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Interstitial Lung Disease and Pulmonary Hypertension Responsive to Low-Dose UVA1 Irradiation in Lupus

Benjamin Jabara, MD^{*}, Mollie Dahlgren, MD^{*}, and Hugh McGrath Jr., MD^{*}

^{*}Department of Medicine, Tulane University Health Sciences Center, New Orleans, LA 70112, U.S.A.

Index terms

lupus erythematosus-systemic; ultraviolet A1; lung disease-interstitial; hypertension- pulmonary; heme oxygenase-1

Concise Report

In three placebo-controlled, double-blind studies, low-dose, full body UVA1 irradiation administered 2-3 times a week had a remedial action in patients with systemic lupus erythematosus (SLE) ¹⁻³. SLE Activity Measure (SLAM) and SLE Disease Activity Index (SLEDAI) scores decreased significantly. The therapy mitigated fatigue, joint pain, rashes, cognitive dysfunction, and photosensitivity within days to weeks, and over the years appeared to maintain these gains ⁴. In only one of these studies was an effect on dyspnea recorded, 4/4 patients experiencing decreases ³. Although the lungs are clearly a target in SLE, there has been no patient with pulmonary disease, prior to this report, monitored for changes in pulmonary measures during prolonged UVA1 irradiation therapy.

Case Report

A 39-year-old woman with SLE of five years duration presented with fatigue, a malar rash, polyarthritis, photosensitivity, dyspnea, interstitial lung disease (ILD) and pulmonary hypertension (PH). She had a history also of mouth ulcers, intermittent leukopenia, pericarditis, and recurrent pleurisy. She had an ANA of 1: 640, an IgM anticardiolipin antibody of 21 MPL U/mL (normal: 0-9), an increased anti-RNP, and prior to entering the study, elevated anti-SSA antibodies. Anti-dsDNA antibodies were absent and the sedimentation rate, CRP, and C3 were normal throughout the study. At the outset of the treatment, the C4 was low at 16 mg/dl (normals 18-45) and the WBC $2.7 (\times 10^3)$, but the C4 became normal and the WBC, ranged from 4-6 ($\times 10^3$) after the start of therapy. She had been taking 8 mg of methylprednisolone a day and 200 mg of hydroxychloroquine twice daily for over a year. The initiation of low-dose (8J/cm²) full body, twice weekly exposures to UVA1 irradiation, as previously described ¹, led to resolution of her fatigue and malar rash within days, polyarthritis and cognitive deficits within weeks, and photosensitivity within months, during which she discontinued her prednisone but continued the hydroxychloroquine. Although the study was not directed at interstitial lung disease (ILD) or pulmonary hypertension (PH), over the long term her pleurisy subsided, dyspnea diminished, restricted pulmonary volume increased, and the DLCO as measured by

Correspondence: Hugh McGrath Jr., Department of Medicine, Tulane University Health Sciences Center, 1430 Tulane Avenue SL-57, New Orleans LA 70112, U.S.A. hmcgrath@tulane.edu.

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single-breath standard technique increased from 14 to 24 ml/min/mmHg (Figure), representing a 65% to 105% increase of predicted. Pulmonary pressures, measured by trans-thoracic ultrasound, decreased from 45 to 25 mmHg. Her ANA remained at 1: 640, ENA and anti-cardiolipin antibodies became negative, and the anti dsDNA, sedimentation rate and CRP remained normal. She gradually discontinued her prednisone and progressed through a successful pregnancy while continuing the UVA1 therapy. Unfortunately, due to an unforeseen and permanent interruption of therapy, her condition deteriorated, the DLCO decreased to 17 mm/min/mmHg (Figure) and the patient required resumption of corticosteroid therapy. Her lung volumes worsened with pulmonary function studies revealing a mild restrictive defect. However, her pulmonary pressures did not deteriorate, the transthoracic ultrasound indicating a pulmonary artery pressure of 28 mm Hg.

Discussion

Decreases in the patient's dyspnea were accompanied by improved measures of underlying ILD and PH, disorders not within the original purview of the study. In addition to bringing about improvement in the non pulmonary disease manifestations, the UVA1 irradiation effected reversal of ILD and PH in this, the only patient with either of these disease manifestations ever treated in this institution with the UVA1 light therapy.

As to mechanisms, the therapy reportedly lowers levels of anticardiolipin antibodies ⁵, as in this patient, these having being cited as contributory to pulmonary hypertension ⁶; it lowers SSA antibodies ⁷, characteristically elevated in the ILD of SLE ⁸; it decreases proportions of cells producing interferon-gamma ⁹, a major effector molecule in SLE ¹⁰; and it promotes macrophage function, impaired in SLE and needed to remove apoptotic bodies, the diminished clearance of which is thought to be central in SLE ^{5, 11}. However, what seems most germane in the specific action of UV-A1 photons on ILD and PH is its unique capacity to generate singlet oxygen, a reactive oxygen species that activates the production of heme oxygenase-1 (HO-1) ¹².

Because wavelengths in the UVA1 range are the longest and most deeply penetrating in the ultraviolet spectrum, they easily reach dermal infiltrating macrophages and cells circulating in the dermis ¹³. Their photon energy is readily absorbed by photosensitizers within cells and transferred to oxygen, raising oxygen to its high energy state, singlet oxygen ¹⁴. Singlet oxygen is highly effective in activating the generation of heme oxygenase-1 (HO-) ¹⁵, a powerful systemic stress enzyme. In fact, the gene whose expression is most enhanced by wavelengths in the UVA (320-400 nm) range is that which encodes this mammalian stress protein/heme-degrading enzyme, HO-1 ¹².

HO-1 breaks down heme into equimolar amounts of carbon monoxide (CO), biliverdin, and iron (Fe) ¹⁵, all having powerful antioxidant and anti-inflammatory actions, seemingly well poised to counter ILD ^{15, 16, 17}. As to PH, these HO-1 products, primarily CO, elicit in the endothelium, anti-apoptotic, vasodilatory, anti-thrombotic, anti-adhesive, and anti-proliferative actions ^{15,16, 17}, all contrasting markedly with the apoptotic, vasoconstrictive, thrombotic, pro-adhesive, and pro-proliferative actions that characterize the endothelium in pulmonary hypertension ¹⁸. Paradoxically, and of further benefit is that CO elicits pro-apoptotic and antiproliferative ^{19, 20} actions in the medial and adventitial cells, actions directly counter to the medial hypertrophy and adventitial thickening that characterizes the walls of hypertensive pulmonary arteries ¹⁸.

Although UVA1 irradiation is dermal, its photons increase HO-1 expression in dermal infiltrating macrophages for as long as three days ²¹, ample time for the HO-1 to act not only locally but in distant tissues ²². Moreover, HO-1-induced CO acts in areas other than close to

where it is generated, this being the basis for using CO releasing molecules (CO-RM) or inhaled CO to bring about CO-induced therapeutic actions in lung, heart, and vasculature¹⁹. This dissemination of singlet oxygen-generated HO-1-induced products offers a means by which UV-A1 dermal irradiation may reach distant sites necessary for actions on PH and ILD.

UV-A1 irradiation remains an unproven but promising inexpensive and readily available therapy in SLE. Other factors, such as the use of hydroxychloroquine and, early on, corticosteroids, may have contributed to this patient's improvement. Nevertheless, the observations appear to extend the potential of full body low-dose UVA1 irradiation to the mitigation of SLE-associated ILD and PH. Although decreases in antibodies to SSA, cardiolipin, and interferon-gamma-secreting cells along with the singlet oxygen-induced promotion of apoptosis may all play a role, UV-A1 radiation's capacity to generate HO-1, a powerful restorer of systemic homeostasis¹⁵ is proposed as uniquely tailored as a pathway along which this modality works in ILD and PH. Further studies are needed to confirm the effectiveness of, and the mechanisms responsible for this potentially promising and gently acting intervention in SLE-based ILD and PH.

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References

1. McGrath H Jr, Martinez-Osuna P, Lee FA. Ultraviolet-A (340-400nm) irradiation therapy in systemic lupus erythematosus. *Lupus* 1996;5:269–274. [PubMed: 8869897]
2. Polderman MCA, Huizinga TWJ, Le Cessie S, Pavel S. UVA-1 cold light treatment of SLE: a double blind, placebo controlled crossover trial. *Ann Rheuma Dis* 2001;60:112–115.
3. Polderman MC, le Cessie S, Huizinga TW, et al. Efficacy of UVA-1 cold light as an adjuvant therapy for systemic lupus erythematosus. *Rheumatology (Oxford)* 2004;43:1402–1404. [PubMed: 15304672]
4. Molina JF, McGrath H Jr. Longterm ultraviolet-A1 irradiation therapy in systemic lupus erythematosus. *J Rheumatol* 1997;24:1072–1074. [PubMed: 9195511]
5. McGrath H Jr. Elimination of anticardiolipin antibodies and cessation of cognitive decline in a UV-A1-irradiated systemic lupus erythematosus patient. *Lupus* 2005;14(10):859–861. [PubMed: 16304728]
6. Nishimaki T, Aotsuka S, Kondo H, et al. Immunological analysis of pulmonary hypertension in connective tissue diseases. *J Rheumatol* 1999;26(11):2357–2362. [PubMed: 10555891]
7. McGrath H Jr. Ultraviolet-A1 irradiation decreases clinical diseases activity and autoantibodies in patients with systemic lupus erythematosus. *Clin Exp Rheum* 1994;12:129–135.
8. Boulware DW, Hedgpeth MT. Lupus pneumonitis and anti-SSA (Ro) antibodies. *J Rheum* 1989;16:479–481. [PubMed: 2664170]
9. Szegedi A, Simics E, Aleksza M, et al. Ultraviolet-A1 phototherapy modulates Th1/Th2 and Tc1/Tc2 balance in patients with systemic lupus erythematosus. *Rheumatology* 2005;44:925–931. [PubMed: 15827034]
10. Theophilopoulos AN, Koundouris S, Kono DV, Lawson BR. The role of IFN-gamma in s systemic lupus erythematosus: a challenge in the Th1/Th2 paradigm in autoimmunity. *Arthritis Res* 2001;3:136–141. [PubMed: 11299053]
11. Nagata S. Autoimmune diseases caused by defects in clearing dead cells and nuclei expelled from erythroid precursors. *Immunol Rev* 2007;220:237–250. [PubMed: 17979851]
12. Pourzand C, Tyrrell RM. Apoptosis, the role of oxidative stress and the example of solar UV radiation. *Photochem Photobiol* 1999;70:380–390. [PubMed: 10546543]

13. Bruls WA, Slaper H, van der Leun JC, et al. Transmission of human epidermis and stratum corneum as a function of thickness in the ultraviolet and visible wavelengths. *Photochem Photobiol* 1984;40:485–494. [PubMed: 6505037]
14. Kochevar, IE. Primary processes in photobiology and photosensitization. In: Krutmann, J.; Elmetts, CA., editors. *Photoimmunology*. Cambridge: Blackwell Science Ltd; 1995. p. 19-41.
15. Soares MP, Bach FH. Hemeoxygenase-1. from biology to therapeutic potential. *Trends Mol Med* 2009;15:50–58. [PubMed: 19162549]
16. Fredenburgh LE, Perrella MA, Mitsialis SA. The role of heme oxygenase-1 in pulmonary disease. *Am J Respir Cell Mol Biol* 2007;36:158–165. [PubMed: 16980551]
17. Freitas A, Alves-Filho JC, Secco DD, et al. Heme oxygenase/carbon monoxide-biliverdin pathway down regulates neutrophil rolling, adhesion and migration in acute inflammation. *Br J Pharmacol* 2006;149:345–354. [PubMed: 16953189]
18. Runo JR, Loyd JE. Primary pulmonary hypertension. *Lancet* 2003;361:1533–1544. [PubMed: 12737878]
19. Peyton KJ, Reyna SV, Chapman GB, et al. Heme oxygenase-1-derived carbon monoxide is an autocrine inhibitor of vascular smooth muscle cell growth. *Blood* 2002;9:4443–4448. [PubMed: 12036874]
20. Xiao-ming, Liu; Chapman, GB.; Wang, H.; Durante, W. Adenovirus-mediated heme oxygenase-1 gene expression stimulates apoptosis in vascular smooth muscle cells. *Circulation* 2002;105:79–84. [PubMed: 11772880]
21. Reeve VE, Tyrrell RM. Heme oxygenase induction mediates the photoimmunoprotective activity of UVA radiation in the mouse. *Proc Natl Acad Sci USA* 1999;96:9317–9321. [PubMed: 10430940]
22. Reeve VE, Domanski D. Immunoprotective haem oxygenase induction by ultraviolet A (320-400 nm) radiation in the mouse is inhibited in interferon-gamma null mice. *Br J Dermatol* 2003;148:1189–1193. [PubMed: 12828748]

ILD Response to UVA1

Figure.

Yearly DLCO measurements were taken while the patient received biweekly, full-body, low-dose UVA1 irradiation at 8 joules/cm² over 30 minutes twice weekly for 5 years. The normal range for DLCO is 20-30 ml/min/mm Hg. (*) indicates cessation of treatment.