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ORIGINAL ARTICLE

Convalescent plasma treatment in severely immunosuppressed patients hospitalized with COVID-19: an observational study of 28 cases

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ABSTRACT

Background: Immunosuppressed patients are particularly vulnerable to severe infection from the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), risking prolonged viremia and symptom duration. In this study we describe clinical and virological treatment outcomes in a heterogeneous group of patients with severe immunosuppression due to various causes suffering from COVID-19 infection, who were all treated with convalescent plasma (CCP) along with standard treatment.

Methods: We performed an observational, retrospective case series between May 2020 to March 2021 at three sites in Skåne, Sweden, with a population of nearly 1.4 million people. All patients hospitalized for COVID-19 who received CCP with the indication severe immunosuppression as defined by the treating physician were included in the study ($n = 28$).

Results: In total, 28 severely immunocompromised patients, half of which previously had been treated with rituximab, who had received in-hospital convalescent plasma treatment of COVID-19 were identified. One week after CCP treatment, 13 of 28 (46%) patients had improved clinically defined as a decrease of at least one point at the WHO-scale. Three patients had increased score points of whom two had died. For 12 patients, the WHO-scale was unchanged.

Conclusion: As one of only few studies on CCP treatment of COVID-19 in hospitalized patients with severe immunosuppression, this study adds descriptive data. The study design prohibits conclusions on safety and efficacy, and the results should be interpreted with caution. Prospective, randomized trials are needed to investigate this further.

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Introduction

In January of 2020, the World Health Organization declared the COVID-19 pandemic a public health emergency of international concern [1]. Although a minority of all persons infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) need hospitalization, immunosuppressed patients are particularly vulnerable to severe infection, and risk prolonged viremia, symptom duration and recurrent infection [2,3].

Particularly persons previously treated with anti-CD20 monoclonal antibodies such as rituximab risk prolonged COVID-19 infection, and a recent French study found a mortality rate of 21% in this group of patients [2,4–7].

Currently, the optimal treatment regime for severely immunosuppressed patients suffering from prolonged or severe infection remains to be investigated.

Convalescent plasma (CCP) has been used for treatment in adult hospitalized patients with covid-19 pneumonia without clinical benefit, whereas CCP within 72 h of symptom onset could reduce the risk of developing severe disease [8–11]. In one randomized controlled study, terminated early for futility, the CCP arm had more adverse events compared to the group that received standard of care [12].

The theoretical antiviral and immunomodulatory effects of CCP are however promising and could possibly be used to reduce morbidity and mortality in severely immunosuppressed patients [13]. To date, no randomized controlled trials have been published investigating the use of CCP in this group of patients, although trials are ongoing. However, previous case series have reported a favourable clinical and virological outcome after CCP in selected groups of severely immunocompromised patients [14–18].

The aim of this study was to describe clinical and virological treatment outcomes in a heterogeneous group of patients with severe immunosuppression due to various causes suffering from COVID-19 infection, who were all treated with CCP along with standard treatment.

Methods

Study design, case definition and setting

This observational, retrospective case series included patients between May 2020 to March 2021 at three sites (Lund, Malmö and Helsingborg) in Region Skåne in the south of Sweden, with a population of nearly 1.4 million people [19]. All patients hospitalized for COVID-19 who received convalescent plasma with the indication severe immunosuppression as defined by the treating physician were included in the study. In Region Skåne, convalescent plasma was available mainly within a randomized controlled study of non-immunocompromised patients [20] but could be made available as compassionate use for patients with severe immunosuppression with inability to achieve virological clearance.

Clinical data

All cases were retrospectively reviewed, applying a predefined study protocol. Comorbidities were assessed according to Charlson Comorbidity Score [21]. Severe immunosuppression was defined by the treating physician and is described in the results section. Clinical improvement was defined as a difference from the day of the first plasma transfusion to day 7 after the first plasma transfusion of at least −1 point of the WHO clinical criteria [22].

In addition, CRP and temperature were registered. A mean reduction of CRP of ≥50% or a normalization of morning temperature for febrile patients to below 38° (with a mean decrease of at least 0.5 °C) between day −3–0 before plasma to day 3–7 after plasma transfusion was considered clinically significant.

Virological improvement of airway or plasma samples was defined as a positive to negative SARS-CoV2 RT-PCR result or an increase of cycle threshold (Ct)-value of ≥5 between samples obtained from the same body site (nasopharynx, sputum, or endotracheal tubes) within 7 days before and after plasma treatment. Relapse was defined as either renewed or increased clinical symptoms in combination with decreasing Ct-values from plasma or airways as defined above, or detectable SARS-CoV-2 virus by PCR from plasma or airways in patients who had previously exhibited evidence of clearing the virus. 30-day mortality was defined as all-cause mortality within 30 days from the first plasma infusion.

Virology samples

All samples from the respiratory tract (nasopharynx, throat, sputum, or samples from endotracheal tubes) and plasma were analyzed at the Department of Clinical Microbiology, Region Skåne by SARS-CoV2 RT-PCR. For positive samples, Ct values were obtained and only samples from the same location were compared. Several RT-PCR methods were in use by the laboratory and for determining positive or negative RT-PCR all results were

deemed reliable, whereas comparison of Ct-values were only made for samples analyzed by the same method or between methods where an evaluation of the relation of Ct-values had been performed by the laboratory (not shown). The Ct-values reported in the study were adjusted accordingly.

Plasma donors

Recruitment and selection of plasma donors, preparing of plasma and detection of neutralizing antibodies (NtAbs) were performed as previously described [20].

In total, 25 donors provided 76 units of convalescent plasma used by patients in this study. Donors had NtAbs titres between 1:40 and 1:1229 with a median value of 1:141.

Three patients in this study received plasma purchased from another regional blood centre in Sweden (Uppsala). Each of these plasma units was produced by pooling plasma collected by apheresis from 4 different donors. Individual serum samples from these donors were not available. NtAbs titres in samples from these pooled plasma units were in a range 1:32–1:39.

Statistical analyses

Continuous data were summarized as median with range and categorical data as absolute numbers and percentage. The statistical analyses were performed using IBM SPSS Statistics for Macintosh, Version 25.0. (Armonk, NY: IBM) and Prism version 7 (GraphPad).

Ethics

This study was granted ethical approval from the Swedish Ethical Review Authority, reference number 2021-00637. All patients received written information about the study with an opt-out approach of consent. No patient denied participation.

Results

Patient characteristics

In total, twenty-eight severely immunocompromised patients who had received in-hospital convalescent plasma treatment of COVID-19 were identified. None of the patients had identifiable SARS-CoV-2- antibodies prior to CCP treatment, but for two patients this had not been investigated. Baseline characteristics of the included patients are presented in Table 1.

Table 1. Patient characteristics.

Baseline characteristics	$n = 28$
Age, median (range)	56 (16–84)
Female sex, *n* (%)	15 (54)
Charlson Comorbidity Index, median (range)	2 (0–5)
Weight, median, (range)	76 (42–133)
BMI, ($n = 20$) median, (range)	25 (21–40)
Underlying immunosuppressive conditions and treatments	
Haematological malignancy *n* (%)	13 (46)
Chronic lymphocytic leukaemia	4
B-cell lymphoma	3
Acute promyelocyte leukaemia	1
Myeloma	1
Waldenström's macroglobulinemia	1
Acute lymphatic leukaemia	1
Chronic neutrophilic leukaemia	1
Leukemic mantle cell lymphoma	1
-Stem cell transplantation *n* (%)	1
Organ transplant *n* (%)	5 (18)
Kidney	4
Liver	1
Primary immunodeficiency *n* (%)	2 (7)
Bruton's agammaglobulinemia	1
Goods syndrome	1
Rituximab treatment* *n* (%), indication	14 (50)
Multiple sclerosis	5
Haematological malignancy	5
Granulomatosis with polyangiitis (GPA)	2
Rheumatoid arthritis	1
DiGeorge's syndrome including GLILD	1

*Immunosuppressive treatment including rituximab. GLILD: granulomatous and lymphocytic interstitial lung disease.

Hospitalization and treatment

The median time from onset of symptoms to CCP treatment was 26 days (range 6–68 days) and 7 of 28 patients received CCP within 14 days of onset of symptoms. After the first dose of convalescent plasma, the median time to discharge from hospital for surviving patients was 8 days (range 2–119 days).

According to the patient records, the indication as stated by the treating physician for receiving convalescent plasma, in addition to immunosuppression, was long duration of symptoms for a majority of the patients ($n = 20$, 71%). Six patients were treated with CCP on the account of having risk for severe COVID-19-disease, and two patients were treated with CCP due to severe disease. Most patients received 3 doses of plasma ($n = 21$) and were also treated with remdesivir ($n = 18$), overlapping with plasma treatment in 10 patients. Corticosteroids were administered to 23 patients but was initiated within 3 days before or after plasma for 6 patients only. Details of hospitalization and treatment are presented in Table 2.

A possible adverse event was noted for one patient, who had shivers 40 min after the convalescent-plasma transfusion. The same patient received two additional convalescent-plasma transfusions during the next two days without complications.

Table 2. Details of hospitalization and treatment.

All patients	$n = 28$
Length of hospitalization, days, median (range)	19 (6–140)
Days from onset of symptoms to CCP, median (range)	26 (6–68)
Days from hospital admittance to CCP, median (range)	10 (2–45)
Days from CCP to discharge, median (range)	8 (2–119)
Indication of convalescent plasma*	
Risk of severe COVID-19-disease	6
Severe COVID-19-disease	2
Long duration of disease	19
Severe COVID-19-disease and long duration	1
Respiratory support on first day of CCP	
Mechanical ventilation	6
HFNC	8
Oxygen, nasal cannula or mask	6
No respiratory support	6
Anticoagulant treatment	27
Corticosteroids	23
Newly administered within +/−3 days of plasma	6
Remdesivir	18
Overlapping with CCP treatment	10
Doses of plasma, median (range)	3 (2–6)

*According to the medical record and in addition to severe immunosuppression.
ICU: intensive care unit; HFNC: high flow nasal cannula.

Table 3. Outcome after CCP treatment.

Outcome	*n* (%)
Within 7 days of CCP:	
Reduced WHO score	13 (46)
Unchanged WHO score	12 (43)
Increased WHO score	3 (11)
Death	2 (7)
Reduced CRP ($n = 20$)	15 (75)
Reduced temperature* ($n = 18$)	14 (78)
Any of reduced WHO score, CRP or temperature	19 (68)
Death within 30 days of CCP	6 (21)
Relapse	3 (11)

*Of febrile patients.

Clinical outcome of CCP

One week after CCP treatment, 13 of 28 (46%) patients showed clinical improvement defined as a decrease of at least one point at the WHO-scale [22]. Out of these 13 patients, 8 were discharged from hospital within 1 week. For three patients (one on mechanical ventilation and two on HFNC), the WHO-scale score increased within one week, of whom 2 patients died. For twelve patients, the clinical status was unchanged according to the WHO-scale.

Of six patients receiving mechanical ventilation on day 0 one died, one was weaned to HFNC and one was weaned off oxygen therapy altogether within 7 days. Three patients remained in mechanical ventilation on day 7. Of the 13 patients with improved WHO score, 8 (62%) received concomitant remdesivir and/or corticosteroids, compared with 5 out of the 15 patients (33%) without improved score.

Of 18 febrile patients, temperatures were normalized within 7 days after CCP for 14 (78%) patients. No afebrile patient developed fever after CCP treatment (Figure 1(a)). The median CRP was reduced by $\geq$50% for 15 of 20 (75%) patients with a CRP measured before and after CCP treatment (Figure 1(b)).

Nineteen (68%) of the patients improved in any of the following parameters; improved WHO-score, decreased CRP or temperature as defined above, and the absence of worsening of any of the parameters.

For three patients, additional CCP was administered during the hospitalization; one patient due to persistent fever and two patients due to sustained RT-PCR positivity for SARS-CoV-2; one of which required continued lymphoma treatment and the other with sustained need for oxygen therapy. Three patients were considered having relapse of the COVID-19. Outcome after CCP treatment is presented in Table 3. Detailed, individual level data on background, clinical characteristics and outcome are provided in Table 4.

Viral outcome of convalescent plasma-treatment

A SARS-CoV-2 PCR from the respiratory tract within 7 days before and 7 days after the CCP treatment was obtained in 14 patients; 11 of these had a negative PCR or a Ct-value increased by $\geq$5 (3 of whom received concomitant remdesivir). In three patients the RT-PCR status remained unchanged, or the Ct value was lower (Figure 1(a)).

SARS-CoV-2 PCR in plasma was analyzed in 24/28 patients at any time before treatment, and of these, 18 (75%) were positive. Immediately after convalescent plasma-treatment, SARS-CoV-2 PCR from plasma was measured in 16 patients; out of which 5 (31%) were positive and 11 (69%) were negative. For patients in whom a PCR from plasma was obtained within 7 days both before and after plasma treatment the Ct value increased by $\geq$5 for 8 of 11 (72%) and unchanged or lower for 3 patients (27%) (Figure 1(b)).

SARS-CoV-2 antibodies were analyzed within 14 days after plasma transfusion for 11 patients only. Two of these patients were positive (obtained 4 and 7 days after CCP), one with a previous negative antibody titre before transfusion and one who was not tested before.

Discussion

This observational case series of 28 patients in Region Skåne, Sweden, aimed to report clinical and virological outcomes for patients with COVID-19 and severe immunosuppression treated with complementary CCP,

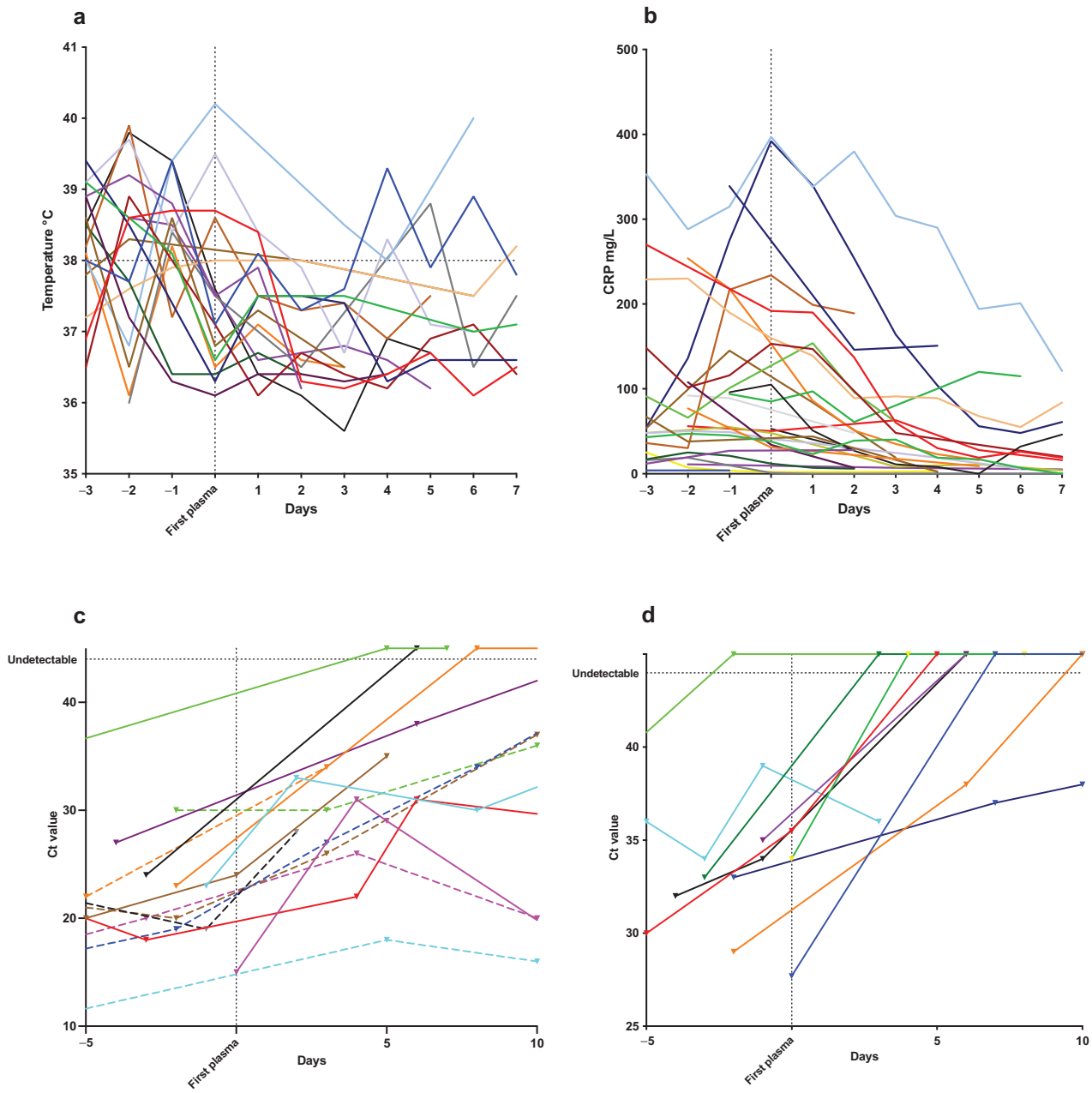

Figure 1. (a) Temperature (for patients with a temperature above 38 °C at least once within 3 days before CCP treatment), (b) CRP, (c) Ct-values of SARS CoV2 PCR from comparable respiratory tract sites. (d) Ct-values of SARS CoV2 PCR in plasma. All patients except one received CCP on 3 consecutive days.

in addition to standard treatment regimes. Half of the patients had previously been treated with rituximab. CCP treatment appeared safe and clinical and virological improvement was achieved in many patients, though a causal relation cannot be proven.

This study contributes with data regarding CCP treatment to immunosuppressed patients hospitalized due to COVID-19 [14–17,23,24]. In one case series of patients with protracted COVID-19 and severe B-lymphocyte depletion, all but one patient improved promptly as measured by a reduction of temperature and CRP after CCP treatment [14]. Two retrospective studies found that CCP reduced mortality and disease severity compared to a control group for patients with haematological malignancies [25,26]. In contrast to some of the previously published case series, the patients of our study had a variety of different underlying conditions or therapies causing immunosuppression. Moreover, the majority of the patients were given CCP late into the course of COVID-19 infection, after a median duration of symptoms of 26 days. However, no differences in outcome could be detected between different groups of immunosuppression or different duration of symptoms before CCP and neither could we associate patient

Table 4. Demographic, clinical characteristics, treatment protocols, and outcomes of all included patients.

Patient	Sex	Age	Length	Weight	CCI	Rituximab treatment	Haematological malignancy	Indication CCP	Maximum level of care	Maximal respiratory support	Anticoagulant	Corticosteroids	Corticosteroids with CCP	Remdesivir	Remdesivir with CCP	Days to CCP*	Death within 30 days	WHO-score day 0	WHO-score day 7	Change in WHO-score	Lower temp if initially febrile	Composite outcome	NtAbs mean
1	W	49	168	82	0	Yes	No	Fever, protracted infection	RW	ONCM	Enoxaparine	No	No	No	No	52	No	5	5	0	No	No change	24
2	M	52	183	112	2	Yes	Yes	Protracted infection	RW	HFNC	Enoxaparine	Yes	Yes	No	No	60	No	6	5	−1	Yes	Improvement	640
3	M	36		77	0	Yes	No	Protracted infection and protracted PCR positivity	ICU	HFNC	Enoxaparine	Yes	Yes	No	No	31	No	6	4	−2	Yes	Improvement	155
4	M	27	172	75	0	No	No	Protracted infection and protracted PCR positivity	RW	ONCM	Enoxaparine	No	No	No	No	27	No	4	2	−2	Yes	Improvement	155
5	W	27		95	0	Yes	No	Protracted infection	RW	HFNC	Enoxaparine	Yes	No	Yes	Yes	27	No	6	5	−1	–	Improvement	238
6	M	59	133	183	4	No	Yes	Immunosuppression	ICU	Mechanical ventilation	Enoxaparine	Yes	Yes	No	No	20	Yes	6	8	2	–	No change	412
7	M	64		69	2	Yes	Yes	Protracted infection	RW	ONCM	Tinzaparin	Yes	No	No	No	29	No	4	2	−2	Yes	Improvement	205
8	W	59	175	58	0	Yes	No	Protracted infection	RW	HFNC	No	Yes	No	Yes	Yes	43	No	5	4	−1	Yes	Improvement	305
9	W	46	177	99	1	Yes	No	Recent rituximab treatment, respiratory support	RW	ONCM	Enoxaparine	Yes	Yes	No	No	11	No	5	2	−3	Yes	Improvement	36
10	M	52		82	2	No	Yes	Protracted infection	RW	HFNC	Enoxaparine	Yes	Yes	Yes	Yes	21	No	6	5	−1	Yes	Improvement	503
11	W	55		55	3	Yes	Yes	Immunosuppression	RW	No respiratory support	Enoxaparine	No	No	Yes	Yes	6	No	4	2	−2	Yes	Improvement	36
12	M	71	176	57	3	No	Yes	Protracted infection	ICU	Mechanical ventilation	Enoxaparine	Yes	No	No	No	25	Yes	8	8	0	No	Improvement	253
13	M	68	163	57	1	No	Yes	Immunosuppression	RW	HFNC	Enoxaparine	Yes	Yes	Yes	No	6	Yes	6	10	4	–	Worsening	183
14	W	47	168	106	0	Yes	No	increasing respiratory support	ICU	Mechanical ventilation	Enoxaparine	Yes	Yes	Yes	Yes	15	No	8	8	0	No	No change	138
15	W	52		56	1	Yes	No	Protracted infection	RW	ONCM	Enoxaparine	No	No	Yes	Yes	25	No	5	2	−3	Yes	Improvement	201
16	W	16		42	2	No	Yes	Mechanical ventilation	ICU	Mechanical ventilation	Dalteparin	Yes	Yes	Yes	No	23	No	8	6	−2	No	Improvement	297
17	W	78	168	69	2	Yes	Yes	recent rituximab treatment, protracted infection	RW	HFNC	Enoxaparine	Yes	Yes	Yes	Yes	13	No	5	5	0	–	Improvement	336
18	M	68	167	63	5	No	No	Protracted infection and protracted PCR positivity	ICU	Mechanical ventilation	Enoxaparine	Yes	Yes	Yes	No	13	Yes	8	10	2	–	Worsening	427
19	W	84	165	68	3	No	No	Protracted infection and protracted PCR positivity	RW	No respiratory support	Enoxaparine	Yes	No	Yes	No	40	No	4	4	0	Yes	Improvement	217
20	M	77	178	65	2	No	Yes	Protracted infection and protracted PCR positivity	ILC	HFNC	Enoxaparine	Yes	Yes	Yes	Yes	21	No	6	6	0	–	Improvement	290
21	W	60	165	85	5	No	No	Protracted infection and protracted PCR positivity	RW	ONCM	Enoxaparine	Yes	Yes	Yes	No	68	No	4	4	0	–	No change	229
22	M	74	175	79	2	No	Yes	Protracted infection and protracted PCR positivity	RW	HFNC	Enoxaparine	Yes	Yes	Yes	Yes	30	No	6	6	0	–	No change	351
23	M	57	170	60	3	Yes	Yes	Protracted infection	RW	HFNC	Enoxaparine	Yes	Yes	Yes	No	40	Yes	4	4	0	–	No change	139
24	W	68	165	87	3	No	No	Protracted infection and protracted PCR positivity	RW	HFNC	Warfarin	Yes	Yes	Yes	No	39	No	5	5	0	–	No change	272
25	M	47		84	1	Yes	No	Mechanical ventilation	ICU	Mechanical ventilation	Enoxaparine	Yes	Yes	Yes	Yes	9	No	7	4	−3	Yes	Improvement	110
26	W	44	170	63	0	Yes	No	Immunosuppression	RW	No respiratory support	Enoxaparine	No	No	No	No	34	No	4	4	0	Yes	Improvement	94
27	M	46	175	91	2	No	No	Immunosuppression, protracted PCR positivity	RW	ONCM	Enoxaparine	Yes	Yes	No	No	20	No	4	2	−2	Yes	Improvement	517
28	M	61	180	78	2	No	Yes	Immunosuppression, pcr positive in blood	ICU	Mechanical ventilation	Enoxaparine	Yes	Yes	Yes	No	8	Yes	8	8	0	Yes	Improvement	95

*From initial symptoms. Composite outcome = decrease in WHO score, temperature or CRP after CCP. ICU: intensive care unit; ILC: intermediate level care; RW: regular ward; HFNC: high flow nasal cannula; ONCM: Oxygen nasal cannula or mask; CCI: Charlson comorbidity index; W: woman; M: man.

outcome with NtAbs titres in donor plasma (data not shown). It is intriguing to speculate if the mortality could have been lower in our cohort of patients, if CCP were administered within the first week of symptoms in all patients. Early administration of monoclonal antibodies has been demonstrated to reduce the need for medical attention, a surrogate for severity of infection, in outpatient patients infected with COVID-19 [27]. For some patients in our study, CCP was administered as rescue treatment in the ICU, and was otherwise commonly used in patients with protracted COVID-19-symtoms which partly explains the long duration before CCP treatment was initiated.

The retrospective nature of this study is the major limitation, as it could result in selection bias. As we did not include a control group, we cannot rule out that the improved clinical and virological outcome is the result of a regression to the mean or other medications given. The majority of the improved patients received concomitant remdesivir and/or corticosteroids which may partly explain the results rather than the given CCP.

The selection of patients treated with CCP in this study could be of considerable importance to the 30-day mortality rate of 21% in our study since severe symptoms, protracted infection or lack of virological clearance were often the indication for clinicians to treat with CCP. This makes mortality comparisons with other studies difficult and thus has to be kept in mind in the following attempt to provide some context to the mortality rate in our study. The overall, pre-vaccine mortality of hospitalized patients with COVID-19 in Sweden was 17.4% [28]. The mortality rate of solid organ transplant recipients in Sweden was 15% for hospitalized patients [29]. Studies from other countries in haematological patients hospitalized due to COVID-19 report mortality rates of 38 and 39% [30,31].

The literature is scarce regarding mortality of rituximab-treated patients with COVID-19. Besides the French study reporting a mortality rate of 21% [7], one small study of thirteen patients (of which eight were hospitalized) reported a mortality rate of 23% [32]. One study on hospitalized haematological patients with severe COVID-19 reported a mortality rate of 54%, where all were given dexamethasone and remdesivir, and 45% also received CCP [33].

The SARS-CoV-2 PCR results from the respiratory tract of this study shows that 79% of the evaluable patients had negative or increasing Ct-values after treatment. Moreover, SARS-CoV-2 PCR from plasma immediately after convalescent plasma-treatment was negative in 69% of patients. However, not all patients could be evaluated in this manner due to missing data, which is a limitation of this study.

Further limitations of our study include small and heterogeneous study sample. The patients differ in age and have a variety of primary diagnoses and comorbidities, which could have affected clinical outcomes. No strict criteria for including patients were used.

Detectable serum antibodies against SARS-CoV2 have been reported immediately after CCP treatment [15,18] in immunocompromised patients, whereas antibodies after CCP treatment were only detected in 2 of 11 tested patients in our study though donor titres were comparable to the above-mentioned studies. However, in our study, antibodies were generally analyzed later after plasma infusion than in the previous reports and may not have detected a possibly transient higher antibody level. Another explanation for undetectable SARS-CoV2 antibodies could be possible higher viral loads causing binding and elimination of antibodies.

In analogy with CCP treatment [11], early treatment with the monoclonal antibody cocktail casirivimab/imdevimab resulted in reduced mortality in out-patients who have not mounted their own immune response [27]. Reduced mortality has also been shown in hospitalized patients who were seronegative at baseline [34]. Compared to CCP, monoclonal antibody preparations provide higher antibody titres and could, especially if given early into the course of the disease, possibly result in greater clinical benefit in immunosuppressed patients compared with CCP.

In case of development of resistance to available monoclonal antibodies, and in lower resource settings without access to monoclonal antibodies, CCP could still play a role in the treatment of COVID-19. In a future viral pandemic, early administration of CCP to patients at risk of protracted or severe infection is a safe, promising treatment regime before more specific treatment is available.

Conclusion

As one of only few studies on CCP treatment of COVID-19 in hospitalized patients with severe immunosuppression, this study adds descriptive data. The study design prohibits conclusions on safety and efficacy, and the results should be interpreted with caution. Prospective, randomized trials are needed to investigate this further.

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Disclosure statement

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