ORIGINAL ARTICLE

# Efficacy of blue light vs. red light in the treatment of psoriasis: a double-blind, randomized comparative study

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## Abstract

**Background** Protoporphyrin IX is present in psoriatic skin without the preceding application of aminolevulinic acid. Therefore, endogenous photosensitizers in psoriasis are a potential target for photodynamic treatment with high-dose visible light.

**Objectives** In the present pilot study, treatment with high-dose blue and red light in psoriasis were analysed with respect to clinical improvement and potential side-effects.

**Methods** In 20 patients, two stable psoriatic plaques were treated with either blue or red light, three times weekly for four consecutive weeks. To remove scaling that could potentially interfere with penetration of the light into the skin, daily application of 10% salicylic acid in petrolatum was started at the screening visit and continued until the end of the study.

**Results** Clinical improvement was seen after treatment with blue as well as after treatment with red light. With respect to scaling and induration, no major differences between both light sources were seen. Improvement of erythema, however, continued in blue light irradiated plaques throughout the whole study period, whereas after red light no significant improvement was seen after six illuminations.

**Conclusions** The clinical improvement of psoriasis, with respect to erythema, in particular after blue light and to a lesser extent after red light indicates that visible light treatment could represent a treatment option for psoriasis.

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## Conflict of interest

P.C.M. van de Kerkhof has consultancy services for Schering Plough, Cellgene, Centocor, Allmirall, UCB, Wyeth, Pfizer, Soffinova, Abbott, Actelion, Galderma, Novartis, Janssen Cilag, and Leo Pharma. P.C.M. van de Kerkhof receives research grants from Centocor, Wyeth, Schering Plough, Merck Serono, Abbott and Philips lighting.

## Introduction

In psoriasis, an unmet medical need for the development of new treatments remains. In particular insufficient efficacy and cumulative toxicity of topical therapies, phototherapy and systemic treatments represent serious limitations for the current treatment options. Over the last few years, phototherapy with visible light in inflammatory skin disease is gaining interest in dermatological practice as a safe alternative for ultraviolet (UV) phototherapy. The absorption of visible light or UV radiation by chromophores in the skin is the main event in commencing biological effects of light on the skin. Endogenous chromophores can be target molecules and may cause direct or indirect damage to adjacent molecules. An increasing number of studies have documented clinical improvement in acne after treatment with different laser- and light-based devices. Irradiation of Proprionibacterium acnes colonies with visible blue light leads to photoexcitation of bacterial porphyrins, singlet oxygen production, eventually bacterial destruction and anti-inflammatory effects on keratinocytes.[1,2] Also in wound healing visible light is used to kill bacteria in infected wounds.[3]

Topical application of aminolevulinic acid (ALA) induces the accumulation of protoporphyrin IX (PpIX). In general, PpIX accumulating skin disorders can be a potential target for photodynamic therapy (PDT). PpIX has a maximum absorption peak at 408 nm (Soret band) and as a result blue light is more effective than red light in activating PpIX. For optimal activation of PpIX not only the maximal absorption spectrum of PpIX but also the absorption characteristics of the skin have to be considered. Therefore, red light is preferred in PDT because of deeper light penetration in the skin.[4] Psoriasis has been shown to accumulate PpIX after application of ALA. Its susceptibility to PDT with red light has been previously studied.[5–10] PpIX is also present in psoriatic

skin without the preceding application of its precursor, because of endogenous levels of PpIX.[11] Consequently, the interaction of blue light and endogenous photosensitizers, like PpIX, in psoriasis may represent a new principle for photodynamic treatment of psoriasis without the application of an exogenous photosensitizer. Recently, Liebmann *et al.* demonstrated that blue light may be effective in treating hyperproliferative skin conditions, because blue light reduces proliferation.[12] In the present pilot study, treatment with high-dose blue and red light in psoriasis were analysed with respect to clinical improvement and potential side-effects to develop a non-carcinogenic alternative to the current treatments with UVB.

## Methods

### Subjects

The local medical ethics committee approved this study. From May 2008 to February 2009, 26 patients with mild chronic stable psoriasis were invited to participate in this study. Finally, 20 patients were included in this study after given their written informed consent (age: 28–74 years, mean 55.7 years ± 11.5 SD; 14 men, 6 women). The studied lesions were located mainly on the extremities (16), on the abdomen (1), back (1) or nates (2). Patients were not allowed to use any systemic psoriatic treatment for at least 2 months before starting phototherapy with visible light. Topical treatment before and during the study was restricted to 10% salicylic acid in petrolatum and emollients. Other topical treatments were not permitted for at least 2 weeks before the study. Medication known to potentially aggravate psoriatic lesions, such as β-blockers, was also not allowed (Table 1).

### Study protocol

At the screening visit, 1 week prior to baseline, two contralateral and clinically identical psoriasis plaques were selected. The two target lesions were located on the trunk or extremities (exclusion of plaques localized on the extension surface of elbows and knees, hands, feet, groin, scalp and genital areas). The size of the selected plaques was at least 4 cm in diameter. One week before baseline, these psoriasis plaques were treated with 10% salicylic acid in petrolatum once daily in order to remove excessive scaling potentially interfering with the irradiation. The salicylic acid in petrolatum was continued on daily base until the end of the study. At random, one psoriasis plaque was illuminated with red light, whereas the contralateral lesion was treated with blue light, starting at baseline, three times weekly for four consecutive weeks. Only the research assistant was informed of the assigned treatment. Two blinded observers were involved in this study. Previous to every light treatment the two plaques to be treated were wetted with water. An emollient was applied after irradiation as phototherapy may aggravate dryness and desquamation.

A disturbing factor in this study is the use of salicylic acid in petrolatum. To assess the added value of visible light to the topical keratolytic treatment of psoriasis, an additional pilot study was performed. Seven patients (age: 37–71 years, mean 55.6 years ± 12.9, 6 men, 1 woman) with chronic stable psoriasis were asked to treat one psoriatic plaque with 10% salicylic acid in petrolatum once daily for four consecutive weeks. In this patient group, no additional therapy with visible light was given.

### Light sources

Patients were irradiated on one plaque with LED's based blue light (420 nm, ∼100 mW/cm$^2$; Philips, Eindhoven, the Netherlands) and LED's based red light (630 nm, ∼50 mW/cm$^2$; Philips) on the other plaque. No UV-filters were used, because measurements of the devices demonstrated an extremely low amount of UVA-radiation (0.0177 mW/cm$^2$).

Each plaque was irradiated for 20 min three times weekly for four consecutive weeks.

### Assessment

At the screening visit, at baseline and during the two weekly control visits a clinical severity score was calculated. To evaluate the clinical response, the sum score, a widely used method to measure the plaque severity, was assessed. In this score erythema, induration and desquamation are scored on a five-point scale as: 0, absent; 1, minimal (very light pink, hardly any elevation, rare scale); 2, mild (light red/pink, slightly elevation, poorly defined scale); 3, moderate (red, moderate elevation, defined scales); or 4, severe (very red, marked ridge, heavy scaling). Finally, a global SUM score (range 0–12) was defined as the sum of all three scores together, reflecting plaque severity. At baseline, psoriasis plaques with a total sum score of less than 5 or with scaling more than 4 were excluded.

At each control visit, possible adverse events, such as pigmentation or erythema, were assessed by a comparable severity scale (0,

**Table 1** Inclusion and exclusion criteria

| Inclusion criteria | Exclusion criteria |
|---|---|
| Stable plaque psoriasis more than 6 months | Severe scaling (≥4) |
| Two symmetrical localized plaques on trunk or extremities with a diameter of ≥4 cm and SUM-score ≥5 | Target plaques localized on extension surface of elbows and knees, hands, feet, groin, scalp and genital areas |
| Total body surface area of ≤10% | Topical treatment for psoriasis ≥2 weeks before start UVB |
| Written informed consent is given | Systemic treatment for psoriasis ≥2 months before start UVB |
| Subject age ≥18 years | Medication potentially aggravating psoriasis (beta-blocker, lithium, prednisone) |
| No other skin diseases | Planned exposure to sun, UVA or UVB affecting psoriasis during study period |

no evidence for pigmentation or burning; 1, minimal pigmentation or erythema; 2, mild pigmentation or marked erythema; 3, moderate pigmentation or marked erythema combined with edema; 4, severe pigmentation or blistering).

### Statistical analysis

To compare the mean sum score and desquamation, erythema and induration separately between the two target lesions a two-tailed student's *t*-test was used. A one-way analysis of variance (ANOVA) for repeated measures was used to analyse difference between time points within the mean sum score. When significant changes were found a two-tailed student's *t*-test was performed for analysis between time points. A *P*-value of <0.05 was regarded statistically significant. Microsoft Excel 2007 (MS Office 2007; Microsoft Corporation, Redmond, WA, USA) and Statistical Package for the Social Sciences 16 (SPSS, Chicago, IL, USA) were used for statistical calculations.

## Results

### Clinical efficacy

Identical sum scores were found at baseline indicating similar clinical severity between both studied groups (sum score of 7.7; SD ±1.3). Generally, the treatment was very well tolerated by all patients. Some patients experienced a slight burning sensation during the irradiation with blue light. No clearance was seen. The psoriatic lesions showed statistically significant clinical improvement during the treatment period, which was reflected in a significant decrease in the clinical plaque severity (sum) score ($P < 0.01$) (Fig. 1). No significant differences in sum score were found between blue (34%) and red light (27%) (Table 2).

Remarkably, the sum score was already significantly decreased based on only one week of pre-treatment with salicylic acid in petrolatum ($P < 0.01$). Both blue ($P < 0.05$) and red light ($P < 0.05$) induced statistically significant decreases in the clinical plaque severity score during the whole study period. However, the psoriatic lesions treated with red light did not show an overall clinical improvement (sum score) anymore after six treatments ($P = 0.26$) (Fig. 2).

After 1 week of pre-treatment, desquamation ($P < 0.01$) as well as induration ($P < 0.01$) decreased, whereas erythema did not change ($P = 0.43$). The decrease in desquamation was maximum after 1 week of pre-treatment ($P < 0.01$) and this effect was maintained by continuing the pre-treatment during the whole study period. Statistically significant improvements of induration and erythema were seen until the end of the study period for both studied groups. However, the decrease in erythema, induced by red light, was not significant anymore at the last treatment ($P = 0.10$) (Fig. 2).

The clinical severity at baseline of the psoriatic plaques in the additional study with salicylic acid in petrolatum as a control group could not be compared with the psoriatic plaques

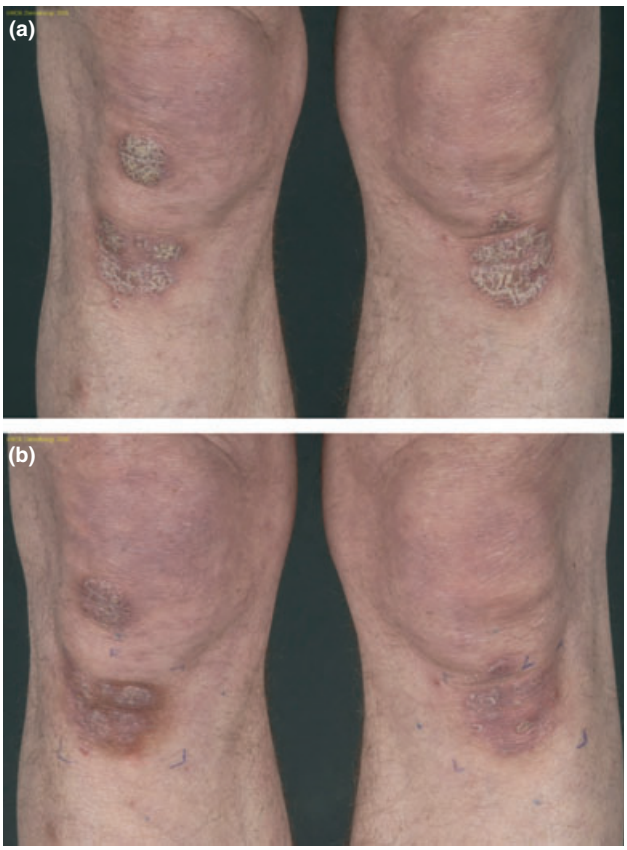


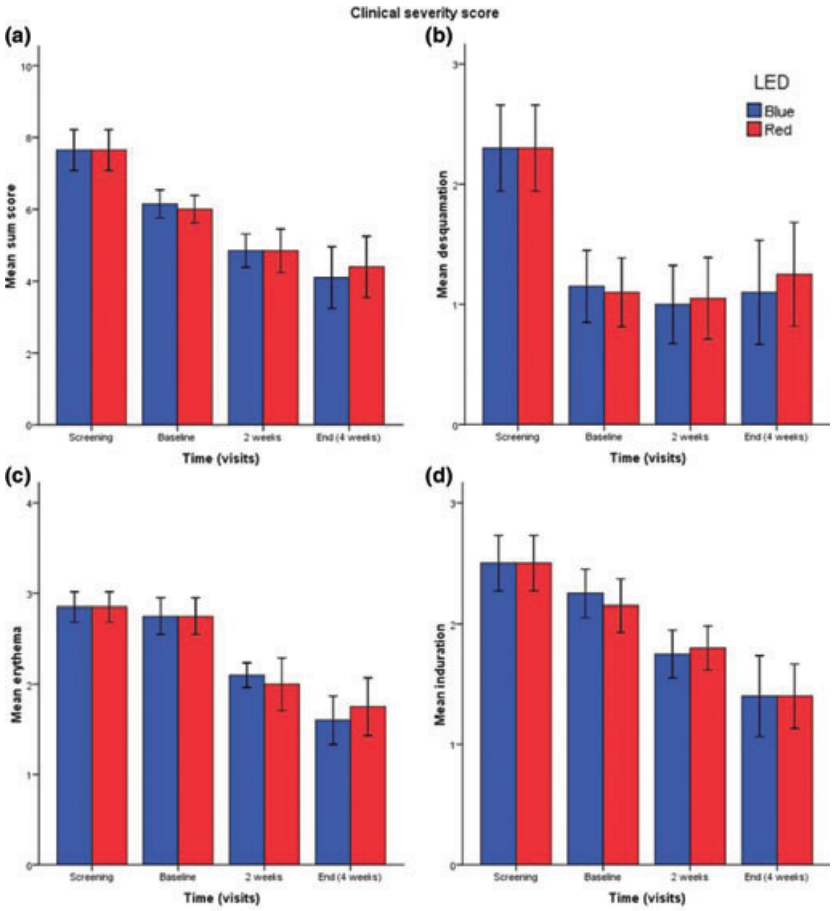

**Figure 1** Before (a) and after (b) treatment photos of psoriasis plaques treated with blue (right leg) and red light (left leg).

**Table 2** Percentage improvement between different time points for salicylic acid in petrolatum as monotherapy during 4 weeks of treatment to evaluate the additional effect of visible light on psoriasis

| Percentage improvement | | 0–2 weeks | 2–4 weeks | 0–4 weeks |
|---|---|---|---|---|
| Total SUM score | Blue | 21.0* | 16.3* | 33.9** |
| | Red | 18.3* | 10.2 | 26.7* |
| | SA | 18.2* | 25.9* | 39.4* |
| Desquamation | Blue | 16.7 | −10.0 | 8.3 |
| | Red | 0 | −18.2 | −18.2 |
| | SA | 43.5* | 46.2* | 69.6* |
| Erythema | Blue | 25* | 23.8* | 42.9* |
| | Red | 28.6* | 10 | 35.7* |
| | SA | −5 | 14.3 | 10 |
| Induration | Blue | 21.7* | 22.2* | 39.1** |
| | Red | 28.6* | 10* | 35.7* |
| | SA | 13.0 | 25** | 34.8** |

*$P \leq 0.01$, **$P < 0.05$.

SA, 10% salicylic acid in petrolatum; −, detoriation.




| Blue light | Screening -Baseline | Screening -2 weeks | Screening -End | Baseline-2 weeks | Baseline-End | 2 weeks-End |
|---|---|---|---|---|---|---|
| Total sum score | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 |
| Desquamation | <0.01 | <0.01 | <0.01 | ns | ns | ns |
| Erythema | ns | <0.01 | <0.01 | <0.01 | <0.01 | <0.05 |
| Induration | <0.05 | <0.01 | <0.01 | <0.01 | <0.01 | 0.05 |
| **Red light** | Screening -Baseline | Screening -2 weeks | Screening -End | Baseline-2 weeks | Baseline-End | 2 weeks-End |
| Total sum score | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | ns |
| Desquamation | <0.01 | <0.01 | <0.01 | ns | ns | ns |
| Erythema | ns | <0.01 | <0.01 | <0.01 | <0.01 | ns |
| Induration | <0.05 | <0.01 | <0.01 | <0.05 | <0.01 | <0.01 |

**Figure 2** Clinical severity score of psoriasis plaques treated with blue and red light. (a) Total sum score, (b) changes in desquamation, (c) changes in erythema and (d) changes in induration. During the whole study period, no significant differences were noted between blue and red light. Addendum of Figure 2. All statistical significant results between the different time points are depicted in this table. ns = not significant.

illuminated with high-dose visible light (Table 3). The sum score at baseline was lower with a strong tendency towards significance ($P = 0.07$). Therefore, improvement between the different time points was calculated in terms of percentage. The total sum score also decreased significantly (39%, $P < 0.01$) after one month of topical keratolytic treatment as monotherapy. This clinical improvement was predominantly based on significant decreases of desquamation ($P < 0.01$), but also induration improved significantly ($P < 0.05$). Compared with treatment with visible light, salicylic acid in petrolatum as a monotherapy has a high impact on the descaling (8% and −18% vs. 70%). No additional effects on induration after treatment with visible light on induration were seen (39% and 36% vs. 35%). Erythema did not change during 4 weeks monotherapy with salicylic acid ointment, whereas both blue and red light induced a significant improvement of erythema (43% and 36% vs. 10%) (Fig. 2 and Table 3). Thus, visible light, especially blue light, improves erythema.

**Table 3** Percentage improvement between different time points

| Percentage improvement | | S-0 | Week 0–2 | Week 2–4 | Week 0–4 |
|---|---|---|---|---|---|
| Total SUM score | Blue | 19.5* | 21.0* | 16.3* | 33.9** |
| | Red | 22.1* | 18.3* | 10.2 | 26.7* |
| Desquamation | Blue | 47.8* | 16.7 | −10.0 | 8.3 |
| | Red | 52.1* | 0 | −18.2 | −18.2 |
| Erythema | Blue | 3.4 | 25.0* | 23.8* | 42.9* |
| | Red | 3.4 | 28.6* | 10.0 | 35.7* |
| Induration | Blue | 8.0** | 21.7* | 22.2* | 39.1** |
| | Red | 12.0** | 28.6* | 10* | 35.7* |

*$P \leq 0.01$, **$P < 0.05$.

−, detoriation; S, screening and start pre-treatment of 10% salicylic acid in petrolatum. Thus, S-0 is solely the effect of 1 week salicylic acid in petrolatum prior to baseline ($t = 0$).

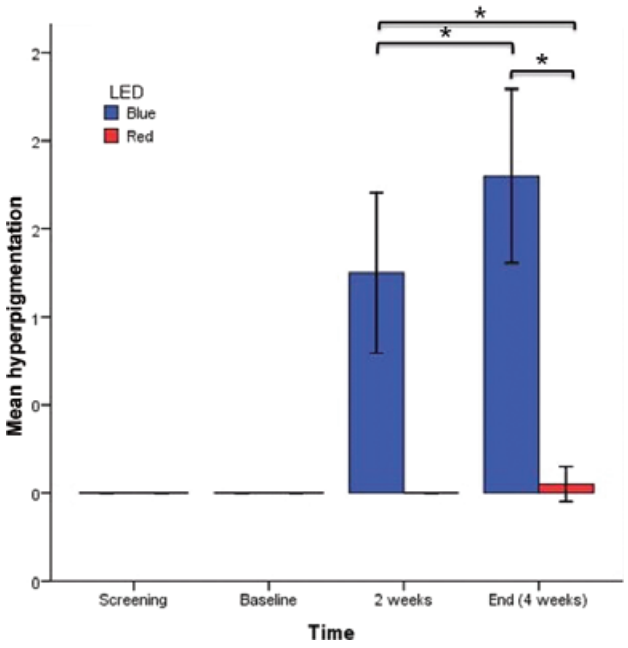



**Figure 3** Hyperpigmentation severity score, *$P < 0.01$.

### Erythema and hyperpigmentation

No erythema surrounding the studied lesions was noticed. Almost all areas treated with blue light showed surrounding hyperpigmentation (16/20, 80%). The severity of the hyperpigmentation increased from minimal to mild according to the number of treatments ($P < 0.01$). Only one patient demonstrated minimal hyperpigmentation of the surrounding skin after illumination with red light (Fig. 3).

## Discussion

Irradiation with high-dose blue as well as with red light, three times weekly for four consecutive weeks, induced improvement of psoriasis. This clinical improvement was identical for both light sources, except for erythema. The clinical improvement during treatment with blue light continued throughout the whole study period. On the contrary, the red-irradiated plaques did not show any significant improvement of erythema during the last six illuminations.

A disturbing factor in this study is the use of salicylic acid in petrolatum on the clinical results. As light does not penetrate into the skin with severe scaling, it is inevitable to use salicylic acid ointments as pre-treatment. Starting 1 week before baseline, the selected psoriatic plaques were treated with 10% salicylic acid in petrolatum once daily to remove excessive scaling. Also on a daily base, 10% salicylic acid in petrolatum was continued until end of the study. It is known that the application of petrolatum and salicylic acid improves psoriasis. Salicylic acid reduces the amount of hyperkeratosis in order to enhance the penetration of light, whereas petrolatum increases hydration and reduces desquamation by normalization of proliferation and differentiation in psoriasis.[13] This study demonstrates that salicylic acid in petrolatum is responsible for a major decrease of desquamation, moreover, also induration decreased significantly. In conclusion, salicylic acid in petrolatum has such a great impact on desquamation, that irradiation with blue or red light does not have an added value on descaling of psoriasis. Also no contributory effect of visible light on the induration of the psoriasis plaques was seen, probably because the amount of hyperkeratosis influences the clinical score of induration and the treatment period of 4 weeks was too short. On the contrary, no significant improvement of erythema was seen after treatment with salicylic acid in petrolatum, whereas treatment with both blue and red light resulted in a significant improvement of erythema. Blue light was superior in improving erythema, as treatment with red light showed no statistically significant improvement of erythema anymore after six illuminations. However, it must be noted that the irradiance of red light was lower.

The results of this study are dissimilar to previous results. In 2002, Maari *et al.* selected 17 psoriasis plaques which were exposed to blue light three times weekly for four consecutive weeks. No significant difference was seen between the irradiated plaque and the control plaque after 12 illuminations.[14] The most plausible explanation is the much lower irradiation dosage used in this study of Maari. Another possible explanation for the failing clinical improvement after irradiation with blue light in the study of Maari could be the fact that no keratolytic pre-treatment had been given to remove excessive scaling, acting as a mechanical barrier and therefore potentially interfering irradiation with visible light. After ALA administration, PpIX accumulation is seen preferentially in differentiating cells in the epidermis.[15,16] Improvement of psoriasis plaque severity after ALA-PDT has been shown in different studies.[7,8,10] Increased PpIX levels have also been demonstrated in psoriasis plaques without the administration of ALA. Endogenous PpIX is mainly present in the stratum corneum of patients with psoriasis.[11] Assuming PpIX to be present in the stratum cor-

neum of psoriasis, it must have been largely removed by keratolytic pre-treatment in this study. However, no improvement of plaque severity was seen after treatment with low-dose blue light without keratolytic pre-treatment in the study of Maari *et al.* and our study with high-dose visible light demonstrated a significant clinical improvement after 1 week of pre-treatment with a keratolytic ointment, implicating a different localization of PpIX or another unknown photosensitizer to be responsible for the clinical results.

PpIX has a maximum absorption spectrum in the blue visible light spectrum (410 nm) with weaker absorption peaks at longer wavelengths (633 nm, spectrum of red visible light). Red light penetrates deeper into the skin and is therefore generally preferred as a light source for activating PpIX, because not only the maximal absorption spectrum of PpIX but also the absorption characteristics of the skin have to be considered for an optimal therapeutic efficacy. However, red light is less efficient in activation of PpIX compared with blue light, but by increasing the total light dose this can be compensated for. As psoriatic plaques are characterized by hyperkeratosis and because its targets for PDT are localized in the deeper layers of the skin, determination of an adequate photodynamic dose is challenging. Red light may also have angiogenesis inhibiting qualities by activating other chromophores in the skin, like haemoglobin, or anti-inflammatory properties by influencing the release of cytokines from macrophages or other cells, but its exact mode of action spectrum is not yet fully understood.[1,2,17,18] This study not only demonstrates clinical improvement of psoriasis after irradiation with deeper penetrating red light, but also, in particular, after treatment with blue light. The clinical effects after treatment with blue light persisted throughout the study, whereas the clinical improvement of the psoriasis plaques irradiated with red light discontinued after 2 weeks. Hypothetically, the concentration of an unknown photosensitizer, responsible for the clinical improvement of erythema in psoriasis after irradiation with high-dose blue light, is highest in the upper part of the epidermis. An endogenous photosensitizer, or perhaps an unknown exogenous agent penetrating the ruptured skin barrier, may be responsible for the demonstrated clinical improvement of erythema in psoriasis after treatment with high-dose blue light. Recently, Liebmann *et al.* demonstrated that blue light may be effective in treating hyperproliferative skin conditions, because blue light reduces proliferation. The reduction in proliferation is attributable to induction of differentiation in skin cells by generation of nitric oxide. Furthermore, they found that irradiation with blue light at 412–416 nm exerts toxic effects only at high or very high fluencies as compared with irradiation with UV light.[12] As UVB irradiation has been proven to have local and systemic immunological effects on the skin,[19] it is attractive to speculate whether the observed effects of this study are caused by systemic effects of visible light. However, these systemic effects have not been demonstrated yet for phototherapy with visible light or photodynamic therapy. Furthermore, only the studied psoriasis plaques were illuminated. The used blue and red light sources could only cover one psoriasis lesion. Therefore, it is almost impossible to explain the observed effects by a systemic one.

A side-effect of using blue light in the treatment of psoriasis is the presence of evident hyperpigmentation of surrounding skin in 80% of the treated psoriatic plaques. In previous studies with visible light, hyperpigmentation affected also some acne patients, but this resolved within 3 months.[20] In 2007, Lee *et al.* showed a significant decrease in melanin level after red irradiation in facial acne patients, whereas with blue light the melanin level increased slightly.[21] However, both UVA and UVB are also capable of inducing delayed tanning. It is known that skin pigmentation is the result of melanin synthesis induced by the activation of enzymes in melanocytes in the basal layer of the epidermis in response to factors, such as UV light. A possible explanation for the hyperpigmentation seen after treatment with blue light could be that wavelengths of blue light are near the wavelengths of UV light. Previous studies have shown that near UVA visible light can result in immediate pigment darkening.[22,23] In a previous study of our group, minimal hyperpigmentation of normal skin of healthy volunteers irradiated with blue light was seen after five irradiations. This clinical finding was confirmed histologically, as also a significant increase in Melan-A positive cells was demonstrated. Both clinical hyperpigmentation and Melan-A expression decreased after cessation of the irradiations with blue light.[24]

A shortcoming of our study is lacking of follow-up data. Although it is not known whether the hyperpigmentation of the surrounding skin noticed in our patient group resolved within a few months, one can expect this to happen. Besides hyperpigmentation, no other complications were noticed. Because no UV radiation is emitted, the chance of side effects as effect of UV radiation, premature ageing and skin cancer, is considered insignificant. The clinical improvement of psoriasis after both blue and red light indicates that visible light treatment can be a treatment option for psoriasis in addition to other conventional therapies. Especially when conventional therapies cannot be considered as a therapeutic option for a particular patient, because of their side-effects profiles or the patient's general condition.

In previous acne studies, mixed blue and red LED phototherapy, probably by combining the antibacterial and anti-inflammatory qualities, showed to be a more effective treatment than blue light alone. Perhaps that combination of both red and blue light may also be a treatment option for psoriasis, inducing the most optimal therapeutic effect in psoriasis by maximum activation of the target photosensitizer and reaching the photodynamic target located in the deep dermis. The next step is to optimize the efficacy of treatment with visible light which depends on several factors, such as dose and frequency of the treatment. In general, clearance of psoriasis is reached after ±30 treatments of narrowband UVB-phototherapy with a three weekly treatment protocol.[25] In this study, patients did not reach clearance after a total number

of 12 treatments, probably because the treatment protocol of three times weekly for four consecutive weeks was too short. Dose finding studies and comparisons of various treatment schedules with different exposition durations, are needed.

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