

The Effectiveness of UV-A1 Phototherapy in Systemic Lupus Challenges Long-Held Tenets in the Pathophysiology of the Disease

Hugh McGrath Jr*

Veterans Administration, New Orleans, LA, USA

*Corresponding author: Hugh McGrath Jr, Veterans Administration, 1601 Perdido St, New Orleans, LA 70112, USA, E-mail: hmcrath2@charter.net

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Introduction

In this month's Lupus, I reported on the therapeutic effectiveness of full body ultraviolet-A1 (UV-A1; 360-400 nm) irradiation of patients with systemic lupus erythematosus (lupus) [1]. In my hands and then of other investigators [1-4], this comfortable and relatively innocuous therapeutic modality significantly reduced the Systemic Lupus Activity Measures (SLAM) and/or the SLE Disease Activity Index (SLEDAI) scores. These were patients with moderately active disease, not requiring chemotherapy, the SLAM dropping from 8.4 ± 2.9 ($p < 0.05$) to 6.7 ± 1.9 ($p < 0.05$) [1] and the SLEDAI from 7.2 ± 5.6 to 0.9 ± 1.8 ($p < 0.005$) [2].

As noteworthy as the effectiveness of the therapy has been, the insights gained are even more far reaching, appearing to push for a re-evaluation of long-held tenets in the disease. For a start, although long-viewed as an autoimmune disease, the effectiveness of UV-A1 photons in reversing disease activity in lupus supports its being a disease of debris spilled into the blood and tissues, due to failed apoptosis, and requiring clearance. The stepped-up immune response so characteristic of lupus, rather than being the engine of disease activity, appears instead to be an attempt to provide clearance of the debris, preventing its noxious and potentially lethal effects.

It is work by Gergely et al. [5] and Godar [6] that had set the background for an understanding of the action and effectiveness of UV-A1 photon therapy in SLE. Gergely describes hyperpolarized ATP deficient mitochondria in lupus, the hyperpolarization rendering the mitochondria refractory to the depolarization needed for initiating apoptosis and the ATP deficiency weakening the capacity of phagocytic cells (macrophages) to remove apoptotic bodies [7]. The failure in apoptosis brings on necrosis, an alternative form of cell death that leads to the spilling of cellular debris into the blood stream and tissues. The ATP deficiency weakens the ability of macrophages to phagocytose apoptotic bodies, that too leading to necrosis.

These aberrancies are nicely-counteracted by UV-A1 photon-activated singlet oxygen, a powerful reactive oxygen species capable of depolarizing the hyperpolarized mitochondria, and doing so in an ATP-independent fashion [5,6]. The depolarization

triggers "immediate apoptosis", a pre-programmed form of apoptosis that spares the cell from necrosis and also spares it from the ATP loss in standard apoptosis. This latter conserves ATP that is needed to fuel macrophages for the removal of apoptotic bodies, preventing their collapse into necrosis.

UV-A1-generated singlet oxygen does more than activate apoptosis and fuel macrophages. It activates the gene for heme oxygenase-1 (HO-1), a powerful enzyme governing body-wide homeostasis [8]. HO-1 has widespread healing actions [9,10]. Most immediately its ultimate breakdown products, carbon monoxide (CO), bilirubin and ferritin down regulate the metabolic disarray resulting from the damaging circulating debris of failed apoptosis as well as the bystander damage deriving from the highly reactive protective immune response called upon to clear the debris.

More specifically, HO-1 and its products counter pulmonary hypertension and interstitial lung disease [11], increase delayed CNS perfusion [12,13] and protect against the damaging effects of SLE in pregnancy [14,15]. Moreover, they have the potential to slow down a progression toward coronary artery disease and the metabolic syndrome [16,17], disorders promoted by lupus and responsible for much of the late term damage and decreased survival in the disease.

Setting aside singlet oxygen, the UV-A1 photons have direct actions in lupus. They reverse solar UV wavelength-induced cisurocanic acid suppression of cell-mediated immunity (CMI) [18]. This may be of benefit in lupus, a disease in which CMI is intrinsically suppressed and in which patients are solar sensitive. UV-A1 reversal of the solar contribution to CMI suppression may be protective.

UV-A1 photon-induced singlet oxygen, through its activation of immediate apoptosis, preempts solar-induced antigen translocation. Antigen translocation is part of a pathway of apoptosis that follows sun exposure. Unfortunately, in lupus there are antibodies to Sjogren's syndrome antigen, which is one of the translocating antigens and this leads to binding of the antigen at the cell surface and an immune complex-activated cell lysis, resulting in an inflammatory reaction known as sub-acute cutaneous lupus [19]. UV-A1-induced immediate apoptosis preempts the need for translocation, eliminating the

ensuing inflammatory reaction. The striking UV-A1-phototherapy-induced reversal of this dermal disorder is nicely illustrated in the McGrath manuscript [1].

Interestingly, the long wavelength photon therapy also reverses the lesions of discoid lupus [20,12], for reasons unknown and even when the lesions are covered [12]. This latter is telling, revealing a systemic component to the disease not previously appreciated.

Then there is then the capacity of UV-A1 irradiation to restore DNA methylation in undermethylated T and B cells [21]. This offers a mechanism by which UV-A1 photons can reverse an epigenetic drift toward lupus, one more mechanism by which the phototherapy works toward a beneficial milieu in lupus.

To be included in UV-A1 irradiation benefits is its alleviation of the noxious effects of lupus in pregnancy. Aside from the benefits accrued from the reduction of overall lupus disease activity, the pregnant lupus patient stands to gain from the UV-A1 activation of HO-1 and its products. Restoration of abnormally low levels of HO-1 toward normal attenuates inflammatory damage in the placenta and reduces the predisposition to preeclampsia [14,15]. UV-A1 photons also to reduce the proclivity to thrombosis in lupus pregnancy.

This latter statement, implicating an effect on antiphospholipid antibody activity, needs further explanation: It seems that phosphatidylserine (PS) on the apoptotic body is "sticky", i.e., prothrombotic [22,23], so that increases in apoptotic bodies in lupus increase coagulability. This increase in apoptotic bodies come about in great part because the energy deficits in lupus diminish macrophages clearance of apoptotic bodies. Corrective of this, singlet oxygen increases macrophage energy stores by eliciting immediate apoptosis, sparing the drain of standard apoptosis on ATP stores and also by supplementing energy stores through singlet oxygen-activation of energy-producing autophagy [24]. There is a third means of energy saving for the macrophage, often available in lupus and that is the presence of anticardiolipin antibody, (aCL), which can act as an opsonin.

Opsonins act as bridges from the macrophage to the body undergoing phagocytosis, reducing the work of phagocytosis, which can be helpful in the low-energy macrophages milieu in lupus. The first of these opsonins is beta 2 glycoprotein 1 (B2GP1), a circulating protein that binds to cardiolipin [25] on apoptotic bodies, altering the structure of this cardiolipin. This alteration generates aCL antibodies. [26], which increase the binding of B2GP1 to cardiolipin thirty-fold and but also act as a powerful opsonins themselves, binding as they do directly to the macrophage Fc receptor. What arises from this is a reasonable supposition that aCL antibodies, rather than facilitating thromboses, as has been long accepted, may to the contrary, act as a deterrent to thrombosis and act even as a sentinel of impending thromboses.

In summary, in what is the first use of UV-A1 photons for a systemic disease, full body UV-A1 radiation had multiple immediate and potential long-term benefits in lupus. As important as its healing action, the effectiveness of the therapy has brought into question the long-held tenet that lupus is an

autoimmune disease with damage being due primarily to immune attack against self. Instead it seems it may be a disease of debris in which the increase in immunity is protective rather than causal. Similarly, the oft present anticardiolipin antibodies, thought to underlie thrombotic proclivities, may protect against, rather than promote thromboses. Finally, and brought forth peripherally, is the unique capacity of UV-A1 photons to activate the gene for HO-1, an enzyme having broad remedial actions not only in lupus but perhaps in other diseases as well.

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