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A review of Narrow-band ultraviolet B radiation in vitiligo

Attwa E. Narrow-band ultraviolet B radiation in vitiligo

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Abstract

Vitiligo is a common, acquired pigmentary disorder of unknown pathogenesis with great impact on patient's appearance and quality of life. It presents a therapeutic challenge to many dermatologists. Photochemotherapy using psoralen and ultraviolet A (PUVA) therapy, topical and oral immunosuppresants, as well as cosmetic camouflage are also commonly employed with varying clinical efficacy. Phototherapy is a popular treatment option, which includes both of the generalized ultraviolet B (UVB) therapies, broadband UVB (BB-UVB) and narrowband UVB (NB-UVB). It has been used favorably, both alone as well as in combination with other agents like topical calcineurin inhibitors, Vitamin-D analogs. Combination therapies are useful and may provide quicker regimentation and treat vitiligo with an additive mechanism of action than UVB phototherapy. Advances in technology may lead to the continuing use of UVB phototherapy as a treatment for vitiligo through the development of sophisticated devices and delivery systems as well as innovative application methods. These will provide increased therapeutic options for all vitiligo patients, particularly those with refractory disease. In this article, we have reviewed the available data pertaining to efficacy and safety issues for NBUVB as monotherapy, its comparison with psoralen plus ultraviolet A and other modes of phototherapy, combination regimens that have been tried and future prospects of NBUVB in vitiligo.

Key words: narrowband ultraviolet B, phototherapy, vitiligo

Core tips: Vitiligo is an acquired depigmentation disorder with great impact on patient's appearance and quality of life. Till date, the etiology of vitiligo remains elusive, which makes it difficult to have curative

therapies. Narrow-band UV-B phototherapy is widely used and produces good clinical results. In this article, we review the journey of NBUVB so far and highlight the current status of other new phototherapy modalities in the treatment of vitiligo.

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INTRODUCTION

The first report of the use of phototherapy in the treatment of skin disorders dates from 1400 BC when patients with vitiligo were given certain extracts of the plants Psoralea corylifolia in India and Ammi majus linnaeus in Egypt in the form of topical application or ingestion, followed by exposure to the sun [1]. The real interest in the use of UV irradiation in the treatment of various skin diseases started in the 19th century when Niels Finsen received the Nobel Prize in 1903 for his therapeutic results with UV irradiation in lupus vulgaris[2].

In 1977, Fischer[3] found that UV light at a wavelength of 313 nm was effective in clearing psoriatic plaques. Diffey and Far,[4] after studying the effects of ultraviolet radiation (UVA, UVB, and UVC), suggested that longer wavelengths added nothing to the therapeutic benefits ,that shorter wavelengths actually detracted from the effectiveness of treatment ,and that UVB was almost effective at 311nm.

A few years later it was determined that the most effective wavelengths were between 295 and 313 nm; within that spectrum, the ratio of the lowest effective daily dose to the minimal erythema dose was smallest for 313 nm, indicating that this wavelength may possess the optimal "phototherapy index" for clearing psoriasis Van Weelden *et al*[5]**.**These studies led to the development of the Phillips TL-01 fluorescent lamp, which emits a narrow peak around 311-312 nm (Figure 1) [6]**.**

Narrow band UVB is a subset of the UVB Wideband or Broadband spectrum. The UVB band comprises the range of wavelengths between 290 nm and 320 nm while UVB Narrowband has a narrow spectrum of emission (310-315nm) wavelengths with a peak at 311 nm[7]**.**

Narrow band -UVB phototherapy cabins contain fluorescent TL-01 (100 W) tubes as the source of irradiation. The cost of a chamber and lamps show considerable variations between countries and distributors. NB-UVB cabins available commercially either incorporate TL-01 alone or in combination with UVA tubes. Combination chambers take longer to administer a treatment dose. Thus, although they provide flexibility, they may represent an unsatisfactory compromise for a busy phototherapy unit [8].

Shorter tubes of NB-UVB have also become available in small area treatment equipments (hand and foot unit, NB-UVB comb) for the therapy of localized body areas[9].

Narrow band -UVB schedules can be tailored according to patient's skin type and local experience. There are two regimens that are most commonly used; the first involves determination of the individual's minimum erythema dose (MED) by means of a separate bank of TL-01 tubes[10]. Another approach, as commonly practiced is the narrow band skin type protocol. It involves standard initial dose according to Fitzpatrick skin phototype (Table 1) with stepwise increases (usually 20%) depending on patient's erythema response.This schedule has proven immensely effective and has been widely distributed and used in a broad selection of phototherapy practices [8].

Minimum erythema dose determination involves exposing small defined areas of sun-protected, clinically uninvolved skin to increasing doses of UV light, the dose to each area typically being 1.4 times the previous dose. A template of UV-opaque, adhesive plastic with eight 2·3cm^2 apertures (ports), affixed to the lower back of the patient may be used,

with each port exposed to a different radiation dose from a panel of TL-01 fluorescent tubes. The rest of the patient's skin is covered during these UV exposure**s**[11].

The dose for each port for NB-UVB phototesting is dependent on the subject Fitzpatrick skin type. For skin types I–III, initial doses of 400, 600, 800, 1000, 1200, 1400 mj/cm^2 are used while for skin types IV–VI, 800, 1000, 1200, 1400, 1600 and 1800 mj/cm^2 are used. The patients are instructed not to receive any natural or artificial UV light to this region of the skin during the next 24 hours and asked to return to the phototherapy centre in 24 hours. The area of the photo-testing should be identified by ink marking at the different dosage sites. A positive reading is considered as identifiable erythema within the margins of the phototesting port. If bright red erythema develops or blistering occurs at the site of any of the phototesting sites, topical corticosteroids can be used to treat the area [12]**.**

Once MED has been determined, the treatment protocol is usually ''percent based''. Often 70% of the MED value is used for the first treatment; thereafter therapy is given three times or more weekly with 40, 20 or 10 % increments depending on local experience, erythema response and skin type tolerance [13, 14]**.**

A semiautomated small hand–held MED tester (Durham MED tester) has become available which generates a fixed sequence of UV doses, based on attenuating foils. The Durham MED tester attenuation sequence approximates a geometric series with a factor of 1·26. Starting from the open aperture (100%), each subsequent aperture is attenuated by a factor of approximately 1·26 [15]**.**

METHODS OF NB-UVB RESEARCH

NBUVB as Monotherapy

Narrow-band UVB phototherapy has been found to be effective and safe for vitiligo [16]. The results of monotherapy with NBUVB have been better in Asian skin. Approximately three-quarters of patients in the series by Kanwar *et al* [17] achieved greater than 75% to complete repigmentation after NBUVB treatment for a maximum period of 1 year. The mean duration of disease was significantly shorter in those who had marked to complete pigmentation compared with those who had poorer response. As with any treatment modality for vitiligo, the best results were observed in lesions on the face and neck, followed by the proximal limbs and trunk. Perifollicular pigmentation was the most common type of initial repigmentation that was observed in approximately three-quarters of patients.

Brazzelli *et al* [18] have studied the effect of NBUVB in vitiligo and the influence of body sites, age of the patients and duration of disease on clinical response. Complete repigmentation was more commonly observed in lesions located on the face, neck and trunk in decreasing order of frequency (68, 57.9 and 50%, respectively). Age of the patients did not influence the response to treatment for facial lesions, while in other areas complete repigmentation was much more commonly observed in younger patients (<20 years). As far as the duration of disease is concerned, lesions over the neck, upper and lower limbs showed the best rate of complete repigmentation (83.3, 33.3 and 28.5%, respectively) in patients with disease of recent onset (<2 years), while

for the lesions over the face, long-standing vitiligo patients responded better. The authors recommend early treatment, as the best results were achieved by young patients with recent-onset vitiligo.

In a randomized, controlled, side-to-side comparison study, mean improvement in the NBUVB was 42.9% compared with 3.3% in the untreated control side, with the severity of disease having been assessed by Vitiligo Area Scoring Index (VASI)[19]. Response to treatment varied greatly between different anatomic sites, with the best response seen over the lower extremities and worst response on the feet. Whereas all patients did not receive treatment for their face, 37.5% of those who opted for treatment of their face had more than 75% repigmentation.

In a large, open, prospective study from India, only approximately a quarter of patients could achieve more than 75% repigmentation[20]. This poor result in Indian patients can be attributed to lower initial dose and twice-weekly treatment. In those patients who had significant pigmentation, it was attributed to good compliance, a greater number of treatments and increasing cumulative dose. Although initial repigmentation was darker, good color matching could be achieved with continued treatment.

Narrow-Band UVB versus PUVA

In Westerhof and Nieuweboer-Krobotova's study comparing twice-weekly topical PUVA versus NBUVB, it was observed that 67% of patients achieved repigmentation in the NBUVB group compared with 46% in the topical PUVA group after 4 months of treatment [21]. After 3 months of NBUVB treatment, 8% of patients showed more than 75% repigmentation, whereas after 12 months of NBUVB treatment, 63% had

such repigmentation. In the first retrospective analysis of comparison between NBUVB and PUVA by Parsad *et al* 41.9% of patients in the NBUVB group and 23.6% in the PUVA group had marked to complete repigmentation after a maximum treatment for 1 year. Color matching was observed in 86% of the NBUVB-treated patients and only 35% in the PUVA group. Stable repigmentation after 1 year of treatment completion was observed in 78.5% of patients in the NBUVB group and 60% in the PUVA group [22].

In the first randomized, double-blind, placebo-controlled trial, the improvement in body surface area affected by vitiligo was greater with NBUVB than placebo after 48 sessions ($p = 0.007$)[23]. While 53% of evaluable patients in the NBUVB group achieved more than 50% repigmentation, 23% in the PUVA group achieved similar repigmentation. After 12 months of cessation of therapy, the superiority in terms of efficacy for NBUVB was maintained, although it was not statistically significant. No association between duration of disease and success of treatment was observed. Although some degree of repigmentation was observed in all patients in the NBUVB group and 92% patients in the PUVA group, color match was excellent in all patients in NBUVB, while it was much poorer with PUVA. The cosmetically unacceptable color matching tended to persist even after a year of treatment cessation.

In a side-to-side comparison study involving 15 patients, an exactly equal number of patients achieved 0–40, 40–60 and 60–75% repigmentation after 60 sessions[24]. The difference in the incidence of side effects such as erythema and blistering was not siginificant between the groups.

In a small retrospective analysis by Scherschun et al., five of their seven patients (70%) achieved more than 75% repigmentation after a mean of 19 treatment sessions. They observed that longer disease duration correlated negatively with response to treatment[16]. In the same setting, NBUVB was found to be more effective compared with PUVA in imparting stability in vitiligo and in repigmentation in both active and stable disease [25].

Vitiligo usually begins in childhood in a proportion of patients, with half of the patients having disease onset before 20 years of age[26]. However, experience of NBUVB in childhood vitiligo is limited. In a prospective study, Kanwar and Dogra[27] recruited 26 children, of whom 20 completed the study. After treatment for a maximum of 1 year, 75% of patients had more than 75% repigmentation. After a mean exposure of 34 times, 50% repigmentation was achieved. Mean duration of disease prior to treatment initiation was less for patients who had marked to complete repigmentation compared with those who had minimal or moderate improvement. The best responses were observed on the face and neck, followed by the proximal limbs and trunk. Although the authors concluded that NBUVB is effective and well-tolerated in children with vitiligo, the long-term outcome for skin conditions in general is not known.

Narrow-band UVB offers major advantages over PUVA which may be important in choosing therapy for patient. It is less time consuming, easier to perform, and does not require the concomitant administration of a photo sensitizer that may cause nausea, cataracts, phototoxic reactions, and unwanted drug reactions[25]. Other advantages also

include the safe use in pregnant women and children and absent drug costs [28,29].

However, short remission rate is one of the greatest disadvantages of NB-UVB compared with PUVA, as for diseases on the palms and soles does not respond to NB-UVB although such disease can at times respond in young children. In comparison, PUVA therapy is often effective at these sites as NB-UVB is less penetrating than UVA radiation[30,31].

Narrow-Band UVB versus Broad-Band UVB

Narrow band-UVB has a relatively monochromatic spectrum of emissin when compared with BB-UVB[32]. Erythema is more commonly produced by BB-UVB than NB-UVB, as NB-UVB is effective at minimal erythema doses much less than those used in BB-UVB treatment [33]. The TL01 lamp is about 5-10 fold less potent than BB-UVB for erythema induction ,hyperplasia, edema ,sunburn cell formation and langerhans cell depletion from the skin [34].

Narrow band-UVB is regarded as more effective with fewer side effects compared with BB-UVB in treating several chronic inflammatory skin diseases as psoriasis and vitiligo.Recently it has been proved to be superior to BB-UVB in treatment of HIV-associated eosinophilic pustular folliculitis with considerable success, especially against the intense itch [35].

Targeted narrowband ultraviolet B therapy

Targeted phototherapy implies delivering light to localized diseased areas of skin. Since only the affected area is exposed to radiation, higher doses of radiation can be used to achieve better and faster results with

lower total cumulative dose and hazards of phototoxicity. Also, it can be used to treat difficult to reach areas like skin folds.

Recently, new UV sources that emit wavelengths effective for the treatment of vitiligo in a targeted fashion are becoming popular. Xenon chloride laser, popularly known as an excimer laser (EL), is a 308 nm laser that was initially used for treating psoriasis[36,37]. However, as its operational wavelength is close to that used in NBUVB, it is used to treat vitiligo as well. This laser offers the advantage of delivering high doses of light to localized areas[38,39]. It was first used successfully in vitiligo by Baltas et al[40] in 2001. In 2002 Spencer et al[39] concluded that the degree of repigmentation in a period of 2-4 weeks is much higher than that achieved with any other current vitiligo therapy.

Taneja et al[41] and Choi et al[42] also showed beneficial results with excimer laser with non acral lesions responding the best. Two studies compared the efficacy of excimer laser to NBUVB, and found that the excimer laser caused more significant and quicker repigmentation[43,44]. However, neither of the two studies was controlled nor used a standardized scoring method.

The monochromatic excimer light (308 nm MEL) may present some advantages over the laser. Firstly, it gives a larger irradiation field that enables to treat larger areas at a time. Secondly, lower power density leads to reduced risk of accidents due to overexposure, suggesting a better safety profile. The excimer lamp was found to give equivalent pigmentation as compared with an excimer laser. In 2003, Leone et al[45] reported that 35/37 (95%) patients showed signs of repigmentation within first eight sittings of MEL and excellent and good repigmentation in 18 and 16 patients, respectively. They also showed that three patients

who did not respond to previous treatments with NBUVB showed excellent repigmentation after 308 nm MEL therapy. They proposed that this might be possible due to the difference in the mode of action of these two sources, with 308 nm MEL device delivering higher energy fluences to the target tissue in less time as compared to NBUVB devices. The repigmentation rate was between 25% and 50% over the entire body, and between 50% and 75% for vitiligo lesions not located at bony prominences or extremities[46]. Interestingly, investigators also noted that MEL induced more erythema than EL suggesting that despite identical 308 nm peak wavelength, EL and MEL might possess different photobiological properties. Similarly, Shi et al[47] also found that the repigmentation rates with excimer lamp were same as those with laser (79% vs. 87.5%, $P > 0.05$). A retrospective study of 80 patients with segmental vitiligo (SV) treated with EL showed that 75-99% repigmentation was achieved in 23.8% of cases and 50-74% repigmentation in 20% of cases[48]. This report indicates that besides surgical methods, EL might be an option for SV patients, with the degree of repigmentation positively correlating with treatment duration, cumulative dose, and shorter disease duration[48].

A recent study was conducted in 40 patients of "stable" vitiligo involving less than 5% body surface area (BSA) who were resistant to conventional oral/topical treatment options. They were treated with a targeted NBUVB device twice-weekly for a maximum of 30 sessions or until 100% repigmentation, whichever was reached first. There were 31 responders (77.5%) who achieved repigmentation ranging from 50% to 100%. The onset of repigmentation was seen as early as the 3(rd) dose in some cases and by the 10(th) dose in all responders. A total of 97 lesions were

treated out of which 45 lesions (46.6%) achieved 90-100% repigmentation. Lesions showing 75% and 50% repigmentation were 14 and 15 in number respectively. 23 lesions failed to show any significant repigmentation at the end of 30 doses. Best response was seen on the face and neck with 20 of the 31 lesions achieving 90-100% repigmentation in this area. Duration of vitiligo was seen to have no statistically significant impact on the repigmentation achieved. Targeted NBUVB phototherapy seems to be an effective treatment option in localized vitiligo with a rapid onset of repigmentation seen as early as 2(nd) week of treatment [49].

Combination Phototherapy

The aims of combination therapy are to reduce the side effects of phototherapy, by potentially facilitating a lower UVB cumulative dose or number of treatments, and to improve efficacy; this involves the concurrent use of an agent that may offer an additive or synergistic effect[50]**.** Compatibility between treatments has to be taken into account, as topical agents may have UVB blocking effects; consequently, it is generally advised that if topical agents are used, they should be applied post-UVB exposure [51].

A) Combination of NB-UVB with topical agents

1. Calcipotriol plus NB-UVB

The role of vitamin D analogues in the management of vitiligo was discovered serendipitously when hyperpigmentation was observed in psoriatic patients who had been treated with a combination of topical calcipotriol and PUVA or NBUVB. Formally, the combination of vitamin D analogue and NBUVB was used first by Dogra and Parsad[52]. The proposed mechanism for vitamin D analogues in vitiligo is two-fold: it

repairs defective calcium uptake in melanocytes and activates vitamin D receptors. Activation of vitamin D receptors leads to stimulation of tyrosinase activity and consequent melanogenesis. Moreover, decreased levels of intracellular Ca2+, as observed in vitiligo, leads to high levels of intracellular reduced thioredoxin, the substrate for thioredoxin reductase and consequent inhibition of tyrosinase activity[50]. As the mechanism of action of NBUVB is different from that of topical vitamin D analogues, hypothetically the combination might be better than either agent alone.

Low levels of vitamin D3 have been noted in patients of vitiligo and other co-morbid autoimmune conditions. A significant body of data suggests that vitamin D3 is strongly immunosuppressive and improves many Th1 triggered diseases i.e. it inhibits the Th 1 phenotype and potentiates the Th2 phenotype; and that low levels are associated with autoimmune conditions including vitiligo. However, the cause of low vitamin D3 in patients with autoimmune conditions remains unknown[53]. Kullavanijaya and Lim[54] observed appreciably better response with the combination compared with NBUVB alone (although not significant) in a side-to-side comparison study. Also, Leone *et al*[55] and Gamil *et al* [56] reported the effectiveness of combination therapy of NB-UVB with calcipotriol in vitiligo and they suggested that treatment with NB-UVB phototherapy in combination with topical calcipotriol may lead to earlier pigmentation with lower initial cumulative NB-UVB radiation in subjects with vitiligo.

Although the combination of topical vitamin D analogues with NBUVB was found to be beneficial, Arca *et al*[57] could not find encouraging differences in the percentage of repigmentation.

2. Tacrolimus plus NB-UVB

Autoimmunity is probably the first etiology proposed for vitiligo. The role of autoimmunity in vitiligo is substantiated by detection of organ-specific autoantibodies in vitiligo patients, antibodies directed to melanocytes and a decrease in T-helper cells, amongst other factors[58]. Topical calcineurin inhibitors having immunomodulatory properties have been found useful in vitiligo as monotherapy, as well as in combination with NBUVB. Direct interaction between pimecrolimus and keratinocytes, creating a favorable atmosphere for melanocyte growth and migration, has been proposed[59].

Castanedo-Cazares[60] and Nordal *et al*[61] reported the efficacy of this combination in the treatment of vitiligo through the activation of pathways influencing melanocyte migration and melanogenesis.They recommended that the addition of topical tacrolimus to NB-UVB should be further investigated, considering its lower carcinogenenic profile compared with systemic administration. Moreover, the use of tacrolimus may be useful to prevent UVB-induced erythema by inhibiting early-phase events of the inflammatory process[62] . The conclusion that can be drawn from the majority of the studies combining topical calcineurin inhibitors with NBUVB is that the combination may increase the efficacy, and probably hasten the response, only for facial lesions.

3. Afamelanotide and Narrowband UV-B Phototherapy

Afamelanotide, an analogue of α–melanocyte-stimulating hormone, is known to induce tanning of the skin. In a recent study involving 4 patients, Grimes *et al*[63] showed that combined therapy of NBUVB and afamelanotide is likely to promote melanoblast differentiation, proliferation and eumelanogenesis leading to faster and deeper

repigmentation (at least > 50%) in each case within 2 days to 4 weeks.

In another recent study, patients with Fitzpatrick skin phototypes (SPTs) III to VI and a confirmed diagnosis of nonsegmental vitiligo that involved 15% to 50% of total body surface area were randomized to combination therapy (n = 28) vs NB–UV-B monotherapy (n = 27). After 1 month of NB–UV-B phototherapy, 16 mg of afamelanotide was administered subcutaneously to the combination therapy group monthly for 4 months while NB–UV-B phototherapy continued; the other group continued to receive NB–UV-B monotherapy. A combination of afamelanotide implant and NB–UV-B phototherapy resulted in clinically apparent, statistically significant superior and faster repigmentation compared with NB–UV-B monotherapy. The response was more noticeable in patients with SPTs IV to VI[64].

B) Combination of NB-UVB with systemic agents:

1. Cyclosporine plus NB-UVB

Combination of NB-UVB and cyclosporine had been reported for the treatment of resistant plaque type psoriasis with satisfactory results as regards the reduction of UV exposures and quick relief of pruritus [32]. Kim et al[65] reported a successful treatment of generalized pustular psoriasis in a two stage regimen, low-dose cyclosporine prescribed for induction and combination of NB-UVB with acitretin for maintenance. However, it was reported that combination of NB-UVB with cyclosporine increase the susceptibility for developing non melanoma skin cancer. Caution of this combination also includes avoid long term therapy, avoid concomitant immunosuppressive therapy and not preferred for those with a past history of skin cancer[66].

2. Acitretin plus NB-UVB

Retinoids have been shown to enhance the therapeutic response of BB-UVB, NB-UVB, and PUVA treatments. This is reflected in the fewer numbers of treatments and cumulative UV doses required to clear lesions than when UV or the retinoid is used alone [67].

The overall approach for the use of systemic retinoids plus UVB therapy seeks to maximize the effect and decrease the potential associated side-effects associated with each of the treatments. Because of the retinoid effect of decreasing the thickness of the stratum corneum and epidermis,there should be a two week initial systemic retinoid therapy before the initiation of NB-UVB .A thinner epidermis would make an individual more susceptible to the effect of UVB[68]. Kirby and Watson [69] mentioned a dramatic response of the combination of NB-UVB with acitretin in the treatment of pityriasis rubra pilaris.

3. Methotrexate plus NB-UVB

The use of methotrexate (MTX) in combination with phototherapy (NB-UVB, and PUVA) are known to cause apoptosis in the infiltrating lymphocytes in psoriatic lesions. It is, thus, not surprising that the combination would be synergistic resulting in faster clearing of lesions [70].Moreover, MTX has been reported to result in reduction in the scaliness and thickness of the lesions, thereby explaining the improved skin optics when UVB phototherapy is given [71].

Asawanonda and Nateetongrungsak[72] reported successful treatment of psoriatic patients with MTX, 3 weeks before standard NB UVB phototherapy was started. They proposed that the combination of MTX and NB-UVB phototherapy is a useful and relatively safe treatment for

plaque-type psoriasis. This combination could be especially useful in developing countries.

Newer Trends

Recently, newer forms of unconventional phototherapy have been tried in the treatment of vitiligo with varying results. In a study published in 2010, Mahmoud *et al* [73] compared the reaction of skin following irradiation with UVA1 (340-400 nm) and broadband visible light in normal individuals with skin types IV-VI. Using diffuse reflectance spectroscopy, the investigators showed that melanin value increased in a dose-dependent manner following UVA1 or visible light exposure. However, in a recent study, El-Zawahry *et al* [74] compared UVA1 phototherapy with NBUVB and concluded that UVA1 was less efficient than NBUVB and thus had a limited value as a monotherapy in vitiligo. Yu *et al*[75] showed that visible light produced by a helium-neon laser (633 nm) was able to induce melanocyte migration and proliferation. Few years later, Lan *et al*[76] used the same low-level laser light source to cause repigmentation in SV. It is believed that the dermatomal distribution of SV implies a neural dysregulation, making it slightly different to treat than NSV. The helium-neon laser has been found to modify the adrenergic dysregulation of cutaneous blood flow seen in SV [77]. Following treatment with helium-neon laser, more than 50% repigmentation was noted in 60% of patients with head and neck SV, repigmentation beginning after 16-17 treatments [75,77]. Recently, Yu *et al* [78] used 635 nm low-energy laser for SV treatment with the main goal to identify factors predicting treatment outcome[78]. In this study, 7 of 14 patients responded to the treatment (response was defined as achieving at least 25% of repigmentation) thus confirming the efficiency, although

limited, of visible light in SV treatment. Importantly, the authors concluded that evaluation of noninvasive cutaneous blood flow with and without prior visible light irradiation on cold-stressed SV lesions may serve as a treatment response predictor [78].

Hartmann *et al* [79] recently tried UVB intense pulse light source with peak emission at 311 nm (Relume-Mode, Lumenis) in a right-left comparative study where phototherapy was given once weekly on left side and tacrolimus was applied twice daily on right side. They concluded that long term treatment with either of the two modalities proved to be comparably effective.

DISCUSSION

The exact mechanism of action of NBUVB in vitiligo is unknown. The predominant type of repigmentation after NBUVB is perifollicular. Therefore, it is at least theoretically justified to believe that it has some relation to the melanocyte reserve in the outer root sheath. A two-step effect of NBUVB has been proposed – both of them may occur simultaneously although[80]. Firstly, there is immunomodulation (local as well as systemic), leading to downregulation of immune attack against the melanocytes. Subsequently, the melanocytes are stimulated to migrate to the epidermis and synthesize melanin [81]. NBUVB phototherapy increases synthesis of IL-1, TNF-α and LTC-4, and these cytokines induce melanocyte mitogenesis, melanogenesis and melanocyte migration [16]. However, the roles of IL-1 and TNF-α in melanogenesis are controversial and contradictory, as has been observed in some studies [82,83].

Englaro et al[84] have proposed that TNF-α inhibits the expression and activity of tyrosinase, the key enzyme in melanin synthesis. This inhibition of melanogenesis induced by TNF-α is secondary to activation of nuclear-factor κB. IL-1 stimulates synthesis of endothelin-1, which is mitogenic and melanogenic. The contradiction is that IL-1β has been found to decrease proliferation of melanocytes and melanogenesis, while IL-1β decreases melanocyte tyrosinase activity without any effect on proliferation [85]. *Imokawa et al*[86] observed increased expression of endothelin-1, IL-1 and tyrosinase in human keratinocytes in vivo and in vitro after UVB irradiation, suggesting the possible mechanism of repigmentation. Release of prostaglandins (PGE2 and PGF2) is another mechanism of action of phototherapy [87]. PGE2 is synthesized in the skin and regulates melanocyte and Langerhans cell function, and promotes melanocyte mitogenesis [88].

The therapeutic action involves a combination of effects in cell cycle kinetics, alterations in cytokine expression, effect on melanocytes and immunomodulation[89,90].

Molecular aspects of NB- UVB irradiation

***Urocanic acid**

Narrow- band UVB has been shown to induce isomerization of urocanic acid (UCA), ''a cutaneous photoreceptor'',from trans to cis form, which may be important in the immunomodulatory effects of TL-01[89]**.** Cis - UCA has been shown to suppress human NK cell activity in a dose dependent manner[54]**.**The immune-suppression properties of cis-UCA may be due to modulation of cytokines such as TNF-α ,IL-10 and IL-12, as

well as LC depletion[91].A further potential in the mechanism of action of cis-UCA includes the stimulation of prostaglandins E2 (PGE2) production [92].

Cellular aspects of NB-UVB

*** NB-UVB induced apoptosis**

The mechanism of action of NB-UVB for treatment of many inflammatory dermatoses is thought to be through the induction of apoptosis and great depletion of T cells. DNA damage is one of the major molecular triggers for UVB-induced apoptosis[93]. Caspases, which are apoptosis associated serine proteases within the cell, are activated and cause a cascade of events that trigger nuclear condensation, DNA fragmentation, and disintegration of the cell [90,94].

In caspase–dependent apoptosis, there are two main pathways involved: the intrinsic pathway(mitochondrial/apoptosome pathway) in which cell death occurs through mitochondrial deterioration and the extrinsic pathway(death-receptor pathway) in which direct activation of death receptors by UVB is involved in UV-induced cell death (Figure 2) [95].

Death receptors belong to a super family of receptors expressed on almost any cell and are characterized by carrying an intracellular death domain[96]. This family comprises CD95 (Fas), the TNF receptor and the TNF-related apoptosis-inducing ligand (TRAIL) receptor [97].

Induction of apoptosis by UVB, however, is not specific for keratinocytes but affects other cells as well including lymphocytes and macrophages[98].Little data has been generated regarding NB-UVB in

keratinocytes.NB-UVB induces apoptosis in T lymphocytes more efficiently than BB-UVB [94]**.**

It is possible that UVB- induced lesional T cell apoptosis is mediated indirectly by CD95L expression on neighboring keratinocytes or by direct cytotoxic effect of UVB [99]**.**

*** NB-UVB induced immunosuppression**

-Antigen presenting cells

Janssens *et al*[100] reported that the effect of UVB on the function of epidermal langerhans cell (LCs) showed a marked suppression of mixed epidermal cell lymphocyte reaction (MECLR) which is used as a measure of immune responsiveness**.**The reduction in MECLR was not paralleled by the changes in LCs numbers or HLA class 2 expression. However**,** Aufiero ***et al***[94] confirmed that multiple exposures of NB-UVB reduced the density of LCs by 20% but on exposure to BB-UVB, LCs morphology was unaffected.Thus,NB-UVB reduces the number of both T lymphocytes and LCs.

- Natural killer cells

Narrow band-UVB radiation causes a dose dependent inhibition of natural killer (NK) cell activity, in association with a decrease in NK-associated cytokines [101-103]**.**

* **Cytokine induction**

Acute exposure to high doses of NB-UVB seems to suppress type-1(IFN-γ)and concomitantly provoke type-2 (IL-4) cytokine expression whereas chronic exposure to low doses of NB-UVB results predominantly in the suppression of IFN-γ expression[104]. Piskin ***et al***[105] also,confirmed that

the expression of IFN-γ inducing cytokines(IL-12, IL-18 ,IL-23 and IL-27)was decreased after chronic NB-UVB exposure.

Ultraviolet-B also stimulates keratinocytes to release the immunosuppressive soluble mediators including IL-10 which abrogates the ability of LCs to present antigens to Th1 clones and even tolerizes them. Therefore, IL-10 shifts the immune response from a Th1 into a Th2 response [34]**.**

Lebwohl and Ali[106]**,**suggested that UVB-induce suppression of Th2 chemokine production suggests that UVB exposure to the skin suppresses infiltration of Th2 cells to the epidermis, so, both BB-UVB and NB-UVB are considered to be effective for the treatment of various Th2-mediated or Th2-infiltrating skin diseases**.** In addition, the effects of NB-UVB on constituent cells of skin other than keratinocytes may participate in the total therapeutic action**.**

Ultraviolet-B radiation has been shown to be a potent inducer of TNF-α gene expression which mediates signaling by human keratinocytes[82]*.* It is suggested that NB-UVB alters the production of cytokines and chemokines as a combined result of its direct and indirect TNF-α-mediated effects[107]**.**

Skiba *et al*[108] examined the effect of UVB irradiation on cytokines(TNF-α,IL-10,IL-1β**,**FasL) by irradiating the spontaneous transformed human epidermal cell line HaCaT to UVA ***(2000*** and 8000 J/cm²) or UVB (200-2000J/cm²) radiation. RNA was extracted from cells at 0,4,8,12,16,24,48h post irradiation for subsequent real time PCR amplification. They found that ,TNF-α m RNA levels were immediately

up regulated (0 hour) after irradiation ,with maximal induction at 8h post 2000 J/m² UVA and 200 J/m² UVB irradiation.

Hino *et al*[107] investigated the effect of NB-UVB on production of chemokines and proinflammatory cytokines by keratinocytes in comparison with BB-UVB.They used the same technique as that of Skiba *et al*[108] and confirmed the previous results of the increased production of TNF-α after UVB irradiation but the augmented effect of NB-UVB was less than that of BB-UVB.

Immunohistochemical examination was done, to assess the TNF-a expression in lesional and perilesional skin as compared to normal control skin, before and after NB-UVB therapy. At baseline, there was a significant increase of TNF-a in vitiligo lesions compared with perilesional and healthy skin which suggests a possible involvement of this cytokine in the depigmentation of vitiligo. The increase in TNF-a expression after NB-UVB phototherapy suggests another role in repigmentation [83].

***Effects on pigmentary system**

Exposure to UV light results in increase in the number of active melanocytes,the rate of melanin synthesis ,and the transfer of pigment granules to surrounding keratinocytes [109]**.**

Sunlight exposure causes increased levels of circulating MSH and ACTH with increased skin darkening[110]**.**It was observed that UVB and MSH act synergistically to increase melanin content in the skin [111].

Ultraviolet-B irradiation causes lipid peroxidation followed by generation of free radicals and depletion of the intracellular pool of reduced glutathione (GSH), resulting in oxidative stress. There is evidence that

the active oxygen species produced by UVB irradiation may play a role in melanogenesis and regulates the epidermal melanin unit by increased expression of melanogenic α-MSH and ACTH peptides[112].

Narrow band-UVB may exert its effects in vitiligo in a two-step process.Both may occur simultaneously. The first being the stabilization of depigmentation process and the second, the stimulation of residual follicular melanocytes [80].However, the molecular mechanisms of these processes remain unravelled [113].

In normal melanocytes, the binding of growth factors, such as b-FGF HGF, and ET-1, to receptors on melanocyte results in the rapid activation of the mitogen-activated protein kinase (MAPK) and ribosomal S6 kinases (RSKs) [114]. In melanocytes, a single growth factor is sufficient to trigger the MAPK cascade but is not able to sustain melanocyte proliferation or viability. At least two different growth factors in combination are necessary to induce melanocyte proliferation [115].

Wu *et al*[115]showed that NB-UVB irradiation stimulated the proliferation of melanocytes with a significant increase in the release of bFGF and ET-1 by keratinocytes. bFGF has been recognized as a natural mitogen for melanocytes,which enhances the growth and survival of melanocytes. ET-1 stimulates DNA synthesis in melanocytes, and has a synergistically stimulatory effect on bFGF-stimulated DNA synthesis of melanocytes

Kawaguchi *et al*[116] reported that NB-UVB is effective in stimulation of proliferation and differentiation of functioning melanocytes in epidermis. The precursor melanocytes seem to proliferate into mature pigmented melanocytes after UV exposure .They differentiate into TRP-2

positive melanocytes by the activation of c-kit receptor then become TRP-1 positive melanocytes.

Narrow-band ultraviolet B stimulates increased expression of the POMC gene which is accompanied by production and release of α-MSH [115,117] .

Adverse effects of NB-UVB

A) Acute effects

1 Erythema

Narrowband ultraviolet B (UVB) is relatively safe, and this is one of the main reasons for it being considered the first choice of treatment of generalized vitiligo in adults, as well as in children. Erythema is the most significant acute side effect of NBUVB, and the incidence varies between 10 and 94% according to the treatment regimen and definition of erythema [116]. However, asymptomatic faint pink erythema is expected to be common, as this is the end point for NBUVB in vitiligo. A greater proportion of patients develop erythema as compared with PUVA, but they are less likely to miss treatment due to a shorter duration of NBUVB-induced erythema.

2 Blistering

Lesional blistering following NB-UVB phototherapy is uncommon, described mainly in psoriatic plaques, and during treatment of pityriasis rubra pilaris. The mechanism of blistering is unclear. George and Ferguson[118] suggested that within psoriatic plaques may be due to rapid loss of scales, exposing lesional skin to a ''phototoxic'' dose in relation to adjacent relatively photo-protected skin causing rapid loss

photoprotection from the lesions thus exposing them to a big dose of radiation.

3 Pruritus

Although also a common side-effects of TL-01 therapy, it sometimes reflects the underlying disease processes [119]. Wallengren,[120] explained this phenomenon by the possibility of the role of prostaglandin E2 which induces itch and potentiates itch induced by histamine release.

4 Infection

Reactivation of herpes simplex virus can occur with NB-UVB treatment and precautionary measures should be taken in those with a history of this condition[121]. The potential effects of NB-UVB on the eyes, in particular exposure-related conjunctivitis or keratitis; need to be taken into account if treating patients with periocular eczema, although treatment can be performed carefully with the eye shut rather than with goggles in this situation [122].

B) Chronic effects

1 Photoaging

Chronic NB-UVB exposure is likely to increase photoaging. There is an increased generation of ROS in skin upon exposure to NB-UVB .These ROS are believed to be critical mediators of the photoaging process. ROS can modify proteins in tissue to form carbonyl derivatives, which accumulate in the papillary dermis of photodamaged skin [123].

2 Carcinogenesis

The long-term risk remains unclear, and questions regarding the risk of carcinogenecity of UVB remain unanswered. Induction of

photodegenerative changes by UVB is well established. UVB is a complete carcinogen and TL-01 has been shown to induce DNA damage in human skin cells and animal models. In a knockout mice model, development of malignant skin tumors was significantly higher for NBUVB than BBUVB following equivalent dose exposure [124]. The formation of cyclobutane pyrimidine dimers (CPD) was significantly higher with NBUVB, while that of photoproduct and 8-oxoguanine was significantly higher following BBUVB. These findings suggested the close correlation between CPD and the higher carcinogenic potential of NBUVB. At least in the setting of psoriasis, it is proposed that this disadvantage of NBUVB vis-à-vis BBUVB can be offset by the fact that the total dose required for clearance of psoriasis is lower than that for BBUVB. The only available human data has a mean follow-up of 5 years [125].

However, there were conflicting data that NB-UVB has been shown to be less[5] equally [126], and more carcinogenic than BB-UVB [6]. Also NB-UVB associated skin cancer risk may be less than that with PUVA [22]. Rivard and Lim, [127]reported that the risk of development of nonmelanom skin cancer has been estimated to be less than 2% per year which is less than that of PUVA .Black and Gavin[128] have suggested that at present, NB-UVB appears to be a relatively safe treatment modality; however, continuous long term follow-up is essential.

The world literature was systematically researched to update information on the skin cancer risk with UVB phototherapy, and Strategies suggested to reduce carcinogenicity during phototherapy [129].

-Skin saving procedure: Parts of the body where no lesions are present (especially the face) should be shielded during treatments. Also, parts that have repigmented satisfactory should, if possible, be shielded during subsequent treatments (for example by wearing trousers as a rule, do not respond to phototherapy)[130]. Genitals should be also shielded because these areas, as a rule, do not respond to phototherapy and genital tumours have been observed after PUVA therapy [22].

-Prevention of unnecessary exposure to natural sunlight on both treatment and non treatment days and the use of UV-blocking agents on sun exposed areas. Also, the use of combined treatments with other modalities to reduce the cumulative dose [131].

-Proper patient selection: and using protocols suitable to each patient with lower cumulative doses [128].

-Chemoprevention: This term is used to minimize the risk of carcinogenesis to UV therapy by using non toxic diet with antitumour properties. For example, black teas extract which contains dimeric faranols, and polymeric polyphenols. These are effective in reducing UVB and UVA mediated DNA damage and expression of early response genes [132].

-Light dose adjustment : This may be the key to limiting the carcinogenesis of NB-UVB. Near erythemogenic doses of NB-UVB clear psoriasis faster than lower doses of NB-UVB,but the later regimen is equally effective with only slightly more treatments [6].

-Less frequent doses: Dawe et al[133] compared thrice –weekly and five times weekly treatments using half body comparison study. In addition to no significant difference in proportion of patients who showed skin

clearing and time to clearance were found between the two regimens. Furthermore, the five weekly groups received higher cumulative doses and had more episodes of well-demarcated erythema.

Advantages of NB-UVB Phototherapy

From the advantages of NB-UVB phototherapy over other phototherapeutics : No topical or oral medication, tests, or special glasses are required[34].Faster response than broad band UVB and similar to PUVA [134].Number of treatments needed for clearing is generally less than broad band UVB and PUVA [22].Safe for children, pregnant women, and lactating mothers[135].Eliminating erythemogenic wavelengths below 311 nm permits higher intensities and longer exposure times resulting in maximum benefit from phototherapy and a shorter course of treatment[22,32].

Longer remission periods after treatment similar to those with PUVA therapy and markedly superior to BB- UVB treatment[33]. Studies show 38-40 % of NB-UVB treated patients requires no additional therapy for at least 12 months[136].

Disadvantages of NB-UVB Phototherapy

Due to the reduced power of narrow band compared to broad band, more lamps are needed to provide timely treatment Standard broad band systems have 8 to 16 lamps, whereas narrow band systems need 24 to 48 lamps[137]. Also NB-UVB lamps appear to have a shorter life expectancy than broad band and therefore, require more frequent replacement. NB-UVB irradiation cabins costs including the lamps are much more expensive[34].Erythema is less predictable than with broad

band UVB, but it may be more intense and persistent. Often lesional only [8].

What Happens to the Quality of Life After NBUVB Phototherapy

Vitiligo is a disease with profound cosmetic and consequent psychological impact, rather than physical disability. The majority of the studies performed so far have assessed the efficacy of NBUVB in the improvement of cosmetic disfigurement – that is, a decrease in the area of depigmentation. Although it is natural to believe that repigmentation following NBUVB would improve the quality of life in vitiligo patients, there is minimal objective assessment to such an effect. In a study of retrospective design, Tjioe et al[138] assessed the quality of life in vitiligo patients after treatment with NBUVB. Although the patients rated their health to be generally good to excellent, phototherapy accounted for only a small improvement in a minority of patients in general well-being. The main problem of phototherapy in fair-skinned individuals is prominence of the vitiligo lesions consequent to tanning of the surrounding normal skin requiring a greater degree of camouflaging until complete repigmentation is achieved in the lesions. In a study in children, quality of life assessed by the Children's Dermatology Life Quality Index did not diminish significantly in children having less than 25% repigmentation, while the reduction was significant in those who had more than 25% pigmentation with a proportional decrease in Children's Dermatology Life Quality Index with improvement grade of repigmentation[130].

Conclusion

Although multiple management options exist for vitiligo, UVB phototherapy is generally the treatment of choice as it is not only effective but has a favorable risk-to-benefit ratio. Conventional BB- and NB-UVB is widely available and useful particularly in widespread disease, although NB-UVB has been more extensively studied with proven efficacy. Combination therapies are also useful and may provide quicker regimentation and treat vitiligo with an additive mechanism of action than UVB phototherapy. Advances in technology may lead to the continuing use of UVB phototherapy as a treatment for vitiligo through the development of sophisticated devices and delivery systems as well as innovative application methods. These will provide increased therapeutic options for all vitiligo patients, particularly those with refractory disease.

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