Convalescent plasma therapy in B-cell-depleted and B-cell sufficient patients with life-threatening COVID-19 – A case series

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ARTICLE INFO

ABSTRACT

Objective: To investigate the effect of convalescent plasma therapy (CPT) on clinical courses of B-cell-sufficient and B-cell-depleted patients with life-threatening COVID-19.

Patients and Methods: In this case series, we retrospectively analysed clinical, laboratory and cardiopulmonary parameters of six patients with life-threatening COVID-19 receiving convalescent plasma (CP) as rescue therapy between April 11, 2020 to October 10, 2020. Clinical and laboratory parameters before and after transfusion were compared in two B-cell-depleted patients and four B-cell sufficient patients (control group).

Results: Both B-cell-depleted patients cleared SARS-CoV-2 virus and survived, while all other patients died within 14 days from intervention despite maximal therapeutic efforts. D-dimer levels increased in both cohorts subsequent to CPT. In control patients, mean Interleukin-6 increased and platelet levels decreased as opposed to decreasing and stable levels in B-cell-depleted patients, respectively. Control patients required increased doses of vasopressor compared to decreasing doses in B-cell depleted patients subsequent to CPT. PO_2/FiO_2 decrease was more pronounced and respiratory deterioration required postinterventional extracorporeal membrane oxygenation in two control patients. Transpulmonary thermodilution revealed a further increase of the Extravascular Lung Water Index upon CPT in control patients.

Conclusion: Use of CP in late stages of life-threatening COVID-19 should be used with caution but may be beneficial in B-cell-depleted patients. Further studies are necessary to assess factors predicting potential therapeutic benefits as well as possible hazards.

1. Introduction

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) results in a wide array of clinical phenotypes ranging from asymptomatic carriage to a potentially deadly systemic disease requiring intensive care in nearly 5% of affected patients. Among several identified risk factors such as age and cardiovascular disease, inherent or acquired immunodeficiency have been associated with unfavourable outcomes [1]. To date, targeted treatment options proven to be effective

for COVID-19 remain limited. Based on immunological considerations, convalescent plasma (CP) has frequently been administered in COVID-19 [2,3]. However, recently published randomized controlled trials failed to show significant clinical improvement for the use of CP in moderate, severe or life-threatening COVID-19 [2,4–7]. While mechanistic details remain to be elucidated, it has been postulated that CP transfusion (CPT) might worsen oxygenation through enhancement of microthrombosis [8].

An intact immune response is considered to be crucial for elimination

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of SARS-CoV-2 through humoral and cell-mediated pathways [9,10]. Accordingly, persistent SARS-CoV-2 infection has been reported in patients receiving B-cell-depleting antibodies such as the anti-CD20 monoclonal antibody rituximab [11–14]. As the effect of CP is mainly attributed to antibodies mediating passive immunity, CP efficacy would be expected to be higher in B-cell-depleted patients though data of CP treatment in immunosuppressed patients are limited [2,4–6,11].

Based on this rationale, we report the longitudinal assessment of the clinical course and antibody responses in four B-cell-sufficient patients compared with two B-cell-depleted patients with life-threatening COVID-19, who received CP as a rescue therapy.

2. Methods

2.1. Study cohort

Data of all patients receiving CP under compassionate-use guidelines at our intensive care unit (ICU) between March and September 2020 were analyzed. One patient was excluded as CP treatment was started in a peripheral hospital. Patients were prospectively included in the COVID-19 registry CoMRI at the University Hospital rechts der Isar of

Technical University Munich (TUM) and consent was obtained according to the study protocol which was approved by the institutional Ethics Committee (221/20S).

2.2. Intervention and monitoring

Patients received CP (2–10 units, see Table 1) with volumes of 180–235 ml and mean SARS-CoV-2 antibodies titers of 1:1256 (range, 1:100 to 1:3200) or IgG antibody levels of 4,5 U/mL (range, 1.74–7.27 U/mL) as determined by an in-house ELISA [15] and the Euroimmune assay, respectively. CP units were transfused 24 h apart and for a maximum of three days in a row.

Patients were continuously hemodynamically monitored by invasive arterial pressure measurement extended with transpulmonary thermodilution (TPTD) and pulse contour analysis (Pulsioflex with PiCCO plus or PiCCO2 monitor, Pulsion Medical Systems, Munich, Germany) as described previously [16] which allows determination of the Global End-Diastolic Volume Index (GEDVI), the extravascular lung water index (EVLWI), as well as pulmonary vascular permeability index (PVPI). The Cardiac Index (CI) is obtained by indexation of cardiac output to body surface area and enables calculation of the Cardiac Power

Table 1
Baseline characteristics, clinical course and outcome of patients treated with convalescent plasma due to life-threatening COVID-19.

	No. 1	No. 2	No. 3	No. 4	No. 5	No. 6	Mean BCdpl	Mean ctrl
Baseline Characteristics								
Age category	65−69	50−54	35−40	50−54	60−64	25−30	58	45
Sex	male	female	male	male	female	male	–	–
Co-existing conditions								
Hypertension	X	–	–	–	X	–	–	–
Diabetes mellitus	–	–	–	–	X	–	–	–
Pulmonary disease	–	–	–	–	X	–	–	–
Chronic kidney disease	MCD	X	–	–	–	–	–	–
Malignant disease	–	FL	–	–	–	X	–	–
No other condition	–	–	X	X	–	–	–	–
Current/former smoker	–	–	–	–	X	–	–	–
B-cell-depleting therapy			–	–				
Cycles of rituximab	11	12	–	–	–	–	–	–
Last administration – COVID-19 diagnosis (d)	75	28	–	–	–	–	–	–
COVID-19 disease								
Symptom onset – presentation (d)	8	8	6	5	2	1	8	3.5
Presentation – transfer to ICU (d)	1	9	0	0	0	2	5	0
Presentation – intubation (d)	2	10	1	0	0	3	6	0.5
SOFA score at admission to ICU	0	3	1	11	6	5	1.5	5.5
Initial CT scan	*2	*3	*3	*3	*4	*1	–	–
COVID-19 directed therapy								
Remdesivir (d)	6	8	1	–	–	–	–	–
Dexamethasone (d)	10	–	–	–	–	–	–	–
CP (units)	5	5	2	10	4	5	5	4.5
Convalescent plasma therapy								
COVID-19 diagnosis – CPT (d)	7	21	10	24	20	5	14	15
Presentation – CPT (d)	4	20	11	24	21	5	12	16
CPT – viral clearance	17	21	2	6	–	–	19	4
Outcome								
Mechanical ventilation (d)	31	63	15	38	27	8	47	21
ECMO (d)	0	0	4	29	0	4	0	4
ADVOS[a] (cycles)	0	41	0	9	27	0	20.5	9
Need for vasopressor support	X	X	–	X	X	X	–	–
CPT – discharge ICU (d)	32	60	–	–	–	–	46	–
CPT – hospital discharge (d)	49	60	–	–	–	–	54.5	–
CPT – death (d)	–	–	5	14	6	6	–	8
ICU admission (d)	35	71	16[b]	38[b]	27[b]	9[b]	66.5	21.5[b]
Hospital admission (d)	53	80	16[b]	38[b]	27[b]	9[b]	66.5	21.5[b]

*1: typical pattern of early staged viral pneumonia. consistent with COVID-19.
*2: typical pattern of COVID-19 pneumonia.
*3: typical pattern of severe COVID-19 pneumonia.
*4: extensive infiltrations. most likely COVID-19 pneumonia.
ADVOS, ADVanced Organ Support; bpm, beats per minute; BCdpl, B-cell-depleted; ctrl, control; CP, convalescent plasma; CPT, convalescent plasma transfusion; d, days; ECMO, extracorporeal membrane oxygenation; FL, Follicular lymphoma; ICU, Intensive Care Unit; MCD, Minimal Change Disease; N/A, not available; SOFA, sequential organ failure assessment.
[a] ADVOS is a hemodialysis approach which combines extracorporeal CO2 removal with continues renal replacement therapy.
[b] died on ICU.

Index (CPI = mean arterial pressure x CI x 0.0022). Post-interventional measurements were missing in patient No. 3. The ratio of partial pressure of oxygen and the fraction of inspired oxygen (pO_2/FiO_2) was compared if patients were continuously on or without extracorporeal membrane oxygenation (ECMO) support.

A standardized laboratory parameter panel was routinely sent for analysis twice a week. IgM and IgG antibodies against SARS-CoV-2 S1 or N protein were detected using a paramagnetic particle chemiluminescent immunoassay (Shenzhen Yhlo Biotech Co., Shenzhen, China). Values ≥10 AU/mL were considered positive according to the manufacturer's instructions. Nucleic acids were extracted from nasopharyngeal swabs or bronchoalveolar fluid and subjected to SARS-CoV-2 polymerase chain reaction (PCR). Viral clearance was defined as two consecutive negative SARS-CoV-2 PCR tests.

2.3. Data analysis

Parameters were retrospectively compiled by chart review and collected the day before (d-1), on the day of first CPT (defined as day0) as well as day2, 3 and 4 ("pre" = mean of d-1 and d0, "post" = mean of d2, 3 and 4). Missing values were omitted. Mean and fold change were determined using Microsoft Excel. Graphs were plotted using GraphPad Prism 9.0 and assembled using Adobe Illustrator 2021. Scatter dot plots visualize means with standard error of the mean.

3. Results

3.1. Patients and clinical courses prior to CP treatment

Six patients hospitalized with life-threatening COVID-19 received CP between April and October 2020 (Fig. 1A, Table 1). Two of them (No. 1 and 2) have received rituximab because of adult-onset minimal change disease and follicular lymphoma grade I, respectively (see Table 1 for details). As circulating B-cells could not be detected by flow cytometry (Supplemental Fig. 1) this subgroup is referred to as B-cell-depleted group in the following (51 and 65 years, one female) and was compared to a control group of four patients with no history of heamatological malignancy or immunosuppression (No. 3 to 6, mean age 47, range 26–60 years, one female). All patients developed severe severe acute respiratory distress syndrome (ARDS), intubation was required 6 versus 0.5 days upon hospital admission, respectively (B-cell-depleted patients: range, 2–10 versus control group: range, 0–3 days). Prone positioning was performed in all patients. Patient characteristics and details of clinical courses are summarized in Table 1 and S1, a chronological synopsis is depicted in Fig. 1A.

3.2. CP therapy

Patients received 5 versus 4.5 (control group, range 2–10) units of ABO-compatible CP (Table 1). Mean time between first positive SARS-CoV-2 PCR to initial CPT was 14 days in B-cell-depleted patients (range, 7–21) and 15 days in control patients (range, 5–24) (Table 1). Except for patient No. 3, all patients remained positive in SARS-CoV-2 PCR testing before CP administration (Fig. 1A). No anti-SARS-CoV-2 antibodies could be detected in both B-cell-depleted patients, whereas three out of four control patients had mounted a specific antibody responses prior to CPT (Fig. 1A, Supplemental Table 1). Post-interventionally, anti-SARS-CoV-2 IgG could be detected in all patients (Fig. 1A, Supplemental Table 1). Viral clearance was noted 17 and 21 days upon CPT in B-cell-depleted compared to 2 (No. 3) and 6 (No. 4) days in control patients, but was never achieved in patient No. 5 and 6 before death (Table 1).

3.3. Outcome

Both B-cell-depleted patients survived: Patient No. 1 could be

discharged home 49 days, patient No. 2 was transferred from ICU to a rehabilitation center 60 days upon CPT (see Table 1 for more details). In sharp contrast, all other patients died within 14 days from CPT. In patient No. 3, a femoral twin double lumen cannula needed to be inserted due to jugular vein thrombosis developing on both sides at the time of cannulation for ECMO support, but failed to prevent death from respiratory failure. Patients No. 4 and 5 died from multi-organ failure (renal, pulmonary and hepatic failure) despite using the extracorporeal multi organ device "ADVanced Organ Support" (ADVOS) (No. 5) combined with ECMO (No. 4). Patient No. 6 died in consequence of subarachnoidal haemorrhage which occurred three days following insertion of a venovenous ECMO device.

To further investigate the striking differences in patient outcomes, respiratory, circulatory and laboratory parameters were longitudinally assessed.
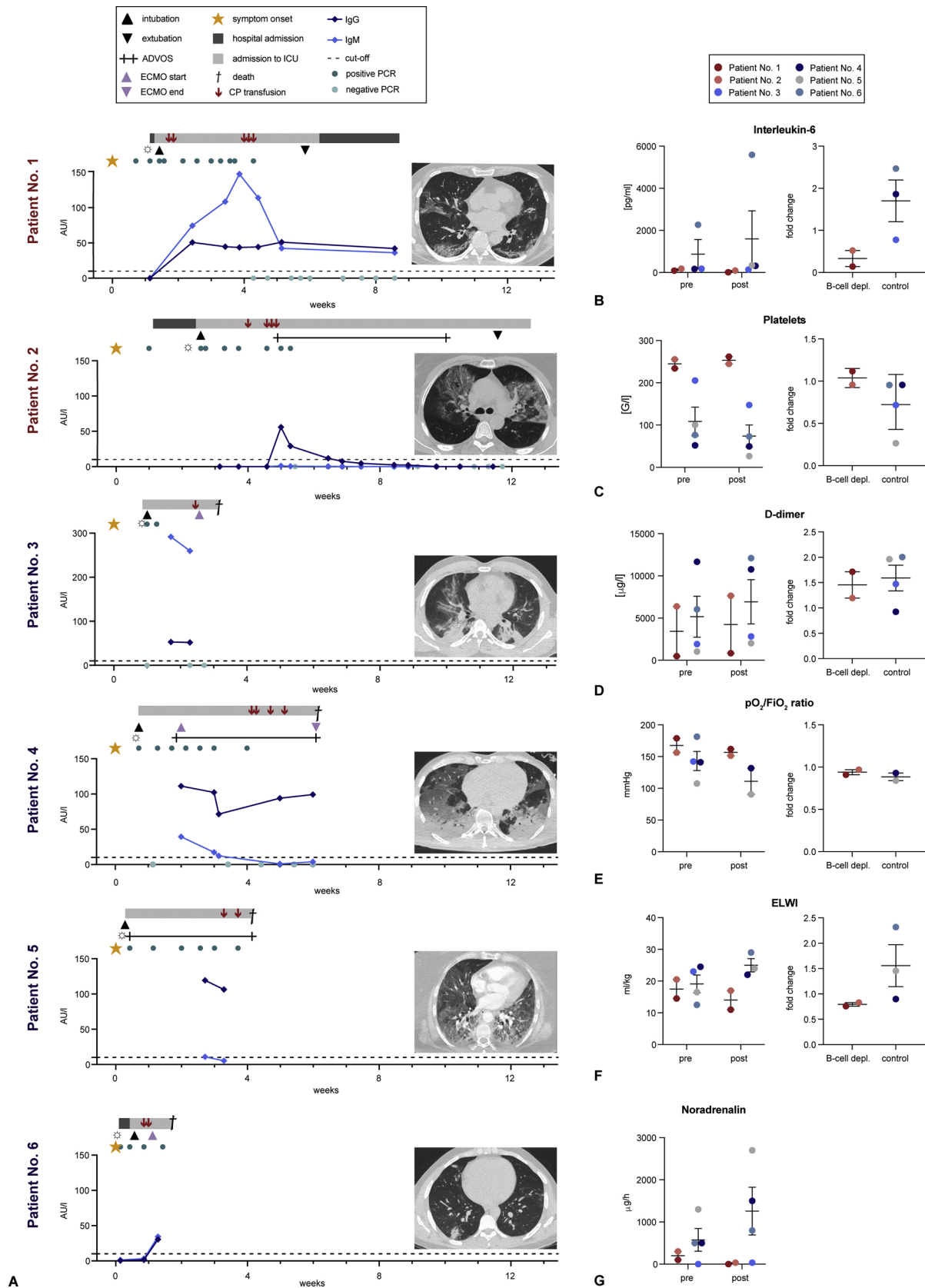
3.4. Analysis of laboratory parameters

Retrospective analysis of inflammatory laboratory parameters showed elevated baseline C-reactive protein (CRP) levels (B-cell-depleted: mean 12.8, range 4.6–21.1 versus control: mean 21.0, range 12.9–43.1, reference <0.5 mg/dl) and procalcitonin (PCT) (B-cell-depleted: mean <0.3, range <0.01 to 0.3, control: mean 3.3, range 0.3–7.6, reference <0.1 ng/mL) in both groups (Supplemental Figure 2A, Supplemental Table 2). Both parameters decreased upon CPT (Supplemental Figure 2A, Supplemental Table 2). Interleukin-6 (IL-6) levels where higher in the control group, particularly in patient No. 6 (control: mean 871.7, range 171–2266 versus B-cell-depleted: mean 134.1, range 88.2–180, reference <7 pg/mL) and showed substantial increase in two out of three control patients (mean 1597.6, range 138–5589.5 pg/ml) in contrast to a decline in B-cell-depleted patients (mean 53.2, range 12.4–94 pg/ml) following CPT (Fig. 1B, Supplemental Table 2). A similar trend was observed for the acute phase protein ferritin (Supplemental Figure 2A, Supplemental Table 2). Platelet counts were low in control patients (mean 108.6, range 52–205.5, reference 150−450 G/l) and further declined upon CPT (mean 74.2, range 26.7–147.3 G/l), while baseline levels were normal in B-cell-depleted patients and remained stable following CPT (Fig. 1C, Supplemental Table 2). D-dimers were elevated in both cohorts (B-cell-depleted: mean 3438, range 490–6386, versus control: 5164.8, range 1035–11663, reference <500 µg/l fibrinogen-equivalent units) and increased subsequent to CPT (Fig. 1D, Supplemental Table 2). Laboratory data are displayed in Supplemental Table 2.

3.5. Analysis of cardiopulmonary parameters

In addition to these laboratory changes, we observed differences in cardiopulmonary status. Acute deterioration of respiratory status required insertion of an ECMO device one and two days upon CPT in patients No. 3 and 6, respectively, limiting the ability to compare the effect of CPT on respiratory parameters in those two patients. PO_2/FiO_2 decreased in both cohorts but less pronounced in B-cell-depleted patients (B-cell depleted: mean 167.6, range, 156.3–178.9, to mean 156.7, range 151.4–162.0 versus control: mean 143.1, range, 107.6–181.4, to mean 115.1, range, 66.6–171.5 mmHg) (Fig. 1E, Supplemental Figure 2B, Supplemental Table 3).

B-cell-depleted patients required less vasopressors (mean noradrenaline dose 200 µg/h, range 100–300) than control patients (575 µg/h, range 0–1300) to reach similar mean arterial pressure (MAP) before CPT (B-cell-depleted: 80.3, range 71–89.5 versus control: 81.9, range 72.0–100.9 mmHg). While noradrenalin doses needed to be increased in control patients subsequent to CPT (1258.3, range 33–2700 µg/h), they could be decreased in both B-cell-depleted patients (16.7, range 0–33 µg/h) (Fig. 1G, Supplemental Figure 2C, Supplemental Table 4). TPTD showed elevated EVLWI in both patient cohorts before (B-cell-depleted: 17.5, range 14.5–20.5, versus control: 19.1, range 12.5–24.5,

(caption on next page)

Fig. 1. Course of clinical and laborarory parameters of six patients with life-threatening COVID-19.

(**A**) Chronological synopsis of the clinical course starting from symptom onset including antibody levels (in AU/l) and SARS-CoV-2-PCR results of both B-cell-depleted (upper 2 panels, red) and control patients (lower 4 panels, blue). The dashed line indicates the cut-off for seropositivity. A representative CT image is depicted, the sun symbol lables the time point of the scan.

(**B-G**) Left panels show mean levels of laboratory and clinical parameters before (mean of d-1 and d0 = pre) and after CP transfusion (mean of d2, 3 and 4 = post). Right panels depict the respective fold changes. Scatter dot plots visualize means of each cohort with standard error of the mean. IL-6 levels were not available for patient No. 5 after CP transfusion. The pO_2/FiO_2 ratio was only compared in patients constantly with or without ECMO support. Post-interventional EVLWI levels were not available for patient No. 3.

ADVOS, ADVanced Organ Support; AU, arbitrary unit; CP, convalescent plasma; CPT, convalescent plasma transfusion; ECMO, extracorporeal membrane oxygenation; EVLWI, Extravascular Lung Water Index; ICU, Intensive Care Unit; PCR, polymerase chain reaction, pO_2/FiO_2, ratio of partial pressure of oxygen and the fraction of inspired oxygen.

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reference range 3−7 ml/kg) and markedly increased levels following CPT in control patients (B-cell-depleted: 14, range 11–17, versus control: 25, range 22–29 ml/kg) (Fig. 1F, Supplemental Table 5). Available PVPI levels were divergent prior to CPT (B-cell-depleted: 2.4 and 4.7, versus control: 5.7 and 2.5) but decreased in B-cell-depleted patients (1.9 and 4.2) in contrast to an increasing trend in control patients following CPT (2.9–5.8). The preload marker GEDVI increased in two out of three control patients (mean 703, range 597–786, to mean 807.8, range 668.3–923, reference range 680−800 ml/m^2) as opposed to declining levels in B-cell-depleted patients. CPI (reference range, 0.5−0.7 W/m^2) and CI (reference range, 3−5 l/min/m^2) values remained within normal ranges. However, an increasing trend was noted in control patients compared to decreased levels in B-cell-depleted patients following CP transfusion (Supplemental Table 5).

4. Discussion

Use of CP has been promoted to be safe with low incidences of serious adverse events [17]. However, data on safety and efficacy of CP treatment in patients suffering from life-threatening COVID-19 remain limited. A study cohort by Li et al. included 28 patients with life-threatening COVID-19 [6], while Liu et al. reported outcomes following CPT in four mechanically ventilated patients [5]. Both randomised controlled trials failed to prove significant improvement in clinical outcome but suggest trends towards a benefit of less severely ill, non-intubated patients [5,6]. Factors contributing to this inferior outcome have not been well studied and patient populations who might benefit from CP therapy remain to be defined [5]. To date, experience on CP treatment in patients with B-cell lymphopenia is limited to a few studies with limited sample size claiming safe and efficient use of CP in B-cell-depleted patients with protracted COVID-19 [11,18,19].

We here present the longitudinal assessment of all COVID-19 patients who received CP while being treated on our ICU. While both B-cell-depleted patients survived, fatal outcomes were observed in all other patients despite maximal therapeutic efforts including extracorporal organ support.

A dysregulated immune response caused by cytokine storm is proposed to be key factor of SARS-CoV-2 pathogenesis. Similar to cascades known from sepsis, systemic hyperinflammation may lead to coagulopathy with microangiopathy, pulmonary damage with subsequent ARDS, as well as multiorgan failure [20–23]. CP contains a plethora of proteins including cytokines and coagulation factors, which might influence both inflammatory responses and coagulopathy: On the one hand, a benefical immunmodulation has been proposed [24,25]. At the same time, concerns have been raised that CP might cause antibody-dependent enhancement of infection and fuel hyperimmune responses via both transfusion and induction of pro-inflammatory cytokines [26–30].

Based on the clinical course following CP administration we hypothesized that CPT might have aggravated systemic hyperinflammation in our B-cell sufficient cohort and thus aimed to analyse clinical, laboratory and cardiorespiratory data.

Signs of systemic hyperinflammation were noted in both cohorts as reflected by elevated inflammatory parameters (CRP, IL-6, PCT and

ferritin), D-dimer levels and the need for vasopressor support in all patients prior to CPT.

Notably, clinical status and laboratory baseline parameters appeared to be worse in the control group: Time from onset of symptoms to hospital admission as well as time to transfer to ICU and to mechanical ventilation were shorter, underlining an accelerated clinical deterioration suggestive of more critical disease. Further, SOFA scores at admission to ICU were higher and levels of inflammatory parameters prior to CPT were markedly elevated in control patients compared to the B-cell-depleted group. Suggesting a systemic prothrombotic state, control patients suffered from more severe thrombocytopenia and D-dimers were concomitantly higher. Moreover, cardiorespiratory baseline situation seemed to be worse as reflected by higher doses of vasopressors, higher FiO$_2$ resulting in a lower mean pO$_2$/FiO$_2$, higher positive end-expiratory pressure, driving pressure (P$_{max}$) and need for ECMO support in one patient before CPT.

Following CPT, several changes in clinical and laboratory parameters could be observed. The increases in both IL-6 and ferritin as well as aggravation of thrombocytopenia underlined an enhancement of systemic hyperinflammation in B-cell sufficient patients. In contrast, CRP and PCT levels decreased, which is in line with previous reports [31]. Fitting with a reduction in peripheral vascular resistance resulting from activated inflammatory cascades, higher doses of vasopressors were required in control patients. Further, an increase in CPI and CI levels were noted, which could be explained by elevated GEDVI upon transfusion and reduced afterload, assuming that cardiac contractility may initially have remained normal [32,33]. EVLWI and PVPI increased in control patients following CPT, pointing out an increased pulmonary oedema, which could be explained by inflammatory-induced alveolar damage. Incidence of postinfusion reactions such as transfusion-associated circulatory overload (TACO) or transfusion-related acute lung injuries (TRALI), which would be difficult to distinguish from progression of SARS-CoV-2 related ARDS, have been reported to be low [34,35]. Underlining a deterioration of respiratory status, we note that two patients required ECMO support following CPT and decreasing pO$_2$/FiO$_2$ were noticed in both other control patients.

In contrast, respiratory status remained almost stable and circulatory situation improved following CPT in B-cell-depleted patients. In addition to declining CRP and PCT, the pro-inflammatory cytokine IL-6 strinkingly decreased in both patients, which is consistend with findings from Hueso et al. [11] and might hint at an anti-inflammatory effect in these patients.

Besides conflicting data on immunomodulatory effects, CP has been suggested to both aggravate and attenuate systemic hypergoaculability in COVID-19 [21,36,37]. In this study, increasing D-dimer levels in both cohorts suggested a prothrombotic role of CP. We noted a distinct procoagulant state in patient No. 3 that led to immediate thrombosis during cannulation for ECMO insertion one day after CPT. Intriguingly, Sanfilippo et al. recently suggested a contributing role of CPT to microthrombosis resulting in pulmonary perfusion abnormalities and subsequent respiratory worsening [8]. In line with this hypothesis we noticed aggravated thrombocytopenia and deterioration of oxygenation in B-cell-sufficient patients.

Altogether, it remains possible that the inferior clinical status prior to

CPT determined severe clinical courses in in control patients. Both thrombocytopenia and D-dimer elevation have been associated with worse outcomes in COVID-19 and may serve as an explanation for the fatal outcomes [38]. On the contrary, CPT might have enhanced the preexistent over-activation of the immune system and thus may be particularly harmful in patients with severe inflammatory responses.

The effects of CP on immunomodulation and coagulation appear to be complex and likely depend on several patient and plasma related factors. In both B-cell depleted patients, viral clearance could be observed suggesting an antibody-mediated beneficial effect of CPT, which may have outweighed potential adverse effects.

4.1. Limitations

Several limitations to this retrospective analysis should be acknowledged: Despite including all COVID-19 patients that received CPT during ICU treatment in this monocentric study, the low number of cases limits the ability to statistically evaluate differences between both cohorts. As patients were treated during different stages of the pandemic, standard therapy varied according to the available evidence and guidelines. Previous treatment with remdesivir and glucocorticoids might have contributed to recovery or interfered with the immune response.

Notably, application scheme and antibody levels differed between patients. With two to ten CP units administered, the amount was higher compared to previous trials [39]. Use of repeated doses has been suggested to be reasonable in individual cases, however, the optimal dosing remains to be investigated [40,41]. Antibody levels of donor plasma were assessed using different assays. Further, mean interval between initial diagnosis via PCR and CPT was 14 days in both cohorts. Three of the control patients had already mounted an antibody response and No. 3 had already been negative on PCR prior to first CPT. Evidence is growing that early administration of CP relative to disease onset is associated with enhanced clinical benefit [5,42,43]. Hence, we cannot exclude that earlier administration may have resulted in better clinical outcome.

4.2. Conclusion

In the presented cohort, CP may have contributed to a fatal outcome by promotion of a procoagulant tendency or boosting of hyper-inflammation in B-cell sufficient patients. Thus, use of CP in late stages of life-threatening COVID-19 should be carefully evaluated considering potential risks and benefits. Data on CP therapy in B-cell-depleted patients affected with life-threatening COVID-19 is scarce. Given the pathophysiological rationale and favourable outcome in both B-cell-depleted patients of this cohort, critical COVID-19 patients with deficient humoral immune responses may draw benefits from CPT, even if administered later in the course of the illness. Further randomised controlled trials including B-cell-depleted patients will be required to investigate efficacy and safety of CPT in life-threatening COVID-19 and assess optimal timing, dosage and plasma characteristics.

Author contributions

Johanna Erber: Formal analysis, Investigation, Data Curation, Writing- Original Draft, Writing – Review and Editing, Visualization; Johannes R. Wiessner, Christina Huberle, Jochen Schneider, Hrvoje Mijočević, Doris von Bomhard: Investigation, Resources, Writing – Review and Editing; Peter Luppa, Roland M. Schmid, Sebastian Rasch: Supervision, Writing – Review and Editing; Tobias Lahmer: Conceptualization, Formal analysis, Resources, Writing- Original Draft, Writing – Review and Editing, Project administration. All authors read and approved the final version.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.transci.2021.103278.

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