Treatment effect of sublingual immunotherapy tablets and pharmacotherapies for seasonal and perennial allergic rhinitis: Pooled analyses

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Background: Data comparing the treatment effect of allergy immunotherapy and pharmacotherapy are lacking.
Objective: We sought to indirectly compare the treatment effect of sublingual immunotherapy (SLIT)-tablets with pharmacotherapy for seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR).
Methods: Pooled data from randomized, double-blind, placebo-controlled trials for the clinical development programs of selected allergic rhinitis treatments were evaluated. Total nasal symptom scores (TNSSs) relative to placebo were compared. Subjects scored symptoms daily during entire pollen seasons in 6 timothy grass SLIT-tablet trials (n = 3094) and 2 ragweed SLIT-tablet trials (n = 658) and during the last 8 weeks of treatment in 2 house dust mite (HDM) SLIT-tablet trials (n = 1768). Subjects scored symptoms daily in 7 montelukast (10 mg, n = 6799), 9 desloratadine (5 mg, n = 4455), and 8 mometasone furoate nasal spray (MFNS; 200 μg daily, n = 2140) SAR or PAR trials. SLIT-tablet trials allowed rescue medication use, whereas most pharmacotherapy trials did not. A fixed-effect meta-analysis method estimated differences in on-treatment average TNSSs.
Results: In grass and ragweed SLIT-tablet trials, overall improvement in TNSSs relative to placebo was 16.3% and 17.1%, respectively. In HDM SLIT-tablet trials, TNSS overall improvement relative to placebo was 16.1%. In the montelukast, desloratadine, and MFNS trials, TNSS overall improvement relative to placebo was 5.4%, 8.5%, and 22.2%, respectively, for SAR trials, and 3.7%, 4.8%, and 11.2%, respectively, for PAR trials.
Conclusions: Although comparisons were limited by study design heterogeneity and use of rescue medications in SLIT-tablet trials, effects on nasal symptoms with timothy grass and ragweed SLIT-tablets were nearly as great as with MFNS and numerically greater than with montelukast and desloratadine for SAR. HDM SLIT-tablet effects were numerically greater than all pharmacotherapies for PAR. SLIT-tablets offer the additional benefit of long-term efficacy. (J Allergy Clin Immunol 2016;138:1081-8.)

Key words: *Allergen immunotherapy, allergic rhinoconjunctivitis, ragweed, grass, house dust mite, sublingual immunotherapy tablet, intranasal corticosteroid, antihistamine, leukotriene receptor antagonists, meta-analysis*

Allergic rhinitis (AR) is a common condition affecting up to 500 million persons worldwide.[1] AR is often undertreated, and there is unfortunately a common misperception by physicians that it is not a consequential disease.[2] However, AR can have a substantial adverse effect on quality of life, emotional health, work and school performance, and sleep characteristics.[3-5] Allergy immunotherapy (AIT) has been demonstrated to reduce symptoms associated with seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR).[6] In contrast to pharmacotherapies, AIT also provides the benefit of inducing allergen tolerance, which results in long-lasting symptom relief for up to several years after treatment is completed.[7,8] Sublingual immunotherapy (SLIT)-tablets are a daily oral alternative to subcutaneous immunotherapy. SLIT-tablets for timothy grass (and related grasses) SAR are approved in North America and throughout Europe,[9,10] and a SLIT-tablet for short ragweed SAR is approved in North America.[11] SLIT-tablets for house dust mite (HDM; 12 SQ-HDM) have also been demonstrated to be efficacious[12-15] and have been approved recently in Europe.

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Abbreviations used
AIT: Allergy immunotherapy
AR: Allergic rhinitis
HDM: House dust mite
INCS: Intranasal corticosteroid
MD: Mean difference
MFNS: Mometasone furoate nasal spray
PAR: Perennial allergic rhinitis
SAR: Seasonal allergic rhinitis
SLIT: Sublingual immunotherapy
SMD: Standardized mean difference
TNSS: Total nasal symptom score

Antihistamines, leukotriene receptor antagonists, and intranasal corticosteroids (INCSs) are the most common pharmacotherapies used to treat symptoms of AR.[16] Although the variable effectiveness among these allergy pharmacotherapy classes has been documented,[17-19] data on the comparative treatment effect of AIT and pharmacotherapy for AR are lacking because few head-to-head trials have been conducted.[20] Indirect comparisons of treatment effects for allergy pharmacotherapies and AIT are difficult because of key methodological differences in trial design/conduct for these products, which might affect signal detection and noise. One of these key differences is that allergy pharmacotherapy trials typically select subjects with confirmed moderate-to-severe symptoms who meet a minimum symptom threshold at baseline when exposed to the allergens at the time of randomization; however, subjects in seasonal AIT trials were typically required to have only a clinical history of AR and documented sensitivity to the allergen under evaluation at the time of randomization without a baseline symptom score or confirmation of a threshold symptom severity during allergen exposure. Another difference, particularly for pollen allergies, is that pharmacotherapy trials generally evaluate efficacy during a 2-week period during the peak pollen season, whereas AIT trials often evaluate efficacy throughout the entire pollen season (approximately 6-12 weeks) with variable pollen levels. These study design differences alone complicate the indirect comparison between AIT and pharmacotherapy.

The most notable difference is in the allowed use of AR rescue medication in the placebo and active treatment groups in AIT trials. The treatment period for AIT trials is weeks or months longer than that of pharmacotherapy, and therefore it is considered unethical for subjects receiving placebo to be unable to treat their AR symptoms. Thus the use of oral antihistamines, ocular antihistamines, INCSs, and occasionally systemic steroids is allowed in all treatment groups. Assuming symptoms across trials are scored similarly, the observed treatment effect for AIT *is in addition to background AR rescue pharmacotherapy use*, which could make the effect appear smaller than that of pharmacotherapy if only an absolute symptom score was used for indirect comparison. Consequently, the treatment effect of AIT products is generally reported as a relative difference from placebo (percentage improvement vs placebo) during the efficacy assessment period.

Two meta-analyses have been conducted comparing the treatment effect of AIT with pharmacotherapy; however, these analyses were either limited to subcutaneous AIT[21] or grass SLIT-tablets for SAR.[22] The objective of these analyses was to indirectly compare, based on nasal symptom scores relative to placebo, the treatment effect of SLIT-tablets with selected pharmacotherapies for SAR and PAR by using pooled clinical trial data.

METHODS

Trials included in pooled analyses

Trials included in the analyses were randomized, double-blind, placebo-controlled trials from the clinical development programs of timothy grass SLIT-tablets (Grastek/Grazax; MK-7243; Merck & Co, Kenilworth, NJ/ALK-Abelló, Hørsholm, Denmark), short ragweed SLIT-tablets (Ragwitek; MK-3641; Merck/ALK-Abelló), HDM SLIT tablets (MK-8237; Merck/ALK-Abelló), montelukast (Singulair; Merck), desloratadine (Clarinex; Merck), and mometasone furoate nasal spray (MFNS; Nasonex; Merck). Numerous trials for these products have been conducted; however, the pivotal registration trials (including trials which did not meet the primary end point) for the SAR and PAR indications with the highest similarity in design and study population were selected to reduce intertrial heterogeneity. Selection criteria for trial design similarity were based on the primary end point, availability of subject-assessed symptoms (as opposed to physician-assessed), and the length of the assessment period. Details of most of the trials included in the analyses have been previously described.[13,15,23-45] Although some of the trials conducted in the 1990s are unpublished, data were obtained from the clinical study reports and *ad hoc* summaries on file. Of the unpublished trials, all met the primary end point (see Table E1 in this article's Online Repository at www.jacionline.org), except for trials C98-225 and P00219 for desloratadine (5 mg). The GT-14 trial for the grass SLIT-tablet also did not meet the primary end point. Subjects in the trials had SAR or PAR, which is in concordance with the main objective of each trial. Some of the trials included subjects with concomitant asthma. Institutional review board or independent ethics committee approval was obtained for each trial, and written informed consent was obtained from all subjects (or the subject's representative).

Treatment

The doses used in these analyses were 2800 bioequivalent allergen units (*Phleum pratense*, 75,000 SQ-T) for timothy grass SLIT-tablets, 12 units of *Ambrosia artemisiifolia* major allergen 1 (Amb a 1-U) for ragweed SLIT-tablets, 12 SQ-HDM for HDM SLIT-tablets, 10 mg of montelukast, 5 mg of desloratadine, and 200 μg of MFNS. All treatments were once daily. In the SLIT-tablet trials, subjects were allowed to use AR rescue medications (see Table E1), if needed. AR rescue medication use was not allowed in the pharmacotherapy trials, except 1 SAR trial and 3 PAR trials with MFNS allowed oral antihistamine use and 2 PAR trials with desloratadine allowed decongestants.

Nasal symptom scoring

Subjects scored the severity of their nasal symptoms daily during the entire pollen season (approximately 6-12 weeks) in the timothy grass and ragweed SLIT-tablet trials and during the last 8 weeks of treatment in the HDM SLIT-tablet trials. In the montelukast trials subjects scored nasal symptoms each evening for the time period since arising that day (ie, daytime symptoms) over a period of 2 weeks for SAR and 4 to 6 weeks for PAR. In the desloratadine SAR trials, subjects scored nasal symptoms each morning and evening for the prior 12 hours over a period of 2 weeks. In the desloratadine PAR trials, subjects scored nasal symptoms each morning and evening instantaneously and reflectively (ie, how they felt at that exact moment and how they felt in the previous 12 hours) over a period of 4 weeks. In the MFNS SAR and PAR trials, subjects scored nasal symptoms each morning and evening for the prior 12 hours over a period of 15 days. In all the trials, nasal symptoms were scored by using a scale of intensity ranging from 0 (none) to 1 (mild), 2 (moderate), and 3 (severe). Different terminology for nasal symptoms was used among the trials; however, all trials assessed the individual symptoms of rhinorrhea/runny nose, nasal stuffiness/congestion/blocked nose, nasal itching, and sneezing. Because of inconsistent data collection between the SLIT-tablet and pharmacotherapy trials, the treatment effect on ocular symptoms was not included in this analysis.