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Journal of Photochemistry and Photobiology B: Biology 38 (1997) 99–106

Journal of PHOTOCHEMISTRY AND PHOTOBIOLOGY B:BIOLOGY

New trends in photobiology (Invited review)

Biological effects of narrow-band (311 nm TL01) UVB irradiation: a review

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Received 12 July 1996; accepted 28 August 1996

Abstract

The narrow-band UVB (TL01) lamp (311 nm emission) was developed for use in phototherapy, as an alternative to a broad-band UVB source and to photochemotherapy, both of which have significant side effects and carry a risk of carcinogenesis. This new lamp has proved to be particularly effective at clearing psoriasis. It is now acknowledged that the TL01 lamp is probably 2–3 times more carcinogenic per minimum erythema dose than broad-band UVB, but the cumulative dose required in therapy is considerably less than when using broad-band UVB sources. In terms of irradiation dose, the TL01 lamp is about 5–10-fold less potent than broad-band UVB for erythema induction, hyperplasia, oedema, sunburn cell formation and Langerhans cell depletion from skin. However, the broad-band UVB to TL01 potency ratio for *cis*-urocanic acid formation in the skin is approximately unity. In addition, the TL01 lamp, as used in phototherapy, has relatively more suppressive effects than broad-band UVB on systemic immune responses as judged by natural killer cell activity, lymphoproliferation and cytokine responses. However, the TL01 lamp is less effective at reducing epidermal antigen presentation, inducing dendritic cell migration to lymph nodes draining irradiated sites and suppressing contact hypersensitivity at the doses tested. Therefore the use of the TL01 lamp in phototherapy should be considered carefully after weighing up its diverse effects on the skin and immune system. ©1997 Elsevier Science S.A.

Keywords: Carcinogenesis; Immunosuppression; UVB irradiation

1. Introduction

The TL01 lamp [1] is used in phototherapy in a number of European dermatology departments as an alternative to broad-band UVB (270–350 nm) or psoralen plus UVA (PUVA). Conventional UVB sources can lead to erythema and may carry a theoretical risk of carcinogenesis, although this has not been confirmed in retrospective studies [2]. PUVA can also cause side effects such as nausea and is contraindicated in pregnancy; it is a recognized carcinogenic treatment, with a up to fifty times the normal risk (unirradiated individuals) of developing cutaneous squamous cell carcinoma [2–4]. Monochromator studies have shown that wavelengths of less than 290 nm are erythemogenic, but not therapeutic, for the treatment of psoriasis [5]. In addition, narrow-band 311 nm UV phototherapy is particularly effective at clearing psoriasis, with a reduced capacity to produce erythema [6]. Therefore it was proposed that it would be desirable to develop a radiation source which excluded the shorter erythemogenic wavelengths and, as the action spectrum for UV carcinogenesis available at the time was thought to parallel that for erythema, would reduce the risk of developing skin cancer [7]. An experimental fluorescent lamp (Philips TL01) was produced in 1984 which emitted a narrow peak of 51% of the radiant energy at 311 nm [1,8]. Its output is shown in Fig. 1. This lamp was significantly better than broad-band UVB irradiation at clearing psoriasis in a shorter period of time, with only a 10% incidence of burning, compared with 28% for conventionally treated patients [9].

Although the narrow-band UVB treatment is used therapeutically, frequently with success, its mode of action is not clear. This article aims to review studies involving the TL01 lamp, but excluding those outlining its use in clinical phototherapy. Although the experiments so far are limited, it is possible to make comparisons with the results from broad-

Abbreviations: CH, contact hypersensitivity; DC, dendritic cells; HSV, herpes simplex virus; γ-IFN, γ-interferon; IL, interleukin; LC, Langerhans cells; MED, minimum erythema dose; MELR, mixed epidermal cell lymphocyte reaction; MLR, mixed lymphocyte reaction; NK, natural killer; PBMC, peripheral blood mononuclear cells; PHA, phytohaemagglutinin; PUVA, psoralen plus UVA; TNF-α, tumour necrosis factor-α; UCA, urocanic acid; UV light, ultraviolet light

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PII S1011-1344(96)07454-4

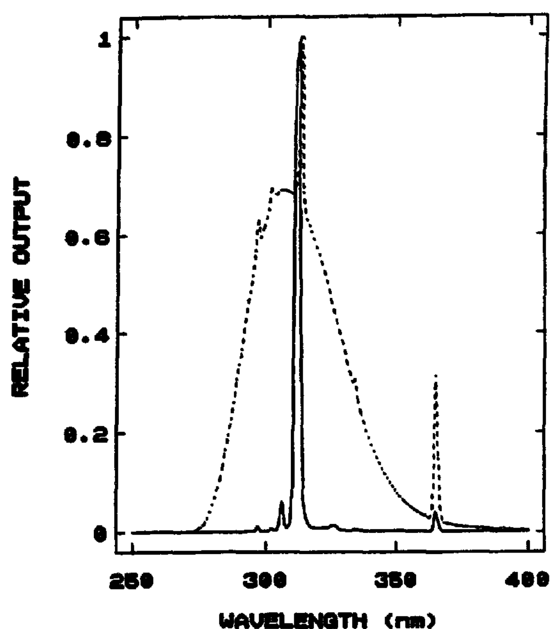

Fig. 1. The relative spectral output of the TL12 (dotted line) and TL01 (full line) fluorescent sources normalized at 312 nm, determined at 1 nm intervals using a Philips Cary 17 spectroradiometer.

band UVB and to reach tentative conclusions regarding the mechanisms and safety aspects. The investigations fall into three categories: the carcinogenic potential of TL01 irradiation, the direct effects on the skin and the effects on the performance of the immune system.

2. TL01 irradiation and carcinogenesis

The first risk assessment of the wavelength dependence of skin cancer induction was based on erythema, and a crude similarity between erythemal effectivity in human subjects and carcinogenicity in mice was noted more than 20 years ago [10]. However, the available data were not sufficient to cover the entire UV range and only in 1993 was an action spectrum constructed using various broad-band UV sources and weighting exposures at different wavelengths according to their effectiveness in skin cancer induction in albino hairless mice [11]. The maximum was at 293 nm and there was a broad shoulder above 340 nm at 10^{-4} of the maximum.

Early work with narrow-band UVB suggested that the TL01 lamp would have a lower carcinogenic potential than broad-band UVB [1,7]. It was concluded that this source was less tumorigenic than the broad-band UVB (TL12) lamp, since the median tumour induction time was significantly longer in animals exposed to TL01 irradiation [12]. However, a more recent study on hairless mice (hr/hr) irradiated with suberythemal doses 5 days per week for 30 weeks using the TL01 lamp or a TL12 source has found that tumours appear earlier with the TL01 lamp [13]. The total irradiation dose is greater with this lamp, but the total minimum erythema dose (MED) is considerably less. The dose required to produce 1 MED in this strain of mouse is 1250 J m^{-2} of TL12 irradiation, but 13 500 J m^{-2} of TL01 exposure, a ratio of 1:10.8. The median tumour induction time is 14 weeks with the TL01 lamp (a dose of 36.3 MED) and 21 weeks with the TL12 lamp (137.6 MED). Another two studies have confirmed this result [14,15]; for example, in mice exposed for 5 days per week to equally oedematogenic doses of TL12 or TL01, the TL01 lamp is significantly more effective at producing primary tumours and multiple tumours at each dose level [15].

Thus the consensus at the present time is that irradiation with TL01 may be more carcinogenic than with broad-band UVB. However, the UV exposure of mice leads to epidermal hyperplasia (thickening of the epidermis) which modifies the UV transmission in a wavelength-dependent manner, shorter wavelengths being obscured to a larger extent [16]. Since TL12 emits more strongly in the wavelength range below 300 nm than TL01, the hyperplasia developing from repeated exposure may explain why the broad-band source is less carcinogenic than the narrow-band source. It has also been noted that longer wavelengths may mitigate the damaging effects of shorter wavelengths in mice. For example, doses of UVA (up to ten times the UVB dose) given simultaneously with UVB protect against UVB-induced cancer [17]. The TL12 source emits 32% UVA [17], whereas the TL01 lamp emits only 12% UVA [18]. This may be an additional reason why the TL01 source is more carcinogenic than expected from its erythemogenic or oedematogenic potential. UVA protection probably occurs via enhanced repair of pyrimidine dimers [19] and a reduction in oxygen radical formation [20]. Finally, a recent investigation has concluded that the TL01 source is more potent at inducing erythema in human skin and the TL12 source less potent than would be predicted from the CIE erythema action spectrum [21]. The ratio of TL12 to TL01 is 1:2.8 instead of the calculated 1:4.2.

Using the mouse carcinogenesis data and taking into account the difference in epidermal thickness between mice and humans, it can be concluded that the TL01 lamp is probably two to three times more carcinogenic per MED in humans than the TL12 source [22]. However, a recent workshop on the use of the TL01 source in phototherapy has noted that the cumulative MEDs of TL01 required to clear psoriasis are usually less than one-third of those required with the TL12 lamp. The participants concluded that the long-term human cancer risk from current regimens should be no greater than that with broad-band phototherapy [23]. Similarly, they suggested that, since PUVA is more carcinogenic than broad-band UVB (there being no direct comparisons between PUVA and TL01), the current trend towards the increased use of TL01 phototherapy is justified.

3. Direct effects of TL01 on the skin

Investigations into the effects of the TL01 lamp on hyperplasia, tanning, oedema, sunburn cell induction, itching and

Table 1
Summary of the broad-band UVB:TL01 dose potency ratios for the induction of local changes in the skin

Parameter	TL12:TL01 potency ratio	Reference
Carcinogenesis	2.8:1	[13]
Erythema	7.5:1	[14]
	2.8:1	[21]
	7:1	[25]
	11:1	[13]
Hyperplasia	5:1	[24]
Oedema	6:1	[28]
	7:1	[29]
Sunburn cell formation	5–6:1	[29]
	6:1	[25]
Cis-UCA induction	0.6:1	[32]
	2.3:1	[29]
Langerhans cell depletion	6:1	[25]

cis-urocanic acid (*cis*-UCA) formation in the skin, as well as on the density of Langerhans cells (LC) in the epidermis, have been performed. A summary of the results is given in Table 1.

3.1. Hyperplasia and tanning

Hyperplasia and tanning occur after prolonged exposure to UV irradiation and these are protective mechanisms. The thicker epidermis and melanin pigment absorb more of the UV radiation, allowing a smaller proportion to penetrate and resulting in a less deleterious outcome. Using three UV lamps, a rough approximation of the hyperplasia action spectrum has been deduced [24]. This shows that the TL01 lamp is approximately fivefold less efficient at inducing hyperplasia than the broad-band UVB source in albino hairless Skh-hr1 mice. It should be noted, however, that a negative feedback loop is present in this system. The epidermal hyperplasia is a biological response to the irradiation stimulus. This irradiation stimulus leads to the thickening of the epidermis which, in turn, reduces the amount of stimulus transmitted into the skin and therefore the rate of thickening. Another study has shown that irradiation of C3H/HeN mice on their shaved backs with 3000 J m^{-2} TL01 (0.3 MED) three times a week over a period of 6 weeks did not lead to any epidermal hyperplasia, whereas irradiation with 500 J m^{-2} TL12 (0.35 MED) led to a 50% increase in the thickness of the epidermis [25]. No erythema or tanning was observed in the TL01 irradiated mice. The TL12 group, however, exhibited erythema and this developed into tanning pigmentation after 3 weeks of irradiation. Others have reported that TL01 exposed lightly pigmented hr/hr hairless mice developed erythema during the first week of irradiation (0.6 MED 5 days per week) [14]. In addition, a more severe erythema was observed in a higher dose TL01 irradiated group than in the TL12 irradiated group (both 1.2 MED 5 days per week), and these mice became more tanned than TL12 exposed mice after 33 weeks of chronic irradiation [14]. These discrepancies may be due to differences in the TL01 doses given or may reflect a variability in the response of different mouse strains. Tanning of the skin is known to reduce the risk of developing basal cell and squamous cell carcinomas which are significantly associated with lighter skin colour [26]. In addition, people who have the ability to develop a tan following UV exposure possess half the risk of skin cancer induction compared with those who have a poor ability to tan [27]. This implies that a UV lamp which stimulates tanning during chronic irradiation is less damaging.

3.2. Oedema

As already stated, the TL12 to TL01 erythema potency ratio has been reported to be 7–10:1 [13,25] in mice and 2.8:1 in human skin [21]. Since it is difficult to assess erythema in mice, skinfold thickness has also been used to measure oedema induction by UV irradiation. An oedema action spectrum has been used to derive an oedema potency ratio between TL12 irradiation and TL01 irradiation of 6:1 [28]. A more direct comparison of the linear dose responses for oedema with the two sources suggests that the TL12 to TL01 potency ratio is approximately 7:1 in Skh-1 (hr/hr) mice [29]. In the same study, the potency ratio to induce sunburn cells, which are thought to be apoptotic keratinocytes, was 5–6:1. Another study confirmed this ratio to be 6:1 [25].

3.3. Itching

UV irradiation provokes itching in humans and in mice. Itching has been induced in mice using four different UV sources, including TL01, and the amount of scratching has been quantified. The same MED was applied using the four UV lamps, but different scratching frequencies were found to be associated with the different sources. If the action spectrum for itching is identical to the erythema action spectrum, all four sources will be expected to provoke an equal amount of scratching. This is not the case, as wavelengths between 315 and 330 nm are more itch provoking than erythemogenic. The TL01 lamp is less itch provoking than the TL12 source and may therefore be preferred for the treatment of itching diseases [30].

3.4. Cis-UCA

The histidine product, UCA, is present as the *trans*-isomer in the upper layers of the epidermis. It acts as a UV chromophore, absorbing irradiation energy, and is thus isomerized from the trans to the cis form. The isomerization is dependent on the dose of UV until the photostationary state is reached, when approximately equal quantities of the two isomers are present. *Cis*-UCA has been implicated as one of the mediators of UVB-induced immunosuppression since it can mimic many of the effects of UV irradiation on the immune system [31]. The action spectrum for *cis*-UCA formation in mouse skin peaks at 300–315 nm, whereas isomerization at 270 nm

is equivalent to that at 325–330 nm [32]. This action spectrum can be used to calculate a theoretical TL12 to TL01 potency ratio of 0.6:1 [29]. In an attempt to compare more directly the ability of the TL12 and TL01 lamps to induce *cis*-UCA, dose–response curves have been derived. All three TL01 doses used (1840, 3200 and 4670 J m^{-2}) produce higher levels of *cis*-UCA than the maximum TL12 dose (780 J m^{-2}). The TL12 and TL01 curves do not overlap and it is therefore difficult to calculate a TL12 to TL01 potency ratio for *cis*-UCA induction. However, this ratio is estimated to be 2.3:1 based on the available data [29].

3.5. Langerhans cells (LC)

LC are very important dendritic antigen presenting cells present in the epidermis which offer the first line of immunological defence. They take up any foreign antigens they encounter and migrate to draining lymph nodes where they present processed fragments to T lymphocytes. The density of LC in the epidermis is thought to be a measure of immunological preparedness, a lower density leading to a more severe outcome in the case of skin infections. For example, a low density of LC results in a more severe herpes simplex virus (HSV) infection [33]. In C3H/HeN mice, a single dose of 960 J m^{-2} TL12 or 7200 J m^{-2} TL01 is capable of significantly reducing the density of LC (by more than 50%) [34]. Only TL12 irradiation, however, changes the morphology of a large proportion of LC from a dendritic shape to a more rounded cell structure.

Multiple UVB doses also reduce LC numbers. Thus TL12 irradiation with 500 J m^{-2} or 1000 J m^{-2} three times weekly results in approximately 50% and 70% reduction in the density of LC after 2–3 weeks. Morphologically, between 20% and 40% of the LC appear to lose their dendrites following 1–4 weeks of TL12 exposure. TL01 exposure with 3000 J m^{-2} results in only a 20% decline in the density of LC after 2 weeks of exposure and there is no effect on the dendritic morphology of LC [25]. Although it is not possible to calculate accurately a TL12 to TL01 LC reduction potency ratio from these data, it can be estimated to be approximately 6:1.

4. Effects of TL01 on immune responses

A variety of tests have been carried out using the TL01 source which indicate its range of activity in modulating both local and systemic immune responses. In almost all cases, its effects are compared with broad-band UVB sources. Although a number of experiments involve mice or murine cells, a few have examined human epidermal cells or samples of blood obtained from patients undergoing phototherapy. The results are summarized in Table 2.

4.1. Antigen presentation

It is known that UVB irradiation in vivo or in vitro decreases the allostimulating capacity of antigen presenting cells. Hurks et al. [35] have produced action spectra over the range 254–312 nm for the suppression in the mixed lymphocyte reaction (MLR) and mixed epidermal cell lymphocyte reaction (MELR) of human cells by irradiating peripheral blood mononuclear cells (PBMC) or epidermal cells as stimulator cells with monochromatic light or TL01 in vitro. It was shown that both responses were maximally suppressed at 254 nm and that the relative sensitivity at 312 nm was 1000 times lower than that at 254 nm. The action spectra correspond closely with those found for the induction of thymine dimers and (6–4) photoproducts in irradiated solutions of calf thymus DNA [36]. A similar result was obtained in a murine system where a comparison was made between the effectiveness of broad-band UVB and TL01 sources to suppress the MELR by the in vitro irradiation of epidermal cells prepared from mouse ears [34]. A reduction of 60% was induced following a dose of 120 J m^{-2} of broad-band UVB, whereas a dose of 3600 J m^{-2} was required from the TL01 lamp to achieve the same percentage reduction.

Broad-band UVB irradiation of C3H/HeN mice in vivo (960 J m^{-2}) resulted in an immediate reduction in the ability of epidermal cells from the exposed site to stimulate the MELR, but irradiation in vivo with the TL01 lamp up to 7200 J m^{-2} had no effect [34]. It is possible that even higher doses may be required to demonstrate an effect. As the two lamps have been shown to be approximately comparable in their potency to induce trans to cis isomerization of UCA (see

Table 2
Comparison of the effects of broad-band UVB and TL01 irradiation on the immune responses

Species	Test	Broad-band UVB	TL01 (comparison with broad-band UVB)	Reference
Human	MLR (in vitro exposure)	Suppression	Suppression (at least ten times less efficient)	[35]
Human	MELR (in vitro exposure)	Suppression	Suppression (at least ten times less efficient)	[34,35]
Mouse	MELR (in vivo exposure)	Suppression	No suppression (at eight times higher dose)	[34]
Mouse	Dendritic cell migration to lymph node	Yes	No	[39]
Mouse	Contact hypersensitivity	Suppression	No suppression (at four to six times higher dose)	[43]
Mouse	Serum IgE	Initial increase	Initial increase (at three times higher dose)	[25]
Human	Immunoglobulin subclasses and IgE	No change	No change	[47]
Human	Peripheral blood mononuclear cell subsets	No change	No change	[48,49]
Human	Natural killer cell activity	Suppression	Suppression (more readily)	[48,49]
Human	In vitro lymphoproliferation	No change	Suppression	[47]

above), this argues against a direct role for *cis*-UCA in the UVB-induced suppression of the MELR. However, such a role has been indicated by three approaches. Firstly, epicutaneous treatment of mice with *cis*-UCA suppressed the MELR when the epidermal cells were tested subsequently as stimulator cells [37]. Secondly, pre-treatment of mice with a monoclonal antibody with specificity for *cis*-UCA before broad-band UVB exposure led to the restoration of the MELR [37]. Thirdly, in vitro addition of *cis*-UCA to a human MLR and MELR resulted in a moderate suppression in the MELR, but not in the MLR, perhaps indicating that epidermal antigen presenting cells are particularly sensitive to the presence of *cis*-UCA [38].

It is difficult to reconcile these various in vivo and in vitro results at the present time. It is possible, however, that some other factor or cellular response in the skin is normally required for TL01 irradiation in vivo to affect the MELR. For example, oedema, in addition to *cis*-UCA formation, may be required before a reduction in the capacity of epidermal cells to present antigen is suppressed by the exposure.

4.2. Dendritic cell (DC) migration

Broad-band UVB irradiation of mice is known to result in the accumulation of DC in lymph nodes draining the exposed site [39]. The number reaches a peak 48 h following irradiation of just less than 1 MED. Furthermore, epicutaneous treatment of mice with contact sensitizers leads to the migration of DC to lymph nodes draining the treated site and a substantial proportion of these are thought to originate in the epidermis [40]. UVB irradiation prior to skin sensitization at the same site enhances DC migration so that there are approximately twice as many DC per lymph node than when using the sensitizer alone [39]. Tumour necrosis factor-α (TNF-α) was shown to be a key cytokine in the migration as pre-treatment with antibodies to TNF-α before exposure eliminated the increase in DC numbers [41]. In contrast with these results, TL01 irradiation at the same or seven times higher dose than broad-band UVB irradiation had no effect on DC accumulation [39]. It is tempting to speculate from this result that the wavelengths emitted by the TL01 lamp do not induce the production or release of TNF-α, and thus DC are not given one of the signals they require to migrate to the lymph nodes draining the site of exposure. Further investigation is required to confirm this suggestion.

4.3. Contact hypersensitivity (CH)

Broad-band UVB irradiation causes the suppression of some cell-mediated immune responses, including delayed hypersensitivity. One of the few instances in which an action spectrum for the immunosuppressive effects of UV radiation has been constructed so far is for CH in mice. De Fabo and Noonan [42] found that the peak was around 260–280 nm and, at 310 nm, an equivalent dose was tenfold less effective. The TL01 lamp has been tried in limited experiments to test its effect on CH. C3H/HeN mice were irradiated on their shaved backs with 1440 or 4320 J m^{-2} TL01 or 1440 J m^{-2} broad-band UVB before being sensitized on their backs with oxazolone 2 days later. When challenged on their ears with oxazolone, the ear swelling response of mice exposed to either dose of TL01 was no different from that of unirradiated control mice ($p>0.1$), whereas that of the mice exposed to broad-band UVB was significantly suppressed ($p<0.01$) [43]. Similarly, another experiment showed that chronic irradiation with 3000 J m^{-2} TL01 (three times weekly for 6 weeks) did not suppress local CH responses to oxazolone, whereas chronic irradiation with broad-band UVB (500 or 1000 J m^{-2}) suppressed this response by over 60% [25]. Another system utilized a series of Kodacel filters to obtain transmitted UV light with progressively less UVB and more UVA, all of which induced the formation of approximately 35% *cis*-UCA in the epidermis of Skh hairless mice [44]. It was found that exposure of the backs to irradiation containing wavelengths below about 310 nm resulted in the suppression of CH to a sensitizer (2,4-dinitrofluorobenzene (DNFB)) applied on the unirradiated abdomen, followed by challenge on the ears.

Thus it is possible that exposure to the TL01 source does not lead to effective suppression of CH, at least at doses below erythemal levels. Reeve et al. [44] noted a correlation between the induction of oedema and the suppression of CH and, as it has been shown that the TL01 lamp is about six times less potent at inducing oedema than the broad-band UVB source (see above), higher doses may be needed to demonstrate that TL01 can suppress the induction of CH. Alternatively, a mediator required in the cascade leading to the suppression of CH may not be produced at the waveband emitted by the TL01 lamp. As noted above, *cis*-UCA is formed from *trans*-UCA most effectively at 300–315 nm in vivo in mouse skin [32]. In addition, Reeve et al. [44] have shown that only the sources richest in short-wavelength UVB can suppress the CH response despite the fact that all sources used can generate 35% *cis*-UCA. These data argue against a direct relationship between the *cis*-UCA concentration and the extent of CH suppression.

Equivalent experiments to test whether TL01 affects delayed-type hypersensitivity responses have not been carried out so far.

4.4. Systemic immune responses

Several reports using mice or murine cells have shown that UVB irradiation results in the promotion of T helper 2 (Th2) responses with anergy of Th1 responses [45,46]. In mice, there is a clear distinction between these Th subsets based on the cytokine profile they produce, so that Th1 cells synthesize interleukin-2 (IL-2), IL-12 and γ-interferon (γ-IFN) and help B cells to produce complement-fixing antibodies (IgG2 and IgG3) and Th2 cells synthesize cytokines such as IL-4, IL-5, IL-6 and IL-10 and help B cells to produce non-complement-fixing antibodies (IgG1 and IgE). The division in

cytokine profiles between these subsets is not so distinct in human subjects.

Two studies have examined immunoglobulin subsets during TL01 irradiation. The first involved the measurement of total serum IgE during chronic irradiation of mice with TL01 or TL12 [25]. Exposure to either 1000 J m^{-2} TL12 or 3000 J m^{-2} TL01 induced a substantial increase in IgE for the first 3 weeks which gradually returned to normal levels after 6 weeks as the irradiation continued. Total immunoglobulin concentrations remained constant throughout, indicating that isotype switching, perhaps through the action of IL-4 produced by activated Th2 cells, occurred during the initiation phase of the chronic irradiation but was not sustained. This could be tested by analysing IL-4 production by activated lymphocytes during irradiation. A second study monitored IgG subclasses and IgE during TL01 phototherapy of patients with psoriasis; no significant changes occurred during 4 weeks of treatment [47]. An initial dose of 70% of the MED was given, followed by exposure three times weekly with an increase of 40% in the dose on each occasion unless erythema occurred.

PBMC from patients with psoriasis have been examined phenotypically and functionally in several ways following TL01 therapy. After 1 and 4 weeks of treatment, the percentages of CD1a, CD3, CD4, CD8, CD57 and MHC Class II-positive cells remained unchanged [48,49]. However, the irradiation reduced the activity of natural killer (NK) cells [49]. This was apparent at all effector to target cell ratios in most patients after 1 week of therapy [48] and was also found to a higher degree after 4 weeks of therapy [49]; 4 weeks after treatment had stopped, the NK cell activity was beginning to recover, although it had not yet regained its initial level. When compared with the effects of broad-band therapy, the kinetics were different. Exposure to the broad-band source induced no significant change in NK cell activity in 4 weeks of therapy, but suppression occurred later after further exposures [49]. Therefore it is possible that, as well as wavelength differences between the two lamps, the total dose of UV may be a critical factor: the patients being treated with the TL01 source received about 66 000 J m^{-2} in 4 weeks, whereas those being treated with the broad-band source received about 18 000 J m^{-2}.

In vitro lymphoproliferative responses of PBMC have also been monitored in patients with psoriasis during TL01 therapy. It was shown that, at the end of the first week of treatment, the responses to the mitogens phytohaemagglutinin (PHA), pokeweed mitogen and concanavalin A and to HSV antigens (in individuals sero-positive for HSV) did not change from the pre-treatment levels [48]. However, as the treatment continued, there was a progressive reduction in the proliferative response to PHA [47]. This was accompanied by a large decrease in the production of the cytokines γ-IFN, IL-2 and IL-10 in vitro, a result which does not support a shift from type 1 to type 2 activity. In contrast, phototherapy with broad-band UVB did not cause changes in the lymphoproliferative response to PHA during 4 weeks of therapy, and the production of γ-IFN, IL-2 and IL-10 in vitro was unaltered [47].

Thus it seems that the TL01 lamp, as used in phototherapy, has more effect than broad-band UVB on the systemic immune responses as judged by NK cell activity, lymphoproliferation and cytokine responses, but no evidence has been obtained to substantiate a differential effect on particular T cell subsets. However, it should be noted that most of these studies have involved patients with psoriasis and, although their PBMC subsets, immunoglobulin classes and NK cell activity are within normal limits [49,50], it is possible that they may respond differently from healthy individuals to TL01 therapy.

5. Conclusions

It may be seen from this review that the effects of exposure to the TL01 source are different in many respects from exposure to the broad-band UVB source. Thus, in terms of absolute dose, the broad-band lamp is approximately 5–10-fold more effective than the TL01 lamp for erythema induction, hyperplasia, oedema, sunburn cell induction and LC depletion from the skin. With regard to immunomodulation, broad-band UVB irradiation suppresses a number of local responses, such as the MLR, MELR and CH, which TL01 does not or only at much higher doses. In contrast, in the few instances in which TL01 has been tested for its effect on systemic immunity during phototherapy, it appears to be more suppressive than broad-band UVB with respect to NK cell activity and the function of mononuclear cells as measured by lymphoproliferation and cytokine production. This may be dose related in addition to being dependent on wavelength. It is not known whether these systemic changes contribute to the success of TL01 treatment in clearing psoriasis. For two other parameters, TL01 is also more effective than expected from its erythemal potential, i.e. *cis*-UCA formation and carcinogenic potential, where the ratios are less than 2.8:1. Whether the induction of *cis*-UCA is linked to the suppression of the systemic immune responses noted and whether *cis*-UCA plays a major role in cutaneous carcinogenesis are not clear at the present time.

Acknowledgements

The spectral output determination was carried out by Dr Neil Gibbs, Photobiology Unit, Ninewells Hospital, University of Dundee. Work in the authors' laboratory is funded by an EC Environment Programme grant.

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