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Review

Passive immunization and its rebirth in the era of the COVID-19 pandemic

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ABSTRACT

The COVID-19 pandemic, caused by SARS-CoV-2, has led to a rapid search for therapeutic and preventive measures because of the potentially severe course of infection. The antiviral drug, remdesivir, and the anti-inflammatory agent, dexamethasone, have shown beneficial effects. As the current COVID-19 vaccines are not yet fully available to everyone, or they may not be readily and universally accepted, various treatment options are being evaluated and will still be needed under these conditions. One of these treatment options, passive immunization, has shown promise in some studies. Further research is needed to determine the utility of immunotherapy with convalescent plasma or artificially produced monoclonal antibodies for the treatment of symptomatic patients, and potentially for use as post-exposure prophylaxis, at least until more effective drugs are available or safe and effective vaccines are distributed and administered to everyone.

1. Introduction and historical background

On June 26, 2020, during one of the White House Coronavirus Task Force press briefings, the U.S. Secretary of Health Human Services, Alex Azar, stated that more than 25 000 COVID-19 patients had received plasma donated by patients who had recovered from infection with SARS-CoV-2. The outcome for these plasma recipients was unclear as no data were provided during the briefing, although this statement was likely referring to ongoing clinical trials. A beneficial outcome in plasma recipients has been reported in China near where the pandemic originated [1,2]. Transfer of antibody-containing plasma or serum-based products has had a long and remarkably successful history as a treatment option for a select group of infections or toxin-induced diseases. The implementation of such a treatment option for patients with COVID-19 may be viewed as a logical course of action, although several relevant issues need to be considered.

The origin of passive immunization was in the latter part of the 19th century when, in 1888, disease manifestations of diphtheria were discovered to be mediated by a toxin. Two years later, Emil von Behring and Kitasato Shibasaburo [3] showed that antitoxin immunity could be transferred using “blood products” from animals that had recovered from experimentally-induced diphtheria. This led to the realization that the same process could be adapted to treat human patients with diphtheria [4]. These results were hailed by some [5] as “the most important advance of the century in medical treatment of acute infective disease”. A few years prior to this achievement, antibody therapy had already been used to treat tetanus through injection of serum from immunized horses into patients with severe disease, which proved to be an effective way to neutralize the tetanus toxin. Prior to the availability of vaccines and antibiotics, specific antitoxin therapy was often the only way to treat toxin-related infections, such as diphtheria, botulism and tetanus. Passive immunization continued to be a first-line therapy for treating certain severe respiratory diseases until the 1930s, even after the first group of antimicrobials, the sulfonamides, were introduced into clinical practice. Interestingly, 60 years after this landmark development, our research group showed that antibody-containing serum from Lyme disease patients was highly protective in preventing infection when administered before *Borrelia burgdorferi* was introduced into mice in an experimental animal-infection model of Lyme disease [6]. Treatment for Lyme disease, and most other bacterial infections, over the past 40-50 years, has relied solely on readily available and effective antibiotics. Human tetanus immune globulin, however, is still being used to protect non-vaccinated or incompletely vaccinated patients from possible tetanus due primarily to wound injuries [7].

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In terms of treating viral infections, in 1945, passively transferred immunoglobulins successfully prevented hepatitis A epidemics that were emerging in summer camps. In the recent past, hepatitis B immune globulin has also proved effective for preventing hepatitis B infection [8]. Prophylaxis against both viruses has now been largely replaced with highly effective vaccines.

2. Passively acquired immunity: basic concepts and clinical application

Protection against infection can be established by administering pre-formed antibody-containing plasma or serum from one donor or from a pool of immune donors who had either recovered from the infection or had been immunized against the pathogen or against the toxin the pathogen produces. Alternatively, prior to transfer, serum or plasma can be purified by separating out the desired immunoglobulins from the other humoral components using various extraction procedures. This procedure could potentially enhance the beneficial effect, reduce the volume of the infusion (usually given intravenously), and lower the chance of adverse effects. The acquired antibodies may combine with the infectious agent or toxin, thus neutralizing an ongoing pathologic process. The protective antibodies are eventually catabolized and the protective effect is lost. Some patients may require a re-infusion of the same immunoglobulins to ensure recovery from the infectious process. The best example of natural transfer of antibodies occurs during pregnancy and after birth. In the first few months of life, when the baby's own immune system is gradually developing, protection against certain pathogens is afforded by maternally-derived antibodies of the IgG isotype acquired by placental transfer to the fetus, and by the presence in the gastrointestinal tract of colostral immunoglobulins, primarily IgA, from breastfeeding.

Other clinical situations where passive immunotherapy currently plays an important role are shown in Table 1. For example, antibody therapy is regularly given as a form of pre-exposure prophylaxis to reduce infectious complications in patients with common variable immunodeficiency. A notable use of passively transferred antibody is for the treatment of individuals who were exposed to the rabies virus, which is supplemented with a vaccine containing dead rabies virus material. Human rabies immune globulin has been available for 50 years and is preferred over whole, unpurified antiserum because it is associated with fewer side effects.

Table 1
Passively transferred therapeutic agents to prevent or treat infectious disease-related conditions in the form of intravenous immunoglobulin (IVIG) or monoclonal antibodies (Mab).

Disease condition	Source
Anthrax	Human Mab
Bone-marrow transplantation	Human IVIG[a]
Botulism	Human IVIG
Common Variable Immunodeficiency	Human IVIG[a]
Diphtheria	Equine IVIG
Hepatitis A	Human IVIG
Hepatitis B	Human IVIG
Rabies	Human IVIG
Respiratory syncytial virus (RSV) infection	Human Mab[b]
Tetanus	Human IVIG; Equine IVIG[c]
Varicella	Human IVIG

[a] For pre-exposure prophylaxis; the other sources are for post-exposure treatment.
[b] A Mab is used to treat RSV infection having replaced a previously used immune globulin.
[c] The equine version is not typically used in the developed world due to the risk of serum sickness, but may be the only intervention available in developing countries.

As well as immune serum-mediated prevention and treatment of certain infectious diseases, antibodies are used to treat a variety of other non-infection related medical conditions. These include therapies with monoclonal antibodies to treat cancer and various inflammatory/autoimmune disorders, such as moderate to severe asthma, rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, and psoriasis. The beneficial effects are based on neutralizing pro-inflammatory cytokines, such as tumor necrosis factor, or blocking checkpoint molecules that interfere with cytotoxic T-cell activity against neoplastic cells.

3. Passive immunization for COVID-19

There has not been such a worldwide concern over a serious biomedical problem like the COVID-19 pandemic since the periodic Ebola virus outbreaks over the past 25 years and the Zika virus epidemic of 2016. Much of this concern can be attributed to the potential morbidity and mortality associated with COVID-19 and the limitations of available drug therapies, although vaccine development has been recently achieved. Some beneficial clinical effects have been demonstrated for the antiviral agent, remdesivir [9], and the anti-inflammatory drug, dexamethasone [10].

Given the limited drug options, clinicians began to use passively transferred immune serum in the hope of rescuing critically ill patients who were at risk of dying from an overwhelming SARS-CoV-2 infection. The rationale for using passively transferred immune serum as a form of immunotherapy for COVID-19 comes from the success achieved in treating other viral infections, such as Ebola [11], SARS-CoV-1, MERS-CoV, H5N1 avian influenza, and pandemic 2009-2010 influenza A H1N1 [12,13]. Initial reports from China, although anecdotal, have been encouraging: infusion of convalescent plasma into critically ill patients has led to clinical improvement as defined by radiologic resolution of pneumonia, reduced viral loads and better survival rates. For example, in one study [1], 5 critically ill patients with laboratory-confirmed COVID-19 and acute respiratory distress syndrome (ARDS) received a transfusion of convalescent plasma containing SARS-CoV-2–specific antibody with a binding titer of >1:1000 and neutralization titer of >40. The convalescent plasma was obtained from 5 patients who had recovered from COVID-19 and was administered to the 5 enrolled patients in the study between 10 and 22 days after hospital admission. Antiviral agents and methylprednisolone were also administered, thus confounding any definite conclusions about the efficacy of plasma treatment. Following plasma transfusion, the clinical condition of the patients improved, including normalization of body temperature within 3 days (in 4 of 5 patients), decrease in sequential organ failure assessment score, rise in PaO_2/FiO_2, resolution of ARDS (4 patients at 12 days after transfusion), success in weaning off mechanical ventilation (3 patients within 2 weeks of treatment), and decline in viral loads with the virus becoming undetectable within 12 days. Of the 5 patients, 3 were discharged from the hospital after a length of stay of 53, 51, and 55 days, respectively, while 2 were in stable condition at 37 days after plasma transfusion. A pilot, non-randomized clinical study [2] of 10 critically ill patients infected with SARS-CoV-2 from 3 different hospitals in Wuhan also reported promising results. In this study, one 200 mL dose of convalescent plasma derived from recently recovered donors with neutralizing antibody titers above 1:640 was transfused into patients in addition to maximal supportive care and antiviral agents. The median time from onset of illness to transfusion was 16.5 days. After transfusion, the level of neutralizing antibody was maintained at a high value in 9 of 10 patients. Clinical symptoms significantly improved along with an increase of oxyhemoglobin saturation within 3 days, and inflammatory responses were reduced. There was also effective neutralization of the virus, with viral load undetectable after transfusion in 7 patients who

had previous viremia. No severe adverse effects were observed. Similarly, in a small clinical trial involving 38 patients in Hartford, CT, convalescent plasma was well tolerated, and there was moderate benefit [14].

Despite these initial encouraging reports, subsequent randomized clinical trials have reported conflicting results on the beneficial effects of passive immunization against COVID-19. In one study [15] from China involving 101 evaluable patients, there was minimal clinical improvement attributable to convalescent anti-SARS-CoV-2 plasma based on lack of statistical significance. Also, a similarly designed study in India [16] in a much larger group of patients showed only a limited survival benefit, although many patients with non-critical conditions experienced improved symptoms and oxygenation, and faster viral clearance relative to controls. A serious limitation of the latter study was the relatively low antibody titers (1:20-1:40) of the transferred plasma, which were much lower than in the Wuhan and Hartford studies [2, 14].

The U.S. Food and Drug Administration (FDA) has approved the conduct of clinical trials involving the use of convalescent plasma in the treatment of COVID-19 patients [17,18], along with testing the efficacy of passively transferred monoclonal antibodies directed against SARS-CoV-2 [19]. The FDA recommended that healthcare providers administer these immune-based products according to standard hospital procedures and institutional medical and nursing practices. The most encouraging results reported so far are from a Phase 2 clinical trial involving 452 participants in which a commercially produced monoclonal antibody for treatment of COVID-19 reduced the need for hospitalization in patients with mild-to-moderate COVID-19 symptoms, compared with untreated control patients [20, 21]. The antibody was directed against the spike protein of SARS-CoV-2, presumably preventing the virus from infecting cells of the treated patients.

By which mechanism is antibody-containing plasma or monoclonal antibodies potentially aiding the recovery of COVID-19 patients? The recovery response is likely based initially on a reduction in the number of virus particles circulating within the key target site for viral replication, the lower respiratory tract. Antibody presumably binds to viral antigens and, in the case of the virus spike protein, would interfere with attachment to the angiotensin-converting enzyme 2 receptor present on alveolar-epithelial type II cells [22]. Consequently, the virus would be unable to enter the host cell and begin the process of producing new virus particles. Another possibility is that antibody can cross-link the viral proteins so that uncoating does not occur, thus preventing viral replication.

The plasma sample goes through several processing steps to ensure its suitability and to optimize its effectiveness before it can be used to treat COVID-19 patients. These steps include rigorous serologic testing to look for high-titer anti-SARS-CoV-2 antibodies based on a detection system approved by the FDA or another governing body, such as an enzyme-linked immunosorbent assay (ELISA) with acceptable levels of specificity. To further guarantee the specificity of a positive test, consideration should be given to following up a positive ELISA with a confirmatory Western blot, as we previously suggested [23]. Following serologic testing, the functional activity of the plasma sample is determined using the plaque reduction neutralization test [24], modified to test for in vitro activity against SARS-CoV-2. Briefly, a suspension of virus is mixed with a plasma or purified antibody sample and then diluted samples are incubated for enough time (usually 1-2 hours) to enable the antibody to react with the virus. Plaque-forming units (PFUs) are counted after the virus-test sample suspension is placed onto a monolayer of cultured human target cells (in this case, a cell line of respiratory origin). After an incubation period lasting a few days, the number of PFUs is counted microscopically or by direct visualization using dyes that react with infected cells. PFUs represent areas of successful viral replication within discrete zones of the cell monolayer. A significant reduction in PFUs is a strong indication that neutralizing antibodies are present in the test sample, and presumably they would be effective against the virus in vivo following transfer.

Other investigators have pointed out additional concerns that need to be considered before widespread use of convalescent plasma is implemented [25]. These include biomedical/clinical, regulatory, and logistical issues, such as donor eligibility and recruitment, ensuring the plasma is free of other infectious agents, cross-match testing to ensure donor-recipient compatibility, defining when and how much of the transfused component should be given, and liability concerns associated with adverse events that may occur following the transfusion process. In most developed countries, however, guidelines and recommendations pertaining to most of these issues have already been standardized. Paramount among these concerns is the optimal timing for administration and how much immunotherapy should be given. Following the experience with rabies, it would seem logical that the best time to start treating COVID-19 patients with immune plasma or monoclonal antibodies would be soon after testing positive and/or during the early stages of infection when symptoms are relatively mild to prevent the patient from becoming severely ill. Depending upon the patient's response to the first transfusion, additional infusions should be considered to promote rapid and full recovery.

Notably, since Alex Azar's statement in June 2020, the number of COVID-19 cases, hospitalizations and deaths has continued to rise globally to exceedingly high levels, particularly in certain parts of the United States, Europe (e.g., Belgium, France, Spain, the Netherlands, and the United Kingdom), India and South America. Unfortunately, there are no signs that this trend will subside substantially in the near future, despite the World Health Organization and recognized international health experts [19, 26] urging constant vigilance in maintaining strict protective measures. Therefore, passive immunization with anti-SARS-CoV-2 plasma or immunoglobulins (either purified or monoclonally-derived) should continue to be a major consideration for evaluation as a therapeutic option against COVID-19. Consideration should also be given for use of this type of immunotherapy for early post-exposure prophylaxis of individuals deemed to be at high risk for severe disease due to pre-existing conditions, such as diabetes, older age, obesity, and cardiac disease. If current ongoing [27] and future clinical trials provide positive results, passive immunization will likely be of much value, at least until more effective drugs, or safe and effective vaccines that can confer long-lasting immunity, become readily available to anyone who wants to receive them (although there is no guarantee vaccines will be universally accepted by the general population) [26].

4. Conclusion

The use of passive immunization is a more than century-old procedure designed to treat an infectious disease-related disorder when a specific antimicrobial agent is either unavailable or its efficacy is insufficient to reverse the disease process and cure the patient. With the lack of highly effective antiviral drugs or enough of a durable vaccine immediately available to everyone, convalescent plasma from patients recovering from a SARS-CoV-2 infection, as well as monoclonal antibodies, are now being seriously considered for treating COVID-19 patients, particularly those who are at risk of becoming critically ill. Although initial reports on the use of convalescent plasma have provided mixed results, additional rigorous clinical research trials are underway to determine whether this form of treatment should become part of routine patient care. A recently published study [28] showed that transfusion of a large cohort of recently hospitalized COVID-19 patients with high titer anti-spike receptor binding domain IgG, present in convalescent

plasma, significantly reduced mortality, and thus further supports the clinical application of immunotherapy as a therapeutic option under these conditions.

Declarations

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