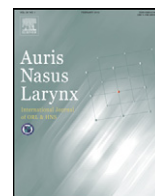




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Intranasal phototherapy versus azelastine in the treatment of seasonal allergic rhinitis

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ABSTRACT

Objective: It has been suggested that intranasal phototherapy represents an alternative choice in the treatment of seasonal allergic rhinitis (SAR). Our aim was to compare the efficacy of intranasal phototherapy with that of azelastine in patients with SAR.

Methods: Seventy seven patients were randomly assigned to the two treatment groups: Group A (phototherapy) and Group B (azelastine). Subjective and objective outcomes were represented by changes in Total Nasal Symptom Score (TNSS), Quality of life scores (Rhinoconjunctivitis Quality of Life Questionnaire – RQLQ), and nasal resistance.

Results: The study demonstrated that both azelastine and intranasal phototherapy are able to significantly improve TNSS, including individual nasal symptoms. Nevertheless, phototherapy reduced nasal obstruction better than azelastine ($p = 0.038$). Both treatments were highly effective in improving RQLQ scores overall and in seven separate domains.

Conclusion: Whether intranasal phototherapy will be a standard treatment of SAR or not should be appraised in future studies and clinical trials.

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1. Introduction

Allergic rhinitis (AR) is an allergen-induced, IgE-mediated inflammatory disease of the nasal mucosa that causes major illness and disability worldwide [1]. It is estimated that the prevalence of AR is between 10% and 30% of adults in the United States and around 25% of the general population in Europe [2,3].

Guidelines issued by the Allergic Rhinitis and its Impact on Asthma group recommend use of second-generation antihistamines as first-line treatment for AR [4]. Intranasal antihistamines can be used as first-line therapy for the treatment of seasonal allergic rhinitis (SAR) [5,6]. Azelastine hydrochloride is a second-generation antihistamine that selectively antagonizes the H1-receptor [7]. In addition to blocking the effects of histamine, azelastine has been shown to inhibit the effects of other chemical mediators of the inflammatory response, including leukotrienes [8], substance P [9], cytokines, and intercellular adhesion molecule-1 [10]. These physiological effects may explain the efficacy of azelastine for treating nasal congestion as well as histamine-mediated symptoms. Several clinical studies with the original

azelastine nasal spray showed its efficacy for the treatment of allergic and nonallergic rhinitis [11].

It has been recently demonstrated that intranasal phototherapy is an effective treatment for SAR. Koreck et al. in a randomized controlled double-blind study demonstrated the efficacy of intranasal phototherapy in ragweed-induced hay fever [12]. A recent prospective, randomized, single-blind, placebo controlled study in AR patients demonstrated a highly significant reduction in the TNSS in the phototherapy group as compared with the placebo group [13]. Rhinophototherapy with low doses of mixed ultraviolet and visible light significantly improve the clinical symptoms of AR by acting at multiple points such as induction of T-cell and eosinophil apoptosis and suppression of release of mediators like eosinophil cationic protein (ECP) and interleukin 5 (IL5) [13,14].

The use of second-generation antihistamines in the treatment of SAR is well established [15]. However, in clinical practice, SAR symptoms are not always satisfactorily controlled by medication and some patients fail to respond to treatment. Furthermore, many patients with allergic rhinitis fail to achieve optimal symptom relief with pharmacologic monotherapy. In fact, a survey conducted by the American College of Allergy, Asthma and Immunology found that 75% of clinicians cited inadequate symptom relief as their reason for changing medications and/or prescribing combination therapy for SAR [16].

The aim of this study was to compare the efficacy of intranasal phototherapy with that of azelastine in patients with SAR.

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Subjective and objective outcomes were represented by changes in Total Nasal Symptom Score (TNSS), nasal resistance, and effects on quality of life (QoL).

2. Materials and methods

This study was approved by the Ethical Committee of “Vasile Goldiș” University of Arad, Romania. All participating patients, adults above 18 years of age, were legally able to give informed consent. A prospective, randomized, open study was performed in patients with a history of at least 2 years of moderate to severe grass pollen-induced SAR poorly controlled by anti-allergic drugs. In addition to clinical symptoms, positive skin prick test results and an elevated level of specific IgE antibody confirmed the diagnosis. Exclusion criteria were: smokers, patients suffering from severe autoimmune disease, neoplastic disease, pregnancy, or had used any of the following drugs – leukotrienes or beta-mimetic drugs, systemic corticosteroids within 4 weeks, topical corticosteroids within 2 weeks, membrane stabilizers within 2 weeks, antihistamines within 1 week, nasal decongestants within 3 days, or immunotherapy within 5 years before the beginning of the study. Patients having significant nasal structural deformities or suffering from perennial rhinitis, acute or chronic rhinosinusitis or nasal polyps were not admitted to the study. The study was conducted in the ENT Department University of Arad between March and August 2009. All consecutive patients fulfilling the inclusion criteria were enrolled after the beginning of the pollen season. Eighty patients were randomly assigned to the two treatment groups: Group A (phototherapy) and Group B (azelastine therapy). The decision of medical therapy or phototherapy was assigned randomly on a 1:1 ratio according to the date of application. These two groups of patients were fairly homogeneous regarding their clinical findings. The demographic data are shown in Table 1.

Patients in Group A received intranasal phototherapy (5% UVB, 25% UVA and 70% visible light-VS) three times a week for 2 weeks ($n = 40$) according to the protocol described by Koreck et al. [12]. Each intranasal cavity was irradiated 3 times a week for 2 weeks with increasing doses of mUV/VIS (starting dose, 1.6 J/cm^2). Irradiations were performed with the Rhinolight 180 mW lamp (Rhinolight Ltd., Szeged, Hungary). The dose was raised by 0.25 J/cm^2 at every second treatment. The top dose was 2.4 J/cm^2 .

Patients in Group B received azelastine hydrochloride nasal spray, two sprays per nostril, once daily with a total dose of 1.1 mg, and continued consistently until the last visit. During the course of the investigation no rescue medication were allowed.

Each patient kept a daily diary of symptoms on a scale of 0–3 (0 indicating no symptoms and 1, 2, 3 indicating mild, moderate and severe symptoms respectively) for nasal obstruction, nasal itching, rhinorrhea, and sneezing during the treatment. TNSS, a sum of scores for sneezing, rhinorrhea, nasal itching, and nasal obstruction, which is considered the most common and best

established parameter for the clinical assessment of AR, was also calculated.

Quality of life was investigated using the Romanian validated form of Rhinoconjunctivitis Quality of Life Questionnaire – RQLQ. The RQLQ has 28 questions in seven domains (activity limitation, sleep problems, nose symptoms, eye symptoms, non-nose/eye symptoms, practical problems and emotional function) [17]. There are three “patient-specific” questions in the activity domain that allow patients to select three activities in which they are most limited by AR. Each item is rated on a seven-point scale (0 = not impaired at all; 6 = severely impaired). The overall RQLQ score is the mean of all 28 responses [18].

Nasal airflow was objectively measured by active anterior rhinomanometry. The investigation was performed with the aid of the Rhinomanometer 300 (ATMOS MedezinTechnik, Lenzkirch, Germany) with a flow meter integrated in the face mask and a pressure transducer fixed in one nostril. All measurements were performed and analyzed by the same specialist (SA) in a standard fashion that has been described previously [19]. Nasal airflow was reported as the sum of recorded airflow through the right and left nostrils in milliliters per second at a pressure difference of 150 Pa across the nasal passage. Each patient had a minim of 4 airflow measurements, and the mean value was recorded.

2.1. Statistical analysis

All data are presented as means $\pm$ SD. The normal distribution of the analyzed data was determined by the Kolmogorov–Smirnov (K–S) test for normality. All results were evaluated by means of the Student’s *t*-test. The Bonferroni correction was employed because of the use of multiple *t*-tests. Value of $p < 0.05$ was considered statistically significant. Sample size was estimated considering the power of the study to be 80% with 5% level of significance. Based on data collected by the author for a previous unpublished study, a mean of 3.55 and a SD of 1.05 for RQLQ were used for calculations. It has been demonstrated that a change of at least 0.5 in RQLQ score is considered to be of clinical significance [20], thus the number of patients in each group would be approximately 36. To compensate for the drop-outs we raised the number of cases to 40 in both arms.

3. Results

In Group A, 39 patients completed the treatment and two patients from Group B did not complete the study. In Group A one patient discarded the treatment because of a modified holiday schedule and in Group B the two dropouts were caused by upper respiratory tract infections. The 2 groups did not differ in age, disease duration, or clinical scores at the beginning of the treatment protocol (see Table 1). The data analyzed in this study was normally distributed (K–S test $d = 0.053$, $p > 0.200$).

Both groups had statistically significant improvements from their baseline TNSS after 2-week treatment (see Table 2). Overall, mean change in TNSS was not significantly different with phototherapy versus azelastine treatment ($p = 0.6$). Individual nasal symptoms such as rhinorrhea, congestion, itching, and sneezing improved similarly in both treatment groups. However, phototherapy reduced nasal obstruction better than azelastine ($p = 0.038$, see Table 2).

The RQLQ scores of the two groups were not significantly different at baseline ($p > 0.05$, see Table 3). The RQLQ measures revealed that both treatments were effective in improving the quality of life overall and in seven separate domains ($p < 0.05$) (Table 3). However, there was a trend toward better results in nasal symptoms and sleep domains for Group A patients (the difference approaching significance, see Table 3).

Table 1
Demographics and baseline characteristics of the treatment groups.

	Group A (N = 39)	Group B (N = 38)	p-Value
Age (yr) ^a	31.42 $\pm$ 11.82	33.56 $\pm$ 12.45	0.15
Women (%)	60%	66%	0.09
Education (yr) ^a	12 $\pm$ 2.4	11 $\pm$ 2.8	0.26
Duration of SAR (yr) ^a	4.68 $\pm$ 2.12	5.15 $\pm$ 2.42	0.36
TNSS ^a	8.87 $\pm$ 2.43	8.42 $\pm$ 1.92	0.37
Nasal obstruction ^a	2.75 $\pm$ 0.70	2.51 $\pm$ 0.83	0.17
Nasal itching ^a	2.71 $\pm$ 0.75	2.56 $\pm$ 0.87	0.38
Nasal discharge ^a	2.62 $\pm$ 0.81	2.43 $\pm$ 0.91	0.36
Sneezing ^a	2.55 $\pm$ 0.72	2.42 $\pm$ 0.65	0.35

SAR, seasonal allergic rhinitis; TNSS, Total Nasal Symptom Score; Group A, intranasal phototherapy; Group B, azelastine therapy.

^a Mean $\pm$ SD.

Table 2

Symptomatic score at baseline and after 14 days of treatment in both treatment groups.

Parameter	Treatment group	Baseline (mean $\pm$ SD)	Day 14 (mean $\pm$ SD)	<i>p</i> -Value*	<i>p</i> -Value#
Nasal obstruction	Group A	2.75 $\pm$ 0.70	0.91 $\pm$ 0.54	<0.00001	0.038
	Group B	2.51 $\pm$ 0.83	1.35 $\pm$ 0.91	<0.00001	
Nasal itching	Group A	2.77 $\pm$ 0.75	0.67 $\pm$ 0.82	<0.00001	0.23
	Group B	2.56 $\pm$ 0.87	0.95 $\pm$ 0.98	<0.00001	
Nasal discharge	Group A	2.62 $\pm$ 0.81	0.85 $\pm$ 0.47	<0.00001	0.25
	Group B	2.43 $\pm$ 0.91	1.05 $\pm$ 0.72	<0.00001	
Sneezing	Group A	2.85 $\pm$ 0.72	0.95 $\pm$ 0.52	<0.00001	0.09
	Group B	2.42 $\pm$ 0.65	0.71 $\pm$ 0.55	<0.00001	
TNSS	Group A	8.87 $\pm$ 2.43	3.75 $\pm$ 2.35	<0.00001	0.6
	Group B	8.42 $\pm$ 1.92	4.15 $\pm$ 2.86	<0.00001	

TNSS, Total Nasal Symptom Score; Group A, intranasal phototherapy; Group B, azelastine therapy.

* The *p*-values of comparisons between baseline and day 14 scores using Student's *t*-test.# The *p*-values of between-group comparisons (Group A versus B) using Student's *t*-test with Bonferroni correction.

The mean total nasal resistance in Group A patients decreased from 0.42 ± 0.18 to 0.36 ± 0.16 Pa/cm³/s ($p = 0.12$), and 0.45 ± 0.15 to 0.37 ± 0.12 Pa/cm³/s in Group B patients ($p = 0.11$) at the end of the therapy. Nevertheless, the difference did not reach significance in neither treatment arm.

Intranasal phototherapy was overall well tolerated. The only side effect was dryness of the nasal mucosa, which occurred in all Group A patients. All patients considered dryness as mild except one in the phototherapy group, and were controlled by emollients. Bitter taste was the only adverse experience that occurred in the azelastine group (5 patients).

4. Discussion

The treatment of SAR, a very common allergic disorder, is a complex problem, including elimination of the inhaled allergens from the patient's environment, specific pharmacotherapy, and immunotherapy. According to the Allergic Rhinitis and Its Impact on Asthma (ARIA) treatment guidelines [4], for moderate/severe rhinitis, intranasal corticosteroids are suggested as first-line therapy in combination with oral or intranasal antihistamines. Nevertheless, the same guidelines acknowledge also that second-generation antihistamines could act as first line therapy for SAR

[4]. In British guidelines for the management of rhinitis, azelastine is not only recommended for its superior therapeutic effects compared with oral antihistamines, but also is acknowledged as a rescue therapy for rhinitis [21]. Because pharmacokinetic studies have suggested that intranasal antihistamines have more rapid onset of action compared with intranasal corticosteroids, azelastine may be considered as primary therapy for patients with rhinitis [22]. As suggested by Kaliner et al., azelastine treats SAR at the site of the disease and limits systemic exposure [23].

A recent study compared the clinical efficacy of phototherapy with the new non-sedating oral antihistamine, fexofenadine hydrochloride [24]. The study was conducted on ragweed-allergic patients, during the pollen season. Phototherapy resulted in a significantly better reduction of individual symptom scores for nasal discharge and obstruction and of TNSS compared with fexofenadine. No significant differences between the two treatments were observed in reducing symptom scores for sneezing, nasal itching, and eye symptoms. However, the authors admit that their study is underpowered and this in fact may explain the results obtained in the antihistamine group.

This is the first study to compare the efficacy of phototherapy with that of intranasal azelastine. Although some mild benefit in the treatment of nasal congestion has been noted with newer

Table 3

Comparison of baseline and post-treatment scores of the RQLQ domains.

	Treatment group	Baseline (mean $\pm$ SD)	Day 14 (mean $\pm$ SD)	<i>p</i> -Value*	<i>p</i> -Value#
Limited activity	Group A	3.81 $\pm$ 1.78	1.70 $\pm$ 0.90	<0.0001	0.4
	Group B	3.47 $\pm$ 1.55	1.91 $\pm$ 0.95	<0.0001	
Sleep	Group A	3.12 $\pm$ 1.44	1.85 $\pm$ 1.12	<0.0001	0.05
	Group B	3.58 $\pm$ 1.63	2.45 $\pm$ 1.20	0.0009	
Non-hay fever symptoms	Group A	2.05 $\pm$ 1.15	1.10 $\pm$ 0.75	<0.0001	0.2
	Group B	2.45 $\pm$ 1.42	1.35 $\pm$ 0.65	<0.0001	
Practical problems	Group A	2.95 $\pm$ 1.65	1.45 $\pm$ 0.85	<0.0001	0.7
	Group B	3.15 $\pm$ 1.40	1.35 $\pm$ 0.75	<0.0001	
Nasal symptoms	Group A	4.10 $\pm$ 2.20	1.75 $\pm$ 1.10	<0.0001	0.047
	Group B	3.85 $\pm$ 2.10	2.30 $\pm$ 1.95	<0.0001	
Eye symptoms	Group A	1.31 $\pm$ 0.77	0.70 $\pm$ 0.60	0.0002	0.6
	Group B	1.45 $\pm$ 0.63	0.55 $\pm$ 0.40	<0.0001	
Emotional functions	Group A	1.88 $\pm$ 1.12	0.80 $\pm$ 0.55	<0.0001	0.7
	Group B	1.90 $\pm$ 1.42	0.60 $\pm$ 0.45	<0.0001	
Overall score	Group A	3.65 $\pm$ 1.39	1.37 $\pm$ 0.74	<0.0001	0.2
	Group B	3.80 $\pm$ 1.75	1.58 $\pm$ 0.85	<0.0001	

TNSS, Total Nasal Symptom Score; Group A, intranasal phototherapy; Group B, azelastine therapy.

* The *p*-values of comparisons between baseline and day 14 scores using Student's *t*-test.# The *p*-values of between-group comparisons (Group A versus B) using Student's *t*-test with Bonferroni correction.

antihistamines, such as desloratadine and levocetirizine, no oral antihistamines have significant effects on reducing nasal obstruction [15]. Conversely, intranasal azelastine can significantly decrease nasal congestion and this is why it was chosen for our assessment.

The study population was quite uniform to provide accurate information and minimize the confounding factors. The patients were randomized 1:1 into the groups, and results were evaluated with strongly recommended objective and subjective measures. This study demonstrated that intranasal phototherapy and azelastine are equally effective in reducing clinical symptoms in patients with moderate to severe SAR. Both in the phototherapy group as well in the azelastine group all symptoms improved significantly. The efficacy of both treatments as assessed in terms of TNSS and in individual symptom scores was found to be similar. However, nasal obstruction was significantly improved with phototherapy weighed against azelastine. This finding could be explained on the base of their means of action. In contrast to antihistamines, which influence predominantly histamine-mediated features of the allergic process, phototherapy has a different, more complex mechanism of action. It was demonstrated that phototherapy operates by inducing T cell and eosinophil apoptosis and suppressing the release of several mediators such as IL-5 and ECP [12]. Similar results concerning eosinophil, ECP, IL-5 levels and T lymphocytes are observed after other well-established therapies of allergic rhinitis, such as topical glucocorticoids or immunotherapy [22].

SAR has a notable negative impact on QoL, sleep and the ability to perform daily activities [25]. The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) was developed to measure the functional problems (physical, emotional, social and occupational) that are most bothersome to adults with allergic or non-allergic rhinoconjunctivitis [17]. RQLQ offers a better registration of changes in disease related problems compared to generic quality of life questionnaires [26]. Azelastine was found to improve RQLQ in patients with SAR [27] while Cingi et al. demonstrated that intranasal phototherapy significantly improves all quality of life variables in patients suffering from allergic rhinitis [28].

Our study demonstrated that both treatments are able to improve RQLQ overall scores. The beneficial effects of therapy on RQLQ (other than nasal congestion) may be the result of a halo effect as improvement in nasal congestion may improve patients' overall sense of well-being and reduce their perception of the severity of other SAR symptoms. RQLQ overall scores were not statistically different between the two groups. However, there was a trend toward better results in nasal symptoms and sleep domains for the intranasal phototherapy group.

There are however some flaws in our study which could sway the results. The outcome measures are mainly based on subjective scores and thus are prone to be affected by placebo-effects and volunteer bias. Further, the absence of blinding may result in a significant bias and moreover it is difficult to compare active therapeutic intervention with pharmacotherapy. These effects are likely to favor the phototherapy group due to a more active intervention and more contacts with health personal. The treating physician (SB) could not be blinded as to the treatment, but we supposed that the effect of this bias was reduced by outcomes assessment by a different investigator (SA). Another flaw is the lack of objective measures. Although rhinomanometry was used, assessment of nasal flow is somewhat uncertain due to the large variability. Nasal lavage should have been performed. However, results for nasal lavages for both phototherapy [12] and azelastine [29] have been previously described. We were interested in providing the clinician with a comparison of treatment results in SAR. Another confounder that was not taken into account is the oscillation in the pollen counts, which may affect the outcome measures. However, Arad is less than 90 km far from Szeged and

our patients were enrolled in the same period when, as previously reported [12,24] pollen counts were greater than 50/m³ in the Szeged area.

Phototherapy is a new and promising therapeutic modality for allergic rhinitis. Multiple studies sustain that phototherapy is able to actively suppresses the effector phase of the allergic reaction at multiple checkpoints. Intranasal phototherapy results in significant improvement of clinical symptoms, even in patients who were unresponsive to conventional anti allergic therapies. Although new antihistamines and local steroids are used with good results, there are cases in which complete resolution of the symptoms cannot be obtained. Moreover, the use of these drugs is controversial in special subsets of patients such as pregnant and breast-feeding women. All these characteristics of SAR highlight the need for effective new treatment options. Therefore, intranasal phototherapy may represent an alternative treatment of allergic rhinitis. This is the reason why recently, Kemeny and Koreck [30] recommended the addition of intranasal phototherapy into the ARIA guideline for those patients with allergic rhinitis, who do not respond well to the conventional antihistamine and intranasal corticosteroids treatments, or for those who cannot take the suggested medication. In addition, phototherapy might be also considered as a future therapeutic approach in other inflammatory and immune mediated mucosal diseases.

5. Conclusion

In the present study we demonstrated that both azelastine and intranasal phototherapy are able to significantly improve individual nasal symptoms such as rhinorrhea, congestion, itching, and sneezing in patient affected by SAR. Nevertheless, intranasal phototherapy reduced nasal obstruction better than azelastine. After a 14 days treatment period, the RQLQ measures revealed that both treatments were effective in improving the quality of life overall and in seven separate domains. However, there was a trend toward better results in nasal symptoms and sleep domains for the intranasal phototherapy group. Whether intranasal phototherapy will be a standard treatment of SAR or not should be evaluated in future studies and clinical trials.

Conflict of interest

We do not have a financial relationship with any organization or any company. No sponsorship was made for this study.

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