BRIEF REPORT

Intravenous Immunoglobulin for Treatment of Severe COVID-19

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Coronavirus disease 19 (COVID-19) was declared a global pandemic in March 2020. The number of cases continues to rise producing an unprecedented global health and economic crisis. The rapid progression of lung involvement, and lack of definitive, effective treatment in patients with severe COVID-19, makes it imperative to develop efficient therapeutic management strategies. The point at which deterioration starts is a critical window of opportunity for intervention. The ability to attenuate acute lung injury and reduce the need for mechanical ventilation would be of great benefit to healthcare systems worldwide. Therefore, it may be useful to consider high-dose intravenous immunoglobulin (IVIG) at the time of initiation of respiratory distress to potentially promote satisfactory clinical recovery and reduce the burden of care for COVID-19 patients.

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On March 11, 2020, the World Health Organization (WHO) declared the coronavirus disease 19 (COVID-19) outbreak a pandemic due to the rapid escalation of cases reported globally.[1] As of April 21, 2020, there are over 2.5 million cases of COVID-19 in 210 countries and territories,[2] and the number of cases continues to rise producing an unprecedented global health and economic crisis.

Although the vast majority of cases are mild, healthcare systems worldwide have been overwhelmed by the demands of patients with COVID-19. Specifically, there have been significant shortages related to mechanical ventilation for patients presenting with severe, life-threatening respiratory symptoms. Therefore, while the spread of the virus continues to escalate, the ability to mediate acute lung injury requiring supplemental oxygen and/or mechanical ventilation would be a huge service to healthcare.

In general, coronaviruses infecting humans can be classified into low pathogenic variants and highly pathogenic variants including severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and, in some cases, COVID-19.[3-5] After infection, patients with COVID-19 may develop mild, moderate, or severe symptoms. Patients with mild disease may be asymptomatic, while patients with moderate disease may exhibit symptoms of fever, nonproductive cough, dyspnea, myalgia, fatigue, and radiographic evidence of pneumonia, but may still have a positive prognosis. In contrast, some patients may develop severe pneumonia, acute respiratory distress syndrome (ARDS), and/or multiple organ failure.[5-7] Highly pathogenic coronavirus presentations pose a substantial threat to public health.

Higher serum levels of pro-inflammatory cytokines (tumor necrosis factor, interleukin-1 [IL-1], and IL-6) and chemokines (IL-8) have been characterized in patients with severe COVID-19 compared to individuals with mild disease, similar to the results in SARS and MERS.[8] Cytokines and chemokines are thought to play an important role in immunity and immunopathology during viral infections. Elevated serum cytokine/chemokine levels and increased neutrophil-lymphocyte ratios in COVID-19 patients are correlated with the severity of the disease and adverse outcomes, suggesting a hyperinflammatory responses in COVID-19 pathogenesis.[4,8] In one study, the level of inflammatory cytokine IL-6 in critically-ill patients was almost 10 times that observed in other patients, and sharply increased IL-6 levels was considered a biomarker of poor prognosis.[6] The extremely high level of IL-6 is a hallmark and important driving force of the severe inflammatory response known as "cytokine storm" which may cause multiple organ dysfunction in critically ill patients.[4,6,9,10]

Currently, there is no vaccine for COVID-19. Although worldwide efforts are concentrated on rapid vaccine development, it could take months or years to reach the global population. Additionally, there are currently no approved treatments for any coronavirus disease, including COVID-19.[7] Therefore, current management of COVID-19 is meticulous supportive care, and respiratory failure from ARDS is the leading cause of mortality.[11]

Intravenous immunoglobulin (IVIG) was first introduced in the United States for the treatment of primary immunodeficiency disorders in the early 1980s, but has increasingly been recognized not only for its ability to fight infections but also for its anti-inflammatory and immunomodulating effects.[12] Approved IVIG products are manufactured via a fractionation process of pooled plasma from thousands of screened donors, and undergo pathogen inactivation steps to optimize product safety and ensure the preservation of functional activities.[13] It is important to distinguish currently approved IVIG products from convalescent plasma (CP) and "hyperimmune" IVIG. Patients who have recovered from a viral infection, such as SARS, MERS, or COVID-19 have antibodies to the disease. Following recovery, patients who meet specific criteria may donate whole blood or plasma for use in development of CP and/or hyperimmune IVIG that would contain COVID-19 antibodies.[14,15] Evidence shows that CP and hyperimmune IVIG can be used as treatment without the occurrence of severe adverse events.[16] However, the availability of these products is extremely limited; the identification, selection, and recruitment of potential donors can be very difficult as convalescent subjects must also meet strict donor selection criteria in compliance with national policies and routine procedures.[17] In contrast, approved IVIG products are currently available for immediate use, and have been found to have broad therapeutic applications for treatment of a variety of autoimmune/neuroimmune, infectious, inflammatory, and viral diseases including idiopathic thrombocytopenic purpura, chronic demyelinating polyneuropathy, multifocal motor neuropathy, neonatal sepsis, postoperative sepsis, Kawasaki disease, dermatomyositis, bullous pemphigoid, lupus, chronic lymphocytic leukemia, respiratory syncytial virus, chronic parvovirus B-19, SARS, and H1N1.[9, 12,18,19]

The mechanism of action of IVIG is not completely understood, but it may modulate the immune response via multiple mechanisms, including blocking a wide array of proinflammatory cytokines that potentially lead to severe inflammatory responses, including cytokine storm, as well as Fc-gamma receptor binding of activated macrophages.[4,11,20]

Clinical and histopathologic characteristics for ARDS are similar across severely affected patients, suggesting a common mode of immunopathogenesis. There may be etiologic substances that have an affinity for respiratory cells and induce lung cell injury in ARDS that originate from pathogens as well as injured host cells. The severity or chronicity of ARDS depends on the amount of etiologic substances and corresponding immune reactions,

Table 1. Published Reports and Planned Studies of IVIG Treatment for COVID-19 in 2020

Authors	No. of Pts.	Overview/Results
Shao et al[21]	325	Retrospective, multicenter study indicating early administration of high-dose IVIG improves the prognosis of critical patients with COVID-19.
Xie et al[22]	58	Retrospective study indicating initiation of IVIG for COVID-19 < 48 hours of admission to the ICU can: 1) reduce the use of mechanical ventilation; 2) reduce length of stay in hospital/ICU; 3) reduce 28-day mortality in patients with severe COVID-19 pneumonia.
Zhou et al[23]	10	Short-term moderate-dose corticosteroid plus IVIG is effective for reversing continued deterioration of COVID-19 patients who failed to respond to low-dose corticosteroid therapy.
Cao et al[24]	3	Three (3) deteriorating patients with severe COVID-19 received high-dose IVIG with satisfactory recovery.
Sakoulas et al[25]	1/20 Planned	One (1) deteriorating patient with COVID-19 successfully treated with IVIG; planned IVIG study currently recruiting approximately 20 COVID-19 subjects.
Lange et al[27]	58 Planned	Planned IVIG study with goal of recruiting approximately 58 COVID-19 subjects.
Jones et al[26]	1	Pediatric patient (6 months of age) diagnosed with Kawasaki disease and COVID-19 was treated with IVIG and discharged within 48 hours.

Abbreviations: No.:number; COVID-19: coronavirus disease 19; IVIG: intravenous immunoglobulin; ICU: intensive care unit.

duration of the appearance of specific immune cells, and/or repertoire of specific immune cells that control the substances. Therefore, treatment with early systemic immune modulators (e.g., IVIG) may reduce aberrant immune responses, and the subsequent inflammatory responses, observed in the severe stages of ARDS.[4,11,20]

Based on this evidence, clinicians hypothesized that IVIG therapy may improve the prognosis of severe and critically-ill patients with COVID-19. There are now a limited number of published reports, as well as planned studies, of IVIG treatment for COVID-19 (**Table 1**).

A retrospective, multicenter cohort study that included 325 adult critical patients from 8 centers, demonstrated that early high-dose IVIG administration (≤ 7 days following admission) improves the prognosis of critical COVID-19 patients.[21] In addition, a retrospective chart review of 58 patients with severe COVID-19 pneumonia compared outcomes in those receiving high-dose IVIG treatment ≤ 48 hours versus > 48 hours after admission to the intensive care unit (ICU).[22] Results demonstrated that high-dose IVIG received ≤ 48 hours after admission to the ICU resulted in reductions in the use of mechanical ventilation, hospital/ICU stay, and 28-day mortality in patients with severe COVID-19 pneumonia.[22]

An observational study was conducted in 10 COVID-19 patients, and results demonstrated that short-term moderate-dose corticosteroid combined with high-dose IVIG effectively reversed severe, deteriorating COVID-19 patients who failed initial low-dose therapy.[23] It's notable that researchers were motivated to employ this therapeutic regimen as it was preliminarily shown to reduce the risk of death in 12 patients with SARS.[19] The authors postulate that corticosteroid use at an early deterioration stage has a timely effect on the suppression of the inflammatory response. More importantly, the combination use of IVIG is believed to strengthen immune function to prevent a potential delay in viral clearance caused by the corticosteroid.[23]

Another study conducted in three (3) deteriorating patients with severe COVID-19 who received high-dose IVIG demonstrated that all experienced a successful recovery with significant improvement in symptoms within 24-48 hours.[24] They also observed that "the first few days of deterioration may present a critical point when potent suppression of the inflammatory cascade could save patients from fatal immune-mediated injuries."

There are two (2) additional case reports of successful recovery following IVIG treatment for COVID-19 in a deteriorating 62-year-old patient with multiple comorbidities.[25] as well as 6-month-old patient who also presented with Kawasaki disease.[26] As a result of these reports, Dr. George Sakoulas, an infectious disease clinician and Associate Editor for the *New England Journal of Medicine - NEJM Journal Watch: Infectious Diseases*, and colleagues have initiated a research study to investigate the use of high-dose IVIG in deteriorating COVID-19 patients. Dr. Sakoulas and his team in San Diego, California, stated in a recent press release that, "The goals of this study are to evaluate three parameters: the rate of subjects requiring mechanical ventilation; number of days patients require oxygen therapy; and length of hospital stay." They plan to recruit approximately 20 patients requiring significant oxygen, but not yet on mechanical ventilation, for the study.[25] A double-blind crossover study has also just been designed by Dr. Daniel J. Lange at the Hospital for Special Surgery in New York City to explore the effectiveness of IVIG in COVID-19 with a planned recruitment of approximately 58 patients.[27] Octapharma has submitted an Investigational New Drug Application (IND) for the study to the FDA. The primary objective of this study is to determine if high-dose IVIG therapy will mitigate deterioration and improve oxygenation and respiratory function in subjects with COVID-19.

The rapid progression of lung involvement and lack of definitive, effective treatment make it imperative to develop efficient therapeutic management strategies for patients with severe, deteriorating COVID-19. Previous experiences with SARS showed that the main pathogenesis of organ dysfunction lay in the overall cytokine dysregulation.[24] Similarly, the point at which deterioration starts in patients with COVID-19 is a critical window of opportunity for intervention. The ability to attenuate acute lung injury and reduce the need for mechanical ventilation would be of great benefit to healthcare systems worldwide.

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