Subcutaneous immunotherapy and pharmacotherapy in seasonal allergic rhinitis: A comparison based on meta-analyses

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Background: Allergen-specific subcutaneous immunotherapy (SCIT) of seasonal allergic rhinitis (SAR) is usually considered a "second-line," slow-acting, disease-modifying treatment.
Objective: We sought to test whether SCIT is as effective as antisymptomatic treatment in the control of symptoms in patients with SAR in the first year of treatment.
Methods: We reviewed meta-analyses with 5 or more randomized, double-blind, placebo-controlled trials of SCIT or antisymptomatic treatment in patients with SAR. We then selected trials measuring the total nasal symptom score (TNSS), the total symptom score (TSS), or both during the first pollen season after treatment initiation. Efficacy was determined as the percentage reduction in TSSs and TNSSs obtained with active treatment compared with placebo (relative clinical impact [RCI]) and the standardized mean difference (SMD) of treatment verses placebo (effect size [ES]).
Results: The weighted mean RCI of SCIT on TNSSs (−34.7% ± 6.8%) was higher than those of mometasone (−31.7% ± 16.7%, $P < .00001$) and montelukast (−6.3% ± 3.0%, $P < .00001$). The weighted mean RCI of SCIT on TSSs (−32.9% ± 12.7%) was higher than that of desloratadine (−12.0% ± 5.1%, $P < .00001$). The overall ES of SCIT in terms of TNSSs (SMD, −0.94; 95% CI, −1.45 to −0.43) was similar to that of mometasone (SMD, −0.47; 95% CI, −0.63 to −0.32; $P > .05$) and higher than that of montelukast (SMD, −0.24; 95% CI, −0.33 to −0.16; $P < .05$). The overall ES of SCIT in terms of TSSs (SMD, −0.86; 95% CI, −1.17 to −0.55) was comparable with that of desloratadine (SMD, −1.00; 95% CI, −1.68 to −0.32; $P > .05$).
Conclusions: Our data provide indirect but consistent evidence that SCIT is at least as potent as pharmacotherapy in controlling the symptoms of SAR as early as the first season of treatment. (J Allergy Clin Immunol 2011;128:791-9.)

Key words: *Seasonal allergic rhinitis, allergen-specific immunotherapy, allergen-specific subcutaneous immunotherapy, nasal corticosteroids, antihistamines, leukotriene antagonists*

According to the Allergic Rhinitis and its Impact on Asthma 2008 update,[1] allergen-specific immunotherapy (SIT) "is the practice of administering increasing amounts of an allergen extract to an allergic subject to ameliorate symptoms associated with the subsequent exposure to the causative allergen." The same document states that subcutaneous immunotherapy against allergic rhinitis is indicated in "patients in whom antihistamines and moderate dose topical glucocorticoids insufficiently control symptoms," "in patients who do not want to be on constant or long-term pharmacotherapy," and "in patients in whom pharmacotherapy induces undesirable side effects."[1] The response to pharmacotherapy appears therefore to be crucial before deciding whether to start SIT in a patient with allergic rhinitis. Most simply, SIT is considered by these guidelines as a sort of "second-line" treatment to be initiated only if pharmacotherapy is unsuccessful, not accepted, or not tolerated. However, pharmacotherapy reduces symptoms of allergic rhinitis without modifying its natural history, whereas SIT would reduce symptoms, especially after some years of treatment.

Clinical guidelines take many parameters into consideration, including costs, safety, acceptance rate, compliance, adherence, and feasibility of different treatments. Is allergen-specific subcutaneous immunotherapy (SCIT), from a merely clinical standpoint, really less efficient than pharmacotherapy in the short-term control of seasonal allergic rhinitis (SAR) symptoms? To answer this question, we analyzed the evidence for the efficacy of SCIT and pharmacotherapy in the control of SAR symptoms.* Unfortunately, only 4 trials directly compared SCIT and antisymptomatic treatment in patients with SAR,[2-5] and they reached conflicting conclusions. Therefore we decided to evaluate a quite large number of double-blind, placebo-controlled trials about SCIT, as well as antisymptomatic treatment, in patients with SAR. To this end, we used 4 meta-analyses published in peer-reviewed journals and examined the efficacy in patients with SAR of SCIT,[6] 1 nasal corticosteroid (mometasone furoate),[7] 1 antihistamine (desloratadine),[8] and 1 leukotriene antagonist (LA; montelukast).[9] In addition, we reviewed relevant studies of additional antisymptomatic drugs (fexofenadine, loratadine, ebastine, fluticasone propionate nasal spray, and ciclesonide).

*We use the old term *seasonal allergic rhinitis* instead of the new term *intermittent allergic rhinitis*[1] because the old term is used by almost all the trials considered in our review.

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Abbreviations used
ES: Effect size
LA: Leukotriene antagonist
MoE: Magnitude of efficacy
RCI: Relative clinical impact
SAR: Seasonal allergic rhinitis
SCIT: Allergen-specific subcutaneous immunotherapy
SIT: Allergen-specific immunotherapy
SMD: Standardized mean difference
TNSS: Total nasal symptom score
TSS: Total symptom score
WAO: World Allergy Organization

METHODS

Selection of meta-analyses, studies, and primary outcomes

Between August and October 2009, we selected, through a Medline search on PubMed (no time limits), 5 meta-analyses of different treatments belonging to 4 different therapeutic approaches to SAR: SCIT (2 meta-analyses dedicated to the total symptom score [TSS]) and total nasal symptom score [TNSS], respectively),[6] nasal corticosteroids,[7] oral antihistamines,[8] and oral LAs.[9] Systematic reviews not following the meta-analysis methodology were not included. We focused on meta-analyses that included at least 5 studies on SAR and that allowed a direct or indirect calculation of the average magnitude of efficacy (MoE) of the considered treatment to be made with both measures: relative clinical impact (RCI) and effect size (ES). Most meta-analyses on pharmacologic treatment of allergic rhinitis include trials on both seasonal and persistent allergic rhinitis; we excluded from our analysis studies without natural exposure (eg, studies based on artificial allergen exposure) and studies on persistent allergic rhinitis. We only selected the meta-analysis with a focus on SAR when 2 or more meta-analyses of a given treatment responded to the selection criteria. Primary outcomes are described in the Methods section in this article's Online Repository at www.jacionline.org. The vast majority of the examined trials included exclusively or almost exclusively adults. Only 1 trial was limited to children.[10]

Analysis of treatment effect

Clinical efficacy in trials of SCIT and trials of antisymptomatic treatment in patients with SAR is generally measured by using different methods (Fig 1). The studies on SCIT commonly evaluate the difference in daily symptom score values recorded throughout the pollen season or during the peak pollen season. By contrast, studies on antisymptomatic treatment of SAR commonly assess baseline values (usually over periods of 1-2 weeks) and treatment values (usually over periods of 2-4 weeks) of the symptom score, and they calculate the absolute and relative improvement of both the placebo and active treatment groups versus baseline values. Efficacy is often estimated as the difference between the percentage of reduction in the active and placebo groups. To compare the efficacy of the 2 therapeutic approaches, we used the means and SDs of the symptom scores recorded during the treatment period (see the Methods section in this article's Online Repository).

ES and RCI

Different scales have been used in the 42 trials contributing to the present study to express the primary outcome variables (TSSs and TNSSs). Therefore we followed the criteria suggested by the World Allergy Organization (WAO)[11] and used the standardized mean difference (SMD) to calculate the ES of individual studies. The overall ES of each category of treatment was calculated as the DerSimonian and Laird method pooled SMD. Both individual and overall SMD values were reported with 95% CIs. χ^2 Tests were performed to assess heterogeneity between studies, with a P value of less than .05 indicating significant differences between studies. Tests of heterogeneity were performed with the I^2 test.

The MoE of treatment versus placebo was also calculated for individual studies and expressed as the percentage reduction in clinical scores (TNSSs or TSSs) in the active versus placebo groups (RCI), as suggested by the WAO.[11] The average RCI of treatment for each category of study (SCIT, mometasone, desloratadine, and montelukast) was calculated by using the weighted mean of the values obtained in each of the studies included in the meta-analyses. Crude unadjusted weights were used.

Individual studies

Individual studies on ciclesonide, fluticasone propionate, fexofenadine, loratadine, and ebastine were selected from those available in the literature on the basis of the following criteria: published in the last 10 years (1998 or later); including at least 100 patients; adopting a randomized double-blind, placebo-controlled approach; and included in the Allergic Rhinitis and its Impact on Asthma update document.[1] For this analysis, we also selected the trial with the largest population among those included in each of the meta-analyses of SCIT, mometasone, desloratadine, and montelukast above reported values.

Comparison of ES and RCI

The ES of SCIT in terms of TNSSs was compared with those of nasal corticosteroids, antihistamines, and LAs and in terms of TSSs to antihistamines. A difference was considered significant when the 95% CI of the overall SMD did not overlap. P values of less than .05 were considered significant. The RCI of SCIT in terms of TNSSs was compared by means of ANOVA with those of nasal corticosteroids, antihistamines, and LAs and in terms of TSSs with those of antihistamines. The Bonferroni correction was applied to the ANOVA posttests. P values of less than .05 were considered significant.

RESULTS

Antisymptomatic effect of SCIT in patients with SAR

For more information on the antisymptomatic effect of SCIT in patients with SAR, see Tables I and II.

In 2007, Calderon et al[6] published a meta-analysis of SCIT for SAR. They examined 276 full-text articles, but only 15 of them[12-26] also met all the criteria for the meta-analysis in terms of the global (nasal, eye, and lung) symptom score. Of these 15 studies, we had to exclude the studies by Walker et al,[26] Corrigan et al,[23] and Jutel et al[25] because they did not report a complete dataset concerning clinical efficacy during the first season after treatment initiation. We included 12 trials, which included 474 subjects receiving active immunotherapy and 348 receiving placebo. In Table I we report the main characteristics of the trials, the TSSs, and the individual and overall RCI and ES values expressed as the SMD. The RCI ranged from −21%[16] to −73%,[15] its weighted mean value was −32.9% (SD, 12.7%; Fig 2, *A*), and its median value was −37.9%. The ES, expressed as the SMD, ranged from −3.06[19] to −0.27,[12] and its overall value was 0.86 (95% CI, −1.17 to −0.55; Fig 2, *B*).

We also analyzed the effect of SCIT on nasal symptoms only. In the meta-analysis by Calderon et al,[6] only 8 studies met the criteria for our meta-analysis in terms of nasal symptom scores.[12,17,21,24,27-30] Of these 8 studies, we had to exclude the studies by D'Amato et al[28] and Dolz et al[29] because it was not possible to extrapolate the data concerning clinical efficacy during the first season after treatment initiation. We included 6 trials, which included 349 subjects receiving active immunotherapy and 236 receiving with placebo. In Table II we report the main characteristics of the trials included, the individual and overall RCI, and the ES values. The RCI ranged from −30%[21] to