Allergic rhinitis, although not life threatening, significantly affects the quality of the patient’s daily life. The three major steps in the treatment of the condition are avoidance of allergens, treatment of symptoms (in particular, antihistamines and topical nasal corticosteroids) and specific immunotherapy. Avoidance of the allergen is usually not possible and symptom relief is often limited, despite the availability of a number of pharmacological options. Specific immunotherapy demands a high level of cooperation on the part of the patient for at least 3 years. Endonasal phototherapy with the Rhinolight® device (Rhinolight Ltd, Szeged, Hungary) for the treatment of immunoglobulin E-mediated allergic rhinitis is a new option that utilizes the immunosuppressive effects of UV radiation. The method directs a combination of UV-B (5%), UV-A (25%) and visible light (70%) into the nasal cavity, and its effectiveness has been demonstrated in one double-blind, placebo-controlled study. The results of additional studies have been presented at various medical conferences and in abstracts. Reports in the literature confirm that phototherapy is a well-established and successful treatment of atopic dermatitis and other skin diseases.

**KEYWORDS:** allergic rhinitis • phototherapy • Rhinolight® • ultraviolet therapy

The severity of the symptoms are to be defined on the basis of their intensity and their effect on the patient’s quality of life:

- **Mild:** symptoms are present but do not impair quality of life
- **Moderate/severe:** symptoms are present and troublesome; quality of life is impaired

In the Allergic Rhinitis and its Impact on Asthma (ARIA) updates, a joint effort of the WHO and the Global Allergy and Asthma European Network (GA²LEN), specific immunotherapy (SIT) is the recommended treatment for the moderate-to-severe intermittent and persistent forms of AR. Apart from allergen avoidance, SIT is the sole causal therapeutic concept for the treatment of IgE-mediated allergic diseases.

**Role of immunotherapy in allergic rhinitis**

The effectiveness of SIT, both in the subcutaneous (SCIT) and sublingual (SLIT) application forms for the treatment of AR, has been confirmed in double-blind, randomized, placebo-controlled studies and in various...
meta-analyses [5,6]. Such studies have shown a high degree of effectiveness against tree-, grass- and cereal-pollen allergies, as well as against those caused by mugwort and ragweed. In the case of perennial allergies, a therapeutic effect has been shown against house dust mites and animal dander [7,8]. Worldwide, SIT for the treatment of allergic diseases is very common outside the USA and the UK. In an official report published in 2007, it was stated that in Great Britain, immunotherapy was not used to its full potential, the reason being partly historical – when early types of immunotherapy were administered, a number of patients had suffered anaphylactic shock [9].

The immunological mechanisms of SIT are not fully known. SIT induces clinical and immunological tolerance to the allergens employed, with a long-term effect that persists beyond the duration of treatment. The development of immunological tolerance is an active response on the part of the immune system, and involves a complex interaction between the allergen administered and the immune system. The success of the treatment is dependent on the quality of the allergen vaccine (immunological activity) and the duration of its application (the total dose of the allergen extract, administered for at least 3 years). Since the allergen extracts differ in terms of the manufacturing process, each manufacturer has its own in-house reference preparation (IHRP) to determine the immunological activity; they cannot be compared directly.

According to the present state of our knowledge, the major target cells of SCIT are T lymphocytes. Their function is inhibited by the activation of regulatory CD4+ T cells, which produce IL-10, TGF-β and mediate tolerance, and by the induction of anergy-reduced responsiveness with decreasing cytokine production, and proliferation after stimulation via the T-cell receptor [10–12]. The result, over the long term, is a shift in the immune response: a dominant TH2 response (e.g., IL-4, IL-5 and IL-13) is replaced by an enhanced TH1 response (IFN-γ) [12,13]. Secondly, the immunoglobulin production of the B lymphocytes changes with induction of the allergen-specific IgG and, in particular, IgG4 production, and possibly a slower reduction in allergen-specific IgE production. The function of effector cells, such as mast cells, and basophilic leukocytes or eosinophilic granulocytes, is inhibited [14]. The immunological mechanisms of SLIT seem to be similar to those of SCIT – with induction of tolerance via antigen-presenting cells (APCs) of the oral mucosa playing a central role [14,15]. Preserving contact of the allergen with the oral mucosa would appear to be critical for the efficacy of SLIT [16]. In comparison with SCIT, administration of an at least 50- to 100-fold subcutaneous dose is recommended for SLIT [17]. However, for SIT to be effective, cooperation on the part of the patient is necessary – he/she must undergo regular, usually monthly, injections in the case of SCIT, and daily administration of the allergen extract when SLIT is employed – and this regimen is generally maintained for a minimum of 3 years. The literature reports compliance figures of between 44 and 88% for SCIT, and between 76 and 97% for SLIT [18,19].

The risk of an anaphylactic reaction to SIT is feared by both physicians and patients alike. Fatalities and serious side effects have been reported both for SCIT and SLIT [20,21]. Although the risk of a serious reaction to SIT is low, the incidence of such reactions has increased since the introduction of standardized and more potent extracts [22]. New routes of application, for example, intralymphatic injection of allergens, are currently being investigated [23].

Rhinophototherapy

Recently, a rhinophototherapy device, Rhinolight® (Rhinolight Ltd, Szeged, Hungary), enabling the application of radiation comprising a combination of UV-B (5%), UV-A (25%) and visible light (VIS; 70%) to the nasal mucosa in AR patients has been developed. The utilization of UV radiation in medicine is nothing new and was first employed at the beginning of the 19th Century, when Finsen successfully applied phototherapy to heal lupus vulgaris [24]. Since then, phototherapy has been used in various modalities (broadband UV-B [290–320 nm], narrowband UV-B [311 ± 2 nm], 308 nm UV-B excimer laser, UV-A [320–400 nm], photosensitizer and UV-A [PUVA], combined UV-A/UV-B, high-dose UV-A1 [340–400 nm] and high-dose VIS [400–800 nm]) in the field of dermatology, for example, to successfully treat atopic dermatitis and numerous skin diseases [25]. UV radiation has a range of biological effects – including local and systemic immunosuppression and immunomodulation – but also undesired effects, such as induction of premature ageing of the skin and skin cancer [26]. The immunosuppressive effect of UV light is due to the induction of apoptosis [27,28], its influence on antigen presentation [29] and the suppression of surface molecules [30] that play a major role in antigen presentation, and the induction of immunosuppressive mediators [31,32].

The working group headed by Kemeny showed that application of the 308-nm UV-B excimer laser in the treatment of AR leads to a significant improvement in total nasal symptom score (TNS), but the wheal induced by the skin prick test was inhibited only at erythematous doses [33]. A study by the same working group demonstrated that irradiation with a combination of UV-B (5%), UV-A (25%) and VIS (70%) at suberythematous doses achieved a similar inhibitory effect on immediate-type skin reaction, as with higher erythematous doses of UVB alone [34]. These findings prompted a randomized, double-blind study in 49 patients with hay fever [35]. By comparison with baseline, the individual scores decreased significantly for sneezing, rhinorrhea and nasal itching, but not for nasal obstruction.

**Technique**

Treatment is applied for 2–3 min, three times a week for 2 consecutive weeks in the seated patient during the pollen season. During treatment, the patient experiences neither a sensation of heat nor pain. A total of six treatments are applied during the 2 weeks but not more than four in 1 week. During a session, both the patient and the physician must wear glasses that protect their eyes against UV light. The first treatment is frequently followed by deterioration in symptoms. Prior to each session, the patient is required to clear his nose. Before phototherapy is begun, the endo-nasal mucosa is treated with decongestant nose drops to ensure that the maximal surface area of the mucosa is irradiated. A nasal
The effectiveness of endonasal phototherapy has been investigated in seven studies involving 537 patients. In a randomized, controlled, double-blind study, 49 patients with ragweed-induced hay fever who were unresponsive to anti-allergy drugs were evaluated [35]. The two groups did not differ in terms of their anthropometric data, disease duration or symptoms score. In comparison with baseline, this study showed a significant improvement in the clinical symptoms of sneezing (p < 0.016), rhinorrhea (p < 0.007), nasal itching (p < 0.014) and TNS (p < 0.004) in the treatment group. None of the scores improved significantly in the control group. Examination of nasal lavage samples showed effects on eosinophils and inflammatory mediators. The authors found significantly lower concentrations of eosinophils, eosinophil cationic protein and IL-5 in the treatment group. In a smaller, double-blind, placebo-controlled study, 67% of the treated patients experienced a significant improvement in symptoms [36]. In an open, multicentric study of 70 ragweed patients, the overall efficacy assessment showed a significant inhibition of the clinical symptoms in 90% of the patients [37]. Another study involving 37 patients (15 with intermittent and 22 with persistent AR) provided similar results [38].

In a study including 59 patients with a history of at least 2 years of ragweed-induced AR treated with endonasal phototherapy, 38 (64%) patients experienced a decrease of more than 50% in the average change in the TNS [39].

In an open study, the effectiveness of endonasal phototherapy was compared with the effect of the antihistamine fexofenadine hydrogen chloride (120 mg) in patients with ragweed AR. TNS was decreased significantly in the endonasal phototherapy group (p = 0.00003) but no significant change was seen in the fexofenadine hydrogen chloride group [40]. Bella et al. investigated the effect of endonasal phototherapy in 243 patients with grass-pollen AR [41]. One group received endonasal phototherapy alone, while the other group received, in addition to endonasal phototherapy, a once-daily oral dose of an antihistamine or a nasal steroid (maximum: 400 μg/day). However, only 75 patients were evaluated. Nasal symptoms were improved significantly in each group. In the group receiving endonasal phototherapy alone, 6% of the patients experienced a worsening of their symptoms compared with 5% in the group receiving phototherapy and medication. No change in symptoms was seen in 19% of the phototherapy versus 8% of the phototherapy plus medication groups. On a visual analog scale, 75% of the patients receiving monotherapy indicated an improvement, in comparison with 87% of the group receiving combined treatment. Cingi et al. prospectively investigated the action of the endonasal phototherapy and its effect on quality of life in 100 patients with intermittent AR [42]. A control group comprising 34 patients was formed. The parameters investigated were the TNS and the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) [43]. The results showed a statistically significant improvement in all the variables in the phototherapy group. In all cases, endonasal phototherapy was well tolerated, the sole side effect being dryness of the nasal mucosa during the treatment, which, however, responded well to emollients. Not a single case of serious side effects occurred.

It has been shown in vivo and in vitro that endonasal phototherapy actively suppresses the effector phase of AR at multiple points:

- Reduction of the antigen-presenting capacity of APCs
- Induction of apoptosis of immune cells (dendritic cells, T-cells, B cells and eosinophils)
- Inhibition of synthesis and release of proinflammatory mediators from eosinophils, mast cells, basophils and T-cells

The major molecular target for UV-induced immunosuppression is UV-induced DNA damage [22]. It is this very point that prompts criticism of endonasal phototherapy, expressed as a fear that endonasal phototherapy might have a carcinogenic effect on the nasal mucosa. A study has investigated the extent of DNA damage prior to and following a 2-week endonasal phototherapy session [44]. The chemical evaluation was performed in the laboratory and immunohistochemical investigations conducted on the nasal cytology samples prior to the initiation of treatment, and immediately after the final session, 10 days thereafter and then 2 months after the last application. A significant increase in DNA damage was found in the mucosa immediately following the last therapeutic session. The damage had decreased significantly 10 days later and was comparable with baseline: 2 months later, the findings were comparable with those seen in healthy control persons. Mitchell et al. investigated DNA damage and repair after a single UV irradiation (combination of UV-C, UV-B, UV-A and some VIS) of human nasal mucosa in 30 adults [45]. Nasal cytology samples were taken prior to, and immediately after, treatment, and 24, 48 and 72 h later. DNA damage in samples taken immediately after UV irradiation was measured in all subjects and was significantly greater than that at baseline. The DNA damage at 24, 48, and 72 h showed no significant difference compared with baseline. In a second investigation in the same study, DNA damage to, and repair of, nasal epithelium was evaluated in nasal cytology samples before and after nine treatments applied over 3 consecutive weeks. At 1 and 4 weeks after the final treatment, DNA damage had returned to the original baseline level. The authors conclude that human nasal mucosa is capable of efficiently repairing UV-induced DNA damage. Earlier studies performed on bronchial fibroblasts and epithelial cells established DNA repair similar to that seen in human skin fibroblasts, suggesting that there is no difference in DNA repair mechanisms among different cell types [46]. Lee et al. evaluated all prospective and retrospective studies identified in Medline between 1966 and June 2002 with a view to estimate the risk of skin cancer associated with UV-B phototherapy, but found no increased skin cancer risk.
associated with UV-B phototherapy [47]. In another, more recent, study involving 3867 patients treated with narrow-band UVB phototherapy, no association was found between narrow band UV-B exposure alone and any skin cancer [48].

The surface area of each nasal cavity per nostril is 20 cm², and UV-A accounts for 25% and UV-B for 5% of the total emission energy. Using the treatment protocol for seasonal AR, comprising six sessions, the total treatment time is 930 s. For six treatments, the cumulated dose of UV-B is 4185 J/m² and of UV-A, 20925 J/m². The average UV exposure of males and females in the southern hemisphere (e.g., 34° South) varies between 29,000 J/m² for indoor workers and 95,000 J/m² per year for outdoor workers [49].

Expert commentary & five-year view
Research into the development of endonasal phototherapy of AR was begun in 1999 by researchers at the dermatological clinic and the Faculty of Science at the University in Szeged, Hungary.

In the meantime, according to the manufacturer of the device, endonasal phototherapy is employed in the following 19 countries: Hungary, Slovakia, Romania, Serbia, Croatia, Poland, Bulgaria, Greece, Austria, Switzerland, the Ukraine, Russia, Germany, Italy, Portugal, Turkey, Hong Kong, South Korea and Japan. Over the last 5 years, approximately 10,000 patients have been treated with this modality worldwide, with half of the treatments being carried out in Hungary. Endonasal phototherapy can readily be performed during the pollen season, does not take long and relieves the patient of their symptoms. Endonasal phototherapy represents an alternative form of treatment in patients who refuse medication (e.g., drugs, SCIT or SLIT), who have experienced a severe side effect with SCIT or SLIT, in whom drug treatment produced no, or only inadequate, effects, or who were unable to undergo SIT owing to contraindications (inadequately treated asthma and/or irreversible airway obstruction, severe cardiovascular disease, local or systemic treatment with β-blockers, inadequate compliance, pregnancy, nursing, or they were a competitive athlete). Contraindications for endonasal phototherapy include anatomical variations, such as a pronounced septal deviation or massive nasal polyposis. Phototherapy is also contraindicated in acute rhinosinusitis, in the presence of tumors of the nasal mucosa, sinuses or nasopharynx. Prior to the application of endonasal phototherapy, it is most important to ensure that the patient is not taking photosensitizing drugs. Advantages of this form of treatment are its good tolerability and repeatability. The application is simple and painless, and possible side effects such as dryness of the nasal mucosa or crusting can readily be treated by appropriate nasal care.

Although investigations into the safety of endonasal phototherapy suggest that UV-induced damage to nasal mucosa is efficiently repaired [44–46], a degree of uncertainty remains with regard to the possibility of carcinogenicity, since long-term investigations are still lacking. The author is, therefore, of the opinion that the number of treatment regimes per patient should be limited to a single regime per year. The equipment has been awarded a Conformité Européenne (CE) mark and thus meets the requirements of the EU guidelines on health and safety. Since endonasal phototherapy is, at present, not performed in the UK, Rhinolight has not been recognized by NICE.

Owing to its novelty and some as yet unresolved questions, endonasal phototherapy should be considered an effective alternative, but not be promoted to, first-line therapy for AR. Allergies are on the increase worldwide, and there is a need to develop treatments that work rapidly on symptoms and do not lose their effectiveness over time. When long-term studies have confirmed the safety of this form of treatment and the persistence of its effect, endonasal phototherapy will play an important role in the treatment of AR – as it already does in the field of dermatology.

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Key issues
- Allergic rhinitis (AR) is an increasing global health problem, and the costs it incurs are substantial. In the UK, direct NHS costs for the management of allergic problems are estimated at more than GB£1 billion per annum.
- Untreated AR has a major influence on a patient’s ability to sleep, their quality of life and cognitive function, and on school/workplace productivity.
- According to the WHO, AR must be considered a risk factor for the development of asthma.
- AR is a symptomatic disorder of the nose induced by IgE-mediated inflammation after allergen exposure of the membranes lining the nose.
- The backbone of its treatment is avoidance of allergens, use of drugs and specific immunotherapy.
- The radiotherapy device Rhinolight® is effective against AR.
- The application of endonasal phototherapy has, to date, been free from serious side effects.
- Endonasal phototherapy is an effective alternative when specific immunotherapy is contraindicated or when antiallergic medication is not tolerated, associated with side effects or is inadequate.
- Data on long-term efficacy and safety are mandatory. Efforts should be undertaken to re-evaluate those patients who have been treated so far.
- Provided that long-term studies confirm the effectiveness and safety of endonasal phototherapy, it will have an important role to play in the future treatment of AR.
References
Papers of special note have been highlighted as:
• of interest
• of considerable interest


• Demonstrates the mechanisms underlying phototherapy.


29 Toews GB, Bergstresser PR, Streilein JW. Epidermal Langerhans cell density determines whether contact hypersensitivity or unresponsiveness follows skin painting with DNFB. *J. Immunol.* 124(1), 445–453 (1980).


• Highlights the mechanisms by which UV radiation causes systemic immune response.


** Describes the efficacy of phototherapy in allergic rhinitis.


** Found that nasal mucosa exposed to UV light posses the capacity to repair UV-induced DNA damage.


** Demonstrates the capacity of airway mucosa to repair after UV-induced DNA damage and compare it with the biological response of a tissue that is not normally exposed to UV-radiation.


** Identifies similar DNA repair in bronchial fibroblasts and epithelial cells as in human skin fibroblasts. The authors conclude that DNA repair mechanisms are equally efficient in all cell types.


** Summarizes the association between narrow band UV-B treatment and basal cell carcinomas, squamous cell carcinomas and melanomas.


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