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REVIEW

Ultraviolet-A1 irradiation therapy for systemic lupus erythematosus

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Systemic lupus erythematosus (lupus, SLE) is a chronic autoimmune disease characterized by the production of autoantibodies, which bind to antigens and are deposited within tissues to fix complement, resulting in widespread systemic inflammation. The studies presented herein are consistent with hyperpolarized, adenosine triphosphate (ATP)-deficient mitochondria being central to the disease process. These hyperpolarized mitochondria resist the depolarization required for activation-induced apoptosis. The mitochondrial ATP deficits add to this resistance to apoptosis and also reduce the macrophage energy that is needed to clear apoptotic bodies. In both cases, necrosis, the alternative pathway of cell death, results. Intracellular constituents spill into the blood and tissues, eliciting inflammatory responses directed at their removal. What results is ''autoimmunity.'' Ultraviolet (UV)-A1 photons have the capacity to remediate this aberrancy. Exogenous exposure to low-dose, full-body, UV-A1 radiation generates singlet oxygen. Singlet oxygen has two major palliative actions in patients with lupus and the UV-A1 photons themselves have several more. Singlet oxygen depolarizes the hyperpolarized mitochondrion, triggering non-ATP-dependent apoptosis that deters necrosis. Next, singlet oxygen activates the gene encoding heme oxygenase (HO-1), a major governor of systemic homeostasis. HO-1 catalyzes the degradation of the oxidant heme into biliverdin (converted to bilirubin), Fe, and carbon monoxide (CO), the first three of these exerting powerful antioxidant effects, and in conjunction with a fourth, CO, protecting against injury to the coronary arteries, the central nervous system, and the lungs. The UV-A1 photons themselves directly attenuate disease in lupus by reducing B cell activity, preventing the suppression of cell-mediated immunity, slowing an epigenetic progression toward SLE, and ameliorating discoid and subacute cutaneous lupus. Finally, a combination of these mechanisms reduces levels of anticardiolipin antibodies and protects during lupus pregnancy. Capping all of this is that UV-A1 irradiation is an essentially innocuous, highly manageable, and comfortable therapeutic agency. *Lupus* (2017) **26,** 1239–1251.

Key words: Ultraviolet-A1; apoptosis; anticardiolipin antibodies; B-cells; pulmonary hypertension; interstitial lung disease; coronary artery disease; carbon monoxide; heme oxygenase-1; discoid lupus; subacute cutaneous lupus erythematosus

Introduction

Falling within the electromagnetic spectrum between X-rays and visible light, the ultraviolet (UV) spectrum is conventionally divided into wavelength bands of increasing length and decreasing energy. Vacuum UV (<200 nm), UV-C (200–280 nm), UV-B (280–320 nm) and UV-A (320–400 nm) comprise the spectrum. The UV-A band has been further divided into UV-A2 (320–340 nm) and UV-A1 (340–400 nm) because UV-A2 shares properties with UV-B[1] and UV-A1 has properties that overlap with visible light.[2] Different chromophores (photon-absorbing molecules) absorb different UV wavelengths, determining their photo-biological effects. These differences account for the healing action of UV-A1 wavelengths when contrasted with the noxious effects of the shorter UV wavelengths in patients with lupus.[3–14]

The primary target of UV photons is the skin. The shortest terrestrial band of wavelengths, UV-B,

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penetrates to the superficial papillary dermis, deep enough to be absorbed by and do damage to epidermal DNA.[15] The DNA damage alters gene translation and function and in lupus triggers anti-double-stranded DNA (anti-dsDNA) antibody production. Repair of the DNA draws on compromised adenosine triphosphate (ATP) stores[16] for repair. In addition, the shorter UV wavelengths such as UV-B suppress cell-mediated immunity (CMI),[17] already suppressed in systemic lupus erythematosus (SLE), and these wavelengths promote antigen translocation, a phenomenon that leads to epidermal cell lysis in patients with lupus.[18–20]

In contrast, UV-A1 photons, which are not absorbed by DNA, penetrate deeply to reach the high levels of immunoreactants observed in the dermal-epidermal junction.[21] Inasmuch as overflow of these immunoreactants into the blood and tissues accounts for much of the systemic expression of disease in patients with SLE, the modulatory effect of UV-A1 photons similarly reaches every organ system.[22]

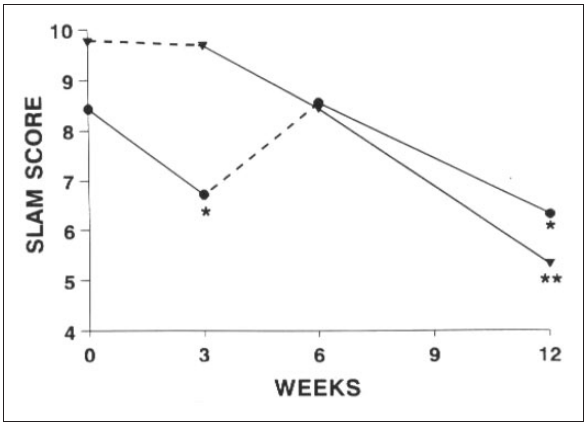

Figure 1 Disease activity during ultraviolet (UV)-A1 radiation therapy, as determined by the systemic lupus activity measure (SLAM) scores. During the first six-week, double-blind, five-day/week phase of the study, Group A patients (black circles) received UV-A1 (__) for three weeks and then received placebo (- - -) irradiation for three weeks. Group B patients (black triangles) received placebo (- - -) irradiation for three weeks and then received UV-A1 (__) irradiation for three weeks. During the unblinded phase of the study beginning at week 6, all patients received UV-A1 irradiation three days/week for six weeks (*$p < 0.05$; **$p < 0.01$).

Early investigations

The mitigating effects of the longest wavelengths of UV radiation on a systemic disease were first observed in a study using the New Zealand Black/New Zealand White (NZB/NZW) mouse model of lupus.[3] In this animal, the UV-A wavelengths not only lacked the toxicity of UV-B wavelengths but unexpectedly attenuated disease activity. UV-A radiation reversed the reduced lymphocyte mitogen responsiveness, decreased the extent of spleen enlargement, reduced the levels of anti-dsDNA antibodies and promoted the survival of the treated mice during the study period, as all of their untreated littermates died along the usual mortality curve for this model. As shown in a follow-up study, the longest UV-A wavelengths comprising the UV-A1 band were responsible for this salutary outcome.[4]

Human studies followed. TL10R Philips lamps, fitted with filters that transmit only UV-A1 wavelengths, were employed. In a series of studies, low-dose, full-body UV-A1 irradiation significantly decreased disease activity (systemic lupus activity measure (SLAM)) scores of patients with lupus (Figure 1), inducing an early reversal of fatigue, depression, and cognitive dysfunction and subsequently decreasing the inflammatory symptoms of pleurisy, joint pain, and mouth ulcers. Photosensitivity exhibited the latest response. The effectiveness persisted and even increased nonsignificantly with less-frequent weekly therapy over several years (Figure 2).

Apoptosis and UV-A1

Apoptosis, or programmed cell death, is the ordered destruction and safe disposal of cells by macrophages and immature dendritic cells.[23] The efficient activation of apoptosis is critical for the maintenance of homeostasis, the avoidance of necrosis, and the removal of excess T and B cells to terminate an immune response.[24–26] The resulting apoptotic bodies must be quickly cleared to avoid necrosis and prevent coagulation.[27,28]

Apoptosis is flawed in patients with lupus. The mitochondria, centers of energy production and governors of intrinsic apoptosis, are abnormal, exhibiting hyperpolarization and ATP deficits.[29,30] The hyperpolarized ATP-deficient mitochondria resist the depolarization required to initiate activation-induced apoptosis. Overexpression of the BCL-2 family of genes, which similarly inhibits activation-induced apoptosis, further increases the mitochondrial resistance to depolarization.[31,32]

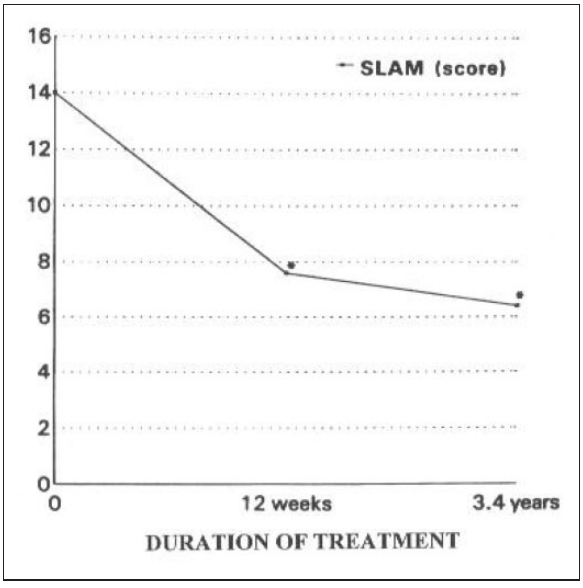

Figure 2 Changes in the systemic lupus activity measure (SLAM) scores from the baseline in patients subjected to long-term treatment with low-dose ultraviolet (UV)-A1 therapy. Six patients from the original group were followed for an average of 3.4 years and received one to two exposures per week, amounting to a total of 6–15 J/m^2 per week. The graph shows the progression of disease activity during and after the initial 12 weeks and for the full 3.4 years ($*p < 0.05$).

These changes result in a shift toward the default mechanism of necrosis, or to spontaneous apoptosis,[33] the latter possibly an escape from the mitochondrial block.

This failure to complete apoptosis and the lack in sufficient mitochondrial ATP to fuel macrophages both predispose to necrosis.[34,35] Necrosis is a toxic form of cell death caused by the release of autologous cell constituents into the blood and surrounding interstitial tissues. These self-or auto-constituents elicit a dendritic cell-coordinated T and B cell-mediated inflammatory immune response directed at preventing the escape of these auto-constituents into the blood and tissues. This protective inflammatory immune response is an autoimmune response as it is the released auto-constituents that drive it.

In contrast to these actions, UV-A1-generated singlet oxygen elicits a state of intense oxidative stress sufficient to activate the intrinsic apoptotic pathway by opening the mitochondrial megapores in the outer mitochondrial membrane.[37,38] This results in a collapse of the electrochemical gradient across the membrane and the subsequent release of apoptosis-initiating factors and cytochrome C, inducing immediate or pre-programmed apoptosis.[37] This apoptotic mechanism is not ATP dependent, fostering, when added to the singlet oxygen-induced activation of energy-generating autophagy,[39] a restoration of the diminished phagocytic cell ATP reserves required for the macrophage-mediated clearance of apoptotic bodies.

Through the ATP-sparing induction of apoptosis and perhaps its activation of energy-generating autophagy,[36,40] UV-A1 irradiation compensates for a low intracellular ATP/adenosine diphosphate (ADP) ratio.[29] In this manner, UV-A1 photons protect against the decreases in macrophage energy required to clear apoptotic bodies. In addition, these photons reduce the overexpression of BCL-2, an inhibitor of apoptosis.[31,32,41]

The drugs currently used to treat lupus highlight the central role of apoptosis, as virtually all are proapoptotic,[42,43] These include glucocorticoids,[42] cytotoxic agents,[44] hydroxychloroquine,[45] mycophenolic acid,[46] and belimumab.[47] Drugs with the opposite action support this paradigm, estrogens and tumor necrosis factor inhibitors facilitating the development of lupus.[47,48]

B cells

Interferon-gamma (IFN-gamma), which induces the release of soluble B-lymphocyte stimulator (sBLyS) by monocytes/macrophages, is overexpressed in peripheral T cells in patients with lupus.[49,50] sBLyS contributes to the immunopathogenesis of lupus by promoting B cell activation and maturation and by inhibiting B cell apoptosis.[51] Increased expression of the sBLyS mRNA directly correlates with increased disease activity in patients with SLE.[52,53] Low-dose, full-body UV-A1 irradiation-induced singlet oxygen production suppresses the secretion of IFN-gamma secretion and parallels the UV-A1-induced mitigation of clinical disease activity in patients with lupus.[11]

In vitro, in vivo, and ex vivo studies *all* support the UV-A1-induced suppression of B cells and B cell activity. In vitro, UV-A1 causes pronounced non-nuclear damage, including cytoskeletal damage.[54,55] Ex vivo, UV-A1 photons decreases B cell activity; 2 J/cm^2 of UV-A1 irradiation delivered through normal skin obtained from cosmetic breast reduction surgery killing 20% of T and B cells and decreasing immunoglobulin (Ig)G, IgM, IgA, and IgE production.[56] In vivo, as mentioned above, singlet oxygen acts to suppress IFN-gamma secretion.[11]

Urocanic acid (UCA)

Although UV-A1 photons suppress humoral immunity, they have the opposite effect on CMI,[57,58] abnormally suppressed in patients with SLE.[59] Exposure to sunlight, which further suppresses lupus-suppressed CMI, may partially account for the toxicity of sunlight in patients with the disease.[60,61] The short solar wavelengths, UV-B and UV-A2, are responsible for the suppression. UV-A1 wavelengths block this suppression[62,63] and even reverse it.[64] This is reminiscent of the NZB/NZW mouse model, in which UV-A1 wavelengths increased CMI and reduced disease activity.[3,4] The contrasting actions of UV-B and UV-A1 wavelengths on CMI parallel the contrasting toxic and remedial actions of UV-B and UV-A1 wavelengths on humans and animals with lupus, suggesting that UCA plays a role in the disease.

UCA is a natural sunscreen that protects against DNA damage. It constitutes approximately 0.05% of the dry weight of the epidermis in humans,[65] reflecting its vital biological role. Solar UV-B photons isomerize UCA from its resting *trans*- form to the active *cis*- isomer, which suppresses CMI. Even the UV-B photons emitted from uncovered fluorescent lamps isomerize UCA to its active *cis* isomer[13] in vitro and increase disease activity in vivo.[66] Teleologically, the suppression of CMI may serve to protect against solar-mediated actinic changes that would predispose patients to immune-mediated rashes and pruritus with every sun exposure. In patients with lupus, who are already CMI suppressed, this added suppression appears to be counter-productive, exacerbating disease activity.

UV-A1 photons first reverse the UV-B (i.e. *cis*-UCA)-induced suppression of CMI through oxidative destruction of *cis*-UCA by singlet oxygen[67] and then through the singlet oxygen-induced expression of the gene encoding heme oxygenase-1 (HO-1), an enzyme that releases CO, a mediator capable of abrogating the suppression of CMI. CO does this by binding and stimulating soluble guanylyl cyclase, a catalyst for the synthesis of cyclic guanosine monophosphate (cGMP).[68,69] Increased cGMP levels parallel the decreases in *cis*-UCA-induced suppression of CMI.[70]

The reason for the innate suppression of CMI in patients with lupus remains unknown. However, because UV-A1 photons, which reverse the suppression, mitigate disease, CMI seems key in disease pathogenesis.

Epigenetics

Epigenetics pertains to environmental influences that modify gene expression without changing the genomic DNA. UV-A1 and UV-B photons have opposing epigenetic effects on patients with SLE. Only 25%–45% of monozygotic twins of a patient with lupus develop the disease, suggesting that the environment regulates changes in the DNA. This has resulted in what is designated twin discordance.[71] The reasons for this discordance are attributed to a number of factors; the principal factor is a deficit in DNA methylation, a reaction that suppresses unwarranted gene expression.[72] Global deficits in DNA methylation are observed in T and B cells from patients with lupus.[73–75] CD4+, but not CD8+, T lymphocytes display this hypomethylation,[75,76] the degree of which correlates with disease activity and anti-dsDNA antibody levels.[77,78] Mice injected with CD4+ cells that have been chemically demethylated exhibit a lupus-like syndrome.[79,80] Even individuals with drug-induced lupus exhibit hypomethylation.[81] The reduced gene methylation in T cells, B cells, and mononuclear cells from patients with lupus renders the patients hypersensitive to IFN-induced inflammation,[82] a hypersensitivity that is preserved through the active stages of the disease and is consistent with the chronic, recurrent nature of SLE.[82]

UV-A1 irradiation counteracts this demethylation of genes in patients with lupus;[78] UV-A1 photons remethylate genes and have even been implicated in global DNA hypermethylation.[83] Accordingly, full-body UV-A1 irradiation has the potential for reversing what may be a major disease mechanism in lupus, i.e. gene demethylation. Not surprisingly, UV-B irradiation, well known to enhance disease activity in lupus, promotes hypomethylation of CD4+ T cell genes in patients with lupus.[84]

HO-1

HO-1 is a powerful homeostatic enzyme that releases products with antioxidant, immunosuppressive, anti-inflammatory, antithrombotic,[85] cytoprotective, and pro-survival actions.[85–87] Its deficiency exacerbates disease states. It is expressed at low levels in patients with lupus,[88] but its levels are increased by UV-A1 photons through the singlet oxygen activation of the encoded HO-1 gene[89–91] and through singlet oxygen-induced reductions in the levels of IFN-gamma, a suppressor of HO-1.[11]

HO-1 is the 32-kDa rate-limiting enzyme in heme catabolism[92] that degrades the highly oxidizing heme moiety into equimolar amounts of biliverdin, iron, and carbon monoxide (CO). These downstream products of heme catabolism mediate the antioxidant, antiapoptotic, antiproliferative, vasodilatory, and anti-inflammatory effect of HO-1[93] that gives it restorative potential in patients with lupus.[86,87,93] Biliverdin reductase converts biliverdin into bilirubin, and both have potent antioxidant and anti-inflammatory activities as reactive oxygen species scavengers. The oxidant Fe elicits the production of ferritin, which can sequester Fe, making ferritin too, a virtual anti-oxidant. CO, a gas with unique anti-inflammatory, neuroprotective, and mitochondrial actions,[94] has the widest therapeutic potential of all the heme degradation products.

HO-1 is expressed in virtually every cell in the body[95] and is upregulated in mammalian tissues in response to a wide variety of conditions, including vascular and immune injury, ischemia, inflammation, cell cycle dysregulation, and both sublethal and lethal cell damage.[96,97] The UV-A1-mediated induction of HO-1 expression begins in the skin, the largest organ in the body and the major site of UV exposure. Dermal phospholipids contain polyunsaturated fatty acids that are highly prone to singlet oxygen-induced peroxidation, forming oxidized phospholipids[98,99] that induce the expression of the HO-1 gene.[100] Although UV-A1 irradiation activates singlet oxygen for only a few nanoseconds, the resulting increase in the HO-1 levels in epidermal cells and cells infiltrating or circulating through the skin lasts for up to three days,[101] sufficient time for HO-1 to act locally and in distant tissues. The low levels of HO-1 in patients with lupus[88] may contribute to the vulnerability of patients to common stressful stimuli, such as viral infections, toxic substances, and lipopolysaccharides,[102] and to their enhanced susceptibility to endothelial damage, all of which are among the aberrations that stand to be remediated by singlet oxygen-generated HO-1.[102]

HO-1 and coronary artery disease

The peak value of HO-1 in lupus may be its impact on coronary artery disease. Patients with lupus have a markedly increased prevalence of coronary artery atherosclerosis and an early age of onset.[103] The incidence of myocardial infarction is up to 50 times the United States national average.[104] Consistent with a role for HO-1 in this disease, animals with low HO-1 levels develop myocardial infarctions (MIs) more readily in response to ischemia than animals with normal HO-1 levels.[105] In HO-1 transgenic animals, the frequency of MI is inversely proportional to the level of HO-1.[106] In humans, the HO-1-mediated catalysis of heme, a powerful antioxidant, into the antioxidant biliverdin, which converts into another antioxidant, bilirubin, reduces post-ischemic and post-infarction myocardial dysfunction.[107] Additionally, HO-1 and its product CO promote neovascularization after MI by modulating the expression of hypoxia-inducible factor-1 (HIF-1), stromal cell-derived factor-1 alpha (SDF-1 alpha), and vascular endothelial growth factor-B (VEGF-B).[108]

HO-1 also downregulates hypertension, hyperlipidemia, diabetes, obesity, and atherosclerosis,[109–111] i.e. metabolic syndrome, actions that contribute to the potential for HO-1 to decrease coronary artery disease. Bilirubin, which is produced from HO-1-generated biliverdin, is negatively associated with hemoglobin A1C levels, metabolic syndrome, and insulin resistance.[112] The capacity of HO-1 to restore homeostasis is well-suited to reverse the disarray induced by coronary artery disease and the metabolic syndrome in patients with lupus.

HO-1 and the central nervous system (CNS)

The effects of HO-1 and its products in the CNS add further to their therapeutic potential in lupus.[6,8,12] For a start, full-body UV-A1 irradiation mitigates "brain fog," a common and often major complaint in patients with lupus.[6,12] This cognitive dysfunction, which presents as decreased attentiveness, memory deficits, diminished problem-solving capability, and decreases in information organization, is frequently the most immediate and gratifying effect of UV-A1 irradiation therapy.[6,8,12] HO-1 exhibits potential neuroprotective effects through the anti-inflammatory,[94,113,114] anti-apoptotic,[115] and vasodilatory properties of CO. In concert with nitric oxide (NO),[116] CO binds to and activates soluble guanylate cyclase (sGC),[117] a heme-containing protein that mediates smooth muscle relaxation, inhibits inflammation, and abrogates ischemic insult to neuronal cells.[118] Increases in the propensity for thrombosis[85] and in cerebral vasospasm[119] are changes observed in the HO-1-deficient mouse. In addition to modulating cerebral vascular resistance, the combination of sGC and

GMP enhances neurotransmission and improves learning and memory, which are commonly impaired in patients with SLE and improved by UV-A1 irradiation.[3–9]

Packaging CO

The extensive benefits of the homeostatic and cytoprotective actions of CO have prompted an onslaught of research into delivery methods for CO.[120–122] In contrast to the currently recommended invasive methods, full-body UV-A1 irradiation is a simpler, safer, gentler, and more physiological means for inducing systemic HO-1. In addition to its effects on lupus, there is compelling evidence that low-dose CO can be therapeutic in a wide array of conditions,[123] pointing to a wider usefulness for its progenitor, UV-A1 irradiation.[124]

Pulmonary disease in SLE

Currently, the only patient with interstitial lung disease (ILD) and pulmonary hypertension (PH) who was treated with UV-A1 irradiation was a 36-year-old Caucasian woman with antinuclear antibody (ANA)/anti-Sjögren syndrome-related antigen A (SSA)-positive lupus for a duration of five years.[13] She had been taking 400 mg of hydroxychloroquine and 6 mg of methylprednisolone for the previous year, without a significant effect. Within weeks of starting triweekly full-body UV-A1 irradiation at 8 J/cm^2, her symptoms of fatigue, malar rash, polyarthritis, mouth ulcers, and intermittent pleurisy abated. The gains were maintained for months with biweekly irradiation treatments, during which time her ILD and PH also responded. She experienced decreases in dyspnea and an increase in the diffusing capacity of the lung for carbon dioxide (DLCO) from 65% to 105% of the predicted value (Figure 3), and her pulmonary artery pressures decreased from 45 to 25 mm Hg. The improvement in both ILD and PH progressed over the years, despite the continued weaning of her corticosteroid treatments from 6 mg to zero per day and the delivery of a healthy baby.

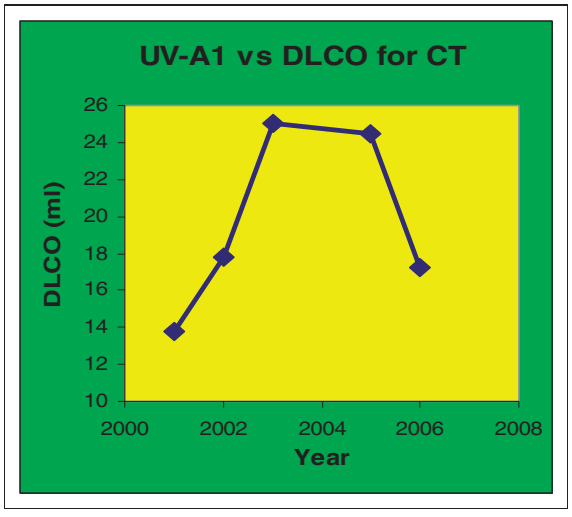

Figure 3 Yearly diffusing capacity of the lung for carbon dioxide (DLCO) measurements from the patient receiving 30-minute biweekly, full-body, low-dose ultraviolet (UV)-A1 irradiation at 8 J/cm^2 for four years at which time the therapy was unavoidably d/c'd, following which the DLCO declined precipitously over the 5th year. CT: computed tomography.

Comment

One team of researchers investigating UV-A1 irradiation reported that four patients with lupus and dyspnea experienced a decrease in their dyspneic symptoms after the UV-A1 irradiation treatment.[9] The present investigator treated the only patient with established ILD and PH[13] and that patient responded with reversal of the ILD and PH therapy.[13] As UV-A1-generated singlet oxygen activates HO-1[125] and HO-1 degrades the powerful oxidant heme, splitting it into products with properties capable of inhibiting interstitial inflammation, endothelial apoptosis, and smooth muscle proliferation,[126–131] three distinguishing characteristics of ILD/PH, it seems reasonable that it was the UV-A1-induced HO-1 underpinning the resolution of disease in this patient.

To explain more fully, HO-1, in degrading the powerful oxidant heme, releases biliverdin, an antioxidant, which is converted to bilirubin, an antioxidant, and Fe, an inducer of ferritin, another antioxidant, the antioxidants having anti-inflammatory activity.[87] CO, through its effects on mitochondrial respiration, downregulates inflammatory processes[94] but perhaps as pertinent, CO reverses established PH in mice[127] by activating p38 mitogen-activated protein kinase (MAPK).[86,128] The activation of p38 MAPK fosters gene-controlled protection of endothelial cells from apoptosis[129] and promotes re-endothelialization,[85] actions that dampen the rheologic disruption that is often central to PH. CO in addition, increases cGMP, which relaxes smooth muscles in the pulmonary arteries[130] and inhibits nuclear factor (NF)-kB-mediated smooth muscle proliferation, both actions running counter to the development of PH.[131]

Less direct, but not to be dismissed as contributing to the mitigation of PH and ILD in lupus, is the role of singlet oxygen in reducing the levels of anticardiolipin (aCL) antibodies,[12] which are linked to thrombosis, sometime contributing to the generation of PH,[132] and the singlet oxygen-related decreases in levels of SSA,[5] elevated in patients with lupus and ILD.[133]

In summary, UV-A1 photons appear to have brought reversal of lupus-related ILD/PH through activation of pathways almost perfectly suited for combatting this disease spectrum.

Subacute cutaneous lupus (SCLE)

Comment

SCLE is a subtype of lupus resulting from apoptosis involving antigen translocation. Normally, following exposure to shorter UV wavelengths, such as UV-B, the extractable nuclear antigens Sjögren syndrome A, Sjögren syndrome B, ribonucleoprotein, and Smith, of human epidermal cells, normally translocate from the nucleus to the cytoplasm and then to the cell membrane during apoptosis.[19,134,135] When these antigens reach developing apoptotic blebs[136] in patients with SLE, they bind to their respective circulating autoantibody on the bleb surface, resulting in either antibody-dependent cytotoxicity and cell lysis[137] or the transport of lupus antigen-antibody complexes into the cell.[133,138] Lysis results in the release of autoantigens, inflammatory mediators, and viruses[136] into circulation, whereas the transport of antigen-antibody complexes into cells promotes cellular dysfunction. In effect, antibodies to Sjögren syndrome A and other nuclear antigens convert translocation, a physiologic process, into a pathologic one in patients with lupus.

Unlike UV-B and the other shorter wavelengths of UV, UV-A1 wavelengths not only fail to activate translocation but counter this action in SCLE[5,139] (Figure 4), primarily by triggering immediate apoptosis,[37,38] which preempts extractable nuclear antigen translocation-induced apoptosis, which is a

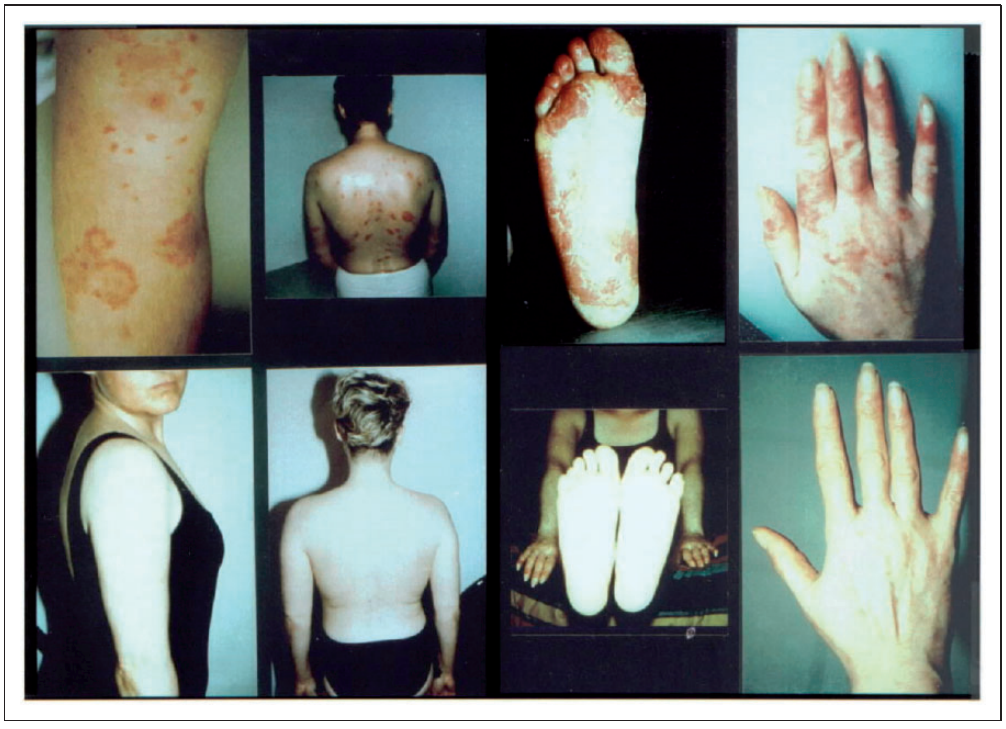

Figure 4 Before and after photos of a 38-year-old woman with subacute cutaneous lupus (SCLE) who was treated with low-dose, full-body ultraviolet (UV)-A1 irradiation. The patient had been disabled and house-bound for four years because of cutaneous eruptions, joint pain, and fatigue that were resistant to three years of prednisone and hydroxychloroquine sulfate treatments. Top left: annular serpiginous cutaneous eruption of SCLE. Top right: palmer erythema and dorsal interphalangeal eruptions on her fingers. Lower panels: the same regions following three weeks of daily low-dose UV-A1 irradiation treatment, showing complete elimination of the SCLE. Her joint pain and fatigue responded concomitantly with the rash. She arose from her sick bed and went back to work for the first time in four years.

delayed apoptosis. The striking response of SCLE to UV-A1 irradiation is another favorable effect of singlet oxygen-induced immediate apoptosis. This rapid apoptosis eliminates the cell before extractable nuclear antigens can migrate to the membrane blebs to effect lysis. UV-A1 wavelengths also reduce the levels of circulating precipitating SSA antibodies that bind to one of the translocating antigens.[5]

Discoid lupus

UV-A1 therapy reversed discoid lesions in a total of three patients.[8,140] However, in the third patient, the discoid lesions were intentionally well-covered during the full-body irradiation.[8] Although the reversal in the first two patients indicated a direct effect of the UV-A1 photons, the remission of the covered rash implicated a systemic UV-A1 effect, making discoid lupus, at least in part, a systemic disease and supporting the systemic action of low-dose full body UV-A1 irradiation therapy.

Antiphospholipid (aPL) antibodies

A 32-year-old woman with lupus and with high levels of aCL antibodies was treated with long-term, low-dose, full-body UV-A1 irradiation.[13] She had a five-year history of progressive memory loss, diminished concentration, and livedo reticularis. Her IgM aCL antibody level was 44 MPL (IgM phospholipid U/ml, normal range: 0–9 MPL/ml), and her IgA and IgG aCL levels were within normal limits. Her score on systemic lupus activity measure–revised (SLAM-R), a validated measure of SLE disease activity, was 14. She was photosensitive, with a malar rash, inflammatory polyarthropathy, chronic cutaneous discoid lupus, and positive for ANA, which comprise the six criteria for the diagnosis of SLE. Her disease began at age 18, with photosensitivity, a malar rash, a biopsy-proven discoid rash and subsequently, severe polyarthritis. Initiation of hydroxychloroquine treatment decreased the joint pain, but not the rash. Intermittent courses of prednisone beginning at age 24 had little effect on her progressive cognitive impairment. At the time of presentation, she was unemployed, having discontinued work because of joint pain, fatigue, memory loss, and other cognitive deficits. She rarely took her hydroxychloroquine, but did use ibuprofen as needed for joint pain. She did not take any other medication. She responded to low-dose, full-body UV-A1 irradiation with a cessation of her progressive dementia, an abatement of the livedo reticularis, a decrease in her aCL levels from 45 to 3 (Figure 5), a reversal of global clinical activity and a cessation of changes in positron-emission tomography during eight months of treatment with biweekly, low-dose (10 J/cm^2) UV-A1 irradiation therapy. The sedimentation rate dropped from 37 to 14 Svedberg units, and the ANA and SSA levels were unchanged at 1:640.

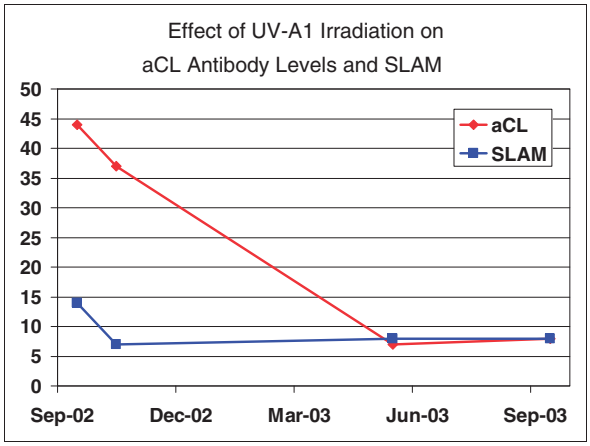

Figure 5 The effects of biweekly, 10 J/cm^2, full-body ultraviolet (UV)-A1 irradiation treatments on the anticardiolipin antibodies (aCL) levels are shown. The aCL levels exhibited a slight decrease during the first month, decreased to normal levels within nine months, and remained at normal levels as the patient continued with weekly irradiation treatments. SLAM: systemic lupus activity measure.

The patient's cognitive function improved as the aCL antibody levels decreased to normal levels and the patient's symptoms and signs of SLE abated during low-dose, full-body UV-A1 irradiation. Livedo reticularis reversed and both clinical and positron-emission tomography scanning revealed a cessation of the patient's progressive cognitive decline. The trio of elevated aCL antibodies, livedo reticularis, and cognitive decline constituted an SLE-related antiphospholipid complex. The virtual elimination of this complex with a parallel improvement in the SLAM-R score in the absence of corticosteroid therapy indicated that the full-body UV-A1 therapy was responsible for the improvements.

In a departure from the accepted paradigm that aCL antibodies induce thrombosis, the results of this study are also consistent with an alternative hypothesis for the pathophysiology, namely, that aCL antibodies protect against thrombosis. Phosphatidylcholine (PS) is a membrane component of apoptotic bodies that is a central mediator

of apoptosis.[141] During apoptosis, PS translocates from the cytosolic side of the membrane to its outer surface in a process catalyzed by the enzyme scramblase.[142] Externalized PS facilitates macrophage engulfment by serving as a bridge that enables macrophages to engulf the apoptotic body.[143,144] However, PS also increases the procoagulant proclivity of apoptotic bodies.[27,145–147] When apoptotic bodies abound, the thrombotic propensity increases.

Beta2 glycoprotein 1 (B2GP1), also known as lipoprotein H, is a positively charged phospholipid-binding serum protein that protects against the prothrombotic apoptotic bodies by binding and thus blocking the negatively charged externalized PS responsible for their prothrombotic proclivity. B2GP1 also acts as an opsonin, enhancing the capacity of macrophages to clear the apoptotic bodies. The binding of B2GP1 induces structural changes in both B2GP1 and membrane-bound cardiolipin, precipitating the generation of antibodies directed against both.[148–151] When bound, these antibodies increase the strength of binding between B2GP1 and the apoptotic bodies 30-fold.[151,152] aCL antibodies, like B2GP1, exhibit opsonic activity;[153,154] the two opsonins facilitate the bridging and subsequent engulfment of apoptotic bodies by macrophages,[149] reducing the procoagulant activity of PS in the membrane. This is consistent with the finding that the injection of apoptotic bodies into mice elicits aCL antibody production.[155] The opsonic activity of aCL antibodies may be more effective than most opsonins because of the direct binding of the antibody to the macrophage Fc receptor.[156]

Consistent with an antithrombotic role for aPL antibodies and B2GP1, aCL antibodies and B2GP1 exhibit anticoagulant activity in vitro and in vivo, respectively.[155,157,158] In summary, although increases in aCL antibody levels have been thought to play a causative role in coagulopathy and thrombosis,[159] they may instead serve as both a sentinel of and a deterrent to thrombosis.

Lupus and pregnancy

The mother and unborn child are protected by the UV-A1-mediated decreases in global systemic disease, as described throughout this manuscript. The removal of apoptotic bodies reduces the thrombotic threat to the placenta. Singlet oxygen-induced activation of HO-1 is of singular value. This enzyme attenuates inflammatory cellular damage in placental villous explants.[160] The induction of HO-1 also compensates for the downregulation of HO-1 in the lupus placenta that predisposes the woman to preeclampsia and recurrent miscarriages.[161] Moreover, the HO-1 products, biliverdin/bilirubin, ferritin, and CO, play augmentative roles in angiogenesis and placental vascular development[162] as well as in the regulation of vascular tone during pregnancy.[160] Elevations of abnormally low HO-1 levels have a telling therapeutic value in pregnant patients with lupus.[161] The UV-A1 irradiation-generated decreases in SSA[5] and aCL[12] antibodies reflect reductions in two major risks in pregnant patients with lupus. Precipitating SSA antibodies are positively associated with neonatal lupus[163] and aCL antibodies are associated with preeclampsia, intrauterine growth retardation, and neonatal antiphospholipid syndrome.[164]

Summary

In the first use of long-wavelength UV irradiation for treatment of a systemic disease, UV-A1 wavelengths had a healing action on SLE, a disease known for its toxic sensitivity to the shorter UV wavelengths. The deeply penetrating UV-A1 photons appear to restore apoptosis and accelerate the removal of apoptotic bodies, both actions acting to prevent necrosis and its sequelae of inflammation and thrombosis. These long wavelengths also suppress B cell activity, enhance CMI, deter an epigenetic march toward SLE, activate the gene for HO-1, ameliorate SCLE and discoid lupus, attenuate PH and ILD, and are associated with decreases in the levels of aCL antibodies. This noninvasive, readily controlled, and relatively innocuous therapy has benefits that justify its continued use and further research into its effectiveness as a treatment for lupus.

Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: HM is working with Christopher Macomber, MD, chief medical officer at UV Therapeutics Inc, to convert the fluorescent lamp-based studies described herein to a light-emitting diode-based model. HM has 50,000 shares of indeterminate stock worth a total of $50.00 in this company's project.

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