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Review

COVID-19 neutralizing antibody-based therapies in humoral immune deficiencies: A narrative review

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ABSTRACT

The outbreak of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), generated an unprecedented global health and social emergency. Despite many efforts from clinicians to develop effective anti-COVID-19 treatment protocols, no specific therapy is currently available. Among anti-viral agents, convalescent plasma (CP) from recovered patients is the object of intense research following the first positive reports in severe COVID-19 patients. Passive immunotherapy the rationale to provide higher benefits in COVID-19 patients with humoral immune deficiencies, such as those with solid and hematologic cancers, patients with primary and acquired immunodeficiencies, and recipients of solid organ and hematopoietic stem cell transplants. The aim of this narrative review will be to critically discuss the literature evidence on CP use in these categories of patients.

1. Introduction

Towards the end of 2019 a novel betacoronavirus, causing a severe acute respiratory syndrome (SARS) and thus named SARS-CoV-2, was associated with an epidemic in Wuhan, China [1]. From there, SARS-CoV-2 spread quickly throughout China and globally generating an unprecedented health, social and economic crisis. On March 11, 2020, the World Health Organization (WHO) declared the rapidly spreading coronavirus outbreak a Public Health Emergency of International Concern [2]. This new virus posed a major challenge among physicians because it had no specific pre-existing therapy. As a consequence, the therapeutic efforts against coronavirus disease 2019 (COVID-19) were initially focused on optimizing respiratory care, managing thrombotic and inflammatory complications by using anticoagulation and corticosteroids, and repurposing existing antiviral therapies [3]. Unfortunately, almost all these initially promising agents (i.e., hydroxychloroquine, lopinavir/ritonavir, and remdesivir) failed to demonstrate a universal beneficial effect [4–6]. Considering the lack of effective anti-SARS-CoV-2 drugs and the pivotal positive experience from China [7], convalescent plasma (CP), an ancient therapy used with apparent success in many epidemics and outbreaks since the 1918 Spanish flu [8, 9], was proposed for COVID-19 [10]. Following the first case-series and

cohort studies suggesting the safety and efficacy of CP in COVID-19 [11–13], a few randomized controlled trials (RCTs) or propensity score-matched control studies have been published on CP therapy against COVID-19, with conflicting results [14].

Although various immune and non-immune mechanisms have been hypothesized to explain the effect of CP, the most important is likely due to the presence of neutralizing antibodies that, thanks to their capacity of inhibiting SARS-CoV-2 entry into target cells, prevent the deleterious consequences of viral replication (i.e., hyper-inflammation and hyper-coagulability) [15]. **It follows that the efficacy of CP for treatment of severe COVID-19 is closely linked to its content of neutralizing antibodies and to the timing of administration, having high titer (>1:160) CP units infused early (within 7 days from symptoms onset) the greatest chance of success [16].** Passive immunotherapy by means of CP transfusion has been particularly attractive for those patients with a defect in humoral immune response (such as patients with solid and hematologic cancers, transplant recipients and patients with congenital and acquired immune deficiencies), and indeed a number of case reports and case-series have been published. **This narrative review will focus on this issue.**

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2. Search methods

As a search literature strategy, the medRxiv, MEDLINE and PubMed electronic databases were searched for publications on the use of CP in COVID-19 patient with immune deficiencies from January 1, 2020 to December 20, 2020, using English language as a restriction. The Medical Subject Headings and key words used were: “convalescent plasma”, “convalescent serum”, “immunosuppression”, “hyperimmune plasma”, “therapy”, “SARS-CoV-2”, “COVID-19”, “coronavirus”, “neutralizing antibodies”, “immune deficiency”, “transplantation”, “congenital”, “alymphocytosis”, “agammaglobulinemia”, “hypogammaglobulinemia”, “cancer”, “malignancy” and “oncohematology”. We also screened the reference lists of the most relevant review articles for additional studies not captured in our initial literature search.

3. Solid and hematologic cancers

Patients with malignancies are particularly vulnerable to infections, including SARS-CoV-2, due to their immunodeficiency status secondary to the underlying disease and anti-cancer chemotherapy [17]. The lack of a significant neutralizing antibody response and the impaired clearance of SARS-CoV-2 in these immunocompromised patients represents the rationale for the use of passive CP immunotherapy [18,19], which has been explored by several investigators [17–33]. The largest published clinical experience is the case series by Tremblay and colleagues [17]. The authors identified, in the frame of an expanded access protocol, 24 patients with cancer, 14 of whom with a hematological malignancy, treated with CP. Most patients (62.5 %) were on anti-cancer therapy at the time of COVID-19 infection. Although 10 of 24 patients (41.7 %) died, non-intubated patients had favorable outcomes. In addition, a significant decrease of inflammatory markers (i.e., C-reactive protein, CRP) was observed after 3 days of CP treatment. Transfusion reactions were uncommon and mild, occurring only in three patients. Based on these results, the authors concluded that CP may be a promising therapy in cancer patients with COVID-19 [17]. The majority of the literature body pertains, however, to patients with onco-hematological disorders, who have an increased mortality risk as compared with the general population [34,35]. Hueso and colleagues [18] reported a series of 17 consecutive patients, of whom 15 had hematological malignancies, with profound B-cell lymphopenia due to anti-CD20 monoclonal antibody therapy and prolonged COVID-19 symptoms, negative SARS-CoV-2 IgG/IgM serology, and positive viral RNA-emia who were treated with 4 units of COVID-19 convalescent plasma. No serious adverse effects were observed during or after CP therapy. Within 48 h of transfusion, all but 1 patient experienced an improvement of clinical symptoms, including reduced oxygen requirements, which correlated strongly with the virological clearance documented in all the 9 patients evaluated. The hyper-inflammatory status faded within a week. Only 1 patient who needed mechanical ventilation for severe COVID-19 disease died of bacterial pneumonia. Interestingly, Betrains and colleagues [31] analyzed 5 patients with COVID-19 and B-cell lymphoma treated with anti-CD20 therapy and demonstrated that B-cell depletion was associated with decreased neutralized antibody formation, reduced viral clearance and protracted clinical manifestations of SARS-CoV-2 infection. Treatment with CP was accompanied by an increase in neutralizing antibody titers in all patients and by a clinical response in all but one patient [31]. Other similar cases have been reported in the literature [28,30,32], suggesting that lymphoma patients with B-cell depletion and protracted SARS-CoV-2 infection may be excellent candidates for passive transfer immunity by COVID-19 CP therapy. In a recent review, Senefeld and colleagues [36] identified 54 patients with hematological malignancies, including lymphoma, leukemia, multiple myeloma and myelodysplastic syndrome, transfused with CP in 18 peer-reviewed reports. A majority of patients recovered following CP transfusion, with many demonstrating rapid clinical improvements shortly after transfusion. Notably, a patient with persistent (> 100 days) COVID-19 and

with lymphoma-associated B-cell immunodeficiency demonstrated rapid reductions in fever, oxygen requirements and lung infiltrates immediately after two CP transfusions separated by approximately 90 days [29].

4. Congenital and acquired immune deficiencies

Immunodeficiency syndromes, being characterized by a blunted endogenous antibody response to infectious agents, including COVID-19, are the ideal setting for evaluating the clinical effect of CP [37–43]. Regarding the primary immunodeficiency, a recent review pre-published by Senefeld and colleagues [36], after a systematic search strategy, identified in the literature 11 patients (1 with autosomal agammaglobulinemia, 6 with X-linked agammaglobulinemia and 4 with common variable immunodeficiency). All patients with agammaglobulinemia demonstrated clinical improvement and symptom resolution following CP transfusion, with 3 patients improving rapidly and demonstrating SARS-CoV-2 serum antibodies after passive immunotherapy [36]. Three of the 4 patients with common variable immunodeficiency and severe or life-threatening COVID-19 survived following CP therapy, including 2 patients under mechanical ventilation or extracorporeal membrane oxygenation (ECMO) [36].

The clinical course of COVID-19 in such immunocompromised individuals is peculiar and particularly dangerous, being characterized in most cases by a prolonged viral shedding with SARS-CoV-2 RNA detected up to 60 days since symptom onset [44]. Van Damme and colleagues [41] reported the impressive case of a 37-year-old male with a common variable immunodeficiency and persisting fever and detection of viral RNA that could be weaned from ECMO and mechanical ventilation within 2 days. Another interesting case was that reported by Mira and colleagues [39]: a 39-year-old male with X-linked (Bruton) agammaglobulinemia developed a life-threatening COVID-19 with bilateral pneumonia refractory to hydroxychloroquine and non-specific intravenous immunoglobulin. Due to the persistence of the viral infection and the documentation at lymphocyte phenotype from bronchoalveolar lavage of an impaired T-lymphocyte and NK-cell activity, in addition to the absence of functional B cells, high-titer (1:320) CP was transfused for compassionate use. The CP administration was followed by a rapid symptom recovery (after 24 h) and viral clearance of the virus (after 48 h), which resulted also in the resolution of bilateral lung lesions (after 1 week). This improvement was accompanied by the restoration of depleted peripheral T-lymphocyte subpopulations.

Patients with acquired immunodeficiencies and COVID-19 are also at increased risk of morbidity and mortality due to the B- and T-cell depletion associated with the autoimmune disorders and to the common use immunosuppressive therapy. Aksoy and Oztugan [42] reported the case of a 46-year-old woman with myasthenia gravis treated with immunosuppressive drugs with severe COVID-19. The use of CP resulted in a rapid clinical improvement, thus avoiding the need for the planned invasive mechanical ventilation. Ye and colleagues [43] reported the case of a 63-years old female with Sjogren syndrome and COVID-19-associated bilateral pneumonia. The treatment with CP was accompanied by the reduction of the density of the multifocal ground glass opacities typical of SARS-CoV-2 infection and the patient was discharged 6 days after CP transfusion.

5. Transplant recipients

Only a paucity of data has been published on the clinical course of COVID-19 in recipients of solid organ and hematopoietic stem cell transplants [45–47]. Even fewer data are available on the possible treatments for viral infection in such immunocompromised patients, including the CP use [48–54].

Regarding passive immunotherapy in hematopoietic stem cell transplantation (HSCT) patients, it should be outlined that an adaptive specific immune response to infection is formed 4–6 months after

allogeneic HSCT and may even be delayed in the case of GVHD and immunosuppressive therapy. Thus, the lack of an immune reconstitution and persistence of secondary immunodeficiency can lead to the severe course and poor prognosis of SARS-CoV-2 after HSCT. Balashov and colleagues [48] reported the case of a 9-month-old girl with juvenile myelomonocytic leukemia who received a haploidentical HSCT and was then chronically treated with steroids and other immunosuppressant agents due to the development of an acute grade III graft versus host disease (GVHD). Forty-three days after the detection of SARS-CoV-2 infection the patient developed a poly-segmental bilateral pneumonia, successfully treated with tocilizumab and 3 doses of CP [48]. The persistence of SARS-CoV-2 infection and the delayed development of lung lesions reported in this interesting case are in accordance with the prolonged impaired immune status after HSCT. Karatas and colleagues [49] reported the case of a 61-year-old man with an Hodgkin lymphoma in remission and a peripheral T-cell lymphoma treated with autologous HSCT. The patient developed a severe SARS-CoV-2 infection and experienced clinical improvement after CP transfusion, although his viral shedding remained positive at reverse-transcription polymerase chain reaction (RT-PCR).

Regarding COVID-19 solid organ transplant recipients, a recent systematic review and meta-analysis by Raja and colleagues [55] identified 215 studies including 2772 transplanted patients (1500 kidney, 505 liver, 141 heart, 97 lung, 1 face, and 43 combined transplants). Although CP was utilized only in a minority of patients (33 patients enrolled in 13 studies), the mortality rate in this subgroup seemed to be lower than that recorded in the entire population of patients (12.9 % versus 18.6 %, respectively). In their recent pre-published review, Senefeld and colleagues [36] identified 9 articles reporting 29 COVID-19 patients receiving immunosuppressive therapies for previous solid organ transplants and transfused with hyperimmune plasma ad. In most case CP administration was accompanied by improved clinical symptomatology and oxygen requirements and reduction in hospital stay. A clinical beneficial effect associated with passive immunotherapy was even seen in the extreme case of a liver transplant recipient with a life-threatening COVID-19: the patient rapidly recovered following a CP transfusion received during a seventeen day medically-induced coma due to COVID-19 complications [56].

6. Conclusions

Only a few descriptions of patients with humoral immunodeficiencies and SARS-CoV-2 infection treated with CP have been published so far. Among them, COVID-19 patients with primary and secondary immunodeficiencies could be the ideal candidates for passive immunization, since a consistent proportion of these patients is unable to mount adequate antiviral responses to SARS-CoV-2 and thus may benefit from the antibody burst supplied by hyperimmune plasma. Also transplanted patients represent a unique group candidate for CP therapy: their long-lasting immunosuppression, indeed, is responsible for the inability to clear the virus and the prolonged viral shedding and exposes them to the risk of severe clinical complications from COVID-19, that can occur also several months from SARS-CoV-2 infection. A concern is related to the duration of SARS-CoV-2 replication in these patients, with accelerated viral evolution reported in several cases [57,58]: neutralizing antibody-based therapeutics exerts selective pressures on the Spike protein. Hence sub-neutralizing doses should be carefully avoided and genomic studies should be promptly initiated in cases with loss of clinical response.

Finally, it should be highlighted that most patients enrolled in ongoing RCTs evaluating CP efficacy are not immunocompromised. Therefore, adequately powered RCTs and registries dedicated to this special groups of patients should be planned in order to assess the clinical beneficial effect of CP therapy.

Declaration of Competing Interest

The authors report no declarations of interest.

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