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COVID-19 Convalescent Plasma: No Definite Answer Yet

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Abstract

The COVID-19 pandemic so far caused millions of deaths, and the therapeutic options for high-risk patients are far from being satisfactory. Active immunization by vaccines against SARS-CoV-2 spike protein provides good protection from a severe course of COVID-19. It has been explored in numerous clinical trials, whether also passive immunization by transfusion of convalescent plasma could positively influence the course of COVID-19. Large randomized clinical trials failed to demonstrate a benefit for patients with advanced disease. However, the antibody dose and timing of transfusion might have contributed to this negative result. Randomized clinical trials are necessary to make evidence-based progress in the development of therapeutic options, and this holds true also for "natural" concepts. However, even high-quality trials are just a tool to test predefined hypotheses. Arguments are presented that convalescent plasma should be further evaluated in clinical trials as proactive, quasi "prophylactic" treatment by giving a sufficient amount of CCP early enough (before massive virus replication). A solid scientific foundation for the principle of target specific and temporarily adapted passive immunization would be very important even beyond COVID-19 as fast and flexible instrument also in future outbreaks of novel pathogens.

Keywords: Convalescent Plasma • COVID-19 • Clinical trials • Respiratory viral

Introduction

Convalescent plasma constitutes a more than 100 years old strategy of passive immunization [1]. It has been widely used for the treatment of severe acute respiratory viral infections [2], and has raised renewed interest due to the COVID-19 pandemic. An excellent review published in July 2020 [3] under the heading "Now Is the Time for Better Science" explored the rationale for and potential harm from COVID-19 Convalescent Plasma (CCP), and expressed the urgent need for Randomized Controlled Trials (RCT). The author rightly pointed out that "failure to study first before wide-scale implementation risks doing harm to both patients and the health care system. "In the meantime numerous clinical studies, including RCTs, have been conducted. But as carefully analyzed in a recent perspective article [4], clinical CCP studies are quite heterogeneous in several important aspects including study size and methodology, donor eligibility criteria and testing of donated plasma, treatment regimens, time between diagnosis and treatment start, patient eligibility criteria, and treatment of controls (supportive care, comedications). Thus, it is not surprising that three meta-analyses so far came to divergent conclusions [5-7]. The authors of one of these meta-analyses [5] including studies published until January 16, 2021 came to a positive conclusion: "Random effects analyses of randomized clinical trials and matched control data demonstrated that patients with COVID-19 transfused with convalescent plasma exhibited a lower mortality rate compared with patients receiving standard treatments". Another meta-analysis [6] including studies published until January 18, 2021 concluded: "CPT could be an effective therapeutic option with promising evidence on the safety and reduced mortality in concomitant treatment for COVID-19 along with antiviral/antimicrobial drugs, steroids, and other supportive care." However, a third recent meta-analysis [7] including studies published until January 29, 2021 came to the conclusion that "treatment with convalescent plasma compared with placebo or standard of care was not significantly associated with a decrease in all-cause mortality or with any benefit for other clinical outcomes". Nevertheless, the so far accumulated clinical evidence from published CCP trials [4-7] does not verify anticipated special hazards such as an Antibody-Dependent Enhancement (ADE) in SARS-CoV2 infection, the safety profile of CCP appears to be comparable to standard plasma transfusion.

The meta-analysis coming to a negative judgement [7] was based to a great extent on the outcome of the large recovery trial [8], which had been published very shortly before as press release only. The CCP study arm of the recovery platform had been terminated for

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futility, since CCP "did not improve survival or other prespecified clinical outcomes". 1399 (24%) of 5795 patients in the CCP group and 1408 (24%) of 5763 patients in the usual care group died within 28 days (rate ratio 1•00, 95% CI 0•93–1•07; p=0•95) [8]. Importantly, this trial involved hospitalized COVID-19 patients, and the median time since symptom onset was 9 (range 6-12) days. The patients in the CP group received two CCP units from two different donors containing SARS-CoV-2 antibodies with a sample to cutoff ratio of 6.0 or more on the Euroimmun IgG Enzyme-Linked Immunosorbent Assay (ELISA). Also another recently published large high-quality RCT [9] involving high-risk outpatients did not find a therapeutic benefit of CCP: "The administration of Covid-19 convalescent plasma to high-risk outpatients within 1 week after the onset of symptoms of Covid-19 did not prevent disease progression." A total of 511 patients were enrolled in the trial (257 in the CCP group and 254 in the placebo group), with a median age of 54 years and median symptom duration of 4 days. The patients received either one unit CCP with a median titer of SARS-CoV-2 neutralizing antibodies of 1:641, or placebo [9]. Obviously, the currently available clinical data indicate CCP is not a "magic bullet" which would cure all stages of COVID-19, but could this really be expected? An old definition coined by the Wildbad Kreuth Initiative in 1999 [10] may be helpful: "Quality in the clinical use of blood products implies administering the right quantity of the right blood product in the right way at the right time to the right patient, and appropriate documentation of both the process and the outcome."

Literature Review

It is firmly established that active immunization by vaccination against SARS-CoV-2 spike protein elicits cellular immunity and robust antibody titers, and provides good protection from infection, and in those patients infected despite vaccination, from a severe course of COVID-19. The hypothesis behind current clinical exploration of CP is that also passive immunization by transfer of antibodies could positively influence the speed of virus replication, the clinical course of a patient and combat the high mortality of severe COVID-19. Notably, another antibody trial published as preprint by the recovery group [11] found a reduction of 28-day mortality after giving a combination of two monoclonal antibodies which bind to two different sites on the receptor binding domain of the SARS-CoV-2 spike protein to seronegative patients (rate ratio 0·80, 95% CI 0·70-0·91, 42 p=0·0010). In this study, the combination (casirivimab 4g and imdevimab 4g) in 250 ml 0.9% saline was infused intravenously over 60 minutes ± 15 minutes; the median time from symptom onset was 7 (range 4-10) days.

What may cause the failure to demonstrate a benefit of CCP in two large recent RCT [8,9] compared to finding a significant reduction of 28-day mortality by the monoclonal antibodies? [11] . It may be relevant whether the patients have already developed antibodies before receiving CCP; in the monoclonal antibody trial [11] the advantage emerged clearly in the patient group without own antibodies, and also in the large recovery CCP trial [8] there was a non-significant trend to a reduced mortality (RR 0.96; range 0.85-1.07) in the antibody negative group, in contrast to a trend to increased mortality in the antibody positive group (RR 1.06; range 0.94-1.19).

Another important point may be the dose: CP is obtained by individual donations, which are obviously heterogeneous concerning amount and specificity of antibodies. Therefore rigorous standardization and dose-finding studies are impractical, whereas established guidelines on CP collection, testing, processing, storage, distribution and monitoring of use are available [12]. The dose of the combination of the two monoclonal antibodies was together 8 g [11], which is corresponding to about the entire amount of immunoglobulins in 1 L of plasma, whereas in the two CCP trials the dose was 400 to 700 mL with a SARS-CoV-2 antibody cutoff ratio of 6.0 or more on ELISA [8], and one unit CCP with a median titer of SARS-CoV-2 neutralizing antibodies of 1:641 [9]. Thus, the relevant antibody dose was probably much higher in the monoclonal antibody trial. In a large retrospective study [13] on the association of CP antibody levels with outcomes, signal-to-cutoff ratios for anti-SARS-CoV-2 IgG antibody levels were categorized as low (<4.62), medium (4.62 to 18.45), or high (>18.45), and transfusion of plasma with higher anti-SARS-CoV-2 IgG antibody levels was associated with a lower risk of death than transfusion of plasma with lower antibody levels. Likewise, CP with a sample to cutoff ratio of 6.0 or higher had been qualified as "high titer" in the recovery trial [8].

A further critical variable could be the time from onset of symptoms until start of treatment. It appears reasonable that the period elapsing before start of any treatment matters; the more time the virus has for replication, binding to crucial receptors and triggering critical host systems which may initiate a deleterious destructive process, the more difficult it will be to stop this vicious cycle. Notably, a RCT including older adult patients within 72 hours after the onset of mild Covid-19 symptoms [14] found a significant benefit of CCP (relative risk, 0.52; 95% Confidence Interval [CI], 0.29 to 0.94; P=0.03) towards the primary end point developing severe respiratory disease. Maybe particularly high-risk elderly patients would need antibodies earlier that their own immune system is able produce them.

Discussion

It is a very reasonable objective to ensure target-oriented clinical research and to avoid spending resources for developing inefficient therapies. Clinical trials aiming at investigating and qualifying new medicines are extremely complex, laborious and costly, and burdened with a high risk of failure; however, there is no other way to make evidence-based progress in the development of therapeutic options, and this holds true also for "natural" concepts like CCP. However, even high-quality RCT are just a tool to test predefined hypotheses.

Concerning the therapeutic value of CCP, the above mentioned RCT [8,9] have tested the hypotheses that one or two units CCP containing the indicated antibody doses would improve the outcome of hospitalized or outpatients with considerably advanced course of COVID-19. However, as discussed above, CCP may still be a therapeutic option when given with higher antibody doses very early to at-risk COVID-19 patients. Therefore, it appears to be worthwhile to give CP a further "fair" chance to be evaluated in clinical trials as proactive, quasi "prophylactic" treatment by giving a sufficient amount of CCP early enough (before massive virus replication). The chances of such an approach would depend on an early diagnosis of COVID-19, ideally before or during onset of symptoms. The currently widely used rapid antigen testing may not be sensitive enough.

However, concepts are available for highly efficient SARS-CoV-2 screening without loss of sensitivity by simultaneously incubating multiple respiratory swabs in a single tube [15], i.e. PCR pool testing to identify asymptomatic virus carriers and patients eligible for early CP treatment, initially as part of a clinical trial, but later on possibly also in wider populations.

Generally, the therapeutic options for severe COVID-19 are far from being satisfactory, and the death toll is still much too high. By collection of CCP a spectrum of polyclonal antibodies can be obtained in close timely and regional connection to prevalent virus, which may be an advantage in view of upcoming variants of concern [16].

Conclusion

Moreover, it would be extremely valuable to obtain a solid scientific foundation for the principle of target specific and temporarily adapted passive immunization, which could be a fast and flexible instrument also in future outbreaks of novel pathogens.

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