Rhinophototherapy: A new therapeutic tool for the management of allergic rhinitis

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Background: Phototherapy has a profound immunosuppressive effect and is able to inhibit hypersensibility reactions in the skin.

Objective: We evaluated whether phototherapy using a combination of UV-B (5%), UV-A (25%), and visible light (70%), referred to as mUV/VIS, is effective in treating allergic rhinitis.

Methods: We conducted a randomized, double-blind study, in 49 patients with hay fever. The study was performed during the ragweed season. Each intranasal cavity was illuminated 3 times a week for 3 weeks with mUV/VIS or with low-intensity visible light. Symptom scores, inflammatory cells, and their mediators were assessed in nasal lavages. *In vitro* effects of mUV/VIS irradiation on T-cell and eosinophil apoptosis and its inhibitory effect on mediator release from basophils were examined.

Results: Rhinophototherapy was tolerated well and resulted in a significant improvement of clinical symptoms for sneezing ($P < .016$), rhinorrhea ($P < .007$), nasal itching ($P < .014$), and total nasal score ($P < .004$). None of the scores improved significantly in the control group. Scores for nasal obstruction slightly improved after mUV/VIS treatment and significantly increased in the control group ($P < .017$). In the nasal lavage, phototherapy significantly reduced the number of eosinophils and the level of eosinophil cationic protein and IL-5. *In vitro* irradiation of T cells and eosinophils with mUV/VIS light dose-dependently induced apoptosis. Furthermore, mUV/VIS irradiation inhibited the mediator release from RBL-2H3 basophils.

Conclusion: These results suggest that phototherapy is an effective modality to treat allergic rhinitis and offer new options for the treatment of immune-mediated mucosal diseases. (J Allergy Clin Immunol 2005;115:541-7.)

Key words: *Allergic rhinitis, phototherapy, eosinophils, T cells, IL-5, apoptosis*

Allergic rhinitis is one of the most common health problems. It is a high-cost and high-prevalence disease with a major effect on the quality of life. It is also considered to be a risk factor for asthma.[1-3] 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.[4] All of these characteristics of allergic rhinitis highlight the need for effective new treatment options.

Allergic rhinitis is an allergen-induced, IgE-mediated inflammatory disease of the nasal mucosa.[5] The development of the disease is characterized by an initial sensitization phase to a specific allergen, when no clinical symptoms are present. At later time points, the encounter of the same allergen by sensitized individuals is followed by the elicitation of an specific immune response and the activation of effector mechanisms. Previous studies have established that a shift toward T_H2 cells plays a role in the initiation and maintenance of the disease.[6,7] Eosinophils, mast cells, and basophils are considered to be the mayor effector cells in hay fever.[8,9] After an allergen challenge, these cells release inflammatory mediators such as histamine, tryptase, leukotrienes, prostaglandins, cytokines, and eosinophil cationic protein (ECP), which are responsible for most of the pathological processes occurring within the nasal mucosa.[5,9-11] Phototherapy has a profound immunosuppressive effect, and phototherapeutic methods using both UV and visible light are therefore widely used

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Abbreviations used
ECP: Eosinophil cationic protein
l-VIS: Low-dose visible light
mUV/VIS: Mixed UV-B, UV-A, and visible light
SPT: Skin prick test
TNS: Total nasal score

for the therapy of various inflammatory skin diseases, including atopic dermatitis.[12-15] The major mechanisms of immunosuppression induced by the various forms of phototherapy in the skin involve the induction of apoptosis in infiltrating T cells, the reduction in the number and function of Langerhans cells, and the induction of immunomodulatory cytokines such as IL-10.[16-20] In a recent study, we have evaluated the effect of phototherapy on immediate-type hypersensitivity reaction by comparing the effects of different wavelengths on wheal formation in skin prick test (SPT) reaction. We found that irradiation with low doses of UV-B, UV-A, and visible light (mUV/VIS), was capable of significantly inhibiting the wheal formation even at suberythematous doses.[21] The same inhibition rate was documented only after higher erythematous doses of UV-B light and could not be obtained with UV-A or visible light irradiation. In a pilot study, we have also found that intranasal irradiation with medium doses of 308-nm UV-B laser resulted in improvement of clinical symptoms of hay fever.[22] It has been shown that there is a good correlation between SPT reaction and nasal symptoms in patients with hay fever and that reduced immediate skin sensitivity is observed after long-term successful immunotherapy.[23,24] Considering that phototherapy using combined wavelengths is successfully used in the treatment of severe atopic dermatitis and that allergic rhinitis and atopic dermatitis are characterized by several common pathogenic features, we sought to investigate whether phototherapy using mUV/VIS light may represent a therapeutic alternative in patients with allergic rhinitis.

We report here that rhinophototherapy with mUV/VIS light significantly reduces the clinical symptoms of hay fever by acting at several points during the effector phase of the allergic process and might therefore serve as a new tool in the therapeutic arsenal for allergic rhinitis.

METHODS

Study design for rhinophototherapy

We conducted a randomized, double-blind study in patients with a history of at least 2 years of moderate to severe ragweed-induced allergic rhinitis that was not controlled by antiallergic drugs. Positive SPT results and an elevated level of ragweed-specific IgE antibody confirmed the diagnosis. The Ethical Committee of Szeged University approved the protocol. All patients gave their written informed consent. We excluded potential subjects from the study if they had any significant nasal structural abnormalities; had asthma, perennial rhinitis, or upper or lower respiratory infection within 4 weeks before the beginning of the study; or had used any of the following 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.

The patients were enrolled after the beginning of the ragweed season, when the pollen counts were greater than 50/m^3 in Szeged area. Seventy-two patients with allergic rhinitis were recruited to participate in the study. After the screening visit, 23 patients were excluded because they did not meet the inclusion criteria. Forty-nine patients were randomly assigned to receive either mUV/VIS irradiation in the active treated group (25 patients) or low-intensity visible light (l-VIS) in the control group (24 patients). Each intranasal cavity was irradiated 3 times a week for 3 weeks with increasing doses of either mUV/VIS (starting dose, 1.6 J/cm^2) or l-VIS (starting dose, 0.06 J/cm^2). Irradiations were performed with the same device (Rhinolight-mUV/VIS lamp [Rhinolight Ltd, Szeged, Hungary]; range: 310-600 nm; see Fig E1 in the Journal's Online Repository at www.mosby.com/jaci). l-VIS irradiation was obtained by using a Schott FG13 filter (Schott AG, Mainz, Germany). In the mUV/VIS group, the patients were treated with the same dose for 2 consecutive dates. Every third treatment day, the dose was raised by 0.25 J/cm^2. The top dose was 2.6 J/cm^2. During the course of the investigation, the only rescue medication allowed was cetirizine. Each patient kept a diary of daily symptoms on a scale of 0 to 3 (0 indicating no symptoms and 1, 2, and 3 indicating mild, moderate, and severe symptoms, respectively) for nasal obstruction, nasal itching, rhinorrhea, and sneezing. An independent investigator examined the patients weekly and performed nasal lavages. At these weekly visits, patients also scored their symptoms. Total nasal score (TNS), 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 allergic rhinitis, was also calculated. Nasal obstruction was also evaluated by using acoustic rhinometry. At the end of the protocol, the overall efficacy of the therapy was assessed on a scale from 1 to 4 (with 1 corresponding to significant, 2 moderate, 3 slight, and 4 no global improvement of symptoms).

Nasal lavage

Nasal lavage was performed by instilling 5 mL prewarmed (37°C) normal saline solution into each nasal cavity, as previously described.[25] The samples were placed immediately on ice and were processed within 2 hours. The nasal lavage fluid was passed through a 40-μm nylon mesh filter (BD Biosciences, Bedford, Mass), and the filtrate was centrifuged at 420*g* for 10 minutes at 4°C. The supernatant was separated from the pellet. A portion of the supernatant (5 mL) was concentrated by using Centriprep concentrators (Amicon; Millipore, Bedfore, Mass) with a molecular cutoff of 3000. A 4× concentration was achieved. The samples were stored at −70°.

Cytologic analysis

The pellet from the nasal lavage samples was resuspended in 0.5 mL PBS containing 0.1% human serum albumin. Two cytospin slides were performed from each sample by using 100-μL aliquots. The slides were fixed with methanol and stained with May-Gründwald-Giemsa for cell differential counts. At least 200 cells were counted in each slide by a reader blind to which treatment had been received. Cells were classified as eosinophils, neutrophils, mononuclear cells, and epithelial cells.

Cytokine assays

IL-4, IL-5, and IL-10 levels in concentrated nasal fluids were quantified by ELISA kits (Quantikine; R&D Systems, Minneapolis, Minn) according to the manufacturer protocols (sensitivity of the