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A clinical trial of IL-15 and IL-21 combination therapy for COVID-19 is warranted

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ABSTRACT

Previous studies of SARS-CoV-2 viral infection suggest that both the humoral and cytotoxic arms of the immune system are weak in patients with severe COVID-19 disease when compared to mild disease. A cytokine storm is also induced in severe disease. IL-15 has been shown to support the cytotoxic arm of the immune response. IL-21 has been shown to support both the cytotoxic and humoral arms of the immune response. In addition, in some settings, Il-21 has been shown to actually decrease IL-6 and TNF-alpha production, reducing the inflammatory proteins involved in the cytokine storm. Furthermore, in other settings, the combination of IL-15 and IL-21 has been shown to be more effective than either interleukin alone in promoting an effective immune response. Therefore, a clinical trial that examines the use of the combination of IL-15 and IL-21 for COVID-19 patients is warranted.

In "*IL-15 immunotherapy is a viable strategy for COVID*-19", Kandikattu *et al.* urged initiation of a clinical trial that examines the use of IL-15 for SARS-CoV-2 patients that present with diminished NK cell or CD8 + T cell counts [1]. While this is certainly a worthwhile endeavor, the combination of IL-15 and IL-21 should be given in one arm of the study. There have been published reports that examined the differences between the immune response that occurred in patients with severe symptoms versus mild symptoms of the viral infection. The research has shown that hallmarks of severe SARS-CoV-2 disease include a cytokine storm, involving elevation of IL-6 and TNF-alpha, elevation of IL-10, a decreased absolute B cell count, and decreased NK cell and/or CD8 + T cell counts [2]. In addition to the decreased B cell count, there is evidence that patients with severe SARS-CoV-2 disease are unable to mount a strong IgG response against the spike proteins on the virus [3]. These findings suggest that both the cytotoxic (NK-cell and CD8 + T cell) and humoral (B cell) arms of the immune system are weak in patients with severe disease. IL-15 has been shown to stimulate the cytotoxic CD8 + T–cell response and the NK cell response, as well as promote memory-phenotype CD8 + T cells [4–7]. Also, in contrast to IL-2, which is already in clinical trials, IL-15 does not cause capillary leak syndrome [7]. IL-21 supports both the cytotoxic and humoral arms of the immune response. It has been shown that IL-21 promotes B cell and plasma cell development, upregulating IgG1 antibody formation. Il-21 also promotes CD8 effector cell proliferation and costimulation of T and NK cell proliferation and function [9–11]. In addition, IL-21 has been shown to actually decrease IL-6 and TNF-alpha production [12]. Furthermore, in other settings, the combination of IL-15 and IL-21 has been shown to be more effective than IL-15 alone in promoting an effective immune response [13,14]. Also, while concerning side effects have been identified in some of the studies of these interleukins [8], they occurred in the relatively long course of treatment required for chronic conditions. These side effects may not be as much of a concern in the short time frame required to treat an acute viral infection.

So, given all of these findings, I urge the combination of IL-21 and IL-15 be given to SARS-CoV-2 patients, particularly to patients that present with diminished B cell and/or CD8 + T cell counts. I would also urge that the trial be conducted on patients early in the course of the disease. If severe disease can be avoided by directing the immune response to arms of the immune system that are known to be most effective in treating the disease, the devastating effects of the infection may be avoided.

Declaration of Competing Interest

The authors report no declarations of interest.

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