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GUIDELINES

An update and guidance on narrowband ultraviolet B phototherapy: a British Photodermatology Group Workshop Report

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Summary These guidelines for use of narrowband (TL-01) ultraviolet B have been prepared for dermatologists by the British Photodermatology Group on behalf of the British Association of Dermatologists. They present evidence-based guidance for treatment of patients with a variety of dermatoses and photodermatoses, with identification of the strength of evidence available at the time of preparation of the guidelines, and a brief overview of background photobiology.

Key words: British Photodermatology Group, guidance, TL-01, ultraviolet B, update

Disclaimer

These guidelines have been prepared for dermatologists by the British Photodermatology Group on behalf of the British Association of Dermatologists and reflect the best data available at the time the report was prepared. Caution should be exercised in interpreting the data; the results of future studies may require alteration of the conclusions or recommendations in this report. It may be necessary or even desirable to depart from the guidelines in special circumstances. Just as adherence to the guidelines may not constitute defence against a claim of negligence, so deviation from them should not necessarily be deemed negligent.

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Introduction

It is almost 20 years since narrowband (311 ± 2 nm bandwidth) ultraviolet (UV) B (NB-UVB, TL-01) lamps were first introduced to Europe, although literature relating to their clinical use was not available until the late 1980s.[1–4] For the purpose of this article, we shall use the term TL-01 for NB-UVB (311 ± 2 nm) throughout. A British Photodermatology Group Workshop in 1996 appraised the developmental phase of TL-01 phototherapy and the findings were published in this Journal.[5]

The use of TL-01 phototherapy in Scotland and, we believe, in the rest of the U.K., has subsequently markedly increased and has surpassed that of psoralen plus UVA (PUVA) photochemotherapy.[6] Indeed, a considerable body of evidence now exists relating to

the therapeutic applications of TL-01. The aims of the recent British Photodermatology Group Workshop (November 2002) were to review the current state of the literature and to provide an evidence-based appraisal of TL-01 phototherapy.

What is the mechanism of action of TL-01?

The major molecular target for UVB is nuclear DNA, with absorption by nucleotides leading to induction of various DNA photoproducts, notably pyrimidine dimers. The inhibitory action of UVB on DNA synthesis is considered to be important in its therapeutic effect in the treatment of hyperproliferative diseases such as psoriasis, with reduction in the proliferating cells in the basal layer and in cell numbers in the hyperproliferative epidermis.[7] Induction of T-cell apoptosis may also be an important mediator of therapeutic effect in diseases such as eczema and cutaneous T-cell lymphoma (CTCL).[8] Several other mechanisms appear to be implicated in the therapeutic actions of TL-01, including other effects on the cell cycle,[9] antimicrobial effects and alteration of skin flora[10] and the induction of anti-inflammatory and immunosuppressive cytokines.[11–13] For example, TL-01 has been shown to induce immunosuppressive effects including induction of interleukin-10, reduced natural killer cell activity and lymphoproliferation. It also induces isomerization of urocanic acid from the *trans* to the *cis* form, which may be important in the immunomodulatory effects of TL-01 for the treatment of skin diseases other than psoriasis.[14–19]

It is therefore clear that the detailed mechanisms of action of TL-01 are not well defined; although it is established that several genetic and molecular events are induced by TL-01,[8] its therapeutic action in different disease states may involve a combination of effects including changes in cell cycle kinetics, alterations in cytokine expression and immunomodulation.

How do action spectra data fit with our use of TL-01?

In an ideal situation the therapeutic action spectra for specific diseases would be established and matched to phototherapy sources with comparable emission spectra. Unfortunately, these studies are difficult to perform in humans and detailed information is not available for diseases other than psoriasis.

In an early study, Fischer[20] examined the efficacy of wavelengths from 254 to 405 nm for clearance of psoriasis, and demonstrated that a narrow waveband at 313 nm was effective for psoriasis clearance, particularly at higher doses. However, other UVB wavelengths were not studied and therefore these data have only limited relevance. Parrish and Jaenicke studied the response of psoriasis to different wavelengths (254, 280, 290, 296, 300, 304 and 313 nm), by irradiating small areas of lesional skin on a daily basis, using various multiples of the minimal erythema dose (MED).[21] No clearance of psoriasis was found with wavelengths of 290 nm or less. Clearance was achieved at wavelengths of 296–313 nm, with some evidence of a better response at 313 nm. However, only four patients were studied, and they were found to have relatively treatment-resistant psoriasis. As wavelengths < 290 nm contribute to burning, but do not appear to be therapeutically effective in psoriasis, it is likely that lamps such as TL-01 that do not significantly emit radiation within this waveband will be therapeutically more useful.

To summarize, existing data show fair evidence based on action spectra studies to support the use of TL-01 for the treatment of psoriasis (*Strength of recommendation B; Quality of evidence I*; Appendix 1). There are insufficient data available for other diseases.

How effective is TL-01 for psoriasis and other diseases?

Psoriasis

The efficacy of TL-01 for the treatment of psoriasis has been demonstrated in several studies; several of these made comparisons with broadband UVB (BB-UVB). A meta-analysis[22] of controlled studies (summarized in Table 1) concluded that TL-01 was significantly more effective than BB-UVB in the treatment of this condition. The majority of these studies compared TL-01 and conventional BB-UVB lamps such as the TL-12 (Philips, Eindhoven, the Netherlands). The TL-12 has significant emission < 290 nm (Table 2) and it is not surprising, based on the action spectrum from Parrish and Jaenicke,[21] that this lamp was less effective than TL-01. However, BB-UVB lamps are available with little emission at or below 290 nm (e.g. UV-6; Sylvania, Brussels, Belgium) (Table 2). Although there are no randomized, MED-based, comparative studies between TL-01 and UV-6 that have followed patients to clearance or minimal residual activity, a study by Storbeck *et al.* suggested that TL-01 was superior.[23] Thus, although there is scope for further comparative studies

Table 1. Controlled studies assessing narrowband ultraviolet (UV) B (NB-UVB) vs. broadband UVB (BB-UVB) for psoriasis (adapted from Dawe[22])

Study (1st author and year)	Controls	Randomized	Observer blinding?	Number of subjects		Overall outcome
				NB-UVB	BB-UVB	
van Weelden, 1984[118]	Historical	No	No	8	8	NB more effective
van Weelden, 1984[118]	Within patient paired	Not reported	Not reported	9	9	NB more effective
Green, 1988[2]	Historical	No	No	52	25	NB more effective
van Weelden, 1988[1]	Within patient paired	Yes[a]	Observer-blind	10	10	NB more effective
Larkö, 1989[4]	Within patient paired	Yes[a]	Not reported	29	29	NB more effective
Karvonen, 1989[3]	Within patient paired	No	Not reported	20	20	NB more effective
Karvonen, 1989[3]	Contemporary, unpaired	No	Not reported	17	23	NB more effective
Barth, 1990[119]	Within patient paired	No	Not reported	22	22	NB more effective
Picot, 1992[65]	Within patient paired	Yes[a]	Double-blind	15	15	NB more effective
Storbeck, 1993[23]	Within patient paired	Yes[a]	Observer-blind	10	10	NB more effective
Storbeck, 1993[23]	Within patient paired	Yes[a]	Observer-blind	13	13	NB more effective
Coven, 1997[24]	Within patient paired	No	No	22	22	NB more effective
Hofmann, 1997[117]	Within patient paired	Yes[a]	Not reported	11	11	Equal efficacy
Walters, 1999[101]	Within patient paired	No	Observer-blind	11	11	NB more effective

The authors of all but one of these studies[117] favoured NB-UVB as more effective than BB-UVB. [a]Method of random allocation not reported.

Table 2. The amount of ultraviolet (UV) radiation of wavelength < 290 nm emitted by different types of lamp, expressed as a percentage of the total UV emission and as a percentage of the erythemally effective emission

Lamp	< 290 nm (%)	Erythemally weighted (%)
TL-12	5·5	21·8
UV-6	0·5	6·9
TL-01	0·1	2·3

between TL-01 and UV-6 or other equivalent BB-UVB sources, ensuring equivalent treatment regimens and treatment to clearance, existing data indicate that, overall, TL-01 is more effective than BB-UVB for the treatment of psoriasis.

In studies comparing PUVA and TL-01 for the treatment of psoriasis (Table 3), PUVA seems to be slightly more effective than TL-01. However, the convenience of TL-01 and the lack of requirement for psoralen suggest that TL-01 could be considered as the first-line phototherapy option with PUVA reserved for treatment failures, for those patients for whom the higher frequency of TL-01 treatment may influence the decision, or possibly for specific types of psoriasis, e.g. palmoplantar pustulosis or pustular psoriasis. However, there is a lack of adequate data relating to the most appropriate phototherapeutic choice for these difficult cases. At present, there are no predictors of the type(s) of psoriasis most responsive to TL-01, and most studies have been performed in caucasian skin types I–III, although patients with skin types IV and V also appear to be suitable candidates for TL-01.[24] Overall, approximately 63–80% of patients will clear with a course of TL-01 phototherapy,[25,26] with equivalent relapse rates for TL-01 and PUVA.[27]

Recent work, which examined the potential systemic effect of TL-01 for the treatment of psoriasis, showed that if any systemic effect was present it was likely to be of minor importance for the clearance of psoriasis, thus justifying half-body comparison studies.[28] Evidence suggests that more exposures are required to achieve clearance with TL-01 than with PUVA,[25] and that TL-01 may be less effective for patients with high baseline Psoriasis Area and Severity Index (PASI) scores.[29] Interestingly, in one study patients with multiple small plaques of psoriasis appeared to respond better to either TL-01 or PUVA compared with those with large plaque disease.[25] However, only 12% of the TL-01-treated group remained clear in that study at 6 months of follow-up compared with 35% in the PUVA-treated group.[25]

To summarize, the available study evidence suggests that TL-01 UVB is more effective than BB-UVB and approaches PUVA in efficacy for the treatment of psoriasis in patients with skin types I–III (*Strength of recommendation A; Quality of evidence I*; Appendix 1).

Eczema

Independent open studies have shown efficacy of TL-01 for the treatment of both adult and childhood chronic atopic eczema when used as monotherapy or when combined with topical steroids. Remission periods appear to be similar to those for psoriasis. In one open prospective study of TL-01 for severe chronic atopic eczema in 21 adults, a 68% reduction in severity scores

Table 3. Published studies comparing narrowband ultraviolet (UV) B (NB-UVB) and psoralen plus UVA (PUVA) for psoriasis

Study (1st author and year)	NB-UVB regimen	PUVA regimen	Comparison	Randomized	Observer blinding?	Number of subjects		Summary results of efficacy
						PUVA	NB-UVB	
van Weelden, 1990[120]	2×/week; MED-based start dose	2×/week; oral 8-MOP	Within-patient paired (inpatients)	Yes (methods not reported)	Yes	10	10	Similar efficacy
Tanew, 1999[29]	3×/week; MED-based start dose	3×/week; oral 8-MOP	Within-patient paired	No	No	25	25	Marginally favoured PUVA, particularly as baseline psoriasis severity increased
Gordon, 1999[25]	2×/week; MED-based start dose	2×/week; oral 8-MOP	Unpaired, stratified (by plaque size and phototype)	Yes	Yes	49	51	PUVA more effective
Markham, 2003[121]	3×/week; MED-based start dose	2×/week; oral 8-MOP or 5-MOP (three patients)	Unpaired	Yes (methods not reported)	Yes	25	29	Similar overall efficacy, although fewer treatments to clear with PUVA
Dawe, 2003[27]	3×/week; MED-based start dose	2×/week; topical (bath) TMP	Within-patient paired	Yes	Yes	29	29	NB-UVB more effective

MED, Minimal erythema dose; MOP, methoxypsoralen; TMP, trimethoxypsoralen.

and 88% reduction in topical steroid use were observed with an MED-based three times weekly air-conditioned treatment regimen over 12 weeks, with continued benefit in the majority 6 months after treatment.[30] Furthermore, in a retrospective study of 40 children with moderate to severe atopic eczema, the same treatment regimen was effective in most subjects, giving relatively prolonged remission in some.[31] Similar response rates have also been shown in an open prospective study in 37 adults with severe atopic eczema, with a twice-weekly skin type-based treatment regimen without air-conditioning.[32]

In a small, open, prospective study of five adults with atopic eczema, five times weekly TL-01 was shown to be effective in all patients in the absence of topical steroid use, although three developed erythema with this regimen.[33] However, in a randomized, investigator-blinded, half-body study comparing TL-01 and bath PUVA, combined with emollients only, in 12 patients with severe atopic eczema, both therapies were effective in 90% of those who completed the study. There was also evidence of prolonged remission in some patients and no significant differences between TL-01 and PUVA.[34] More recently, in a randomized, controlled, blinded comparison study, twice-weekly TL-01 was shown to be superior in efficacy to low-dose broadband UVA or visible light placebo. Treatment was in conjunction with topical steroid use in 73 adults with moderate to severe atopic eczema; significant reduction in disease extent, activity and maintained improvement 3 months after treatment were seen in those treated with TL-01.[35]

At present we do not have predictors of therapeutic response for patients with eczema and there is no evidence on which to define an optimal treatment regimen. A study of BB-UVB in the treatment of eczema showed that a very low dose regimen (equivalent to a 20% increment over the treatment course) was superior to a more conventional higher incremental dosage regimen in patients with atopic eczema.[36] However, the two study groups were not directly comparable and similar studies for TL-01 are not yet available. Comparative studies with UVA1 phototherapy, which appears to be more effective in acute flares of eczema,[8] will be important. A small study in nine patients with chronic atopic eczema has indicated that TL-01 may be more effective than medium dose (up to 50 J cm^{-2}) UVA1 in this patient group,[37] although further studies are required. Seborrhoeic dermatitis has been shown to respond to TL-01 in an open, prospective study in 18 patients. However, although all patients improved or

cleared with treatment, all those followed up ($n = 11$) had rapidly relapsed by a median of 21 days (range 12–40) after treatment was discontinued, which may limit its use in this condition.[38] There is good evidence to support use of TL-01 in chronic atopic eczema (*Strength of recommendation A; Quality of evidence I*; Appendix 1).

Other diseases

Details are given in Table 4.

Photodermatoses. Efficacy of TL-01 has been shown for the prophylactic treatment of the photodermatoses. A randomized, controlled comparative study of TL-01 with PUVA in 25 patients showed equivalent efficacy for the desensitization of polymorphic light eruption (PLE).[39] In a separate report in 20 patients with photodermatoses, TL-01 was shown to be effective for desensitization of actinic prurigo ($n = 6$), hydroa vacciniforme ($n = 4$) and for cases of idiopathic solar urticaria ($n = 1$), amiodarone phototoxicity ($n = 1$) and cutaneous porphyria ($n = 8$), in particular erythropoietic protoporphyria (six of the eight cases).[40] A standard psoriasis treatment approach has been applied, although the optimal regimen and length of the treatment course for desensitization in photodermatoses are undefined and further studies are required. The mechanism of action for desensitization in photodermatoses is unknown, although it is likely that immunomodulation, in addition to stratum corneum thickening and increased melanin production, is important.

Vitiligo. The efficacy of TL-01 in the treatment of vitiligo has been examined. In one study, TL-01 was compared with topical PUVA in a total study group of 281 patients.[41] Two patient groups were investigated. The first part of the study compared 4 months of treatment with topical PUVA ($n = 28$) or TL-01 ($n = 78$). A second group, treated twice weekly with TL-01, was followed for up to 12 months. The study showed a trend to improved repigmentation responses (67% of the patients treated with TL-01 in the first part of the study had some response compared with 46% with PUVA after 4 months of treatment) and in the nature of the induced skin pigmentation in the TL-01-treated group, with lower cumulative TL-01 exposure compared with PUVA. Improved responses were seen with long-term TL-01 treatment; 63% of TL-01-treated

Table 4. Other diseases that have been treated with TL-01

Condition	References	Best study evidence	Strength of recommendation/ quality of evidence[a]	Comparators (in controlled studies)
Atopic dermatitis	30,31,34,35	RCT	A I	UVA1 Visible light (placebo); BB-UVA;
Seborrhoeic dermatitis	38	Open, uncontrolled study	B III	NA
Nodular prurigo	122	Case report	C III	NA
Vitiligo	41,43,44,122,123	Controlled trial without randomization	B IIi	PUVA
Mycosis fungoides	47–49,122	Open, uncontrolled study	B III	NA
Lichen planus	124,125	Case series	C III	NA
Subcorneal pustular dermatosis	126,127	Case reports	C III	NA
Alopecia areata	128,129	Case reports	C IV	NA
Granuloma annulare	128	Case report	C IV	NA
Acquired perforating dermatosis	130	Case report	C IV	
Pityriasis rubra pilaris[b]	122	Case report	D IV	NA
Photodermatoses				
Polymorphic light eruption	39	RCT	A I	PUVA
Erythropoietic protoporphyria	40,131	Case reports	B III	NA
Actinic prurigo	40	Case reports	B III	NA
Hydroa vacciniforme	40	Case reports	C IV	NA
Drug-induced photosensitivity	40	Case reports	C III	NA
Pruritus				
of polycythaemia vera	132	Open, uncontrolled study	B III	NA
of infiltrating breast cancer	133	Case report	C III	NA
Other generalized itch	122	Case series	C III	NA

BB-UVA, broadband ultraviolet (UV) A; RCT, randomized controlled trial; NA, not applicable. [a]See Appendix 1. [b]Other reports suggest that narrowband UVB may be contraindicated in adult pityriasis rubra pilaris; it should certainly be used with caution.

subjects experienced >75% repigmentation by 12 months compared with 8% at 3 months. The authors concluded that TL-01 was safe and effective for vitiligo.

In a separate retrospective analysis of seven patients with vitiligo who were treated with TL-01, including three with skin types IV and V, five achieved >75% repigmentation with a mean of 19 treatments.[42] Furthermore, Tjioe *et al.* showed up to 100% repigmentation in 92% of 27 patients with vitiligo treated three times weekly with TL-01.[43] Treatment of children with vitiligo may also be effective; in an open trial of twice-weekly TL-01 for up to 1 year in 51 children with generalized vitiligo, 53% achieved >75% repigmentation and stabilization of disease was reported in 80%.[44]

However, others have reported a lack of efficacy of TL-01 for vitiligo.[45] In general, facial and small areas of vitiligo involvement are more responsive than larger areas of vitiligo or disease at acral sites, for both TL-01 and PUVA. The mechanism of action appears to be by increased melanin production, although again, immunomodulation may be implicated and further studies are required to examine this. (TL-01 for vitiligo: *Strength of recommendation B; Quality of evidence IIi*; Appendix 1).

Cutaneous T-cell lymphoma. Efficacy of TL-01 for the treatment of patch- and plaque-stage CTCL has also been reported. In one study of TL-01 given three to four times weekly to 20 patients with small plaque parapsoriasis or early stage CTCL, 19 patients showed clinical and histological clearance after a mean of 20 treatments. However, all relapsed by a mean of 6 months.[46] In a further study of eight patients with patch-stage CTCL, TL-01 given three times weekly for a mean of 26 treatments resulted in complete clearance of disease in six patients, four of whom had prolonged remission.[47] More recently, Gathers *et al.* studied 24 patients with early stage CTCL treated three times weekly with TL-01, and reported complete response in 54%, partial response in 29% and no response in four subjects.[48] Biopsies from 10 subjects who had achieved complete clinical response showed histological clearance in nine. After treatment was discontinued four patients who had reached clearance relapsed, with a mean relapse time of 3 months. Furthermore, in a retrospective study of 56 patients treated with either TL-01 ($n = 21$) or PUVA ($n = 35$), 81% of TL-01-treated subjects achieved complete remission compared with 71% with PUVA, with mean remission periods of 25 and 23 months, respectively.[49] Thus, TL-01 is an effective and well-tolerated therapy for early stage CTCL. However, the identification of UVB signature mutations in the p53 gene in six of 17 patients with tumour-stage CTCL but in none of 12 patients with plaque-stage CTCL is of potential concern.[50] The presence of these mutations in tumour-stage CTCL does not prove that UVB can contribute to causation of progression from plaque stage but raises the possibility that it can do so. (TL-01 for CTCL: *Strength of recommendation B; Quality of evidence III*; Appendix 1).

Other dermatoses. TL-01 has been used in an extensive list of diseases (Table 4) with encouraging results for some, e.g. pruritus, subcorneal pustular dermatosis, alopecia areata, granuloma annulare and lichen planus.

Is combination therapy beneficial?

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. 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. Study design for the examination of the effects of combined therapies has involved addition of a therapeutic agent to a phototherapy regimen, and conversely, addition of phototherapy to a therapeutic agent regimen.

In an open randomized study of TL-01 with and without systemic etretinate in 45 patients with chronic plaque or guttate psoriasis, no real advantage was seen for combination treatment.[51] A reduction in the cumulative UVB dose was seen but there was no effect on overall numbers of treatments, and an increased relapse rate was seen in the retinoid treatment group. Psoralen increases the erythemal response to TL-01 and, in 10 subjects, combined 8-methoxypsoralen plus TL-01 resulted in faster lesion clearance than TL-01 alone.[52] A combination of psoralen sensitization with TL-01 was shown to be as effective in psoriasis as PUVA in a bilateral comparison study[53] and in a randomized controlled trial in 100 individuals.[54] However, there are concerns regarding the potential carcinogenicity of this novel combination because more than one type of DNA photoproduct is likely to

be produced, and further clinical studies have not been performed. (Systemic retinoids plus UVB: *Strength of recommendation D; Quality of evidence I*; Appendix 1).

Half-body topical application studies have been conducted in an open manner to compare TL-01 alone vs. TL-01 and topical agents. These suggested a greater reduction in PASI score when TL-01 was combined with tazarotene,[55,56] while there were conflicting data concerning combination with calcipotriol. For example, one study showed no additional benefit of introducing calcipotriol to TL-01 phototherapy,[57] whereas a separate study showed improved responses if TL-01 were combined with a topical calcipotriol regimen.[58] From a systematic review of the literature, it appears that cumulative exposure to UVB might, in general, be reduced by vitamin D_3 analogues.[59–62] Further bilateral comparison studies suggest that TL-01 in combination with dithranol is as effective as BB-UVB with dithranol,[3,23] but there have been no reported studies comparing dithranol or coal tar and TL-01 with TL-01 alone. One randomized controlled trial of balneotherapy showed no significant effect of saline spa water on the efficacy of TL-01 alone.[63] Further adequately designed studies are required to examine standard topical therapies in combination with TL-01, particularly with respect to potential reduction of UVB dose or treatment number. (Combination therapy: *Strength of recommendation C; Quality of evidence I*; Appendix 1).

What are the adverse effects of TL-01?

Acute

The acute side-effects of TL-01 therapy include erythema, which has been shown to have similar characteristics to that induced by BB-UVB.[64] The incidence of erythema with TL-01 varies according to treatment regimen and definition of erythema, but figures of between 10% and 94% have been quoted.[2,24,25,51,65–68] In a study of patients with PLE, this was provoked in some during treatment with TL-01, although this appears no more likely to occur than with PUVA.[39] Lesional blistering of psoriatic plaques has been observed mid-way through a TL-01 treatment course, requiring dose reduction;[69,70] the same phenomenon has also been reported during treatment of pityriasis rubra pilaris with TL-01.[71] Perilesional erythema was not reported and the mechanism for blistering is unclear. Pruritus, although also a common side-effect of TL-01 therapy,[51] sometimes reflects the underlying disease process. Interestingly, there is one case of vitiligo occurring at lesional sites during treatment of psoriasis with TL-01,[72] although this appears to be an extremely rare occurrence.

Reactivation of herpes simplex virus can occur with UVB treatment[73] and precautionary measures should be taken in those with a history of this condition. No data are available for the effect of TL-01 on human immunodeficiency virus (HIV) promoter expression, although it is known to be activated by BB-UVB.[74–76] Clinical data indicate that TL-01 is an effective therapy in patients with HIV infection[77] but further studies are required because with BB-UVB the HIV RNA levels have been shown to increase in a UVB dose-dependent manner.[78,79] The potential effects of TL-01 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 eyes shut rather than with goggles in this situation. This would not be advised routinely but only in specific situations.

Chronic

The longer-term risks of TL-01 remain unclear and the question as to the carcinogenicity of UVB is unanswered. Induction of photodegenerative changes by UVB is well established.[80,81] Reduced dermal hydroxyproline levels and induction of gelatinases and elastin cross-links have been shown. The action spectrum for induction of photodamage and photocarcinogenesis in animals is maximal in the UVB region.[80–84]

The carcinogenic risk of BB-UVB in humans is recognized but not well defined.[85–89] A meta-analysis of studies using BB-UVB showed an excess of skin cancers of up to two per 100 patients treated with UVB per year; the risk was much less than that for PUVA.[85,90,91] UVB is a complete carcinogen and TL-01 has been shown in human skin, cell and animal models to induce DNA damage;[92,93] it is more carcinogenic than BB-UVB in animal models.[1,94–96] It has been estimated by extrapolation from animal studies that TL-01 is probably two to three times more carcinogenic than BB-UVB, per MED delivered, in terms of nonmelanoma skin cancer (NMSC). In a commentary article,[97] it was suggested that this risk is offset by the fact that the number of MEDs required to clear psoriasis with TL-01 is less than a third of the number required with BB-UVB. However, the assumption of a large MED difference in clearance has not been confirmed in randomized studies and the risk with TL-01 remains potentially higher than that with

BB-UVB. Due to this likely but as yet unquantified skin cancer risk, it is therefore recommended that TL-01 should be used as limited duration courses in situations where simpler topical therapies have failed or are inappropriate.

The only available human data have a mean 5-year follow-up to date.[98] No significant increase in squamous cell carcinoma or malignant melanoma was seen in those patients treated with TL-01 and only a small increase in basal cell carcinoma, which appeared unlikely to be related to treatment as several of the tumours were discovered in the first 3 months of the study.[98] Concern remains regarding the increasing use of topical immunomodulators such as tacrolimus, as the combined effect of TL-01 and tacrolimus may theoretically enhance photocarcinogenicity.[99] Until further data are available with respect to TL-01 follow-up, precautionary measures should be taken with shielding of high-risk areas such as the face, and improved efficacy of treatment in order to reduce the amount of UVB exposure per treatment course.[24,100,101] Combination therapies, although no convincing evidence exists to show superior efficacy, may potentially reduce the cumulative UVB dose and hence the UVB-induced skin cancer risk and should therefore not be dismissed without further study.

Which equipment should be used?

A wide variety of TL-01 equipment is routinely available. It can be categorized into: whole-body cabins, whole-body panels, small panel irradiators and point sources, each with their advantages and disadvantages (Table 5). The most commonly used equipment and manufacturers are listed in Table 6. The use of simple machines with timers is encouraged. Dedicated equipment for either UVB or UVA therapy is desirable, rather than combined-wavelength treatment cabinets, which require longer treatment times and for which safety issues may also be a problem. The spectral emission of the lamp must match that of the calibration equipment, and the manufacturers should specify the output.

What guidance is there regarding dosimetry and metering?

Recent U.K. and Scottish guidelines for dosimetry and calibration in UV radiation therapy have been proposed and are discussed in detail elsewhere.[102,103] Due to patient shielding (see discussion below), a variable but approximately 20% difference occurs between direct and indirect methods of comparison of irradiance. The preferred option is therefore for each centre to determine their own correction factor, which is usually of the order of 0·8–0·9. It is important that a UV meter has the correct wavelength response (280–320 nm), a cosine angular response, a directional error f_2 of $< 10\%$[104,105] and a dynamic range of 0·1–50 mW cm^{-2}. It is also essential that a standard bank of lamps is available at the centres where calibration is performed in order to allow comparison with one or more recommended sources. Close involvement of medical physicists is therefore essential in order to establish and maintain accurate dosimetry. Meters should be sent to an appropriate test centre for annual calibration, either with spectroradiometry or with a reference meter method, to provide sufficient accuracy.

Currently, TL-01 calibration is problematic, with discrepancy of up to $\pm 40\%$ between specialist centres.[106] With spectroradiometric or reference meter calibration it should be possible to improve accuracy to within $\pm 10\%$. A direct measurement in which the investigator measures irradiance on his/her body surface is preferable from a dosimetric point of view, but some people may find that this is inconvenient to perform on a routine basis and there is a potential risk of exposure. Skin and eyes must be protected from UV exposure, for example by use of a UV-protective suit. Other indirect methods may be used provided a correction factor is applied to account for the occupancy effect of the patient inside the cabin.[107] Automated systems can provide a reproducible technique for measurement of irradiance over a range of directions in a whole cabin and provide more detailed information on dose distributions.[108] Correction factors may be derived from comparison of direct and indirect measurements. Mannequins provide an alternative technique for derivation of the correction factor, which avoids the necessity for a person to enter a cabin.[109]

How should it be used?

The delivery of TL-01 phototherapy is potentially dangerous. Approximately 50% of successful litigation for dermatology claims in Scotland relates to phototherapy events.[110] Phototherapy is principally a nurse-led service, with increasing involvement of trained nursing staff, which will continue with the development of nurse practitioners.

Table 5. Characteristics of narrowband ultraviolet (UV) B irradiator types (·, lowest; · · ·, highest)

Irradiator type	Size	Cost	Area treated	Hazards	Convenience	Comments
Whole-body cabins with UV sensors	· · · to · · · ·	· · ·	Whole body	Negligible radiation hazard; dosimetry unreliable and often cannot be adjusted	Efficient, restricted space in smaller cabins	Automatic compensation for lamp fluctuations; *fixed* calibration standard
Whole-body cabins without UV sensors	· · · to · · · ·	· ·	Whole body	Negligible radiation hazard	Efficient, restricted space in smaller cabins	No compensation for lamp fluctuations; *any* calibration standard
Long upright panels/columns	· ·	·	Partial whole-body	Significant UV hazard to others in front of the panel	Patients must move around to treat whole body	Care needed to avoid over- or under-dose at overlaps
Small area/canopy devices	· ·	·	Limited areas, extremities	Possible UV hazard from 'open' radiation source	Larger areas require multiple exposures with risk of overlap	Care needed to avoid over- or under-dose at overlaps
Very small area and 'point-source' devices	· to · ·	· to · · · ·	Localized high dose possible	Possible UV hazard from 'open' radiation source	Avoids unnecessary area irradiation	Care needed to avoid over- or under-dose at overlaps
MED/test devices	·	·	Test areas only	Possible UV hazard from 'open' radiation source		UV spectrum and calibration standard must match treatment

MED, minimal erythema dose.

Assessment of the minimal dose required to cause just perceptible erythema, the MED, allows the detection of unsuspected photosensitivity and is desirable before proceeding to whole-body therapy. Although uncommon, some photoactive medications, such as nonsteroidal anti-inflammatory agents, calcium-channel blockers and phenothiazines, may lower the TL-01 MED.[111] Evidence relating to the erythemal time-course for TL-01, showing a peak erythemal response at 12–15 h,[112] supports the rationale for use of a 50% MED start dose in order to minimize the risk of burning.

It is highly desirable that dedicated nursing staff with continuity of care and adequate training are available to perform MED testing and readings. In the absence of staff familiar with performing MEDs, a TL-01 test dose is desirable. For psoriasis, evidence exists to support the use of a three (or two) times weekly regimen, with an incremental regimen of 20% reducing to 10% (rather than 40% reducing to 20%) increments with each treatment, as there is an increased incidence of painful erythema with the latter approach to increments,[26,66,67] rather than a less than twice weekly,[28,113] four[114] or five times weekly regimen or 40% increments. It also seems that near-erythemal treatment courses are not essential and that suberythemal treatment may be as effective, although this may take longer to achieve clearance.[100]

The optimal maximum dose for each treatment is not defined, although it is partly determined by the amount of time a patient can comfortably spend in the cabinet. It is also important that patients receiving phototherapy are treated in the same cabinet each time. Further studies are required with respect to the dose escalation required for the most effective treatment.

Should there be a ceiling on the number of TL-01 exposures based on current knowledge?

The recorded incidence data on risk of phototherapy-induced skin cancer in humans as a consequence of therapy are not yet available and it will be a decade or more before we can expect them. In the meantime, the most defensible approach is to incorporate mathematical models of NMSC incidence with estimates of human exposure to both sunlight and therapeutic UVB in order to arrive at risk estimates.

In recommending a ceiling number of treatments based entirely on these calculations, we need to consider what is an 'acceptable' increased risk of skin cancer resulting from TL-01. For example, if we assume that an average patient would be prepared to take a

Table 6. Distributors and manufacturers of ultraviolet therapy equipment in the British Isles

U.K./Ireland distributor	Contact details	Manufacturers represented	Websites
Athrodax Healthcare International Ltd	Hawthorn Business Park, Drybrook, Gloucestershire GL17 4HP Tel.: + 44 (0) 1594 544440 Fax: + 44 (0) 1594 545800	Waldmann Medizintechnik GmbH (Germany)	http://www.athrodax.co.uk http://www.waldmann-medizintechn.com
Cosmedico UK	11 Laburnum Way, Loughborough LE11 2FB Tel.: + 44 (0) 1509 554044 Fax: + 44 (0) 1509 554045	Cosmedico Medizintechnik GmbH (Germany)	http://www.cosmedico-medizintechnik.de E-mail: cosmedico.uk@ntlworld.com
Hospital Lamp Supplies (division of Hybec Ltd)	Barrington Industrial Estate, Leycroft Road, Leicester LE4 1ET Tel.: + 44 (0) 116 235 8818 Fax: + 44 (0) 116 235 8810	Hybec Ltd (U.K.)	http://www.hybec.com
Lumenis (UK) Ltd	1st Floor, Merit House, The Hyde, London NW9 5AB Tel.: + 44 (0) 20 8324 4200 Fax: + 44 (0) 20 8324 4222	Lumenis Inc. (U.S.A.)	http://www.aesthetic.lumenis.com
Medical Physics, Ninewells Hospital	Department of Medical Physics, Ninewells Hospital, Dundee DD1 9SY Tel.: + 44 (0) 1382 632604	Medical Physics, Ninewells Hospital (U.K.)	http://www.dundee.ac.uk/medphys/

50% increased risk for the development of NMSC, Diffey has predicted that a ceiling number of treatments of 450 would be recommended for a patient who received one treatment course per year, with the face unshielded.[115]

These estimates assume that TL-01 has equal efficacy to sunlight in inducing NMSC for the same erythemal exposure. However, this may not be the case. If, on an erythema-for-erythema basis, TL-01 is twice as carcinogenic as sunlight (as may be inferred from animal studies comparing response to BB-UVB and NB-UVB[97]), then the maximal number of treatments recommended would be less than one-half of those quoted.[115]

The recommendation of a ceiling number of TL-01 exposures depends not only on objective estimates of skin cancer risk (and the uncertainties associated with these estimates for TL-01) but also on factors such as whether or not the face is shielded during phototherapy, the frequency with which treatment courses are repeated and, not least, each patient's attitude to an acceptable risk of treatment. Limitation of the frequency of treatment courses and shielding of habitually exposed sites, if clinically appropriate, may reduce risk.

It should be emphasized that these figures should be treated with caution until epidemiological data emerge from human TL-01 cancer studies that are currently in progress. Particular caution should be taken in skin type I/II, blond/red-haired subjects, and it is prudent to identify and follow up patients considered to be 'at risk'. Finally, it should be recognized that these ceiling estimates must be used in conjunction with clinical judgement in cases of severe psoriasis where the alternative to TL-01 might be other potent agents such as methotrexate or ciclosporin. It must be stressed that recommended ceiling dose estimates are just guidelines and that inflexible adherence to them is inappropriate.

Few absolute contraindications to TL-01 phototherapy exist, but include xeroderma pigmentosum and lupus erythematosus. In a small proportion of cases where there is geographical demand, TL-01 phototherapy with home delivery may be appropriate, although adequate patient and nurse training is required.[116]

Development of National Managed Clinical Networks can help to standardize phototherapy between centres and to monitor long-term outcomes; this is currently being introduced in Scotland. The establishment and overall management of a phototherapy unit should be consultant-led, although adequate patient training and nursing support is required. Although there are guidelines for instruction of dermatology trainees in phototherapy, there are no firm guidelines for the experience required by a consultant in charge of a phototherapy unit, and this would be desirable for the future. Defined Nursing National Standards are also required for this purpose. It is essential that phototherapy is performed by staff with appropriate training and with experience of assessment of treatment of patients with skin disease, and also that dedicated time is available.

Conclusions and future work required

The use of TL-01 has markedly increased since its introduction in the 1980s and it is now widely used to treat a range of skin diseases. Its mechanism of action includes antiproliferative, anti-inflammatory and immunosuppressive effects, the relative importance of each presumably depending on the disease treated. Action spectra studies support its use in psoriasis and its clinical efficacy is proven for both psoriasis and eczema. Efficacy for other diseases, including CTCL, PLE and vitiligo, has been demonstrated, although further studies are required to confirm its role in the treatment of other conditions. Combination therapy offers no clear advantages over TL-01 monotherapy, but this area remains under study. TL-01 is generally well tolerated in the short term; the long-term cancer risk in humans is unclear at present but is likely to be less than that of PUVA. Optimization of treatment is essential in order to maximize therapeutic efficacy, while minimizing the adverse effects of treatment, and this requires a multidisciplinary approach between medical and nursing staff and medical physicists.

Summary of main conclusions

- There is fair evidence, based on action spectra (*Strength of recommendation B*), and good evidence based on clinical studies (*Strength of recommendation A*), to support the use of TL-01 for the treatment of psoriasis (both *Quality of evidence I*).
- There is good evidence to support the use of TL-01 in chronic atopic eczema (*Strength of recommendation A; Quality of evidence I*).
- There is fair evidence to support the use of TL-01 in vitiligo (*Strength of recommendation B; Quality of evidence IIi*) and in CTCL (*Strength of recommendation B; Quality of evidence III*).

Possible audit points

- Equipment to measure radiation output from TL-01 equipment should be calibrated annually.
- The initial dose should normally be a percentage (50–70%) of the MED or determined by a small area test dose.
- The number of doses per treatment course and the total number of doses should be recorded.
- There should be a record that possible skin cancer risks have been discussed with the patient.
- Regular review by an expert panel will be required to keep guidance updated.

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Appendix 1

This guideline has been prepared by the British Photodermatology Group on behalf of the British Association of Dermatologists (BAD). The writing committee comprised experts in clinical photomedicine/photobiology, medical physicists, and a representative of the BAD's Therapy Guidelines and Audit Committee (TGA). Evidence was searched from medical databases and from previous publications; the recommendations formulated from the evidence, and the strength of the evidence on which they are based, use the ranking system previously applied by the TGA and listed below. The limitations and side-effects of treatment have been taken into account in making these recommendations. However, this document is specifically aimed to provide guidance on narrowband ultraviolet B and, other than for comparative purposes, other treatments for the conditions discussed have not been addressed in detail.

The strength of recommendations and quality of evidence gradings are as follows:

Strength of recommendations

A There is good evidence to support the use of the procedure.
B There is fair evidence to support the use of the procedure.
C There is poor evidence to support the use of the procedure.
D There is fair evidence to support the rejection of the use of the procedure.
E There is good evidence to support the rejection of the use of the procedure.

Quality of evidence

I Evidence obtained from at least one properly designed, randomized controlled trial.
IIi Evidence obtained from well-designed controlled trials without randomization.
IIii Evidence obtained from well-designed cohort or case–control analytical studies, preferably from more than one centre or research group.
IIiii Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments could also be regarded as this type of evidence.
III Opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees.
IV Evidence inadequate owing to problems of methodology.