

Is response to allergen immunotherapy a good phenotypic marker for differentiating between allergic rhinitis and mixed rhinitis?

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ABSTRACT

This study was designed to determine if patients with allergic rhinitis (AR) and mixed rhinitis (MR) subtypes have similar treatment outcomes after a full course of allergen immunotherapy (AIT). A historical pre- and posttreatment study design was used to identify all AR patients in a large allergy practice who started AIT in 2001 and completed at least a 3-year course. One reviewer compiled data through chart review using a standardized form that recorded allergic and nonallergic irritant triggers, symptoms, and medication requirements before and after completion of ≥ 3 years of AIT. Other than age, there were no significant differences in baseline demographic characteristics, allergic triggers, or rhinitis symptoms between the AR and MR groups. Both groups experienced reduced episodes of sinusitis after AIT. Although both groups also had a significant decrease in the mean number of rhinitis medications after AIT ($p < 0.001$), the reduction in number of medications was significantly greater for the AR versus the MR group (1.24 ± 1.09 versus 2.09 ± 1.55 ; $p = 0.0023$). AIT is a very effective treatment for AR and MR patients. However, these data support the classification of MR as a distinct rhinitis phenotype because MR patients required significantly more medications after a full course of AIT to control their nonallergic-induced symptoms.

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The diagnosis of a pure seasonal allergic rhinitis (SAR) and/or perennial AR (PAR) phenotype should not be trivialized. Current criteria for diagnosis of SAR and PAR include a detailed history of rhinitis symptoms that correlates with specific IgE testing (skin-prick testing or serum-specific IgE).^{1,2} However, the diagnosis of AR is complicated in that up to 50% of patients with AR may also have a significant nonallergic component termed mixed rhinitis (MR).³ In fact, a recent study in which a validated non-AR questionnaire was administered to an SAR population revealed that >50% of these individuals experienced significant rhinitis symptoms in response to nonallergic triggers.^{4,5}

Currently, there is no consensus on an objective method for differentiating irritant-induced symptoms secondary to nonspecific nasal hyperresponsiveness due to underlying AR inflammation from irritant-induced symptoms induced through distinct nonallergic pathways.^{6,7} Treatment response to medications and allergen immunotherapy may be one way to clinically differentiate between these two chronic rhinitis subtypes.⁸

A primary consideration for initiating allergen immunotherapy (AIT) requires an accurate diagnosis of AR to ensure that selected patients will achieve optimal therapeutic benefits.⁹ Ideally, patients are considered to have had a good response to AIT if they have reduced upper respiratory symptoms, reduced medication requirements, reduced complications such as sinus infections, and are able to tolerate environments, such as being outdoors during the peak pollen season that would have otherwise not have been possible.⁹ The purpose of this study was to determine if treatment response with AIT could differentiate between AR and MR patient phenotypes.

METHODS

Recruitment and Enrollment

A historical pre- and posttreatment study design was used. Medical records were reviewed from an academic allergy practice to identify all AR patients who started AIT in 2001. Patients were included in the study if they then completed at least 3 years of AIT. Because this was a retrospective study, rhinitis was managed by the physician as clinically relevant with the goal to control symptoms while minimizing medication use. Likewise, AIT was managed by the physician as appropriate according to Joint Task Force Practice Parameter guidelines on AIT and was only continued if patients felt they were achieving a subjective improvement in symptoms and quality of life.⁹ Allergens for AIT were chosen for each individual based on skin-prick test results. Indi-

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vidual allergen extracts from ALK-Abelló (Round Rock, TX) were used in the AIT vials per the standardized AIT guidelines.⁹

Data Collection

One reviewer compiled data through chart review using a standardized form that captured data regarding allergic and nonallergic triggers, symptoms, and medications pre- and posttreatment ≥ 3 years of AIT. In addition, information was collected regarding each patient's personal and family history of atopy, the age of onset of symptoms, specific allergic triggers (pets or animals, high pollen counts, seasonal changes, and high mold counts) and nonallergic triggers (weather changes, strong odors or perfumes, tobacco smoke, solvents, and temperature changes), and any other relevant demographic information such as home exposures to cats and tobacco smoke. Quantitative rhinitis symptom scores were calculated by summing the number of individual rhinitis symptoms experienced by the patient, which included sneezing, ocular pruritus, rhinorrhea, nasal congestion, headache, postnasal discharge, sinus pressure, and ear symptoms at baseline and after ≥ 3 years of AIT. A symptom severity score was not possible because this was not routinely recorded by the treating physicians. Patients were classified as MR if they had significant symptoms in response to irritant triggers. Specific sensitization to aeroallergens was confirmed by historical skin-prick test results and/or specific IgE results. A positive skin-prick test was defined as a wheal of ≥ 3 mm than a negative saline control with a histamine-positive control.⁹ A medication score was calculated for each patient by adding the absolute number of concurrent medications related to their rhinitis condition in conjunction with immunotherapy.

Outcome Definitions

The outcomes of this study were changes in clinical rhinitis symptoms and changes in the number of medications used. For rhinitis symptoms the outcomes were the presence or absence of symptoms. For medication use, the outcomes were whether the patient was using or not using a medication as well as the number of medications they were using. Sinusitis was defined as symptoms of sinus pressure, headache/facial pain with or without fever, and purulent discharge unresponsive to intranasal and/or oral medications that required treatment with antibiotics.

Rhinitis Subtype Definitions

The patients in this study were categorized as having AR or MR subtypes. AR was defined as having at least one rhinitis symptom along with at least one positive skin-prick test that correlated with their symptom(s). MR was defined as having at least one rhinitis symp-

Table 1 Demographic characteristics of the study population at baseline ($n = 98$)

Age, yr (mean $\pm$ SD; $p = 0.0016$)	AR: 31.8 ± 15.5 MR: 41.4 ± 12.8
Male gender, n (%) [*]	43 (44%)
White race, n (%) [*]	83 (85%)
Family history of atopic disease, n (%) [*]	61 (66%)
Presence of MR, n (%) [*]	65 (66%)
Tobacco smoke exposure, n (%) [*]	14 (16%)
Number of medications used for rhinitis symptoms at baseline (mean $\pm$ SD) [*]	3.1 ± 1.3

^{*}No significant difference between AR and MR patients.
AR = allergic rhinitis, MR = mixed rhinitis.

tom that correlated with at least one positive skin-prick test and rhinitis symptom(s) that were worsened by at least one irritant trigger (tobacco smoke, perfumes/fragrances, temperature changes, weather changes, and/or solvents). The irritant triggers were chosen based on a published Irritant Index Scale (Appendix 1)¹⁰ and simplified to five main factors based on a cluster analysis. Based on published data that showed 89% accuracy,¹⁰ one irritant trigger was used to define the irritant component of MR.⁵

Data Analysis

The data analysis was performed with SAS software (Version 9.1 for Windows; SAS Institute, Inc., Cary, NC). The relationship between rhinitis subtype and outcomes including changes in symptoms and medication use were analyzed. Student's t -test was used for the comparison of means (number of symptoms and number of medications). Chi-squared analysis was used for the comparison of distributions (presence or absence of symptoms or medications between rhinitis subtypes). McNemar's test was used to evaluate for treatment effect with immunotherapy (change in rhinitis symptoms or medications). A two-sided value of $p < 0.05$ was considered statistically significant.

RESULTS

Demographics of the Study Population

Of the patients seen at an academic allergy practice in 2001, 98 with chronic rhinitis were started on AIT and continued on this treatment for at least 3 years (Table 1). Of the 98 patients, 65 (66%) were categorized as having MR based on the definition of this rhinitis subtype. Patients were predominantly white (85%), and male patients composed 44% of the study population. The majority of patients had a family history of atopic disease (66%) and required on average three medications to con-

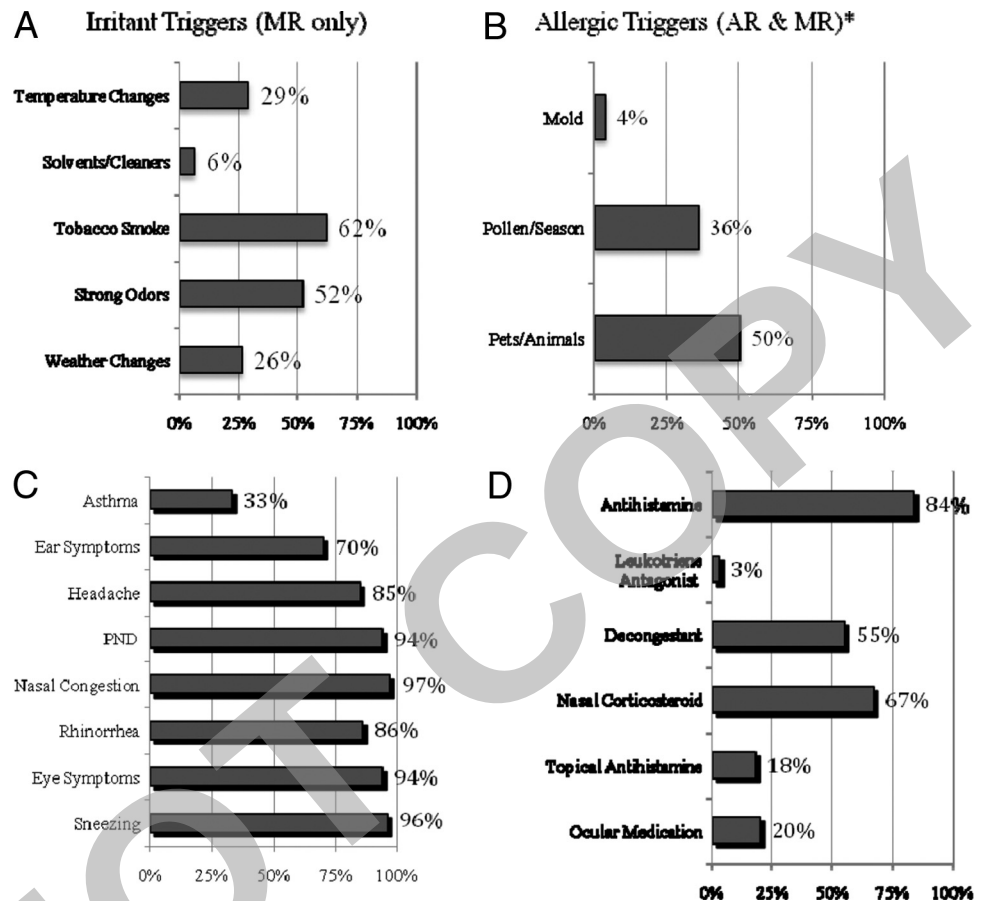


Figure 1. Baseline triggers, symptoms, and medications in the allergic rhinitis (AR) and mixed rhinitis (MR) groups. (A) Rhinitis irritant triggers at baseline. (B) Rhinitis allergic triggers at baseline. No significant difference in proportions with allergic triggers between AR and MR. (C) Symptoms at baseline (AR and MR). No significant difference in proportions with symptoms between AR and MR. PND, postnasal drip. (D) Medication use at baseline (AR and MR). No significant difference in proportions with symptoms between AR and MR).

trol rhinitis symptoms at baseline. Tobacco smoke exposure, either primary or second hand, was reported in only a minority (16%) of patients. Other than age, there were no significant differences in baseline demographic characteristics between AR and MR patients. The AR patients were younger on average compared with MR patients (31.8 versus 41.4 years; $p = 0.0016$).

Baseline Characteristics of the Study Population

Three categories of baseline characteristics were analyzed for differences between the AR and MR patients (Fig. 1). Irritant rhinitis triggers were by definition seen only in the patients with MR (Fig. 1 A). The most frequently reported irritant triggers at baseline were tobacco smoke (62%) and strong odors (52%). Symptoms after sudden temperature or weather changes as triggers were reported in approximately one-quarter of patients (29 and 26%, respectively).

There were no significant differences in the number of patients reporting allergic triggers between the AR and MR groups (Fig. 1 B). One-half of the patients (50%) reported pets or animals as a trigger of rhinitis symptoms, and over one-third (36%) reported pollen or seasonal rhinitis triggers. Only a very few patients reported mold exposure as a trigger (4%).

A wide variety of symptoms were reported at baseline. There were no significant differences in the proportions of patients reporting rhinitis symptoms between the AR and MR patient groups (Fig. 1 C). Asthma was reported in one-third of patients (33%) whereas headache, postnasal discharge, nasal congestion, rhinorrhea, ear symptoms, and sneezing were all reported in at least 85% of patients.

On average, three medications were required to control rhinitis symptoms in these patients at baseline (3.1 ± 1.3). The three most commonly used medications were antihistamines, decongestants, and nasal corticosteroids (Fig. 1 D). There were no significant differences in the proportions of patients on each medication from baseline to end of study between the AR and MR patient groups.

Change in Symptoms with Immunotherapy

To evaluate for improvement of rhinitis symptoms (listed in Fig. 1 C), an analysis of change in symptoms before and after AIT was performed by rhinitis subtype. No statistically significant changes were seen in the proportion of patients reporting sneezing, rhinorrhea, headache, postnasal discharge, nasal congestion, or ocular symptoms from baseline to end of study

(after AIT; data not shown). Interestingly, of those AR patients reporting recurrent sinusitis at baseline, 67% reported resolution of recurrent sinusitis after immunotherapy ($n = 12$; $p = 0.058$ by McNemar's test) whereas for those MR patients reporting recurrent sinusitis at baseline, 72% reported resolution of recurrent sinusitis after immunotherapy ($n = 18$; $p = 0.045$ by McNemar's test). The MR group had a statistically significant greater resolution of recurrent sinusitis when compared with the AR group ($p = 0.045$ by Cochran-Mantel-Haenszel analysis).

Change in Medication Use with Immunotherapy

Significant changes in medication use were seen in both the AR and the MR groups after at least 3 years of AIT (Fig. 2). A significant proportion of AR patients were able to stop antihistamines ($p = 0.004$), decongestants ($p = 0.021$), nasal corticosteroids ($p < 0.0001$), and ocular medications ($p = 0.03$) and still maintain symptom control (Fig. 2A). A significant proportion of MR patients were also able to stop antihistamines ($p = 0.002$), decongestants ($p = 0.003$), and nasal corticosteroids ($p < 0.0001$). However, a significantly greater proportion of AR patients (87%) were able to discontinue nasal corticosteroids compared with the MR patients (63%; $p = 0.049$; odds ratio, 0.25; 95% CI, 0.065–0.99).

The total number of rhinitis medications used after AIT was significantly greater in the MR group compared with the AR group (Fig. 2B). Based on the distribution of number of medications after immunotherapy, the number of medications used was dichotomized to less than three medications or three or more medications for analysis. Patients with MR comprised a significantly greater proportion of those requiring three or more medications to maintain control of rhinitis symptoms after immunotherapy compared with AR patients ($p = 0.043$).

The number of medications used decreased for both groups, but this decrease was significantly greater in the AR group compared with MR. At baseline, there were no significant differences in the mean number of medications used for rhinitis symptoms (Table 1; Fig. 2C; $p = 0.35$). For both groups, there was a significant decrease in the mean number of medications used after AIT ($p < 0.001$). However, the AR group had a greater decrease than the MR group after AIT (1.24 ± 1.09 versus 2.09 ± 1.55 ; $p = 0.0023$).

DISCUSSION

Previous studies confirm that management of patients with AR and/or allergic asthma by allergists provides more effective and cost efficient clinical outcomes.^{1,10–13} This could be attributed to a more accurate diagnosis of allergic disease, resulting in more appropriate treatment and, ultimately, reduction of associated

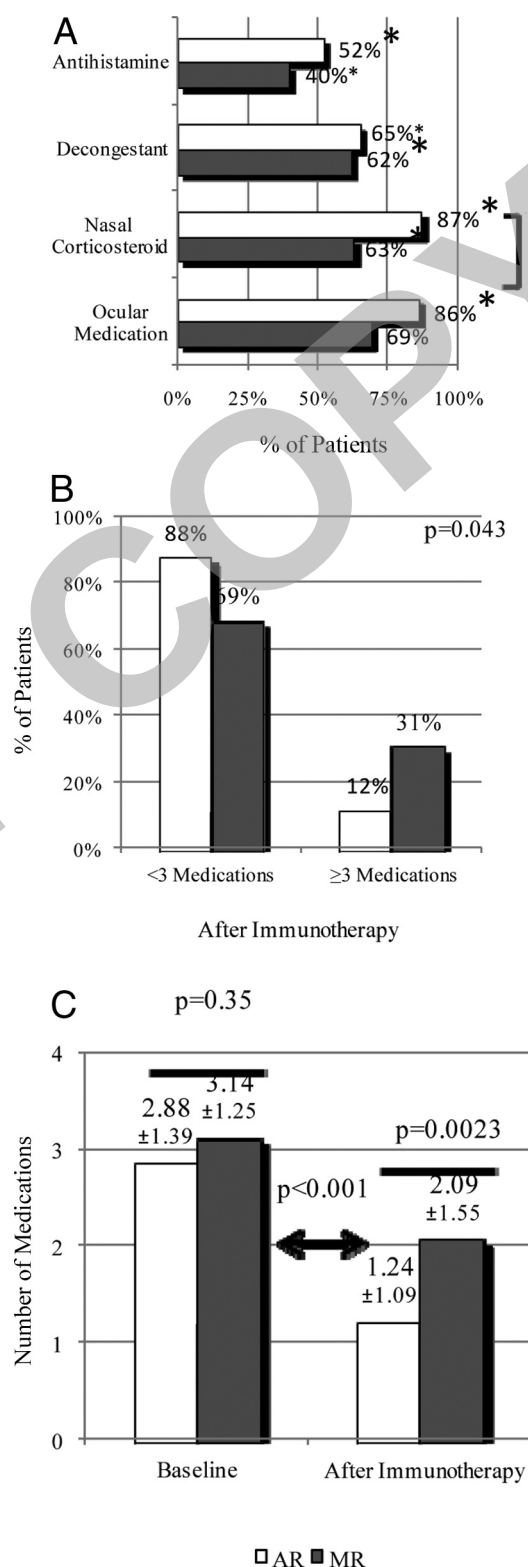


Figure 2. Change in medication use with immunotherapy. (A) Patients stopping medication after immunotherapy. * $p < 0.05$ for change from baseline; § $p = 0.049$ for difference between change in nasal corticosteroid use in allergic rhinitis (AR) and mixed rhinitis (MR). (B) Number of medications used after immunotherapy. (C) Change in mean numbers of medication used with immunotherapy.

complications such as sinusitis and asthma.^{12,13} In the present study, we have shown that characterization of chronic rhinitis subtypes using well-defined criteria can identify AR patients who are more likely to have a better outcome as defined by reduced medication requirements after a full course of AIT. Although both groups were able to reduce medication requirements after AIT, the AR group was able to reduce the number of medications to a significantly greater extent compared with the MR group. This effect was seen for each class of medication including antihistamines (both nasal and oral), nasal corticosteroids, decongestants, and ocular medications. Interestingly, the MR group had a greater reduction in the number of sinus infections experienced compared with the AR group. One could speculate that AIT had an immunomodulatory effect on the AR component of MR that was effective at attenuating symptoms induced by nonallergic triggers. However, whether this was a direct effect of AIT, the use of more medications throughout the course of AIT or both was not possible to discern.

There are several limitations of this study that warrant further discussion. First, the lack of consensus definitions for differentiating AR from MR has been a limitation in accurately classifying patients with these phenotypes. To obviate this potential problem, we chose a very conservative definition for MR in this study. The results of this study are quite remarkable considering the conservative definitions of AR and MR used in this analysis. Recently, we have developed an irritant index score that can discriminate more accurately between AR and MR patients.¹⁰ Future longitudinal treatment response studies in AR patients should incorporate an objective instrument such as the Irritant Index Scale to ensure a more accurate classification of AR and MR subtypes.¹⁰ Second, this analysis would have benefited from having a larger study population sample size to allow for multivariate analyses. However, despite the small population size, there were no measured demographic or other baseline clinical characteristic differences between the AR and MR groups other than age that significantly biased our findings. A younger mean age for the AR group compared with the MR group is not unexpected because AR begins at a younger age compared with nonallergic rhinitis (a component of MR), which begins at an older age.¹⁰ Finally, although this was a historical pre- and posttreatment study design, all chart reviews were conducted by the same investigator, and strict prestudy definitions were consistently adhered to while analyzing the data.

In summary, AIT was perceived by both AR and MR patients as being an effective treatment because both groups continued treatment for at least 3 years. The reduction in medication requirements by the AR group indicates that treatment response to AIT may be a useful way of differentiating between AR and MR subtypes. Interestingly, despite the differential require-

ment for medications by the MR group, they still achieved a therapeutic benefit from AIT manifested as a reduction in the number of sinusitis episodes experienced during this time period. It is probable that the cost associated with a greater requirement for medications by the MR group was offset by their reduction in sinus infections. This study supports the need for larger longitudinal investigations to determine whether use of more objective criteria for differentiating AR from MR subtypes impacts treatment response outcomes to specific medications being investigated or already approved for the treatment of AR including AIT.

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APPENDIX 1

Cincinnati Irritant Index Scale

Instructions. Please rate on a scale of 0–10 the degree to which the following irritants cause or aggravate any upper respiratory symptoms or headaches:

A degree of “0” means that the irritant has no effect on creating or aggravating upper respiratory symptoms or headache, and “10” means that the irritant has a maximal effect. If it does not provoke the disease at all, write “0”.

If you avoid the irritant because it aggravates your symptoms, please rate what your reaction was when you were exposed to the irritant in the past.

Upper respiratory symptoms may include the following: stuffy nose; runny nose; itching of the nose; sneezing; itchy, red, and watery eyes; postnasal drainage.

Irritant Upper Respiratory Symptoms

1. Perfume
2. Hair spray

3. Cosmetics (including aftershave lotion)
4. Antiperspirants/deodorants
5. Fresh newsprint
6. Cooking/frying odors
7. Bleach (Clorox)
8. Soap powders (*i.e.*, laundry soap)
9. Ammonia (*i.e.*, Lysol and Windex)
10. Household cleaners (*i.e.*, Tilex and Comet)
11. Christmas tree odors or Pine-Sol
12. Varnish
13. Solvents (turpentine, alcohol, and/or nail polish remover)
14. Paints
15. Sawdust
16. Crude oil (gasoline, diesel, and/or kerosene)
17. Periods of high air pollution
18. Cold air
19. Weather (rain, dampness, and/or temperature changes)
20. Tobacco smoke/wood smoke (burning logs)
21. Mold/mildew odors

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