COVID-19 Convalescent Plasma Therapy

Subjects: Respiratory System

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Translating the experience from previous viral epidemics, passive immunotherapy by means of plasma from individuals recovered from COVID-19 has been intensively investigated since the beginning of the pandemic.

Keywords: convalescent plasma ; COVID-19 ; hyperimmune plasma ; SARS-CoV-2 ; therapy

1. Introduction

Coronavirus disease 2019 (COVID-19) is a still ongoing pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), initially discovered in Wuhan, China, at the end of 2019 and quickly disseminating all over the world [1]. As of 1 March 2021, the infection had already affected approximately 120 million people and caused nearly 2,500,000 deaths worldwide, and the rates are still increasing, according to World Health Organization (WHO) bulletins [2]. Unfortunately, current treatment options are limited. Corticosteroid therapy has been shown to significantly reduce 28-day all-cause mortality in severely ill COVID-19 patients compared with usual care or placebo (odds ratio (OR) 0.66; 95% confidence interval (CI), 0.53−0.82]; $p < 0.001$) [3]. Among the few available therapeutic options, the use of plasma from COVID-19-recovered donors has been the object of an intense research from investigators during the last 12 months [4][5]. Convalescent plasma (CP), containing neutralizing anti-viral antibodies, is a form of passive immunotherapy that has been used for the treatment and prevention of infectious diseases for more than 100 years [6]. CP was successfully used in the treatment of severe acute respiratory syndrome (SARS) in 2002, Middle East respiratory syndrome (MERS) in 2012, and the 2019 H1N1 pandemic [6]. A meta-analysis of 32 SARS and severe influenza studies showed that CP treatment was associated with a significant reduction of mortality (pooled OR 0.25; 95% CI, 0.14−0.45) [7].

Following the negative results from certain randomized controlled trials (RCTs) [8][9], some scientists have claimed that CP does not work against COVID-19. However, in our opinion, the issue is wrongly posed. Indeed, assuming that CP containing high-titer anti-COVID-19 neutralizing antibodies is effective in suppressing viral replication [10][11], the correct question these scientists should pose is “why does CP not work in our study?”. This is probably because there are some critical issues in the study design. However, to respond correctly to this question, one must take a step back, separately analyzing the three key factors determining the clinical effects of CP therapy. We have called them “pillars”, translating our transfusion experience in the patient blood management (PBM) setting. The three “pillars” of CP therapy are the treatment (hyperimmune plasma), the disease (COVID-19), and the patients (Figure 1). This narrative review aims at elucidating the clinical role of these three CP-related factors.

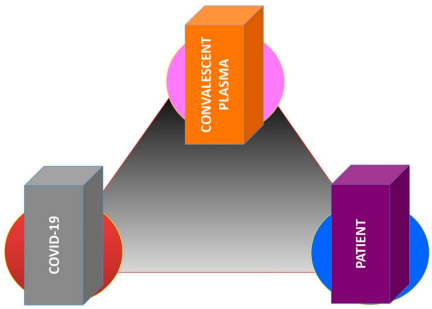

Figure 1. The three pillars of anti-COVID-19 convalescent plasma therapy.

2. The Disease

A critical issue for assessing the CP efficacy is its timing of infusion in COVID-19 patients. At the beginning of the pandemic, CP was transfused in more critical patients, such as those hospitalized in intensive care units (ICU) and under mechanical invasive ventilation. For these patients, indeed, there was at that time no therapeutic chance. The RCT by Li and colleagues [12], published as early as August 2020, did not demonstrate a statistically significant difference in 28-day mortality between the CP-treated and standard treatment groups. However, stratifying patients by disease severity

(severe or life-threatening COVID-19), the researchers observed a statistically significant difference in time to clinical improvement within a 28-day period in the group treated with hyperimmune plasma. Therefore, this study highlighted that CP must be administered at an early stage of the disease and not in an advanced phase in order to have the maximum effect. This observation is also plausible with the high replication kinetics of SARS-CoV-2 and with the mechanism of action of hyperimmune plasma, considering that the blocking of viral replication during the initial phase of COVID-19 is also able to prevent the activation of inflammatory and coagulative cascade, often irreversible, which instead characterizes the advanced stage of the disease where, unfortunately, the viral anti-replicative activity of CP is, at that stage, ineffective. In other words, it is essential to prevent the COVID-19 from progressing through the early administration of hyperimmune plasma and the patient from undergoing invasive mechanical ventilation and being transferred to the ICU. In fact, once intubated and in the ICU, the patient is at a very high risk of mortality linked above all to superinfections favored by immunosuppression caused by virus-associated lymphopenia [12]. Paradoxically, a consistent number of critically ill COVID-19 patients die without having SARS-CoV-2 infection (negative search for SARS-CoV-2 nucleic acid), but for its deleterious consequences. Another RCT conducted by Libster and colleagues [13] enrolled older individuals with COVID-19 who were identified in the outpatient setting within 48 h of symptom onset. The patients who were given CP within 72 h of symptom onset had a 48% reduced risk of progression to severe respiratory disease. The benefit of administering CP early in the disease course is further corroborated by data from observational studies. An analysis of a cohort of 3082 patients in the U.S. Expanded Access Program (EAP) found that high-titer CP given less than 72 h after hospital admission conferred a survival benefit when compared to those receiving CP later in their hospital stay [14]. A matched propensity score study published by Salazar and colleagues found the greatest effect when patients were given CP within 44 h of hospital admission [15]. Thus, thanks to these and other similar studies [16], nowadays we are aware that CP must be administered early, possibly within 72 h from symptom onset [17]. Other RCTs [18][19] did not find clinical benefit from later CP administration. On the basis of the newer literature evidence, the U.S. Food and Drug Administration (FDA) recently revised the Emergency Use Authorization (EUA) of COVID-19 CP, authorizing its use at high titer for the treatment of hospitalized COVID-19 patients early in the course of disease and those hospitalized with impaired humoral immunity [20]. Finally, clinical studies are needed to verify the possible resistance of viral mutations to CP therapy observed by in vitro studies [21].

3. Conclusions

After a careful analysis of the published literature studies regarding the main factors implicated in CP clinical efficacy, i.e., the CP product and the characteristics of COVID-19 patients and of the disease, we realized that there are still some gray zones and unanswered questions in this area. Nevertheless, the great majority of available literature agrees on the efficacy of CP in blocking promptly SARS-CoV-2 viral replication. That said, it is unlikely that this biological activity by CP has no clinical consequences—it is only a question of knowing how to identify them. The current literature evidence is clearly summarized by the recent interim recommendations from the AABB [18]. Besides the safety of CP, which has been considered comparable to standard non-hyperimmune plasma, researchers have pointed out high-titer and transfusion as close to symptom onset as possible as the main predictors of effectiveness of CP. Thus, considering the results from the literature supporting the efficacy of early treatment of COVID-19 patients, an outpatient CP transfusion approach in order to treat earlier COVID-19 patients preventing hospitalization (with all the risks associated with immobilization and hospital co-infections) could be reasonable. This argument is, however, not speculative but based on the clinical practice observation that CP transfused to elderly patients with moderate-severe COVID-19 living in long-term care facilities is safe and effective in blocking disease progression and reducing the mortality risk by 65% [22]. Unfortunately, in Italy (and other European countries), CP can be administered only in hospitals within experimental trials or for compassionate use, and this greatly limits its widespread and potentially more appropriate clinical use.

Since we would have to live with COVID-19 for a few more months before reaching mass immunity with vaccines, we hope that on the basis of further clinical evidence also in Europe, as in the USA, governments will take the necessary actions in order to favor the emergency use of CP even outside the hospital setting. In parallel, dose-finding trials aimed at better tailoring CP therapy to patients' characteristics are welcomed.

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