

## Rationale of using CytoSorb therapy in critically ill COVID-19 patients

### **Background**

There are two problems in severe COVID-19 infection. First, the virus infects the lower respiratory tract, causing direct pulmonary injury through viral replication, leading to viral pneumonia and pneumonitis. The virus can also be detected in the bloodstream, and may cause direct cardiac injury, liver injury, and other remote organ injury.

The second problem, as seen in influenza, other coronavirus infections (e.g. SARS, MERS), and now COVID-19 infection, is the development of a cytokine storm, driving a severe systemic inflammatory response syndrome (SIRS), capillary leak syndrome, organ injury, and other complications. In critically-ill patients in the ICU, this contributes to a high risk of death due to a high incidence of complications such as ARDS (61%), shock (31%), kidney injury (8%), acute cardiac injury (22%) and arrhythmias (44%), and other organ dysfunction.<sup>1)</sup> A report by Huang et al., documents significantly higher cytokines in patients with serious illness in the ICU vs. non-ICU patients.<sup>2)</sup> Meanwhile Ruan et al., observed a significant difference in IL-6 in COVID-19 patients who die (mean 11,400 pg/mL) and those who survive (6,800 pg/mL),  $p < 0.001$ , and significant increases in the mean of other inflammatory markers in those who die, including C-reactive protein (CRP; 126.6 vs 34.1 mg/L,  $p < 0.001$ ) and ferritin (1,297.6 vs 614 ng/mL control,  $p < 0.001$ ).<sup>3)</sup> Though not definitive, the cytokine and inflammatory marker profile associated with COVID-19 disease severity resembles secondary hemophagocytic lymphohistiocytosis (sHLH), a severe hyperinflammatory syndrome, which in nearly 30% of cases stems from a viral infection as the underlying condition.<sup>4,5)</sup>

The mortality rate for critically-ill patients is very high and is directly related to age. The reported mortality of ICU patients in an early study was 38%, but did not include the outcomes for many patients who still required hospitalization.<sup>2)</sup> Based on statistics that 5% of all COVID-19 patients in China required ICU care, and a 3.4% reported mortality of all cases in China, and assuming all critically-ill patients were treated in the ICU, that would imply an ICU mortality of 68%. In Italy, the mortality rate of all patients contracting COVID-19 is approximately 8%. The overall mortality worldwide is between 1-4%.

### **Rationale**

CytoSorb is a European Union-approved extracorporeal cytokine adsorber, designed to broadly reduce cytokine storm and other inflammatory mediators in the blood that could otherwise lead to uncontrolled systemic inflammation, organ failure, and death in many life-threatening illnesses. CytoSorb is broadly indicated for use in situations where cytokines are elevated, which includes the treatment of COVID-19 complications. CytoSorb has been used safely in more than 80,000 treatments worldwide, primarily in the treatment of systemic hyperinflammation in a wide variety of life-threatening conditions such as septic shock, influenza, ARDS, secondary HLH, trauma, liver failure, pancreatitis and many others.

In the majority of reported cases, CytoSorb therapy has been used safely to treat many of the complications of organ dysfunction and failure in bacterial and viral sepsis, seen also in patients with COVID-19 infection, including ARDS, shock, and other complications. For example, CytoSorb therapy is associated with hemodynamic stabilization and a reversal of shock, as indicated by a reduction in vasopressor need and improvement in lactate clearance in many studies.<sup>6-15)</sup> CytoSorb has also been used safely with positive clinical outcomes in the treatment of ARDS with both CRRT and ECMO.<sup>16-23)</sup> Animal and cell culture studies support a potential role of CytoSorb in protecting endothelial tight junctions against hyper-inflamed serum, which may translate into reduced capillary leak syndrome, as well as a modulation of pulmonary metabolism, edema formation, and cell-mediated infiltration and injury to the lungs.<sup>24-26)</sup>

CytoSorb therapy has also been used successfully in documented cases of secondary HLH.<sup>27-29)</sup> Recent recommendations on the management of HLH patients<sup>30)</sup> mention cytokine adsorption, which may aid in rescuing critically-ill patients from a deleterious cytokine storm.

### **Experience in Treating Patients with COVID-19 infection**

The rationale of using blood purification to treat cytokine storm in critically-ill COVID-19 patients was recently detailed by a recent publication that concluded, "Finally, a sepsis-like syndrome might occur frequently due to the virus itself or to a superimposed bacterial infection and in this case, since pharmacological approaches have shown poor results, new extracorporeal organ support therapies including haemoadsorption and haemoperfusion, with new sorbent cartridges designed to remove cytokines and other circulating mediators, should be considered."<sup>31)</sup>

To date, more than 65 critically-ill patients with COVID-19 infection have been treated with CytoSorb in various centers in Italy, China and Germany. Although patient level data is not yet available due to the extraordinary circumstances in these countries, the positive results in Italy have led to the formal recommendation by the Italy Brescia Renal COVID Task Force and published by the Italian Society of Nephrology and ERA-EDTA, to specifically use CytoSorb in severe COVID-19 patients with Stage 3 AKI receiving Continuous Renal Replacement Therapy (CRRT).<sup>32)</sup> Also, the recent National Guidelines on adult COVID-19 patients from Panama recommend CytoSorb therapy.<sup>33)</sup> In addition, the recent Handbook of COVID-19 Prevention and Treatment from Zhejiang University School of Medicine, China, is also recommending blood purification to treat cytokine storm in critical cases of COVID-19 infection.<sup>34)</sup>

### **Conclusion**

In the light of all this, CytoSorb therapy may be a promising and important therapeutic option to help manage the serious complications caused by cytokine storm and hyperinflammation in critically-ill COVID-19 infected patients.

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