusions were possible because of the wide variation in allergens, dosage schedules, patient selection, and types of outcome measures.¹⁰ In 2006, the results of three large, double-blind, placebo-controlled trials of a grass-pollen tablet for sublingual immunotherapy were published.¹¹⁻¹³ These trials, which included more than 1600 patients, showed a 35 to 40% reduction in clinical symptoms in the first year of treatment and a similar reduction in the use of rescue medication. A total of 82% of patients receiving active therapy reported feeling better or much better, as compared with 55% of patients receiving placebo.

CLINICAL USE

Specific immunotherapy can alter the sensitivity of patients to inhaled allergens and improve allergic symptoms that do not respond to standard pharmacotherapy.¹⁴ Injection immunotherapy is routinely used, and it is the only form of specific immunotherapy approved by the Food and Drug Administration (FDA). However, this form of immunotherapy has a number of limitations. Efficacy is usually partial, and patients continue to need to use some drugs for the relief of symptoms. Adverse reactions are well recognized. Most of these reactions are minor, but a few fatal reactions, including death from anaphylaxis, occur each year.¹⁵ In addition, this risk creates a logistical issue, since injections have to be given in a doctor's office by someone familiar with injection immunotherapy and with managing anaphylaxis. Patients have to stay in the doctor's office for at least 30 minutes after each injection. Many potential patients are unable to find the time for injections. Sublingual immunotherapy has therefore been adopted in many European countries for patients who might otherwise be considered for conventional injection immunotherapy.

For either form of specific immunotherapy, the patient's symptoms must be shown to be due to one or a few dominant allergens. These allergens are then selected for immunotherapy with the expectation that the patient will not have substantial residual disease caused by other allergies. If the patient's symptoms are due to multiple or poorly defined allergens, then he or she will probably do better with pharmacotherapy, which should deal with symptoms regardless of which allergen is responsible. There are some differences of perspective in this



regard between allergists in the United States, who tend to view all sensitizations as being relevant, and European allergists, who tend to focus on allergens with the highest degree of sensitization.

The only agent that is currently commercially available for sublingual immunotherapy (Grazax, ALK-Abelló) is the extract of the grass pollen (*Phleum pratense*) that was studied in the trials mentioned above.¹¹⁻¹³ Therefore, only patients for whom grass pollen is the sole or dominant allergen re-

sponsible for symptoms can be treated with a standardized commercial form of sublingual immunotherapy, and only this product has thus far been approved for clinical use by European regulatory agencies. Other agents, such as an extract of cat dander,¹⁶ have undergone more limited study and have not received regulatory approval, but they are nonetheless in fairly widespread clinical use in Europe. The FDA has not approved any agent for sublingual immunotherapy.

Sublingual immunotherapy is not recommended in patients with active autoimmune or malignant conditions. There is no hard evidence that these conditions can be made worse by immunotherapy, but the precautionary approach seems wise. Moreover, managing the other condition is likely to take clinical priority over managing the allergy. Because of potential difficulties in treating anaphylaxis, injection immunotherapy is usually contraindicated in patients taking beta-blockers for clinically significant cardiac disease. However, on the basis of currently available data, anaphylaxis appears to be extremely unlikely with the use of sublingual immunotherapy.

Treatment with sublingual immunotherapy may be started at the full maintenance dose, without the gradual increase in dose that is usual with the administration of injection immunotherapy. Earlier trials incorporated a dose-increase phase, but this has been shown to be unnecessary. For the commercially available grass-pollen extract, a single sublingual tablet taken once daily constitutes the standard dose. Treatment works best if it is initiated at least 2 months, and preferably 3 to 4 months, before the pollen season.

In the trials of the grass-pollen tablet described above, about half the patients experienced some local irritation with the first dose. Such irritation is minor and generally does not require a reduction in subsequent doses. About half the patients with initial side effects had lost them by the eighth day of treatment; only 1 in 25 of all patients had continuing local side effects after 3 months of treatment.¹³ On the basis of available data, the risk of anaphylaxis appears to be extremely low. However, it is recommended that the first dose of sublingual immunotherapy should be given in a doctor's office so that any side effects can be discussed and explained. Subsequent doses are taken at home. The appropriate duration of therapy has not been clearly established, and practices and recommendations differ (see Areas of Uncertainty, below).

Although sublingual immunotherapy has been shown to be effective both in the clinical trials cited above and in practice, the majority of patients will continue to require other medications such as antihistamines and decongestants for more effective relief of symptoms. The use of inhaled or systemic corticosteroids might be expected to interfere with the efficacy of sublingual immunotherapy, but there is no evidence that this is the case.

The application of sublingual immunotherapy

in clinical practice has included a variety of approaches that are not based on sound evidence from well-conducted trials. Such approaches include the use of untested or inadequately tested allergens, low or homeopathic doses of allergens, and combination or multiple-allergen preparations. Because such practices are so widespread, it is essential to distinguish them from the evidence-based use of established agents, which to date includes only the commercially available grass-pollen tablet described above. Other approaches cannot be endorsed until better data are available. Specific details of some of these untested approaches are discussed further below.

The cost of the commercially available grass-pollen tablet for sublingual immunotherapy varies somewhat in the countries in which it is available. In the United Kingdom, the cost of 1 year of treatment is approximately £800 (\$1,650),¹⁷ whereas in Germany the current cost is €1,100 per year (\$1,700).¹⁸

ADVERSE EFFECTS

The most common side effect of sublingual immunotherapy is local irritation in the mouth and under the tongue; clinical trials have shown that the rate of local irritation was 47% and 52%. This side effect presumably reflects local allergic reactions to the allergen extract, although the tablet itself may play some part, since these symptoms were also reported by a minority of patients receiving placebo. Local pruritus affects about 50% of all patients, but it is usually transient and does not progress to anaphylaxis. Very few subjects cited this irritation as a reason for withdrawing from the clinical-trials program. Patients who have local irritation can be reassured that they have a 50% chance that this side effect will disappear within 8 days after treatment, whereas only 1 of 12 patients will still have ongoing local symptoms after 3 months of treatment. Other local side effects reported occasionally include ear pruritus, palatal edema, and throat irritation. If troublesome, these side effects may be managed by empirical premedication with antihistamines.

No systemic allergic reactions were reported in the clinical trials of commercial airborne-allergen extracts. However, there have been three case reports of anaphylaxis after sublingual immunotherapy. None of these reactions occurred with the commercially available grass-pollen tablet. Two reports describe anaphylaxis after administration of individualized mixtures of allergens^{19,20};

the third case was reported in a trial of sublingual immunotherapy for an allergy to latex.²¹

AREAS OF UNCERTAINTY

The development of a reliable, consistent, and reproducible approach to allergen dosing for immunotherapy has been constrained by the fact that accurate standardization is lacking. For many years, the biochemical composition of most common allergens was heterogeneous and not precisely determined. The standardization of extracts used for injection immunotherapy has been based on a biologic standard of IgE-binding potencies. Individual manufacturers use their own unique units, preventing comparison among products. An international system of quantification and standardization is currently being undertaken by a European Union project called CREATE (Development of Certified Reference Materials for Allergenic Products and Validation of Methods for their Quantification).²²

The issue of precision in measurement further complicates the determination of appropriate dosing for sublingual immunotherapy. Quantification is often expressed in terms of the dose that would be used in injection immunotherapy, since such doses are themselves not precisely defined. In the randomized trials of the commercially available grass-pollen extract, effective doses of allergens were 20 to 400 times the total dose that would be given in a course of injection immunotherapy. There is no evidence that giving smaller or homeopathic doses sublingually has any clinical effect whatsoever. Unfortunately, in the field, some clinicians have prescribed significantly smaller doses than those used in clinical trials. Given the large placebo effect seen in the clinical trials of high-dose sublingual immunotherapy, it is not surprising that some patients receiving low-dose sublingual immunotherapy feel better. However, such practices cannot be endorsed given the lack of data from properly designed trials.

The use of immunotherapeutic agents containing multiple allergens is another approach that is common in clinical practice, especially in the United States. This technique has arisen on the basis of the belief that patients should be treated for the full range of sensitivities that they show on skin testing, rather than for the effects of one or a few dominant allergens. Such therapeutic agents are usually formulated in the allergist's office from bulk material, and they contain multiple ingredients, the proportions of which are adjusted accord-

ing to the patient's skin-test sensitivities.²³ However, there are no systematic data confirming the efficacy of such preparations, and there is the theoretical concern that the absorptive capacity of the sublingual mucosa may be too limited to ensure proper exposure to multiple allergens administered together.²⁴ Therefore, this approach also cannot be endorsed.

The optimum duration of sublingual immunotherapy has not been defined. Recent clinical trials have confirmed the initial impression that sublingual immunotherapy is effective in the first 2 years of use, but it remains unclear whether its benefits persist after discontinuing treatment, and if they do persist, for how long. The manufacturer of the only licensed product recommends starting treatment 4 months before the first grass-pollen season and continuing throughout the year for 3 years. However, most of the clinical trials were short term (6 to 12 months), and there are thus few data providing support for this recommendation. Most open-label use has been intermittent — starting 2 to 3 months before the grass-pollen season and stopping at the end of the season.

The relative efficacy of sublingual immunotherapy and injection immunotherapy has not been determined. The only published comparative studies were far too small to give meaningful results.^{25,26} On the basis of the effect size seen in the meta-analyses,^{10,27} it seems likely that sublingual immunotherapy has between 60 and 100% of the efficacy of injection immunotherapy, although it is difficult to make a true comparison.

Efficacy in children has not yet been shown, and the results of some negative trials have been published.²⁸ However, in some countries such as Italy, up to 85% of children who are prescribed specific immunotherapy receive sublingual immunotherapy rather than injections. Although it is difficult to conduct double-blind, randomized, placebo-controlled trials involving children, it is wrong to extrapolate from studies performed in adults, especially given the tendency for remission of allergic disease in children.

GUIDELINES

Although sublingual immunotherapy is mentioned in several guidelines for the treatment of allergic rhinitis, no specific protocols for its use have been endorsed. The British Society for Allergy and Clinical Immunology notes in guidelines published in January 2008 that “sublingual immunotherapy has been

shown to be effective in both rhinitis and asthmatic patients and to have a good safety profile.²⁹ The lack of more precise or broadly authorized guidelines likely reflects the lack of an international consensus to date about the role of this form of therapy.

RECOMMENDATIONS

The patient described in the vignette is a suitable candidate for injection immunotherapy, since he has tried various medications with limited benefit and he has a predominant sensitization to one allergen (grass pollen). However, he is unable to make time to visit the allergist's office for the required sequence of injections. Therefore, he is an appropriate candidate for sublingual immunotherapy. As a practitioner in the United Kingdom, where a tablet of grass-pollen

extract (Grazax) is commercially available and approved for use, I would recommend that he start treatment with that agent 3 months before the onset of the grass-pollen season, continuing daily through the pollen season. He should receive the first dose in the physician's office. I would make certain that he is informed about the potential, typically minor, side effects and the theoretical risk of anaphylaxis. He should be advised that the need for additional medication such as antihistamines is likely for optimal control of his symptoms. He will need to be reevaluated at the end of the grass-pollen season in order to decide whether he should receive a full 3-year course of therapy.

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