

ORIGINAL ARTICLE

Author Proof

Olfaction in patients with allergic rhinitis: an indicator of successful MP-AzeFlu therapy

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Background: The purpose of this study was to investigate the effect of MP-AzeFlu on olfaction and the interaction between severity of allergic rhinitis and olfactory improvement after therapy.

Methods: A prospective, multicenter, observational study was performed on 47 patients with persistent allergic rhinitis. Duration and severity of allergic rhinitis was diagnosed and classified using the modified Allergic Rhinitis and its Impact on Asthma (ARIA) criteria and the proof of allergen sensitization from positive skin-prick tests, specific immunoglobulin E (IgE) in serum, and nasal provocation response. Patients were treated with MP-AzeFlu (1 spray/nostril twice daily) over 3 months. Olfactory function was assessed at baseline and at 1 and 3 months of therapy using the "Sniffin' Sticks" test. In addition, a nasal symptom score was recorded on a visual analog scale (VAS) at each given time-point.

Results: MP-AzeFlu was found to be associated with a significant improvement in TDI score, from 23.7 at baseline to 34.2 at 1 month ($p < 0.001$) and 37.1 at 3 months ($p < 0.001$) of treatment. Furthermore, a highly

significant improvement of symptoms over time ($p < 0.001$; VAS at baseline: 84.3; 1 month: 32.4; 3 months: 26.2) could be demonstrated. Most importantly, there was a highly significant interaction between the severity of allergic rhinitis and olfactory function ($p < 0.001$) and VAS ($p < 0.001$).

Conclusion: MP-AzeFlu is associated with olfactory improvement in persistent allergic rhinitis patients. Further, the modified ARIA severity classification is an indicator of patients' olfactory function. Moreover, assessment of olfaction seems to be a reliable indicator of the clinical success of antiallergic/antiinflammatory therapy. © 2016 ARS-AAOA, LLC.

Key Words: allergic rhinitis; olfaction; olfactory disorders; olfactory test; steroid therapy; therapeutics

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Allergic rhinitis (AR) is a global health problem with increasing prevalence and has a major impact on a person's quality of life (QoL).¹ Olfactory dysfunction is among the key symptoms of allergic rhinitis and seems to rise in frequency with increasing duration and severity of AR.² The importance of olfaction on QoL and mental health was shown, for example, by Katotomichelakis et al, who demonstrated a positive correlation between these factors.³ The underlying mechanism of impaired olfaction in AR is not fully understood, but it seems to result from mechanical as well as inflammatory components within the nasal mucosa.^{4,5}

AR was reclassified in 2001 using the Allergic Rhinitis and its Impact on Asthma (ARIA) criteria, where classification was based on duration ("intermittent"/"persistent") and disease severity and later updated. Severity was based on 4 items that impair QoL, namely sleep disturbance; impairment of daily activities, leisure, and/or sports;

impairment of school or work; and troublesome symptoms. Two different categories could be distinguished: mild (patients with none of the items affected) and moderate/severe (patients with 1 or more items affected).⁶ Because the moderate/severe group was very heterogeneous and included patients with wide-ranging severity, a modified classification of AR severity (or modified ARIA [m-ARIA] severity level) with 3 levels had been developed using the same 4 ARIA items: mild (no items affected); moderate (1 to 3 items affected); and severe (all 4 items affected).^{7,8} Several validation studies showed partly controversial outcomes,^{9–11} but correlation of ARIA classes with olfaction or olfactory changes after AR therapy has not been investigated so far.

A recent review¹² on olfaction in AR revealed that antihistamines and topical steroids, at least to some extent, had a beneficial effect on olfaction. However, due to mainly the use of self-rated symptom scores in the studies reviewed, a reliable assessment of olfaction was difficult, as self-ratings seemed to correlate with nasal breathing abilities rather than with olfactory function.¹³ Therefore, there remains a strong need for studies using standardized quantitative assessment tools.

MP-AzeFlu, a combination of azelastine and fluticasone, is a new topical AR therapy that has been shown to be superior to topical antihistamine and topical steroid alone for symptom relief.¹⁴ As of now, however, no study has investigated olfactory outcomes in AR patients treated with MP-AzeFlu.

The aim of the present study was to investigate: (1) the effect of MP-AzeFlu on olfactory function in patients with allergic rhinitis; and (2) the correlation between severity of the disorder and olfactory function and/or improvement after therapy.

Patients and methods

This study was performed in accordance with the Declaration of Helsinki and approved by the ethics committee of the Medical Faculty of Mannheim University. All patients were recruited in the course of a multicenter study coordinated by the Mannheim University Hospital and Center for Rhinology and Allergology, Mannheim and Wiesbaden, Germany. After a detailed explanation of the study and a thorough evaluation regarding inclusion and exclusion criteria, patients provided written informed consent.

Participants

Inclusion/exclusion criteria

Patients meeting the following criteria were eligible to participate in the study:

- Female and male outpatients between 18 and 70 years of age.
- A diagnosis of persistent allergic rhinitis (PAR) classified using the m-ARIA criteria.

- Sensitization to perennial inhalational allergens (mites and/or molds and/or animal dander) as evidenced by positive tests in skin prick (weal for allergen at least as large as histamine dihydrochloride 0.1% = 1 mg/mL control reaction) and positive immunoglobulin E (IgE) in serum EAST/CAP class ≥ 2 and positive nasal provocation response.

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Radioallergosorbent/
Carrier-Polymer-System (RAST/CAP)

Patients meeting any of the following criteria had to be excluded from the study:

- Ongoing allergen-specific immunotherapy to any allergen in question in any formulation.
- Any kind of nonallergic rhinitis or infections of the respiratory tract.
- Treatment with systemic corticosteroids, antihistamines, or other medication that may interfere with symptoms of PAR.
- Severe psychological disorders.
- Any contraindication for application of the study drug according to the medicinal product's professional information.
- Drug or alcohol abuse.
- Female patients seeking to become pregnant, pregnancy, or in lactation period.
- Concurrent participation in any other clinical trial or participation in any other clinical trial during the previous 30 days before inclusion.
- Low compliance or inability to understand instructions/study documents.

Removal of patients from therapy or assessment

In accordance with the Declaration of Helsinki, patients were allowed to discontinue their study participation at any time without giving a reason and without adversely affecting their further treatment. In addition, patients should be withdrawn by the investigator for the following reasons:

- In cases of an adverse event (including pathologic laboratory parameters) when continuation of treatment would constitute an unacceptable risk for the patient.
- If the patient is not willing to adhere to the study requirements (severe lack of compliance).
- If there is relevant protocol violation.

All patients who discontinued the study were regarded as "drop-outs" and the circumstances of withdrawal or discontinuation had to be recorded in the CRF.

After thorough evaluation regarding the criteria, a total of 47 patients (25 women, 22 men) with PAR were eligible for inclusion in the study. The average age was 31 years (standard deviation, 7.8 years), ranging from 18 to 67 years.

According to disease severity, PAR patients were classified using the m-ARIA severity levels of mild, moderate, or severe rhinitis. Further information is presented in Table 1. On the basis of this modified classification, 6 subjects were

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case report form

TABLE 1. Classification of allergic rhinitis severity according to the modified ARIA levels

Level	Description of AR severity
Mild	- Nasal and ocular symptoms - None of the following affected: sleep disturbance, impairment of daily activities, leisure and/or sport, impairment of school or work, troublesome symptoms
Moderate	- Nasal and ocular symptoms plus - One to three of the following affected: sleep disturbance, impairment of daily activities, leisure and/or sport, impairment of school or work, troublesome symptoms
Severe	- Nasal and ocular symptoms plus - All four of the following affected: sleep disturbance, impairment of daily activities, leisure and/or sport, impairment of school or work, troublesome symptoms

graded as having mild, 27 as having moderate, and 14 as suffering from severe rhinitis.

Short form of fluticasone propionate is FP,
so please change to FP

Treating allergic rhinitis

Q5 To treat symptoms of AR, patients had to apply MP-AzeFlu at 1 spray per nostril in the morning and evening (total daily doses: Aze = 548 μ g; Flu = 200 μ g) over a period of 3 months. No other medication was used during this time.

Nasal symptom rating

All patients had to rate the severity of their nasal symptoms at baseline and at 1 and 3 months of MP-AzeFlu therapy on a visual analog scale (VAS). Patients were asked to mark on a 100-mm horizontal line (0 mm—"not at all bothersome" to 100 mm—"highly bothersome") how they felt in response to the question, "How bothersome were your nasal symptoms today?"

Olfactory testing

Olfactory testing was done at baseline and during MP-AzeFlu therapy at 1 and 3 months using the "Sniffin' Sticks" test kit.¹⁵ This test consists of 3 subtests, where odor threshold, odor discrimination, and odor identification are tested.

Odor threshold was tested using 16 different concentrations of phenylethylalcohol (PEA) beginning from a 4% stock solution (solvent propylene glycol, dilution ratio 2:1). A triplet of pens were presented randomly for 2 seconds each about 2 cm in front of the nostrils. One pen contained PEA odor, whereas the other 2 pens were odorless propylene glycol. Subjects were blinded for this test and had to detect the odorized pen relying solely on their olfactory

ability. Because it was a 3-alternative, forced-choice procedure (3-AFC) patients had to decide on 1 pen even if it was a guess. Concentration was increased if patients could not detect the PEA odor and was decreased if the answer given was correct twice in a row. Odor threshold was defined as the average of the last 4 turning points from a total of 7 turning points.

Odor discrimination, a suprathreshold test, was investigated again using 16 triplets of felt-tip-pen-like odor dispensers. By presenting as a triplet, patients had to discriminate 2 identical odors from 1 different odor. Subjects had to find the single different odor and were again forced to give an answer even if they did not know.

The odor identification task was based on a 4-alternative, forced-choice procedure (4-AFC), where patients had to identify 16 different odors from a list of 4 descriptors presented with each pen. Within each subtest a maximum of 16 points could be achieved. The sum of all 3 subtests was defined as the TDI score (threshold, discrimination, identification) with a maximum score of 48 points. Normosmia was defined as having >30.5 points, hyposmia between 16.5 and 30.5 points, and functional anosmia as $\leq$ 16.5 points.¹⁶

Statistical analysis

Data were analyzed using SPSS version 23.0 (SPSS, Inc., Chicago, IL). Significance level was set at $p = 0.05$. Analysis of variance (ANOVA) was used to highlight possible interaction between factors "time" (baseline, 1 and 3 months) and ARIA classification (olfactory function within severity levels). When an interaction was observed, a post-hoc Tukey multiple-comparisons test was used to compare each level of the factors.

Results

Nasal symptoms

The main effect of time was highly significant [$F(2, 88) = 897.8$, $p < 0.001$], meaning that all patients, independent of their classification, had improved nasal symptoms over time. Starting from an average symptom score of 84.3 ($\pm$ 10.9) on the VAS at baseline, patients improved to 32.4 ($\pm$ 7.6) after 1 month and to 26.2 ($\pm$ 7.2) after 3 months of therapy. Hence, at 1 month after therapy, 45 of 47 (96%) patients showed symptom scores of <50 mm (cut-off for well-controlled symptoms) on the VAS. Those 2 patients who could not improve sufficiently belonged to the group of severe and moderate PAR patients. Nevertheless, 13 of 14 (93%) patients with severe PAR and 26 of 27 (96%) patients with moderate PAR improved to levels of <50 mm on the VAS after 1 month.

Most importantly, a significant interaction between time and severity classification emerged [$F(4, 88) = 8.4$, $p < 0.001$]. In looking at the post-hoc comparison, the data show that each AR severity level improved significantly over time ($p < 0.05$ for all).

Olfactory function

In looking at the TDI score, the main effect of time was again highly significant, showing that all patients, regardless of their assigned severity levels, improved significantly after 1 and 3 months [$F(2, 88) = 274.2, p < 0.001$; φ TDI at baseline: $23.7 (\pm 3.9)$; 1 month: $34.2 (\pm 2.4)$; 3 months: $37.1 (\pm 2.2)$].

In looking at the subtests, a significant improvement over time for every single subtest (at 0, 1, 3 months: threshold φ 5.5, 8.4, 9.5; discrimination φ 8.5, 12.6, 13.5; and identification φ 9.7, 13.2, 14.1) could be observed after 1 and 3 months of MP 29-02 application [$F(2, 92) = 287.1, p < 0.001$]. Furthermore, a significant interaction between the main effect of time and test [$F(4, 184) = 4.1, p = 0.003$] showed that the rate of improvement at different time-points (1 and 3 months) varied between the tests. Although discrimination and identification improved by 4.1 and 3.5 points, the threshold score improved by 3.0 points after 1 month. After 3 months of therapy, in comparison to 1 month, there was less improvement seen within all tests, ranging from 0.9 to 1.1 points (T: 1.1 points; D: 0.9 point; I: 0.9 point). In total, 44 of 47 (94%) patients treated with MP-AzeFlu showed full olfactory recovery, with a TDI score of >30.5 points after 1 month, and all 47 (100%) patients becoming normosmic after 3 months.

Olfactory function and m-ARIA severity level

In grouping patients according to m-ARIA severity levels we could show again a significant improvement of the TDI score after 1 and 3 months of MP-AzeFlu therapy for all severity levels [$F(4, 88) = 13.2, p < 0.001$] (Figure 1). Although severe PAR patients had an average TDI score of 20.0 points at baseline, this improved to 34.7 and 37.1 points after 1 and 3 months, respectively. Likewise, moderate PAR patients, starting from an average score of 24.4 points at baseline, improved to 34.0 (1 month) and 36.8 (3 months) points. Thirteen of 14 (93%) patients with severe PAR and 26 of 27 (96%) with moderate PAR showed a normal sense of smell with a TDI scores of >30.5 points after 1 month of MP-AzeFlu therapy. Normosmia was seen in all (100%) patients after 3 months.

Regardless of the m-ARIA severity classification, a significant improvement in all subtests after 1 and 3 months was observed [S: $F(2, 88) = 114.9, p < 0.001$; D: $F(2, 88) = 139.6, p < 0.001$; I: $F(2, 88) = 117.8, p < 0.001$]. A significant interaction between the main effect of time and classification showed that, similar to the TDI improvement, the improvement of threshold [$F(4, 88) = 4.0, p < 0.005$], discrimination [$F(4, 88) = 5.5, p < 0.01$], and identification [$F(4, 88) = 10.7, p < 0.001$] differed significantly between the various levels of m-ARIA severity. In looking at the post-hoc comparison, the data show significant improvement in discrimination over time in moderate and severe PAR patients, with mild PAR patients improving only by 1.8 and 2.8 points. Similar findings could be elucidated for the identification test (severe: 5.5 and 6.1 points; mild: 1.5

and 2.3 points) and odor threshold test (severe: 3.5 and 4.9 points; mild: 1.5 and 3.5 points).

Discussion

We have obtained the following results in our study of patients using MP-AzeFlu to treat PAR for 3 months: (1) there was a highly significant improvement of symptoms over the entire time period; (2) there was a highly significant improvement in olfaction (TDI score) after 1 and 3 months; (3) there were similar improvements within each subtest (threshold, discrimination, identification) over time; (4) there was a highly significant interaction between the olfactory function (TDI) and m-ARIA severity levels; (5) there was a highly significant interaction between symptom score (VAS) and m-ARIA severity levels; and (6) and $>90\%$ of patients with full olfactory recovery and reaching a state of well-controlled AR (VAS <50 mm) within the first month.

The effect of AR therapy on olfaction using topical steroids or antihistamines was studied in the various groups. Quantitatively assessed improvement was thus far limited to odor threshold and odor identification using topical steroids.^{17,18} Olfactory improvement shown from the use of topical antihistamine was based on symptom score,¹⁹ which is known to represent nasal breathing ability rather than olfactory function,¹³ at least under some conditions. Our study was the first to investigate the effect of MP-AzeFlu, a combination of azelastine and fluticasone, on olfaction in AR patients using a quantitative assessment method (Sniffin' Sticks). There was consistent improvement in olfaction (TDI and all subtests T, D, and I) and a significant relief from nasal symptoms, which was sustained over the entire course of treatment. Reaching an average VAS score of 26 mm at 3 months highlighted MP-AzeFlu's ability to control symptoms when cut-off score for well-controlled AR patients is set at 36 mm,²⁰ or even <50 mm according to the latest AR treatment algorithm.²¹ Based on the fact that $>90\%$ of the patients regained a normal sense of smell and reached scores of well-controlled AR symptoms within 1 month of MP-AzeFlu, this time frame seems to be the optimal duration of PAR therapy. In demonstrating such improvement rates, not only in mild but also in moderate and severe PAR patients, our data highlight the efficacy of MP-AzeFlu in the treatment of severe allergic rhinitis. We have confirmed the safety of MP-AzeFlu²² and its superiority in symptom relief¹⁴ as described previous studies, and our additional findings of olfactory and general symptom improvement support previous recommendations considering MP-AzeFlu as a first-line therapy for AR patients, specifically those with moderate to severe PAR.

Further, we have shown, for the first time, a clear interaction between the m-ARIA severity levels and olfactory function. With increasing severity of AR, olfactory function decreased; that is, the higher a patient's m-ARIA severity level, the worse the olfactory function at baseline. At the same time, we could show an m-ARIA severity level-dependent improvement in olfaction with AR therapy, with higher

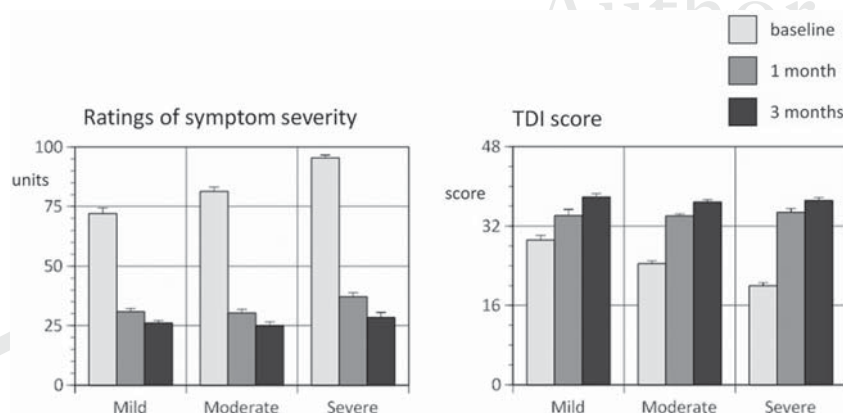


FIGURE 1. Improvement of symptom severity and TDI score (expressed as mean and standard error of the mean) separately over time for the m-ARIA severity levels. m-ARIA = modified Allergic Rhinitis and its Impact on Asthma (criteria); TDI score = threshold, discrimination, identification (score).

olfactory improvement in patients diagnosed with a higher m-ARIA severity level, especially within the first month of therapy. Similar interactions could be shown between m-ARIA levels and symptom score, meaning that, the higher the patients' m-ARIA severity level, the greater the rate of improvement, whereas the main improvement was again found within the first month of therapy. These findings allow m-ARIA severity levels to be a valid for predicting improvement in olfactory and general symptoms after AR therapy. On the other hand, the interaction between m-ARIA severity level and olfactory function shows us that assessment of olfaction may be considered a reliable indicator of the clinical success of an antiallergic/antiinflammatory therapy. Thus, we believe olfactory testing should be implemented in the daily routine diagnostics of AR patients.

Olfactory impairment in AR patients seems to result from a combination of conductive and sensorineural

dysfunction. Due to swollen mucosa and/or increased mucus secretion,²³ odor molecules cannot reach olfactory receptor neurons, which leads to olfactory impairment. Further, inflammatory processes in AR at the level of the olfactory epithelium have been shown to be associated with olfactory dysfunction.^{4,24} Considering the present results, it appears that assessment of olfactory function is a reliable indicator of the clinical success of an antiallergic/antiinflammatory therapy.

In conclusion, our data suggest the following: First, use of of MP-AzeFlu in AR therapy is effective for symptoms in general, but for olfaction in particular. Second, m-ARIA severity classification is an indicator of olfactory function and its improvement after MP-AzeFlu therapy. Third, assessment of olfactory function may be considered a reliable indicator of the level of clinical success of an antiallergic/antiinflammatory therapy. ③

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