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The Disillusioned Comfort with COVID-19 and the Potential of Convalescent Plasma and Cell Therapy

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Abstract

Coronavirus disease 2019 or COVID-19 is highly infectious, which can lead to acute and chronic debilitating symptoms, as well as mortality. The advent of safe and effective vaccines or antiviral drugs remains distant in the future. Practical public health measures, such as social distancing, hand washing, and wearing a face mask, are the current recommended guidelines by the Centers for Disease Control and Prevention for limiting the spread of the virus. Weakened immune system and aberrant inflammation represent a major pathological symptom of COVID-19 patients. Based on the unique immunomodulatory properties of both convalescent plasma and stem cells, we discuss here their potential use for treating COVID-19.

Keywords

virus, mesenchymal stem cells, vaccine, immunoglobulin, convalescent plasma

The Disillusioned Comfort

Three common vices to avoid: smoking, gambling, and riding a motorcycle! The dire statistics in the United States prove staggering, in that these vices lead to life-threatening diseases, financial losses, and bodily injuries.

Smoking stands as the main cause of lung cancer, contributing to 80% and 90% of lung cancer deaths in men and women, respectively[1]. Men and women who smoke are 23 times and 13 times, respectively, more likely to develop lung cancer compared to never smokers[1].

The average debt generated by a man addicted to gambling ranges from $55,000 to $90,000, while women gamblers average $15,000 of debt[2]. In extreme cases, gambling can result in serious legal problems or financial ruin. Indeed, more than 20% of compulsive gamblers end up filing for bankruptcy because of gambling losses[2].

In the United States, motorcyclists are about 26 times more likely to die in a crash than someone riding in a passenger car and are five times as likely to be injured[3]. The lack of any substantial protective barriers between a motorcycle and the road, as well as the difficulty that other motorists may have in anticipating and seeing a motorcycle, leave riders prone to serious injury in the event of an accident[3].

Currently, the world, which is under virus attack, has added another form of vice that can be as devastating as these three vices. This new vice refers to "disillusioned comfort," defined as our ignorance of the dangers of the virus, giving us a false blanket of security that we can continue to live life as it is. As of July 20, 2020, according to data collected by Johns Hopkins University, there are about 15 million confirmed coronavirus cases and close to 615,000 deaths worldwide[4]. The United States now leads the world with about 3.8 million confirmed COVID-19 cases, and more than 140,000 deaths. The US numbers have reached the estimates made by Dr Anthony Fauci of the National Institute of Allergy and Infectious Diseases, who projected in late March 2020 that there will be at least 100,000 deaths in America even in a best-case scenario compared to the originally reported 14 American cases on February 26, 2020[5]!

The projected deaths seemed initially unfathomable with only a few known cases in early 2020[5]. Many scenarios may contribute to the rapid uncontained virus spread, but the majority of the multifold increments in infections and deaths

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may be likely accounted for by human behavior, especially those who do not take seriously the Centers for Disease Control and Prevention (CDC)-recommended public health practices of social distancing and proper hygiene, i.e., washing of hands with soap and water. Moreover, the virus-associated microdroplets can stay airborne for up to 3 h[6], necessitating the need for wearing a face mask to protect ourselves and others. The combination of 6-feet social distancing, 20-s hand washing, and wearing N-95 or other CDC-recommended face masks has been reported to curve the spread of virus[7,8], but quantifying the risk of reducing these strategies remains debatable. Notwithstanding, the CDC continues to stress practicing social distancing, hand washing, and wearing a face mask in order to inhibit future deaths from the virus. Otherwise, we are living in our "disillusioned comfort," similar to the misguided security blanket we afford to negative consequences of smoking, gambling, and riding a motorcycle.

The Spanish Flu

A historical review of virus-related pandemics reminds us of the 1918 Spanish flu, which infected 500 million and estimated to have killed about 17 million to 50 million people[9]. The Spanish flu resembles COVID-19: both are respiratory viruses with the precursor viruses mutating in animals thereafter infecting humans, and with fast-progressive cases from infection to symptom onset with viral consolidation in the lung and eventually mortality primarily from pneumonia[9–12]. Eerily enough, the key promoters of such high mortality rate of Spanish flu were overcrowding and poor hygiene—the same two factors that define our disillusioned comfort for COVID-19. Human behavior to the Spanish flu outbreak stands as the major determinant for the pattern of the pandemic's high mortality rate[13]. Again, the same human response, or lack thereof, that faces COVID-19.

A Spanish flu vaccine was not available during the 1918 pandemic, with the virus remaining largely unknown for almost a century when the molecular underpinnings of the virus were finally characterized in 2005[14]. Similar to COVID-19, the 1918 Spanish flu was first detected in the month of January, but after the second wave in August of that year, the number of cases dropped significantly and almost disappeared by the year's end. Without a vaccine, the rapid decline in infection and mortality after the second of the two lethal waves of Spanish flu was attributed to better treatment of pneumonia and the virus mutating to a less dangerous strain.

Three key lessons from the Spanish flu pandemic are worthy of consideration. First, those who survived the first wave developed immunity against the virus; thus, these individuals were immune to the second wave of the Spanish flu, providing us a glimpse on the future of passive immunity-based treatment against the virus. Indeed, clinical trials have recently been initiated using plasma collected from recovered COVID-19 patients based on the concept that these individuals have likely harbored strong immune responses such as antibodies that target the proteins found on COVID-19[15]. Second, that the end of Spanish flu cases by 1920 might have signaled the eradication of the pandemic may not be completely true. Evidence of slow-progressive cases of Spanish flu has been linked to secondary bacterial pneumonia, possibly affecting the brain, which results in neurological disorders, in particular encephalitis lethargica, that recorded its outbreak in the 1920s, in children[16], which was suggested to manifest in adulthood as Parkinson's disease[17] but such a pathological link being merely coincidental has been debated[18]. Similarly, the potential long-term consequences of COVID-19 to brain disorders, and other comorbid diseases, warrant critical research avenues as we tackle this pandemic and its associated not-so-apparent mini outbreaks. Third, that overcrowding in military camps and lack of sanitation due to poverty during World War I contributed to Spanish flu pandemic draws our attention to the key pressing issue of human behavior.

The Potential of Convalescent Plasma

Regenerative medicine may play a key role in treating COVID-19. The ongoing clinical trials of infusing convalescent plasma stand as a potent cell therapy for COVID-19 patients. This investigational treatment uses plasma that contains antibodies to severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2, the virus that causes COVID-19. Plasma therapy entails the use of plasma or specific, fractioned, antibodies, along with other immunoglobulins (IGs) and possibly other therapeutic molecules harvested from immunized individuals or convalescent persons[19]. Plasma therapy has a long history of safety, and even efficacy, since the Spanish flu in 1917–1918[19,20]. While the mechanism of action of plasma therapy remains not fully understood, the functional benefits have been largely ascribed to the purified neutralizing antibodies of the convalescent plasma[19,20]. A meta-analysis of English-language journals from 1918 to 1925 reveals that the overall mortality rate was 16% among treated patients compared to 37% among controls, indicating difference in fatality between the treatment and control groups at 8% to 26%[20]. Note that the meta-analysis study[20] was based on only eight studies with many methodologic limitations, including lack of blinding, randomization, or placebo-controlled arm. Subsequent to the Spanish flu pandemic, the treatment with convalescent plasma has been studied in similar outbreaks of respiratory infections, such as the 2003 SARS-CoV-1 epidemic, the 2009–2010 H1N1 influenza virus pandemic, and the 2012 MERS-CoV epidemic[19,20]. Whereas small clinical trials and anecdotal accounts of convalescent plasma suggest safety and efficacy of plasma treatment in these previous outbreaks[21], its potency in COVID-19 requires carefully designed and rigorous assessment of these clinical trials as discussed subsequently.

The still limited evidence but massively accumulating interest in the safety and efficacy of convalescent plasma treatments may provide the basis for compassionate use of these therapies for COVID-19 in the United States. Indeed, a review of the literature from 2020 alone shows that there are already 152 publications, although most are review and commentary articles, and protocol descriptions, on the theme of convalescent plasma treatments for COVID-19. Notable clinical research reports include: (1) The small study on six Chinese patients diagnosed with COVID-19, who subsequently received ABO-compatible convalescent plasma, demonstrating immediate increase of antibody titers in two patients and elimination of the virus in two other patients[22]. (2) Another small study on ten severe COVID-19 Chinese patients revealed that nine patients displayed increased neutralizing antibody titers, and the viral load in seven patients becoming undetectable by day seven post-infusion of convalescent plasma, but only 3 exhibited improved respiratory function[23]. (3) Another study on five critically ill COVID-19 patients revealed viral loads decreased and became negative by day 12, and three patients were discharged by about 50 days, while 2 patients remained in stable condition at 37 days after convalescent plasma infusion[24]. (4) In six end-stage COVID-19 patients, convalescent plasma effectively induced viral shedding with the SARS-CoV-2 RNA undetectable by day 3 post-infusion of convalescent plasma, but five patients eventually died[25]; (5) In South Korea, two severe COVID-19 patients treated with convalescent plasma with both showing favorable outcomes including being weaned from mechanical ventilators and/or extubated with SARS-CoV-2 negative after days 20–26 of convalescent plasma infusion[26].

From these five small clinical case reports, the following protocol specifics may require optimization in order to further assess the safety and efficacy of convalescent plasma treatment for COVID-19. (1) The small number of patients is clearly a limiting factor in all these studies. (2) Once the number of patients to be enrolled is increased, there is a need for proper control and randomization of treatments, as well as blinding of the treating physicians. (3) The timing of convalescent plasma infusion and its doses and the need for booster shots will require careful considerations. For example, in Duan's study[23], patients were infused with convalescent plasma at around 16 days of symptom onset, while in Shen's study[24], patients received convalescent plasma at around 21 days after symptom onset. The recognition of positive outcomes may depend on the early initiation of convalescent plasma infusion and may be the need for subsequent booster treatment. Additionally, in Duan's study[23], one dose of 200 ml of convalescent plasma with the neutralizing antibody titers above 1:640 was specified. In Shen's study[24], it was 400 ml of convalescent plasma with the neutralizing antibody titer set at 1:1000. Finding the optimal timing and dose will improve the safety and efficacy of convalescent plasma. (4) Related to the timing of convalescent plasma infusion, the severity of the disease is likely to impact on the treatment outcomes. In all these five clinical studies, it is understandable that because convalescent plasma treatment remains experimental, the target population is initially the severe or critically ill patients, who have high mortality and worst morbidity, which may mask the potential functional benefits of the treatment. Future treatments may need to enroll those mild COVID-19 patients or those who are in the early stages of the disease. (5) The treatment profile of the patients will need to be carefully charted, noting the drugs and ventilator supportive care among others, in order to delineate the true effects of convalescent plasma infusion or the possibility of additive effects of convalescent plasma with antiviral agents and immunomodulatory drugs. (6) The patient's preexisting health condition is equally an important factor in treatment outcomes and disease progression. In addition to COVID-19, immune-related diseases may worsen the presenting pathology, which will likely require not only eliminating SARS-CoV-2 but also addressing the multifactorial manifestations of disease. (7) The age, gender, ethnicity, genetic factors, and other pertinent patient profiles will need to be factored into the final analysis of the treatment outcomes as this will further guide optimization of the convalescent plasma treatment. Clearly, there remain several factors in order to advance the widespread use of convalescent plasma for treating COVID-19. However, at the minimum, the transparency in reporting the detailed methods and treatment outcomes will ensure rigorous assessment of the true functional effects of convalescent plasma. A glance at the clinicaltrials.gov website reveals 173 ongoing clinical trials on the use of convalescent plasma for COVID-19. Recognition of the factors mentioned earlier will allow direct comparisons of protocols and safety and efficacy readouts across these clinical trials and further evaluate the potential of convalescent plasma for COVID-19.

The Emerging Science and Clinical Trials of Stem Cell Therapy

As noted earlier, plasma therapy involves the use of convalescent plasma, but also the plasma-active components specifically IGs. Under the guise of passive immunity against pathogens in viral epidemics, convalescent plasma is considered the first-line passive immunotherapy since the 1918 Spanish flu and the modern viral epidemics (2003 SARS-CoV-1, 2009–2010 H1N1, and 2012 MERS-CoV), and now Covid-19[27,28]. The last several decades have witnessed advancements in molecular technology toward the purification and manufacture of plasma-derived IG as a drug therapy[27,28]. Toward this end, human IG formulations have been advanced as the second line of passive immunotherapies against these diseases[27,28]. The rationale of human IG for intravenous use (IVIG) is thus based on the similar etiology and inflammatory pathogenesis of SARS-CoV-2 infection to diseases for which the use of IVIG has already been approved by the FDA[29]. According to clinicaltrials.gov,

there are 40 trials using IG for COVID-19. Similar to convalescent plasma treatment, the mechanism of action ascribed to IG therapy is to boost the immune response of the body against SARS-CoV-2.

Along this line of boosting the immune system of COVID-19 patients, mesenchymal stem cells (MSCs) possess secretory functions of robust immunomodulatory biologics[30–34]. Because COVID-19 manifests a massive inflammatory pathology in the lung, characterized by pulmonary edema and an over-reactive immune response, which can lead to hypoxia, respiratory distress, and lung damage, finding a treatment designed to sequester this aberrant inflammation and immune response may prove beneficial against COVID-19[33]. Accordingly, cognizant that abrogating COVID-19 may depend on the patients' properly functioning immune system, the transplantation of MSCs has been proposed to propel the host immune system to effectively eliminate the virus. MSCs display potent anti-inflammatory and immunomodulatory properties. Indeed, our group and many others have shown that MSCs exert anti-inflammatory effects and even repair lung damage[34]. Although MSCs have been the major cell type for cell therapy in COVID-19, non-MSC stem cells, such as umbilical cord blood monocytes[35,36], that similarly target the inflammatory and immune pathways and promote other regenerative mechanisms (e.g., tissue repair), are also being tested. Interestingly, intravenous administration of MSCs has the natural preponderance to migrate preferentially to the lungs allowing for the first-pass treatment of pulmonary diseases[33,34], such as COVID-19. Moreover, the long track record of safety profile of MSCs for hematologic diseases may expedite their clinical entry for novel indications; indeed, clinicaltrials.gov reveals 31 ongoing studies using stem cell therapy for COVID-19. Preliminary reports in China and the United States suggest solid safety outcomes in patients who have received MSCs and their exosomes[31,32]. Together with convalescent plasma and IG treatments, stem cell therapies may offer an innovative approach in fostering immunomodulatory regulation of COVID-19. Moreover, although the lung stands as the main pathological organ in COVID-19, recent studies have implicated extra-lung organs, including the heart and the brain, as well as the gut, suggesting that targeting these organs may prove beneficial in treating the disease. Indeed, combining the envisioned vaccines and immunomodulatory treatments with novel strategies, such as altering the gut microbiome[37–41], will likely enhance the overall prognosis of COVID-19.

Conclusions

Science and medicine may take time to advance a vaccine, antiviral drug, convalescent plasma treatment, and IG and stem cell therapies to the clinic. Mortality rate ranges from 0.1% to as high as 10%, with the elderly (>65 years of age) and those with preexisting immune-related and inflammatory diseases (hypertension, diabetes, heart diseases), showing higher incidence of mortality[42–44]. Given the morbidity not only in the acute stage, but the realization of equally devastating long-term effects, including cardiovascular and cerebrovascular consequences[45–49], warrants immediate action to at least lessen the spread of the virus. Without access to the vaccine and other proven therapies, just like in 1918 Spanish flu era, the best course of action for the meantime is practicing social distancing and good hygiene, which represents a logical strategy to curve the course and to address the disillusioned comfort of COVID-19.

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