A recent correspondence posed a call to arms in the battle to increase survival in COVID-19 patients. The request is for existing effective treatments to calm the hyper-inflammatory response known as the cytokine storm.[1] Calming the cytokine storm may be key to turning COVID-19 into a non-lethal infection.

We propose an immediate randomized trial for a safe, non-invasive, low-cost treatment with existing global regulatory clearances which may mitigate the development of a cytokine storm from COVID-19: ultraviolet B-band (UVB) (290-320nm) light therapy. UVB has been safely calming the cytokine storm in patients with numerous auto-immune diseases and improving survival in critically ill allogeneic hematopoietic stem cell transplantation (HSCT) patients for 20 years. [2]

The HSCT patient is at risk to develop Graft versus Host Disease (GvHD) and its associated deadly cytokine storm. HSCT patients acquiring acute GvHD have a 16.2% in-hospital mortality rate. [2] Post-transplant, the immune system is not strong; rather, it is considered to be dysregulated, leading to an aberrant pro-inflammatory response. In a meta-analysis of UVB and GvHD, a response rate was found in excess of 70% and side effects isolated to minor cutaneous burns. [3] Prophylactic arrowband-UVB (NB-UVB) (311-313nm) exposure (6 sessions prior to transplant) for HSCT patients results in significantly higher 25-hydroxyvitamin D3 serum levels and higher numbers of circulating CD4+ FoxP3+ regulatory T cells. [4] The first randomized control Phase II trial is underway in Japan to further validate the clinical benefit of UVB-NB in acute GvHD. [5]

The predominant mechanisms of UVB-induced immunosuppression include decreased number and function of antigen-presenting cells (APCs) in the skin, induction and activation of immunosuppressive Tregs, and increased release of systemic inhibitory cytokines, such as tumor necrosis factor (TNF-a) and IL-10.[6] Therapeutic UVB has been documented in the autoimmune setting of psoriasis to suppress the type 1 (proinflammatory) axis of IL-12, IFN-gamma, and IL-8 and selectively reduce proinflammatory cytokine production by individual T cells. [7] The overall impact is positive immune modulation and improved Th1/Th2 balance in the immune system. Figure 1 compares the levels of five cytokines from two studies. The top chart illustrates the cytokine data from patients from Wuhan, China. These include a control group and 522 COVID 19 patients split between those who went to the ICU and those who remained able to breathe on their own (No ICU). The bottom chart illustrates the cytokine data from a murine model investigation of the use of UVB to treat GvHD. [10] These data are split into three groups: controls, those with GvHD, and those with GvHD treated with UVB. The murine model is chosen over patient data in the following figures as the visual comparison is direct and appropriate.

For example, the objective is to calm cytokine IL-2 in the COVID-19 ICU patients from ~9pg/ml to ~6pg/ml (a ~33% reduction). In the matching GvHD data, UVB treatment reduced elevated IL-2 from ~50pg/ml to ~25pg/ml (a ~50% reduction). UVB’s proven ability to reduce inflammatory cytokines and increase anti-inflammatory cytokines like IL-10 may provide sufficient treatment benefit to keep patients out of the ICU and increase survival.
COVID-19’s age discrimination is also consistent with research on the development of chronic inflammation evident in the aging process. Epigenomic changes that impact immune dysregulation occur in men at ~63-years of age and women at ~68-years of age and affect health and lifespan disparities between the sexes. [12] This age-dependent baseline inflammation may contribute to elevating the COVID-19 cytokine storm to the critical tipping point of Acute Respiratory Distress Syndrome (ARDS). Aging, vitamin D deficiency, and immune functioning levels of vitamin D, 1,25-(OH)2D3 are closely correlated, yet presently unreported in the COVID-19 risk profile.

In short, given that UVB has a known safety profile and the ability to improve survival by heading off the cytokine storm in disorders like GvHD -- and given the marked similarity between COVID-19’s cytokine storm and that of GvHD -- we hypothesize that UVB should be effective in heading off the cytokine storm from COVID-19.

Our response to the Lancet’s call is to perform two randomized trials, devices and training at centers willing to test this hypothesis and offer this therapy to their high-risk, >60-year-old patients with comorbidities or an elevated ferritin level. One trial will investigate whether a NB-UVB treatment will result in high-risk ambulatory patients (n=300) avoiding intubation and ICU level care. The second trial is for patients (n=50) already intubated and design of a phase II study of narrow-band ultraviolet B phototherapy for cutaneous steroid-refractory acute graft-vs-host disease following allogeneic stem-cell transplantation. Medicine: 98: e16372.

Figure 2: COVID-19 patients show a decrease in T cell numbers based on disease severity.[10]

In GvHD patients refractory to corticosteroids, NB-UVB treatment creates a fivefold expansion in the absolute numbers of regulatory T cells (Tregs) at 2 weeks. [11]

This means the NB-UVB treatment response time may fit within the 3-5 day window between when COVID-19 patients present at a hospital and when they escalate to needing respiratory support. Once patients need respiratory support, survival is 50:50.

The COVID-19 pandemic has transcended affecting the global health of our communities to impacting our social interactions, our economies, and even our political systems. We all agree that health of our communities to impacting our social interactions, even our political systems. We all agree that we should act now and evaluate viable present therapeutics like our proposed trials while others proceed on future solutions like vaccines and antivirals.

References
1. https://doi.org/10.1016/S0140-6736(20)30628-0

Copyright: ©2020 Joxel Garcia. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.