



Assessment of specific immunotherapy efficacy using a novel placebo score–based method

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ABSTRACT

Background: In trials of allergen immunotherapy, allergen exposure is typically assessed by pollen counts, but these may misrepresent exposure if performed remotely from multiple study centers.

Objective: To assess whether symptomatology in placebo-treated patients is a better measure of local allergen burden at individual centers in such trials.

Methods: Data from a multicenter, placebo-controlled trial of preseasonal grass pollen immunotherapy were reanalyzed to identify the 4 weeks at each center in which the placebo-treated subjects had the highest combined symptom/medication scores (CSMS). The difference in CSMS between active and placebo groups was compared during the 4 peak placebo score weeks (PISW) and the 4 peak pollen count weeks (PoCW).

Results: The benefit of immunotherapy over placebo in the PISW analysis (18.5%) was greater than in the PoCW analysis (13.6%), with increased statistical significance ($P = .0001, .0038$, respectively). Similar improved discrimination was observed when analyzing benefits in subgroups of patients with severe symptoms, a high disease burden, and in different geographical locations.

Conclusion: This novel PISW analysis results in better discrimination of the effects of allergen immunotherapy compared with placebo and may be widely applicable in similar studies, both prospectively and retrospectively.

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Introduction

Allergic disease remains a major health care challenge for modern society, because it affects individuals' quality of life¹ and creates a high socioeconomic burden.² The prevalence of allergy has increased considerably in recent decades,³ with allergic rhinoconjunctivitis being the most common allergic disease in adults.⁴

Allergen-specific immunotherapy involves repeated, systemic administration of allergen extracts to allergic individuals and results in sustained relief from symptoms caused by allergen exposure.^{4,5} This is, in turn, attributed to modifications in the immunologic response to the allergen. Specific immunotherapy is the only

treatment for allergic rhinoconjunctivitis considered to target the cause of the disease.⁶

During studies of the benefits of allergen immunotherapy in seasonal allergic rhinoconjunctivitis, allergen exposure can be experimentally simulated by local challenge or in exposure chambers.⁷ However, ultimately the effects of immunotherapy must be investigated during natural exposure to pollen during the pollen season. Although mimicking “real life” conditions, there are several problems with this type of investigation. In particular, the perceived benefits of treatment depend on the severity and duration of symptoms, which, in turn, depend on local pollen exposure. Local pollen exposure is usually measured by counting pollen grains caught in traps and retrospectively identifying the weeks when these pollen counts are at their highest. The problem is that such traps may be situated at considerable distances from study centers, so that the pollen counts they produce may bear little relationship to the actual exposure of patients in the vicinity of the centers.

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In this novel analysis of data from a randomized, multicenter, placebo-controlled trial of grass pollen immunotherapy, we set out to identify the 4 weeks at each center when the placebo-treated patients experienced the most symptoms and used the most rescue medications, as captured by a combined symptom and medication score (CSMS), making the assumption that these were the 4 weeks when the local allergen burden at each center was at its highest.^{8–11} These 4 weeks were then redefined as the presumptive periods of maximum allergen exposure, rather than relying on remote pollen counts used in the original outcome analysis. The time period of 4 weeks was prespecified as time for analysis of the primary endpoint (combined symptom/medication score) in the original analysis.¹² We then compared data from each analysis.

Methods

We undertook a retrospective analysis of the data from a large randomized, multicenter, double-blind, placebo-controlled study of preseasonal grass pollen immunotherapy for grass pollen-induced seasonal allergic rhinoconjunctivitis with Grass MATA MPL (Pollinex Quattro, Pollinex Complete; Allergy Therapeutics, London, United Kingdom) (NCT00414141, EudraCT trial 2005–004959–35). This is a grass pollen allergoid vaccine containing monophosphoryl lipid (MPL) adjuvant and L-tyrosine as depot mediator. The trial protocol has previously been described in full.¹² The trial was conducted in 84 centers (58 US, 17 Canada, 6 United Kingdom, 3 Austria) during the 2007 grass pollen season. It was approved by all relevant regulatory and ethics authorities, and all participants provided written, informed consent. Participants were adults aged 18 to 59 years with a history of moderate/severe seasonal allergic rhinitis or conjunctivitis caused by grass pollen and incompletely controlled by standard medications (antihistamines, topical steroids, leukotriene modifiers), and sensitized to grass pollen as shown by positive skin prick and serum immunoglobulin E tests. Exclusion criteria and randomization methodology were described previously.¹²

All investigational centers recorded the local pollen counts for trees, grasses, and other relevant local allergenic plants at least 3 times per week for a period extending well beyond the beginning and end of each pollen season. Commencement of the grass pollen season at each center was defined as a grass pollen count of at least 5 grains/m³ for at least 2 of 7 days.¹³ This was when the subjects began daily electronic symptom and medication diaries, which were continued until the end of the pollen season and used to derive daily CSMS as described.¹² The end of the season was defined as a grass pollen count of less than 5 grains/m³ for 2 consecutive weeks (approximately 10 weeks later).¹³

In the study, eligible subjects were randomized 1:1 to receive subcutaneous injections of grass MATA MPL in 3 escalating dosages and 1 booster dose or identical-looking placebo, which contained no grass pollen or MPL (both Allergy Therapeutics UK Ltd) administered at 2- to 4-weekly intervals. Injections were completed at least 3 weeks before the start of the grass pollen season.¹⁴

Placebo score weeks analysis

For this analysis, we considered the CSMS scores of the subjects who had been treated with placebo. For each center, 4 weeks were defined where the placebo-treated subjects had the highest mean CSMS. These weeks were not necessarily consecutive and did not necessarily correspond in absolute time between centers.

Pollen count weeks analysis

In this case, the 4 peak weeks of the pollen season at each center were defined as in the original analysis¹² as those with the highest mean weekly pollen counts. As with the placebo score weeks (PISW) analysis, the peak weeks were not necessarily consecutive.

Efficacy analysis

We determined the difference in CSMS in patients on active and placebo therapy for the 4 weeks defined by PISW and pollen count weeks (PoCW) analysis. The selection criteria for subjects in the PISW and PoCW populations were identical. In addition to the entire patient population, we also analyzed differences in subgroups: (1) subjects with particularly severe symptoms at screening defined as a Disease Severity Questionnaire (DSQ) score of at least 9 or 10; (2) centers with a high burden of disease (defined as those in which the median CSMS in the placebo-treated subjects during the 4 peak weeks defined by PISW or PoCW analysis was higher than the grand median of all the centers); (3) subjects with additional symptoms of asthma or cough; (4) subjects recruited at European centers. We also compared the proportions of well subjects (defined as median CSMS < 2 in the respective peak weeks) and severely affected subjects (median CSMS > 10 in the respective peak weeks) in the active and placebo-treated groups.

Statistical analysis

Both analyses were conducted in 2 data sets, an intention-to-treat (ITT) set, which included all subjects commencing therapy, and a complete data set, which included all subjects with 28 complete diary entries for the 4 relevant PISW or PoCW weeks. For the PoCW analysis, missing diary card data were imputed using a matched pair technique. The ITT population for the placebo score analysis was defined as all subjects with data available during the peak placebo score weeks. The same population was used in both analyses.

Treatment group differences in CSMS were assessed by analysis of covariance (ANCOVA). For the PISW analysis, CSMS was the dependent variable, treatment group, sex, and region were factors, and age was a covariate. For the PoCW analysis, treatment differences were assessed by ANCOVA with CSMS as the dependent variable, treatment group, sex, and region as factors, and age and average pollen count (per center) during the 4 peak weeks as covariates. Efficacy data were log-transformed before the ANCOVA to achieve a normal distribution. Two-sided tests were performed at the 5% level. Adjusted geometric means for group and intergroup differences were calculated with the corresponding 95% confidence intervals (CI). Treatment differences in the number of well or severely affected subjects were assessed by χ^2 test, with significance at the 5% level.

Results

Subject disposition

In total, 2,180 subjects were screened, of whom 1,028 were randomized at 84 study centers. The numbers of subjects included in the ITT and complete data populations for the PISW and PoCW analyses are shown in Figure 1. Of the 875 subjects with information on location available (437 Grass MATA MPL, 438 placebo), 92.3% lived within a 16-km radius and could be considered matched for allergen exposure conditions.^{8,9}

Comparison of the response to grass MATA MPL during the four peak placebo score weeks and the four peak pollen count weeks

Of the possible 336 peak placebo score weeks (4 weeks per center), a median of 75% were identical to the 4 peak pollen count weeks (62.5% in North America and 75% in Europe).

In the PISW analysis, active treatment with Grass MATA MPL ($n = 477$) was associated with an 18.5% reduction in CSMS compared with placebo ($n = 489$; $P = .0001$) (Table 1). This was greater than that observed in the PoCW analysis, in which active treatment ($n = 514$) led to a 13.6% reduction in CSMS compared with placebo ($n = 514$; $P = .0038$).

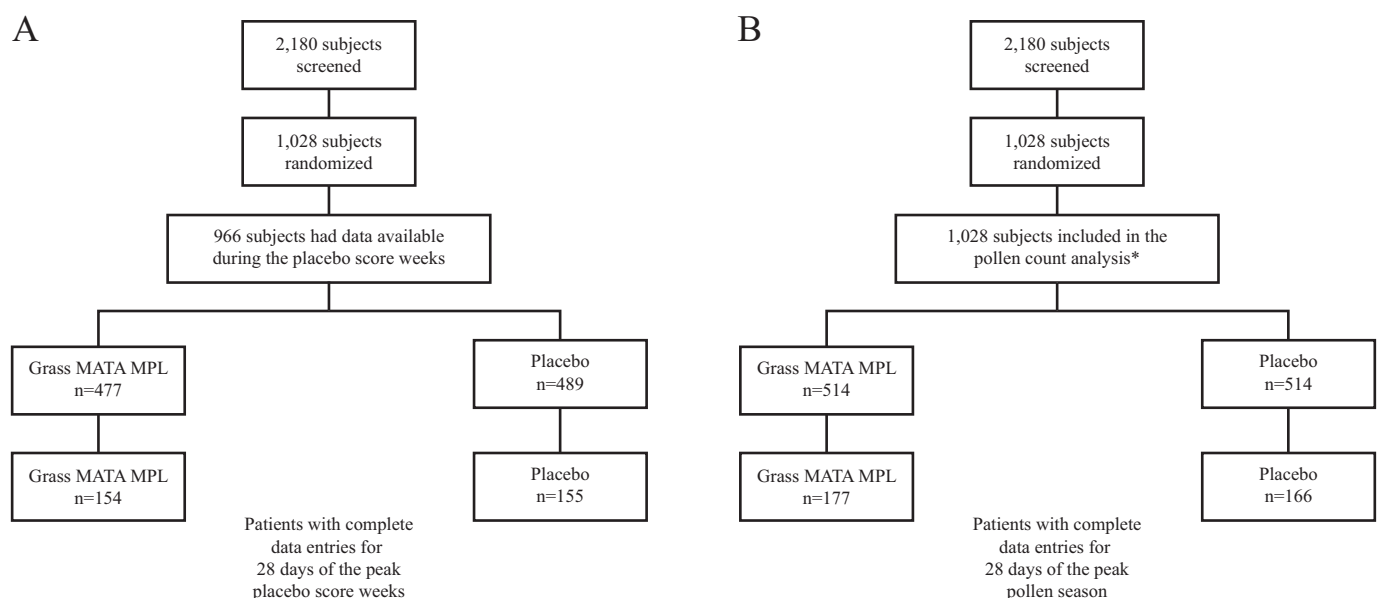


Fig. 1. Disposition of subjects in the placebo score (A) and pollen count (B) analyses. *1,028 subjects analyzed, missing data imputed.

The mean CSMS using both PoCW and PISW analyses showed a high correlation of 0.96. The mean CSMS using PISW significantly increased for placebo-treated subjects (95% CI: 0.4–0.7) and also increased for active-treated subjects but to a lesser degree and missed statistical significance (95% CI: 0–0.4) as compared with PoCW. The mean treatment difference between placebo- and Grass

MATA MPL-treated subjects was statistically significantly greater in the PISW vs the PoCW analysis ($P = .0007$, 95% CI: 0.2–0.6).

In the PISW analysis, subjects with particularly severe symptoms ($DSQ \geq 9$) receiving Grass MATA MPL ($n = 265$) showed an 18.1% reduction in CSMS compared with placebo ($n = 267$; $P = .0057$), and those with DSQ of at least 10 ($n = 202$) a 19.6% reduc-

Table 1
Difference in CSMS during the 4 peak placebo score weeks and in the 4 peak pollen count weeks in the Grass MATA MPL and placebo groups (ITT analysis, all patients with data available)

Analysis	Treatment group	N	Mean	Median	SD	Superiority (Grass MATA MPL vs placebo)		
						Relative difference in AGM, %	Hodges-Lehmann for median of differences 95% CI, %	2-sided <i>P</i> value
Difference in CSMS in the grass MATA MPL and placebo groups								
Placebo score	Grass MATA MPL	477	7.39	6.01	6.03	18.5	8.6–25.4	.0001
	Placebo	489	8.60	7.62	5.92			
Pollen count	Grass MATA MPL	514	7.21	6.00	5.57	13.6	4.6–20.8	.0038
	Placebo	514	8.05	7.06	5.57			
Differences in CSMS in the grass MATA MPL and placebo groups in subjects with DSQ ≥9								
Placebo score	Grass MATA MPL	265	8.22	6.51	6.73	18.1	4.2–27.0	.0057
	Placebo	267	9.32	8.18	6.37			
Pollen count	Grass MATA MPL	269	8.00	6.66	6.23	13.5	0.1–23.4	.0433
	Placebo	267	8.85	7.45	6.25			
Difference in CSMS in the grass MATA MPL and placebo groups in subjects with DSQ ≥10								
Placebo score	Grass MATA MPL	202	8.45	6.54	6.91	19.6	3.8–29.9	.0089
	Placebo	185	9.62	8.56	6.18			
Pollen count	Grass MATA MPL	207	8.23	6.70	6.26	13.2	–1.6–25.3	.0852
	Placebo	184	9.06	7.77	6.01			
Difference in CSMS in the grass MATA MPL and placebo groups in centers with a high burden of disease^a								
Placebo score	Grass MATA MPL	259	7.70	6.01	6.57	35	22.4–40.6	<.0001
	Placebo	265	10.46	9.99	6.08			
Pollen count	Grass MATA MPL	244	7.55	5.99	6.23	31	18.5–38.7	<.0001
	Placebo	248	9.83	9.09	5.93			
Difference in CSMS in the grass MATA MPL and placebo groups in subjects with grass pollen-induced cough or asthma								
Placebo score	Grass MATA MPL	187	8.02	6.01	6.74	16	6.1–31.1	0.0384
	Placebo	175	8.97	8.42	5.44			
Pollen count	Grass MATA MPL	193	7.74	6.23	6.12	13.4	–3.0–28.8	0.0787
	Placebo	175	8.54	7.88	5.24			
Difference in CSMS in the grass MATA MPL and placebo groups in subjects recruited in Europe								
Placebo score	Grass MATA MPL	53	8.69	6.19	7.32	27.3	2.9–41.1	0.0280
	Placebo	60	10.26	8.68	7.29			
Pollen count	Grass MATA MPL	55	8.31	6.99	6.91	22.0	–7.8–38.6	0.0845
	Placebo	62	9.54	8.15	7.07			

Abbreviations: AGM, adjusted geometric mean.

^aCenters with a high burden of disease were defined as sites with CSMS >7.6 in the placebo group in the placebo score analysis and CSMS >7.06 in the placebo group in the pollen count analysis.

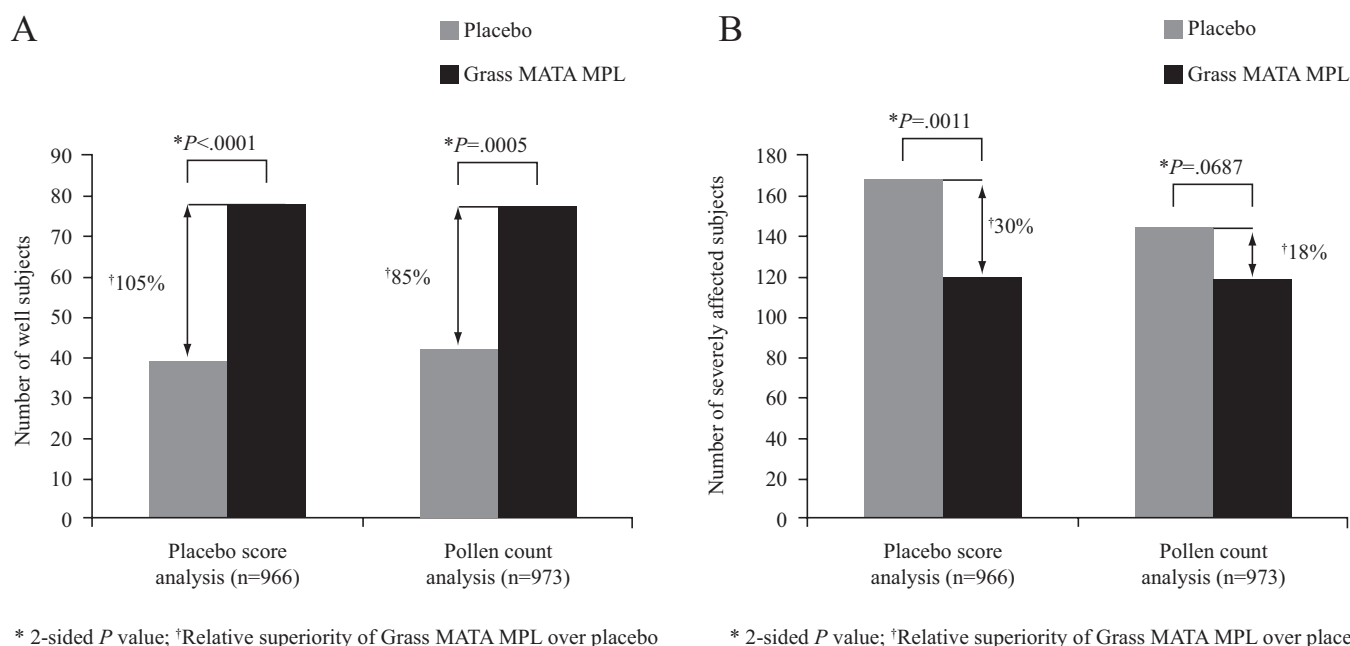


Fig. 2. Difference between Grass MATA MPL and placebo in the number of well subjects (A) and number of severely affected subjects (B) during the 4 peak placebo score weeks and the 4 peak pollen count weeks.

tion compared with placebo ($n = 185$; $P = .0089$) (Table 1). In the PoCW analysis, these differences were less marked (13.5%; $P = .043$ and 13.2%; $P = .0852$, respectively) (Table 1).

Using the PISW analysis, the median CSMS in the placebo-treated patients across all centers was 7.6. Centers with a median CSMS greater than 7.6 in the placebo group were, therefore, identified as those with a high burden of disease presumably resulting from a higher allergen load or recruitment of patients with more severe disease. The geographic distribution of these sites is shown in eTable 1. In the PoCW analysis, centers where placebo-treated patients had a median CSMS greater than 7.06 were considered to have a higher burden of disease. At these centers, reduction in CSMS with active compared with placebo treatment was 35% ($P < .0001$) using the PISW analysis compared with 31% ($P < .0001$) using the PoCW analysis (Table 1).

In the subgroup of patients with additional seasonal symptoms of grass pollen-induced cough or asthma, active treatment was superior to placebo, with a relative improvement in CSMS of 16% ($P = .0384$) by PISW analysis and 13.4% ($P = .0787$) by PoCW analysis (Table 1). For patients enrolled in Europe, a 27.3% benefit of Grass MATA MPL over placebo ($P = .0280$) was observed with PISW analysis, whereas the PoCW analysis showed a benefit of 22%, which was not statistically significant ($P = .0845$).

Compared with patients given placebo, twice as many patients given active treatment had median symptom scores of 2 or less in the PISW analysis and were considered to be well subjects (Fig 2A). Similarly, fewer patients in the Grass MATA MPL group had median symptom score of 10 or more in the PISW analysis and were considered to be severely affected (Fig 2B). The same benefit of active treatment in terms of symptom score was evident in the PoCW analysis, although the difference between Grass MATA MPL and placebo was not as great as in the PISW analysis.

For most of these outcome measures, reduction in CSMS by active treatment compared with placebo was greater in the complete data population than in the ITT population. As seen in the ITT analysis, the relative benefit of Grass MATA MPL over placebo was greater and of greater statistical significance in the PISW analysis than in the PoCW analysis in all populations (Fig 3). The benefit of

Grass MATA MPL over placebo was 26.4% ($P = .0012$) in the PISW analysis compared with 24.3% ($P = .0031$) in the PoCW analysis.

Figure 4 shows the CSMS in the Grass MATA MPL and placebo groups together with the pollen count at a representative site. Although pollen counts increased, subjects needed time to develop their symptoms (priming), so there was a delay in CSMS increase after exposure to allergen. In addition, between days 28 and 35, symptoms remained high despite a trough in the pollen count. At the end of the pollen season, the pollen counts were very low, but symptoms were still high, in particular in the placebo group (persistent mucosal inflammation). These different profiles resulted in different peak weeks being identified in the PISW than in the PoCW. At the representative site, the 4 peak weeks were days 14 to 28 and 35 to 49 in the PoCW analysis and days 21 to 49 in the PISW.

Discussion

Specific immunotherapy is the only treatment for allergic rhinoconjunctivitis that manages the underlying cause of the disease. It does this by desensitizing subjects to the allergen responsible for the allergic symptoms, although the exact mechanism remains unknown.⁴

Although the literature on specific immunotherapy for seasonal allergic rhinoconjunctivitis is extensive, before 2005 very little data from randomized, controlled trials were available, and most studies involved small numbers of patients. More recently, several large international studies have been published that have not only ratified the efficacy, tolerability, and safety of allergen immunotherapy for allergic rhinoconjunctivitis but have also given rise to discussion about the optimal design of immunotherapy studies and how the data they produce should be interpreted.^{10,15}

In this study we have explored a novel approach for the analysis of outcome data. The original analysis of this study, which showed a significant benefit of Grass MATA MPL over placebo, was based on comparisons of CSMS during the 4 peak weeks of the pollen season defined on the basis of pollen counts from pollen traps near the study centers. Several studies have, however, confirmed what seems intuitively likely, that pollen counts may vary significantly between the site of the pollen trap and the subject's place or

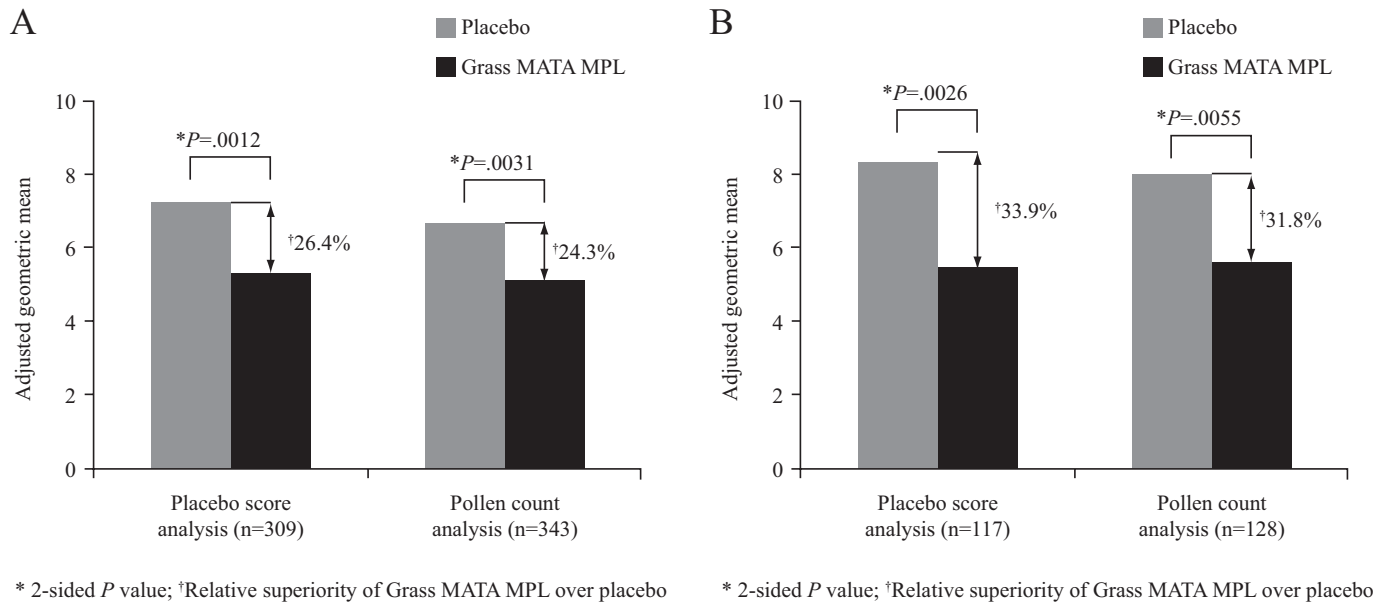


Fig. 3. Difference in CSMS in the Grass MATA MPL and placebo groups in the placebo score and pollen count analyses in the complete data population. (A) Overall population and (B) subjects with cough or asthma.

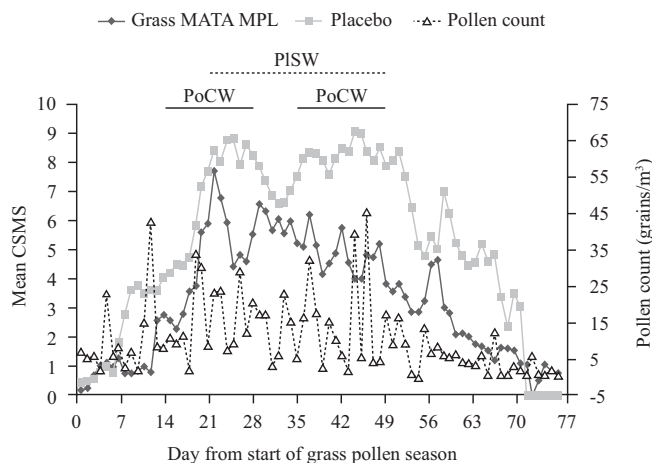
residence.^{8,9} In these analyses by Dalan et al, pollen counts were shown to be relevant to subjects living within 16 km of the pollen counting station, but variability is likely for patients living more than 16 km away. Furthermore it has been noted, for example, in a study of reactions to birch pollen,¹⁶ that some sensitized subjects report severe symptoms even on days with apparently low birch pollen counts and that on some days the difference between estimated allergen exposure based on pollen counts and determination of allergen concentrations in the atmosphere by immunoassay may vary by as much as 10-fold.¹⁷ The authors of this latter study attributed this variance to a large increase in expression of the birch pollen allergen *Bet v1* just before pollination. Consequently, the precise time at which the pollen grain is released during ripening will affect its allergen content. These studies suggest that even in locations close to the pollen traps, pollen counting may not closely reflect allergen exposure. In the current analysis, we demonstrated a delay in

subjects developing allergic symptoms after an increase in pollen exposure. In addition, patients' symptoms continued even when pollen levels had decreased. This latter effect was particularly apparent in the placebo group and may reflect mucosal inflammation that persisted as a result of lack of treatment. These observations highlight that pollen counting may not be the most appropriate method to determine the times in the pollen season most associated with symptoms, whereas a method based on response in placebo-treated patients may be more suitable.

With this in mind, we reanalyzed the Grass MATA MPL data, defining for each center the 4 peak weeks of allergen exposure as those associated with the highest CSMS in the placebo-treated subjects. This obviously involves a number of assumptions; first that the times when the CSMS is highest in the placebo-treated patients reflect times of the heaviest local allergen load^{8–11} and also that there is a reasonable geographic mixing of placebo and actively treated subjects around any given center.^{8,9} In the current analysis, more than 90% of each treatment group lived within a 16-km radius and could be considered matched for allergen exposure conditions.^{8,9}

Nevertheless, we believe that it allows a more realistic estimate of the allergen burden at each study center. The technique seems to have internal validity in the sense that peak allergen load weeks defined by PISW and PoCW corresponded approximately 75% of the time, and there was an even distribution of placebo and Grass-MATA MPL-treated subjects across study centers.

This PISW analysis improved the apparent efficacy of Grass MATA MPL over placebo for the primary outcome measure (reduction in CSMS during the peak 4 weeks of the pollen season) and the subgroup analyses, where some previously insignificant differences became statistically significant. These observations are compatible with the hypothesis that this novel analysis offers a substantial gain in discriminatory power when analyzing the efficacy of pollen allergen immunotherapy compared with an approach based on pollen counts. We offer this technique as an alternative paradigm for assessing the effect of any therapy (compared with placebo) on seasonal symptoms caused by any pollen allergen as an alternative to performing pollen counts. This technique also might prove useful in retrospective analysis of existing studies.



* Solid lines represent 4 peak weeks in the PoCW analysis; Dashed line represents the 4 peak weeks in the PISW analysis

Fig. 4. The time course of CSMS in Grass MATA MPL and placebo groups and pollen count at a representative study center.

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Supplementary Data

Supplementary data associated with this article can be found, in the online version, at [10.1016/j.anai.2012.08.013](https://doi.org/10.1016/j.anai.2012.08.013).

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ETable 1
Centers with a high burden of disease (defined as median CSMS >7.6 in the placebo score analysis)

Country	Total number of centers	Centers with median CSMS >7.6 in the placebo group, n (%)
Austria	3	2 (66.7)
Canada	15	6 (40.0)
United Kingdom	6	5 (83.3)
United States	55	27 (49.1)
Total	79	40 (50.6)