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Clinical Insights

Management of COVID patients with convalescent plasma: Do we have the final word?

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ABSTRACT

Immunotherapy with convalescent plasma (CP) has been used in the past in several different infectious diseases and proposed as a potential therapeutic option in patients with COVID-19. However, a clear benefit was never demonstrated and randomized clinical trials (RCTs) conducted in different populations of COVID-19 patients showed contrasting results. In general, current evidences suggest that CP in patients with moderate to severe COVID-19 does not reduce the progression to severe respiratory failure or death within 30 days. However, currently published RCTs have several limitations. The administration of plasma with low titer of neutralizing antibodies (NAbs), the use of suboptimal surrogate serological tests to determine NAbs titer, the delayed administration of CP from the onset of COVID-19 symptoms and the lack of information about antibody titer of recipients before CP infusion, are all limiting factors that may have affected the study results. Thus, a potential benefit of early (within the first 72 h from onset of symptoms), high titer CP in patients with mild COVID-19 (pO2/FiO2>300) cannot be definitively excluded. However, immunotherapy with monoclonal antibodies developed from CP demonstrated efficacy in reducing progression to severe COVID-19 and hospitalization and are today recommended in the early phase of COVID-19.

1. Introduction

Immunotherapy with convalescent plasma (CP) has been used in the past in several infectious diseases (influenza, SARS, MERS) with the aim to shorten or stop the phase of viral replication and to improve the patient outcome. However, a clear benefit was never demonstrated.

More recently, patients with COVID-19 have been frequently treated with CP drawn from people recovered from COVID-19, usually within 30 days and with an adequate level of neutralizing antibodies (NAbs) directed against the Spike-protein of SARS-CoV2 ($\geq$ 1:160). Although CP generally showed a good safety profile, the evidence of relevant clinical benefit in reducing the rate of disease progression or death is scanty and limited to specific subgroups of patients treated early and, in particular, before the development of a serological antibody response. Several randomized clinical trials (RCTs) have been already published [1–11] [13][24] or are available as pre-print version [12,14] and, with few exception [9,10], they did not show a clear benefit of CP in reducing the risk of disease progression or death (Table 1). It is noteworthy that, great heterogeneity exists among the available RCTs in terms of enrolled population, timing of plasma infusion, NAbs titer, outcomes and study results. In fact, a relationship between NAbs titer and a more favorable clinical outcome have been suggested [8,15] and CP was associated with a decreased 28-days mortality rate when high titerCP was used [9] or when CP was administered early in the course of the disease [10].

Available RCTs have several limitations, including:

- The administration of plasma with low titer of NAbs.
- The use of suboptimal surrogate serological tests to determine NAbs titer.
- The delayed administration of CP from the onset of COVID-19 symptoms.
- Lack of information on recipients' antibody titer before CP infusion.

The Food and Drug Administration (FDA) limited the use of CP to high titer products only to be administered to hospitalized patients early in the course of COVID-19 (< 72 h) and to those with impaired humoral immunity who are unable to produce an adequate antibody response. Since CP with low levels of antibodies has not been shown to be helpful in COVID-19, the use of this product was not authorized under this FDA EUA recommendation [16].

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The aim of this paper was to review the current literature and to discuss the experimental conditions leading to discordant results in the available trials.

2. Defining the outcome measures

The choice of the primary outcome measure in a RCT evaluating CP is challenging for several reasons: (1) CP may be administered to patients with different risk profile for progression and in different moment of the disease course; (2) CP is usually given in combination with other therapies (antivirals, corticosteroids, LMWHs) administered at various time points in the disease process; (3) the RCTs are usually not appropriately powered to conduct meaningful secondary and subgroup analyses ; (4) the outcome "mortality" may be influenced by several concomitant factors, including age, the presence of comorbidities, the disparities among different national health systems.

The vast majority of the RCTs used a composite endpoint including disease progression, as documented by worsening of the respiratory failure, and death at 30 days. Table 1 summarizes the study results and distinguishes findings about the pre-specified composite endpoints (surrogate of disease progression) and mortality.

Table 1
Clinical trials exploring the use of CP in COVID-19 patients.

Reference	Study population	Days from onset of symptoms to CP infusion	Number of patients CP/ controls	Primary Outcome CP vs controls	Mortality CP vs controls
Li et al. [1]	Severe COVID-19 SaO2 of 93% or less on room air PaO2/FIO2 < = 300	Median 30 days	52/51	Clinical improvement within a 28-day period: 51.9% vs 43.1%, $p = 0.26$	15.7% vs 24%, $p = 0.3$ (28-day)
Agarwal et al. [2]	Severe COVID-19 SaO2 <=93% on room air PaO2/FiO2 200–300	Median 6 days	235/229	Composite of PaO2/FiO2<100 or all-cause mortality: 19% vs 18% (RR 1.04, 95% CI 0.71 to 1.54)	15% vs 14% (RR 1.04, 95% CI 0.66 to 1.63) (28-day)
Simonovich et al. [3]	Severe COVID-19 SaO2< = 93% on room air PaO2/FIO2 < = 300	Median 8 days	228/105	Clinical status 30 days after the intervention (ordinal scale): $p = 0.83$	10.9% vs 11.43% (risk difference −0.46, 95% CI, −7.8 to 6.8) (30-day)
Horby et al. RECOVERY [4]	COVID-19 (all patients)	Median 9 days	5795/5763	-	24% vs 24%, $p = 0.95$ (28-day)
AlQahtani et al. [5]	Severe COVID-19 SaO2 < = 92% on room air PaO2/FiO2 < = 300)	NA	20/20	Requirement for NIV or MV: 20% vs 30% $p = 0.72$	5% vs 10% $p = 0.55$ (in-hospital)
Balcells et al.* [6]	Severe COVID-19 No MV	< = 7 days (median 6 days)	29/28*	Composite of MV, hospitalization for >14 days, or death: 32.1% vs 33.3%, $p > 0.999$	17.9% vs 6.7%, $p = 0.246$ (in-hospital)
Korley et al. [7]	Outpatients	< = 7 days (median 4 days)	257/254	Disease progression (composite of hospital admission, seeking emergency or urgent care, or death) within 15 days: 30% vs 31.9%, risk difference 1.9; 95% CI, −6.0 to 9.8	1.9% vs 0.4%, risk difference, −1.6, 95% CI −4.2 to 0.50 (30-day)
Körper et al. [8]	Severe COVID-19 (including non-invasive or invasive MV or ECMO)	Median 7 days	53/52	Survival and no longer fulfilling criteria for severe COVID-19 on day 21: 43.4% vs 32.7%, $p = 0.32$	77.9% vs 68.1%, $p = 0.21$ (60-day survival)
Bajpai et al** [12]	Severe COVID-19	< = 3 days	14/15	% of patients remaining free of mechanical ventilation on day 7: 21.4% vs 6.7%, NS	21.4% vs 6.7, $p = 0.33$ (28-day)
Avendaño-Solà et al.*** [13]	Severe COVID-19	< = 12 days (median 8 days)	38/43	% of patients who need for non-invasive or invasive MV or who died at day 15: 0vs 14%, $p = 0.57$	0% vs 9.3% (in-hospital)
Ray et al. [14]	Severe COVID-19 PaO2/FiO2 100–300 No MV	NA	40/40	–	No difference
O'Donnell et al. [9]	Severe COVID-19 SaO2< = 94% on room air (including noninvasive or invasive MV and ECMO	< = 14 days (median 9 days)	72/147	Clinical status at day 28 (on an ordinal scale): $p = 0.18$	12.6% versus 24.6%, $p = 0.034$ (28-day)
Libster et al. [10]	Mild/moderate COVID-19 > = 75 years old	<=72 h	80/80	Progression to severe respiratory disease (> 30 breaths/min or SaO2< = 93% on room air): 16% vs 31%, $p = 0.03$	2% vs 5%, RR 0.50, 95% CI 0.09–2.65 (in-hospital)
Menichetti et al. (TSUNAMI) [11]	Moderate to severe COVID-19 PaO2/FIO2 200–350	< = 10 days (median 7 days)	232/241	Worsening respiratory failure (defined as a PaO2/FiO2 ratio<150) indicating the potential need for mechanical ventilation, or death: 25.5% vs 28%, $p = 0.54$	6.1% vs 7.9%, $p = 0.43$ (30-day)
REMAP-CAP Investigators [24]	Severe COVID-19	median 42 hours ****	1078/909	Organ support–free days up to day 21: 0 vs 3 (median-adjusted OR 0.97 (95% CrI, 0.83 to 1.15)	37.3% vs 38.4% (in-hospital)

* Early vs deferred CP therapy: the early plasma group received the first plasma unit at enrollment. The deferred plasma group received CP only if a prespecified worsening respiratory function criterion was met during hospitalization (PaO2/FiO2 < 200) or if the patient still required hospitalization for symptomatic COVID-19 >7 days after enrollment.

** CP versus frozen plasma.

*** Trial stopped after first interim analysis due to the fall in recruitment.

[d] from hospital admission

2.1. Disease progression (worsening of respiratory failure)

Several of the published trials [3,7,9,11] failed to demonstrate a benefit of CP in reducing the risk of disease progression. The TSUNAMI trial, a large RCT performed in Italy, did not shows a difference in disease progression, defined as a ratio of PaO2/FiO2 <150 indicating the need for non-invasive or invasive mechanical ventilation, in patients who received CP plus standard therapy (ST) compared to those who received ST alone. The RCT by Libster et al. is the only trial highlighting a beneficial effect of CP in reducing the risk of disease progression (> 30 breaths/min or SaO2< = 93% on room air) [10]. However, this trial has been specifically conducted in elderly patients treated with CP within 72 h from onset of COVID-19 symptoms.

2.2. Mortality

Several published [1–8,10,11] and unpublished RCTs [12,14] lack to demonstrate any beneficial effect of CP on mortality. The RECOVERY trial, the largest RCT on CP including 16.287 patients with COVID-19, showed no difference in 28-day mortality between patients who received CP and controls (24.1% vs 24.4%, $p = 0.95$) [4]. In the TSUNAMI trial, 30 days mortality was 6.1% for the CP recipients and 7.9% for the control group. These striking differences are probably due to several factors: difference in the population median age, difference in the risk factors for progression to severe COVID-19, time lapse between disease onset and CP transfusion, different comprehensive patient management, and, perhaps, better quality of our CP (NAbs titer ≥ 1:160).

3. Neutralizing antibodies titer of CP

It has been suggested that the benefits of CP may depend from the plasma nAbs titer [15], and that using CP with a low titer (i.e.:< 1:160) could explain negative results. Potential plasma donors are usually selected among patients completely recovered from symptomatic COVID-19 having required hospitalization showing an adequate antibodies titer. The ideal time for plasma donation is within thirty days from complete recovery (no symptoms and two consecutive negative nasopharyngeal swabs). However, the amount of antibodies and the virus neutralizing activity in convalescent serum is highly variable among donors [17]. A recent study compared three methods to determine the SARS-CoV-2 neutralizing activity of human CP (life virus neutralization by plaque reduction assay, a lentiviral vector based pseudotype neutralization assay and a competition ELISA-based surrogate virus neutralization assay) [18], and demonstrated that neutralization activity correlated among the different assays. However, in the published RCTs on CP in COVID-19 several different methods to evaluate the CP antibodies titer were used and they were not always comparable. The PLACID study used commercial qualitative immunoassays for SARS-CoV-2 antibodies on chemiluminescent immunoassay or enzyme linked immunosorbent assay [2]. The RECOVERY study used the EUROIMMUN IgG enzyme-linked immunosorbent assay (ELISA) targeting the spike glycoprotein [4]. Some studies did not qualify the CP [5], while others used some assay (SARS-CoV-2 Spike S1-RBD IgG enzyme-linked immunosorbent assay detection kit, GenScript) as surrogate of virus neutralization [10]. The TSUNAMI trial used qualified CP only, with a NAbs titer =/> 1:160, directly assessed with a micro-neutralization assay [11,19] and 36% of the patients (83) were treated with CP units with NAbs titers ≥1:320. In this trial the occurrence of the primary endpoint did not differ between the CP and the control group, even in the subgroup of patients who received CP with NAbs titers ≥320; however, the TSUNAMI trial was not powered for an accurate subgroup analysis and the results are inconclusive.

4. Early use of CP

It has been suggested that antibody-based therapies are likely to be most effective in the early stages of COVID-19, when viral replication dominates. Libster et al. showed that high-titer CP, administered to older adults within 72 h of the onset of mild COVID-19, reduced the progression of the disease: severe respiratory failure developed in 16% (13/80) of patients treated with CP and 31% (25 of 80) of those who received placebo ($p = 0.03$), with a relative risk reduction of 48% [10]. In the TSUNAMI trial the median time from the onset of COVID-19 to CP administration was of 7 days and this may have limited the CP efficacy [11]. It is noteworthy that, in the TSUNAMI trial, in the subgroup of patients with a PaO2/FiO2 ratio≥ 300 at randomization, worsening of respiratory function and deaths at 30 days occurred in 11.6% of patients who received CP + ST and 21.9% of those who were treated with ST alone [11]. This difference, although not statistically significant, (OR 0.47; 95% CI 0.19–1.18; $P = 0.059$) seems to confirm the strong relationship between early administration and clinical benefit of CP [11].

5. Presence of anti-spike antibodies in the recipients at the time of CP infusion

The presence of anti-SARS-CoV-2 IgG antibodies in recipients before receiving CP has also been listed as a possible reason for the lack of a documented CP efficacy. Several of the published RCTs evaluating CP in COVID-19 suffer for this methodological shortcoming. In the study by Agarwal, patients with a median pre-transfusion NAbs titer of 1:60 were transfused with CP units with a median titer of 1:40 [2]. This certainly represents a major drawback, because neither a virological nor a clinical beneficial effect should be expected with these experimental conditions. It is noteworthy that, in the RECOVERY trial, patients receiving CP having negative anti SARS-CoV2 IgG antibodies at the time of transfusion had a better outcome (death or mechanical ventilation) with respect to those not receiving CP (OR 0.90, 95% CI 0.82–0.97, $p = 0.01$) [4].

6. CP safety profile

The safety profile of CP in the published trials is good and the observed adverse events are generally not severe. Moreover, thrombotic adverse events have not been reported. Pathak suggests that CP may be prothrombotic and its use , in the context of a thrombophilic disorder like COVID-19, might represent a serious risk [20]. While it is true that most trials published to date had a short follow-up to detect thrombotic events, much controversy exists on the prothrombotic activity of CP: several authors have speculated that antithrombin III replacement achieved with CP units could favor efficacy of heparin therapy. However, at present, this has not been formally demonstrated *in vivo*. Moreover, convalescent donors have no history of thrombosis, and the small reinfused CP volume only alters 15% of the recipient's plasma total volume.

7. CP with antibodies active against dominant variant of concern

The efficacy of CP is likely to depend on the 'match' between the strain-specific transfused anti-SARS-CoV-2 antibodies in donor plasma and the infecting virus variant in the recipient. The SARS-CoV-2 variant (B.1.1.7) detected in England in December 2020, spread rapidly to become the dominant SARS-CoV-2 variant in most European countries, including Italy [21]. Whilst B.1.1.7 has changes in the spike glycoprotein that could theoretically modify antigenicity, only modest reductions in neutralization by CP have been reported. The majority of RCTs were conducted when the dominant variant was represented by the D614G. The role of CP against more recently described and today largely dominant VoC (i.e.: Delta variant) is unknown.

8. Perspectives

Treatment of patients with COVID-19 changes according to setting of care, disease severity and phase of disease [25]. Current evidences suggest that CP treatment of patients with moderate to severe COVID-19 does not reduce the progression to severe respiratory failure or death within 30 days. However, the favorable trend, observed in some subgroups of patients (patients treated within the first 72 h from onset of symptom, those with a PaO2/FiO2 ratio $\geq$ 300) suggests a potential benefit of earlier, high titer, CP in mild COVID-19 [22]. However, in the field of immunotherapy, alternative treatments are now available. Hyperimmune globulin was manufactured from a large number of CP donors and consists of a concentrated immune globulin fraction with well-defined properties, tested in a small group of patients, showed to be safe but without significant clinical benefit [23]. More interestingly, monoclonal antibodies (mAbs) developed from CP, directed against specific target of SGP and selected on the basis of antiviral potency and target affinity showed efficacy in reducing the risk of disease progression and death. Currently approved mAbs have not the same activity against VoC [21]. Ongoing clinical trials are evaluating the safety and efficacy of second-generation mAbs with activity against circulating VoC and more easily administered by IM route. Moreover oral antiviral drugs seem to represent a promising option for early outpatient treatment for COVID-19. Identification of predictors of poor outcome and severe prognosis in patients with COVID-19 who are cared for at home or who need hospitalization may allow physicians to start a more tailored therapy [26]. Finally, efforts to identify predictors of lack of response to vaccines and new preventive strategies, such as immunotherapy for prevention of COVID-19 or post-exposure intervention, are warranted and explored in the future [27][28]

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