Immune Plasma for the Treatment of COVID-19: Lessons Learned so far

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Abstract

COVID-19 convalescent plasma (CCP) has been explored as one of the treatment options for COVID-19. Results of many cohort studies and clinical trials have been recently published. At first glance, the results of the CCP studies appear to be inconsistent. However, it became clear that CCP is not beneficial if CCP with low anti-SARS-CoV-2 antibody concentrations is used, if it is administered late in advanced disease stages, and to patients who already mounted an antibody response against SARS-CoV-2 at the time of CCP transfusion. On the other hand, CCP may prevent progression to severe COVID-19 when very high-titer CCP is given early in vulnerable patients. Immune escape of new variants is a challenge for passive immunotherapy. While new variants of concern developed resistance to most clinically used monoclonal antibodies very rapidly, immune plasma from individuals immunized by both a natural SARS-CoV-2 infection and SARS-CoV-2 vaccination retained neutralizing activity against variants. This review briefly summarizes the evidence on CCP treatment to date and identifies further research needs. Ongoing research on passive immunotherapy is not only relevant for improving care for vulnerable patients in the ongoing SARS-CoV-2 pandemic, but even more as a model for passive immunotherapy in case of future pandemics with a newly evolving pathogen. Compared to other drugs, which must be newly developed in a pandemic (e.g., monoclonal antibodies, antiviral drugs), convalescent plasma is rapidly available, inexpensive to produce, and can be adaptive to viral evolution by selection of contemporary convalescent donors.

Keywords
- immune plasma
- convalescent plasma
- COVID-19
- vaccination

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has caused more than 6.5 million deaths worldwide (https://coronavirus.jhu.edu/map.html). Mortality is 40% or more for hospitalized patients from clinically vulnerable groups.[1–4]

COVID-19 convalescent plasma (CCP) has been considered as one of the treatment options for severe COVID-19 already very early in the SARS-CoV-2 pandemic. The approach was based on considerations of its mechanism of action [5–7] and the encouraging reports of use of convalescent plasma for

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other severe viral respiratory infections including severe acute respiratory syndrome (SARS), middle-east respiratory syndrome (MERS), and influenza.[8]

During the SARS-CoV-2 pandemic, CCP has been broadly used in an expanded access program[9] in the United States and preliminary reports on signals of efficacy and safety led to an emergency use authorization in the United States in August 2020.[10,11] In Europe, a broad spectrum of actions from CCP collection to monitored access programs and clinical trials have been implemented (www.support.eu). In the following, we focus on lessons learned so far. Other treatment options which have been developed include monoclonal antibodies[12,13] or antiviral drugs (molnupiravir,[14] nirmatrelvir plus ritonavir,[15] or remdesivir[16]).

In this review, we summarize the results of clinical trials of CCP, the identification of subgroups more likely to benefit from CCP, and the improvement of CCP over time. The term "convalescent" plasma continues to be used in the literature. However, highest titers and broadest immunological reactivity even against variants is achieved in plasma from individuals immunized by both infection and vaccination. The established term "convalescent" plasma describes only a partial aspect. The term "immune plasma" seems more appropriate to describe the multiple immunization events (►Fig. 1). Treatment with immunoglobulins[17,18] which are isolated from such immune plasma units are not within the scope of this review.

Clinical Trials of CCP for COVID-19

A large number of clinical trials on CCP have been initiated since the start of the pandemic. The majority of trials included patients with moderate to severe COVID-19, that is, patients in stages 4 to 7 of the WHO 8-point ordinal severity scale. A common feature of a majority of clinical trials so far is the inclusion of hospitalized patients only.[19–43] Very few trials enrolled outpatients.[30,44–48]

Clinical data on efficacy have been heterogeneous. Recent guidelines based on living systematic reviews of controlled randomized clinical trials concluded that CCP was not significantly associated with a decrease in all-cause mortality or with any other benefit for other clinical outcomes compared with placebo or standard of care in unselected hospitalized patients with moderate to severe COVID-19.[49] The overall certainty of evidence was high.[49] In contrast, the same clinical practice guidelines suggested to use CCP in hospitalized patients who do not have SARS-CoV-2 antibodies detected at admission and to use CCP for hospitalized patients with COVID-19 and preexisting immunosuppression.

Other meta-analyses concluded that patients with COVID-19 transfused with CCP had a lower mortality rate compared with patients receiving standard treatments[50] and early transfusion of higher titer plasma was found to be associated with lower mortality.[51]

The heterogeneous results can be explained by various aspects of the study design and methodology: The volume of transfused CCP was low in some of the trials which administered a total CCP volume of 200 mL,[19] 200 to 250 mL,[40] 250 mL,[52] 300 mL,[53] 400 mL,[23,25,32,39] 500 mL,[9,26,41] and 550 mL.[38] Only very few trials administered higher plasma volumes (e.g., the CAPSID trial [median volume: 846 mL]).[35]

Only a few studies defined a minimum anti-SARS-CoV-2 titer for CCP. The content of antibodies in CCP units was poorly characterized or only measured post hoc in some of the trials. The assays used for measuring anti-SARS-CoV-2 antibody concentrations varied substantially. Besides, most

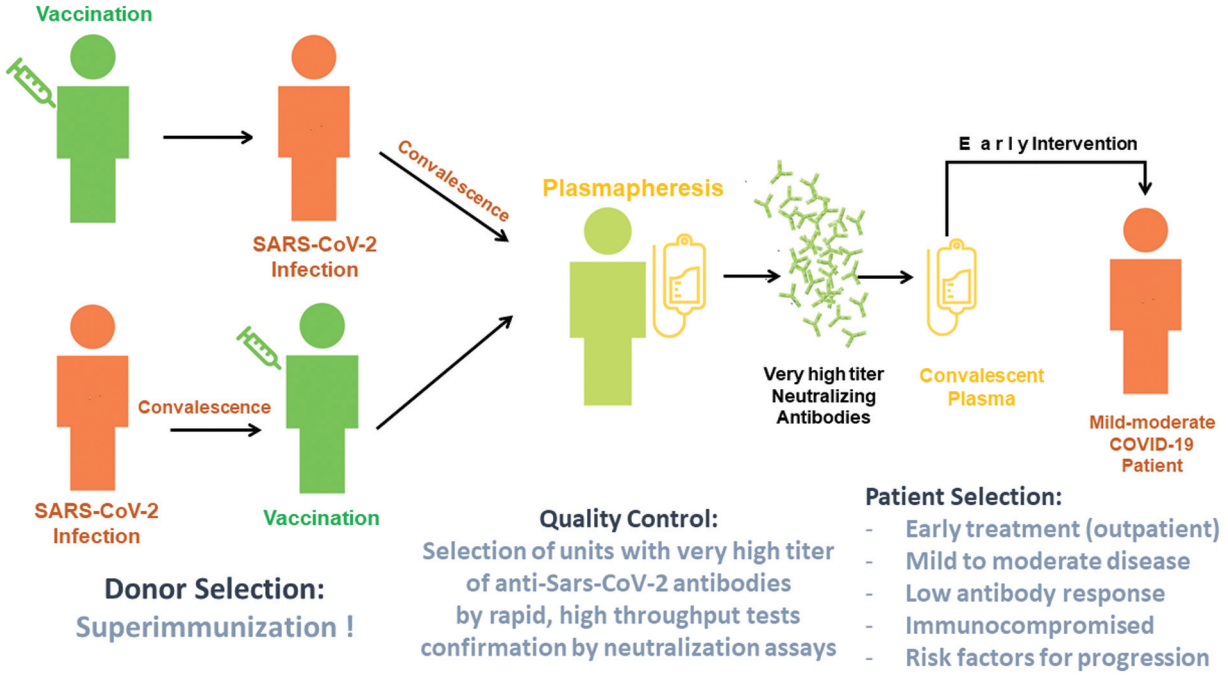

Fig. 1 Advanced concept of treatment with hyperimmune plasma from superimmunized donors, that is, donors who are convalescent from a SARS-CoV-2 infection and who are also immunized by SARS-CoV-2 vaccination—irrespective of the order of these immunizing events.

of these trials were initiated in spring 2020 when availability and information on comparability of antibody tests were limited[54,55] and antibody titers were low compared to what can be achieved now in plasma from superimmunized donors. CCP is not a "magic bullet" which can rescue severely sick COVID-19 patients and even when given late in the course of the disease. There is now growing evidence that CCP can be an important component in the therapeutic armamentarium if it is given (1) *early*, (2) *at very high dose* (i.e., with high antibody content), and to (3) *vulnerable patients* who are at risk of progression to severe COVID-19.

Therefore, in the following we summarize current evidence on potential benefit of early, very high titer CCP treatment of vulnerable patients and highlight future research needs.

Timing of CCP Treatment: Early Treatment Can Prevent Progression of COVID-19

In the randomized clinical trial INFANT COVID 19 from Argentina (NCT04479163), CCP was administered within 3 days after the onset of symptoms of COVID-19 in vulnerable patients. This approach reduced the risk of progression to severe respiratory disease, compared to a control group by about 50% (16% after CCP vs. 31% in control group; relative risk of 0.52, 95% confidence interval [CI]: 0.29–0.94; $p = 0.03$).[44] A modified intention-to-treat analysis that excluded six patients who had a primary end-point event before transfusion of CCP or placebo showed a larger effect size (relative risk, 0.40; 95% CI, 0.20–0.81).

A U.S. multicenter, double-blind, randomized, controlled trial enrolled symptomatic adults ($\geq$18 years of age) who had tested positive for SARS-CoV-2, regardless of their risk factors for disease progression or vaccination status (NCT04373460).[45] Participants, most of whom were unvaccinated, were enrolled within 8 days after symptom onset and were randomized to receive CCP or control plasma within 1 day after randomization. In the prespecified modified intention-to-treat analysis that included only participants who received a transfusion ($n = 1{,}181$), COVID-19-related hospitalization occurred in 17 of 592 participants (2.9%) who received CCP and 37 of 589 participants (6.3%) who received control plasma (absolute risk reduction: 3.4 percentage points; 95% CI: 1.0–5.8; $p = 0.005$). This corresponded to a relative risk reduction for hospitalization of 54%. The results of a prespecified subgroup analysis suggested that point-estimate outcomes were better in participants who received a transfusion within 5 days after the onset of symptoms than in those who received a transfusion later.[45]

The SIREN-3PO Trial enrolled 511 patients who were either 50 years of age or older or had one or more risk factors for disease progression (NCT04355767).[30] Disease progression occurred in 77 patients (30.0%) in the CCP group and in 81 patients (31.9%) in the placebo group (risk difference, 1.9 percentage points; 95% credible interval, −6.0 to 9.8; posterior probability of superiority of CCP, $p = 0.68$). Twenty-five patients reached the primary endpoint (hospital admission) during the index visit even before administration of plasma. In a post hoc sensitivity analysis that excluded these patients, the posterior probability of superiority of CCP plasma was 93% in the intention-to-treat population.[30]

Two other multicenter, double-blind randomized trials which were conducted in Spain (COnV-ert, NCT04621123)[47] and the Netherlands (CoV-Early; NCT04589949)[48] were merged for analysis ($n = 797$).[46] Outpatients aged $\geq$50 years and symptomatic for $\leq$7 days were included and randomized to receive standard of care ($n = 392$) or CCP ($n = 390$) (volume: 200–300 mL). The odds ratio of CCP for improved disease severity scale was 0.936 (CI: 0.667–1.311). The odds ratio for hospitalization or death was 0.919 (CI: 0.592–1.416). CCP effect on hospital admission or death was largest in patients with $\leq$5 days of symptoms (odds ratio: 0.658, 95% CI: 0.394–1.085). CCP did not decrease the time to full symptom resolution.[46] All patients seroconverted immediately after transfusion. However, the median virus neutralization titer only rose to 1:40 which was four times lower than the median titer in immunocompetent convalescent COVID-19 patients[53] and up to 100 times lower than titers observed after treatment with monoclonal antibodies.[56] The authors postulated that the range of neutralizing antibody titers present in the plasma may well have been too low.[46] Thus, underdosing may partially explain these findings.[46,57] In addition, it must be noted that one of the trials, COnV-ert, used methylene-blue–treated plasma. Methylene blue which is used for pathogen inactivation has been reported to interfere with immunoglobulin function.

SARS-CoV-2 Antibody Concentration in CCP Matters

There are several trials which demonstrate a dose–effect of CCP. Significantly better results of CCP-treated patients compared to the control group were observed only in patients who had received CCPs with higher titers.

In the INFANT-COVID-19 trial in elderly vulnerable patients, a subgroup analysis by the concentration of SARS-CoV-2 S IgG titers in the transfused CCP units revealed a significant reduction of progression to severe respiratory disease only in recipients of CCP with a titer at or above the median: risk reduction of 73% in the high-titer group compared to 31% in the low-titer group.[44]

The CAPSID Trial in Germany enrolled hospitalized patients with severe COVID-19 (NCT04433910).[35] Patients were randomized to receive CCP or no CCP (control group) in addition to standard of care. There was no significant difference in the dichotomous composite primary outcome at day 21 (survival and no longer severe COVID-19): 43% of patients in the CCP group and 32% in the control group reached the primary outcome (n.s.).[35] The 1-year survival was 78.7% in the CCP and 60.2% in the control group ($p = 0.08$). Since the total amount of neutralizing antibodies depends on both the volume and the antibody titer of CCP, the cumulative amount of "neutralizing units" was calculated to take into account both variables. In a prespecified subgroup analysis, the CCP group was divided into a "high-

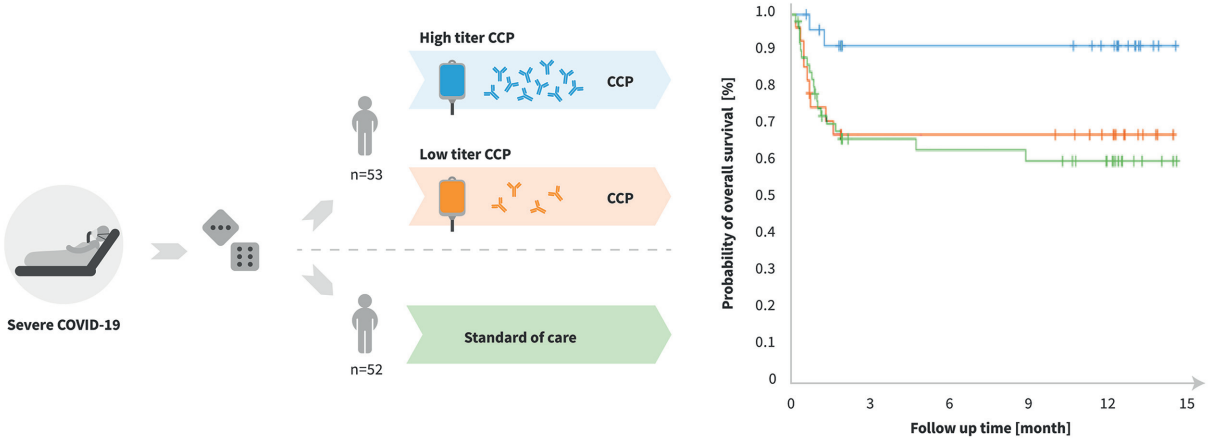

Fig. 2 Long-term follow-up of CAPSID trial (NCT05271929; EudraCT 2021-006621-22): overall survival compared in the COVID-19 convalescent plasma (CCP) subgroup that received a low cumulative amount of neutralizing antibodies (solid red line), the CCP subgroup that received a high cumulative amount of neutralizing antibodies (solid blue line), and the control group (solid green line). Censored patients are indicated by +. High amount versus control: $p = 0.011$ and high amount versus low amount: $p = 0.032$ (log-rank test).[58]

titer" subgroup (> median) and a "low-titer" subgroup (≤ median).[35] The subgroup treated with a higher cumulative amount of neutralizing antibodies showed a better 1-year survival compared to the control group (91.5 vs. 60.2%; $p = 0.01$) and the subgroup that was treated by a low cumulative amount of neutralizing units (1-year overall survival: 67.4%; 95% CI: 46.6–81.5%; $p = 0.03$; ►Fig. 2).[58] Among those who received a high or low cumulative amount of neutralizing units, the primary outcome occurred in 56.0% and in 32.1%, and in 30.8% in the control group ($p = 0.046$ high titer vs. control).[58]

In a retrospective analysis based on the U.S. National Registry of the Early Access Program (E.A.P.), death within 30 days after plasma transfusion occurred in 22.3% of patients who had received high-titer CCP, 27.4% in the median-titer group, and 29.6% in the low-titer CCP group in a patient subgroup who had not received mechanical ventilation before transfusion (relative risk: 0.66, 95% CI: 0.48–0.91). Signals of a dose–effect were also observed in further trials.[59,60]

Antibody-Negative or Immunocompromised Recipients Are More Likely to Benefit from CCP

In the planning period of the "first generation" of clinical trials, it was assumed that enrolled patients will be SARS-CoV-2 antibody-naive and that the passive transfer will convert patients from an antibody-negative to a positive status. It turned out that a substantial proportion of patients in trials which enrolled hospitalized patients already had mounted a humoral immune response by the time of inclusion in the CCP trials.[24,26,35,38,40,53,61] Among hospitalized patients who lacked SARS-CoV-2 antibodies at baseline, CCP decreased the need for mechanical ventilation or mortality compared with standard of care or placebo.[20,21,34,38,49,62]

Even more, in immunocompromised patients the antibody response might be absent or delayed. Clinically vulnerable patients, such as patients with congenital immunodeficiency or patients who are immunocompromised due to underlying disease and/or immunosuppressive therapy, are at high risk of progression to severe COVID-19. These patients are also likely to have persistent SARS-CoV-2 infection and may shed infectious SARS-CoV-2 particles for a prolonged time[63,64] and experience recurrence of symptoms while posing a risk of sustained onward transmission and so may gain additional benefits from early therapeutic intervention.[65]

There is evidence for efficacy of CCP in immunocompromised patients both from cohort studies and subgroup analyses of randomized clinical trials.

In a matched-pair analysis, 143 patients with hemato-oncologic diseases that were treated with CCP were compared to 143 matched controls selected from a total of 823 patients. More than 85% of the patients had lymphoid neoplasms, the majority with active disease. Only a small proportion of approximately 30% were in remission. Treatment with CCP showed lower mortality at 30 days compared with matched controls (hazard ratio [HR]: 0.52; 95% CI: 0.29–0.92). In contrast to the data in non-immunosuppressed patients (see above), this benefit was also seen in patients severely affected by COVID-19 who received intensive care (HR: 0.40; 95% CI: 0.20–0.80) or mechanical ventilation (HR: 0.32; 95% CI: 0.14–0.72).[66]

In a matched-pair analysis from the French controlled CCP program, all patients with B-cell neoplasms treated with CCP were retrospectively identified. Patients with B-cell neoplasms who had not received CCP for the treatment of their COVID-19 disease that occurred during the same period were then identified at participating centers. This approach matched 81 patients treated with CCP to 121 control patients. The primary endpoint of the analysis was 90-day overall survival. No antibodies were detectable in 83% of the included patients. In the overall population, CCP reduced mortality by 50% ($p = 0.001$). This effect was most pronounced in patients receiving anti-CD20 therapy (mortality reduced by 63%, $p < 0.002$).[67]

A retrospective analysis of a cohort of 23 patients with hematological malignancies who had received CCP very early after diagnosis (48–72 hours) compared to 22 control patients without CCP treatment demonstrated significantly higher survival and faster recovery in the CCP-treated group.[68] However, two other cohort studies could not confirm the positive effect of CCP on mortality in patients with hematological malignancies[69] or kidney transplant patients.[70] This might be explained by sample size, delayed treatment, and use of a low proportion of high-titer CCP.

A meta-analysis of three randomized trials which also included patients with preexisting immunosuppression (cancer, corticosteroids, B-cell depleting therapies; $n = 2{,}210$) [20,21,53] demonstrated no difference in mortality at 28 days among immunocompetent patients who received CCP versus standard of care or placebo.[49] However, among the subgroup of immunosuppressed hospitalized patients at baseline, CCP decreased mortality compared with standard of care or placebo (RR: 0.71 [CI: 0.51–0.98]).[49]

Two further randomized trials which included a subgroup of immunosuppressed patients are available only as congress abstracts or preprints so far.[71,72] A total of 133 patients were included in the German RECOVER trial (NCT05200754), 71 patients with hematological malignancies, other cancers, or immunosuppression. Patients were randomized (1:1) to receive standard therapy alone or with CCP. In the overall population, the cumulative improvement rate was not significantly different between the CCP and control group with a nonsignificant shorter time to improvement in the CCP group compared to the control group (12.5 vs. 18 days, $p = 0.29$). In the cohort with malignancies or immunosuppression, the patients in the CCP arm had a significantly shorter median time to clinical improvement of 13 days versus 32 days ($p = 0.01$).[71]

The CORIPLASM trial in France included 120 patients receiving standard therapy with CCP or without CCP (NCT04345991). The mortality rate at day 28 was not significantly different in the overall cohort (7% in the control group vs. 20% in the plasma group; HR: 0.51; CI: 0.2–1.32). In contrast, the subgroup of 49 patients with hemato-oncologic disease showed a significant survival advantage for the CCP group (HR: 0.37; CI: 0.14–0.97).[72]

An updated meta-analysis of CCP for the treatment of immunocompromised patients with COVID-19 by Senefeld and colleagues included 9 controlled studies (535 treated patients and 1,365 controls, including 4 randomized controlled trials), an individual patient data analysis of 125 case reports/series (265 patients), and a descriptive analysis of 13 uncontrolled large case series without individual patient data available (358 patients). The meta-analysis of controlled studies showed a mortality risk ratio of 0.65 comparing treatment with CCP versus standard of care for immunosuppressed COVID-19 patients.[73]

Plasma from Convalescent and Vaccinated Patients Provides Higher Antibody Titers and Breadth of Anti-SARS-CoV-2 Activity

It has been demonstrated that the combination of natural infection and a SARS-CoV-2 vaccination causes both an enhancement of all aspects of the humoral immune response and a broad immune reaction against new variants.[74–76] The underlying mechanisms involve ongoing antibody somatic mutation, memory B cell turnover, and development of antibodies that are resistant to SARS-CoV-2 receptor binding domain (RBD) mutations, including those found in variants of concern.[74] B cell clones expressing broad and potent antibodies are selectively retained in the repertoire over time after infection and expand after vaccination.[74] Immunity in convalescent individuals is very long-lasting and convalescent individuals after vaccination will produce antibodies and memory B cells that should be protective against circulating SARS-CoV-2 variants.[74–76]

New variants might escape passive immunotherapy since they can evade neutralization by sera from vaccinated and convalescent individuals and by monoclonal antibodies *in vitro*. [77–81] Delta and omicron were not efficiently neutralized *in vitro* by sera of convalescents from the first and second surge of the SARS-CoV-2 pandemic. However, in convalescents, just one dose of SARS-CoV-2 vaccination could restore *in vitro* neutralization capacity against delta and omicron.[82] This broad reactivity against new variants was observed even in donors who had been infected with previous variants and who had been vaccinated with the first generation of SARS-CoV-2 vaccines against the wild type.[82] It was suggested that even without adaptation of currently available vaccines, the broader immune repertoire in superimmunized (i.e., vaccinated and convalescent) individuals can cover novel variants.[74,82] Antiviral activity of immune plasma should be confirmed by neutralization assays. However, systematic screening of convalescent, vaccinated donors using commercially available high-throughput serological assays (anti-SARS-CoV-2-QuantiVac-ELISA [IgG]; Elecsys anti-SARS-CoV-2 S) can identify plasma donors with very high SARS-CoV-2 antibody concentrations, who also have very high in vitro neutralizing titers against variants.[82]

Thus, plasma from superimmunized individuals may have advantages in terms of both antibody concentrations and cross-neutralization of variants. This also means a transition from merely convalescent donors to multiple immunized donors which provide CCP with neutralizing potency against different variants (►Fig. 1).

Lessons Learned So Far and Future Clinical Trials

We now know that the use of CCP in an unselected hospitalized population with COVID-19 is not beneficial—at least not when CCP with low antibody titers is used as in previous clinical trials. Much higher anti-SARS-CoV-2 titers can now be achieved by appropriate selection of superimmunized donors as compared to the rather low titers of CCP units used in the "first generation" of CCP trials.[19–41,44–48] What titers exactly separate high-titer and low-titer plasma cannot be defined based on existing data. No dose-finding human trials were ever performed.[57] Neutralizing capacity of CCPs used in clinical trials has either not been reported or the titers have

been measured with in-house test whose results are difficult to compare between centers.[57,83] Therefore, the use of quantitative standardized assays or comparison between laboratories by exchange of reference samples is important to ensure better comparability of antibody content and activity in future clinical trials.[83] Such activities are ongoing in the European Consortium Support-E (www.support-e.eu).

There is growing evidence for efficacy of high-titer CCP from convalescent, vaccinated donors if it is given early and at very high titers to vulnerable patients who are in particular at risk for progression to severe COVID-19. However, some of this evidence is derived from cohort studies or subgroup analyses of randomized trials. Therefore, additional prospective randomized trials are still needed.

Two ongoing trials may provide additional clarity regarding the use of CCP in patients with COVID-19: the REMAP-CAP trial (NCT02735707) and the COVID-19 trial (Early High-Titre Convalescent Plasma in Clinically Vulnerable Individuals with Mild COVID-19; NCT05271929; EudraCT 2021-006621-22).

In the immunoglobulin domain of the REMAP-CAP trial (NCT02735707), the investigators plan to enroll hospitalized immunocompromised patients.

The COVID-19 trial is a multinational, randomized clinical trial comparing early administration of CCP with standard of care in vulnerable patients with COVID-19 who are at high risk of progression to severe COVID-19. It studies the hypothesis that early high-titer CCP therapy will significantly reduce the risk of hospitalization and death. The trial will enroll two cohorts: (1) patients $\geq$70 years or with a COVID age $\geq$70 years (assessed by ALAMA risk calculator); (2) adult patients with primary or secondary immune deficiency. Patients will be randomized (1:1) to receive CCP with very high-titer neutralizing anti-SARS-CoV-2 antibodies within 7 days after onset of symptoms or standard of care. CCP will be collected from donors who have recovered from a SARS-CoV-2 infection *and* have received at least one dose of SARS-CoV-2 vaccine. This increases all components of the immune response including neutralizing breadth against variants. The impact of variants on response and potential immune escape will by studied (SARS-CoV-2 sequencing; cross-neutralization analysis *in vitro*). At the time of writing of this article (October 2022), the trial is ongoing.

Ongoing research on these topics is relevant for several reasons. Despite the availability of vaccines and despite lower pathogenicity of newer variants, there is a subgroup of patients, who are still at risk for severe COVID-19. Thus, there is still a medical need to improve care for vulnerable patients in the ongoing pandemic. Convalescent plasma has never been studied before in such detail as during the SARS-CoV-2 pandemic. We must continue to explore CCP as a model for passive immunotherapy, also in light of potential future pandemics with newly evolving pathogens. The lessons learned so far regarding donor selection, antibody titer, dose of immune plasma, timing of administration, and selection of the target population that most likely benefits from passive immune therapy can already now guide future strategies. This can and should be further refined to support a preparedness plan that allows immediate implementation of convalescent plasma for future pandemics.

Conflict of Interest

None declared.

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