Clinical reviews in allergy and immunology

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# Sublingual or subcutaneous immunotherapy for allergic rhinitis?

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**Overall Purpose/Goal:** To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

**Target Audience:** Physicians and researchers within the field of allergic disease.

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**Activity Objectives:**

1. To review the efficacy and safety of subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) based on randomized placebo-controlled trials.
2. To compare the efficacy and safety of SCIT versus SLIT based on indirect evidence and evidence from randomized head-to-head comparative trials.

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**Allergen immunotherapy is effective in patients with allergic rhinitis (AR) and, unlike antiallergic drugs, has been shown to modify the underlying cause of the disease, with proved long-term benefits. Subcutaneous immunotherapy (SCIT) has been the gold standard, whereas sublingual immunotherapy (SLIT) has emerged as an effective and safe alternative. Previous Cochrane systematic reviews and meta-analyses have confirmed that both SLIT and SCIT are effective in patients with seasonal AR, whereas evidence for their efficacy in patients with perennial disease has been less convincing. Recent large, adequately powered trials have demonstrated reductions in both symptoms and use of rescue medication in patients with seasonal and those with perennial AR. Here we appraise evidence for SCIT versus SLIT based on indirect evidence from Cochrane reviews and recent well-powered double-blind, randomized controlled trials versus placebo and the limited direct evidence available from randomized blind head-to-head comparisons. At present, based on an overall balance of efficacy and side effects, the patient is in equipoise. Pending definitive comparative trials, choice might be determined largely by the local availability of SCIT and SLIT products of proved value and personal (patient) preference. (J Allergy Clin Immunol 2016;137:339-49.)**

***Key words:*** *Allergic rhinitis, immunotherapy, sublingual immunotherapy, subcutaneous immunotherapy*

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Allergic rhinitis (AR) is a common disease.[1] Its prevalence in the United States is about 15% based on physician diagnoses and up to 30% based on self-reported symptoms.[2] In Europe the prevalence ranges from 17% to 29%, with an overall prevalence of 23%.[3] AR is frequently associated with bothersome symptoms,

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*Abbreviations used*
AR: Allergic rhinitis
ARC: Allergic rhinoconjunctivitis
RCT: Randomized controlled trial
SAR: Seasonal allergic rhinitis
SCIT: Subcutaneous immunotherapy
SLIT: Sublingual immunotherapy
SMD: Standardized mean difference
SR: Systematic review

which can impair quality of life, productive time at work and school, quality of sleep, and decreased involvement in outdoor activities.[2,3] Often, this condition is associated with comorbidities, including asthma.[4] Standard medical therapy consists of allergen avoidance where possible and pharmacotherapy, which generally includes the use of nonsedating oral antihistamines, topical nasal antihistamines, and intranasal corticosteroid sprays.[1,2,5] Suboptimal responses to antiallergic drugs are frequently caused by poor adherence such that patient education on the proper technique and need for regular use of nasal steroid sprays is important. These medications, although effective, must be repeated when symptoms recur because the underlying allergic disease remains unaffected.[1,6] Furthermore, some population surveys have reported that up to 29% of children and 62% of adults have partial or poor relief with pharmacotherapy alone.[7,8]

For patients with AR whose symptoms remain uncontrolled despite a supervised trial of medical treatment, allergen immunotherapy should be considered.[1] Subcutaneous immunotherapy (SCIT) has been shown to be highly effective, particularly for seasonal pollinosis but also for perennial disease in patients with mite allergy.[9,10] Nevertheless, this route of administration can occasionally be associated with allergic side effects and therefore needs to be administered in a specialist setting with access to adrenaline and other resuscitative measures.[11,12] Sublingual immunotherapy (SLIT) has emerged as an effective and safe alternative to the subcutaneous route for patients with seasonal allergic rhinitis (SAR),[1,13] whereas, until recently, evidence for efficacy in perennial mite allergy has been less convincing, particularly in children.[14] Sublingual treatment is commonly associated with local itching and swelling in the mouth, which can occasionally be bothersome and persist for weeks.[11] SLIT has an impressive safety profile in clinical trials[15,16] and postmarketing surveillance of large cohorts.[17] Although there have been isolated reports of more severe allergic side effects, including anaphylaxis, there have been no fatalities.[18] Adherence to sublingual treatment has also been raised as a potential issue,[19] and regular 3-month follow-up for repeat prescriptions has been shown to be effective in improving compliance.[20]

Both SCIT and SLIT, in contrast to antiallergic drugs, have been shown to have disease-modifying properties with clinical benefits that can persist for 2 to 3 years after discontinuation of therapy.[15,21] Three long-term double-blind, placebo-controlled studies of SLIT[6,11,15,16,22-24] and 3 studies of SCIT[21,25-28] for seasonal pollinosis are described in detail in Tables E1 and E2 in this article's Online Repository at www.jacionline.org.[6,11,15,16,21-28] Briefly, 3 years of treatment with sublingual drops of a 5-grass-pollen extract was effective 1 year after discontinuation.[22] Two studies of grass pollen allergen tablet immunotherapy administered daily either pre-coseasonally[16,23,24] or continuously[6,11,15] for 3 years (cumulative annual dose of the Phl p 5

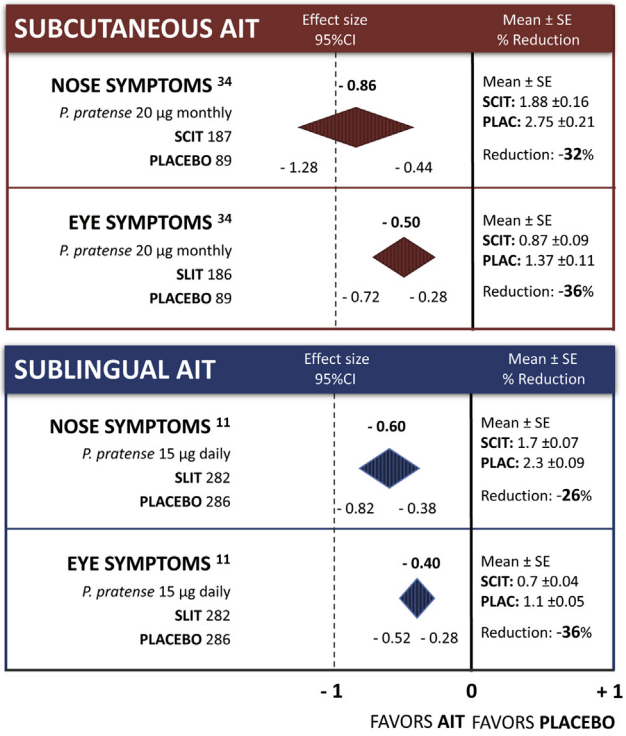


**FIG 1.** Two well-powered RCTs of SCIT and SLIT for SAR. *AIT,* Allergen immunotherapy.

major allergen for both studies was around 5-6 mg annually) produced remarkably similar results. In both studies there was an approximate 30% to 40% reduction in symptoms and rescue medication use during 3 years of therapy and a 20% to 30% reduction during 2 years off treatment when double-blinding was maintained. Local side effects were common but generally well tolerated, and there were no serious adverse events reported. Three previous double-blind, placebo-controlled trials of subcutaneous ragweed,[25] grass pollen,[21,26,27] and *Parietaria* species[28] immunotherapy produced similar results. Although studies were small (with 10-20 participants per group), 3 to 4 years of treatment resulted in persistent improvement in symptoms and/or reductions in rescue medication at 3 years in 1 study after double-blind withdrawal[21] and in 2 studies at 1 year after discontinuation of immunotherapy.[25,28] There is also evidence that SCIT can prevent disease progression to asthma in children with pollen-induced AR[29] and possibly prevent onset of new allergic sensitizations,[30,31] with similar results for sublingual treatment.[32] Evidence for prevention is less robust, and a current double-blind, placebo-controlled trial of grass pollen sublingual tablet immunotherapy on asthma prevention in 812 children with SAR will be reported in 2016.[33]

An important question is whether the balance of effectiveness and side effects is in favor of either the subcutaneous or sublingual route. Two well-powered randomized controlled trials (RCTs) by Frew et al[34] using subcutaneous grass pollen immunotherapy and Dahl et al[11] using sublingual grass pollen tablet immunotherapy had very similar study designs and were conducted with similar methodology. Participants had moderate-to-severe grass pollen SAR for at least 2 years. The studies used the same standardized single-allergen *Phleum pratense* extract. The SCIT was administered in a cluster updosing regimen followed by monthly maintenance injections of alum-adsorbed extract that contained