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RHINOLOGY

Endonasal phototherapy significantly alleviates symptoms of allergic rhinitis, but has a limited impact on the nasal mucosal immune cells

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Abstract The literature documents the fact that UV irradiation of cutaneous Langerhans cells (LC) in vivo prevents the development of contact allergy and produces long-lasting immunosuppression. However, not much is known about the effect of UV irradiation on the LC of the nasal mucosa and their connection with clinical scores. Local antigen presentation may be necessary for both primary and recall T cell responses to birch pollen in patients with hay fever. Endonasal phototherapy combination of UVB (5%), UVA (25%) and visible light (70%) utilises the immunosuppressive effects of UV irradiation. The aim of this study was to correlate clinical symptom scores with possible changes in the LC of the nasal mucosa induced by UV radiation. The clinical effectiveness of this form of treatment is discussed. Nasal biopsies were obtained from ten birch pollen-sensitive patients with seasonal rhinitis before and after endonasal phototherapy. All patients showed a significant clinical benefit post-treatment as assessed by standardised instruments, including total nasal symptom score, nasal congestion score, nasal itching score, sneezing score, nasal secretion score and impairment-to-health score. However, we found no significant morphological changes, to, or quantitative differences in, the CD1a+, CD4, CD8 or CD31 cells before and 14 days after treatment. Despite the positive clinical effect, the study revealed no effect of UV irradiation on the LC and other analysed cells of the nasal mucosa immune system. Possible reasons for this are discussed.

Keywords UV radiation · Endonasal phototherapy · Nasal Langerhans cells · CD1a · Allergic rhinitis

Introduction

Our knowledge of the therapeutic effect of ultraviolet (UV) irradiation has a long history extending back to the ancient Egyptians [1]. In 1893, the physician, Niels Finsen, developed one of the first appliances to enable the production of artificial sunlight, which he successfully employed to treat lupus vulgaris [2]. Margaret Kripke was the first author to describe the immunosuppressive effect of UV irradiation in a series of transplantation experiments on murine skin cancers induced by UVB radiation [3]. The last decades have seen an increase in our knowledge regarding the range of indications for, and the therapeutic modalities of broadband UVB (290–320 nm), narrow-band UVB (311 ± 2 nm), endonasal phototherapy, 308-nm UVB excimer laser, UVA (320–400 nm), photosensitisers and UVA (PUVA), combined UVA/UVB, high-dose UVA1 (340–400 nm) and high-dose visible light (400–800 nm) [4]. Koreck et al. [5] reported the results of a randomised controlled double-blind study aimed at investigating the efficacy of endonasal phototherapy in ragweed-induced hay fever.

A recent prospective, randomised, single-blind, placebo-controlled study investigating the effects of this form of treatment on allergic rhinitis found a highly significant

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reduction in the TNSSs in the active treatment group *vis-à-vis* the placebo group [6].

Endonasal phototherapy involves the irradiation of the nasal mucosa in patients with allergic rhinitis employing a combination of UVB (5%), UVA (25%) and visible light (70%). Although the mechanisms of the therapeutic effect, for example, in the treatment of atopic dermatitis employing phototherapy, have not yet been established in detail, the scientific consensus is that immunosuppressive effects have a major part to play. The working group headed by Cooper [7] showed that immunosuppression can be induced virtually in any healthy patient by exposure to UV light, and that represents a physiological reaction to UV radiation.

UV radiation induces a number of biological effects on Langerhans cells (LC). Numerous publications have shown that UVB irradiation of LC in vivo prevents the development of contact allergy, and induces long-lasting immunosuppression. In murine models, low-dose UVB exposure of LC resulted in a depletion of their numbers. These irradiated LC were no longer able to trigger a delayed-type immune response. The antigen specific- tolerance induced in T cells by the UVB irradiation of the LC persisted long after the exposure [8–12].

Weiss et al. [13] showed that UV irradiation leads to a dose-dependent suppression of the expression of both surface molecules (e.g. MHC class II and adhesion molecules) and important costimulatory molecules (CD80 [B7.1] and CD86 [B7.2]). In vitro experiments revealed that UV radiation causes apoptosis of LC [14]. Takashima et al. [15] showed in mice that apoptosis of LC is induced by UVB radiation via, among other things, the production of oxygen species. In 30 healthy volunteers, Kölgen et al. [16] investigated the cause of LC depletion after irradiation with artificial UVB radiation. With the aim of establishing whether this is caused by apoptosis or migration of the LC, they raised suction blisters on the skin in vivo and "captured" the migratory LC in the blister fluid. Their findings indicate that UVB-induced depletion of LC cells in human skin is more likely to be due to migration than apoptosis.

Since LC are responsible for antigen presentation, their presence is necessary for the induction of an immune response in the skin. In addition, it must be assumed that LC are intimately involved in antigen presentation at other sites too. LC are found in large numbers not only in the epidermis, but also in the oral and nasal mucosa [17–19].

Although the effects of UV radiation on the skin are well documented in the literature, no investigations have been carried out to determine the effect of UV irradiation on these cells in the (somewhat harder to study) nasal mucosa. In the present work, we investigated the effect of endonasal phototherapy on the LC at this site.

Materials and methods

Subjects

The study was approved by the Ethics Commission at the University of Witten/Herdecke. Ten volunteers (six men and four women aged 18–55 years) with an at least 2-year history of monosensitisation to birch pollen gave their written informed consent to participate in the study after first being fully informed as to its purpose. In addition to their clinical symptoms, allergy was further verified by the demonstration of IgE-mediated sensitisation, the skin prick test and nasal provocation testing. A positive reaction to the prick test was defined as a wheal diameter of at least 3 mm greater than in histamine controls. A positive in vitro test was determined by the use of laboratory reference standards. In the case of the nasal provocation test, rhinomanometry had to show a flow reduction of more than 40% over baseline (to be considered positive). Exclusion criteria were as follows: age <18 or >65 years, known polymorphous photodermatosis, use of photosensitising medication, severe autoimmune disease, malignant neoplastic disease, pregnancy, use of leukotrienes or beta-mimetic drugs, ongoing specific immunotherapy or antiallergic medication before the start of the study (systemic glucocorticoid therapy <4 weeks, topical glucocorticoid treatment <2 weeks, topical antihistamines <3 days, systemic antihistaminics <10 days, topical cromoglycin acid <1 week).

Patients suffering from perennial rhinitis, acute or chronic rhinosinusitis or rhinosinusitis with nasal polyps were not admitted to the study.

Nasal epithelial specimens

Before the start of endonasal phototherapy, and 2–3 days after the last session, nasal mucosal biopsies were obtained from the lower edge of the inferior turbinate, about ca. 2 cm posterior to the front edge, employing a forceps having a cup diameter of 2.5 mm using the method described by Fokkens [20]. To induce local anaesthesia, a cotton wool pledget soaked in oxybuprocaine hydrochloride was applied below the inferior turbinate taking care not to allow it to come into contact with the biopsy site. When the biopsy site had healed, the mucosa was irradiated with the rhinophototherapy device (Rhinolight Ltd., Szeged, Hungary) according to the protocol described by Koreck et al. [5]. A total of six treatments, each lasting for 2–3 min, were applied during two consecutive weeks.

Histological analysis and immunohistochemistry

Biopsy specimens were fixed in paraformaldehyde (4% in PBS) and embedded in paraffin. For histological analyses,

3-μm sections were stained with haematoxylin and eosin (Varistain 24-4ThermoFisher, Dreieich, Germany) according to the manufacturer's instructions.

For immunohistochemistry, the following monoclonal anibodies were used: O10 (murine IgG1κ-directed against human CD1a; Immunotech, Marseille, France), F7.2.38 (murine IgG1κ-directed against human CD3ε; DakoCytomation, Glostrup, Denmark, France), 1F6 (murine IgG1 κ-directed against human CD4; Novocastra Laboratories, Newcastle upon Tyne, UK), C8/144B (murine IgG1κ-directed against human CD8a; DakoCytomation) and JC70A (murine IgG1κ-directed against human CD31; DakoCytomation). 3-μm sections were stained following the Immunostar 80 protocol in accordance with the manufacturer's instructions (ThermoFisher).

Morphometric evaluation and statistical analysis

From each biopsy specimen, a number of positive cells per mm epidermis were counted using a microscope equipped with a 20× lens (Zeiss Axioscope, Göttingen, Germany). All statistical analyses were performed using the Excel software (Microsoft GmbH, Munich, Germany). Data are displayed as means of all evaluated sections (±SD). P values were determined using the two-tailed t test, and $P < 0.05$ (confidence interval 95%) was considered statistically significant.

Efficacy evaluation and statistical analysis

The nasal symptomatology was recorded in the form of TNSS, with the symptoms "sneezing", "nasal secretion", "nasal secretion" and "itching" being recorded separately on a scale ranging from 0 (no symptoms) to 3 (severe symptoms). For the psychometric evaluation, a visual analogue scale (VAS) extending from 0 (non-impairing) to 10 (intolerable) was employed as recommended [21, 22]. Data were collected at three time points: Before treatment (pre), after treatment, i.e., 14 days after the pre measurement (post), and on the occasion of the (at the follow-up examination) i.e., 10 days after the post measurement. Variables analysed: TNSS, the individual variables contained in the TNSS and the VAS score. Data evaluation of each variable employing simple variance analysis with repeated measurement, post hoc analysis employing Duncan's test.

Clinical efficacy of endonasal phototherapy

The variance analytical evaluation of the TNNS showed that the data obtained at the various time points differed highly significantly ($p \leq 0.001$) (Fig. 1a). The post hoc analysis revealed a highly significant reduction in pre-treatment symptom severity, both on completion of treatment and at follow-up, but no significant difference in the figures of the last two measurements (post and follow-up) (Table 1). Evaluation of the variance analysis of nasal congestion showed that the figures obtained at the various time points differed significantly ($p \leq 0.02$) (Fig. 1b). The post hoc analysis revealed a significant reduction in pre-treatment symptom severity at the end of treatment, and at follow-up, with no significant differences (to be seen) between the last two measurements (post and follow-up) (Table 1). Evaluation of the variance analysis for the symptom nasal itching revealed significant differences between the figures obtained at the three time points ($p \leq 0.02$) (Fig. 1c). The post hoc analysis revealed a highly significant reduction in symptom severity at end of treatment and follow-up *vis-à-vis* the pre figures; no significant differences were seen between the post and follow-up figures (Table 1). Evaluation of the variance analysis for the symptom sneezing showed that the measurements made at the various time points differed significantly from one another ($p \leq 0.05$) (Fig. 1d). The post hoc analysis revealed a significant or tendentially significant reduction in pre-treatment symptom severity; no significant differences were seen between the post and follow-up figures (Table 1). The evaluation of the variance analysis for nasal secretion revealed highly significant differences between the figures obtained at the different time points ($p \leq 0.001$) (Fig. 1e). The post hoc analysis revealed a highly significant reduction in symptom severity at treatment end and follow-up *vis-à-vis* the pre figures; no significant differences were seen between the post and follow-up figures (Table 1).

The evaluation of the variance analysis for the VAS showed that the measurements made at the various time points differed highly significantly from one another ($p \leq 0.01$) (Fig. 1f). The post hoc analysis revealed a (highly) significant reduction in symptom severity at treatment end and follow-up *vis-à-vis* the pre figures; no significant differences were seen between the post and follow-up figures (Table 1).

Impact of endonasal phototherapy on cells of the mucosal immune system

The average size of the biopsy specimens was 3 mm^2. Before treatment, all samples showed an intact epithelium. CD1a is the best-established marker for detecting epithelial LC. CD1a-positive cells were detected in all pre-treatment samples (7 cells/mm; range 5–11 cells/mm) and with one exception, in all post-treatment samples (8 cells/mm; range 5–11 cells/mm). A number of CD1a-positive cells were of the same order of magnitude as reported in the literature [24]. The numbers of pre-treatment CD1a-positive cells did not differ significantly from the post-treatment counts (Figs. 2, 3).

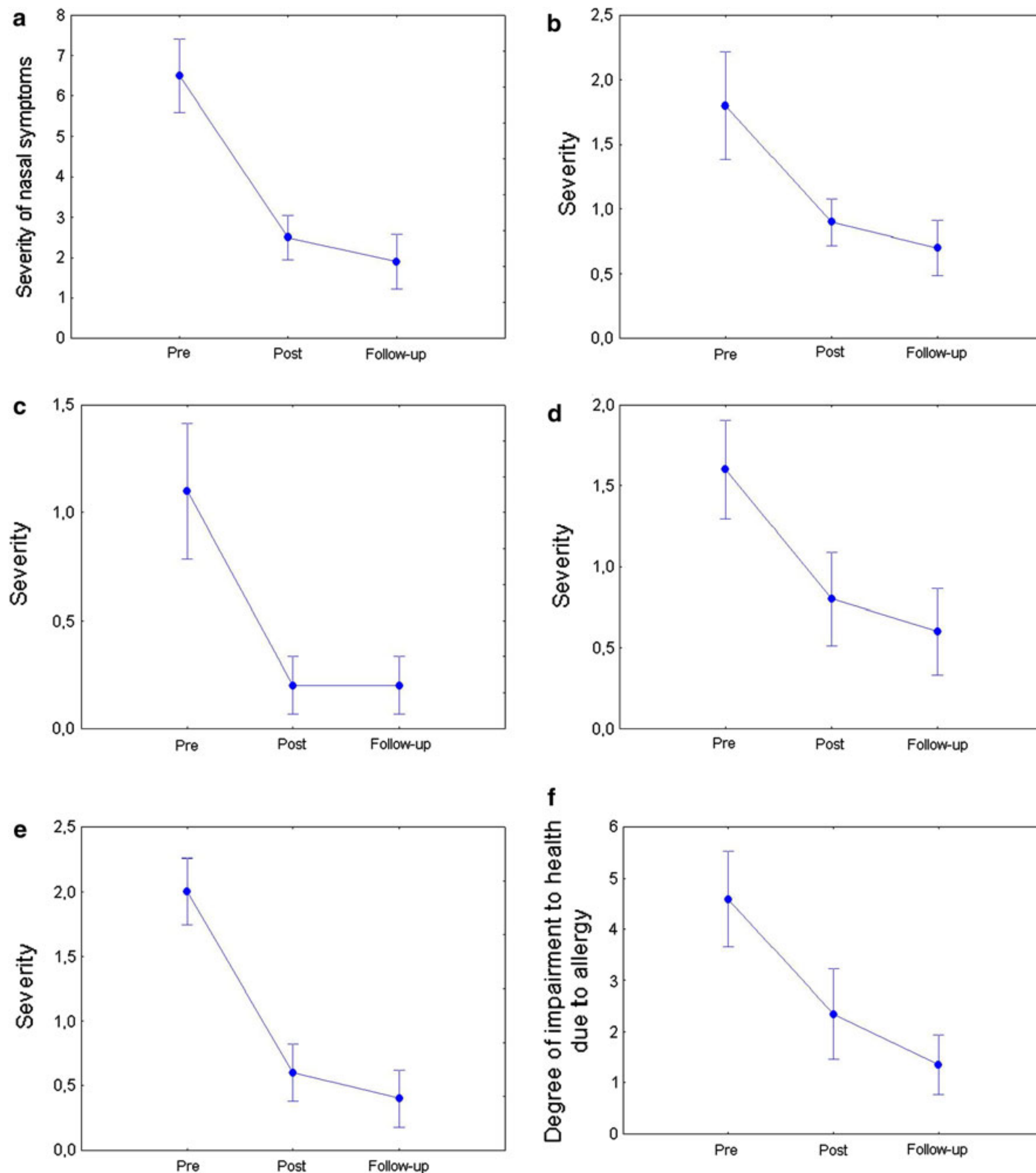

Fig. 1 Evaluation of the variance analysis of symptom scores. **a** Mean (SEM) total nasal symptom score (symptom severity range 0–12). **b** Mean (SEM) nasal congestion score (symptom severity rating 0–3). **c** Mean (SEM) nasal itching score (symptom severity rating 0–3). **d** Mean (SEM) sneezing score (symptom severity rating 0–3). **e** Mean (SEM) nasal secretion score (symptom severity rating 0–3). **f** Mean (SEM) impairment-to-health (visual analogue scale 0–10)

Examination under the light microscope of the samples stained with haematoxylin and eosin revealed no significant histological differences between the untreated epithelium and the epithelium 14 days after treatment. In particular, no inflammatory changes or epithelial abnormalities were detected (Fig. 2). The demonstration of CD3 is highly specific for T lymphocytes, and is one of the earliest signs of the involvement of the T cell system. We were unable to find any statistically significant difference between the pre- and post-phototherapy situation (data not shown). The CD4 antigen is preferentially expressed by T helper cells in the tissue, while detection of cytotoxic T cells was achieved with the CD8 antibody. No statistically significant treatment-related changes were seen either in T helper cells or cytotoxic T cells (Figs. 2, 3). Finally, the mucosal vascularization, as an overall parameter for inflammatory changes, was assessed using a CD31-directed monoclonal antibody. In addition, no significant treatment-related changes were

Table 1 Descriptive statistics: mean, standard deviation, minimum and maximum obtained at the three measurement points

	N	Minimum	Maximum	Mean	Standard deviation
Sneez1	10	0	3	1.60	0.966
Sneez14	10	0	3	0.80	0.919
Sneez24	10	0	2	0.60	0.843
Secret1	10	1	3	2.00	0.816
Secret14	10	0	2	0.60	0.699
Secret24	10	0	2	0.40	0.699
Cong1	10	0	3	1.80	1.317
Cong14	10	0	2	0.90	0.568
Cong24	10	0	2	0.70	0.675
Itch1	10	0	3	1.10	0.994
Itch14	10	0	1	0.20	0.422
Itch24	10	0	1	0.20	0.422
Tnss1	10	3	12	6.50	2.877
Tnss14	10	1	6	2.50	1.716
Tnss24	10	0	6	1.90	2.132
VAS1	10	1	9	4.59	2.954
VAS14	10	0	8	2.34	2.798
VAS24	10	0	6	1.35	1.855

detected 14 days after endonasal phototherapy when compared with the untreated situation (Figs. 2, 3).

Discussion

The present study shows for the first time, the effect of phototherapy on nasal LC. On average, some 10,000–12,000 L of air daily pass through the nose of an adult human. This means that, in addition to a large quantity of potentially injurious gases, aerosols and particles, the latter is also exposed to native allergens. Specific nasal defences also include the LC. These cells have an important role to play, not only in the development, but also in the treatment of allergic rhinitis. Till et al. [23] reported a depletion of LC in patients with allergic rhinitis treated with a topical glucocorticoid; while in the placebo group, a statistically significant increase in LC occurred during the pollen season. The differences in the LC of the skin, oral mucosa and nasal mucosa have been thoroughly investigated [19, 25]. Nasal and oral mucosa contains various different dendritic cells which they share in FcεRI expression; otherwise, differ in phenotype and functional properties [25].

The effect of UV radiation on the LC of the skin has been well documented in the literature. Depending on the UV dose, the disappearance of LC from the skin is likely to be due to either migration or induction of apoptosis. Accordingly, endonasal phototherapy should also produce

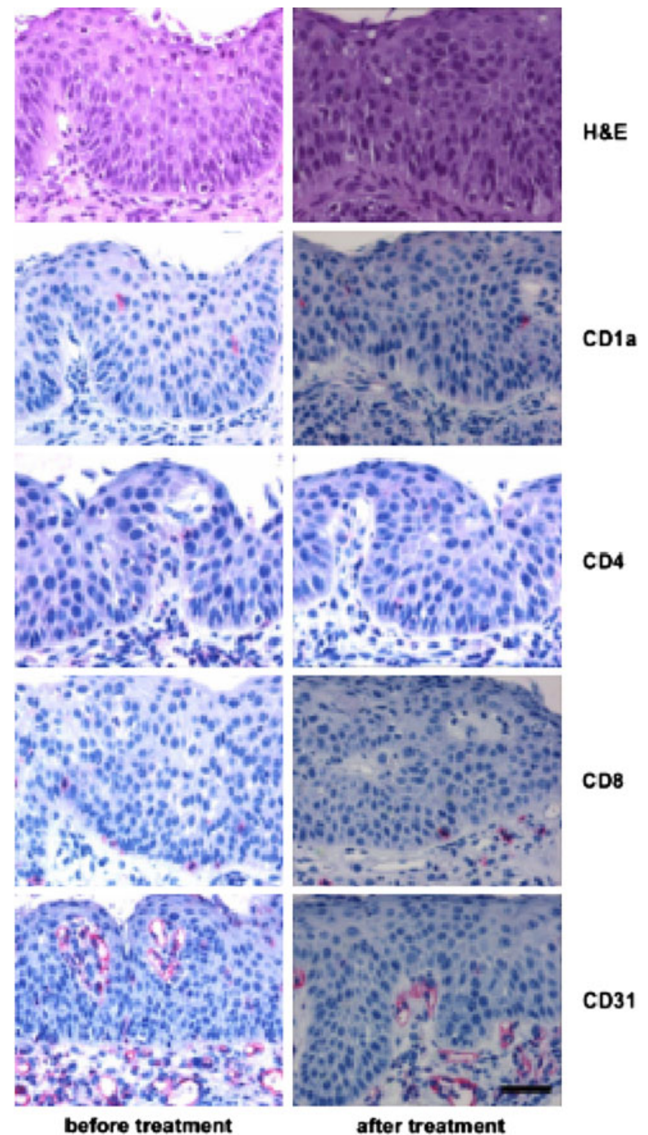

Fig. 2 Distribution of immune cells and vascularization before and after endonasal phototherapy. Patients were treated by endonasal phototherapy as described in "Materials and methods". Biopsy specimens of the nasal mucosa were obtained before and after 14 days endonasal phototherapy. Paraffin-embedded sections of representative tissues were stained with haematoxylin and eosin (*top*) or antibodies directed against CD1a (detecting Langerhans cells), CD4 or CD8 (detecting T cell subsets), or CD31 [detecting PECAM-1 (platelet endothelial cell adhesion molecule-1) on blood vessels] as indicated. *Scale bar* 50 μm

an observable effect on the LC of the nasal mucosa. Without exception, all 10 patients profited significantly from the endonasal phototherapy, and this outcome is supported by the results of other studies involving larger numbers of patients, as well as in those of a randomised controlled double-blind study [26]. This form of treatment has a positive effect also on the quality of life in patients with allergic rhinitis has recently been shown by Cingi et al. [27]. Despite the obvious clinical effect, we were unable to detect any

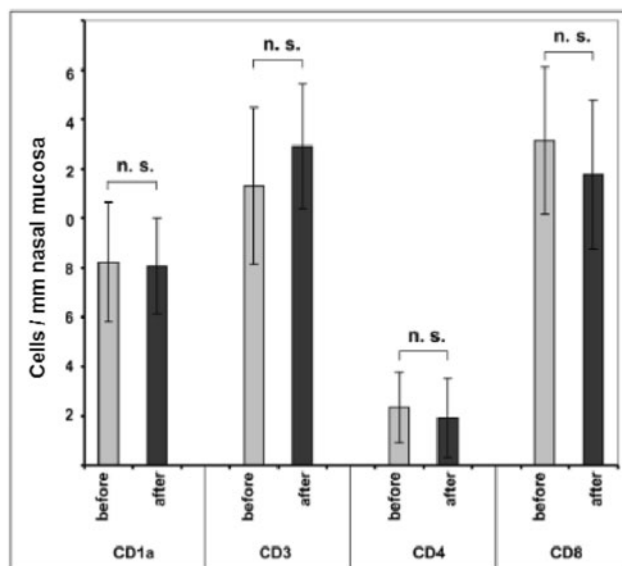

Fig. 3 Quantitative analysis of cells of the immune system within the nasal mucosa before and after endonasal phototherapy. Biopsy specimens of the nasal mucosa obtained from 10 patients before (*light grey bars*) or after 14 days endonasal phototherapy (*dark grey bars*) were stained as described in the legend of Fig. 1. Cells reactive with the indicated antibodies were counted microscopically (depicted as cells per millimeter epithelium). Values shown represent average counts from 10 patients (±SD); *ns* indicates not statistically significant

statistically significant morphological changes in, or differences in the number of, LC before and after endonasal phototherapy. This suggests three possibilites:

1. Nasal LC are not actively involved in allergic rhinitis.
2. The UV dose (usually) employed is too small to have an effect on the nasal LC.
3. We failed to identify the correct time point for the biopsy to allow changes in the nasal LC to be detected.

It would appear unlikely that the LC of the nasal mucosa play no part in allergic rhinitis. In their study, Godthelp et al. [28] demonstrated a significant increase in the number of nasal LC following nasal provocation in patients with an isolated grass pollen allergy. In patients with perennial allergic rhinitis (house dust mite) KleinJan et al. [23] found a greater number of LC than in healthy controls. In the patients with AR, the LC had a more mature ($CD86^+$) phenotype and were seen to be closely associated with T lymphocytes. Furthermore, in the AR patients greater numbers of CD11c+ LC were seen than in the controls. Based on their findings, the authors conclude that nasal LC are definitely involved in AR.

Endonasal phototherapy applies to the mucosa a cumulative dose of 20,925 J/cm^2 UVA and 0.418 J/cm^2 UVB. A single irradiation with UVA and UVB at a dose of 40 J/cm^2 reduces the number of LC in the epidermis, and leads to morphological changes (distorted and less dendritic cells) [29]. Thus, it is conceivable that the dose employed for endonasal phototherapy is too low to exert a detectable influence on the nasal LC.

The samples were obtained 2 days after the last irradiation. Aberer et al. [29] showed that epidermal LC were already depleted 3 h after UVA and UVB irradiation, and 48 h after the final irradiation the number of LC had decreased by more than 80%. However, these observations reported in cutaneous LC do not formally exclude the possibility that the time point chosen for biopsy of the nasal mucosa in our study had missed quantitative changes of immune cells. It is, therefore, possible that LC in the nasal mucosa differ from their cutaneous counterparts in the dynamics of their reaction to UV light challenge.

In the present study we were unable to find a statistically significant difference in the numbers of dendritic cells, T lymphocytes (CD3+), the T helper cell subset (CD4+), or the T suppressor cells (CD8+) in the nasal mucosa before and after endonasal phototherapy. Since the clinical effectiveness of this form of treatment has been confirmed in numerous studies, including our own; we conclude that other immunological mechanisms are also involved or that dynamic changes of nasal mucosal immune cells differ from those reported for the skin.

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