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Annals of Vaccines and Immunization

Commentary

Combining Therapeutic Plasma Exchange with Virus Neutralizing Antibodies for Treatment of Severe COVID-19

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Submitted: 11 May 2018

Accepted: 26 May 2018

Published: 29 May 2018

ISSN: 2378-9379

TO THE EDITOR -

The pandemic spread of coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) requires very urgently to identify effective therapies and prophylaxis. After early promise, disappointing findings have been reported with drugs repurposed for COVID-19, including hydroxychloroquine, [1] lopinavir-ritonavir [2] and remdesivir [3] Currently, there is no effective therapeutics for the treatment of severe COVID-19; as of May 25, 2020, 5,304,772 people had tested positive for COVID-19 and 342,029 people had succumbed to the disease [4].

Blanco-Melo et al. [5] studied host responses to SARS-CoV-2 and found weak innate antiviral defenses coupled with inappropriately high inflammatory cytokine levels were key entities driving the etiopathogenesis of COVID-19. They conclude their article (quote): "Because our data suggest that numerous chemokines and ILs are elevated in COVID-19 patients, future efforts should focus on U.S. Food and Drug Administration (FDA)-approved drugs that can be rapidly deployed and have immunomodulating properties." Indeed, many COVID-19 patients develop sepsis-like syndromes and recent clinical observations [6,7] further validate the inferred role of virally-driven hyperinflammation with fulminant hypercytokinemia in severe COVID-19.

Given the potential key pathogenic role of the host response to SARS-CoV-2 in severe COVID-19 rather than the viral replication in host cells per se provides the rationale for targeting this response by therapeutic plasma exchange (TPE). The purpose here is to remove the excess of cytokines in the plasma causing the clinical signs and symptoms. This concept of potential extracorporeal removal of pathogenic substances and its relative safety and efficacy have a long history [8-11] and currently, TPE is an effective treatment in many clinical situations [12,13]. During a typical TPE procedure, which takes about 2 hours, the patient's blood is passed through an apheresis machine (on the order of 1 to 1.5 blood volumes) and the separated plasma is collected by the instrument and eventually discarded. The cellular blood components are mixed with a replacement fluid (typically an isotonic solution of ~5% human albumin) and returned to the patient.

The recent COVID-19 studies in Italy suggested that no individual anti-inflammatory treatment targeting a single cytokine molecule had any substantial therapeutic effects (Giuseppe Ippolito, personal communication). This is not very surprising, because in comparison with healthy adults, COVID-19 patients display elevated plasma concentrations of many cytokines, including interleukin (IL)-1β, IL-1 receptor antagonist, IL-7, IL-8, IL-9, IL-10, basic fibroblast growth factor, granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, interferon-γ, interferon-γ inducible protein 10, monocyte chemoattractant protein-1, macrophage inflammatory protein 1-α, macrophage inflammatory protein 1-β, platelet-derived growth factor, tumor necrosis factor-α and vascular endothelial growth factor [14]. Performing single or repeated TPE treatments in severe COVID-19 would eliminate a significant proportion of all of these elevated plasma cytokines. In fact, a recent pilot study in septic shock demonstrated that the key proinflammatory cytokines and permeability factors (e.g., IL-1β, IL-6, and angiopoietin-2) were significantly reduced after TPE, while the levels of protective antipermeability factor angiopoietin-1 were unaffected [15] This TPE part of the proposed combination therapy may have beneficial effects in all severe COVID-19 patients, [16] particularly in those with acute respiratory distress syndrome (ARDS).

An important feature of coronaviruses such as SARS-CoV-2 is the presence of 3'-5' exoribonuclease (ExoN) enzymatic activity. ExoN can excise incorporated nucleotide analogs typically targeting viral RNA-dependent RNA polymerases, rendering resistance to these types of antivirals. On the other hand, the proofreading capability of ExoN diminishes the accumulation of mutations, which is favorable for effectiveness of virus-neutralizing (VNAbs) antibodies and vaccines. Similar to the concept of extracorporeal removal of pathogenic substances, the idea of using antibodies to nullify pathogenic entities [17] including viruses [18-21] has a long tradition.

Recently, Shen et al. [22] reported 5 critically ill and mechanically ventilated COVID-19 patients with severe ARDS, who received VNAbs-containing convalescent plasmas between 10 and 22 days after admission. This resulted in body temperature normalization within 3 days in 4 of 5 patients and on day 12 in the fifth patient. The Sequential Organ Failure Assessment (SOFA) score decreased similar to viral loads measured by quantitative RT-PCR. One patient became PCR-negative on post transfusion day 1, two patients became PCR-negative on day 3 and two patients became negative on day 12 after the plasma transfusion. After 53, 51, and 55 days of stay, three patients were discharged from the hospital and two patients remained in stable condition at 37 days after plasma transfusion.

These remarkable results strongly suggest that replacing 400 ml of the isotonic human albumin solution during the TPE procedure with 400 ml of ABO-matched convalescent plasma [22] containing high titers of VNAbs would effectively complement the TPE treatment of severely ill COVID-19 patients. Wu et al. [23] studied virus-neutralizing antibody (VNAb) responses in 175 COVID-19 recovered patients using pseudotyped-lentiviral-vector-based neutralization assay. Ten COVID-19 patients had undetectable levels of VNAbs. Interestingly, significantly higher ($P<0.0001$) titers of VNAbs were present in elderly and middle-age patients than in young patients and the VNAb titers corelated positively with the plasma C-reactive protein levels and negatively with the lymphocyte counts at the time of admission [23].

Many hospitals probably cannot perform the true virus-neutralization assay (for measuring the presence or absence of VNAbs in convalescent plasmas), which requires a BSL-3 or 4 lab. Therefore, either a suitable BSL-2 pseudotyping-variety neutralization assay [24] or selections of convalescent plasmas with high titers of antibodies binding to the S1-RBD, S1-NTD and S2 should be performed. Testing by ELISA (or another suitable assay) can replace the virus neutralization assay, because practically all known VNAbs are binding to one of these three SARS-CoV-2 regions and interfere with binding to ACE2 or with S2-mediated membrane fusion [25]. Alternatively, VNAbs-containing allogeneic plasma could be replaced with cross-neutralizing SARS-CoV RBD-specific (human or 'humanized') antibodies [26] or SARS-CoV-2-specific monoclonal VNAbs [27] The whole TPE-VNAbs procedure can be repeated as needed.

This combination TPE-VNAbs treatment of critically ill COVID-19 patients could be very effective and free of most toxic side effects associated with many antiviral drugs currently tested. After adjusting the used doses of VNAbs to eliminate the potential prozone-like effects [28,29] the only potential side effect could be an allergic reaction towards an unknown component in the allogeneic plasma. These reactions are known to occur but are not extremely frequent. Although one additional hypothetical risk could be a possible VNAb-mediated attenuation of humoral immunity, [30] the above-mentioned study [22] does not support this possibility, because the VNAb titers in the 5 convalescent plasma recipients ranged between 40 and 160 before the therapeutic plasma transfusions and beneficially increased to ranges of 80-320 and 160-480 on day 1 and day 7 after transfusion, respectively. While lacking any effective therapies and vaccines for COVID-19, novel treatment strategies are needed to decrease mortality. Given the relevant data briefly discussed above, the TPE-VNAbs combination therapy, ideally initiated as soon as possible after symptom onset in severe COVID-19 patients, may be considered as a therapeutic option.

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Cite this article

Malkovsky M (2020) Combining Therapeutic Plasma Exchange with Virus Neutralizing Antibodies for Treatment of Severe COVID-19. Ann Vaccines Immunization 5(1): 1017.