

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 hypersensitivity 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 major 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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Supported by a grant of the Hungarian Ministry of Health (ETT-419/2003) and a grant of the Hungarian Ministry of Education (OMFB-01620) to Dr Kemeny.

Disclosure of potential conflict of interest: Lajos Kemeny, Attila Dobozy, Zsolt Bor, Gabor Szabo, and Ferenc Ignacz are cofounders of a company that will produce the light source for treatment and have submitted a patent application on this topic (patent pending).

Received for publication June 8, 2004; revised November 3, 2004; accepted for publication November 4, 2004.

Available online January 4, 2005.

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0091-6749/\$30.00

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doi:10.1016/j.jaci.2004.11.005

Abbreviations used

ECP:	Eosinophil cationic protein
I-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/m³ 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 (I-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/cm²) or I-VIS (starting dose, 0.06 J/cm²). 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). I-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/cm². The top dose was 2.6 J/cm². 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- μ m nylon mesh filter (BD Biosciences, Bedford, Mass), and the filtrate was centrifuged at 420g 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, Bedford, Mass) with a molecular cutoff of 3000. A 4 \times concentration was achieved. The samples were stored at -70°C.

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- μ L 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

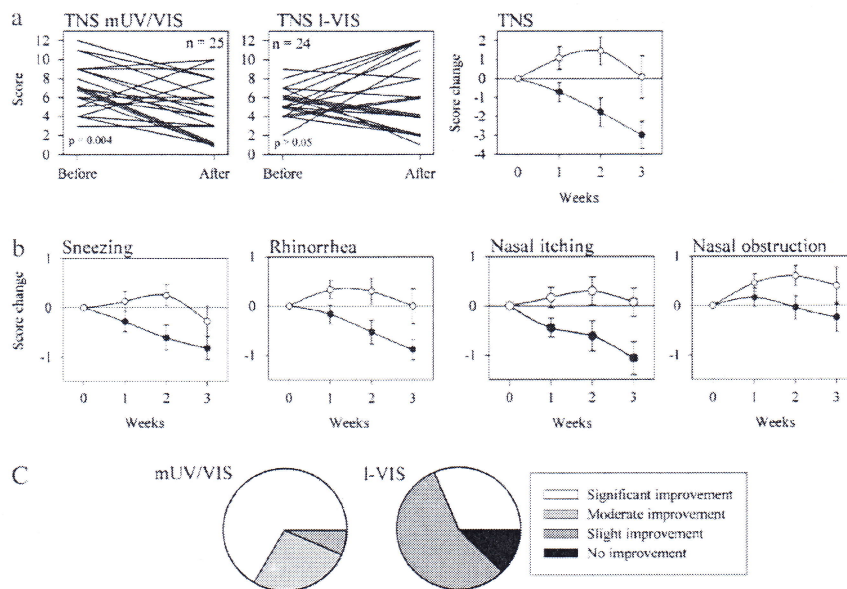


FIG 1. Effects of phototherapy on clinical symptoms of allergic rhinitis. TNS values before and after treatment in mUV/VIS irradiated and control groups (A). Changes from mean baseline values for TNS (A), sneezing, rhinorrhea, nasal itching, and nasal obstruction (B) in mUV/VIS-irradiated and control groups. Scoring of the global outcome of treatment in mUV/VIS irradiated and control groups (C).

assays was less than 0.13 pg/mL for IL-4, less than 3.0 pg/mL for IL-5, and less than 3.9 pg/mL for IL-10). We also measured ECP levels in nasal lavage samples by ELISA kit (sensitivity of the assay was 0.125 ng/mL; MBL, Nagoya, Japan). All of the values reported have been converted to levels in unconcentrated nasal fluid lavage.

In vitro irradiation and flow-cytometric detection of T-cell, eosinophil, and RBL-2H3 cell apoptosis

We isolated eosinophils by a negative immunomagnetic procedure, the StemSep™ procedure (StemCell Technologies, Vancouver, British Columbia, Canada), and cultured them in the presence of IL-5 (Sigma, St Louis, Mo). PBMCs were isolated by Ficoll density-gradient centrifugation. The rat basophil leukemia cell line RBL-2H3 was cultured as previously described.²⁶ Eosinophils, PBMCs, and RBL-2H3 cells were irradiated with increasing doses of mUV/VIS (60, 120, and 240 mJ/cm²). Because only a part of the incident light penetrates in the tissues where immunologic active cells are present, the dosages used for *in vitro* studies might correspond to the *in vivo* situations.¹⁹ After 20 hours, the cells were stained with mAbs specific for Apo2.7 (phycoerythrin (PE)-conjugated; Immunotech, Marseille, France) and, in the case of PBMCs, also with antibodies specific for CD3 (fluorescein isothiocyanate [FITC]-conjugated; Dako, Glostrup, Denmark). Apoptosis of memory and naive T cells was also assessed by using antibodies specific for CD3 (allophycocyanin [APC]-conjugated), CD45RO (FITC-conjugated), and CD45RA (FITC-conjugated). Samples were analyzed with a FACSCalibur flow-cytometer (BD Biosciences, San Jose, Calif). In each case, 3 independent experiments were performed.

Irradiation of RBL-2H3 cells and β-hexosaminidase assay

The effect of mUV/VIS light irradiation on histamine release was investigated by using an *in vitro* model on RBL-2H3 cells in which the release of β-hexosaminidase from the cells correlated with

histamine release.²⁶ The assay was performed as described previously.²⁶ Briefly, we sensitized RBL-2H3 cells by incubating them with dinitrophenyl-specific IgE. The cells were irradiated by using increasing doses of mUV/VIS (15, 30, 60, 120, and 240 mJ/cm²) and were challenged with DNP-conjugated to BSA. After incubation for 2 hours, β-hexosaminidase release was determined by reading the optical density of the color reaction at 405 nm.

Statistical analyses

Differences in baseline characteristics of patients between the mUV/VIS and the control group were evaluated by using the Mann-Whitney rank-sum test. The Wilcoxon sum of ranks test was used to assess the statistical significance of clinical symptom changes and the overall efficacy. The all available data approach was applied. All analyzed data correspond to pollen counts higher than 50/m³. We used the Student *t* test to determine the significance of cell count and cytokine level changes. *P* values less than .05 were considered statistically significant.

RESULTS

Effects of phototherapy on clinical symptoms of allergic rhinitis

Forty-nine patients received intranasal phototherapy, either with mUV/VIS light (25 patients) or I-VIS (24 patients). The 2 groups did not differ in age, disease duration, or clinical scores at the beginning of treatment protocol (see Table EI in the Online Repository at www.mosby.com/jaci). TNS significantly decreased after mUV/VIS (*P* = .004) and slightly increased after I-VIS treatment (*P* > .05; (Fig 1, A). In the mUV/VIS group, the individual scores decreased compared with baseline for sneezing (*P* = .016), rhinorrhea (*P* = .007), and nasal itching (*P* = .014). The scores for nasal obstruction

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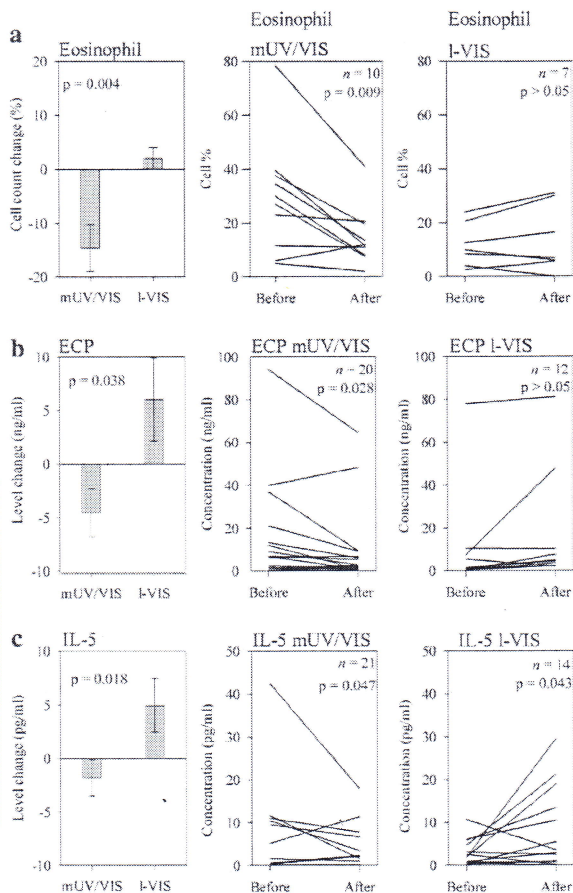


FIG 2. Effects of phototherapy on local inflammatory cells and mediators. Comparison of changes from mean baseline values for eosinophils (A), ECP (B), and IL-5 (C) in nasal lavages of mUV/VIS-treated and control groups. The percentage of eosinophils (A), the concentration of ECP (B), and IL-5 (C) in nasal lavages before and after treatment in mUV/VIS-irradiated and control groups.

improved slightly during phototherapy, but changes did not reach statistical significance ($P > .05$; Fig 1, B). In the control group, none of the scores improved significantly at the end of treatment. In fact, a significant increase was observed in the score for nasal obstruction ($P = .017$; Fig 1, B). No improvement of nasal obstruction was recorded by using acoustic rhinometry (data not shown). In the overall efficacy assessment at the end of the treatment, mUV/VIS proved to be significantly more efficient than l-VIS ($P = .004$; Fig 1, C).

The therapy was well tolerated. The only side effect was dryness of the nasal mucosa, which occurred in all patients from the mUV/VIS group and in 6 patients from the control group. All patients except 1 from the mUV/VIS group scored the dryness as mild. In these patients, dryness was controlled with emollients. In 1 patient who scored the dryness as severe, the treatment was stopped.

The dropout rates in the active treatment versus the control group did not differ. In the mUV/VIS group, we had 5 dropouts (1 because of lack of efficacy, 1 because of

dryness of the mucosa, 1 for lack of compliance, and 2 because of a modified holiday schedule). In the control group, we had 4 dropouts (2 because of lack of efficacy, 1 for lack of compliance, and 1 because of an upper respiratory infection). In the control group, a significantly higher consumption of rescue medication was recorded compared with the mUV/VIS group (93 tablets in the control group vs 57 tablets in the mUV/VIS group).

Effects of phototherapy on eosinophils and inflammatory mediators in the nasal lavage

In the mUV/VIS group the percentage of eosinophils and the ECP level in the nasal lavage decreased significantly during therapy ($P = .009$ and $P = .028$, respectively), whereas both the eosinophil cell count and the ECP level increased slightly in the control group ($P > .05$; Fig 2, A and B).

The nasal fluid IL-5 levels decreased after treatment in the mUV/VIS group ($P = .047$) and increased in the control group ($P = .043$); in change from the mean baseline values, the difference between the 2 groups was statistically significant ($P = .018$; Fig 2, C). A slight decrease of IL-4 levels was observed in nasal lavages from patients treated with mUV/VIS light and a slight increase in the samples from the control group, but changes did not reach statistical significance ($P > .05$).

In the majority of the concentrated nasal lavage samples, the IL-10 level was below the detection limit of the kit.

Effects of phototherapy on T-cell, eosinophil, and RBL-2H3 cell apoptosis

mUV/VIS irradiation induced a dose-dependent increase in both apoptotic T cells (Fig 3) and eosinophils (Fig 4). No proapoptotic effect of l-VIS irradiation was observed in either T cells or eosinophils. Moreover, a dose-dependent increase of both CD3⁺CD45RO⁺ and CD3⁺CD45RA⁺ was observed after mUV/VIS irradiation (see Fig E2 and Fig E3 in the Online Repository at www.mosby.com/jaci). RBL-2H3 cells were resistant to mUV/VIS-induced apoptosis (see Fig E4 in the Online Repository at www.mosby.com/jaci).

Effect of phototherapy on mediator release from RBL-2H3 cells

We found that after mUV/VIS irradiation, the β -hexosaminidase release was inhibited (Fig 5). Even low doses of mUV/VIS (15-60 mJ/cm²) induced a significant decrease of β -hexosaminidase release, and higher doses (240 mJ/cm²) had a complete blocking effect. In contrast, no inhibitory effect of l-VIS irradiation was observed.

DISCUSSION

The goal of our study was to assess the efficacy of phototherapy in allergic rhinitis. Our data reveal that mUV/VIS significantly suppressed the clinical symptoms of allergic rhinitis. Phototherapy locally reduced the

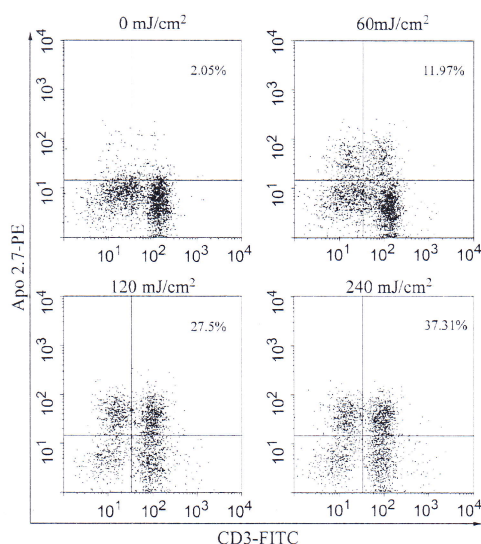


FIG 3. *In vitro* effect of mUV/VIS light on T lymphocytes. Peripheral mononuclear cells were irradiated with increasing doses of mUV/VIS. Apoptosis was detected by using monoclonal antibodies specific for Apo 2.7. Three different experiments were performed. In each case, 20,000 events were acquired. Results of one of these experiments are shown. A dose-dependent increase of apoptotic T cells was detected.

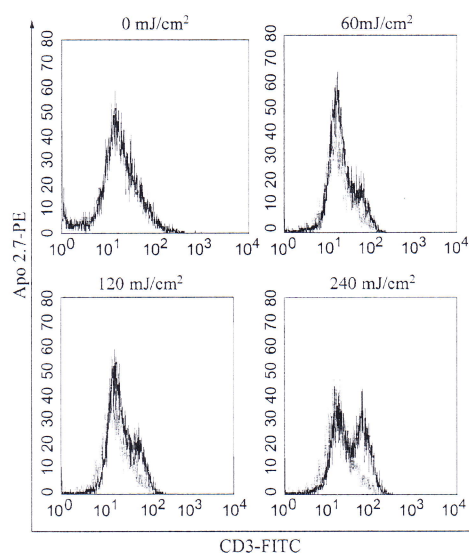


FIG 4. *In vitro* effect of mUV/VIS light on eosinophils. Human eosinophils separated from peripheral blood were cultured in the presence of IL-5. The cells were irradiated with increasing doses of mUV/VIS. Apoptosis was detected by using mAbs specific for Apo 2.7. In each case, 20,000 events were acquired. Three different experiments were performed. Results of one of these experiments are shown.

number of inflammatory cells and the level of mediators. Rhinophototherapy was tolerated well and significantly reduced the clinical scores for sneezing, rhinorrhea, and nasal itching as well as the TNS.

Recently, we could show in a pilot study that intranasal phototherapy with 308-nm xenon chloride laser was effective in allergic rhinitis.²² The results presented here confirm that phototherapy is effective for the treatment of allergic rhinitis and suggest that the different wavelengths used in combination, as in mUV/VIS, have a synergistic effect, permitting the use of lower UV-B doses for successful treatment of allergic rhinitis.

We have also studied the mechanism by which phototherapy was able to inhibit the symptoms of allergic rhinitis. Allergic inflammation is associated with a shift in the cytokine balance toward a T_H2 predominance.⁷ Several data indicate that T_H2 cytokines (IL-5 and IL-4) are present in increased amounts in the nasal mucosa of patients with allergic rhinitis.^{6,7} IL-5 is a cytokine that promotes the maturation, activation, and prolonged survival of eosinophils, the main effector cells in hay fever.²⁷ The suppression of prolonged eosinophil survival induced by IL-5 is a potential therapeutic strategy for the resolution of allergic rhinitis. In our study, irradiation of the nasal mucosa resulted in a significant decrease in local IL-5. T lymphocytes are major sources of IL-5.²⁸ Thus, apoptosis of these cells after phototherapy might be the basis of the underlying mechanism of decreased IL-5 production. Memory T cells have an important role in the perpetuation and maintenance of allergic process. Apoptosis of these cells after phototherapy might have a long-term beneficial effect. Phototherapy also resulted in a decreased number

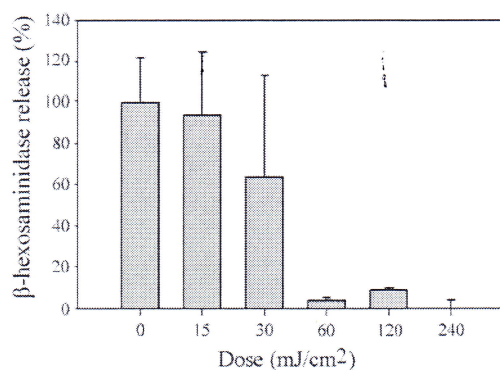


FIG 5. *In vitro* effect of mUV/VIS light on mediator release from RBL-2H3 cells. RBL-2H3 cells sensitized with DNP-specific IgE were irradiated by using increasing doses of mUV/VIS. The results were calculated as a percentage of total β -hexosaminidase release after correction for spontaneous release of unstimulated cultures. Results are expressed as the means \pm SEMs of 3 independent experiments.

of eosinophils and a decreased level of ECP in the nasal lavage fluid. This might be attributed to the direct proapoptotic effect of mUV/VIS on eosinophils and to the decreased local IL-5 level. Similar results concerning eosinophil, ECP, and IL-5 levels and T lymphocytes are observed after other well-established therapies of allergic rhinitis, such as topical glucocorticoids or immunotherapy.^{6,24,29,30} Allergic rhinitis is also accompanied by an elevated level of IL-4 in the nasal mucosa. IL-4 is essential in promoting the commitment of T-cell precursors to

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produce T_H2 cytokines, and it activates the IgE isotype switching of B cells.⁵ However, the role of IL-4 in modulating eosinophil survival and function is not yet clear. IL-4 could regulate the production of CCL11/eotaxin, a potent eosinophil chemoattractant promoting tissue eosinophilia, but it is also an inducer of apoptosis of peripheral blood eosinophils.^{31,32} The proapoptotic effect of IL-4 is more dramatic in eosinophils separated from atopic individuals compared with those from nonatopic subjects. Wedi et al³² have suggested that IL-4-mediated eosinophil apoptosis may be of physiological relevance if the eosinophil is not primed by the survivor cytokines (IL-5, IL-3, or GM-CSF). These data suggest that the quantitative relation of IL-4 and IL-5 produced during inflammation may determine the apoptosis rate of eosinophils at the site of allergic inflammation. Our study did not reveal significant changes in IL-4 levels in the nasal lavage samples. Similar results were reported after topical glucocorticoid therapy of allergic rhinitis.²⁵ Thus, the reduction of IL-5 in nasal mucosa after phototherapy together with the persistence of IL-4 might further promote phototherapy-induced eosinophil apoptosis.

Not only T cells and eosinophils but also mast cells and basophils have important roles in the effector phase of the allergic reaction.⁹ They are the principal source of different mediators and especially of histamine. The role of histamine in allergic rhinitis has been well studied and is mirrored by the wide use of antihistamines in the treatment of allergic rhinitis.³³ In our study, we demonstrated that mUV/VIS irradiation is able to inhibit mediator release from RBL-2H3 cells. It has been shown that β -hexosaminidase release after allergen challenge of RBL-2H3 cells passively sensitized to murine IgE correlates with histamine release and SPT results.²⁶ Several other agents used for the therapy of allergic rhinitis and asthma have been already tested in this *in vitro* model of histamine release and have been shown to be potent in inhibiting IgE-mediated histamine release.^{34,35} Our findings are in concordance with previous studies in which the inhibitory effect of UV-A and UV-B light on histamine release was assessed.³⁶ It has been shown that UV-A light significantly inhibited histamine release from human basophils and a human mast cell line and that UV-B light had an inhibitory effect only on mast cells.³⁷ The effect of *in vitro* UV-A irradiation of basophils is characterized by a biphasic dose-dependent action on histamine release: low doses are followed by a significant inhibitory effect; in contrast, high doses are followed by histamine liberation.³⁶ The use of mUV/VIS, which is characterized by low-dose UV-A and low-dose UV-B, is followed by a very strong inhibitory effect, and in fact, a complete blocking effect could be achieved at certain doses.

The data reported here demonstrate that phototherapy was able to inhibit the effector phase of the allergic reaction at multiple checkpoints. In contrast with antihistamines, which influence predominantly histamine-mediated features of the allergic process, phototherapy with mUV/VIS light has a different, more complex action spectrum, such as inducing T-cell and eosinophil apopto-

sis and suppressing the release of mediators like ECP and IL-5. This suggests that intranasal phototherapy might also be an alternative for patients with symptoms not controlled by antihistamines. Our data support this indication considering that all enrolled patients were nonresponders to conventional therapies, including the latest generation of antihistamines. In conclusion, our findings indicate that phototherapy represents an efficient therapeutic modality for the treatment of patients with allergic rhinitis.

We thank Annika Scheynius from Karolinska Institute, Stockholm, Sweden, for helpful discussions and critical reading of the manuscript.

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