CLINICAL REVIEW
ULTRAVIOLET IRRADIATION IN SYSTEMIC LUPUS ERYTHEMATOSUS: FRIEND OR FOE?

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SUMMARY

The long established notion that UV irradiation is always harmful to patients with systemic lupus erythematosus has been challenged by some recent reports of benefit using a form of phototherapy with UV-A. In the review we discuss the different types of UV radiation, the links between certain forms of such radiation and clinical manifestations and consider the mechanisms involved.

KEY WORDS: Systemic lupus erythematosus, Photosensitivity, Ultraviolet radiation, UV-A, UV-B.

EXPOSURE to sunlight has long been associated with exacerbation of systemic lupus erythematosus (SLE). Photosensitivity occurs in ~45% of patients and remains a diagnostic criterion of SLE [1, 2]. Photo-induced cutaneous disease appears mainly on sun-exposed areas as macular, papular or bullous lesions as well as classic erythema [3]. Although new lesions may result from exposure to sun or fluorescent light, pre-existing skin disease is more likely to be aggravated [4, 5]. Systemic flare may occur and is reported as weakness, fatigue, fevers or joint pain, but this may not be related to more severe overall disease and does not necessarily correlate with physician or laboratory parameters of increased disease activity [6].

Photosensitivity results mainly from ultraviolet (UV) radiation rather than visible light [7]. UV wavelengths consist of UV-C (200–290 nm; far UV, germicidal UV), UV-B (290–320 nm; midrange UV, sunburn radiation) and UV-A (320–400 nm; near UV, black light) (Fig. 1). Because UV-C is absorbed by the Earth’s ozone layer, its effects are negligible [3, 5]. Daily exposure to UV-A is much greater than to UV-B, although UV-A-induced erythema in normal skin requires 1000 times more energy than from UV-B [5]. Different photobiological effects from UV-A radiation are thought to be significant in the pathogenesis of photoinduced systemic disease; however, recent studies have shown that longer wavelengths of UV-A, but not UV-B, may be beneficial in SLE and in the photosensitive lupus subset, subacute cutaneous lupus erythematosus (SCLE) [8–11]. These surprising findings warrant a re-appraisal of light exposure, photosensitivity and SLE.

CLINICAL EFFECTS

Typically, clinical investigation of photosensitivity is performed by phototesting small areas of skin with UV radiation. Most studies of SLE have examined the effects of UV-B radiation, with 30–50% of patients developing a skin reaction upon phototesting [12–14]. Systemic disease is induced rarely, perhaps due to the small area of irradiation. Patients with a UV-B-invoked reaction develop erythema at the phototest site 24 h–3 weeks after irradiation, and this can persist for weeks [15, 16]. Although UV-A may exacerbate skin disease, some studies report no effect [12, 14, 15, 17–19]. In a study of 20 patients with SLE, characteristic lesions were reproduced in a quarter of those irradiated, mainly with UV-B or UV-B with UV-A, but in one patient with UV-A alone [14]. Moreover, a history of photosensitivity does not necessarily predict positive reactions on phototesting. One-third of patients with SLE will have no phototest reaction despite a history of photosensitivity, whereas positive phototests may occur in patients with no previous photosensitivity [14].

PATHOGENESIS OF PHOTOSENSITIVITY

Amongst the mechanisms that may determine photosensitivity following UV irradiation, circulating antibodies to the Ro/SSA antigen [ribonucleoprotein (RNP) particles linked to particular small cytoplasmic RNA species] have been associated with photoinduced lesions and may confer an increased risk compared to other antibodies [20, 21]. There is no difference, however, in the frequency of antibodies to Ro/SSA among patients with positive and negative phototest reactions [15, 18, 21]. Photosensitivity is diagnostic for SCLE and 75% of patients have antibodies to Ro/SSA antigen, although titres do not correlate with skin activity [22–24]. This strong association of Ro/SSA antibody in SCLE has served as a model for investigation of the immunopathogenic mechanism of photosensitivity [25]. In human skin grafted onto nude mice, injection of sera having anti-Ro/SSA antibodies, but not anti-DNA antibodies, resulted in Ro antibody deposition in the skin [26, 27]. UV-B, but not UV-A, increases the expression and binding of autoantibody to Ro/SSA and, to a lesser extent, RNP and Sm antigens, but not to DNA, while concomitant radiation of UV-B with UV-A appears to have no effect on
Members of the heat shock protein (hsp) 70 family, migration of memory and activated T cells [41]. Lectin in dermal endothelial cells which may promote similar, UV irradiation increases E-selectin expression on keratinocytes which, in turn, may facilitate cellular interaction, recognition and subsequent cytoxicity [25, 38-40]. Similarly, UV irradiation increases E-selectin in dermal endothelial cells which may promote migration of memory and activated T cells [41]. Members of the heat shock protein (hsp) 70 family, 72 kDa and 70 kDa proteins, are increased by UV radiation [42, 43]. These proteins may serve as molecular chaperonins with a role in Ro/SSA translocation, although overexpression of hsp 70 decreases UV-induced IL-1 and IL-6 release, and increases cell viability after UV-B irradiation [43]. While prostaglandin production and release may be enhanced by UV light, UV-irradiated antibodies to Ro/SSA may contribute to changes in vascular dilatation and may increase blood flow [44, 45].

Unlike cutaneous photosensitivity, the pathogenesis of systemic photosensitivity is not clearly understood, and may be due to causes other than Ro/SSA autoantibody and ADCC (Fig. 2). In contrast to Ro/SSA antigen—antibody binding, the binding of anti-DNA antibodies to DNA is not increased after UV-A or UV-B irradiation [46]. UV-B radiation induces thymine dimers as products of DNA damage, while UV-A induces single-strand DNA breaks [47, 48]. Antibodies to UV-altered DNA (UV-DNA) are increased in sera of patients with SLE compared with normal controls, but again this does not correlate with a history of photosensitivity [49, 50]. Interestingly, i.v. injection of UV-DNA can result in glomerular nephritis (GN) in New Zealand albino rabbits with anti-DNA glomerular deposition [51]. Effects of direct UV irradiation on animal models of SLE are variable, although generally there is increased morbidity and antibody production [52]. Furthermore, UV effects on cutaneous immune function may contribute to systemic photosensitivity. UV-induced cytokine production by keratinocytes may result in systemic inflammation, while UV-B can activate a skin-derived mediator, cis-urocacin, which results in profound suppression of systemic cell-mediated immunity [53]. UV-B may affect Langerhans cells (LC) in several ways, e.g. by decreasing the number of these cells or changing their morphology and function, and decreasing their ability to stimulate T cells, particularly CD4+ Th1, thus resulting in unopposed Th2 cell stimulation of B cells [54, 55]. In addition, UV-B-irradiated epidermal macrophages activate CD4+CD45RA+ suppressor-inducer cells which results in a predominantly suppressor effector T-cell response in circulating lymphocytes [56]. That UV-A has different photobiological effects than UV-B may be significant in systemic photosensitivity (Table I). Unlike UV-B, UV-A penetrates the dermis and dermal vasculature, and may have a more direct effect on systemic immunity. Although lymphocytes cultured from patients with SLE showed increased susceptibility to UV-B irradiation as well as decreased

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**Fig. 1.**—The spectrum of UV radiation, by wavelength. The diagram is not to scale.

<table>
<thead>
<tr>
<th>Wavelength (nanometers)</th>
<th>UV-C</th>
<th>UV-B</th>
<th>UV-A1</th>
<th>UV-A1</th>
<th>Visible light</th>
</tr>
</thead>
<tbody>
<tr>
<td>200-290</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>400-700</td>
</tr>
<tr>
<td>290-320</td>
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<td>400-700</td>
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<td>320-340</td>
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<td>400-700</td>
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<tr>
<td>340-400</td>
<td></td>
<td></td>
<td></td>
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<td>400-700</td>
</tr>
</tbody>
</table>

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DNA repair synthesis, UV-A had either no effect or increased DNA repair synthesis [57]. Although UV-B may be more efficient in causing damage to DNA through direct absorption, UV-A has little effect on DNA without sensitization or activation of a secondary molecule ('chromophore') which forms a DNA cross-linking agent that may inhibit lymphocyte proliferation [7]. In skin as well as in lymphocytes, chromophore action is partly mediated by activated oxygen species which may contribute to damage of cell membranes or DNA [7, 58, 59]. Splenocytes from SLE murine models appear to be more sensitive to UV-A-induced oxidative stress than normal splenocytes [8, 9]. Interestingly, pre-irradiation of skin fibroblasts with UV-A results in decreased oxidative membrane damage upon subsequent UV-A exposure, and haem oxygenase 1 and ferritin may mediate this adaptive response [60].

THE BASIS OF PHOTOTHERAPY

The principle of chromophore activation is the basis of photochemotherapy, and has been used in the investigation and treatment of SLE. Photochemotherapy induces an autoregulatory response in the recipient that may deactivate abnormal T-cell idiotypes and alter T-cell receptor specificity [61-63]. Modification of lymphocyte function with UV-A-activated psoralens (PUVA) is the most common form of photochemotherapy, but requires direct skin irradiation.

Most intriguing is that UV-A alone may be beneficial without a known chromophore. UV-A irradiation of (NZB × NZW)F1 mice resulted in increased survival and decreased circulating anti-DNA antibodies [64]. A mechanism for the beneficial effect of UV-A is unclear, although it may be due to the absence of a chromophore and subsequent lack of effect on DNA. Furthermore, longer wavelengths of UV-A, UV-A1 (340-400 nm), do not affect LC function, perhaps resulting in decreased stimulation of B-cell function [65].

EFFECTS OF PHOTOTHERAPY

In SLE, extracorporeal photochemotherapy (photopheresis) has been used in order to avoid potentially harmful effects of direct light exposure. Photopheresis of MRL/l mice and a murine model of lupus-like graft-versus-host disease resulted in delayed progression of autoimmune disease [63, 66]. In an

<table>
<thead>
<tr>
<th>Specific effects</th>
<th>UV-A</th>
<th>UV-B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location of maximum effect</td>
<td>dermis</td>
<td>epidermis</td>
</tr>
<tr>
<td>Phototest response</td>
<td>mixed</td>
<td>positive</td>
</tr>
<tr>
<td>Ro/SSA</td>
<td>no effect</td>
<td>increased</td>
</tr>
<tr>
<td>Antigen expression</td>
<td>no effect</td>
<td>increased</td>
</tr>
<tr>
<td>Antibody binding</td>
<td>no effect</td>
<td>increased</td>
</tr>
<tr>
<td>Langerhans cells</td>
<td>no effect</td>
<td>decreased</td>
</tr>
<tr>
<td>Number</td>
<td>no effect</td>
<td>decreased</td>
</tr>
<tr>
<td>Morphology</td>
<td>no effect</td>
<td>decreased</td>
</tr>
<tr>
<td>T-cell stimulation</td>
<td>no effect</td>
<td>decreased</td>
</tr>
<tr>
<td>DNA damage</td>
<td>minimal without chromophore</td>
<td>+</td>
</tr>
<tr>
<td>Role of O2 radical damage</td>
<td>increased</td>
<td>unknown</td>
</tr>
<tr>
<td>Antioxidant response</td>
<td>increased</td>
<td>decreased</td>
</tr>
<tr>
<td>DNA repair synthesis</td>
<td>unchanged</td>
<td></td>
</tr>
</tbody>
</table>
uncontrolled trial of photopheresis in eight patients with SLE, seven had significant clinical improvement, including decreased joint scores, improved skin lesions, and minimal side-effects [67]. In some, improvement was maintained up to 1 yr after treatment.

Following direct UV-A<sub>1</sub> phototherapy of patients with SLE and SCLE, without a chromophore, photosensitive skin lesions, constitutional symptoms and arthritis improved with no activation of skin or systemic disease [11, 68]. Patients with anti-Ro/SSA antibodies appeared to have a greater response and no patient developed disease exacerbation. Improvement was maintained with decreased phototherapy sessions. Paradoxically, patients having photosensitive lesions, particularly SCLE, appeared to have the best response with either photopheresis or UV-A<sub>1</sub> [11, 68].

**SUMMARY**

Despite the prevalence of photosensitivity amongst lupus patients, light may be harnessed to benefit some patients. Unlike UV-B, UV-A has photobiological effects that may be beneficial. While we treat patients at present with potentially toxic medication, UV-A<sub>1</sub> and photopheresis appear to be safe therapies without exacerbation of skin or systemic disease. In fact, photopheresis appears to have no effect on normal cell-mediated immune function [63]. The notion of clinical improvement after UV-A<sub>1</sub> treatment is provocative and contradictory to the maxim that light harms the SLE patient. The mechanism of this therapy is unclear, although UV-A<sub>1</sub> does not affect LC function and therefore may not allow B-cell stimulation. Could repetitive irradiation with low-dose UV-A<sub>1</sub> result in decreased oxidative damage? Further laboratory investigation may clarify the mechanism by which light affects disease activity, while large, controlled clinical trials are needed to confirm the safety and efficacy of therapy, in which at last some forms of light are no longer a foe, but a friend to those with SLE.

**ACKNOWLEDGEMENT**

The authors thank Dr Sanj Menon for critical review of the manuscript.

**REFERENCES**


