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Transfusion and Apheresis Science 59 (2020) 102855

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

Extracorporeal blood purification treatment options for COVID-19: The role of immunoadsorption

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ARTICLE INFO

Keywords:
Blood purification therapies
COVID-19
Hypercytokinemia

ABSTRACT

The activation of the innate and adaptive immune systems by SARS-CoV-2 causes the release of several inflammatory cytokines, including IL-6. The inflammatory hypercytokinemia causes immunopathological changes in the lungs including vascular leakage, and alveolar edema. As a result of these changes in the lungs, hypoxia and acute respiratory distress syndrome occur in patients with COVID-19. Even though there are clinical trials on the development of therapeutics and vaccines, there are currently no licensed vaccines or therapeutics for COVID-19. Pharmacological approaches have shown poor results in sepsis-like syndromes caused by the hypercytokinemia. Suppressing the cytokine storm is an important way to prevent the organ damage in patients with COVID-19. Extracorporeal blood purification could be proposed as an adjunctive therapy for sepsis, aiming to control the associated dysregulation of the immune system, which is known to protect organ functions. Several extracorporeal blood purification therapies are now available, and most of them target endotoxins and/or the cytokines and aim improving the immune response. For this purpose, plasmapheresis and immunoadsorption may be an important adjunctive treatment option to manage the complications caused by cytokine storm in critically ill patients with COVID-19.

1. Introduction

The highly pathogenic Coronaviruses (CoVs), Severe Acute Respiratory Syndrome CoV-1 (SARS-CoV-1) and Middle East Respiratory Syndrome CoV (MERS-CoV), infect the lower respiratory tract and cause severe pneumonia, sometimes leading to fatal acute lung injury [1–3]. At the end of 2019, a cluster of patients with viral pneumonia was started to be observed in Wuhan, China [4]. Soon after, researchers revealed that the cause of these pneumonia cases were the 2019 Novel CoV (2019-nCoV) [5]. On February 11, 2020, the disease was officially named as COVID-19 and 2019-nCoV was named as SARS-CoV-2 [6,7]. The disease was declared a pandemic by the WHO on March 11, 2020. As of 23 April 2020, worldwide, there have been 2,510,177 confirmed cases of COVID-19, including 172,241 deaths, as reported to WHO [6].

In a study from China, it was reported that, among all patients with COVID-19, 5% had critical disease (respiratory or multiorgan failure), 14 % had severe disease (> 50 % lung involvement on imaging within 24–48 hours, or hypoxia) and 81 % had mild symptoms [7]. The rate of severe and critical disease or mortality may vary according to geographic location. In mid-March, in Italy, the estimated case fatality rate was 7.2 % whereas it was 0.9 % in South Korea. There are some factors that have impact on the rate of case fatalities such as, proportion of elderly population in that country, previous exposure to other CoV variants and the quality of healthcare system. For example, the median age of patients with COVID-19 was 64 years in Italy, whereas in Korea the median age was in the 40 s [8–10]. In a report from China, including 44,500 patients with confirmed COVID-19, 87 % of patients were between 30 and 79 years old. In this report, older age and/or the presence of any comorbidity was also associated with increased mortality. The case fatality rate was 8% in patients aged 70–79 years whereas it was 15 % in patients 80 years or older [7].

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https://doi.org/10.1016/j.transci.2020.102855

The activation of innate and adaptive immune system by SARS-CoV-2 causes the release of several inflammatory cytokines, including IL-6 [11–13]. IL-6 induces proliferation and differentiation of B cells. While stimulating Th17 cells. IL-6 inhibits regulatory T cell (Treg), and promotes CD4 T cell response [14–16]. Additionally, high levels of expression of other cytokines such as IL-1B, IFN-γ, IP-10 and monocyte chemoattractant protein-1 may activate the T-helper type 1 cell response. The severity of the disease is correlated with the increased serum levels of IL-2R and IL-6 in patients with COVID-19 [17]. In one study, the researchers showed that the COVID-19 patients in the intensive care unit (ICU) had higher levels of granulocyte colony-stimulating factor, IP-10, monocyte chemoattractant protein-1, macrophage inflammatory protein-1A, and TNF-α compared to COVID-19 patients in general wards [18]. The inflammatory hypercytokinemia causes immunopathological changes in the lungs including vascular leakage, and alveolar edema. As a result of these changes in the lungs, hypoxia and acute respiratory distress syndrome (ARDS) occur in patients with COVID-19 [19,20]. In COVID-19, the median time from first symptom to dyspnea was 5 days, to hospital admission was 7 days, and to ARDS was 8 days [21–23].

In severe disease, if the pharmacological treatment is not efficacious, extracorporeal treatment options seem to be a good aproach. In order to prevent progression of the pathologic changes in COVID-19, inflammatory cytokines should be reduced [24,25]. Therapeutic options for hypercytokinemia include steroids, selective cytokine inhibition (anakinra, tocilizumab), JAK inhibition, and blood purification treatments (BPTs). Tocilizumab is a recombinant humanized anti-IL-6 receptor IgG1 antibody [26]. The efficacy of tocilizumab has been shown in patients with COVID-19 and elevated IL-6 levels in a multicentre randomised controlled trial in China [27]. The (BPTs) including plasma exchange (PE), immunoadsorption (IA), perfusion, blood/plasma filtration, etc., can eliminate inflammatory factors from the blood and reduce the effects of hypercytokinemia. The BPTs can be used in the early and middle phases of the disease in severe and critical patients with COVID-19 [28]. Through application of specific devices BPTs may also be used to support lungs, heart, kidneys, and liver [29]. However, the use of extracorporeal BPTs remains controversial because of the conflicting results observed in randomized controlled studies [30].

As mentioned above, in organ dysfunction syndromes, when pharmacological treatments are not available or efficacious, mechanical ventilation along with hemodynamic support and BPTs seem to be the only possible strategy [24]. Historically, the efficacy of BPT in removing pathogenic antibodies or cytokines has been proven in a various of diseases, but not in COVID-19 patients [31,32]. Therefore, in this review, we aimed to discuss the role of different BPT options and focus on the IA methods to remove both endotoxins and cytokines in patients with COVID-19.

2. Therapeutic plasma exchange (TPE)

TPE removes inflammatory cytokines, stabilizes endothelial membranes, and improves the hypercoagulable state. Although previous studies suggest that the use of TPE in sepsis is safe, there are only limited evidence as to whether TPE is beneficial for sepsis, and not studied in ARDS [33–35]. In the largest randomized controlled study evaluating the efficacy of TPE in sepsis, a lower 28-day mortality rate was shown in the patients who had TPE performed compared to the patients who received standard therapy. However, with additional TPE, when controlled for other contributing factors, no significant difference was found regarding the mortality rate between 2 groups [8]. Previous reports including a total of 194 patients showed insufficient evidence of benefit using TPE as an adjunctive therapy in patients with sepsis [36]. The American Society for Apheresis (ASFA) recommends that the decision about the use of TPE in the treatment of sepsis with multiorgan failure should be individualized because the optimum role of apheresis therapy is not established [37].

The effect of TPE has not been studied in patients infected with SARS-CoV-1 and MERS. However, there are a limited number of studies on the use of TPE in patients with COVID-19 to reduce the levels of inflammatory cytokines. Ma et al. ([38]) reported 3 cases with critically ill patients with COVID-19. 1 patient was treated with plasmapheresis, the others had undergone continuous renal replacement treatment. After performing plasmapheresis, clinical condition was improved and the patient was extubated. Shi et al. ([39]) reported a 50 year old critically ill patient with COVID-19 refractory to pharmacological treatment, who received TPE followed by intravenous immunoglobulin (IVIG) and showed that performing TPE prevented the progression of the disease and reduced the need for intensive supportive care [39]. Limited case reports demonstrated beneficial effect of TPE in pateints with COVID-19, but whether or not this effect is seen after using TPE should be confirmed in controlled studies.

3. Double-filtration plasmapheresis (DFPP)

DFPP removes the immunoglobulin fraction from the serum selectively [40]. DFPP has been used for several indications such as hyperacute rejection in ABO-incompatible kidney transplantation, and in the treatment of anti-neutrophil cytoplasmic antibody-associated vasculitis with severe kidney dysfunction [41,42]. In the literature, DFPP has not yet been performed in sepsis and ARDS, and also in COVID-19 yet, and how it will affect the course of the disease is not known.

4. Immunoadsorption

IA is a safe and well-tolerated treatment that can provide both biochemical and clinically objective improvements by selectively removing cytokines in patients with severe sepsis. It has been suggested that hemoadsorption devices could also adsorb leukocytes, mainly activated monocytes and neutrophils, in addition to cytokines and/or endotoxins. When used in patients with severe sepsis, it was shown that IA reduced inflammatory markers, norepinephrine requirement, the duration of ventilation and ICU stay [43,44]. Therefore, IA may be an important adjunctive treatment option to reduce the complications caused by hypercytokinemia in critically ill patients with COVID-19. Worldwide, more than 200 critically ill patients with COVID-19 have been treated with IA. In previous studies, in severe and critical patients with COVID-19 in ICUs, a significant benefit was observed with the use of hemoperfusion with cartridges containing highly biocompatible sorbents and microporous resins [23,45,46]. Although there is no randomised study, the Italian Society of Nephrology and ERA-EDTA recommended the use of IA in severe COVID-19 patients receiving Continuous Renal Replacement Therapy [47]. Also, the recent National Guidelines on adult COVID-19 patients from Panama recommend IA therapy [48]. On the 13 April 2020, the United States Food and Drug Administration (FDA) issued an Emergency Use Authorization for emergency use of IA to treat patients 18 years of age or older with confirmed COVID-19 admitted to the ICU with confirmed or imminent respiratory failure [49].

In conclusion, ARDS is responsible for the majority of deaths in patients with COVID-19. Hypercytokinemia is responsible from the majority of symptoms in severe and critical patients. Therefore, reducing the levels of inflammatory cytokines is an important way to prevent the organ damage. In severe disease, if the pharmacological treatment is not efficacious, extracorporeal BPT options seem to be a good approach to reduce the levels of cytokines. Randomized prospective clinical trials are needed in order to show the efficacy of these aproaches.

Declaration of Competing Interest

All authors declare that they do not have any potential conflict of interest that could inappropriately influence the present study.

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