

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;■■■:■■■-■■■.)

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

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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 efficacious¹²⁻¹⁵ and have been approved recently in Europe.

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

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

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 AIT²¹ 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 (Clarinet; 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.

Statistical analysis

The average total nasal symptom score (TNSS) within the double-blind treatment period (ie, on treatment) for the total of 4 nasal symptoms (maximum, 12) was calculated *a priori* for SLIT-tablets and *post hoc* for pharmacotherapies. For the current analyses, the average on-treatment TNSS was calculated *post hoc* in the same manner as for the SLIT-tablet trials (relative difference to placebo) at the treatment group level as the sum of the baseline TNSS and the average change from baseline TNSS. The original TNSS

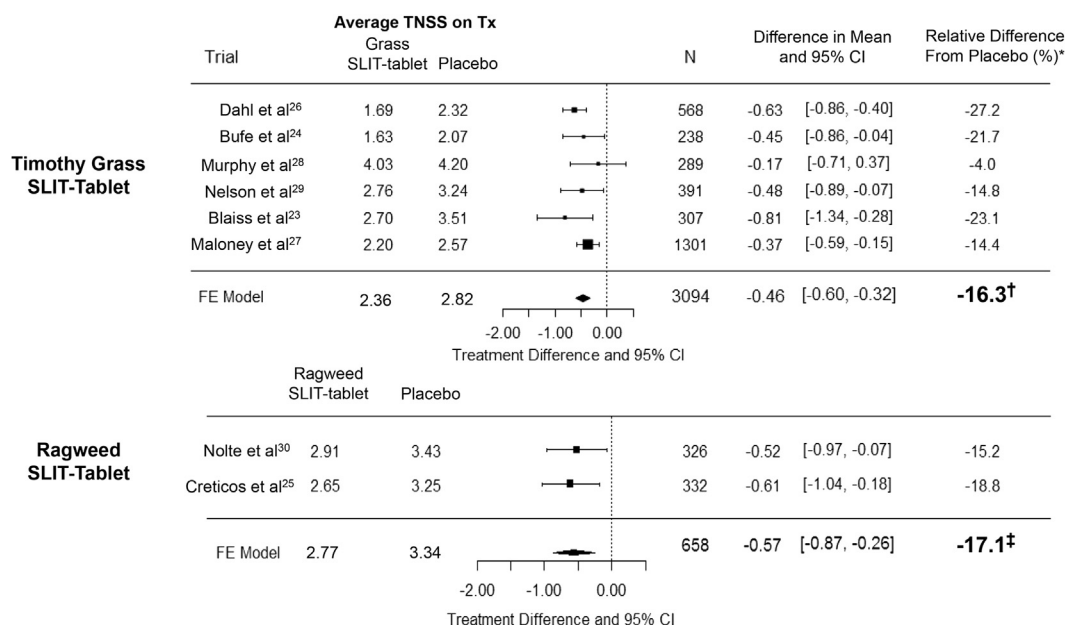


FIG 1. TNSS improvements with timothy grass and ragweed SLIT-tablets relative to placebo for SAR. *Calculated as follows: $(\text{Active treatment} - \text{Placebo}) / \text{Placebo} \times 100\%$. †Relative percentage improvement in rhinoconjunctivitis daily rescue medication score ranged from 27% to 38% in the trials. ‡Relative percentage improvement in rhinoconjunctivitis daily rescue medication score was 38% and 46% in the 2 trials. FE, Fixed effects.

analyses in the pharmacotherapy trials were based on comparing the average change from baseline symptom scores between treatment groups. In the original montelukast trials, the TNSS was calculated as the average of the 4 nasal symptom scores rather than the sum of the scores. In the current analyses, the montelukast data were adjusted to the “sum” scale by multiplying the originally reported results by 4. The variability of the on-treatment TNSS was determined as 95% CIs calculated *a priori* in the SLIT-tablet trials, SDs calculated *a priori* for MFNS, and SDs calculated *post hoc* for desloratadine. For the montelukast trials, SDs for the on-treatment TNSS were not originally calculated, and therefore the pooled SD of the change from baseline quantity was used as a proxy to estimate the variability of the on-treatment quantity for each trial included in the meta-analysis.

A simple fixed-effect meta-analysis method using the number of evaluable subjects as weight was used to estimate the overall effect size. A fixed-effects model was chosen instead of a random-effects model because it is closer to the approach that would be used in a pooled analysis when subject-level data are available. In addition, because of the use of evaluable subjects as weights, point estimates of the overall absolute treatment difference will be the same for both models, and only the associated 95% CI differs. Because of the different reporting conventions on TNSSs between SLIT-tablet and pharmacotherapy trials, effect size based on the mean difference (MD) metric used the between-treatment difference (with 95% CIs) as the input for the SLIT-tablet trials and treatment group means (with SDs) as the input for the pharmacotherapy trials. The overall average on-treatment TNSS from placebo-treated subjects was estimated as the weighted (by number of evaluable subjects) average of the individual placebo symptom scores. The overall relative treatment difference was then calculated for each AR treatment by dividing the meta-analytic treatment difference by the weighted on-treatment TNSS from placebo subjects as follows:

$$([\text{Active treatment} - \text{Placebo}] / \text{Placebo}) \times 100\%.$$

Software used for the analysis was based on R (version 3.1.0) with the package metaphor (version 1.9-7).

Effect sizes based on the standardized mean difference (SMD) metric were calculated as a supplemental method of demonstrating the treatment effect in which we accounted for differences in the range of TNSSs and the variability of the end point across trials. The overall absolute treatment difference based on the SMD metric for each therapy was estimated by using a fixed-effects

model, with the number of evaluable subjects as weight. Effect size calculations used treatment group means (SDs) of TNSSs as input for each trial. The variability estimate (ie, SDs) for the TNSSs was calculated per protocol in the SLIT-tablet and MFNS trials. Data were extracted *post hoc* from the 9 desloratadine trials to calculate the SDs for TNSSs. The SDs from montelukast trials were estimated based on the results available in the clinical study reports using the assumption that the pattern of variability would be similar among the pharmacotherapy trials.

RESULTS

A total of 23 SAR trials and 11 PAR trials were included in the analyses, representing 18,914 subjects. Characteristics of the trials are shown in Table E1. Subjects included in the trials ranged in age from 5 to 85 years. All of the trials were conducted in North America, Europe, or both; 2 studies also had sites in Latin America.

Treatment effect for SAR

The treatment effects in the timothy grass and ragweed SLIT-tablets were similar. In the 6 timothy grass SLIT-tablet trials, TNSS improvement relative to placebo ranged from 4.0% to 27.2%, with an overall improvement of 16.3% (Fig 1).^{23,24,26-29} In the 2 ragweed SLIT-tablet trials, TNSS improvement relative to placebo was 15.2% and 18.8%; overall improvement was 17.1% (Fig 1).^{25,30} Treatment effects with SLIT-tablets were numerically greater for SAR compared with montelukast and desloratadine. In the 5 montelukast SAR trials, TNSS improvement relative to placebo ranged from 0.6% to 10.3%; overall improvement was 5.4% (Fig 2).³¹⁻³⁵ In the 6 desloratadine SAR trials, TNSS improvement relative to placebo ranged from 1.7% to 12.5%, with an overall improvement of 8.5% (Fig 3).^{36,39,46} In contrast to montelukast and desloratadine, the treatment effect size with MFNS for SAR was numerically greater compared

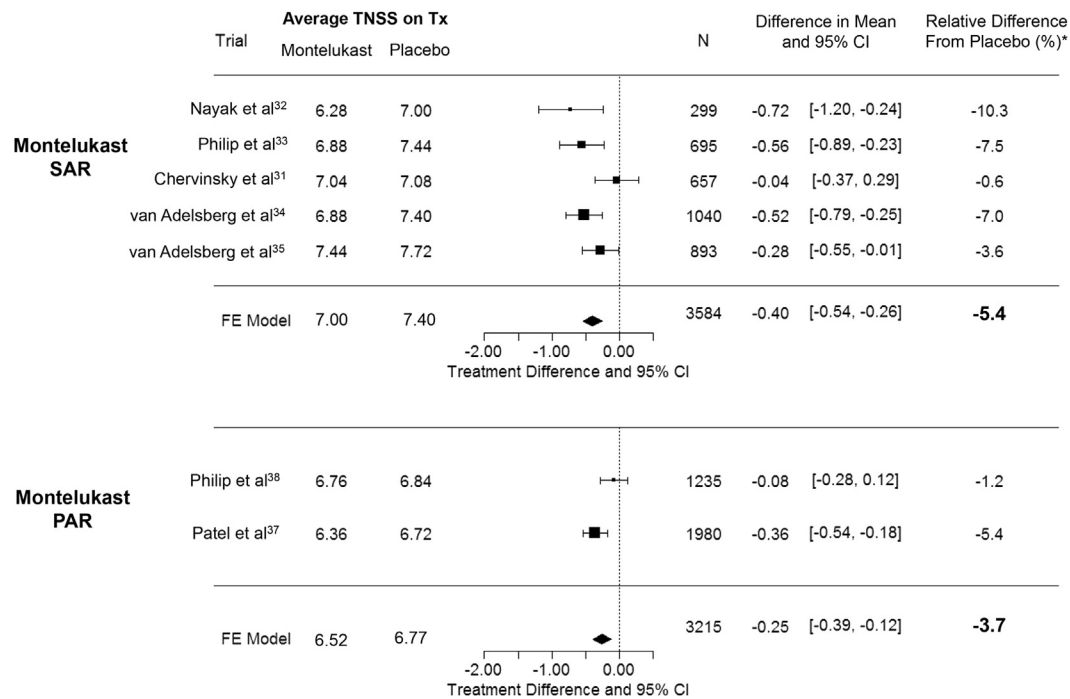


FIG 2. TNSS improvements with montelukast relative to placebo for SAR and PAR. *Calculated as follows: $([\text{Active treatment} - \text{Placebo}]/\text{Placebo}) \times 100\%$. FE, Fixed effects.

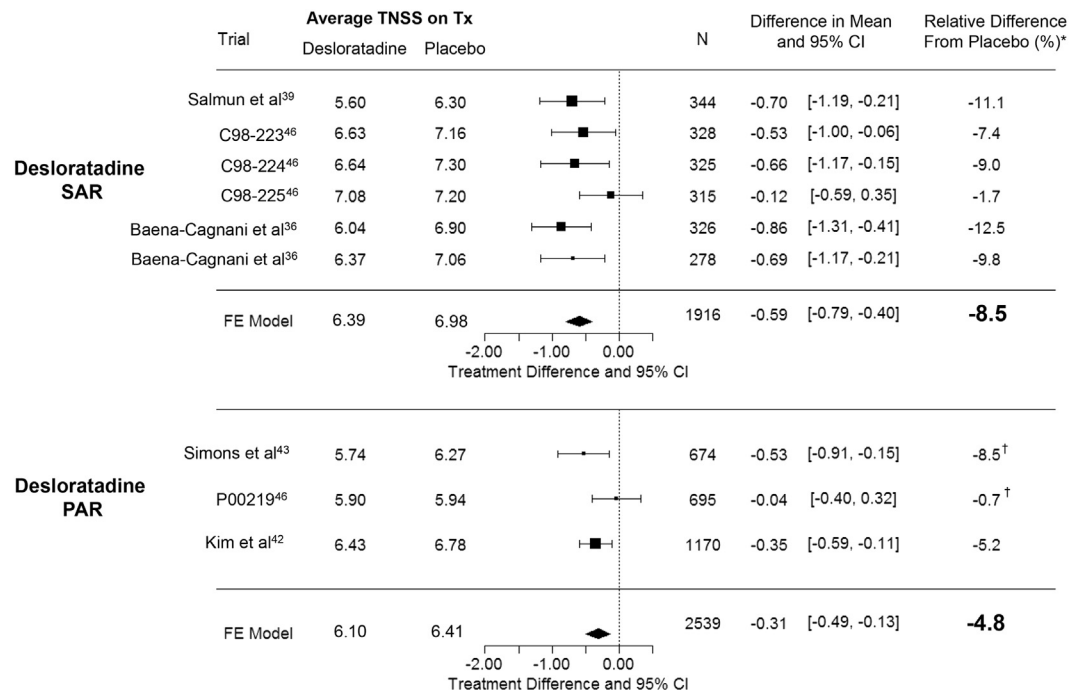


FIG 3. TNSS improvements with desloratadine relative to placebo for SAR and PAR. *Calculated as follows: $([\text{Active treatment} - \text{Placebo}]/\text{Placebo}) \times 100\%$. [†]Trial allowed decongestant use. FE, Fixed effects.

with that for SLIT-tablets. In the 4 MFNS SAR trials, TNSS improvement relative to placebo ranged from 13.1% to 28.1%, with an overall improvement of 22.2% (Fig 4).^{40,41,46} The absolute treatment differences across therapies for SAR based on SMDs are shown in Table I.

Rescue medication use for rhinoconjunctivitis was allowed in the timothy grass and ragweed SLIT-tablet trials in both the active treatment and placebo groups (see Table E1). In the 6 timothy grass SLIT-tablet trials, improvement in the weighted daily medication score for rhinoconjunctivitis ranged from 27% to 38% with

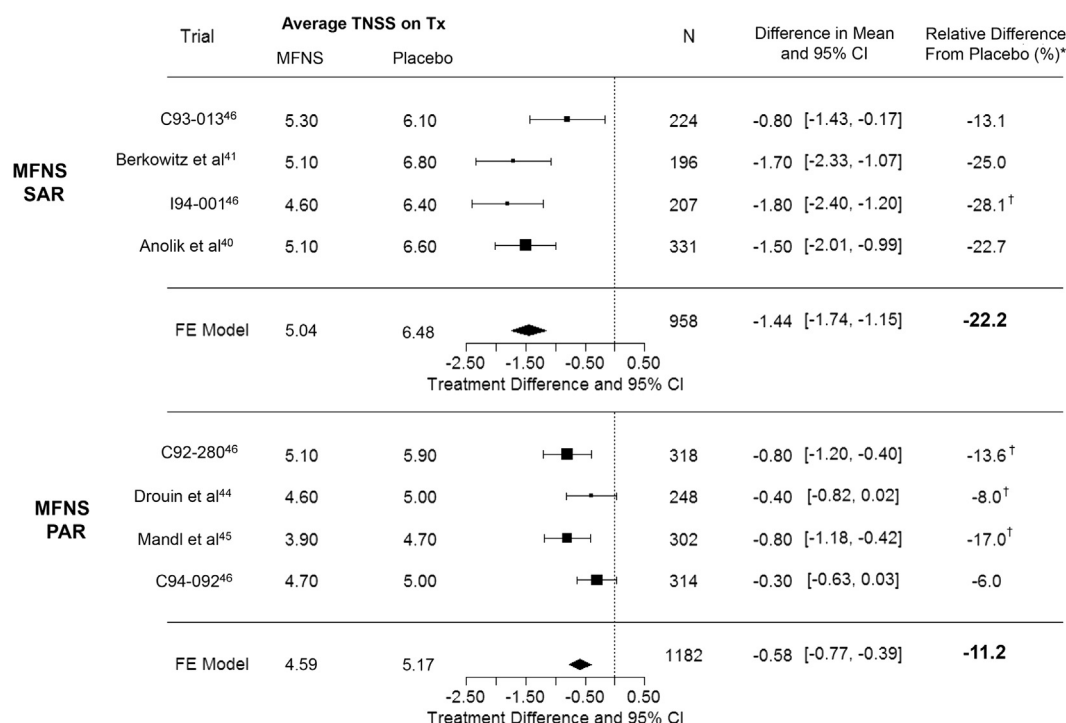


FIG 4. TNSS improvements with MFNS relative to placebo for SAR and PAR. *Calculated as follows: $[(\text{Active treatment} - \text{Placebo}) / \text{Placebo}] \times 100\%$. [†]Trial allowed antihistamine use. FE, Fixed effects.

TABLE I. SMDs for SLIT-tablets and pharmacotherapies for SAR and PAR

Treatment	SAR SMD (95% CI)	PAR SMD (95% CI)
Timothy grass SLIT-tablet	-0.26 (-0.33 to -0.19)	
Ragweed SLIT-tablet	-0.29 (-0.44 to -0.13)	
HDM SLIT-tablet		-0.24 (-0.33 to -0.14)
Montelukast	-0.18 (-0.25 to -0.12)	-0.12 (-0.19 to -0.05)
Desloratadine	-0.25 (-0.34 to -0.16)	-0.13 (-0.20 to -0.05)
MFNS	-0.61 (-0.74 to -0.48)	-0.28 (-0.40 to -0.17)

active treatment relative to placebo, and in the 2 ragweed SLIT-tablet trials, improvement was 38% and 46% with active treatment relative to placebo.

Treatment effect for PAR

In the 2 HDM SLIT-tablet trials, TNSS improvement relative to placebo was 16.0% and 16.4%, with an overall improvement of 16.1% (Fig 5).^{13,15} The treatment effect with HDM SLIT-tablets for PAR was numerically greater than that of montelukast, desloratadine, and MFNS. In the 2 montelukast PAR trials, daytime TNSS improvement relative to placebo was 1.2% and 5.4%; overall improvement was 3.7% (Fig 2).^{37,38} In the 3 desloratadine PAR trials, TNSS improvement relative to placebo ranged from 0.7% to 8.5%; overall improvement was 4.8% (Fig 3).^{42,43,46} In the 4 MFNS PAR trials, TNSS improvement relative to placebo ranged from 6.0% to 17.0%; overall improvement was 11.2% (Fig 4).⁴⁴⁻⁴⁶ The absolute treatment differences across therapies for PAR based on SMD are shown in Table I.

In the 2 HDM SLIT-tablet trials, improvement in the weighted daily medication score for rhinitis was 18% and 21% with active treatment relative to placebo.

DISCUSSION

The results of these meta-analyses indicate that nasal symptom improvement relative to placebo with SLIT-tablets was nearly as great as with MFNS and numerically greater than montelukast and desloratadine for patients with SAR. The effects of HDM SLIT-tablets were numerically greater than all the pharmacotherapies in PAR trials. The effect sizes with SLIT-tablets were nearly identical for SAR and PAR, whereas the effect sizes of pharmacotherapies for PAR were approximately 1.5- to 2-fold less than those observed for SAR. These findings need to be interpreted within the context of background AR rescue medication use (ie, oral antihistamines and INCSs) by subjects in both the active treatment and placebo groups in the SLIT-tablet trials, which would tend to underestimate the improvements of SLIT-tablets versus placebo when compared with the allergy pharmacotherapy trials. All but 1 of the SAR trials for the pharmacotherapy products prohibited AR rescue medication use, and therefore the placebo group was a “true” placebo. Although the SLIT-tablet trials did not enrich the trial populations with highly symptomatic subjects based on a symptom score threshold during allergen exposure, one can reasonably assume that because of the allowed use of AR rescue medication, the placebo groups in the SLIT-tablet trials had low symptom scores compared with the pharmacotherapy trials, which makes a treatment effect more difficult to detect. Therefore an observed effect size of 15% to 20% above placebo within the context of background AR rescue medication use is notable when pharmacotherapy trial results are used as a reference (ie, montelukast, desloratadine, and MFNS effect size of 5.4%, 8.5%, and 22.2%, respectively, for SAR trials, and 3.7%, 4.8%, and 11.2%, respectively, for PAR trials).

The treatment effects for SAR with timothy grass SLIT-tablets and pharmacotherapies observed in the current analysis were numerically similar to those calculated in a previously published

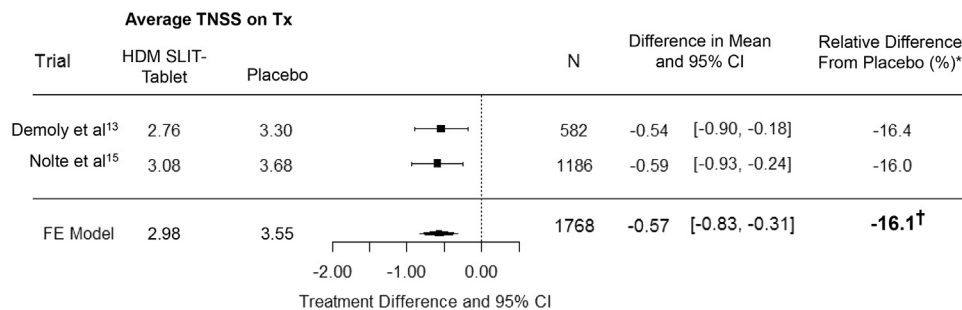


FIG 5. TNSS improvements with HDM SLIT-tablets relative to placebo for PAR. *Calculated as follows: $[(\text{Active treatment} - \text{Placebo})/\text{Placebo}] \times 100\%$. [†]Relative percentage improvement in rhinitis daily rescue medication score in the 2 trials was 18% and 21%. FE, Fixed effects.

meta-analysis. In the meta-analysis by Devillier et al,²² the treatment effect relative to placebo for symptom scores (nasal only or nasal plus ocular scores based on each trial's primary end point) was 19.2% with timothy grass SLIT-tablets, 6.5% with montelukast, 15.0% with oral antihistamines, and 23.5% with INCSs. In turn, both the current analyses and those of Devillier et al are in agreement with a meta-analysis conducted by Matricardi et al,²¹ which demonstrated that the effect on symptoms with subcutaneous immunotherapy was superior to montelukast, antihistamines, and INCSs. The current analyses showed that ragweed SLIT-tablets also have nearly as great or greater relative treatment effects on nasal symptoms versus pharmacotherapies.

This is the first analysis to indirectly compare treatment effects on nasal symptoms between AIT and pharmacotherapy for PAR. The treatment effect with the HDM SLIT-tablet was numerically greater than with montelukast, desloratadine, and MFNS. Demonstration of treatment effects in PAR trials is considered more challenging than in SAR trials. Indeed, for all of the pharmacotherapies evaluated, the treatment effects were approximately 1.5- to 2-fold less than those observed for SAR. Three of the 4 PAR trials for MFNS and 2 of the 3 PAR trials for desloratadine allowed rescue medication use, which might have contributed to the reduced treatment effect observed compared with SAR.

MFNS had the highest treatment effect for SAR and PAR among the pharmacotherapies, particularly for SAR. This pattern has been noted in other meta-analyses.^{21,22,47} Beneficial effects with montelukast, oral antihistamines, and nasal corticosteroids are the relatively quick onset of effect and significant symptom relief. In contrast, AIT induces immunologic tolerance relatively slowly, with a decrease in symptoms and AR rescue medication use after approximately 8 weeks.^{14,48} The advantages of AIT are the generally greater magnitude of effects plus the long-term tolerance induction that has been demonstrated for up to 2 years after completing 3 years of treatment with timothy grass SLIT-tablets.⁴⁹ Statistical modeling has indicated that within 6 years of starting AIT, this form of treatment becomes more cost-effective than pharmacotherapy.⁵⁰ Furthermore, AIT has been demonstrated to reduce asthma symptoms, reduce the need for asthma medications, and prevent the development of asthma.⁵¹⁻⁵⁵

These analyses are limited by heterogeneity in study designs among trials. Nasal symptoms in all the trials were scored on the same 0- to 3-point scale, although the time of day of symptom scoring varied among the trials. Differences in study populations, duration of the efficacy evaluation period, and, in particular, use

of rescue medication in the SLIT-tablet trials makes the direct comparison of absolute treatment differences inappropriate. Consequently, the placebo score must be taken into account when examining a treatment effect for AIT trials. In a meta-analysis of grass SLIT-tablets, the SMD (difference in means between SLIT and placebo divided by the pooled SD) for symptom and medication scores was gauged for the magnitude of effect, and the authors concluded that only a small clinical benefit was observed.⁵⁶ However, use of the SMD alone does not take into account the effect of AR rescue medication use on symptoms in the placebo group. Without rescue medication use, placebo symptom and medication scores would be higher, and the SMD would be expected to be greater. In the current analysis the absolute treatment difference estimated based on the SMD metric corresponded to the relative treatment difference based on the MD metric for the pharmacotherapies but undervalued the absolute treatment difference for the SLIT-tablets. For example, based on relative and absolute treatment metrics, respectively, MFNS had a 2.3- and 2.2-fold greater effect size for PAR than desloratadine and a 3.0- and 2.3-fold greater effect size than montelukast. However, based on relative and absolute treatment metrics, respectively, the HDM SLIT-tablet had a 3.4- and 1.8-fold greater effect size for PAR than desloratadine and a 4.4- and 2.0-fold greater effect size than montelukast. Thus among pharmacotherapies, the fold differences under relative and absolute treatment metrics were similar, whereas for the SLIT-tablets, the fold differences under the absolute treatment metric were less than those under the relative treatment metric. Therefore the current analysis focused on a relative treatment effect as expressed by the change in score relative to placebo.

In conclusion, although comparisons were limited by study design heterogeneity, timothy grass and short ragweed SLIT-tablets had nearly as great an effect on nasal symptoms compared with an INCS (MFNS) and had a numerically greater effect compared with a leukotriene antagonist (montelukast) and an antihistamine (desloratadine) in SAR trials. The HDM SLIT-tablet had a numerically greater effect compared with a leukotriene antagonist, an antihistamine, and an INCS in PAR trials. It is important to consider that the effect size of SLIT-tablets is in addition to background allergy rescue pharmacotherapy use, which would tend to diminish the detectable effect size compared with placebo use. This supports the complementary use of AIT in the treatment of SAR and PAR. A distinct advantage afforded by AIT in the treatment of SAR and PAR, as opposed to pharmacotherapy, is the ability to achieve a long-lasting therapeutic benefit through immunologic tolerance.^{8,49}

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Clinical implications: Treatment effect size with SLIT-tablets is in addition to background allergy rescue pharmacotherapy use. Demonstrated effect sizes with SLIT-tablets versus pharmacotherapies support complementary use of AIT in AR treatment.

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TABLE E1. Characteristics of trials used in the pooled analyses

Lead author and/or protocol no.	Trial registration no.	Total no. randomized	Region of study sites	Age range included (y)	Nasal symptoms scored	Primary end point(s)	Duration of analysis for primary end point	Allergic rhinitis rescue medication use allowed
Timothy grass								
SLIT-tablet								
Dahl et al, 2006 ^{E1}	NCT00227279	634	EU	18-65	Runny nose, blocked nose, sneezing, itchy nose	Average AR/C DSS and DMS for entire GPS	Mean GPS, 58 d	Oral antihistamine; INCS; oral corticosteroid
GT-08 (year 1)								
Murphy et al, 2013 ^{E2}	NCT00421655	329	NA	18-65	Runny nose, blocked nose, sneezing, itchy nose	Average AR/C DSS for entire GPS	Mean GPS, 43 d	Oral antihistamine; ocular antihistamine
GT-14								
Bufe et al, 2009 ^{E3}	NCT00408616	253	EU	5-16	Runny nose, blocked nose, sneezing, itchy nose	Average AR/C DSS and DMS for entire GPS	Mean GPS, 81 d	Oral antihistamine; ocular antihistamine; INCS; oral corticosteroid
GT-12								
Blaiss et al, 2011 ^{E4}	NCT00550550	345	NA	5-17	Runny nose, blocked nose, sneezing, itchy nose	TCS averaged for entire GPS	Mean GPS, 53 d	Oral antihistamine; ocular antihistamine; INCS; oral corticosteroid
P05238								
Nelson et al, 2011 ^{E5}	NCT00562159	439	NA	18-65	Runny nose, blocked nose, sneezing, itchy nose	TCS averaged for entire GPS	Median GPS, 56 d	Oral antihistamine; ocular antihistamine; INCS; oral corticosteroid
P05239								
Maloney et al, 2014 ^{E6}	NCT01385371	1501	NA	5-65	Runny nose, blocked nose, sneezing, itchy nose	TCS averaged for entire GPS	Mean GPS, 54 d	Oral antihistamine; ocular antihistamine; INCS; oral corticosteroid
P08067								
Ragweed SLIT-tablet								
Nolte et al, 2013 ^{E7}	NCT00783198	565	NA	18-50	Runny nose, blocked nose, sneezing, itchy nose	TCS averaged for peak RPS	Peak RPS, 15 d*	Oral antihistamine; ocular antihistamine; INCS; oral corticosteroid
P05233								
Creticos et al, 2013 ^{E8}	NCT00770315	784	NA/EU/Russia	18-50	Runny nose, blocked nose, sneezing, itchy nose	TCS averaged for peak RPS	Peak RPS, 15 d†	Oral antihistamine; ocular antihistamine; INCS; oral corticosteroid
P05234								
HDM SLIT-tablet								
Demoly et al, 2016 ^{E9}	NCT01454544	992	EU	18-65	Runny nose, blocked nose, sneezing, itchy nose	TCRS during the last ~8 wk of the 1-y treatment period	~8 wk	Oral antihistamine; ocular antihistamine; INCS
MERIT								
Nolte et al, 2016 ^{E10}	NCT01700192	1482	NA	≥12	Runny nose, blocked nose, sneezing, itchy nose	TCRS during the last ~8 wk of the 1-y treatment period	~8 wk	Oral antihistamine; ocular antihistamine; INCS
Montelukast, 10 mg								
SAR								
Nayak et al, 2002 ^{E11}	NCT00963599	907	NA	15-85	Rhinorrhea, congestion, sneezing, itching	Mean change from baseline in daytime TNSS	2 wk	None
P117								
Philip et al, 2002 ^{E12}	NCT00979901	1302	NA	15-85	Rhinorrhea, congestion, sneezing, itching	Mean change from baseline in daytime TNSS	2 wk	None
P162								
Chervinsky et al, 2004 ^{E13}	NCT00960141	829	NA	15-85	Rhinorrhea, congestion, sneezing, itching	Mean change from baseline in daytime TNSS	2 wk	None
P192								
Van Adelsberg et al, 2003 ^{E14}	NCT00972738	1214	NA	15-85	Rhinorrhea, congestion, sneezing, itching	Mean change from baseline in daytime TNSS	2 wk	None
P235								
Van Adelsberg et al, 2003 ^{E15}	NCT00963469	1079	NA	15-82	Rhinorrhea, congestion, sneezing, itching	Mean change from baseline in daytime TNSS	2 wk	None
P240								

(Continued)

TABLE E1. (Continued)

Lead author and/or protocol no.	Trial registration no.	Total no. randomized	Region of study sites	Age range included (y)	Nasal symptoms scored	Primary end point(s)	Duration of analysis for primary end point	Allergic rhinitis rescue medication use allowed
PAR								
Philip et al, 2007 ^{E16} P246	NCT00974571	1365	NA	15-85	Rhinorrhea, congestion, sneezing, itching	Mean change from baseline in daytime TNSS	4 wk	None
Patel et al, 2005 ^{E17} P265	NCT00092118	1992	NA/EU	15-85	Rhinorrhea, congestion, sneezing, itching	Mean change from baseline in daytime TNSS, not including itching	6 wk	None
Desloratadine 5, mg								
SAR								
Salmun et al, 2002 ^{E18} C98-001	NR	1036	NA	≥12	Rhinorrhea, stuffiness, sneezing, itching	Mean change from baseline in averaged morning/evening TSS	2 wk	None
C98-223 ^{E19}	NR	496	NA	≥12	Rhinorrhea, stuffiness, sneezing, itching	Mean change from baseline in averaged morning/evening TSS	2 wk	None
C98-224 ^{E19}	NR	492	NA	≥12	Rhinorrhea, stuffiness, sneezing, itching	Mean change from baseline in averaged morning/evening TSS	2 wk	None
C98-225 ^{E19}	NR	475	NA	≥12	Rhinorrhea, stuffiness, sneezing, itching	Mean change from baseline in averaged morning/evening TSS	2 wk	None
Baena-Cagnani et al, 2003 ^{E20} P00214	NR	501	NA	≥15	Rhinorrhea, stuffiness, sneezing, itching	Mean change from baseline in averaged morning/evening TSS and FEV ₁	2 wk	None
Baena-Cagnani et al, 2003 ^{E20} P00215	NR	423	NA	≥15	Rhinorrhea, stuffiness, sneezing, itching	Mean change from baseline in averaged morning/evening TSS and FEV ₁	2 wk	None
PAR								
Simons et al, 2003 ^{E21} P00218	NR	676	NA/Germany	≥12	Rhinorrhea, postnasal drip, stuffiness, sneezing, itching	Mean change from baseline in average morning/evening (instantaneous) TSS, excluding stuffiness	4 wk	Decongestant
P00219 ^{E9} P00219	NR	698	NA/LA	≥12	Rhinorrhea, postnasal drip, stuffiness, sneezing, itching	Mean change from baseline in average morning/evening (instantaneous) TSS, excluding stuffiness	4 wk	Decongestant
Kim et al, 2006 ^{E22} P02772	NR	1179	NA/International	≥12	Rhinorrhea, stuffiness, sneezing, itching	Mean change from baseline in average morning/evening (reflective) TSS, including stuffiness	4 wk	None
MFNS, 200 µg								
SAR								
C93-013 ^{E19}	NR	345	NA	≥12	Rhinorrhea, stuffiness, sneezing, itching	Mean change from baseline in averaged morning/evening TNSS	15 d	None
Berkowitz et al, 1999 ^{E23} C93-184	NR	201	NA	≥12	Rhinorrhea, stuffiness, sneezing, itching	Onset time of relief	3 d (2 wk used for TNSS)	None
I94-001 ^{E19}	NR	313	NA	≥12	Rhinorrhea, stuffiness, sneezing, itching	Mean change from baseline in averaged morning/evening TNSS	15 d	Oral antihistamine

(Continued)

TABLE E1. (Continued)

Lead author and/or protocol no.	Trial registration no.	Total no. randomized	Region of study sites	Age range included (y)	Nasal symptoms scored	Primary end point(s)	Duration of analysis for primary end point	Allergic rhinitis rescue medication use allowed
Anolik et al, 2008 ^{E24} C94-145	NR	704	NA	≥12	Rhinorrhea, stuffiness, sneezing, itching	Mean change from baseline in averaged morning/evening TNSS and morning/evening TSS	15 d	None
PAR C92-280 ^{E19}	NR	491	NA	≥12	Rhinorrhea, stuffiness, sneezing, itching	Mean change from baseline in averaged morning/evening TNSS	15 d	Oral antihistamine
Drouin et al, 1996 ^{E25} I92-293	NR	427	NA/EU	≥12	Rhinorrhea, stuffiness, sneezing, itching	Mean change from baseline in averaged morning/evening TNSS	15 d	Oral antihistamine
Mandl et al, 1997 ^{E26} I94-079	NR	550	NA/LA/EU	≥12	Rhinorrhea, stuffiness, sneezing, itching	Mean change from baseline in averaged morning/evening TNSS	15 d	Oral antihistamine
C94-092 ^{E19}	NR	334	NA	≥65	Rhinorrhea, stuffiness, sneezing, itching	Mean change from baseline in averaged morning/evening TNSS	15 d	None

All treatments were administered once daily.

AR/C, Allergic rhinitis with/without conjunctivitis; DMS, daily medication score; DSS, daily symptom score; EU, European Union; GPS, grass pollen season; LA, Latin America; NA, North America; NR, not registered; RPS, ragweed pollen season; TCRS, total combined symptom and medication rhinitis score; TCS, total combined symptom and medication rhinoconjunctivitis score; TSS, total symptom score (includes ocular symptoms).

*Entire season used for TNSS in current analysis (mean, 44 days).

†Entire season used for TNSS in current analysis (mean, 46 days).