PERSPECTIVE

Heterogeneity in COVID-19 Convalescent Plasma Clinical Trials

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Due to the outbreak of the coronavirus disease 2019 (COVID-19) pandemic, clinical trial (CT) research for efficacy and safety evaluation of convalescent plasma (CP) accelerated globally. In trial planning and approval, clinical researcher and regulatory agencies worldwide are challenged by limited evidence from the use of convalescent plasma in previous outbreaks of viral diseases and by different possible study approaches. We analyzed CT designs to identify potential opportunities for data aggregation and to facilitate generation of decision-relevant evidence.

CP therapy has a long-standing history in the post-exposure prophylaxis and treatment of infectious diseases, including outbreaks of various respiratory infections, such as the 2002–2004 severe acute respiratory syndrome-coronavirus (SARS-CoV) pandemic, the 2009 H1N1 influenza virus pandemic, and the 2012 Middle East respiratory syndrome coronavirus (MERS-CoV) epidemic. Unfortunately, evidence of its efficacy from rigorously controlled CTs is still limited.[1]

The number of CTs evaluating CP therapy in patients suffering from coronavirus disease has rapidly grown in response to the COVID-19 pandemic in the absence of a vaccine and a specific antiviral therapy. Over 140 CP-CTs have been registered by a COVID-19 specific CT database.[2] Different study concepts and designs are required for a comprehensive evaluation of the quality, efficacy, and safety aspects of CP therapy. The disadvantage, however, is that this increases the risk of conflicting study results and thus complicates informed decision making in the treatment of patients with COVID-19.[3] Available meta-analyses already pointed to the methodological heterogeneity, the risk of study bias, and the general lack of controlled CTs.[4,5] In addition, in case of pandemic waning, a high number of CTs may augment recruitment issues. Indeed, some CTs already had to be terminated early.[6,7]

COVID-19 CP THERAPY IN CLINICAL TRIALS

The goal of this article is to evaluate the potential opportunities of CT data aggregation to improve informed decision making for physicians, researchers, regulators, and policy makers.

A comparative analysis of COVID-19 CP related CTs was performed using a revised and extended dataset originally derived from a real-time dashboard of clinical trials for COVID-19.[2] Only publicly available data were used. Data modeling, analysis, and plotting was performed using Microsoft Excel 2016, and statistical analyses were conducted using Stasols nQuery sample size software.

CP is the third most frequent therapy and the second most frequent discrete investigational medicinal product evaluated in COVID-19 related CTs (**Figure 1a**). As of January 15, 2021 and of 2,533 globally tracked CTs,[2] 6.5% were related to plasma-based therapies. One hundred forty-four CTs specifically evaluating CP therapy were included in our final analysis set (**Table S1**). A summary of CT locations and designs is shown in **Table 1**.

The majority of CP-CTs is conducted in North America (38%), Asia (29%), and the European Union (15%). The main countries by frequency are the United States (29.9%), Iran (9.7%), China and Mexico (both 6.3%). Fifty-six percent of the CTs have a randomized controlled trial (RCT) and 11% a nonrandomized controlled design, 28% are single-armed, and 5% are not specified. Overall, 27,495 patients are planned for enrollment with 70% (~ 19,000 subjects) to be included in RCTs. Of the RCTs, 86% will be conducted in a single province with a mean recruitment size of 240 subjects and a mean duration of 9.5 months. The majority of RCTs is open label (31% of total CTs) and evaluates patients in the hospital (39% of total CTs) or intensive care unit (ICU) setting (9% of total CTs). A similar setting applies for nonrandomized and single-armed CTs. A minority of RCTs is using a blinded study design (23% of total CTs). Eighty-five percent of all CTs recruit exclusively adult patients, 12% also include children, and 2% are primarily pediatric

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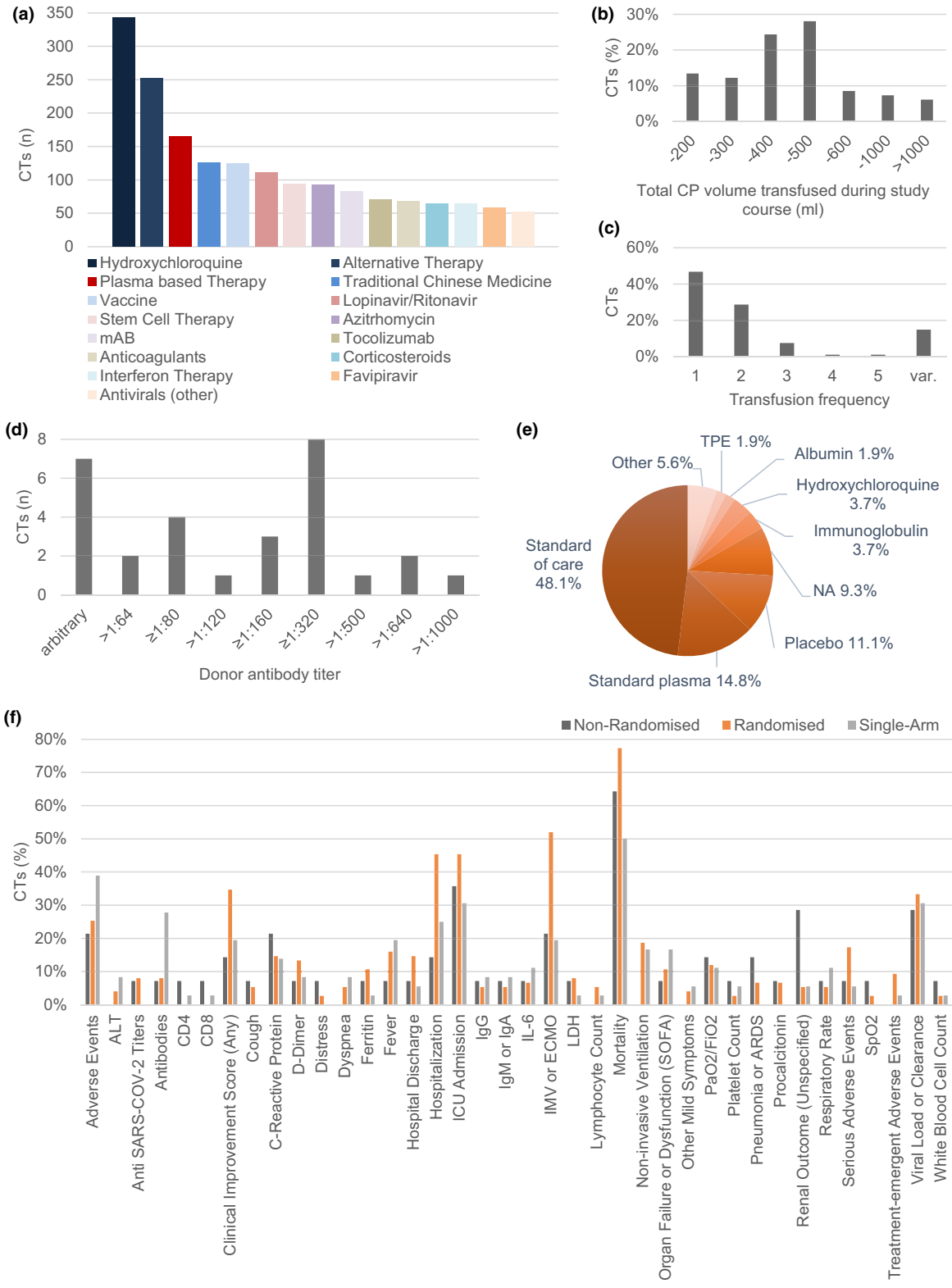

Figure 1 Ranking, transfusion regimen, comparators and endpoints of convalescent plasma (CP) clinical trials (CTs). (**a**) Fifteen globally most frequently investigated COVID-19 therapies (as of January 2021). (**b**) Total CP volumes transfused during study course (upper limits). (**c**) CP transfusion frequency (data in **b** and **c** aggregated from CTs enrolling adult subjects exclusively). (**d**) Donor antibody titer (absolute numbers of CTs are shown due to sample size). (**e**) Type and frequency of comparators used in controlled CTs (randomized and nonrandomized CTs, multiple comparators present in some studies. NA, no data available; TPE, therapeutic plasma exchange). (**f**) Frequency of outcome measures by study design (outcome measures with a maximum frequency of < 5% in any group are left out intentionally. IMV, invasive mechanical ventilation).

Table 1 Overview of COVID-19 convalescent plasma related CTs

Region/country	CTs (*n*)	%
Africa	6	4.2
Egypt	4	2.8
Nigeria	1	0.7
Kenya	1	0.7
Asia	41	28.5
Bahrain	1	0.7
Bangladesh	1	0.7
China	9	6.3
India	6	4.2
Indonesia	2	1.4
Iran	14	9.7
Iraq	1	0.7
Kuwait	1	0.7
Pakistan	3	2.1
Saudi Arabia	1	0.7
Vietnam	2	1.4
Australia	1	0.7
Europe (EU)	21	14.6
Belgium	1	0.7
France	2	1.4
Germany	5	3.5
Greece	1	0.7
Hungary	1	0.7
Italy	5	3.5
Netherlands	2	1.4
Spain	2	1.4
Sweden	2	1.4
Europe (other)	5	3.5
Macedonia	1	0.7
Russia	1	0.7
Switzerland	2	1.4
Turkey	1	0.7
North America	55	38.2
Canada	1	0.7
Mexico	9	6.3
United States	43	29.9
US + other countries	2	1.4
South America	15	10.4
Argentina	3	2.1
Brazil	1	0.7
Chile	2	1.4
Columbia	7	4.9
Ecuador	1	0.7
Peru	1	0.7
Total	144	100.0

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Table 1 (continued)

Study design		Nonrandomized	Randomized	Single-arm	Unspecified	All CTs
Number of CTs		16 (11.1%)	81 (56.3%)	40 (27.8%)	7 (4.9%)	144 (100.0%)
Subjects	*N* total (%)	3,572 (13.0%)	19,442 (70.7%)	4,289 (15.6%)	192 (0.7%)	27,495 (100.0%)
	N mean (range)	223 (12–700)	240 (15–2,400)	107 (10–2,000)	192 (192–192)	199 (10–2,400)
Province	Single (%)	93.8%	85.7%	92.5%	–	89.3%
Mean duration	Months (range)	8.8 (1–26)	9.5 (1–34)	9.1 (2–51.1)	–	9.3 (1–51.1)
Blinding	Double	–	14 (9.7%)	–	–	14 (9.7%)
	Open–Label	14 (9.7%)	45 (31.3%)	39 (27.1%)	–	98 (68.1%)
	Quadruple	–	7 (4.9%)	–	–	7 (4.9%)
	Single	–	3 (2.1%)	–	–	3 (2.1%)
	Triple	–	9 (6.3%)	–	–	9 (6.3%)
	Unspecified	2 (1.4%)	3 (2.1%)	1 (0.7%)	7 (4.9%)	13 (9.0%)
Patient setting	Healthy exposed	–	2 (1.4%)	2 (1.4%)	–	4 (2.8%)
	Hospital	7 (4.9%)	56 (38.9%)	25 (17.4%)	2 (1.4%)	90 (62.5%)
	ICU	7 (4.9%)	13 (9.0%)	9 (6.3%)	4 (2.8%)	33 (22.9%)
	Outpatient	1 (0.7%)	5 (3.5%)	–	–	6 (4.2%)
	Unclear	1 (0.7%)	4 (2.8%)	4 (2.8%)	1 (0.7%)	10 (6.9%)
	NA	–	1 (0.7%)	––	–	1 (0.7%)
Eligible subjects	Adults	12 (8.3%)	72 (50.0%)	34 (23.6%)	5 (3.5%)	123 (85.4%)
	Adults and children	4 (2.8%)	7 (4.9%)	4 (2.8%)	2 (1.4%)	17 (11.8%)
	Children	–	1 (0.7%)	2 (1.4%)	–	3 (2.1%)
	NA	–	1 (0.7%)	–	–	1 (0.7%)
Age range (adults)	18 to < 60	–	1 (0.8%)	2 (1.6%)	–	3 (2.4%)
	18 to < 70	–	5 (4.1%)	2 (1.6%)	–	7 (5.7%)
	18 to < 80	–	7 (5.7%)	2 (1.6%)	–	9 (7.3%)
	18 to < 90	1 (0.8%)	7 (5.7%)	4 (3.3%)	–	12 (9.8%)
	18 to ≥ 90	10 (8.1%)	44 (35.8%)	22 (17.9%)	5 (4.1%)	81 (65.9%)
	20 to ≤ 60	–	2 (1.6%)	–	–	2 (1.6%)
	21 to ≤ 70	–	–	1 (0.8%)	–	1 (0.8%)
	21 to > 70	–	1 (0.8%)	–	–	1 (0.8%)
	25 to 55	1 (0.8%)	–	–	–	1 (0.8%)
	30 to ≤ 70	–	–	1 (0.8%)	–	1 (0.8%)
	30 to > 70	–	1 (0.8%)	–	–	1 (0.8%)
	40 to NA	–	1 (0.8%)	–	–	1 (0.8%)
	50 to 70	–	1 (0.8%)	–	–	1 (0.8%)
	65 to NA	–	2 (1.6%)	–	–	2 (1.6%)

Comparative description of nonrandomized, randomized, and single-arm CTs. Relative data are calculated as percentage of all CTs.
COVID, coronavirus disease; CT, clinical trial; EU, European Union; NA, not applicable; US, United States.

studies. Adult age ranges show notable heterogeneity. Lower limits vary between 18 and 65 years, and upper age limits are between 45 and 99 years. Other eligibility criteria (e.g., disease severity or comorbidities) could not be assessed consistently.

The putative optimal CP treatment regimen is frequently debated among practitioners and regulators. In earlier CP-CTs, there was large variation among treatment schemes, which was partially caused by its use in different indications (i.e., treatment and prophylaxis).[8] In fact, heterogeneity of treatment algorithms is a strong limiting factor in the comprehensive meta-analysis of CP-CT data. We compared the treatment schemes of CTs enrolling adults exclusively, including the total CP volumes transfused during the course of the studies (**Figure 1b**, $n = 89$) and transfusion frequencies (**Figure 1c**, $n = 94$). Upper limits of total volumes are most frequently between 200 and 500 mL, although the data show large variability (range: 180–5,250 mL). Variability of transfusion frequencies is also notable, but the majority of study participants receive the total volume within one to two transfusions. The planned average transfusion volume for single administration is 270 mL. Data on the minimum donor antibody titer required were available for few CTs

only (**Figure 1d**, $n = 29$). It should be noted, however, that for many CTs, the availability of appropriate antibody or neutralization tests was limited at the time of their initiation, but such qualifying criteria may have been introduced later and are not recorded in databases or registries. Despite this limitation in our analysis, the available data indicate a considerable heterogeneity among CTs in this regard. In addition to the treatment regimen, the use of comparators was analyzed in the controlled CTs (**Figure 1e**). The most frequent control groups are standard of care (SOC) therapy (48%), standard plasma (16%), and placebo (11%), the latter being defined most often as saline or lactated ringer's solution. The most frequent outcomes for the investigation of CP efficacy and safety are shown in **Figure 1f** and include adverse events, clinical improvement scores, hospitalization, ICU admission, mechanical ventilation or extracorporeal membrane oxygenation (ECMO), mortality, and viral load or clearance. No substantial discrepancy is noted among different CT designs.

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Positive prospects and statistical considerations

Various CTs are required to resolve important open questions of CP therapy in general and in COVID-19. The most appropriate study endpoints, patient eligibility criteria, and study size must be determined as well as optimal treatment algorithms, including neutralizing antibody titers, transfusion volumes, and timing of treatment. Given the continuing lack of consensus for CP therapy,[4] these questions could not be answered with only very few CTs. In particular, the importance of controlled CTs must be emphasized in supporting the concept and addressing regulatory needs in the authorization of CP therapy.

In the RCTs ($n = 81$), SOC, standard plasma, and placebo are considered appropriate comparators taking into account the unestablished efficacy of other treatment options (see **Figure 1e**) and safety considerations. Among RCTs which meet these criteria ($n = 70$), the slightly larger proportion is open-label ($n = 37$) and the smaller part blinded ($n = 30$, data not available $n = 3$). Fifty-one of these 70 RCTs include patients in the outpatient or hospital setting (open-label $n = 28$, blinded $n = 23$), and 57 RCTs include patients in the hospital or ICU setting (open-label $n = 32$, blinded $n = 25$).

Heterogeneity is added by use of different endpoints. However, some show a consistent association, such as mortality and the Delta Sequential Organ Failure Assessment (SOFA).[9] Among all RCTs, study endpoints (**Figure 1f**) most often refer to mortality (77.3%), mechanical ventilation or ECMO (52.0%), hospitalization (45.3%), ICU admission (45.3%), and clinical improvement score (34.7%).

Of all RCTs, 89% have 2 study arms, 8.1% follow a 3-armed design, and 1.2% are 4- and 6-armed, respectively. The mean size per study arm is 105. This size is sufficient to demonstrate an odds ratio = 0.3 (e.g., for mortality, ventilation requirement, or non-discharge from the ICU). This consideration assumes event rates of 25% and 10% in the control and treatment group, respectively, with 5% significance level and 80% power by means of a two-sided χ^2 test, and is inferred by unpublished and published statistical analyses.[10] The same sample size could also detect a 1 point difference in SOFA score, as calculated using a 2-sided t-test for 2 means with $\alpha = 0.05$, 80% power, an effect size of 0.38, and an SD of 2.64.[9] Likewise, an odds ratio of 0.4 for the development of severe respiratory disease assuming event rates of 50% and 30% in the control and treatment groups, respectively, could be detected. Indeed, a risk reduction of 48% with event rates of 31% and 16% in the placebo and treatment groups (relative risk = 0.52, $P = 0.03$, $N = 80$ per group) for development of severe respiratory disease has been found in a RCT evaluating elderly outpatients treated with CP-IgG titers above 1:1,000 within 72 hours since symptom onset.[7] However, a recent meta-analysis suggests that any potential treatment effects may be substantially smaller in other settings, especially in hospitalized patients.[5] Consequently, a larger number of CTs may be statistically underpowered.

Negative prospects

Data aggregation will be complicated by different treatment regimen, timings between diagnosis and treatment start, eligibility criteria, and national or regional study procedures (e.g., related to supportive care and comedication). Different CP quality characteristics will produce additional uncertainty in CT data interpretation and synthesis, in particular, due to differences in donor eligibility criteria and in testing of donated plasma. Used plasma antibody titer for CP therapy will only be partially comparable and differences among antibody assays may worsen the situation. The US Food and Drug Administration (FDA) and the European Commission release updated recommendations to health care providers, investigators, and blood establishments for the collection and transfusion of CP. However, there are currently no robust data for cut-off levels of neutralizing antibody titers.

Outlook

About 70 COVID-related CTs of different therapies and vaccines have been approved in Germany with recruitment needs of approximately 900 patients in the ICU.[2] According to the German DIVI-Intensivregister ~ 5,000 patients with COVID-19 in ICUs have been registered as of January 15, 2021. The current ratio of available and needed study participants suggests that sufficient evidence can now be generated worldwide to definitively clarify the efficacy of CP therapy. Stronger evidence of CP-related quality, safety, and efficacy is important for any future prophylactic or therapeutic use of CP and corresponding hyperimmunoglobulin therapies. This may be particularly important for low- and middle-income countries that may have limited or delayed accessibility to future vaccines.

SUPPORTING INFORMATION

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CONFLICT OF INTEREST

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