COMMENTARY

Active Therapy with Passive Immunotherapy May Be Effective in the Fight against COVID-19

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Passive immunity against pathogens in epidemics has historical roots. Convalescent plasma (CP), plasma collected from individuals who have recovered from an infectious disease, has been used to confer therapeutic benefits in previous epidemics, including measles, mumps, and influenza, and remains the first-line passive immunotherapy in emerging diseases, including the H1N1 influenza pandemic (2009) and now coronavirus disease 2019 (COVID-19).[1] Over the last several decades, as technology has developed to purify and manufacture plasma-derived immunoglobulin (IgG) as a drug therapy, hyperimmune globulin (H-IG) formulations have been used as the second-line of passive immunotherapies against these diseases. H-IGs are preparations of immunoglobulins with known titers of neutralizing antibodies against specific infectious agents, such as rabies, hepatitis B, and cytomegalovirus.

CP or H-IG treatments have demonstrated clinical benefits in previous coronavirus epidemics. In severe acute respiratory syndrome (SARS), caused by SARS-coronavirus (CoV), highly homologous to SARS-CoV-2, CP or H-IG reduced mortality and hospital stay.[2] In a meta-analysis involving 32 studies of SARS or severe influenza, passive immunotherapy lowers mortality, especially if administered early in disease (within 5 days of symptoms). Yet, these studies often lacked control groups or had high risk of bias.[3]

COVID-19 is a historic pandemic that is testing populations, healthcare systems, and the biopharmaceutical industry in previously unimagined ways. We now are seeing new drug developers, including biopharmaceutical companies, government agencies, academicians, and private foundations, come together in full force to consider approaches to treat and prevent infection with SARS-CoV-2. Vaccines, which if effective will result in mass active immunity, are now in clinical trials. The most advanced vaccines (Moderna and Oxford/Astra Zeneca) could be available via emergency use authorization as early as Fall 2020. The first wave of therapies, such as remdesivir (Gilead), are completing clinical trials and the second wave, including repurposed existing drugs and new drug candidates, are now entering clinical trials. Until vaccines and new therapeutics are widely available, passive immunotherapies to manage COVID-19 may prove to be effective agents in the fight against SARS-CoV-2 and COVID-19.

PASSIVE IMMUNITY IN THE CONTEXT OF COVID-19

Passive immunity is conferred by the transfer of pathogen-specific antibodies and, in the case of CP, innate humoral immune factors, to patients at-risk of developing or actively suffering from infection. The pathogen-specific antibodies include all immunoglobulin isotypes (IgG, IgM, IgA, and IgE) and nonspecified humoral innate immunity factors in CP or high purity polyclonal IgG and its subclasses in H-IG. In viral diseases, antibodies exert effect by viral neutralization (blocking viral cell entry and, therefore, replication), complement activation, opsonization, and antibody-dependent cellular cytotoxicity mediation. Viral neutralization is antigen-specific; other antiviral activities are antigen-nonspecific and are effected in part via Fc:FcReceptor interactions. In SARS-CoV-2 infection, the principle target antigen associated with neutralization is the Spike protein, which is responsible for SARS-CoV-2 attachment to epithelial cells, including pneumocytes. The antibodies in COVID-19 passive immunotherapies are polyclonal in nature, with multiple epitopes against SARS-CoV-2 paratopes, including the receptor-binding domain in the Spike protein.

Both CP and H-IG depend on plasma collected from patients who have recovered from the diseases. The US Food and Drug Administration (FDA) has provided nonbinding recommendations for CP donation: donors must have had documented infection with SARS-CoV-2 (real-time polymerase chain reaction or serology) and at least 28 days from resolution of symptoms or at least 14 days without symptoms and a negative real-time polymerase chain reaction test.[4]

CP has been used compassionately in this pandemic and is currently in clinical trials via an expanded access program in the United States, managed by the COVID-19 Convalescent Plasma Project (CCPP19.org). In a published report of 10 critically ill patients in China, 200 mL of plasma with titers of at least 1:640 on top of supportive care improved signs and symptoms in critically ill patients.[5] Assuming an average normal level of IgG, 200 mL equates to ~ 2 g of IgG, or 0.03 g/kg in a 70 kg adult. The process for using CP as a therapy is straightforward and efficient: one or two units of fresh, frozen, and virus-inactivated plasma (~ 250–500 mL, or up to ~ 5 g of IgG) collected from individual convalescent patient(s) is administered to blood group-matched patients.

Although CP is screened for neutralization titers, the titers are not standardized, and the dose of antibodies (including IgG) and other immune factors is unknown. The FDA recommends that CP neutralization titers are at least 1:160.[4]

H-IG is a drug derived from convalescent plasma. H-IG is produced following normal IG production processes, via a fractionation process that results in a purified mix of IgGs in subclass ratios that mimic human IgG subclass mixtures (in this case, to ratios in COVID-19 convalescent patients). The product will have a diverse set of polyclonal antibodies against SARS-CoV-2, with a standard, measured neutralization titer prior to release. The final product is finished to a precise concentration of IgG (10% solution is common). As a drug, H-IG is regulated by health authorities, and several biopharmaceutical companies with specific infrastructure to produce plasma-derived therapies have announced H-IG programs.

H-IG HAS THE POTENTIAL TO BE A SUSTAINABLE IMMUNOTHERAPY

Manufacturing clinical and commercial supply of H-IG depends on plasma collection. In the United States, Europe, Japan, and China, there is established and highly regulated plasma collection infrastructure that is being mobilized now to collect plasma from the increasing number of convalescent patients in these regions. Once collected and pooled, plasma is manufactured into H-IG through a series of steps that can take several months: fractionation, purification, incubation, release testing, finishing, and packaging. The process ensures product purity, pathogen safety, and adequate titers of neutralizing antibodies before release for clinical use. H-IG may be stored up to 3 years depending on conditions. Further, H-IGs may be manufactured at commercial scale, following the process outlined above, with manufacturing runs that can process up to 20,000 L of plasma.

The H-IG is expected to behave pharmacokinetically like IG (i.v.). **Table 1** shows an example of pharmacokinetic (PK) characteristics for a commercially available IG (i.v.) product.[6] The short time of maximum plasma concentration (T_{max}) and long T1-2 suggest that a single infusion of H-IG may be sufficient for treatment in the acute disease settings. In upcoming studies, it is important to confirm that the PK of SARS-CoV-2 specific antibodies

administered therapeutically in an active disease state is similar the PK of IG (i.v.).

To assess PDs, animal models may be a key mainstay in COVID-19. Preclinical studies using human transgenic ACE2 mice and non-human primates will provide prospective understandings of minimal protective titers that can substantiate human dosing, evaluate efficacy in a therapeutic setting, and address key safety risks (as discussed below). Ongoing preclinical experiments can substantiate the proposed clinical dose through pharmacometric modeling of the PK/PD relationship. However, due to the urgency of the pandemic and the speed of clinical development in this situation, these experiments will run concurrently with pivotal clinical trials. Thus, the early reads on PD may come from human therapy trials.

Although the clinical dose will be defined in clinical trials, *in vitro* neutralization titers of the finished product will inform dose selection. Based on assessments done in our own laboratories, the current estimate is that the dose will range from 0.1 to 0.5g/kg, given i.v. once (every 28 days if used for prophylaxis). The experience to date with CP as therapy suggests that a lower dose may be effective: this will be tested in randomized clinical trials.

To date, no high-quality clinical trial has demonstrated convincing efficacy and safety of H-IG in coronavirus epidemics. Thus, randomized controlled trials are needed now to establish the benefit-risk balance of this intervention for COVID-19 and to guide future H-IG use in new, emerging epidemics. Target indications for the COVID-19 H-IG include treatment and prevention. In coronavirus diseases, including COVID-19, endogenous antibody production is nondetectable early in disease (< 5–7 days). In COVID-19, ~ 95% of patients convert within 14 days of symptom onset, and IgM and IgG seroconversion seems to occur simultaneously and plateaus after 6 days.[7] Thus, patients who have rapidly progressing yet early disease may benefit from the antibody boost that would come from H-IG. Randomized, placebo controlled clinical trials in treatment paradigms are anticipated to begin in Summer 2020.

In prevention, the initial targeted population could be pre-exposure prophylaxis in front-line healthcare providers (HCPs). To date, several hundred HCPs have died from COVID-19.[8] High infection rates in HCPs translate to direct and indirect harm: as the individual HCP is infected and suffers from the disease and is a potential fomite for new infection, additional HCPs are called in to care for patients and are at higher risk for infection.

ANTIBODY-DEPENDENT ENHANCEMENT AND SAFETY CONCERNS

In general, i.v. IgG is well-tolerated and the safety profile is well known. Common adverse reactions are mild and self-limiting, but severe adverse effects, including thrombosis, renal dysfunction, and death, are known to occur in high-risk patients. Little is known about the safety of CP or H-IGs when used to manage coronavirus infections. There is a theoretical concern that H-IG against coronavirus, including SARS-CoV-2, may potentiate disease via a mechanism called antibody-dependent enhancement (ADE), and earlier studies of H-IG in SARS and Middle East respiratory

Table 1 Select pharmacokinetic parameters and estimates of IgG levels after infusion of a commercially available IVIG 10% (200–800 mg/kg, mean dose 453 mg/kg) at 4 week intervals (Melamed *et al.*[6])

Parameter	Median (min, max)
C_{min}, g/L	9 (6.8, 20.6)
C_{max}, g/L	16.5 (12.7, 26.0)
T_{max}, hours	2.5 (1.8, 26.3)
$T_{1/2}$, days	37.4 (18.7, 131.7)
Vd, L/kg	0.09 (0.0, 0.2)

C_{max}, peak plasma concentration; C_{min}, minimum plasma concentration; IgG, immunoglobulin; IVIG, intravenous immunoglobulin; $T_{1/2}$, terminal half-life; T_{max}, time to peak plasma concentration; Vd, volume of distribution.

syndrome (MERS) have not provided enough information to extrapolate to COVID-19.

ADE describes two basic phenomena mediated by virus-specific antibodies: enhanced viral infection and enhanced immunologic response in the advanced disease, independent from viral load. There are no data to date to suggest that ADE occurs in COVID-19, but research in this space is relatively immature. The strongest set of data on ADE in coronavirus infections come from SARS-CoV. *In vitro* data suggest that although anti-Spike protein serum inhibits viral entry into epithelial cells incubating in SARS-CoV inoculated medium, there is enhanced uptake of virus in immune cells via FcgammaRII (not ACE2)[9]: whether this uptake enhances immune pathology requires scientific evaluation. Additional *in vivo* results from a macaque model showed that induction of anti-SARS-CoV Spike IgG resulted in enhanced-acute lung injury, related to enhanced pro-inflammatory morphological changes in alveolar macrophage.[10] Additional preclinical animal studies are needed to understand whether H-IGs at high neutralization titers will enhance antibody-dependent immune pathology. Human data to correlate these findings do not exist, yet, it is important to note that in SARS ~ 80% of patients developed acute respiratory distress syndrome (ARDS), coincidentally with IgG seroconversion. Preclinical and clinical correlation in COVID-19 are needed.

PASSIVE IMMUNOTHERAPY AS A PLATFORM FOR THIS AND FUTURE EPIDEMICS

Passive immunotherapy from convalescent plasma and H-IG drugs may be effective in future epidemics caused by novel or known pathogens, to target pathogens against which no existing direct antiviral therapy exists. These approaches may be standardized and scaled, and we are actively learning how to initiate collections, supply, clinical trials, and distribution network in order to mobilize agilely for the next epidemic. As H-IG therapies become available, rapid and cost-effective distribution needs to be ensured to optimize the full potential of this therapy.

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