

Post-Infectious Sequela of SARS-CoV-2 Infection in Adults and Children: An Overview of Available Agents and Clinical Responsiveness

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Abstract

The SARS-CoV-2 2019 pandemic has created challenges to managing the post-infectious autoimmune consequences of a disease that leads to the high case fatality in adults and children. The spectrum of agents available to modulate and suppress the immune system in combination with other appropriate antiviral antibiotics and life support measures is reviewed. All of the agents envisioned to treat Covid-19 disorders, including a newly recognized pediatric multi-system inflammatory syndrome, impact post-infectious mechanisms in keeping with the multiplier effect of infection, immunity and inflammation known as I-Cubed (I³).

Keywords: SARS-CoV-2; Covid-19; Intravenous immune globulin; IVIg

Comment

The 2019 novel coronavirus (2019-nCoV [Covid-19]) pandemic caused by coronavirus 2 (SARS-CoV-2), is the third known zoonotic coronavirus disease after severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) [1]. The virus probably originated in bats from which it transmitted to humans and epidemically spread by human-to-human [2]. The exact route by which SARS-CoV enters the body is unknown. However, an early phase of intranasal viral penetration [3] precedes the commonest symptoms of fever, dry cough and shortness of breath followed soon after by dysregulated post-infectious autoimmunity and disease worsening that coincides with intensive unit (ICU) care and the need for life-saving ventilator support [4] analogous to the cytokine storm of severe viral influenza illness [5]. A pediatric multi-system inflammatory syndrome is ascribed to Covid-19 [6]. Recognizing the importance of a given patient's immune response to the SARS-Cov-2 exposure, subjects are being activity recruited to participate in studies to examine B- and T-cell repertoire and immune responses during the acute and resolved phases of Covid-19 infection at home and in the hospital (ClinicalTrials.gov Identifier: NCT04362865).

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Three potential therapies to stem the Covid-19 pandemic target the immune system. The oral antimalarial drug hydroxychloroquine decreases the secretion of cellular proteins responsible for immune-mediated chemotaxis, phagocytosis and superoxide production by neutrophils and inhibits SARS in vitro [7]. It was administered in an open-label, non-randomized clinical trial of 20 patients with severe Covid-19 illness with improvement, and later made widely available as prophylaxis [8]. A phase IIB study to evaluate the efficacy of hydroxychloroquine and azithromycin to prevent hospitalization and death in symptomatic adult outpatients with Covid-19 caused by SARS-CoV-2 infection has not yet started recruiting subjects (ClinicalTrials.gov Identifier: NCT04358068).

Remdesivir, a nucleotide analogue prodrug that inhibits viral RNA polymerases that has shown in vitro activity against SARS-CoV-2 treated a cohort of 61 patients compassionately leading to improvement in two-thirds [9]. A clinical protocol allowing expanded access to remdesivir (ClinicalTrials.gov Identifier: NCT04323761) and several clinical studies have begun recruiting subjects in a randomized, open-label, controlled clinical trial, in collaboration with the World Health Organization (WHO) (ClinicalTrials.gov Identifier: NCT04330690). A phase III randomized study comparing the safety and efficacy and antiviral activity of two remdesivir regimens with respect to clinical status is recruiting subjects (ClinicalTrials.gov Identifier: NCT04292899). An open label study to evaluate the safety and antiviral activity of remdesivir with moderate Covid-19 compared to standard of care treatment is recruiting subjects (ClinicalTrials.gov Identifier: NCT04292730).

Convalescent plasma transfusion of SARS-CoV-2-specific IgG and neutralizing antibodies was administered in an uncontrolled case series of five critically ill patients with Covid-19 with clinical improvement [10]. These preliminary findings suggest a role for transfusion therapy in the treatment of critically ill patients with COVID-19. A pilot prospective study collecting plasma to measure neutralizing antibodies to SARS-Cov-2 in recovered subjects has not yet started recruiting participants (ClinicalTrials.gov Identifier: NCT04344977).

Intravenous immune globulin (IVIg) therapy has a presumptive role in the treatment of post-infectious disorders due to its immunomodulatory actions in keeping with the multiplier effect of infection, immunity and inflammation known as I-Cubed (I^3) [11]. The potentially devastating outcome of uncontrolled post-infectious autoimmunity due to SARS-CoV-2 exposure is more severe and long lasting than the infection itself, especially in vulnerable patients that are older or have comorbid diseases. Treatment with 2 grams per kilogram high-dose IVIg therapy administered to three patients over 4-5 consecutive days in the early stages of clinically apparent SARS-Cov-2 viremia, alone (1 patient), or in association with antiviral and antibacterial antibiotics, showed clinical stabilization and were uneventfully discharged from the hospital [12]. A single-center, randomized, open-label, controlled study in Peking China, to evaluate the safety of IVIg in conjunction with their standard care for severe 2019-nCov pneumonia has not started recruiting subjects (ClinicalTrials.gov identifier NCT04261426). No similar studies are available in the US.

An anecdotal prospective analysis of 55 subjects receiving maintenance (400 mg/kg monthly) or high-dose (2 gm/kg) IVIg therapy to treat diverse acquired and post-infectious autoimmune neurological disorders, and stratified by a single home infusion service at the height of the Covid-19 pandemic (when it was impermissible for a nurse to enter the home), found no new cases of SARS-CoV-2 infection. These uncontrolled observations suggest that IVIg therapy not only treats both active

Covid-19 illness, but may mitigate the illness in vulnerable and susceptible patients, such as those with comorbid diseases. A longer period of follow-up of this cohort will be necessary to confirm these observations, as are further controlled studies to identify the dose and frequency of IVIg treatment to confer prophylactic efficacy.

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