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Sublingual Immunotherapy for Allergic Rhinitis Is 2-Year Treatment Sufficient for Long-term Benefit?

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Allergen-specific immunotherapy (AIT) is a desensitizing and potentially curative therapy that has been used since 1911 to treat allergic rhinitis and asthma.¹ Immunotherapy involves



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repeated administration of the identified allergen(s) over time with the goal of inducing sustained allergen-specific tolerance. The proportion of patients treated with AIT who achieve sustained allergen-specific tolerance varies from 0% to 55%, depending on factors including type of allergen, treatment duration, and the definition of relapse.²

AIT typically involves administering unmodified allergen extracts derived from natural sources (eg, grass pollen) or cultures (eg, house dust mites) over a 3- to 5-year treatment course. Short-course (4-6 injections) AIT with various modifications that include changing the allergen structure (eg, T-cell epitope peptides) or addition of immunostimulatory adjuvants (eg, CpG oligodeoxynucleotides, monophosphoryl lipid A) have been largely unsuccessful in achieving tolerance to the allergen. Systemic allergic reactions are the most concerning risk associated with AIT, occurring in approximately 0.1% of injections in approximately 2% to 5% of patients.³

Subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) are the most widely prescribed delivery routes for aeroallergen immunotherapy AIT. A direct correlation between allergen dose and adverse effects has been reported with SCIT but not with SLIT. In general, the incidence of SCIT-induced systemic allergic reactions occurs in approximately 0.1% of injections, and most of these reactions (~70%) are classified as mild (World Allergy Organization Grade 1).⁴ In

contrast, no fatalities and only a few cases of SLIT-associated anaphylaxis have been reported in the more than 3 decades of SLIT use worldwide. Due to the potential risk of a serious systemic allergic reaction, clinical practice guidelines recommend that SCIT be administered "... in a facility with the appropriate equipment, medications, and personnel to treat anaphylaxis."³ The favorable safety profile of SLIT allows for administration outside of a medical center provided that the patient is knowledgeable regarding self-administration and management of adverse reactions.⁵

Numerous well-designed, randomized clinical trials have demonstrated that both forms of AIT reduce allergic rhinitis symptom-medication scores—the most commonly investigated primary outcome. The magnitude of benefit required for an AIT product to be considered effective, according to the World Allergy Organization, is a 20% or greater improvement in outcomes compared with placebo.⁶ Although antiallergy medications (eg, antihistamines, nasal corticosteroids) are effective in relieving symptoms of allergic rhinitis, these medications do not achieve sustained benefits after treatment is discontinued.

Because allergic rhinitis is a chronic condition, the cumulative costs of symptomatic drug treatment for perennial or seasonal allergic rhinitis can be significant over time. In a 2013 systematic review and economic evaluation, economic modeling suggested that AIT, compared with symptomatic treatment, may become cost-effective at a threshold of £20 000 to £30 000 (equivalent to US \$24 533-\$36 829) per quality-adjusted life-year from approximately 6 years after treatment initiation.⁷ The AIT treatment duration was 3 years

in most of the studies included in this review. This suggests that AIT cost-effectiveness may not be fully appreciated until some time after therapy completion, when the costs of the AIT therapy are exceeded by the savings from avoiding anti-allergy medications. The authors of the review and economic evaluation also concluded that there would likely be greater savings if the disease-modifying effects of AIT were considered: “potential cost savings resulting from future cases of asthma avoided were not included in the analysis, but would likely lead to an increase in cost-effectiveness.”⁷ However, few studies have considered the effects of AIT vs symptomatic drug treatment alone on the indirect costs related to poorly controlled allergic rhinitis and its comorbid conditions (eg, missed work or school, poor sleep quality causing daytime fatigue, unscheduled medical visits for sinusitis or asthma). It is likely that these indirect costs are at least as great as the direct costs.⁸

Inherent to any AIT cost-benefit assessment is the duration of treatment required for optimal long-term efficacy. The time commitment requirement may be an important factor in patients’ decisions to initiate therapy. Few studies have been designed to define the optimal duration of AIT for achieving long-term clinical tolerance. To date, no randomized clinical trials have compared the long-term efficacy of different durations of AIT treatment.

Retrospective studies provide some evidence that 3 years of AIT may be associated with long-term clinical benefit, and AIT courses of less than 3 years’ duration may be associated with greater relapse rates.^{2,9} Double-blind, placebo-controlled trials with SLIT and SCIT have demonstrated that 3 years of continuous AIT resulted in clinical benefits and immunological changes consistent with allergen-specific tolerance sustained for at least 2 years after treatment discontinuation.¹⁰⁻¹³ Current clinical guidelines recommend at least 3 years of therapy for both forms of AIT.^{3,14} Whether a shorter course of AIT treatment provides long-term efficacy is not known.

In this issue of *JAMA*, Scadding and colleagues¹⁵ attempt to address whether a shorter course of therapy can achieve benefit at 3-year follow-up. In this clinical trial, the authors assessed the efficacy of a 2-year course of grass-pollen SLIT, with outcomes assessed at 3 years. Adults with moderate to severe seasonal allergic rhinitis were randomized to receive 2 years of treatment with SLIT ($n = 36$), placebo ($n = 34$), or SCIT ($n = 36$, included to serve as a positive control for tolerance and mechanistic studies). All 3 groups were administered a tablet (SLIT or placebo) daily and received a monthly injection (placebo or SCIT) for 2 years. Active treatment used the same dosing regimen and formulations as in previous SCIT and SLIT trials that established the persistent benefits of 3 years of continuous treatment.^{11,12}

The primary outcome was long-term efficacy, determined by response to a grass-pollen nasal challenge 1 year after completing the 2-year SLIT treatment course. Nasal allergen challenges were performed at baseline, after the first and second treatment year, and 1 year after the end of treatment. The primary outcome was the weighted average of Total Nasal Symptom Score (TNSS) per hour during the challenge. The TNSS is a

composite of 4 nasal symptoms rated by the patient on a scale of 0 to 3, with 3 representing most severe symptoms.

Secondary and exploratory outcomes included change in nasal inspiratory flow rates after the challenge; weekly general and disease-specific quality-of-life assessments during allergy season using the visual analog scale and the Mini Rhinoconjunctivitis Quality-of-Life Questionnaire (mini-RQLQ); and end-of-season assessment of rhinitis severity, seasonal medication use, change in late- and early-phase skin test response, and allergen-specific IgE and IgG.

The trial demonstrated that 2 years of continuous SLIT therapy did not provide significant posttreatment efficacy at 3-year follow-up. For the primary outcome, the imputed mean TNSS scores at pretreatment and at 3 years for the SLIT group were 6.36 and 4.73 and for the placebo group were 6.06 and 4.81, between-group difference (adjusted for baseline) was -0.18 (95% CI, -1.25 to 0.90 ; $P = .75$). Exploratory analysis revealed a similar lack of efficacy in the SCIT group with between-group difference compared to placebo at -0.90 (95% CI, -1.96 to 0.16 ; $P = .10$).

In contrast, in secondary exploratory outcomes there was significant improvement in response to nasal rechallenge compared with placebo at the end of the second treatment year with both forms of AIT. A significant improvement in nasal challenge was also observed after the first treatment year with SCIT but not with SLIT. The effect of both forms of AIT on seasonal allergic rhinitis symptoms was inferred by the improved mini-RQLQ and global severity evaluations compared with placebo in both treatment years. This treatment effect was not sustained in the posttreatment assessment. It should be noted that the recorded grass-pollen counts during the peak pollen season were at least 2 times greater in the second treatment year compared with the first treatment and posttreatment years. Lower grass pollen counts may have resulted in less symptomatic allergic rhinitis in all 3 groups, diminishing any treatment effect during this assessment period. This effect has been the postulated reason for several studies investigating novel AIT therapies for seasonal allergic rhinitis that failed to meet their primary outcome of reduced symptoms and medications during pollen season. In some instances, further development of the AIT product was abandoned despite earlier studies demonstrating significant clinical efficacy. Because this study did not evaluate seasonal symptoms scores, it is not known if the lower pollen counts in the third year of the study resulted in less allergic rhinitis symptoms in the placebo group.

However, both AIT routes were associated with significant changes in the secondary exploratory objective assessments of allergen-specific tolerance, the early- and late-phase skin test reactivity, and allergen-specific IgG during treatment and 1 year after therapy was completed.

These objective measures of allergen-specific response are included as secondary outcomes in most AIT clinical trials and are often considered surrogate markers of AIT efficacy. Although the mechanism responsible for persistent AIT efficacy after discontinuation is unclear, the expected outcomes of effective AIT therapy include reduced allergen skin test reactivity and increased allergen-specific IgG levels. An AIT

therapy failing to induce significant changes in either parameter would raise questions about its therapeutic efficacy or require an alternative mechanism to explain allergen-specific tolerance. Although 2 years of SLIT treatment did not achieve clinical efficacy at 3-year follow-up, in exploratory analyses, the study demonstrated benefit of SLIT during treatment and also demonstrated evidence of sustained immunological tolerance after 2 years of SLIT. As reported in other studies,¹⁶ the clinical efficacy of SLIT appears to increase over time during the treatment period, with greater improvement seen in the second year compared with the first year of therapy.

Overall, the results of the study by Scadding et al suggest that 2 years is not sufficient for SLIT treatment to induce long-term clinical efficacy. These results support current practice guidelines^{3,14} recommending that at least 3 years of SLIT therapy are required for induction of long-term clinical efficacy and tolerance, and provide an important contribution to the evidence regarding immunotherapy for allergic rhinitis. With the emergence of SLIT therapy over the past decade, it is important to clearly define the duration of therapy necessary to improve symptoms and clinical outcomes for patients with allergic rhinitis.

ARTICLE INFORMATION

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