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Controversies in COVID-19 pandemic: the case of convalescent plasma

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Abstract

The SARS-CoV-2 pandemic has caused an unprecedented health and social crisis worldwide. In this paper we summarized the different therapeutic actions planned from the two sides of the Atlantic Ocean (USA and Europe) to fight the initial phase of COVID-19 pandemic, with an emphasis on passive immunotherapies such as convalescent plasma and anti-Spike monoclonal antibodies. The lessons derived from the critical analysis of that period could drive our treatment decisions for the next pandemics.

Editorial

During the 4-year period from December 2019 to December 2023, the COVID-19 pandemic has caused more than 770 million confirmed cases and 7 million confirmed deaths worldwide, with an unprecedented global health impact and social crises [1].

Along with oxygen supplementation, the treatment of patients hospitalized for severe COVID-19 initially included the use of repurposed drugs with different mechanisms of action: corticosteroids and tocilizumab for their anti-inflammatory properties, low-molecular-weight-heparins for their anti-thrombotic activity, and remdesivir and lopinavir/ritonavir for their antiviral effect [2]. Along with these therapeutic agents, which represented the standard of care during the first months of the pandemic, collection of plasma from individuals who had recovered from SARS-CoV-2 infection (COVID-19 convalescent plasma, CCP) was rapidly deployed around the globe to treat patients with SARS-CoV-2 infection at different stages of disease severity, considering the positive clinical experience in previous viral outbreaks [3]. CCP has been the most intensively studied treatment against COVID-19, with nearly 50 published randomized controlled trials (RCTs) that have provided evidence to assess its correct placement in the anti-COVID-19 therapeutic armamentarium. These studies indicate that CCP has a beneficial clinical effect when administered at high titer (>160) of virus-neutralizing antibodies and early in the course of disease (i.e. within 5 days from symptom onset). Immunocompromised patients (i.e., patients with solid or hematological cancer, congenital or acquired immune deficiency, transplant recipients) who are not able to mount a sufficient antibody response after SARS-CoV-2 infection or vaccination are those who mostly benefit from CCP therapy, largely an antibody replacement therapy [4-6].

Since SARS-CoV-2 was declared a public health emegency of international concern by the WHO, the main initial hurdles have been creating cost-effective diagnostic methods to rapidly and correctly identify the presence of the virus and generating effective treatments to combat COVID-19. While the first task has been successfully accomplished, the therapeutic strategies implemented during the first wave of the COVID-19 pandemic largely varied from country to country and depended on economic resources, organizational capabilities and scientific and political decisions by individual states. The greatest variability was observed regarding the use of CCP.

In the United States, the Food and Drug Administration (FDA) began granting requests for emergency single-patient investigational new drug (IND) use in late March 2020, and first issued guidance for CCP use as an IND in April 2020. Such decision was taken considering the lack of alternate options at that time and its potential effectiveness based on the experience in previous epidemics. At the same

time, FDA made an alliance between major blood suppliers, the Mayo Clinic and transfusion services to create the National Expanded Access Program (EAP). Although CCP was considered an experimental biological product (and currently remains an experimental medicine), the EAP was determinant to permit the use of CCP in patients without having to apply for an IND for each patient [7]. At the same time CCP was being collected from COVID-19 recovered donors on a large scale across the United States, the Mayo Clinic initiated the EAP with the primary goal of assessing CCP safety in hospitalized patients. Following the publication of the initial 20,000 cases treated with CCP under EAP, documenting a lower rate of overall and serious adverse reactions [8], FDA on August 2020 issued the emergency use authorization (EUA) of CCP in hospitalized patients with COVID-19. Subsequent EUA updates on CCP regarded the criteria for CCP donation from vaccinated donors (January 2021) and the clinical use of high-titer CCP units in hospitalized patients early in the course of the disease or in those with impaired humoral immunity (February 2021) [7]. Thanks to the EUA, more than 500,000 hospitalized COVID-19 patients have been treated with CCP during the last four years in the United States, with a substantial clinical benefit documented by the inverse correlation between mortality and CCP use [9].

In Europe, a project from the European Commission was set up in mid-2020 to promote and financially support the laboratory and clinical studies on CCP. Apart from these initial efforts, many individual European countries were reluctant to use CCP. In Italy, for example, although the National Blood Center provided the rules for the collection and biological validation of CCP already in March 2020 [10], the Superior Health Council advised caution in using CCP until there was evidence on its efficacy from RCTs. As a consequence, differing from the United States, the emergency use of CCP was never authorized in Italy and the transfusion of this biological product was restricted to hospitalized COVID-19 patients in the frame of experimental trials or after the authorization for each patient by the local ethical committee and the hospital management. Such bureaucratic obstacles resulted in a substantial delay between the COVID-19 symptom onset and CCP treatment, which enormously limited CCP effectiveness in Europe [11]. It is well known, indeed, that the antiviral effect of CCP is maximum in the peak phases of SARS-CoV-2 replication (i.e., 3-5 days from symptom onset), fading thereafter. In addition, the early communication in April 2021 (i.e., 6 months before the final publication!) by the Italian Agency of Drug (AIFA) of the negative results of the Italian RCT TSUNAMI on CCP use provoked a sudden neglect of this biological product, which was almost no longer collected and utilized in our country and in the rest of Europe [12]. In the meanwhile, anti-Spike monoclonal antibodies (mAbs) and small-molecule antivirals had been authorized for clinical use and had replaced CCP as early (outpatient) treatment against COVID-19. However, the

immune evasion due to the new variants of SARS-CoV-2 undermined the efficacy of anti-Spike mAbs: while they were progressively deauthorized by the FDA, the EMA never took action and their (inappropriate) use declined more slowly in Europe. With anti-Spike mAbs ineffective against newer SARS-CoV-2 variants and CCP no longer available, a dangerous therapeutic void as created that affected first of all the immunocompromised COVID-19 patients, leaving them without antibody-based antiviral therapies and with poor response to vaccine boosts.

Since 2022 robust evidence gathered about the safety [13] and efficacy of CCP in both outpatients [14] and inpatients [5]. In addition, there is unprecedented availability of hybrid CCP (i.e. CCP collected from donors that are both vaccinated and convalescents) among regular donors [15], which shows preserved efficacy against novel variants [16]. Accordingly, CCP remains in 2024 the single antiviral treatment with supporting evidence in immunocompromised patients from a randomized controlled trial [4].

Thus, at the end of the pandemic and considering what happened, it was profoundly wrong to prematurely remove CCP from the list of therapeutic options against COVID-19 without considering the possible immune escape of SARS-CoV-2. An important lesson for the future.…

Declarations

Conflict of Interest

The Authors declare that there is no conflict of interest.

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