M. Menzel wrote the paper and designed the study, B. Weide collected the samples, P. Bauer performed the cDNA synthesis and the sequencing, D. Meckbach and C. Garbe critically reviewed the manuscript, and O. Kohlbacher and J. Bauer designed the study and reviewed the manuscript.

Conflict of interest

The authors state no conflict of interest.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Materials.

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Letter to the Editor

Efficacy of excimer light therapy (308 nm) for palmoplantar pustulosis with the induction of circulating regulatory T cells

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Abstract: In this open-label study, we investigated the efficacy of excimer light (308 nm) with a filter to cut off wavelengths below 297 nm for the treatment of palmoplantar pustulosis (PPP). Twenty patients with PPP were recruited and treated once a week for a total of 30 sessions. Patient response was assessed every 10 sessions based on the Palmoplantar Pustulosis Area and Severity Index (PPPASI) score. Levels of Th17 cells and regulatory T cells (Treg) in the peripheral blood in patients with PPP were also evaluated. Mean PPPASI score was 19.5 at baseline, 13.2 at 10 treatments, 10.9 at 20 treatments and 9.5 at 30 treatments. Th17 levels after excimer therapy were not significantly different from those at baseline. In contrast, Treg levels after excimer therapy were significantly higher than those at baseline.

Key words: excimer light – open-label study – palmoplantar pustulosis – regulatory T cells – Th17 cells

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Background

Monochromatic excimer light therapy for psoriasis was first reported in 1997 (1). The excimer lamp (308 nm) allows for targeted therapy that irradiates only the affected area and prevents UV exposure of unaffected skin. Excimer light effectively treats resistant and localized psoriasis lesions, requires fewer treatments and produces a lower cumulative UVB dose compared with narrow-band UVB (NB-UVB) (2). Excimer light has advantages over NB-UVB for the treatment for palmoplantar pustulosis (PPP).

Circulating Th17 levels are increased in patients with psoriasis (3). Other important factors may also be produced by the epidermis (4). Patients with PPP have significantly more circulating Th17 than healthy controls and fewer circulating regulatory T cells (Treg). Th17 was inversely correlated with Treg (5). In patients with psoriasis, the number of Treg in the peripheral blood increases after bath-psoralen UVA treatment (6).

Questions addressed

We evaluated the efficacy of excimer light with a filter to cut off wavelengths below 297 nm for the treatment of PPP. We also analysed the levels of $CD4^+CD25^+$ Treg and Th17 before and after therapy to determine whether the therapeutic effects of excimer light for PPP are related to Treg, Th17 and other parameters.

Experimental design

Twenty patients with clinically and histologically diagnosed PPP were enrolled in this open-label study (Table S1). The patients were resistant to topical corticosteroids or topical vitamin D3 ana-

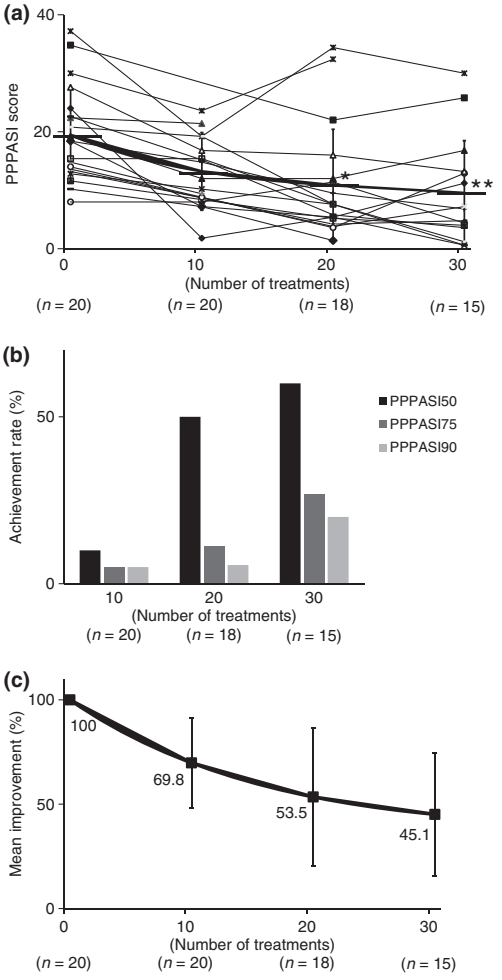

Figure 1. (a) Changes in Palmoplantar Pustulosis Area and Severity Index (PPPASI) score after every 10 treatments with excimer light. We compared the PPPASI scores using the Wilcoxon signed-rank test. Results are presented as mean ± SD $*P < 0.05$ and $**P < 0.01$. (b) Proportion of patients with at least 50%, 75% or 90% improvement in the PPPASI score after every 10 treatments with excimer light. (c) Mean (95% confidence interval) percentage improvement in PPPASI score after every 10 treatments relative to the baseline score.

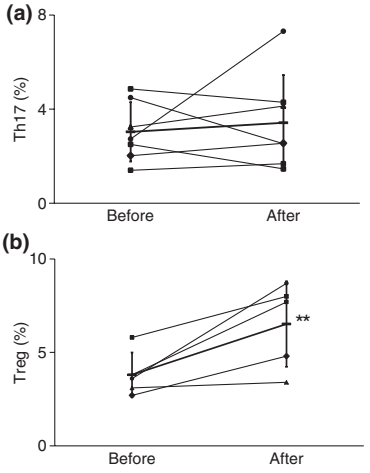

Figure 2. Continuous variables of the proportion of Th17 and Treg before and after excimer therapy were compared using the paired *t* test. The frequency of Treg significantly increased. The results are presented as the mean ± SD $*P < 0.05$ and $**P < 0.01$.

logues. One patient who had taken etretinate discontinued the drug 2 weeks before starting excimer light therapy. Exclusion criteria included as follows: a history of malignant skin tumors and photosensitivity disorders.

The 308-nm excimer light (TheraBeamUV308, Ushio, Japan) releases a power density of 40 mJ/cm^2 with a spot size of 120 cm^2. Although the peak wavelength is 308 nm, the excimer light also emits shorter wavelengths ranging between 290 and 300 nm. For psoriasis, wavelengths <296 nm are not only ineffective, but also induce erythema and increase the risk of photocarcinogenesis (7). Therefore, this excimer light was attached to an excimer filter to cut off wavelengths below 297 nm. We previously demonstrated that the use of an excimer light with a filter significantly decreased the number of cyclobutane pyrimidine dimer-positive cells (2). The initial dose was 0.3 J/cm^2 with 20% increase each session to a final dose of 2 J/cm^2 according to the standard NB-UVB regimen (8). Based on our preliminary experience, treatments were given once a week. Patients continued to use moisturizers, and the same topical treatments were used before this study. Clinical evaluation was based on the Palmoplantar Pustulosis Area and Severity Index (PPPASI) score (9). Clinical photographs were taken and assessed by two of the authors (T. F. and C. S.) independently.

Peripheral blood mononuclear cells were obtained at before and after treatment from the patients with PPP after obtaining written informed consent: 7 for Th17 assessment and 5 for Treg assessment. The study was approved by our university ethics committee. Two additional patients for Th17 assessment and 1 for Treg were obtained before treatment. $CD4^+$ Tcells were isolated using magnetic beads (Miltenyi Biotec, Auburn, CA, USA), incubated with phorbol 12-myristate 13-acetate and ionomycin (Sigma Aldrich, St. Louis, MO, USA) and then stained with a monoclonal antibody against CD3 (BD Bioscience, San Jose, CA, USA) and interleukin (IL)-17A (eBioscience, San Diego, CA, USA), and $CD3^+$ IL-$17A^+$ T cells were defined as Th17 cells by fluorescence-activated cell sorting analysis (FACS Calibur™; Becton Dickinson, Franklin Lakes, NJ, USA). The frequency of IL-$17^+CD3^+CD4^+/CD3^+CD4^+$ cells was investigated as Th17 cells. The frequency of $CD4^+CD25^+Foxp3^+/CD4^+$ cells was investigated as Treg.

Results

Of the 20 initially recruited patients, 15 completed all 30 treatments, two patients discontinued treatment after achieving partial or complete remission and three discontinued treatment because of either moderate pain and itching after each treatment ($n = 1$) or erythema on treatment day ($n = 2$). The symptoms in these three patients improved without specific treatment within a few days after discontinuing excimer therapy.

At baseline, the mean (±SD) PPPASI score was 19.5 (±8.1) and it decreased steadily throughout the treatment period: 13.2 (±6.6) at 10 treatments, 10.9 (±9.6) at 20 treatments and 9.5 (±8.9) at 30 treatments. The PPPASI score was significantly lower after 20 treatments than at baseline ($P < 0.05$) and even lower after 30 treatments ($P < 0.01$; Fig. 1a).

After 10 treatments, 2 patients had achieved PPPASI 50 and one patient achieved PPPASI 90. After 20 treatments, 9 (50%) of the patients achieved PPPASI 50. At 30 treatments, 9 (60%) of the patients achieved PPPASI 50 and three (20%) achieved PPPASI 90 (Fig. 1b).

Mean percentage improvement in PPPASI score was evaluated at every 10 treatments. At 10 treatments, the PPPASI score decreased 30% from baseline, at 20 treatments it had decreased 47% and at 30 treatments it had decreased 55% (Fig. 1c, Table S2). Representative clinical pictures are shown in Fig. S1.

The Th17 frequency in the peripheral blood after excimer treatment did not differ significantly from baseline values. In contrast, the Treg frequency increased significantly ($P = 0.004$; Fig. 2). Th17 levels were significantly correlated with disease duration ($r = -0.749$), but not the PPPASI score ($r = -0.05$; Fig. S2).

Conclusion

Our results are comparable with those of previous studies (10,11). We used an excimer light with a filter that cuts off wavelengths below 297 nm (2), which seemed to be as effective as other excimer light treatments. Irradiation without wavelengths below 297 nm improves the safety of excimer light treatment.

There were no significant changes in Th17 levels after excimer therapy, but the Treg population significantly increased. Treg might better reflect PPP severity than Th17. Th17 levels correlated with the disease duration, which might relate to the pathogenesis in the early stage of this disease.

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T.F, K.T. and A.M. designed the research and analysed the data. E.N and H.K. recruited the patients and collected the data. S.C. monitored statistical data. T.F. and A.M. wrote the manuscript.

Conflict of interest

The authors declare no conflict of interest.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Clinical pictures of patient No.6 at baseline, and after 10, 20 and 30 treatments. Excimer light was sometimes effective already in the early stages.

Figure S2. Relationship between PPPASI, Th17 and disease duration. Th17 levels were not significantly correlated with the PPPASI ($r = -0.050$), but were significantly correlated with disease duration ($r = -0.749$). Correlation analyses were performed using the Pearson product-moment correlation coefficient.

Table S1. Patient characteristics.

Table S2. PPPASI reduction.

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Letter to the Editor

Elevated MMP-7 levels in patients with systemic sclerosis: correlation with pulmonary involvement

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Abstract:

Background: Fibrosis is characterized by an excessive accumulation of connective tissue because of an imbalance between synthesis and degradation of extracellular matrix proteins. Systemic sclerosis (SSc) is a prototypic chronic inflammatory disease leading to a severe fibrosis of the skin and many internal organs.