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RHINOLOGY

Rhinophototherapy in persistent allergic rhinitis

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Abstract Previous published results have revealed that Rhinolight® intranasal phototherapy is safe and effective in intermittent allergic rhinitis. The present objective was to assess whether phototherapy is also safe and effective in persistent allergic rhinitis. Thirty-four patients with persistent allergic rhinitis were randomized into two groups; twenty-five subjects completed the study. The Rhinolight® group was treated with a combination of UV-B, UV-A, and high-intensity visible light, while the placebo group received low-intensity visible white light intranasal phototherapy on a total of 13 occasions in 6 weeks. The assessment was based on the diary of symptoms, nasal inspiratory peak flow, quantitative smell threshold, mucociliary transport function, and ICAM-1 expression of the epithelial cells. All nasal symptom scores and nasal inspiratory peak flow measurements improved significantly in the Rhinolight® group relative to the placebo group and this finding persisted after 4 weeks of follow-up. The smell and mucociliary functions did not change significantly in either group. The number of ICAM-1 positive cells decreased non-significantly in the Rhinolight® group. No severe side-effects were reported during the treatment period. These results suggest that Rhinolight® treatment is safe and effective in persistent allergic rhinitis.

Keywords Intercellular adhesion molecule-1 expression · Intranasal phototherapy · Mucociliary clearance · Nasal inspiratory peak flow · Persistent allergic rhinitis · Rhinolight®

Introduction

Allergic rhinitis (AR) has become the most common chronic disease worldwide [1, 2], with over 500 million diagnosed cases. The WHO data suggest that half of the population of Europe may well become hay-fever sufferers by 2015 in consequence of explosive rise in incidence. Studies in Hungary have similarly reported a significant increase in prevalence [3, 4]. The social and economic importance is immense as severe and/or persistent cases are associated with an increased prevalence of asthma and with marked deteriorations in nighttime resting and daytime activities, and a resultant decline in the quality of life.

Currently, the most successful way to alleviate the harmful consequences is to apply effective treatment modalities. Allergic Rhinitis and its Impact on Asthma (ARIA), compiled in cooperation with the WHO, summarizes the latest knowledge on the issue, defines the diagnostic and therapeutic principles, analyses the risks and courses of accompanying diseases, and presents alternatives for the treatment of the disease [1, 2, 5, 6]. Oral antihistamines, nasal steroids, and, in some selected cases, immunotherapy provide the basis of progressive treatment adjusted to the grades of severity. The diverse appearance forms of the disease, the presence of individual genetic and environmental factors, and the occurrence of therapy-

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resistant cases reflect the need for the development and introduction of new treatment options. A number of paramedicinal products have been advocated, but their applicability awaits confirmatory evidence [6]. The authors have studied the literature about the other two methods of rhinophototherapy: Allergy Reliever SN206 and the Bionase device, but they have no personal experience with them. Bionase (Syro Technologies Ltd., Jaffa, Israel) is a device which emits a visible red light at a single wavelength of 660 ± 3 nm [7].

Allergy Reliever SN206 (Lloyds Pharmacy Ltd, Coventry, UK) emits infrared light delivering 0.54 J/cm^2 per a 3-min cycle. The manufacturer claims that the 652- and 940-nm infrared light delivered via the nasal probes suppresses release of histamine promotes and increased blood flow, respectively [7].

The significant local and systemic immunosuppressive effect of phototherapy has been known for decades [8–10]. Methods of phototherapy [ultraviolet (UV) irradiation and visible light (VIS)] are widely used for the treatment of various inflammatory, immune-mediated skin diseases, e.g., atopic dermatitis, psoriasis, and vitiligo. In a prospective randomized clinical trial, Tatar et al. found that rhinophototherapy plus medical therapy was better than purely medical therapy in patients with persistent and moderate/severe allergic rhinitis with respect to quality of life and symptoms improvement [11].

The first in vitro and then in vivo studies to assess the applicability of UV phototherapy in AR were conducted at the Department of Dermatology and Allergology in Szeged [12–15].

The efficacy of a combination of UV-B, UV-A, and high-intensity VIS (Rhinolight®) as intranasal phototherapy (RL) in seasonal AR was proven in a randomized, double-blind, placebo-controlled clinical study [13, 14, 16, 17] (Hungarian Medical Research Council (ETT-TUKEB) certification on the application of Rhinolight as a medical therapeutic procedure, File No.: 351/KO/02, Certificate No: 60008/20/ETT/2002). However, the effect of phototherapy in persistent AR has not yet been studied.

Objectives

The goal of the present randomized, double-blind, placebo-controlled, prospective clinical study was to establish the efficacy and safety of RL in the treatment of PAR. Determination of quantitative changes in the clinical symptoms, the nasal inspiratory peak flow (PNIF) parameters, the smelling ability, and the mucociliary function served as primary endpoints. The secondary endpoint was a comparison of the quantity of oral antihistamine (levocetirizine) taken by the patients during the study in the RL and the placebo groups. Another secondary endpoint was an assessment of the duration of the therapeutic effect of phototherapy. The follow-up was based on the nasal symptoms collected in the patient's diary and the PNIF changes.

Materials and methods

Between November and March, 34 patients with moderate or severe PAR were enrolled and randomized. Allergy to house dust mite and mould was confirmed with a specific immunoglobulin E (IgE) or prick test.

The patients enrolled were randomized into RL and placebo groups in a 2:1 ratio, respectively (visit 1). Nine patients (seven in the RL group and two in the placebo group) dropped out because of their poor compliance or withdrawal, thus 25 patients (fourteen in the RL group and eleven in the placebo group) completed the study (female/male ratio = 7/18; average age 34.6 years); data from the drop-outs are not included in the evaluation. Patients who were taking drugs (i.e., photosensitizers, non-steroidal anti-inflammatory drugs, and antibiotics) were excluded. Washout periods for these drugs (nasal or systemic steroids: 1 month; antihistamine: 2 weeks; oral or intranasal decongestants: 2 weeks; leukotriene antagonists: 1 month) were strictly considered.

Enrolment, randomization, and follow-up visits took place at the Department of Otorhinolaryngology and Head and Neck Surgery, while the phototherapy and the laboratory evaluation of nasal mucosa samples were performed at the Department of Dermatology and Allergology. All the treatment visits were performed at the department by a highly trained assistant. The subjects were in the prone position. Figure 1 shows the device for phototherapy. The probe of the light source was inserted into the right nostril first and then into the left one. The light was spread over the mucosal surface evenly by constant and gently movements within the nose. The subjects were scheduled for eight treatment visits. Treatment duration was 2 min, 2 min 15 s,

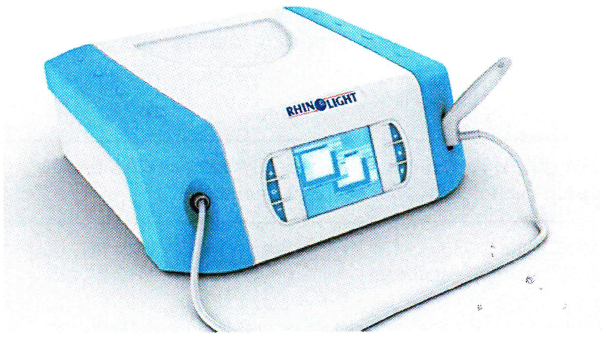

Fig. 1 Rhinolight device (Rhinolight Ltd., Szeged, Hungary)

2 min 30 s, and 2 min 45 s on Treatment Visit 1, Treatment Visit 2, Treatment Visit 3, and Treatment Visit 4, respectively, and 3 min for the remaining treatment visits.

The target population comprised patients with symptom scores of 4 or more on a VAS scale of 0–10 for at least two symptoms (one of which was either nasal obstruction or rhinorrhoea) during 4 consecutive days (moderate or severe PAR).

The patients received a total of 13 intranasal treatments during 6 weeks (three times in week 1 and then twice weekly for 5 weeks). On a random basis, in a double-blind manner, 2/3 of the patients received RL treatment, in a dose of 1.6–2.7 J/cm^2/nostril/treatment (RL).

In the other group (placebo group), low-intensity VIS was administered. Low-intensity VIS was achieved by insertion of a special light filter (Schott GG420). Patients had medical check-ups by an ENT specialist on week 3 (visit 2), 24 h after the last treatment (visit 3), and one month later (visit 4) (Table 1).

During the run-in period, patients recorded their nasal symptoms in the morning and evening, and scored their nasal symptoms on the basis of the preceding 12 h (on a VAS scale of 0–10).

During the treatment and follow-up periods, patients kept a symptom diary twice a day, immediately after waking up and before going to bed, based on the previous 12 h (rhinorrhoea, nasal itching, sneezing, and nasal obstruction on a VAS scale of 0–10). For the examination of nasal breathing, measurements were made of PNIF, a stable, well-reproducible, fast, and cost-effective method which can easily be learnt by the patient [18]. Patients measured the flow twice a day in their homes (the highest value of three measurements was recorded) with a Youlten (Clement Clark, England) instrument.

Application of supplementary medication, i.e., oral antihistamine (levocetirizine 1 × 5 mg/day), side-effects, and adverse events were also recorded.

For quantitative assessment of the smell threshold, the standardized Smell Threshold Test developed by the University of Pennsylvania was used. The threshold was determined by stimulating the olfactory nerve with a standardized solution series of phenylethylalcohol, separately in each nostril, in several steps. The average determined threshold concentration of each nostril was then compared with the average for the age group in the healthy population [19].

The mucociliary transport function was measured by means of a saccharin test. Sodium Saccharin (3 × 3 mm) is placed on the anterior surface of the inferior nasal concha. The saccharin first dissolves in the mucus and undergoes mucociliary transport to the pharynx, where it generates a pronounced sweet flavour. The time passing is called the saccharin time, which correlates well with the mucociliary function [20].

Eighteen patients consented to nasal mucosal sampling for determination of the intracellular adhesion molecule 1 (ICAM-1) expression of the nasal mucosal epithelial cells. ICAM-1 is a very sensitive marker of nasal mucosal inflammation in AR [21, 22] and is, therefore, suitable for objective determination of the efficacy of intranasal phototherapy. Nasal mucosal scrapings were obtained from the anterior part of the inferior nasal concha with a Rhinoprobe® Nasal cytology curette which was exclusively

Table 1 Course of the study

Evaluation	Screening	Inclusion (visit 1)	Treatment phase weeks 1–6	Treatment phase, end of week 3 (visit 2)	24 h after last treatment (visit 3)	1-month follow-up visit (visit 4)
Informed consent	X					
Inclusion/exclusion criteria	X	X				
Pregnancy test		X			X	
Nasal symptom score (0–10)		X	X	X	X	X
Quantitative smell test		X			X	X
Mucociliary transport (saccharin test)		X			X	X
ENT physical examination	X			X	X	X
PNIF	X	X	X	X	X	X
Nasal scraping		X			X	X
Recording of adverse events			X	X	X	X
Drugs	X	X	X	X	X	X

produced for this purpose [23]. Samplings were obtained before start of treatment (visit 1), after completion of the treatment period (visit 3) and at the end of the follow-up phase (visit 4). Seven of the eighteen patients received placebo, and eleven received RL treatment. The findings at visits 3 and 4 were compared with those at visit 1.

Nasal mucosal epithelial cells were used for ICAM-1 staining: Nasal mucosa samples were centrifugated, and smears were prepared from the cellular sediment. The cells were then fixed in acetone and stored at 20 °C. After rinsing with a phosphate buffer and then a TBST (Tris-Buffered Saline + 0.1% Triton X) solution, the specimens were blocked for 30 min in TBST containing 0.5% bovine serum albumin, and subjected to double fluorescent staining. The anti-ICAM-1 antibodies (monoclonal anti-human ICAM-1 Alexa Fluor 647, Santa Cruz Biotechnology, 10410 Finnell Street, Dallas, TX 75220 USA) were diluted 1:50. The specimens were also stained for cytokeratin (monoclonal anti-mouse cytokeratin 5/8 Alexa Fluor 488, Santa Cruz Biotechnology, 10410 Finnell Street, Dallas, TX 75220 USA) to distinguish epithelial cells unequivocally. The anti-cytokeratin antibodies were used in a 1:50 dilution. For each sample and sampling time, isotype controls were applied to establish the specificity of the stainings. The sections were incubated overnight at 4 °C. The following day, after multiple rinsing and cell core staining with 4′,6-diamidino-2-phenylindole (Sigma-Aldrich Chemie GmbH, Industriestrasse 25, CH-9471 Buchs SG, Switzerland), the sections were mounted with Fluoromount G. The stained sections were evaluated with the Tissue FAXS (TissueGnostics GmbH, Taborstrasse 10/2/8, A-1020 Vienna, Austria) method. At least ten pictures (from spots deemed suitable) were taken from each section with a Zeiss Axio Imager microscope equipped with a PCO PixelFly camera. The images were assessed with the image analysis software of the Tissue FAXS system (TissueQuest, TissueGnostics GmbH). The number and percentage of ICAM-1 and cytokeratin 5/8-positive cells of each sample were determined relative to the isotype control samples [21].

Statistical analysis

The effects of RL treatment as compared with placebo, and the changes in time at the end of the treatment and the follow-up in each group as compared with the baseline were assessed by Repeated-Measures ANOVA. To confirm differences between the RL and placebo groups at different stages, Fischer LSD (Post hoc) tests were performed (Table 2) at visits 3 and 4.

Results

Both the initial morning and evening nasal symptom scores improved significantly in the two groups by the end of the treatment compared with baseline ($p < 0.05$), and this was observed during the 1-month follow-up (Table 2; Fig. 2).

By the end of the treatment phase, the morning scores for sneezing ($p = 0.034$), rhinorrhoea ($p = 0.0019$), nasal obstruction ($p = 0.021$) and the calculated total nasal score (TNS) ($p = 0.019$) and PNIF ($p = 0.0019$), and the evening scores for sneezing ($p = 0.017$) and PNIF ($p = 0.0077$) demonstrated a significant improvement in the RL group relative to the placebo group. By the end of the 4-week follow-up, a significant improvement was seen in the morning and evening scores for nasal itching ($p = 0.004$ and $p = 0.0003$, respectively), the evening rhinorrhoea score ($p = 0.0034$), and the TNS ($p = 0.0017$) in the RL group. By the end of the follow-up, there was no

Table 2 Average changes in nasal symptoms and PNIF at the end of the treatment phase (week 6), and the follow-up (week 10) as compared with the pretreatment scores (*M* in the morning, *E* in the evening)

	Week 6		RL vs placebo	Week 10		RL vs placebo
	RL	Placebo	*p*	RL	Placebo	*p*
Sneezing_M	−2.16	−1.44	0.03	−1.97	−1.43	0.12
Itching_M	−2.04	−1.95	0.78	−2.40	−1.47	0.00
Rhinorrhoea_M	−2.46	−1.38	0.00	−3.16	−1.75	0.00
Obstruction_M	−2.24	−1.52	0.02	−3.16	−1.99	0.00
TNS_M	−8.84	−6.30	0.02	−10.62	−6.66	0.00
PNIF_M	19.31	6.79	0.00	27.28	11.82	0.00
Sneezing_E	−2.36	−1.57	0.02	−2.35	−1.72	0.06
Itching_E	−2.28	−1.95	0.32	−2.73	−1.53	0.00
Rhinorrhoea_E	−2.07	−1.54	0.10	−2.93	−1.99	0.00
Obstruction_E	−1.69	−1.47	0.49	−2.47	−1.91	0.08
TNS_E	−8.38	−6.54	0.08	−10.47	−7.19	0.00
PNIF_E	20.85	11.56	0.01	28.14	13.30	0.00

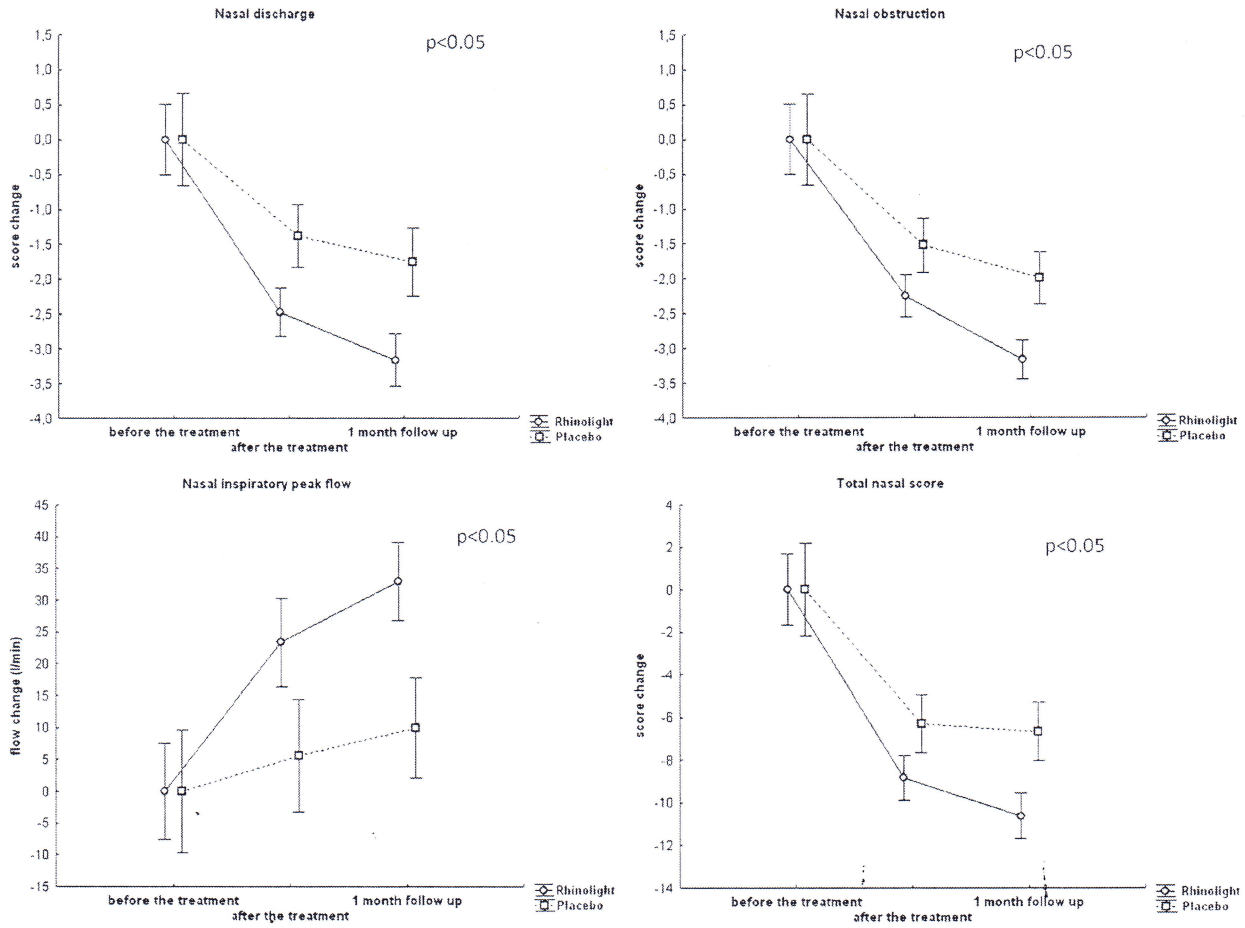

Fig. 2 Changes in PNIF and nasal symptoms (nasal obstruction, rhinorrhoea, and changes in TNS) in the morning: relative to the baseline, at the end of treatment (week 6), and the follow-up period (week 10) (created with MS Office)

significant difference between the morning and evening sneezing scores, both of which had improved significantly ($p = 0.12$ and $p = 0.077$, respectively).

The evening nasal obstruction proved to be the most resistant symptom. Although it improved considerably, it did not improve significantly as compared with the placebo group at any time examined.

The measured mucociliary function and quantitative smell threshold data exhibited considerable variation and no significant change was observed either in time or in intergroup comparisons ($p > 0.05$).

The permitted levocetirizine consumption per person did not differ significantly in the RL group (4.21 tbl/person/treatment cycle) and in the placebo group (3.45 tbl/person/treatment cycle) ($p > 0.05$).

The number of ICAM-1-positive cells was appreciably lower in the RL group than in the placebo group even at visit 3 and the difference became more marked at visit 4, yet it did not reach a significant level at any time (Fig. 3).

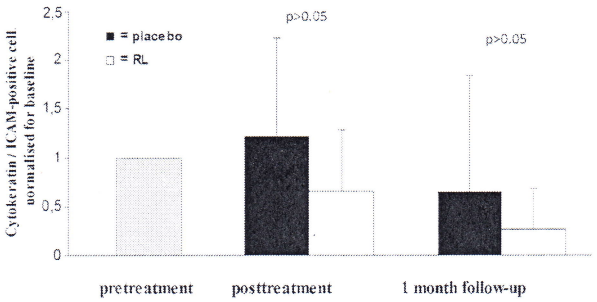

Fig. 3 Proportions of ICAM-1-positive cells in the nasal mucosa in the RL and placebo groups (created with MS Office)

No severe side-effects were found. Three patients in the RL group reported mild dryness of the nasal mucosa, which disappeared in a few days with the use of Coldastop™ nasal drops. Two patients in each group experienced mild nosebleed when blowing the nose; this was not directly treatment-related, and did not require any particular treatment. Temporary and spontaneously resolving nasal pain

occurred in three patients in the RL group, and in two patients in the placebo group, while headache and diarrhoea occurred in one patient in each group. There was no statistically measurable difference between the frequencies of the side-effects in the two groups.

Chi-square and two-tailed Fisher's exact test proved that the light therapy had no significant effect to the number of drop-outs ($p = 0.249$ and $p = 0.4267$, respectively; $p > 0.05$).

Discussion

More than 70% of Rhinolight® light fall into the range of VIS. UV-A light emission accounts for <25% and UV-B for <5% of the total light [10, 11, 14, 15]. Clinical studies have revealed that RL phototherapy inhibits antigen-induced histamine release in mast cells, and it induces apoptosis in T-lymphocytes and eosinophil cells, thus the number of eosinophil cells and the eosinophil cationic protein and interleukin-5 levels will be reduced [9, 14]. An earlier randomized, placebo-controlled, double-blind study demonstrated that RL treatment is effective in the treatment of ragweed-induced seasonal AR [16, 17]. The present investigation was designed to establish, whether RL can be used safely and effectively in moderate or severe PAR.

The symptom diary kept by the patients served as the basis for the treatment assessment. The records of the symptoms for the preceding 12 h separately characterized the severity of symptoms during the daytime (activity) and night (resting) periods. Data collection twice a day promoted the sensitive follow-up of the daily, weekly, and monthly changes, and the interpretation of the individual (occasionally markedly different) data.

The clinical (nasal) symptom scores in these PAR patients improved significantly as the treatment proceeded in both the RL and the placebo groups. The significant improvement in the placebo group may be explained by the fact that the continuous medical attendance (a total of 13 phototherapy sessions, 4 medical visits and, whenever necessary, repeated contact by phone and psychological guidance) had a significant positive impact on the subjective symptoms, too. By the end of the treatment and follow-up periods, the RL treatment proved to be significantly more effective than placebo light as related to the morning nasal obstruction, rhinorrhoea and calculated TNS values, and both the morning and evening PNIF (Table 2; Fig. 2). The differences between the two treatment modes (significance levels) further increased for all the above symptoms and PNIF by the end of the follow-up. This latter phenomenon can be explained either by the gradual disappearance of the placebo effect of treatment in the follow-up period or by the efficacy of RL treatment extending beyond the treatment period. These presumptions are confirmed by the fact that certain symptom scores (nasal itching in the morning and evening, and rhinorrhoea in the evening) and the evening TNS significantly differed between the RL and placebo groups by the end of the follow-up period. The morning and evening sneezing scores improved by the end of the treatment in the RL group, but its degree proved to be non-significant by the end of the follow-up period. The evening nasal obstruction proved to be the most resistant symptom: its change did not reach the level of significance by the end of either the treatment or the follow-up period. However, the objective measurement of nasal breathing with the PNIF values indicated that the treatment was effective in the evening hours, too. The frequent contradiction between the subjective sensation of nasal obstruction and the objective parameters reflecting nasal breathing (e.g., PNIF values) has long been known [24].

We observed similar results previously in ragweed allergy patients, when the 4-week RL treatment proved to be significantly more efficient than placebo on all nasal symptoms and the TNS values, except for nasal obstruction [13, 14, 16, 17]. In our current study, the sensitivity of recorded changes in symptoms is significantly reduced by the well-known fact that the symptoms are of lower intensity on average in patients with persistent moderate allergy or severe allergy as compared with seasonal (e.g., ragweed) AR. Patients find it more difficult to evaluate the less extensive changes during the treatment. The improvement of the recorded symptom scores exceeding 50% in the placebo group may suggest the biological efficacy of low-intensity VIS, and this might question its applicability as placebo light. However, the previous in vitro studies on cell cultures unequivocally proved the therapeutic difference of RL and VIS with regard to the main apoptosis-inducing therapeutic effect [9, 14]. The results of these basic studies encouraged us to apply the VIS treatment as placebo both earlier and in the present work.

Our previous safety studies aimed at the determination of the extent of UV-B-induced DNA damage and the risk of carcinogenicity [15, 25]. The results of Koreck et al. suggest that UV damage induced by intranasal phototherapy is efficiently repaired in nasal mucosa [15]. Mitchel et al. observed significant levels of DNA damage immediately after treatment and efficient removal of the damage within a few days, but no residual damage was seen in human subjects exposed to multiple UV-B treatments several weeks after the last treatment [25]. This study was the first to allow the examination of the smelling ability in a standardized manner. Smelling is a physiological function of the neuroectodermal endonasal epithelial structure, which was exposed during the treatment [19, 26, 27]. We

observed a tendency for the smell function to improve in response to the RL treatment, but this did not reach the level of significance. The low number of cases and the high variability made the assessment difficult. The improvement observed can primarily be attributed to the alleviation of the allergy symptoms [28, 29]. The fact that no decrease in smell function was observed in any of the patients indicates that intranasal RL treatment in the applied dose does not damage the olfactory epithelium. It is worth continuing the observations in seasonal-type AR, where comparisons in the asymptomatic and symptomatic periods before and after treatment in the various seasons can provide more accurate results. The impact of allergic symptoms on the smell function and the effects of RL on the olfactory epithelium can be examined with the exclusion of allergic symptoms. The effects of RL on the mucociliary function have also been examined for the first time. The saccharin time is a good indicator of the mucociliary function. A number of publications have dealt with the inhibition of this function by AR and with the regeneration of the reversibly damaged function after the termination of the seasonal symptoms [20]. We observed a non-significant improvement of the mucociliary clearance function in the RL group. Phototherapy did not affect either the mucociliary or the smell functions detrimentally, which is further evidence of the safety of the RL treatment. The improvement of the nasal symptoms indicates the decrease in the inflammatory process of the nasal mucosa and the decrease in oedema and secretion. In parallel with this, we expected improvements in smell and mucociliary functions, which, in fact, were well observed in individual patients, though in the overall group, the changes were not significant.

The number of ICAM-1-positive cells decreased in the RL group relative to the placebo group. The decline in the ICAM-1 expression of the olfactory epithelium in the RL group implies a decrease in the inflammatory process, which coincides with the decrease in allergic symptoms, though this difference is statistically not significant. The comparatively high deviation may have been due to the low number of patients enrolled.

It has been observed clinically that if the medical treatment (local steroid and/or antihistamine) of PAR patients is suspended, they become more susceptible to upper-airway infections [2]. In this study, the treatment period unfortunately overlapped with an influenza pandemic, and more than a quarter of the randomized patients had to be excluded because of upper-airway infection.

Nasal dryness was the only treatment-specific side-effect in the RL group [13, 15, 16, 25], but it was not observed in the placebo group. The nasal dryness was not severe, and did not increase the likelihood of nasal bleeding. Our previous studies and clinical experience indicated a 50–70% incidence of nasal dryness during the 2-week three sessions per week treatment. Regular treatment of the nasal mucosa with Coldastop^{TM} nasal drops during an elongated, only two sessions per week treatment reduces the probability of nasal dryness.

In view of the pronounced placebo effect, analysis of the differences during the 4-week follow-up is particularly important. When the placebo effect is no longer exerted, a significant difference can be seen between the two groups. Statistical evaluation is difficult because of the low number of cases. A larger, multicenter study is necessary to confirm our preliminary results and further assess the efficacy and safety of intranasal phototherapy in PAR.

In cases involving severe symptoms, its special mechanism of effect and narrow side-effect profile permit the ready combination of RL phototherapy with other therapeutic modalities already applied. Our study suggests that RL phototherapy may represent even an effective monotherapy for the treatment of PAR.

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Compliance with ethical standards

Conflict of interest The authors do not have any financial interest in relation to the work or any financial support provided by companies toward the completion of the work.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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