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REVIEW

# Phototherapy for vitiligo, what's new?

Andrea PARO VIDOLIN, Caterina AURIZI, Giovanni LEONE *

San Gallicano Dermatological Institute, IRCCS, Rome, Italy

*Corresponding author: Giovanni Leone, Istituto Dermatologico San Gallicano, via Elio Chianesi 53, 00144 Rome, Italy. E-mail giovanni.leone@ifo.gov.it

ABSTRACT

Vitiligo is a disorder characterized by the development of depigmented macules and patches. Existing treatments include topical and systemic immunosuppressants, topical vitamin D analogues in monotherapy or in association with phototherapy, phototherapy and surgical techniques, which together may serve to halt disease progression, stabilize depigmented lesions, and encourage repigmentation. Narrow-band UVB (NB-UVB 310-315 nm) radiation is now considered as the "gold standard" for the treatment of diffuse vitiligo. This article provides a brief overview of the different phototherapy based treatments in vitiligo.

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**Key words:** PUVA therapy - Phototherapy - Vitiligo.

Vitiligo is an acquired cutaneous depigmentation disorder affecting approximately 1% to 2% of the world population with no predilection of age, gender or racial background. Familial occurrence is found in about 30% of the patients.[1] Although not life-threatening, vitiligo is a disfiguring disorder and can have deep psychological consequences.[2] The progressive depigmentation of the skin that characterizes vitiligo is associated with loss of melanocytes from the basal layer of the epidermis.

Present therapies require many months to years of treatment and sometimes result in disappointing outcomes. Photochemotherapy with the photosensitizer psoralen plus ultraviolet A (PUVA) is an effective treatment but carries the potential risk of skin carcinomas such as squamous cell carcinoma and malignant melanoma.[3, 4] An alternative for PUVA therapy is narrow-band ultraviolet B (NBUVB) phototherapy using lamps that have a maximum emission at 311-312 nm. NBUVB can be used alone or together with topical / systemic treatments to accelerate and increase the therapeutic response to phototherapy. In addition there is the melanocites autologous transplant and, as emerging treatment modality, Afamelanotide, which is a potent synthetic analogue of the naturally occurring alfa-melanocyte-stimulating hormone.[5, 6] The optimal treatment of vitiligo will depend on the subtype of the disease and the percent of body surface area (BSA) involved.

## Photochemotherapy: PUVA therapy

Synthetic compounds like 8-methoxypsoralen or 8-MOP, 5-methoxypsoralen or 5-MOP, and trimethylpsoralen (TMP) are used in modern photochemotherapy regimens in the form of topical agents (creams, gels and solutions) or orally, followed by exposure to natural sunlight (so-called PUVASOL) [7, 8] or to artificial UVA radiation (PUVA). The exact mechanism of action of methoxsalen is not known. The best-known biochemical reaction of methoxsalen is with DNA. Methoxsalen, upon photoactivation, conjugates and forms covalent bonds with DNA which leads to the formation of both monofunctional (addition to a single strand of DNA) and bifunctional adducts (crosslinking of psoralen to

both strands of DNA). Reactions with proteins have also been described.

For PUVA, the patient is required to ingest 0.4-0.6 mg/kg of 8-MOP and the lesions are then exposed to UVA after 2 hours when the levels of psoralen have peaked in the blood. Recently an ultramicronised formulation has been introduced and it is better and more consistently absorbed, in countries where it is available it is usually the preferred formulation of the 8-methoxypsoralen. In this case, the preparation has to be administered 1 hour prior to UVA exposure, because of its more rapid absorption.

For all psoralen preparations, the time interval required to achieve peak blood levels can vary with intake of food, especially fatty foods. The peak blood levels show also a wide interindividual variation from patient to patient. The kind of pharmaceutical preparation also plays an important role in absorption. Interpatient variability in peak plasma concentration after an oral dose of methoxsalen ranges from 6 to 15 fold.

Topical PUVA has to be done cautiously to avoid photo-toxicity and koebnerization (appearance of new lesions at blistered sites). Nonetheless, treatments can in fact be done very carefully, using lower concentrations of methoxsalen (0.1% and below). The preparation, which is usually in solution or cream form, is applied directly to the lesions, which are then exposed to UVA after 20 minutes. Better results are obtained with topical preparations containing trimethylpsoralen, that is more commonly used for topical PUVA in countries in northern Europe. Initial doses are about 0.25 J/cm$^2$, with the same increments, for every treatment, until mild erythema is achieved in the lesions. Even if topical PUVA is correctly performed, in most cases perilesional hyperpigmentation can be observed, and can represent an obstacle for continuing the treatment.

PUVAsol, which is commonly used in countries where sunlight is in abundance and where the facilities for artificial sources of light are often lacking, works on the same principle except that natural sunlight is used instead of UVA. The same types of oral and topical preparations are used. The initial exposure is of a short duration and subsequent exposures are gradually increased until satisfactory erythema is achieved.

In sunnier climates, like that in India, treatments can be done all year and this kind of treatment is still quite popular. PUVAsol was also popular in Italy until a few years ago. Now, due to availability of artificial sources for PUVA and narrow band UVB this rather empiric procedure should be discouraged due to its potentially dangerous and frequent side effects.

PUVA is contraindicated in patients with history of skin cancer (melanoma or non-melanoma), premalignant skin lesions, cataracts, alteration of liver function,[9] skin type I, pregnancy and lactation, obesity (increased risk of erythema), concomitant immunosuppressive therapy or associated phototoxic treatments. In order to avoid the potentially dangerous side effects PUVA is being more and more frequently replaced with Narrowband UVB (NBUVB).

## NBUVB phototherapy

The introduction of NBUVB in the early eighties of the last century has evolved into one of the major accomplishments in the field of phototherapy. It is a more recent form of phototherapy, which was initially used for psoriasis and has since also been used for vitiligo.

In addition to its immunosuppressive effects, NBUVB induces melanocyte differentiation and melanin production.[10] In the last decade, NBUVB has become the first-line therapy for extensive, progressive vitiligo because of its superiority to PUVA and its relative paucity of side effects. It can also be used safely in children and those who are pregnant or lactating. When used alone, repigmentation rates ranging from 40% to 100% have been reported, depending on the location of the lesions.[11-15] Patients should be treated with an optimized, aggressive approach, starting at a safe, low dose (*i.e.*, 200 mJ) 2 to 3 times per week with 10% to 20% dose increments. When asymptomatic, light pink erythema lasting 24 hours is achieved, the optimal dose has been reached and treatment should continue at this dose until erythema disappears. The dose should then be increased again until it returns. The maximum dose of NBUVB varies depending on Fitzpatrick skin phototype and photosensitivity. Recently expert recommendations for the administration of NBUVB phototherapy in vitiligo were created.[16] A lack of response after 6 months suggests a nonresponsive patient, and discontinuation of treatment should be considered.[17]

In 1981 Parrish and Jaenicke found that 311 nm wavelength UVB radiation was most effective for the treatment of psoriasis.[18] This finding provided the im-

petus for developing the Philips TL 01 fluorescent bulb, the NBUVB light source. Currently, there are several clinical indications for NBUVB phototherapy including psoriasis, atopic dermatitis, desensitization therapy for photodermatoses and patch stage cutaneous T cell lymphomas.

The use of NBUVB phototherapy for vitiligo was first reported by Westerhof *et al.* in 1997 [19] who compared twice-weekly topical PUVA to twice weekly NBUVB phototherapy. They showed that after 4 months of therapy, 67% of patients undergoing NBUVB phototherapy developed repigmentation compared with 46% of patients receiving topical PUVA. The extent and rates of repigmentation among patients receiving NBUVB were further examined in a separate subset of patients. In this subset, 8% of patients repigmented greater than 75% after 3 months of treatment and 63% did so after 12 months. The authors concluded that NBUVB was slightly, but not significantly, more effective than topical PUVA.The lower cumulative dose and the fewer side effects were considered to be the major advantages of the use of NBUVB over PUVA. It was concluded that compared with topical PUVAtherapy, NBUVB was equally effective and was associated with fewer side effects as well. Since no photosensitizer is used, ocular or gastrointestinal side effects are non-existent.

After this study, the same authors conducted an open trial [15] on the treatment of children with generalized vitiligo with NBUVB. In this study 51 children were treated on a twice weekly schedule for up to 1 year and 53% achieved >75% repigmentation and stabilization of disease was reported in 80%.

## Narrow band UVB *versus* PUVA

After the establishment of NBUVB phototherapy for vitiligo an obvious challenge was to assess its therapeutic efficacy relative to that of other phototherapeutic modalities, in particular, photochemotherapy. To this end several trials have been performed so far. In a first bilateral comparison study NBUVB was compared with PUVA in 15 adult patients with symmetrical vitiligo. After 60 sessions the clinical response to both treatments did not differ significantly.[20] A retrospective comparison of 38 patients on oral PUVA and 31 patients on NBUVB showed a significantly better outcome for NBUVB. In the PUVA group, marked to complete improvement was observed in 23.6%, moderate improvement in 36.8%, no to mild repigmentation in 32.6% andworsening in 7% of patients. The respective figures for the NBUVB group were 41.9%, 32.2%, 25.9% and 0%.[21] Another study compared randomly allocated treatment with thrice weekly NBUVB and oral TMP-UVA in 50 consecutive non-segmental vitiligo patients. The mean treatment duration was 6.3 months for NBUVB and 5,6 months for TMP UVA. Both in terms of stability achieved and efficacy in active and stable disease NBUVB was found to be superior to TMP-UVA.[22] Recently the first randomized, double-blind trial was published on the efficacy of NBUVB *vs.* oral 8-MOP (or 5-MOP) UVA in 50 patients with non-segmental vitiligo. Treatment was given twice weekly and assessments were performed after every 16 sessions. At the end of the study, the PUVA group had received a mean number of 47 treatments as opposed to 97 treatments in the NBUVB group. This difference was suspected to be due to differences in efficacy and adverse effects; 64% of patients in the NBUVB group had >50% improvement compared with 36% of patients in the PUVA group. Also when only those patients were considered who completed ≥48 sessions the reduction of body surface area affection was significantly greater for NBUVB than for PUVA. The color match of repigmented skin was excellent in all patients treated with NBUVB but in only 44% of those treated with PUVA. The clear conclusion of this study was that NBUVB is superior to oral PUVA in non-segmental vitiligo.[23] A small, open, four-quarters comparison study evaluated NBUVB *vs.* BB UVB in combination with topical calcipotriol *vs.* placebo in 9 patients with generalized symmetrical vitiligo: NBUVB was delivered to the upper part of the body until the navel and BB UVB to the lower part of the body. Irradiations were done thrice weekly during the first months and twice weekly thereafter, additionally, calcipotriol was applied once in the evening on vitiligo lesions on the right side of the body and placebo ointment on lesions the left side. After 6 months of treatment, none of the patients showed repigmentation on the lower part of the body indicating that neither BB UVB and calcipotriol alone nor their combination had been therapeutically effective.Brod band UVB was then discontinued and NBUVB applied to the whole body. At the end of treatment, after 12 months, no difference in repigmentation was apparent

between calcipotriol and placebo-treated sites indicating that calcipotriol failed to enhance the response to NBUVB.[24]

In summary, the majority of comparison studies have shown that NBUVB is more effective than other phototherapeutic modalities. Therefore most treatment centers nowadays consider NBUVB phototherapy as the first line treatment for generalized vitiligo. Its distinct advantages over PUVA include the lack of psoralen related side effects and precautions, cosmetically better color match, and its safety in children. However, the relative stability of NBUVB induced repigmentation over PUVA, its maximum safe duration, and, cumulative dose allowed still remain to be determined.

## Irradiation protocols for NBUVB

Narrow band UVB is currently the first choice treatment for inducing repigmentation in generalized vitiligo affecting multiple or large areas of the body and it may stop disease progression in active vitiligo. However, the adoption of a personalized irradiation protocol for each patient is necessary to achieve optimum treatment results. There is no universally accepted protocol for NB-UVB, so treatment protocols differ from site to site. There is a widespread belief that vitiligo patients, in terms of photosensitivity, behave as skin type I and, consequently, they have been treated with very low initial NBUVB doses ranging from 150-250 mJ/cm$^2$ [19] to avoid sunburn. In a recent study, however, this approach has been challenged. It was shown that the erythemal sensitivity in vitiliginous skin depends on the skin type, with darker skin types tolerating higher UVB doses than subjects with a fair complexion. In addition, the minimal erythemal dose (MED) values in vitiligo skin were, on average, only 35% (95% CI: 31-39%) lower than in normal skin of the same individual.[25] The importance of stratum corneum thickening, as a protective mechanism against UV [26] has been emphasized in vitiliginous skin. Recently it has been shown that vitiliginous skin, treated with targeted phototherapy, undergoes progressive photoadaptation with a corresponding increase in the MED;[27] a positive correlation was also found between skin phototype and MED, that reflects the increased NBUVB tolerance shown by the higher skin types. In normal skin, the same finding may be attributable to the increase in melanogenesis; in vitiliginous skin, which is deficient in melanin, this may be due to photoprotective mechanisms other than melanin. The data published by El-Khateeb *et al.* in 2010 [28] confirm that, in vitiliginous skin, photoprotective mechanisms other than melanin, including epidermal layer thickness, optical properties and chromophores, may play a major role. This has to be kept in mind when starting a phototherapy course in an individual with a dark skin type where vitiliginous patches show a proportionally higher resistance to NBUVB irradiation as compared to that of a lower skin type. Apart from the photoadaptation phenomenon and the efficacy of defense mechanisms other than melanin in vitiliginuous skin, another study showed that doses close to the MED are the most effective in determining the induction, *in vitro*, of soluble mediators like Endothelin 1 (ET-1).[29] On the basis of these data and of our personal experience, we initiate vitiligo treatment with higher NBUVB doses, as compared to the phototherapy protocols that were earlier described, *e.g.*, 70% of the MED determined on normally pigmented skin, or 50% in the case of lighter skin types (I e II). We adopt the twice weekly schedule: dose increments at each treatment session are adjusted following the photoadaption of the irradiated skin by dose increments of 10-40% with the aim to induce and maintain a faint erythemal reaction in lesional skin. In the majority of the studies, the dose is stabilized when mild erythema develops. Generally, after the first few sessions, the rate of increase in UVB dose is individualized for each patient.

In practice, we increase by 10-20% for skin type I-II, 30% for skin type III, 40% for skin type IV and eventually 50-60% for the darker skin types. Skin type I usually does not require treatment and, on the other hand, phototherapy is hardly tolerated, the potential side effects being more numerous than the benefits. If symptomatic erythema or blistering develops treatment is omitted (once or twice) and when treatment is resumed the last dose is decreased by 20%.

Treatment is continued as long as there is ongoing repigmentation. We interrupt the treatment if no repigmentation is achieved within 3 months of treatment, or, if after 6 months, only minimal repigmentation is obtained (<25%) with continuous NBUVB exposure.

In some cases, where the response to phototherapy is slow and scarce, an interruption of the treatment followed by a resumption after 2 months may be tried. This is based on the concept that intermittent irradiation

might induce a more effective stimulation of melanocyte proliferation than a continuous treatment schedule. There is currently a trial that is investigating the effects of such a protocol ("stop and go") and the preliminary data seem to be encouraging.[30]

### NBUVB in combination with systemic treatments

Folic acid, vitamin B12 and sun exposure were used in an open label study for a minimal period of 3-6 months in 100 patients with vitiligo during summer and together with UVB irradiation in winter: improvement occurred in 52 patients and total repigmentation was observed in six others.[31] This finding was not confirmed in a parallel group study in which the addition of folic acid and vitamin B12 to NBUVB was assessed: 27 patients with stable vitiligo were randomized to receive either NBUVB alone or NBUVB combined with vitamin B12 and folic acid for 1 year. Although repigmentation was notable on face, trunk and extremities it was minimal on hands and feet, and vitamin B12 and folic acid did not seem to improve the effect of NBUVB.[32]

Because oxidative stress has been implicated in the pathogenesis of vitiligo, the combination of NBUVB with agents that have antioxidative properties has been suggested to increase the effectiveness of phototherapy. Recently, we have treated 35 patients with NBUVB and an oral antioxidant pool (AP) containing alpha-lipoic acid, vitamins C and E and polyunsaturated fatty acids, in a randomized, double-blind, placebo-controlled multicentre trial.[33] The therapeutic response with the AP and NBUVB, revealed 47% of the patients achieving >75% repigmentation against 18% in the placebo group; the average number of treatments required to induce 50% repigmentation was 18 in the AP group and 23 in the placebo group. We hypothesize that therapy with the AP may significantly have improved the clinical effectiveness of NBUVB by reducing oxidative stress. Another study [34] focused on the effect of vitamin E in association with NBUVB phototherapy: 24 patients were treated either with NBUVB plus oral vitamin E or with NBUVB alone in a randomized study. Vitamin E increased the effectiveness of NBUVB, and this was attributed to its ability to prevent lipid peroxidation in the cellular membrane of melanocytes. The antioxidative and photoprotective plant extract Polypodium leucotomos (PL) has been found to have also immune modulator properties: it is able to modulate the immune response after trauma, inhibiting Th2 pathway activation.[35] Given the pathogenic role of oxidative stress and autoimmunity in vitiligo, the therapeutic potential of PL in combination with NBUVB has been evaluated in a double-blind, placebo-controlled trial: 50 patients were randomized to receive either 250 mg PL capsules or placebo three times daily in conjunction with twice weekly NBUVB. At week 26, there was a body area-dependent trend towards more repigmentation in the PL + NBUVB group. The mean cumulative NBUVB dose was similar for both groups. Patients with skin type II and III appeared to benefit more from PL than darker skin types.[36]

At present, antioxidants should be used as co adjuvant rather than as a first line therapy.

NBUVB in combination with topical treatments

Corticosteroids, calcineurin inhibitors, vitamin D analogues and preparations containing pseudocatalase or a combination of catalase and superoxide dismutase have all been used as topical treatments for vitiligo with different and sometimes equivocal results. In addition to their use as a monotherapy, a number of studies have investigated the combination of these agents with NBUVB with the aim to accelerate and increase the therapeutic response to phototherapy.

A case report from India first described the use of thrice weekly NBUVB in combination with calcipotriol cream on the right and placebo cream on the left lower limb. At the end of 6 months, repigmentation was almost complete over the right limb whereas it was less than 50% on the placebo-treated side.[37] Subsequently, several other trials assessed the usefulness of a once or twice daily combination of NBUVB with calcipotriol (calcipotriene) or tacalcitol in small patient cohorts. Most of these trials were open and uncontrolled and did not extend over more than 6 months. In one of these, NBUVB thrice weekly in combination with calcipotriol twice daily applied to all vitiligo lesions on the left side of the body gave better results in 6 out of 17 patients. The study period was not clearly specified, apparently up to 116 treatments (or more) of NBUVB were received by some patients.[38] In another open trial on 24 patients, twice daily application of calcipotriol was found to potentiate the efficacy of NBUVB. About two thirds of the patients had an earlier onset of repigmentation with the combination. After 6 months of treatment the overall response rate was 51% for the combination

and 39% for NBUVB alone.[39] A greater extent of repigmentation and an increase in response rate was also reported for NBUVB in combination with tacalcitol: we performed a randomized, investigator-blinded bilateral comparison study on 32 pairs of symmetrical vitiligo lesions that were exposed twice weekly to NBUVB. In addition, a standard dose of tacalcitol was applied once daily in the evening on one of the paired lesions. Throughout the whole observation period, the combination led to significantly higher repigmentation scores than NBUVB alone. Lesions treated with combination regimen repigmented both earlier and to a greater extent.[40] In contrast, no effect of twice daily calcipotriol cream in addition to twice or thrice weekly NBUVB was observed in an investigator-blinded study on 20 patients after 6 to 12 months of treatment.[41] Two further studies also reported negative findings. Calcipotriol once daily did not enhance NBUVB-induced repigmentation when given over a period of 1 year.[24] Another trial compared monotherapy with NBUVB (24 patients) with NBUVB plus twice daily calcipotriol (13 patients). No significant difference in repigmentation was found between the two groups after 30 sessions of phototherapy.[42]

A small, randomized, placebo-controlled, double-blind trial compared NBUVB plus tacrolimus vs NBUVB plus placebo in the treatment of generalized vitiligo: paired vitiligo lesions in 9 patients were treated thrice weekly with NBUVB plus twice daily application of either 0.1% tacrolimus or petrolatum, over a total period of 12 weeks. Overall, both sides improved without a statistically significant difference between tacrolimus and placebo.[43] In an open, uncontrolled trial including 110 patients with 403 lesions tacrolimus ointment once daily was combined with twice weekly NBUVB for 16 weeks. Greater than 50% repigmentation was observed in 42% of the lesions. Due to the uncontrolled nature of the study it is not possible to assess the additional effect, if any, of tacrolimus to NBUVB in this trial.[44] A recent prospective single blind study on 80 patients with generalized, symmetrically distributed, vitiligo has demonstrated that addition of topical tacrolimus increases the extent of overall repigmentation achieved with NB-UVB therapy and reduces the cumulative NB-UVB dose needed to achieve a therapeutic benefit in affected patients.[45]

There has been a wide debate in the last few years about the possible risk of this association and, namely, the possibility that its use might increase the carcinogenic risk of phototherapy. In a recent paper Lerche [46] reviewed the available data and concluded that the risks have been overestimated. Other publications confirm this position. The principal objections are: the scarce ability of these molecules to penetrate in vitiligo skin, due to their high molecular weight, and the fact that all the data on carcinogenesis have been collected, so far, in animals that underwent massive applications of these topical drugs.[47] Also in our hands, calcineurin inhibitors have proven to be effective together with phototherapy in vitiligo, but further studies are needed to exclude definitely the long side effects and validate a therapeutic protocol that may minimize the risks (application frequency, dosage, etc.), and, for the moment, this association should not be routinely recommended

There is evidence that the vitiligo epidermis shows oxidative stress that is believed to have a fundamental role in the pigment cell degeneration found in vitiligo.[48] On the basis of such findings, Schallreuter *et al.*[49] have argued that excess hydrogen peroxide in the vitiligo epidermis leads to inactivation of catalase, and also identified calcium deficiency in vitiligo keratinocytes [50] suggesting that the correction of catalase deficiency could be a valid therapeutic approach. After an early report on the benefit of pseudocatalase in combination with short-term UVB exposure, no effect of a combination of pseudocatalase with NBUVB was found in a later investigation. Both studies were small, open and uncontrolled.[51, 52] Bakis-Petsoglou *et al.*[53] report a clinical trial of a pseudocatalase cream *vs.* placebo over a 24-week period, with patients in both arms of the study receiving NBUVB. The authors found that the use of pseudocatalase cream with NBUVB was not superior to the use of placebo cream with NBUVB. The therapeutic role of pseudocatalase, alone or in combination with UV is controversial.[54] A small, double-blind, intraindividual comparison study on NBUVB in combination with either a gel containing catalase and superoxide dismutase (Vitix®) or placebo (the excipient only) suggested some effect of the verum preparation.[55] A recent small study [56] also described the use of this product in combination with NBUVB. Due to the open, uncontrolled design of the study the relevance of the data cannot be interpreted.

There is only one report [56] on the combination of NBUVB with topical corticosteroids: the combination

of topical clobetasol together with NBUVB was tested against placebo with NB-UVB and no significant differences could be shown.

In summary, there is some evidence that concurrent treatment with topical vitamin D analogues and calcineurin inhibitors might accelerate and increase the response to NBUVB in a proportion of patients. However, controlled, larger scale trials with longer treatment periods are required to corroborate this contention. Available data on the combination of NBUVB with other topical treatments are scarce and of low evidence level thus precluding a well-founded assessment.

## Duration of repigmentation and predictors of response

Several variables significantly influence repigmentation in patients with vitiligo. These include age, patient motivation, number of treatments, maintenance of adequate lesional erythema, location of lesions, type of vitiligo, skin type, and the presence of residual lesional melanocytes. Usually maximal repigmentation occurs in children with vitiligo. Two to three months of treatment with NB-UVB are usually required before new pigment becomes evident; however it is not uncommon to observe patients with rapid responses (in our series >50% of the patients have experienced repigmentation within the first three months of treatment). Follow-up data of patients after termination of a NB-UVB phototherapy course are limited. In their series, Nicolaidou *et al.*[57] followed up 25 patients for up to 4 years after stopping phototherapy. Relapse was observed in 44% of them within 1 year after treatment cessation. In 14.3% of patients, no new vitiligo lesions appeared within the repigmented areas 4 years after treatment. Sitek *et al.*[58] followed up 11 patients with more than 75% overall repigmentation after a course of NB-UVB and reported that 45% of patients were in full remission 2 years after the end of treatment. Natta *et al.*[59] followed up 9 patients for up to 2 years and reported 25% and 43% relapse rates in 1 year and 18 months, respectively, whereas in the series by Kanwar *et al.*,[60] 4 of out of 8 patients relapsed within 3 months. Recently Kumar [61] reported the results of a study on 150 Indian patients treated with NBUVB with a follow up period of six months after cessation of therapy for stability of repigmentation: only three patients developed depigmentation of repigmented sites during follow-up. There is general agreement on the fact that those who relapse usually respond to a second course of treatment. The duration of the disease is inversely correlated with repigmentation percentage in the face, trunk and limb lesions but not for acral lesions which could be explained by the exhaustion of the melanocytes storage present in the outer root sheath of the hair follicle that occurs progressively with time in areas other than the extremities, where the follicular reservoir is insufficient from the beginning. This is in agreement with the findings of Njoo *et al.*[15] who reported that early lesions respond better than old ones suggesting that the follicular melanocytes are also destroyed by disease process. Also in our patients undergoing treatment with NBUVB we have noticed that vitiligo of recent onset responds better to UV treatment.[62, 63] This was not confirmed by the study of Natta *et al.*[60] who found that the duration of the disease had no impact on the response. In general, facial and small areas of vitiligo involvement are more responsive to NBUVB phototherapy than larger areas of vitiligo [64] or disease at acral sites, like hand skin where the poor response is related to low hair follicle density.[65] An open, uncontrolled study from Greece [58] reported on 70 patients with non-segmental vitiligo who were treated over a maximum period of 1.5 years. Cosmetically acceptable repigmentation (>75%) was achieved in 34.4% of patients with lesions on the face after a mean treatment period of 6 months but in only 7.4% of patients with lesions on the body after a mean treatment period of 9.2 months. Hand and feet vitiligo showed minimal or no repigmentation and lesions on the elbows and knees responded less than lesions on the trunk but better than acral vitiligo. Predictors of a good response, in this study, were darker skin types (III-V) and early initial repigmentation; 25 patients were followed for up to 4 years: 7 patients (28%) remained stable over 1 to 4 years, whereas 18 patients (72%) relapsed after 1 to 3.5 years. In vitiligo, repigmentation may spread inwards from the borders of the lesion or from the hair follicles in the lesion. Kim *et al.*[66] demonstrated that the involved site and the duration of vitiligo are important determining factors in the manifestation of repigmentation patterns in vitiliginous patches. Some [67] have noticed that old lesions showed white hairs and no response to phototherapy contrary to the lesions that had appeared more recently. It could be hypothesized that, the longer the duration of vitiligo, the

higher the possibility of having white hairs. Because the melanocytes in the hair follicles are a major source of repigmentation, the existence of white hairs in vitiligo lesions suggests that vitiligo may be resistant to phototherapy.[68] Thus, the poor response of phototherapy in old vitiligo may be related to white hairs, suggesting that in vitiligo early treatment is required before these white hairs appear. The evaluation of white hairs using a portable digital microscope may predict the response of phototherapy.[69]

## Targeted phototherapy

Targeted phototherapy (excimer lasers and excimer lamps) can be considered when 10% of BSA is affected.[70] This therapy is attractive for patients who wish to avoid skin darkening caused by NB-UVB. Although effective in the repigmentation of stable lesions, this focal therapy typically fails to stabilize vitiligo because clinically unaffected skin is not treated. In the segmental variant, excimer laser seems to be the most beneficial treatment when used early in the disease course.[21] In a recent retrospective study, 59 patients with the segmental variant, which is typically refractory to treatment, responded well to excimer laser, topical tacrolimus, and short-term systemic corticosteroids for 3 months; almost 50% of patients achieved 75% repigmentation.[71]

## Lasers

### *Helium-neon laser*

Low-energy helium-neon (He-Ne) lasers (632.8 nm) have been employed in a variety of clinical treatments including vitiligo management. Light-mediated reaction to low energy laser irradiation is referred to as biostimulation rather than a thermal effect. A first report was published in 2003.[72] This study investigated the effect of He-Ne laser both *in vitro* and *in vivo*. *In vitro* studies revealed a significant increase in basic fibroblast growth factor release from both keratinocytes and fibroblasts and a significant increase in nerve growth factor release from keratinocytes.[73] It has also been shown that melanocyte migration was enhanced either directly by He-Ne laser irradiation or indirectly by the medium derived from He-Ne laser treated keratinocytes. Furthermore, 30 patients with segmental-type vitiligo on the head and/or neck were enrolled in this study. He-Ne laser light was administered locally at 3.0 J/cm$^2$ with point stimulation once or twice weekly. After an average of 16 treatment sessions, >50% repigmentation was observed in 60% of patients.[72] A recent study by the same group [73] demonstrated that He-Ne laser induced a growth stimulatory effect on functional melanocytes via mitochondria-related pathways and suggested that other minor pathways including DNA damage may also be inflicted by laser treatment on irradiated cells. Despite the interesting results obtained in cell cultures and the clinical improvement noted in patients with segmental vitiligo, further clinical studies are required on larger series, also including non-segmental vitiligo, to confirm the indication for the use of He-Ne laser in vitiligo.

### *Excimer laser 308 nm*

The excimer laser represents the latest advance in the concept of selective phototherapy. It emits a wavelength of 308 nm and shares the physical properties of lasers: a monochromatic and coherent beam of light, selective treatment of the target, and the ability to deliver high fluences. The 308-nm excimer laser was first used in dermatology for treating psoriasis. Since then, many studies have evaluated this new device in a number of dermatologic disorders. Psoriasis and vitiligo have each been further investigated, and the use of excimer lasers for both conditions is now approved by the US Food and Drug Administration.

The excimer laser emits a wavelength of 308 nm produced using xenon and chlorine gases. Transmission of the beam of light is achieved by using a liquid light guide (LLG). Spot size is variable from 14 to 30 mm in diameter depending on the model used. These technical characteristics provide this laser with many advantages over conventional phototherapies. High fluences can be emitted, which can be useful in thick plaques of psoriasis but not in vitiligo where only low fluences are used. It is also possible to selectively turn the beam of light and thus to treat the specific area involved, sparing healthy skin. In vitiligo, this selectivity limits the unsightly tanning of perilesional skin, which is commonly observed with other phototherapies. The LLG also makes it easier to reach areas that are usually difficult to treat, such as folds and mucosa. Disadvantages include the fact that the limited size of spots can be unpractical for treating large surfaces (>20% of total surface body

area) and that purchase and maintenance costs of these devices is rather expensive. Due to its selectivity and pro-pigmentary properties, the 308-nm excimer laser represents an interesting new approach for treating vitiligo. The use of the 308-nm excimer laser in treating vitiligo was first reported by Baltas *et al.*[74] Since then, many studies have shown the efficacy of this laser for repigmenting vitiligo lesions. Spencer *et al.*[75] recently reported that the 308-nm excimer laser may represent a new therapeutic option for the management of vitiligo, resulting in repigmentation of vitiligo patches in less time than that required with current modalities. With this treatment, pigmentation can start after only five sessions and increase with continuation of treatment. Low fluences (from 50 to 200 mJ/cm$^2$) have been used in one to three sessions a week for 1 to 6 months, depending on the study. Among factors that can influence the clinical response to treatment, localization of the lesions seems to play a crucial role.[76] In their study, Taneja *et al.*[77] report repigmentation of at least 75% in all the lesions located on the face *vs.* none on the hands and feet. The variability of some results reported certainly depends on the localization of target lesions. Sessions can be performed once, twice, or three times a week. The repigmentation rate seems to be linked to the total number of sessions and not to their frequency.[78] It is difficult to know if repigmentation is stable with time because the follow-up of existing series is short or non-existent. A recent study reports no depigmentation 1 year after the end of sessions.[79] On the other hand, Passeron and Ortonne, in a recent review article [80] report that in their series about 15% of new depigmentation is observed 1 to 3 years after the end of treatment. Tolerance of treatment is usually very good, and immediate side effects are limited to erythema and in rare cases blistering. Phototherapy with the excimer laser may represent a valuable therapeutic option in children with vitiligo. In a group of children with vitiligo Hui Lan *et al.*[81] showed that the combination of topical pimecrolimus and excimer laser is statistically better than excimer laser alone: combined therapy may lead to faster repigmentation than excimer laser monotherapy for facial lesions only. In the same study the authors concluded, that 308-nm excimer laser was effective, safe, with minimal side-effects for childhood vitiligo. Topical tacrolimus has been shown to increase the efficacy of excimer laser phototherapy in vitiligo. Two pilot prospective studies [82, 83] have compared the efficacy of the excimer laser combined with 0.1% tacrolimus ointment with excimer laser monotherapy or laser associated with a placebo. In the first series, two sessions per week were performed *vs.* three in the second. In both cases, a total of 24 sessions were carried out and 0.1% tacrolimus ointment was applied twice a day. Results were comparable and clearly showed a greater efficacy and shorter response to treatment with combined therapy as compared with excimer laser alone. Such a combination might not be used routinely since there is an ongoing debate whether tacrolimus might increase the risk for UV-induced cutaneous cancers. Another possible association could be with topical corticosteroids: in a recent study Sassi *et al*. showed that twice as more patients had more than 75% repigmentation when using hydrocortisone 17-butyrate during 308 nm excimer laser treatment as compared to patients treated with the laser alone.[84]

The possible mechanisms of action of NBUVB radiation in vitiligo have already been discussed, but additive actions can be advocated in the case of the new potent monochromatic light sources used for targeted phototherapy. Photobiologically, the wavelengths of the excimer laser (308 nm) and NBUVB (311 nm) are very close to one another, and the therapeutic effects may well be similar. The biological effects of coherent and collimated laser light may differ from those of incoherent light of the same wavelength. Conventional UVB sources emit polychromatic, continuous, incoherent light, whereas the excimer laser emits coherent, monochromatic, UVB light in short pulses. These photophysical properties of the excimer laser could account for its greater effectiveness as compared to conventional NBUVB in the treatment of vitiligo. Namely, the possibility to deliver high doses in a short interval of time may account for the differences between the biologic effects of conventional NBUVB and those of the monochromatic excimer sources. Even if the Bunsen-Roscoe law (BRL) of reciprocity states that a certain biological effect is directly proportional to the total energy dose, irrespective of the administered regimen, in some cases it has been shown not to hold and this could be also the case for the effects of the excimer laser. Recently, the mechanism of the excimer laser's high efficacy in psoriasis treatment has been investigated; on the other hand, data on the autoimmune origins of vitiligo underline the probable implications of the immunosuppressive action of UV in

treating vitiligo and thus the intense pro-apoptotic effect of the 308 nm wavelength on T cells, that has been demonstrated in psoriasis, could play a role also in vitiligo: among UVB light sources, the XeCl excimer laser is the strongest inducer of apoptosis in T cells.[85] Novak *et al.* also compared seven spectral distributions of UVB light in the spectral region of 290-311nm: the 308 nm XeCl excimer laser more strongly induced apoptosis at a dose six times less than that of NB-UVB.[86] Another study on psoriasis patients,[87] based on an immunohistochemical evaluation of T cells and the expression of various molecules associated with apoptosis, demonstrated that the 308 nm Excimer Lamp (see next paragraph) effectively depleted T cells in psoriatic hyperproliferative skin after treatment. In the previously cited study by Noborio [29] on the ability of different light sources in the UVB range to induce secretion of ET-1, the excimer laser irradiation induced high levels of ET-1 secretion compared to the other sources.

## Non laser light sources

### *Monochromatic Excimer Lamp/ Excimer Light 308 nm (MEL 308 nm)*

The 308 nm monochromatic radiation can also be delivered by excimer lamps. The effectiveness of a new 308 nm monochromatic excimer source, with emission close to that used in NBUVB phototherapy, has been initially described in the treatment of recalcitrant palmoplantar psoriasis.[88, 89]

A pilot study [90] that we have carried out, using such a device reports that 18 out of 37 vitiligo patients achieved 75% or more repigmentation after 6 months of treatment. The source in this study was a 308-nm XeCl MEL device with a power density of 48 mW/cm$^2$ at a distance of 15 cm from skin and, the irradiation field covered an area of 504 cm$^2$ with rectangular shape (36 cm x 14 cm). Interestingly, a satisfactory response on the hands was noted: two patients achieved grade 3 repigmentation. This finding is not significant because of the limited number of patients that received treatment on the hands in this study (N.=3), but it may suggest the efficacy of higher NBUVB fluencies on these locations that usually respond poorly to conventional treatment. The 308 nm MEL may present some advantages over the laser: lower power density and consequently reduced risk of accidents due to overexposure; the larger irradiation field that allows to treat larger areas at a time, with shorter treatment duration. More recently devices that deliver 308 nm MEL to the skin by means of an optic fiber or with a smaller hand piece have been introduced: this offers the possibility to treat both small and large lesions.

Apart from calcineurine inhibitors that proved to enhance the efficacy of UV treatment in the majority of the published studies, other topical treatments have been associated with 308 nm MEL phototherapy in vitiligo and may variably increase its effectiveness: good results have been reported with topical tacalcitol [91] in a half body comparison study; topical khellin has been evaluated in association with 308 nm MEL: the results were better than excimer light alone.[92] The cost of these devices is lower than that of the lasers and maintenance is less frequently required, with a favorable cost-benefit ratio. The short term and long term side effects should be the same as conventional NBUVB. Nevertheless, the carcinogenic risk of MEL 308 nm has been questioned in a recent paper [93] due to the presence of erythemogenic and carcinogenic wavelengths, and the use of appropriate filters to improve the risk/benefit ratio has been suggested; the data were obtained on irradiated cultured T cells on which apoptosis and cyclobutane pyrimidine dimers (CPDs) were measured. These findings need to be confirmed with clinical studies on humans, and, in any case, the risks are counterbalanced by the fact that the irradiation strength of the excimer lamp is stronger, and thus less irradiation time is required for treatment, with the comparative advantages of fewer treatments and a lower cumulative UVB dose.

## Excimer laser/lamp *vs.* NBUVB, ecximer laser vs/excimer lamp

In the last years, studies have been published that compare the excimer laser or light with conventional NBUVB phototherapy. A first paper [94] compared the efficacy of the laser with that of the lamp and also with NBUVB in psoriasis: there were no significant differences between the excimer lamp and the laser, but both were more effective than NBUVB, as long as an aggressive protocol was used and also the cumulative UV dose was reduced as compared to NBUVB. In vitiligo, a first study demonstrated the greater efficacy of the 308-nm excimer laser over NBUVB, with more rapid and profound repigmentation induced by the laser. The

comparison was made on 23 patients with symmetrical vitiligo patches treated with the 308 nm laser or NBUVB on a two week sessions schedule for a maximum of 20 treatments.[95] A similar, but multicentre study, has been published by our group comparing the therapeutic effectiveness of MEL 308 nm and conventional NBUVB phototherapy in twenty-one vitiligo patients. Symmetrical vitiligo lesions on one body side were treated twice weekly for six months, while NBUVB was used to treat lesions on the opposite site. At the end of the study 37.5% of lesions treated with 308 nm MEL and only 6% of lesions treated with NBUVB achieved an excellent degree repigmentation.[94]

These two comparative studies both suggest that treatment with the excimer laser or MEL 308 nm may allow repigmentation within a shorter period of time than NBUVB phototherapy does, while limiting exposure to only selected areas. Also, the rapid onset of repigmentation may play an important role in supporting patients' motivation and compliance, and, what may be of great importance, the cumulative UV dose at the end of the treatment is significantly lower than with conventional NBUVB. Le Duff *et al.*[95] published, in 2010, a study on 20 vitiligo patients were the aim was to compare the effects of 308 nm excimer laser treatment and the excimer lamp treatment: the design was that of a randomized monocentric study where one lesion was treated with the 308-nm excimer laser and its counterpart with the 308-nm excimer lamp. The results showed that the 308-nm excimer lamp and laser had a similar efficacy in treating vitiligo. For the same fluence, the lamp induced more erythema suggesting photobiological differences between the two devices. This is not a surprise if the output of the sources is compared from a photophysical point of view, looking at the spectrum: the laser exhibits more "pure" monochromaticity; neverheless these differences do not seem to influence the biologic effect and the therapeutic outcome. The types of repigmentation pattern obtained with NBUVB phototherapy or targeted phototherapy using a 308 nm excimer laser were compared in a recent study.[91] These patterns according to location, age, duration of lesions, and speed of response showed similarities in both the NBUVB and excimer laser-treated groups, the most frequent being the perifollicular type in both groups treated with NBUVB or excimer laser followed by marginal, diffuse, and combined; nevertheless the marginal pattern was more frequent in the early response group. The Authors did not find significant differences in the repigmentation pattern according to the location of lesions, patient 'sage, or duration of lesions.

### Mercury arc lamps

Different devices equipped with high-pressure mercury arc lamps are now available for targeted phototherapy. Usually the light is delivered to the skin by means of an optic fiber. Due to the emission spectrum of these lamps this is also referred to as "targeted broad band UVB". Interesting results have been described in vitiligo, with a high-pressure mercury lamp capable of emitting either UVB or UVA (Dua-Light, Thera Light Inc. Carlsbad, CA USA). The UVB spectral output of this light source includes peaks at 302 and 312 nm, with an average weighted erythemal wavelength of 304 nm. The high output of this device allows irradiation of 100 mJ/cm$^2$ of UVB to take place within approximately 0.7 s. Ultraviolet radiation is delivered through a square aperture sized 1.9 cm x 1.9 cm. Asawanonda *et al.*[96] reported their experience on six patients: twenty-nine vitiligo lesions were treated with targeted, broadband UV-B phototherapy. Treatments were carried out twice weekly for 12 weeks. Some degree of repigmentation occurred in all subjects. Onset of repigmentation was as early as 3 weeks of treatment in some subjects. According to these results, targeted broadband UVB could be an efficacious and safe modality for the treatment of localized vitiligo. The same authors in a subsequent study reported that there were no differences between targeted broad band UVB and targeted NBUVB (non-laser), obtained with the adjunctive filtration of the beam.[97] In the case of non-laser devices emitting UVB, the results may differ from those that can be obtained with a monochromatic source such as an excimer laser. A possible advantage is that these mercury arc lamps are less expensive and require minor maintenance as compared to the excimer devices. Another device, similar to the aforementioned, has been used with interesting results in psoriasis [98] and a recent report has been published concerning its use in vitiligo.[99] The B Clear-Targeted PhotoClearing System (Lumenis Inc, Santa Clara, CA, USA) uses a UVB lamp to deliver targeted broad band UVB, filtered incoherent pulsed or continuous UVB light at 290-320 nm. Peak irradiance occurs between 310 and 315 nm. The 16 x

16 mm spot size emits a pulse width of 0.5-2.0 s with a fluence range of 50-800 mJ/cm$^2$. The authors reported on a group of 12 patients good results on vitiligo lesions located on the face, to a lesser degree on the trunk, and with no response in acral lesions; there were minimal adverse effects that did not require discontinuation of treatment. A system, named "UVB microphototherapy" (300-320 nm, peak at 311 nm), with a focused beam of broad band UVB light with a 311 nm peak, 2-3 times per week, has been reported as an alternative to NBUVB and PUVA for localized vitiligo. From 734 patients, 510 (69.48%) achieved >75% repigmentation of treated areas and 112 were totally repigmented; other 155 patients (21.12%) achieved 50-75% repigmentation and 69 (9.40%) showed <50% repigmentation.

## Plasma lamps

A phototherapy device, the MultiClear® system (Cure Light Ltd. USA), has been recently introduced.[88] It is based on Selective Photo Clearing (SPC™), a proprietary technology generating, by means of high-power plasma light source, emission of different wavelengths: 296-315 nm, 360-370 nm, 405-420 nm (blue light PDT). The system allows to select high intensity of UVB, UVA, and a blend of targeted UVB and UVA1 delivered by means of a flexible light guide, with a treatment spot of 23 mm x 23 mm: UVA1 and UVB could act synergistically to induce repigmentation in vitiligo according to the producer's specifications (unpublished data). Clearly, all these sources do not have the peculiar advantages of the high intensity monochromatic NBUVB peaking at 308 nm, nevertheless, light is selectively targeted to the skin, and this is an advantage as compared to whole body NBUVB. The spectra of the different sources may be slightly different from case to case with a variable presence of the shorter more erythemogenic UVB wavelengths. In some of these devices the emission is filtered to eliminate erythemogenic radiation, but this can considerably reduce the power density.

## Phototherapy as an adjuvant to surgical treatment in vitiligo

With cultured melanocyte grafts, repigmentation is attained several months after surgery, and PUVA contributes to provide faster and deeper repigmentation.[42]

A recent report on 17 vitiligo patients with stable focal or segmental vitiligo has demostrated that combination treatment with split-skin-thickness grafting and postsurgical exposure to 308-nm excimer laser can lead to fast, cosmetically good, long-lasting results. PUVA, NBUVB phototherapy and excimer laser phototherapy may be used after surgical procedures in vitiligo to accelerate repigmentation and improve the aesthetic results.

## Conclusions

Phototherapy remains an essential treatment option for vitiligo. Treatment of vitiligo with phototherapeutic modalities may halt disease progression and induce significant repigmentation in vitiligo. Most treatment centers nowadays consider NBUVB phototherapy as the first line treatment for generalized vitiligo because of its relatively good efficacy and excellent tolerance as compared with systemic and topical PUVA therapy. The efficacy of NBUVB, in vitiligo, can be further enhanced with associated topical or systemic treatments. Many investigations have documented the benefits of targeted phototherapy systems, including 308 nm xenon chloride excimer lasers, which offer several advantages over conventional NBUVB units that irradiate both diseased and normal skin whereas targeted sources deliver high intensity light exclusively to depigmented areas. Rapid therapeutic responses have been reported after targeted phototherapy which may contribute to the reduction of the cumulative UV dose.

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