Article title: Cytokine Removal and Immunomodulation in COVID-19 Severe Pulmonary Respiratory Infection

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Cytokine Removal and Immunomodulation in COVID-19 Severe Pulmonary Respiratory Infection

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The World has never seen such a large group of scientists working together in so many countries at the same time for the same goal: saving patients from SARS-CoV-2 acute respiratory syndrome. Old drugs and new drugs are being tested. Efforts are being made to discover which drugs and in which dose can be used effectively, or a gap in the pathophysiological path of this disease that could help direct treatments. There are more than 2,000,000 cases reported around the world. In some countries, 10% of infected patients require management in an intensive care unit, with a total mortality rate that varies between 3% and 5%.¹ Those who develop a severe form of the infection require respiratory support with mechanical ventilation.

Data from severe sepsis syndrome's patients have shown that viruses can produce a cytokine storm like bacteria.² Colleagues in Wuhan, have evaluated multicenter retrospective series of cases of patients with coronavirus infection in China. In some patients the higher viral load produced a hyper inflammation reaction to the host, increasing cytokines levels of IL-2, IL-6, IL-7, IL-10 granulocyte-colony stimulating factor GCS, interferon γ , monocyte chemoattractant protein 1, macrophage inflammatory protein 1- α and tumor necrosis factor- α .³ The non-survivor patients had elevated ferritin, IL-6 and erythrocyte sedimentation rate levels, suggesting that this inflammatory reaction could be contributing to the severe condition.⁴

Cytokines are low molecular weight proteins that are produced in response to bacteria or virus stimulus. There are 3 groups of cytokines: the immunoregulatory cytokines, involved in growth and differentiation; the pro-inflammatory cytokines, produced in response to infectious agents (TNF α , IL-1 β , IL-6, IL-8); and the anti-inflammatory cytokines (IL-4, IL-6, IL-10, IL-13)⁵. In patients seriously affected, the body cannot manage to restore balance and homeostasis is lost. Some cytokines, like IL-6 can be pro or anti-inflammatory and persist in plasma much longer than other cytokines, making it a measurable marker of inflammation. During acute infections, IL-6 can activate Janus kinase signal transducer (JAK), induce thrombosis by enhancing the release of von Willebrand's factor, induce gut barrier dysfunction and regulate synthesis of ACTH in the pituitary gland.⁶ In the evaluation of patients with multiple system organ failure, persistence of elevated levels of cytokines has been associated with worst prognosis, like in the case of coronavirus infected patients.⁷

In this cytokine storm syndrome, produced by coronavirus infection, removal of inflammatory molecules could help restore a balance among pro inflammatory and anti-inflammatory response. There are some extracorporeal blood purification techniques for immunomodulation used in other pathologies as sepsis, SIRS (systemic inflammatory response syndrome), pancreatitis or AKI (acute kidney injury).⁸

Hemofiltration uses convection with an ultrafiltrate replacement solution to achieve solute clearance of middle size molecules, maintaining volume control and hemodynamic stability.⁹ Another technique is the use of adsorption columns, Cytosorb®; where substance removal from whole blood is based on pore capture and surface adsorption, with evidence of reducing levels of broad spectrum of cytokines, including IL-6.¹⁰ Cytokines accumulates in blood as well as in all organs. The use of adsorption columns would remove cytokines in blood, and as it is explained by the peak cytokines concentration, hypothesized by Ronco and colleagues¹¹, would remove the most predominant cytokine found in blood; and the use of hemofiltration would remove cytokines transported by lymphatic circulation.¹²

High Volume Hemofiltration in pulses, has been used as a rescue therapy in severe hyperdynamic septic shock patients, in short courses, resulting in a safe, feasible therapy, with a decrease in noradrenaline requirements, improvement in clinical parameters and decrease of IL-1, IL-4, IL-6, IL-10 values; with a benefit in survival.^{13,14,15} Prescription of 6 to 8 hours for 1 to 3 days in doses of ≥ 85 ml/kg/h, would require less nursery staff time because of reduced hours of treatment.¹⁶ This approach should be used early in the post admission hours to Intensive Care Unit, and not as a salvage therapy for refractory shock, where probabilities of controlling inflammation would be lower. Time for initiation of therapeutic intervention might be crucial. The combination of Pulse High-Volume Hemofiltration with adsorption columns at the same time for short periods, could remove the majority of cytokines from blood and lymphatic circulation with the purpose of controlling inflammation.

The use of steroids as therapeutic options for downregulation of pro-inflammatory immune response has been used in patients with severe sepsis and septic shock for years. Studies evaluating the time course and clinical signs of coronavirus infection, have described that the hyperinflammation phase produces pulmonary involvement, with evidence of alveolar edema, hyalosis and fibrin deposition with immune cell infiltration, as data from post mortem analysis has evidenced.^{17,18} Using models of sepsis, the elevated levels of cytokines could produce recruiting of monocytes, lymphocytes and macrophages to the lung, causing an excessive immune reaction in the lung endothelium, with alveolar disability. Corticosteroid, in vitro, produce an increased migration of anti-inflammatory monocytes to sites of inflammation or infection, limiting tissue damage because of antioxidative properties and high capacity for phagocytosis of proinflammatory stimuli,¹⁹ as in this case, the coronavirus stimuli. The Chinese Thoracic Society has made a consensus statement on the use of corticosteroids in patients with coronavirus pneumonia at a low-moderate dose (0.5 – 1 mg/kg per day methylprednisolone or equivalent) and for short duration (less de 7 days)²⁰ for patients with moderate or severe infection. Low dose steroids could be used before initiating extracorporeal treatment and up for 5 days, as a complement treatment for immunomodulation.

Coronavirus infection produces a cytokine storm in some patients, developing a moderate to severe clinical condition that is associated to increased mortality mainly because of severe pulmonary involvement. In this patients, clearance of cytokines with extracorporeal therapies in short pulses and immunomodulation treatment with steroids could help remove inflammatory cytokines allowing a downregulation of the inflammatory response, giving an opportunity for the host to reach homeostasis, decreasing lung damage and improving survival.

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