April 25, 2020

Re: The Immunopathogenesis and Treatment of COVID19

Dear Dr. Fauci and Dr. Lane,

I am a pediatric rheumatologist who also specializes in the study and treatment of Susac syndrome (SuS). The latter is an immune-mediated, hypoxia-producing, occlusive microvascular endotheliopathy/basement membranopathy that causes ischemic injury to the brain, retina, and inner ear. My experience with "cytokine storm" in systemic juvenile idiopathic arthritis and my experience with SuS have informed my thoughts about COVID.

I am concerned that two immune-mediated complications of COVID19 may not be receiving adequate attention.

The first is the possibility that in many cases of COVID the hypoxia may be primarily due to a Susac-like immune-mediated, hypoxia-producing, occlusive microvascular endotheliopathy/basement membranopathy within the pulmonary microvasculature. This is only a hypothesis, but one for which there is some evidence and precedence.[1-3]

The second immune-mediated complication of COVID is the proven "cytokine storm" that develops in severe cases.[4-9] **My concern is that cytokine storm in COVID is often not being treated as promptly, aggressively, and imaginatively as needed.**

<u>Immune-mediated microvascular endotheliopathy/basement membranopathy in the pulmonary microvasculature of patients with COVID---An Hypothesis</u>:

An appropriate hypothesis is that the dyspnea and hypoxia in COVID, especially when out of proportion to radiographic abnormalities and/or out of proportion to the extent of decreased lung compliance, could be due, primarily, to diffuse, Susac-like immune-mediated microvascular endotheliopathy/basement membranopathy within the pulmonary microvasculature. If this is true, lung biopsy or autopsy (with Electron Microscopy) would reveal the same occlusive microvascular endothelial disease and potential gross basement membrane thickening that we have documented in our EM study of Susac syndrome (SuS).[1] And, this pathology, if present, could, of course, cause hypoxia, even before radiographic abnormalities appear.

If this hypothesis is correct, a possibly effective treatment for hypoxic COVID patients would be immunosuppression designed to shut down this immune-mediated pulmonary microvascular endotheliopathy as early in its course as possible, before it causes regrettable ischemic damage to the lungs and pulmonary microvasculature---using pulses of IV methylprednisolone and/or IVIG as first line therapy. Such treatment might prevent need for mechanical ventilation.

I have attached an article on pulmonary microvascular endothelial cell involvement in H5N1-associated ARDS; a rare article on the lung pathology in COVID; our published article on EM findings in SuS; and my unpublished hypothesis about possible harmful up-regulation of the immune system within the microvascular endothelial cells in SuS.

The concept is that the virus enters the pulmonary microvascular endothelial cells; the immune system within those cells (starting with excessive upregulation of type 1 interferon) grossly over-reacts to the viral threat; a cascade of ever-amplifying multi-dimensional immune activation follows; immune-mediated damage to the pulmonary microvasculature results---e.g. endothelial cell injury (including occlusive endothelial cell swelling) and potential basement membrane thickening (with defective diffusion); and the end-result is hypoxic and inflammatory damage to the alveoli and bronchioles (as well as potential permanent damage to the pulmonary microvasculature).

Cytokine storm in COVID:

There is growing evidence that "cytokine storm" often plays a major role in the deaths of patients with COVID19.[4-9] In particular, it is possible that many of the deaths that have occurred in relatively young and previously healthy adults (e.g. physicians, nurses, and other health care workers) have been due to inadequately treated cytokine storm, rather than simply to the virus itself.

As a pediatric rheumatologist who has had considerable experience with successful treatment of cytokine storms, I want to strongly support and encourage hospitalists and physicians in Emergency Departments and ICUs to promptly think of cytokine storm when they encounter patients (particularly younger patients) who are seriously ill with COVID19. For such patients it is essential to promptly test for cytokine storm and promptly consider aggressive treatment, if evidence of cytokine storm is found.

Life-threatening cytokine storm is relatively easy to diagnose and can be successfully treated, particularly if it is promptly recognized and aggressively treated before it becomes advanced and causes irreversible multi-organ injury (including lung injury).

As you know, early (and easily obtained) laboratory indicators of cytokine storm include: elevated serum ferritin; elevated D-dimers; a falling platelet count and falling ESR, despite high CRP; low WBC; low Hgb; AST and ALT elevation; triglyceride elevation; low fibrinogen; INR >1.5, and low serum albumin.

More sophisticated confirmatory tests (if needed), but less readily available, are tests for: elevated IL-1, IL-6, IL-18, and interferon gamma levels; elevated soluble IL-2 receptor; elevated soluble TNF receptor I and II; soluble CD163; decreased IL-10/TNF alpha ratio; elevated High Mobility Group Box 1 (HMGB1).

Currently available treatment options for cytokine storm include: initial pulses of IV methylprednisolone (IVMP); either IV anakinra (anti-IL-1) or IV tocilizumab (anti-IL-6); and cyclosporine (CSA). Of these, CSA is probably the least important.

Understandably, there is a natural reluctance to treat patients who are suffering from a primary viral infection with aggressive immunosuppression. The concern, of course, is that the immunosuppression might interfere with the immune system's ability to fight off the viral infection. However, if the patient's life is threatened primarily by an excessive immune reaction to the virus, the patient's survival will depend on suppression of that reaction.

A conceivable approach to treatment of COVID19 that has been complicated by cytokine storm---an approach that may be worthy of consideration, but has not been tested---would be a combination of treatments:

- An anti-viral drug, such as remdesivir, or a better alternative---to help subdue the virus.
- IVMP (x 3-5 days); either anakinra or tocilizumab; with or without CSA---to shut down the life-threatening cytokine storm.

- Consider also treating with interferon alpha 2b (to help subdue the virus). If used, the interferon alpha 2b could be given only initially and briefly, lest it potentially fuel the cytokine storm.

Some patients with COVID might have cytokine storm, without immune-mediated pulmonary microvascular endotheliopathy; others might have immune-mediated pulmonary microvascular endotheliopathy, without cytokine storm; and some might have both of these immune-mediated complications.

IVIG does not seem to help with cytokine storm, but is promptly and dramatically effective for the microvascular endotheliopathy/basement membranopathy of SuS. If a patient with COVID appears to have both cytokine storm and pulmonary microvascular endotheliopathy, then IVIG could be added to the cytokine storm treatment.

Many health care workers are currently risking their lives while attending to patients with COVID19. The least we can do to thank them is to make sure we consider ways to maximally help them, if they contract COVID19 and become gravely ill. It is in that spirit that I offer the above considerations.

Consideration should also be given to organizing clinical trials, including randomized trials, to assess which of the above treatments or combinations of treatments, are most effective and, yet, sufficiently safe in the treatment of severe COVID19. The knowledge gained from treating COVID19 might also help us to better treat patients who become gravely ill with seasonal flu---which has been causing between 12,000-61,000 deaths, annually, in the USA alone, including children. Knowledge gained from treating cytokine storm (and possible immune-mediated pulmonary microvascular disease) in COVID19 might also be applicable to treatment of future novel viral infections.

Again, my concern is that immune-mediated complications of COVID19 may not be receiving adequate attention---at the level of research and the level of treatment. I worry that these complications, particularly cytokine storm, are often not being treated as promptly, urgently, aggressively, and imaginatively as needed.

Robert M. Rennebohm, MD
Pediatric Rheumatology (semi-retired)
Port Townsend, WA
(Formerly at Cleveland Clinic)

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