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Phototherapy for Allergic Rhinitis

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1 Introduction

Allergic Rhinitis (AR) affects 10% - 20% of the global population and is a major respiratory health problem[1], especially in developed countries. Moreover, the prevalence of allergic rhinitis continues to increase in most countries.[2] In addition to the clinical symptoms like sneezing and runny nose, AR affects the quality of life, sleep, cognition and even work and school performance for patients with severe symptoms. [3, 4] People with AR have an increased risk of asthma and other comorbid conditions. Different treatments and remedies like intranasal corticosteroids and antihistamines are available; however, their use may be limited due to side-effects or may not be appropriate for certain patient populations.[5] For example, the side effects of nasal antihistamine include bitter aftertaste, headache and anticholinergic effects like dry mouth, tachycardia, and blurred vision limiting their use in elderly patients. The use of corticosteroids may trigger adverse effects like nasal stinging, burning, dryness and bleeding.[6, 7] These medications do not cure AR, although available treatments reduce the severity of symptoms and improve the patients' quality of life. Prevention of seasonal allergic rhinitis especially by avoiding exposure to allergens outdoors is recommended although it is difficult to implement in practice. The symptoms of allergic rhinitis become milder with age and the allergic skin reactivity decreases in the elderly.[4]

This paper reviews the epidemiology, symptoms and pathophysiology of allergic rhinitis, relevant guidelines and current pharmacologic treatments. Phototherapy is introduced as a new treatment option for the disease. Available devices on the market are described in terms of the technology, wavelengths, energy emitted and recommended treatment regimen. The safety and efficacy of phototherapy for AR is described based on published clinical studies. The paper reviews some of the mechanisms proposed for explaining the symptomatic relief provided by phototherapy.

2 Allergic Rhinitis

Allergic rhinitis is an immunoglobulin E (IgE) mediated inflammatory condition that occurs due to exposure to allergens. Such exposure leads to inflammation of the membranes lining the nasal cavity. AR is primarily characterized by the symptoms of nasal discharge (rhinorrhea), sneezing and nasal obstruction.[8, 9] The development of AR is characterized by sensitization to a specific allergen without the presence of any clinical symptoms. Upon encountering a similar allergen at a later time, the body elicits a specific immune response along with activation of effector mechanisms. Memory cells play an important role in maintaining established antibody responses. Eosinophils, mast cells and basophils are considered the major effector cells in AR. They release inflammatory mediators such as histamine, cytokines and eosinophil cationic proteins that are responsible for the pathological processes occurring within the nasal mucosa.[6, 10]

The commonly used classification for the types of allergic rhinitis is seasonal and perennial allergic rhinitis. Seasonal allergic rhinitis (SAR), also known as hay fever, is related to seasonal allergens like tree (spring), grass (summer) and weed pollens (fall) found outdoors.[6] In 2011, 16.9 million adults (7.3%) aged 18 and over in the U.S. were diagnosed with hay fever over the preceding 12 months. During the same time period 6.7 million children (9.0%) reported hay fever.[11] The prevalence of SAR is more common in children and adolescents than in adults.[4] Perennial allergic rhinitis (PAR) is related to the exposure to house dust mites, animal dander and other such allergens found indoors. [6]

The American Academy of Allergy, Asthma & Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) established a Joint Task Force in 2008, for updating the practice guidelines related to the diagnosis and management of AR. The Joint Task Force used the seasonal and perennial classification for patients with AR.[9] Similarly, the U.S. Food and Drug Administration (FDA) used the SAR/PAR classification in its guidance for clinical development programs for drug products.[7]

Due to the global prevalence of the disease, national and international agencies have published guidelines for its diagnosis and treatment. The Allergic Rhinitis in Asthma (ARIA) guidelines, which is a collaborative effort of the World Health Organization, Global Allergy and Asthma European Network (GA^2LEN) and AllerGen*, concluded that the seasonal/perennial classification was not satisfactory and hence proposed in 2008[4] a new classification based on the frequency of the symptoms (intermittent or persistent) and the severity of symptoms (mild or moderate/severe). The new classification uses four groups:

1. mild intermittent,
2. mild persistent,
3. moderate/ severe intermittent
4. moderate/ severe persistent

If the symptoms are present for less than four days per week or less than four consecutive weeks, then AR is categorized as intermittent. It is categorized as persistent if symptoms continue for more than four days per week and more than four consecutive weeks. The severity of AR is classified as mild or moderate/ severe. The classification framework and practice guidelines by ARIA have been adopted by many governmental health agencies and scientific societies including the European Medical Agency.[4, 8]

* AllerGen NCE Inc. is a joint initiative of the Natural Science and Engineering Research Council, the Canadian Institutes of Health Research, the Social Sciences and Humanities Research Council and Industry Canada.

The two classification schemes do not map exactly into each other; for example, SAR and intermittent AR define different patient populations.[3]

In 2012, the Agency for Healthcare Research and Quality began a systematic comparative effectiveness review of available treatments (FDA-approved drugs) for SAR. The review report (released in July 2013) stated that treatment effectiveness was comparable. It cited lack of sufficient evidence for any conclusions regarding the adverse effects of the drugs. The report highlighted the need for standardization and validation of the symptom rating scales. It identified the lack of evidence to support anchor based minimum clinically important differences (MCID) (based on the symptom scales), as a research gap. Increased methodological rigor in SAR research was emphasized as the greatest need.[3]

The management of AR typically follows a progressive treatment algorithm. It begins with the diagnosis of allergic rhinitis, based on the assessment of symptoms like rhinorrhea, sneezing, nasal obstruction and other nasal or ocular symptoms. Skin prick tests are widely used to demonstrate an IgE-mediated allergic reaction and confirm the diagnosis. The frequency and severity of the symptoms are assessed in order to classify AR as intermittent/persistent, and mild or moderate/severe. The treatment strategy is based on the severity and duration of the disease, patient preferences and lifestyle limitations, efficacy of available medications, cost, etc. The management of AR includes patient education, pharmacotherapy and allergen-specific immunotherapy. The general consensus of allergen avoidance resulting in symptom improvement for AR needs further clinical evidence.[4, 12] Medications used for AR are typically administered either intranasally or orally. Intranasal corticosteroids (anti-inflammatory drugs) are typically prescribed as the first line of therapy for the treatment of persistent AR.[1, 9] Antihistamines are also used frequently to treat AR where they bind to H1 histamine receptors selectively or non-selectively. Second generation antihistamines are used for mild intermittent AR symptoms. Specific immunotherapy involves administering small amount of allergen extract to ameliorate the symptoms. It is used for moderate or severe persistent AR patients that aren't responsive to usual treatments.[4, 13]

The selection of allergy medication is often based on the degree of symptom relief.[13] Many of the drugs have systemic and local adverse effects especially following long term treatment. Corticosteroids have adverse effects like inhibition of growth in children, metabolism disorders, and behavioral changes due to the systemic exposure. Intranasal corticosteroids may have local adverse effects including nosebleeds, stinging, taste abnormalities and burning sensation. Long-term use of nasal decongestants may lead to rhinitis medicamentosa as well as headaches, insomnia, and hypertension while the use of antihistamines is associated with bitter aftertaste as an adverse effect. Immunotherapy is not appropriate for children or elderly patients.[6, 14]

Published studies summarizing different treatment modalities include subjective and objective outcome measures used to assess treatment efficacy. The two commonly used standard measurement tools are:

- Total Nasal Symptom Score (TNSS) – used in most of the clinical trials for drugs and devices where change from baseline is used as the efficacy endpoint. TNSS is a 0-12 point scale where four nasal symptoms (runny nose, nasal itching, sneezing, and congestion) are graded on a 0-3 categorical severity scale (0 = absent, 1 = mild, 2 = moderate, and 3 = severe).
- Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) – used to assess the impact of allergic rhinitis. It has 28 questions in seven domains (activity limitation, sleep problems, non-nose/eye symptoms, practical problems (e.g. the need to blow nose repeatedly), nose symptoms, eye symptoms, and emotional function) on a 7-point scale (0 = no impairment and 6 = severe impairment).

The established AR treatment for a given patient depends on the individual symptoms, and is typically based on the use of medication such as antihistamines, corticosteroids, decongestants or immunotherapy. However, recent reports described the use of phototherapy, i.e. the emission of light into the nasal cavity, as a new treatment modality. This paper is focused on the examination of the scientific evidence for the use of phototherapy as a safe and effective treatment of AR symptoms.

Passalacqua et al. published a systematic review of complementary and alternative medicine for rhinitis and asthma in 2006 as part of the ARIA guidelines.[15] The review identified two randomized controlled trials using phototherapy for treating AR. One device (Bionase) used a narrow-band red light intranasal therapy in PAR patients while the other (Rhinolight®) used a combination of UVA, UVB and visible light for SAR patients. ARIA used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to provide a uniform scale for assessing the quality of different publications. Assessments of the quality of evidence for each outcome considered the study design, risk of bias, consistency of evidence across studies, indirectness of evidence and the precision of the estimate of the effect. Based on this GRADE approach, ARIA classified the publications using phototherapy as very low quality evidence. The 2010 revision of ARIA guidelines stated that clinicians should not administer and patients should not use phototherapy or other physical techniques for the treatment of AR. This conditional recommendation placed more value on avoiding the potential adverse effects of phototherapy and less on the uncertain effect of phototherapy on symptoms of AR.[1]

3 Phototherapy for Allergic Rhinitis

3.1 Method and Results

We conducted a search of the U.S. National Library of Medicine (PubMed) with the MeSH terms 'phototherapy allergic rhinitis' which produced a list of 36 citations from May 1977 until July 2013. The first clinical trial on phototherapy for AR was by Neuman and Finkelstein[16] in 1997. Although this shows the small number of clinical evidence studies available on this topic, considering that 29 of these citations were published in the last 10 years indicates a growing interest. Seven papers published in languages other than English and other articles that were deemed not relevant (animal studies (1), dermatology related phototherapy article (4), KTP/532 laser (1), neonatal jaundice (1)) were excluded from this review. One publication on PUVA phototherapy by Koreck et al. (2010) was available only as an abstract. Pertinent studies, clinical guidelines and review articles were studied and are summarized in the following sections.

3.2 Phototherapy in Allergic Rhinitis

Kemeny and Koreck published in 2007 a review article that summarized the potential of phototherapy for treating AR. The complex mechanism of action of intranasal phototherapy involving apoptosis induction and inhibition of inflammatory mediators was described. The authors provided an overview of the clinical efficacy of combined ultraviolet-A (UVA), ultraviolet-B (UVB) and visible light. The article proposed the addition of intranasal phototherapy into the ARIA Guidelines[4] for patients who do not respond well to antihistamine and intranasal corticosteroid treatments.[17]

Leong[18] published a review article in 2011, focused on the assessment of intranasal phototherapy as a treatment of AR. The article evaluated three medical devices: Bionase (Bionette), Rhinolight® and Allergy Reliever SN206. 14 full-text articles were studied in this review. The review article highlighted the differences in the quality of the supporting clinical studies and concluded that the level of clinical evidence for recommending phototherapy for AR patients was weak. Although there are inherent challenges in conducting masked studies of phototherapy, recent publications contribute to the growing number of studies suggesting that phototherapy may present a viable treatment modality for some AR patients.

3.3 Available Phototherapy Devices

Four phototherapy devices, tested in clinical studies for safety or efficacy, utilize ultraviolet (UV), visible light and infrared (IR) wavelengths within the electromagnetic spectrum as shown schematically in Figure 1. None of these devices were cleared by FDA for use in United States. Three devices, Bionase, Rhinolight® and Allergy Reliever SN206 are CE marked, and therefore can be marketed and sold in the European Union.

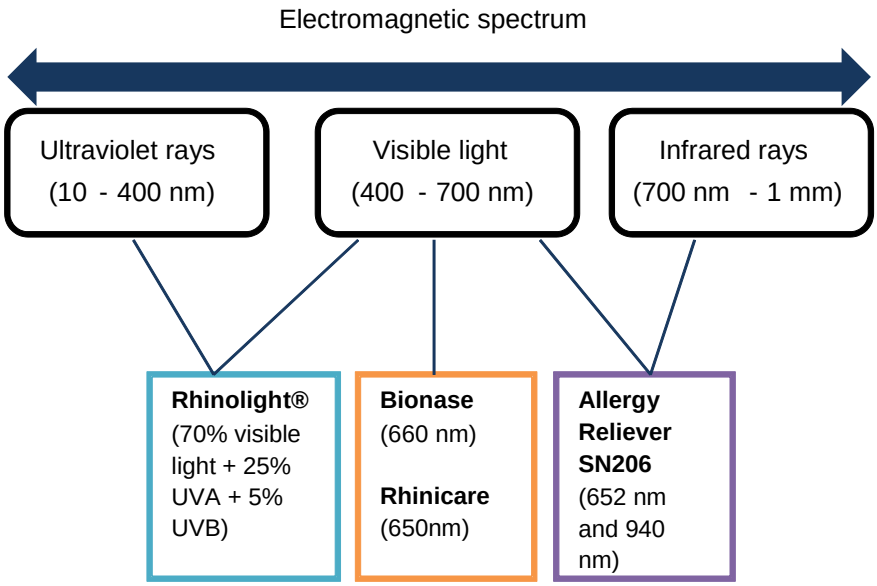

Figure 1. Phototherapy medical devices for treating allergic rhinitis

Figure 2. Bionette phototherapy device

Bionette (by SyroLight, Ltd. of Israel) is the first phototherapy device to use LED light. It is based on a pocket sized device (Figure 2) that uses visible red light (630 nm) to treat AR patients. The device consists of a control box and two light emitting diode probes for intranasal use. The treatment is self-administered by the patient three times a day for 4.5 minute treatment sessions, for a treatment period of two weeks.[19]

Neuman and Finkelstein investigated an earlier version of the device (660nm wavelength), for the efficacy of treating patients with PAR and nasal polyposis. They concluded that in uncomplicated cases of AR (no polyps or other anatomical deformities of nasal structures), red light illumination led to marked alleviation of symptoms.[16]

The double-blind, randomized, prospective study, included patients with PAR and nasal polyposis. All patients had daily symptoms of AR despite antihistamines and local steroid spray treatments. TNSS scale was used to determine the severity of the symptoms. Patients maintained a diary of AR symptoms throughout the study period of 14 days. Skin prick tests were performed for diagnosis of AR, and video endoscopic examinations of the nose was used for objective measurements. A sham illumination device was used in the placebo group. The placebo control group consisted of 29 patients while the active treatment group had 50 patients. Mild improvement

of symptoms was experienced by 44% and marked improvement by 29% of the patients in the active treatment group. The improvement of symptoms was most pronounced for rhinorrhea and nasal obstruction. 24% of the patients in the placebo control group also reported mild or marked improvement. Patients in the study were followed up for a year and none showed any adverse side effects of phototherapy. This is the only clinical study that documented the efficacy of the Bionette device in adults.

Moustafa et al. [20] compared the efficacy of phototherapy using the device and laser acupuncture in the management of AR in children. 40 PAR patients between the ages of 7-18 years old, were included in the study. Patients were randomly assigned to either the phototherapy or laser acupuncture groups. Phototherapy patients received treatment four times per session, twice a week for six weeks, while the laser acupuncture group received treatment twice a week for six weeks. The most severe symptoms at baseline were nasal obstruction and rhinorrhea. Both groups showed improvement in the severity score symptoms. The phototherapy group showed significant improvements one month after therapy for patients with severe symptoms, however there was a regression in the symptom improvement score for mild to moderate symptoms after three months and one year. The serum IgE levels were significantly reduced one month and three months after therapy.

Figure 3. Rhinolight® phototherapy device

Rhinolight® (by Rhinolight Ltd. of Szeged, Hungary) is a desktop device (Figure 3) which uses a combination of ultraviolet and visible light (mUV/VIS) to treat AR patients. The device emits light which consists of 70% in the visible spectrum (400–700 nm), 25% – UVA (320–400 nm) and 5% in the UVB light (290–320 nm) spectrum. The device consists of a single probe and the treatment is administered under medical supervision in clinics. The treatment is applied for 2-3 minutes/nostril, three times a week for two consecutive weeks.[21]

This device has the largest number of clinical studies documenting its safety and efficacy.

Koreck et al.[10] conducted a double-blind study of intranasal phototherapy using the Rhinolight® device for the treatment of patients with SAR during the ragweed pollen season. 49 patients were randomly assigned to receive either mUV/VIS irradiation in the active treatment group (25 patients) or low intensity visible light in the control group (24 patients). Each patient kept a diary of daily symptoms measured using TNSS. Nasal obstruction was assessed using acoustic rhinometry and nasal lavage was analyzed for cytokines and eosinophil cationic proteins (ECP) concentration. The symptoms scores for sneezing, rhinorrhea, nasal itching and TNSS in the active treatment group decreased significantly while the control group did not show any significant improvements. The symptom scores for nasal obstruction improved slightly but did not reach statistical significance in the active treatment group. The number of eosinophils, ECP and IL-5 were significantly reduced in the active treatment group. The side effect of dryness of the nasal mucosa was reported by all patients in the active treatment group. The authors concluded that the device significantly reduced clinical symptoms of AR and the number of local inflammatory cells in the nasal lavage of the patients.

Cingi et al.[22] investigated the efficacy of phototherapy using Rhinolight® on 79 patients with PAR in a prospective, randomized, single-blind, placebo controlled study. The control group (38 patients) received

low intensity visible light irradiation, while the active treatment group (41 patients) received irradiation using the Rhinolight® device. TNSS significantly decreased in both groups but the decrease was highly significant ($p<0.001$) in the active treatment group compared to the placebo group.

Cingi et al.[23] conducted another prospective study in 100 patients using the Rhinolight® device to investigate the effect of phototherapy on the quality of life of patients with AR. The efficacy of treatment was assessed by clinical findings, TNSS and RQLQ. The phototherapy device was used three times a week for 2 weeks with increasing doses. There was a significant difference between TNSS scores before and after treatment. Similarly, significant differences in all quality of life variables before treatment, compared to one and three months after treatment were reported.

A recent study by Garaczi et al.[24] compared the efficacy of intranasal phototherapy using Rhinolight® to that of fexofenadine hydrochloride (antihistamine). In addition to blocking the H1 receptors, fexofenadine reduces the allergic inflammatory responses mediated by mast cells, basophils, epithelial cells, eosinophils and lymphocytes. Thirty one SAR patients (symptoms triggered by ragweed pollen) were randomly assigned to receive either phototherapy or the antihistamine treatment. All patients kept a daily diary of the symptoms for nasal obstruction, nasal itching, sneezing, rhinorrhea and palate itching. During the two weeks treatment, changes from baseline values were calculated at day 1, day 7 and day 14. The individual TNSS scores significantly decreased in the rhinophototherapy group at the end of the treatment. Other than sneezing, none of the symptom scores decreased significantly for the antihistamine group. The side effect of mild nasal dryness of the nasal mucosa was observed in all patients treated by rhinophototherapy.

Brehmer and Schon[25] studied 10 volunteers with monosensitisation to birch pollen, who received phototherapy for two consecutive weeks. The values for TNSS showed significant reduction in severity of the symptoms following treatment and at follow-up (10 days after the treatment). There were no significant differences (compared to baseline) in the numbers of dendritic cells, T lymphocytes, T helper cells or T suppressor cells in the nasal mucosa following phototherapy treatment.

Albu and Baschir[26] compared the efficacy of intranasal phototherapy to azelastine in the treatment of SAR patients. Azelastine hydrochloride is a second generation antihistamine that selectively antagonizes the H1 receptor. Seventy seven SAR patients were randomly assigned to receive either phototherapy or azelastine (antihistamine) therapy. TNSS and RQLQ were used for measuring allergy symptoms and rhinomanometry was used for objectively measuring nasal airflow. The study demonstrated that both intranasal phototherapy and azelastine were equally effective in reducing symptoms in patients, however phototherapy reduced nasal obstruction better than azelastine ($p=0.038$). Both treatments improved the overall RQLQ scores. The authors recognized certain flaws in the study like the subjective outcome measures used (possibly affected by placebo effects) and volunteer bias, absence of blinding and the lack of objective measures.

Figure 4 summarizes TNSS improvement in AR patients after phototherapy treatment based on the clinical studies for Rhinolight®.

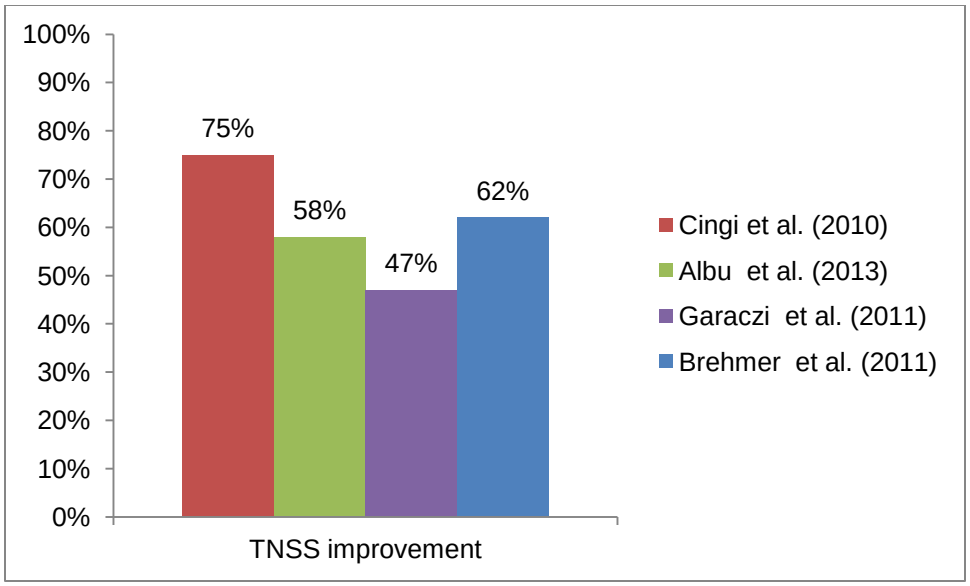

Figure 4. TNSS improvement for allergic rhinitis patients using the Rhinolight® phototherapy device

Figure 5. Allergy Reliever SN206 phototherapy device

The Allergy Reliever SN206 (by Lloyds Pharmacy of United Kingdom) (Figure 5) is a pocket size device (similar to Bionette) used for treating AR patients. The device has two intranasal probes which emit light at 652nm and 940nm. The device is suitable for use up to 3-4 times per day, with 5-6 hours between treatments.[27]

Emberlin and Lewis[28] studied intranasal phototherapy using the Allergic Reliever, for the treatment of adult SAR (triggered by grass pollen) patients. The double-blind, placebo controlled study, included 101 patients. All used the device for three minutes, three times per day, 5-6 hours apart for 14 days prior to the pollen challenge. The placebo device was identical to the active unit but emitted low intensity visible light. Treatment compliance was monitored by a subjective diary of allergy symptoms filled by the patients, and by interviews with the patients. Samples of nasal secretions were analyzed for ECP and measurements of nasal peak inspiratory flow (PIFn) and nasal peak expiratory flow (PEFn) were performed. The placebo control group consisted of 51 patients while the active treatment group had 50 patients. Symptoms scores after the pollen challenge were taken at 0.5, 6, 15, 30, 45, 60, 90, 120 and 150 minutes. The device significantly reduced hay fever symptoms (sneezing, runny nose, running eyes and itchy mouth/palate). No significant differences were found in the symptom scores for itchy eyes, itchy throat, itchy nose, ECPs, PIFn and PEFn for the two groups. The symptoms scores on average were higher for the placebo group compared to the active treatment group. There was a significant difference in these scores between the placebo and active groups ($p \leq 0.05$). This is the only clinical study supporting the safety and efficacy of the Allergy Reliever device.

Advertising Standard Authority (UK's independent regulator of advertising across all media) had commissioned an independent clinical trial to investigate the claims in the marketing advertisement of this device. They analyzed the claims by the manufacturer of Allergy Reliever SN206, Lloyds Pharmacy, and

concluded that the advertisement had breached the advertising standards. The following problems were cited in this study: [29]

- The study was performed outside the pollen season
- The buildup of pollen exposure that occurred during a real pollen season was not recreated in the study and only high doses of pollen were administered
- Study showed that the device did not have an effect on other symptoms of hay fever, including itchy eyes, nose and throat
- There was no baseline assessment and only subjective reporting of the effect of pollen on symptoms
- The information on the treatment effect of the device on low or medium pollen count days was missing
- No information was available on whether the treatment effects would persist beyond the two week treatment period and last for the entire pollen season

Figure 6. Rhinicare phototherapy device

Rhinicare (by SM Medical Co. of Seoul, Korea.[30]) (Figure 6) is a pocket size device which uses visible red light at 650nm to treat AR patients.

Lee et al.[31] conducted an open label, single center pilot study to evaluate the safety and efficacy of phototherapy device in PAR patients.

The study included 42 PAR patients. The protocol required use of the device twice daily for less than a minute for four weeks. The symptoms of rhinorrhea, sneezing, nasal obstruction and itching were recorded based on the TNSS tool. RQLQ was completed by all the patients before and after treatment. Testing at four weeks post treatment showed significant improvement in the clinical symptoms by 68% of the patients, while the overall RQLQ scores significantly improved by 45% compared to baseline values. There was a significantly high correlation between the changes in sleeping state and daily activities ($r=0.84$, $p < 0.001$), changes in nasal symptoms and daily activities ($r=0.746$, $p < 0.001$) and changes in vitality state and systemic symptoms ($r=0.517$, $p=0.004$). No adverse events were reported during the treatment period. The limitations acknowledged in this study included the absence of a control group and lack of clinical trial evaluation to reconfirm the effects of phototherapy after 6 months. This is the only clinical study supporting the safety and efficacy of the Rhinicare device.[31]

There are a few other devices mentioned in some parts of the world like Allergy Reliever – AR1, Kinetik Medical Devices, Warwickshire, England. However, we have not been able to identify clinical studies focused on those devices.[32]

3.4 Mechanism of Phototherapy

As described in the sections above, phototherapy for the treatment of AR is the application of light, generally of specific wavelengths, intensity and energy to reduce inflammation. Although the focus of this review article is on the use of phototherapy for AR, it is also used in other clinical applications, based on the same underlying mechanism of action. For example, phototherapy has been routinely used for

treating some skin disorders like psoriasis and eczema (atopic dermatitis). Atopic dermatitis and AR share many common pathogenesis factors and both are mediated by IgE.[17]

The main mechanism of immunosuppression induced by phototherapy was demonstrated for a combination of ultraviolet and visible light. It includes the induction of apoptosis in infiltrating T-cells, the reduction in the number of Langerhans cells and the induction of immunomodulatory cytokines. The cytokines IL-5 which promote the maturation, activation and survival of eosinophils, are present in increased amounts in the nasal mucosa of patients with AR. Irradiation of the nasal mucosa using phototherapy results in a significant decrease in levels of IL-5. T-cells play an important role in the maintenance of allergic process, therefore the apoptosis of these memory T-cells following phototherapy might disrupt a key element of the allergic response. Phototherapy also reduces the number of eosinophils and the concentration of ECP in the nasal lavage fluid. Irradiation of the nasal mucosa using a combination of ultraviolet and visible light inhibits the mediator release from RBL-2H3 basophils that are implicated in the effector phase of the allergic reaction.[10]

UV light has been used in dermatology to treat skin diseases. The narrow band 308 nm xenon chloride (XeCl) laser was used for the treatment of psoriasis. UVA and UVB light irradiation have shown an inhibitory effect on histamine release and the irradiation using UV light in phototherapy exhibits local and systemic immunosuppression in skin diseases. The irradiation doses used for phototherapy are low doses of UV light and the risk of carcinogenesis is very low. Csoma et al.[33] investigated the tolerability and efficacy of UVB irradiation in AR patients using the 308 nm XeCl laser. In an open label study, 18 SAR patients were enrolled and divided into two groups, low dose XeCl and medium dose XeCl. The eight patients in the medium-dose XeCl group showed significant improvement in the clinical symptoms for AR after the two week treatment period, while the patients in the low dose XeCl showed no significant change. The TNSS symptoms of sneezing, rhinorrhea and nasal congestion were significantly reduced by more than 50% for patients in the medium-dose XeCl group. The UVB irradiation suppressed the allergen induced wheal formation in the skin prick test reaction. All the patients tolerated the treatment well and no severe side effects were observed.[33] UVB irradiation of cutaneous Langerhans cells (LC) prevents the development of contact allergy and induces long-lasting immunosuppression. In a study by Brehmer and Schon[25], there was no effect of UV irradiation on the LC of the nasal mucosa even though all AR patients showed a significant clinical benefit after phototherapy treatment. Brehmer and Schon used the Rhinolight® device to study the impact of phototherapy on nasal mucosal immune cells. The possible reasons suggested for the findings (no effect of UV irradiation on LC) were that low dose UV used in the phototherapy device could not exert a detectable effec on nasal LC or that an incorrect time point was selected to detect immunocellular changes.

In another open label study, Csoma et al. [34] used (photochemotherapy) psolaren with UVA light (PUVA) for treating patients with SAR. PUVA treatments are widely used in various inflammatory skin disorders. Thirteen patients completed the three week treatment and showed a significant decrease in the clinical scores for sneezing, rhinorrhea, nasal itching, nasal blockage and TNSS. The treatment also suppressed the hypersensivity reaction in the skin. The same research group conducted a pilot study in seven patients with nasal polyposis.[35] Following PUVA treatment for six weeks, eosinophils significantly decreased in the nasal lavage while there was a decreasing trend in the levels of IL-5 and ECP in these patients.

In a pilot study, Koreck et al. investigated the effects of intranasal phototherapy on nasal mucosa in patients with AR, specifically assessing UV light induced DNA damage and repair process in nasal mucosa. A combination of visible light and ultraviolet light was used to irradiate the intranasal cavity three times a week, for two weeks in eight patients. Nasal cytology samples were collected before starting

therapy, immediately, 10 days and two months after last treatment. The presence of UV specific photoproducts cyclobutane pyrimidine dimers (CPD) in the nasal cytology samples was assessed. DNA damage was higher immediately after the last treatment although it decreased significantly after 10 days and cytology samples contained no CPD positive cells after two months. UV light induced DNA damage in the irradiated nasal epithelium cells; however, the damage was repaired over time.[36] Mitchell et al. found similar results where the nasal mucosa was able to efficiently repair UVB induced DNA damage in 26 AR patients. One week after the last treatment, the DNA damage had returned to the original baseline level and two months after the treatment no morphological changes were attributed to UV exposure.[37]

A number of studies have shown that visible and infrared light have biochemical, cellular and other functional effects. Visible light is responsible for a cascade of metabolic events at the level of respiratory chain of the mitochondria through photochemical reactions. Red light has an antihistamine like effect that suppresses the cells that release histamine thereby reducing inflammation; while the infrared light promotes increase in blood flow circulation to the area.[38] In addition to the reduction of oxygen radicals, light affects the calcium mobility due to changes in calmodulin-dependent protein kinases II (Ca^{2+}). Allergic symptoms are strongly dependent on the formation of reactive oxygen species and on Ca^{2+} changes in neutrophils, eosinophils or mast cells.[16] Another mechanism proposed for the improvement in AR symptoms following phototherapy, is based on the changes in the mucosal blood supply and inflammatory effects[28] induced by the heat generated by the intranasal probes emitting light at 652nm and 940nm. The reviewed clinical studies indicate that the immunosuppression due to phototherapy as a result of irradiation with combined UV and visible light has the most supporting data. As mentioned above, the apoptosis of immune cells and inhibition of inflammatory mediators are probably at the core of the therapeutic results of combining UVA, UVB and visible light.[17]

4 Discussion

Phototherapy has received growing interest as a therapeutic alternative for patients with AR. In the last 5 years (since 2009), 19 articles (of the total 36) were published on this topic which characterizes the growing interest in this treatment modality. Table 3 summarizes the safety and efficacy results from the supporting clinical studies for the four phototherapy medical devices for treating AR. Based on the reviewed clinical studies, the effectiveness of Bionase has been investigated in 99 patients, Rhinolight® in 345 patients, Allergy Reliever SN206 in 101 patients and Rhinicare in 42 patients. Phototherapy was well tolerated in all AR patients and other than the side effect of dryness inside the nose for Rhinolight® which can be addressed by applying emollients, there weren't any other short term adverse events reported.

TNSS is a recognized standard for assessing treatment efficacy and is utilized by most of the pharmaceutical companies in AR drug clinical trials. All the AR patients studied showed significant improvements in TNSS after phototherapy treatment. AR patients treated with Rhinolight® in four different clinical studies showed an average TNSS improvement of over 50% in following phototherapy treatment (Figure 4).[22, 24-26] Although the MCID for TNSS does not have an accepted threshold, these improvements indicate significant benefits in the clinical symptoms of sneezing, rhinorrhea, nasal itching and nasal congestion. The beneficial effects of phototherapy for AR patients in improving quality of life, such as the ability to perform daily activities, were measured by RQLQ. AR patients had more than 40% improvement in the overall RQLQ score following phototherapy treatment.[23, 26, 31]

The duration of the effect of phototherapy treatment is variable. The efficacy of Rhinolight® phototherapy as measured by RQLQ was higher at the end of the first month compared with the results at the end of the third month.[23] The improvement in clinical symptom scores subsided after three months and one year of treatment using the Bionase device for children with PAR.[20] Adult PAR patients that had responded favorably to the phototherapy treatment using the Bionase device showed continued benefits for a year.[16] There are no reports of long-term side effects associated with phototherapy; however, the small size of these studies suggests that additional research is needed to establish the long-term effects of the treatment.

Second generation antihistamines are frequently used as therapy for SAR patients and the ARIA treatment guidelines indicate that these could be used as first line therapy for such patients. The therapeutic potential of phototherapy was described in two comparative studies involving phototherapy and the new generation antihistamines. The combination of ultraviolet and visible light in the treatment of SAR patients was more effective than fexofenadine HCl (antihistamine) in reducing clinical symptoms for sneezing, nasal itching, rhinorrhea, palate itching and nasal obstruction.[24] The other study showed that both intranasal phototherapy and antihistamine azelastine were equally effective in reducing clinical symptoms of SAR, however, nasal obstruction was significantly improved with phototherapy compared to azelastine.[26]

Several studies have shown significant reduction in the number of inflammatory cells and the level of mediators following phototherapy. Reported changes included reduction in the number of eosinophils and the concentration of ECP in nasal lavage.[10] However, another study found no differences in ECP concentrations between active and placebo groups.[28] Similarly, no effect of UV irradiation on the LC of the nasal mucosa was reported by Brehmer and Sohn[39] although Koreck et al. demonstrated the capacity

of the nasal mucosa to efficiently repair DNA damage after UV light irradiation[36] Such findings need to be reconciled and further objective measurements need to be included in the supporting clinical studies for phototherapy devices. Some of the contradictory findings can be attributed to the differences in the clinical study protocols. In a review article, Brehmer[39] described that phototherapy suppresses the effector phase of AR through reduction of the antigen presenting capacity of antigen cells, induction of apoptosis of immune cells (dendritic cells, T-cells, eosinophils) and inhibition of inflammatory mediators from mast cells, eosinophils, basophils and T-cells.

Passalacqua et al.[15] published a systematic review of the literature supporting complementary and alternative medicine for rhinitis and asthma in 2006. The scoring system developed by Jadad et al.[40] was used for assessing the quality of the clinical trials. The score ranges from 0 to a maximum of 5 (2 points for correct randomization, 2 points for correct blinding and 1 point for description of withdrawals and dropouts). The review article by Leong used the same scoring system. The score for the clinical studies for AR varied from 0 to 5 (majority had a score of less than 3) which indicates the lack of methodological rigor in the research. For example, the Emberlin and Lewis[28] study was conducted outside the pollen season and did not have any baseline assessment. Lee et al.[31] did not include a control group or blinding, Albu and Baschir[26] used the subjective outcome measures which were possibly affected by placebo effects and volunteer bias and Cingi et al.[23] did not specify some details of the study such as the number of patients that completed the study. Clinical studies of phototherapy can be improved by ensuring blinding for patients and clinicians, randomization of patients, placebo controlled trials, post-treatment follow-up to determine the effect of phototherapy and the incorporation of objective measures.

Other than Rhinolight®, all other phototherapy devices are small pocket size devices, self-administered by the patients. Rhinolight® treatment is administered under medical supervision in clinics. The Bionase, Rhinicare and Allergy Reliever SN206 devices are battery powered and operate with an on-off switch. The treatment is administered over a couple of weeks, and the devices are used either 2-3 times every day or every week. Bionase and Allergy Reliever SN206 deliver 1J/cm^2 and 0.54J/cm^2 of light energy respectively per treatment session.[16, 28] Rhinolight® and Rhinicare irradiate the nasal cavity using increasing doses over the course of a treatment and the highest dose is 2.4J/cm^2 – 2.6J/cm^2.[17, 31]

The use of phototherapy for the treatment of AR has now been documented in clinical trials covering ~500 patients. The safety record of the procedure and significant symptomatic improvement, reported in studies using multiple devices, different wavelengths, treatment periods and energies delivered, suggest that phototherapy may offer an alternative treatment for AR patients. The specific effects of different wavelengths, energy emitted (in a single treatment and over the entire course of treatment) and the timing of the treatment in relation to the level of allergens are all topics that require further study, in order to determine the potential of phototherapy as a viable treatment modality for AR.

Study Size / (Active Group)	Patient Population	Study design (R, B)	Control Group	Safety	Efficacy (TNSS)	Efficacy (RQLQ)	Efficacy (Objective Measures)	Duration of Treatment (Weeks)	Authors / Year	Journal
Bionase (Bionette)										
40 (20)	PAR	R	Comparative group – laser acupuncture (20)	-	Significant improvement of clinical symptoms NO and ND one month after treatment (p=0.001)	-	Serum IgE levels significantly reduced after therapy	6	Moustafa et al. 2013[20]	International Journal of Pediatric Otorhinolaryngology
79 (50)	PAR	R, DB	Yes (29)	No side effects for a year after treatment	Improvement of symptoms (ND, NO, S, NI) in 72% of PAR patients in active treatment group	-	Nasal endoscopy / 61% improved in NO; 65% improved in ND	2	Neuman et al. 1997[16]	Annals of Allergy, Asthma & Immunology
Allergy Reliever SN206										
101 (50)	SAR	R, DB	Yes (51)	No adverse events during treatment period (2 weeks)	Significant reductions in severity of symptoms for S, ND, RE, and IM (p≤0.05)	-	No differences for ECP, PIFn and PEFn	2	Emberlin et al. 2009[28]	Current Medical Research and Opinion

Table 1: Comparison table of clinical studies for phototherapy devices

Note: R = Randomization, B = Blinding, SB = Single Blind, DB = Double Blind, NO = Nasal Obstruction, ND = Nasal Discharge (Rhinorrhea), NI = Nasal Itching, S = Sneezing, RE = Running Eyes, IM = Itchy Mouth

Study Size / (Active Group)	Patient Population	Study design (R, B)	Control Group	Safety	Efficacy (TNSS)	Efficacy (RQLQ)	Efficacy (Objective Measures)	Duration of Treatment (Weeks)	Authors / Year	Journal
Rhinolight®										
77 (39)	SAR	R	Comparative group – azelastine; (38)	Dryness of the nasal mucosa	Both groups had significant improvements of symptoms (ND, NO, S, NI) after treatment ($p<0.0001$)	Both treatments improved RQLQ scores	No significance in either treatment arm for nasal resistance	2	Albu et al. 2013[26]	Auris Nasus Larynx
10	SAR	None	No		Symptoms (ND, NO, S, NI) reduced significantly after treatment compared to pre-treatment severity ($p \leq .001$)		No significant changes in CD1a+, CD4, CD8 or CD31 cells after treatment	2	Brehmer et al. 2011[25]	European Archives of Oto-Rhino-Laryngology
31 (18)	SAR	R	Comparative group – fexofenadine Hcl; (13)	Dryness of the nasal mucosa	All individual symptoms of ND, NO, S, NI and palate itching significantly decreased compared to baseline (≤ 0.005)	-	-	2	Garaczi et al. 2011[24]	Journal of Photochemistry and Photobiology

Table 1 (Continued). Comparison table of clinical studies for phototherapy devices

Note: R = Randomization, B = Blinding, SB = Single Blind, DB = Double Blind, NO = Nasal Obstruction, ND = Nasal Discharge (Rhinorrhea), NI = Nasal Itching, S = Sneezing, RE = Running Eyes, IM = Itchy Mouth

Study Size / (Active Group)	Patient Population	Study design (R, B)	Control Group	Safety	Efficacy (TNSS)	Efficacy (RQLQ)	Efficacy (Objective Measures)	Duration of Treatment (Weeks)	Authors / Year	Journal
Rhinolight® (continued)										
79 (41)	PAR	R, SB	Yes (38)	Dryness in the nose	TNSS decreased significantly in active treatment group compared to placebo ($p<0.001$)	-	-	2	Cingi et al. 2010[22]	Therapeutic Advances in Respiratory Disease
7	Nasal polyposis	None	No	-	-	-	Eosinophils decreased significantly after 6 week treatment	6	Koreck et al. 2010[35]	Roumanian Archives of Microbiology and Immunology
100	AR	None	No	-	Significant differences for ND, NO, S, NI and turbinate edema after treatment	All RQLQ variables improved significantly one month after treatment ($P<0.05$)	-	2	Cingi et al. 2009[23]	European Archives of Oto-Rhino-Laryngology

Table 1 (Continued). Comparison table of clinical studies for phototherapy devices

Note: R = Randomization, B = Blinding, SB = Single Blind, DB = Double Blind, NO = Nasal Obstruction, ND = Nasal Discharge (Rhinorrhea), NI = Nasal Itching, S = Sneezing, RE = Running Eyes, IM = Itchy Mouth

Study Size / (Active Group)	Patient Population	Study design (R, B)	Control Group	Safety	Efficacy (TNSS)	Efficacy (RQLQ)	Efficacy (Objective Measures)	Duration of Treatment (Weeks)	Authors / Year	Journal
Rhinolight® (continued)										
8	SAR	None	No	-	-	-	Significant decrease in DNA damage after 10 days compared to data obtained immediately after finishing the treatment protocol	2	Koreck et al. 2007[36]	Journal of Photochemistry and Photobiology
17	SAR	None	No	Mild dryness of the nasal mucosa observed in three patients	All individual symptoms (ND, NO, S, NI) and TNSS significantly reduced after treatment (p≤0.01)	-	-	3	Csoma et al. 2006[34]	Journal of Photochemistry and Photobiology
49 (25)	SAR	R, DB	Yes (24)	Dryness of nasal mucosa	Significant improvement of symptoms for S, ND and NI (p<0.05)	-	Nasal lavage analysis – significant reduction in number of eosinophils, ECP, IL-5	3	Koreck et al. 2005[41]	Journal of Allergy and Clinical Immunology
18	SAR	None	No	Mild dryness of the nasal mucosa observed in some patients	Symptom scores for S, ND and NO reduced significantly in the medium dose XeCl laser group by more than 50% after treatment (p<0.05)	-	Skin prick tests showed inhibition of allergen induced wheal formation	2	Csoma et al. 2004[33]	Journal of Photochemistry and Photobiology

Table 2 (continued). Comparison table of clinical studies for phototherapy devices

Note: R = Randomization, B = Blinding, SB = Single Blind, DB = Double Blind, NO = Nasal Obstruction, ND = Nasal Discharge (Rhinorrhea), NI = Nasal Itching, S = Sneezing, RE = Running Eyes, IM = Itchy Mouth

Study Size / (Active Group)	Patient Population	Study design (R, B)	Control Group	Safety	Efficacy (TNSS)	Efficacy (RQLQ)	Efficacy (Objective Measures)	Duration of Treatment (Weeks)	Authors / Year	Journal
Rhinicare										
42	PAR	None	No	No adverse events during treatment period (4 weeks)	Improvement of symptoms (NO, ND, S, NI) in 68% of patients (p≤ 0.005)	RQLQ improved by 45% from baseline after 4 weeks of treatment in PAR patients	Nasal endoscopic assessment showed normal nasal mucosa after 4 weeks of treatment	4	Lee et al. 2013[31]	Journal of Photochemistry and Photobiology

Table 3 (continued). Comparison table of clinical studies for phototherapy devices

Note: R = Randomization, B = Blinding, SB = Single Blind, DB = Double Blind, NO = Nasal Obstruction, ND = Nasal Discharge (Rhinorrhea), NI = Nasal Itching, S = Sneezing, RE = Running Eyes, IM = Itchy Mouth

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