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Editorial

Development of passive immunity against SARS-CoV-2 for management of immunodeficient patients—a perspective

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The recent coronavirus disease 2019 (COVID-19) pandemic raises serious concerns about potential prophylaxis and therapy in a naive population, particularly in patients with primary or secondary immunodeficiencies. The former mainly includes patients with defects in T-cell–mediated immunity and, to a lesser extent, those with antibody deficiencies and immune dysregulation. The latter includes patients undergoing therapy with immunosuppressive drugs, such as stem cell transplanted patients. In addition, patients with B-cell malignancies and autoimmune disorders treated with selected forms of targeted therapy (such as anti-CD20) may develop secondary immunodeficiency characterized by hypogammaglobulinemia. Although many drug candidates have been identified through *in vitro* viral neutralization experiments or based on clinical observations, thus far, there are no specific therapeutic agents to treat COVID-19. The antiviral drug remdesivir has shown some effects during compassionate use in patients with COVID-19[1]; however, randomized, placebo-controlled clinical trials have yet to prove its value. Another combination of antiviral drugs (lopinavir-ritonavir) did not provide any benefit for hospitalized patients with COVID-19 with severe disease in a randomized, controlled, open-label trial.[2] The antimalaria drug chloroquine/hydroxychloroquine has also been reported to show positive clinical results. However, recent studies showed no beneficial effects but rather a negative influence on cardiac function, with an increased mortality in the high-dose group.[3]

Because immunodeficient individuals are unlikely to respond to active vaccination, there is an urgent need for additional forms of therapy. Many of these patients are currently receiving substitution with intravenously or subcutaneously administered gammaglobulin preparations. However, because the available lots were manufactured before the appearance of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), they are unlikely to provide protection because they do not contain any specific antibodies against this new virus. Low levels of cross-reactive antibodies may exist because of previous exposure to other types of coronavirus, but at nonneutralizing titers. Thus, preparations enriched in specific antibodies against SARS-CoV-2 are needed for these patients.

Passive immunotherapy, using preformed antibodies, is a century-old treatment modality, which is still used today for selected infections using polyclonal antibodies, preferably as a hyperimmune preparation from convalescent donors. To identify individuals who have recovered from COVID-19, novel tests are currently entering the market and used for analyzing the presence of antibodies against the virus. These antibodies are initially of the IgM class, followed by IgG (preferentially IgG_3, a subclass usually associated with viral infections) and IgA.[4] The target antigen chosen for serological assays is most often the spike protein or subunits thereof (S1). The receptor-binding domain, which confers binding to angiotensin-converting enzyme 2, may be of particular interest in this context. Yet, even antibodies that interfere with the fusion process (and which will not directly interfere with binding) may also be of therapeutic interest and should therefore be investigated. To date, no systematic study has been made to address which antigen would be optimal for screening of convalescent donors for therapeutic antibodies.

Plasma obtained from convalescent donors could be rapidly used as a therapy against virus infections and has been used previously in patients with various infections, including 80 patients in Hong Kong, infected with SARS-CoV-1 during the 2003 outbreak,[5] resulting in a reported lower mortality rate (12.5%) compared with patients not treated with plasma (17%). Plasma therapy in small noncontrolled series of patients with SARS-CoV-2 infections (Table I)[6-8] has recently also been reported, with suggested beneficial effects. However, no controlled clinical study of the potential benefit of plasma therapy has been conducted to date in patients with COVID-19 and neither the timing of the infusions, nor the dose of antibodies needed has as yet been established. Furthermore, because single donations are used for a given patient, there are individual differences in the content of specific antibodies (titer and neutralizing capacity). Thus, characterization of plasma-neutralizing activity as well as the number, volume, and timing of plasma infusion should represent mandatory requirements in the clinical trials design. A trial is currently ongoing in Italy, using plasma from convalescent patients with neutralizing titers greater than 1:160, and results will be available very soon. However, as of today, nobody can predict

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TABLE I. Plasmatherapy in patients with COVID-19

Study	No. of patients	Age (y)	Dose (mL)	Days from symptom onset	Neutralizing titer*	Outcome	Reference
1	5	36-65	400 in 2 divided doses	14-24	>1:40	No death. Fever normalized within 3 d in 4 of 5 patients; viral loads became negative within 12 d; 3 patients discharged and 2 were in stable condition	[6]
2	4	31-73	200-2400 in 2-8 divided doses	15-23	Not given	No death. Three patients discharged and 1 patient with virus undetected and moved to unfenced ICU	[7]
3	10†	34-70	200 in 1 dose	10-20	>1:640	No death. Clinical symptoms and paraclinical criteria improved markedly within 3 d; viral load was undetectable in 7 patients who previously had viremia	[8]

ICU, Intensive care unit.
*Measured as reduction of SARS-CoV-2–infected cells. Study 1 used the isolated viral stain BetaCoV/Shenzhen/SZTH-003/2020 in Vero cells, and study 3 used the isolated viral strain 2019-nCoV BetaCoV/Wuhan/WIV04/2019 in VERO E6 cells.
†The clinical results were compared with a recent historic control group (n = 10 patients) showing a significantly ($P < .001$) improved outcome in the plasma-treated group.

TABLE II. Comparison of different passive immunotherapy approaches

Approach	Samples and donors needed	Antibody titers	Safety issues	Time to clinic practice
Plasma therapy	Plasma samples from 1 or a few convalescent donors to treat individual patients, blood type matched	Variable titers between donors	Transmission of infections; transfusion-related risk; unknown factors in the donor's plasma; antibody-dependent enhancement of infection	Immediate to weeks
Hyperimmune gamma globulin	Plasma samples from hundreds to thousands of convalescent donors for production of 1 batch of gammaglobulin	Enriched titers, standardized	IVIG-related risks	Months to 1 y; requires clinical trials
Broad neutralizing human recombinant mAbs	Blood samples from selected convalescent donors; isolation of antibodies from single B cells or by using phage display, followed by the screening of hundreds of candidates	Broad and potent neutralizing antibodies, standardized	Not envisaged	More than 1 y usually; requires animal model testing and clinical trials

IVIG, Intravenous immunoglobulin.

how long these titers can last. Thus, delays in collecting sufficient amount of hyperimmune plasma doses might result in a shortage in the unfortunate event of COVID-19 recrudescence. However, hyperimmune plasma collection campaigns must rely on screening of large groups of recovered patients, something that might be difficult to achieve. Finally, the presence of other plasma components may theoretically affect the clinical outcome. Of particular concern is the presence of low levels or low-affinity antibodies that may be associated with augmentation of the infection due to antibody-dependent enhancement.[9]

Intravenous polyclonal hyperimmune IgG preparations is another attractive form of therapy both for critically ill SARS-CoV-2–infected individuals and as prophylaxis in immunocompromised patients. This would provide a standardized pharmaceutical product that could be available within the near future, provided that a sufficient number of convalescent donors could be rapidly collected. This necessitates large-scale serological screening by the collection centers (preferably using improved and standardized detection kits) to identify suitable donors and pooling of resources and plasma by the major industrial stakeholders to speed up the collection process. On April 6, 2020, a collaboration between the major gammaglobulin producing companies in the world to meet this need was announced (https://www.cslbehring.com/newsroom/2020/covid-19-hyperimmune), providing a glimpse of hope for successfully combating the disease within the foreseeable future. In addition to a higher titer of the specific antibodies, the hyperimmune IgG products, such as the standard preparation of normal gammaglobulin for intravenous use (intravenous immunoglobulin), may also confer anti-inflammatory effects and could thus theoretically be beneficial for patients with COVID-19 to mitigate or prevent the IL-6–associated cytokine release syndrome. However, other potential beneficial factors that may exist in the convalescent plasma, such as anticoagulation factors and anti-inflammatory cytokines, will be lost after the gammaglobulin purification process.

mAbs against SARS-CoV-2 have also been considered for therapy in patients with COVID-19, following the successful development of human/humanized mAbs against recently emerging infections, including Zika and Ebola. Some of the mAbs raised against SARS-CoV-1 have shown cross-reactivity against SARS-CoV-2[10] and novel mAbs against the new virus have also been generated with an astonishing speed. Unlike polyclonal antibodies generated during natural infection or vaccine-induced antibodies, mAbs can be engineered precisely and

optimized for potent and broad neutralizing activity, meanwhile addressing the safety concerns such as antibody-dependent enhancement. The highly effective mAbs, however, usually take a longer time to develop, because substantial testing in appropriate animal models is required before being used clinically.

In summary, passive immunotherapy is a promising tool for the management of immunodeficient patients during the COVID-19 pandemic. Before a specific antiviral therapy or an effective vaccine is available, polyclonal and monoclonal antibodies may also provide protection for the high-risk group of individuals such as elderly persons and health care workers as well as a therapy for severely ill patients with COVID-19. Different approaches of passive immunotherapy have their own risk and benefit issues that need to be considered (Table II) and their safety and efficacy beyond standard care should be tested in controlled, randomized clinical trials.

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