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Brief Report

CLINICAL TRIALS AND OBSERVATIONS

Convalescent plasma therapy for B-cell–depleted patients with protracted COVID-19

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KEY POINTS

- As a proof of concept, COVID-19 convalescent plasma represents an interesting approach in B-cell–depleted patients with protracted COVID-19.
- COVID-19 convalescent plasma induces a decrease in temperature and inflammatory parameters within 1 week associated with oxygen weaning.

Anti-CD20 monoclonal antibodies are widely used for the treatment of hematological malignancies or autoimmune disease but may be responsible for a secondary humoral deficiency. In the context of COVID-19 infection, this may prevent the elicitation of a specific SARS-CoV-2 antibody response. We report a series of 17 consecutive patients with profound B-cell lymphopenia and prolonged COVID-19 symptoms, negative immunoglobulin G (IgG)-IgM SARS-CoV-2 serology, and positive RNAemia measured by digital polymerase chain reaction who were treated with 4 units of COVID-19 convalescent plasma. Within 48 hours of transfusion, all but 1 patient experienced an improvement of clinical symptoms. The inflammatory syndrome abated within a week. Only 1 patient who needed mechanical ventilation for severe COVID-19 disease died of bacterial pneumonia. SARS-CoV-2 RNAemia decreased to below the sensitivity threshold in all 9 evaluated patients. In 3 patients, virus-specific T-cell responses were analyzed using T-cell enzyme-linked immunospot assay before convalescent plasma transfusion. All showed a maintained SARS-CoV-2 T-cell response and poor cross-response to other coronaviruses. No adverse event was reported. Convalescent plasma with anti–SARS-CoV-2 antibodies appears to be a very promising approach in the context of protracted COVID-19 symptoms in patients unable to mount a specific humoral response to SARS-CoV-2. (*Blood*. 2020;136(20):2290-2295)

Introduction

Anti-CD20 monoclonal antibodies (MoAbs), such as rituximab, represent the cornerstone of treatment for most patients with B-cell malignancies and, to a lesser extent, patients with autoimmune disease.[1,2] Repeated administrations of rituximab may lead to prolonged B-cell depletion, which impairs the adaptive immune response and the ability to produce neutralizing antibodies.[3,4] Patients with hematological malignancies or autoimmune diseases may be at higher risk for severe forms of COVID-19.[5-7] Those patients are often excluded from clinical trials testing COVID-19 drugs and urgently need therapeutic options.

In the past, convalescent plasma transfusion (CPT) has been used for numerous viral epidemics, such as severe acute respiratory syndrome, Middle East respiratory syndrome, or influenza.[8] This therapeutic strategy appears to be promising for severe COVID-19, as well.[9-12] As a proof of concept, this approach should be of particular interest in patients who are unable to produce neutralizing antibodies. In this article, we report the safety and efficacy of CPT in 17 patients with profound B-cell lymphopenia and protracted COVID-19 disease.

Study design

This nationwide, observational, and multicenter study was conducted in 13 French hospitals from 1 May 2020 to 30 June 2020. All patients presenting with a B-cell immunodeficiency and prolonged COVID-19 symptoms, confirmed by SARS-CoV-2–specific reverse transcription polymerase chain reaction (RT-PCR) in respiratory samples and without seroconversion, were eligible for CPT. The severity of COVID-19 disease was evaluated using the World Health Organization classification.[13] Patients gave their written informed consent for the retrospective data collection, and ethical clearance was obtained from the French Infectious Diseases Society.

Convalescent donors were eligible for plasma donation 15 days after resolution of COVID-19 disease. Collected apheresis plasma underwent pathogen reduction (Intercept blood system; Cerus, Concord, CA) and standard testing, as per current regulations in France. Additionally, anti–SARS-CoV-2 antibody content was assessed in each donation, with a requirement for a SARS-CoV-2 seroneutralization titer $\geq$ 40 and/or an immunoglobulin G (IgG) enzyme-linked immunosorbent assay (EUROIMMUN, Bussy-Saint-Martin, France) ratio $>$ 5.6 as further described in the supplemental Data (available on the *Blood* Web site).[14]

Convalescent plasma was delivered through the National Early Access Program[15].

SARS-CoV-2 serology was performed using the IgG enzyme-linked immunosorbent assays in use in the different hospitals.[16] SARS-CoV-2 RNAemia was quantified using droplet-based digital RT-PCR (ddPCR) technology (Stilla Technologies, Villejuif, France), based on a COVID-19 Multiplex Crystal Digital PCR detection kit (ApexBio, Houston, TX).[17,18]

Virus-specific T-cell responses were analyzed before CPT in peripheral blood mononuclear cells using an interferon-γ (IFN-γ) enzyme-linked immunospot assay after the addition of individual 15-mers 11-aa overlapping peptide pools of different SARS-CoV-2 proteins or of common coronavirus proteins.[19]

Each patient received 2 consecutive transfusions of 2 ABO-compatible convalescent plasma units (200-220 mL each) at days 0 and +1. The Elisa ratio and neutralization titers of transfused convalescent plasma units are detailed in supplemental Table 1. Clinical parameters (temperature and oxygen need) were collected daily from day +5 before to day +7 after the last plasma transfusion. Biological parameters, including inflammatory markers (C-reactive protein [CRP], ferritin) and circulating lymphocyte subpopulations, were also assessed. When available, plasma interleukin-6 (IL-6) was quantified in a subset of patients who did not receive tocilizumab.

Results and discussion

Seventeen consecutive patients treated with CPT were included (Table 1). Fifteen patients were treated for hematological malignancies, 1 patient was treated for multiple sclerosis, and 1 patient was diagnosed with common variable immune deficiency during COVID-19 disease. Fifteen patients had received anti-CD20 MoAbs within the last 2 years (median number of cycles, 7; range, 4-18), with an interval between the last rituximab injection and symptom onset of 4 months (range, 3-6).

Patients had protracted COVID-19 symptoms for a median of 56 days (range, 7-83). The patient with symptomatic COVID-19 for only 7 days (following chemotherapy) experienced a prior asymptomatic phase over the previous 8 weeks (as evidenced by positive nasopharyngeal swab), suggesting that he was, in fact, experiencing a protracted form of COVID-19. Ten patients required oxygen by nasal prongs or noninvasive ventilation, and 2 required mechanical ventilation. Specific treatments had been administered before CPT in 11 patients. Three had shown a temporary clinical improvement following remdesivir (n = 2) or tocilizumab (n = 1) but had relapsed within a few days after treatment completion.

A severe hypogammaglobulinemia (median, 3.5 g/L; range, 1.8-14) was noted in 15 patients, whereas the remaining 2 patients received gamma globulin supplementation. No patient previously treated with anti-CD20 MoAbs had detectable circulating B cells. Two patients with pancytopenia had a positive SARS-CoV-2 RT-PCR in the bone marrow aspirate (Table 1).

No serious adverse effect was observed during or after CPT. Almost all patients experienced a very fast clinical improvement. Fever abated within the first 48 hours, and all 10 oxygen-dependent patients could be weaned from the oxygen mask or noninvasive ventilation within a median of 5 days (range, 1-45) after CPT. Among the 2 patients requiring mechanical ventilation, 1 died 7 days after CPT from ventilation-associated pneumonia, and 1 could be weaned from mechanical ventilation, although he still required oxygen. Biological parameters improved, in particular, CRP, ferritin, and IL-6 levels. All 16 living patients were asymptomatic for COVID-19 2 weeks after CPT.

Although RT-PCR on nasopharyngeal swab remained positive in 5 patients, monitoring of circulating SARS-CoV-2 using ddPCR technology performed in 9 patients showed a decrease in RNAemia within 7 to 14 days, which correlated with clinical improvement.

Table 1. Patient characteristics (N = 17)

Characteristics	Data
Age, median (range), y	58 (35-77)
Females/males, n	5/12
Hematological malignancies	15 (88)
Diffuse large B-cell lymphoma	4 (28)
Mantle cell lymphoma	3 (20)
Follicular lymphoma	3 (20)
Chronic lymphocytic leukemia/Richter syndrome	3 (20)
Marginal zone lymphoma	1 (6)
Waldenström macroglobulinemia	1 (6)
Nonhematological malignancies	2 (12)
Multiple sclerosis	1 (6)
Common variable immune deficiency	1 (6)
Disease status	
Complete response	11 (65)
Partial response	3 (18)
Progressive disease	2 (12)
Not attributed	1 (5)
Last chemotherapy	
R-chemotherapy*	6 (35)
Rituximab/obinutuzumab maintenance	7 (42)
Other†	3 (18)
Not attributed	1 (5)
Previous treatment with anti-CD20 therapy	15 (88)
Cycles of anti-CD20 therapy, median (range)	7 (4-18)
Gammaglobulinemia, median (range), g/L‡	3.5 (1.8-14)
Time between COVID-19 symptoms onset and last anti-CD20 therapy, median (range), mo	4 (3-6)
COVID-19 severity (WHO score)	
4	5 (29)
5-6	10 (59)
≥7	2 (12)
Previous COVID-19–specific treatments	11 (65)
Steroids	8 (72)
Hydroxychloroquine	5 (45)
Tocilizumab	4 (36)
Remdesivir	3 (27)
Lopinavir-ritonavir	2 (18)
Time from COVID-19 symptoms onset to CPT, median (range), d	56 (7-83)
Oxygen weaning (NIV or nasal prong)	10 (100)
Time for oxygen weaning after CPT, median (range), d	5 (1-45)
Length of hospital stay after CPT, median (range), d	7 (2-14)
Overall survival	16 (94)

Unless otherwise noted, data are n (%).

NIV, noninvasive ventilation; WHO, World Health Organization.

*R-chemotherapy was composed of several regimens combining rituximab with bendamustine (2 patients), high-dose aracytine + cisplatin (2 patients), fludarabine + cyclophosphamide (1 patient), and ifosfamide + cyclophosphamide + etoposide (2 patients).

†Other treatments were ibrutinib (1 patient), venetoclax (1 patient), or chimeric antigen receptor T cells (1 patient).

‡Two patients had gamma globulin supplementation. The normal range for gamma globulin is 7 to 14 g/L.

Quantification of SARS-CoV-2–specific T cells secreting INF-γ before the first plasma administration. As shown in Figure 1, a strong positive response was detected, in particular, toward peptides of the Spike glycoprotein (CoV-S1). In 2 patients, a high response was also detected to the N nucleoprotein and M membrane protein. The response to peptides from other common β coronaviruses (OC43-S1 and OC43-S2) and α coronaviruses (229E-S1 and 229E-S2) was negative in 2 patients, whereas the third patient exhibited a positive response to peptides of a common α coronavirus (229E-S2).

This case series reports the clinical benefit of CPT in 17 consecutive patients with profound B-cell lymphopenia and protracted COVID-19 disease. While COVID-19–specific treatments induced a transient decrease of fever or CRP, all failed to improve sustainably the course of the disease. Conversely, CPT was associated with a striking improvement of clinical symptoms and biological parameters in 16 out of 17 patients and a decrease of SARS-CoV-2 RNAemia within 7 to 14 days. The possibility that some patients were recovering before CPT cannot be totally excluded. However, the deleterious clinical course in all 17 patients before CPT, the close temporal association between plasma administration and clinical improvement, as well as the extent of the clinical responses make this possibility unlikely.[20]

In our series, almost all patients had a profound hypogammaglobulinemia associated with an absence of circulating B cells, and none had mounted a neutralizing antibody response after several weeks of symptoms. This suggests that prior treatment with anti-CD20 MoAbs or innate immunodeficiency resulted in a severely impaired adaptive humoral response that was responsible for persistent SARS-CoV-2 shedding and a protracted SARS-CoV-2 infection.[21] The only patient who had detectable circulating B lymphocytes was receiving ibrutinib for chronic lymphocytic leukemia. It is likely that these remaining B cells actually represent residual chronic lymphocytic leukemia B-cell clones that are unable to produce specific SARS-CoV-2 antibodies.[22]

Interestingly, the rapid clinical improvement observed after CPT correlated strongly with virological clearance, as demonstrated by the decrease of SARS-CoV-2 RNAemia using an innovative ddPCR technology that allows precise quantification of SARS-CoV-2 RNAemia.[23,24] These results support the concept that passive immunotherapy in such patients provides the neutralizing SARS-CoV-2 antibodies that are mandatory for viral clearance. By contrast, virus-specific T-cell responses tested in 3 patients prior to plasma injection revealed a very high number of circulating SARS-CoV-2–specific IFN-γ–producing T cells. One must note the prominent response to the structural spike (S) glycoprotein that expresses the specific immunodominant epitopes of SARS-CoV-2, which is the target of the neutralizing SARS-CoV-2 antibodies. Conversely, a poor cross-reacting response to other coronaviruses was detected.[25] These ancillary results suggest that specific T-cell responses to SARS-CoV-2 are not sufficient to control viral infection in the absence of neutralizing antibodies. It remains possible that these T cells might work synergistically with the antibodies brought by CPT.

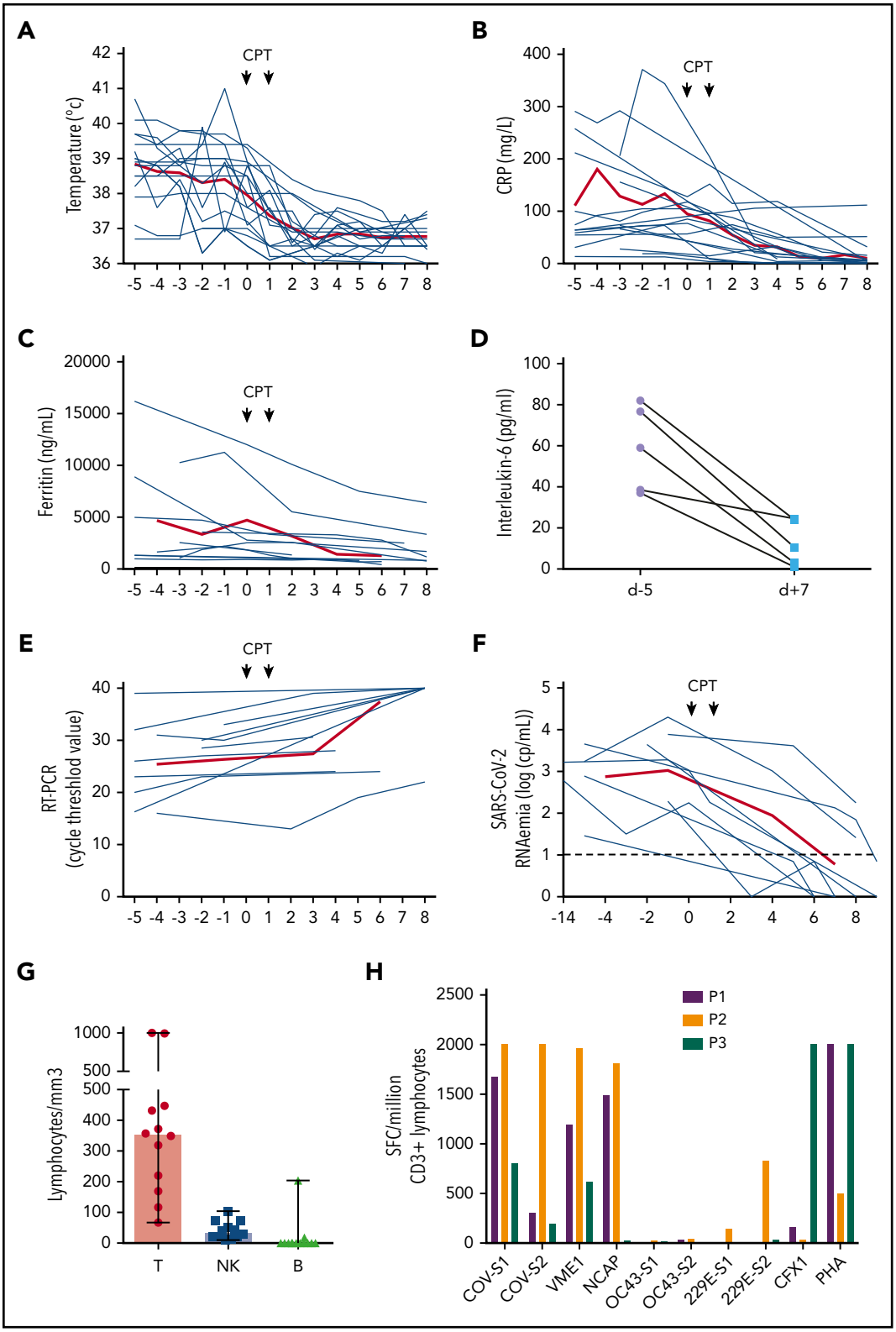

Figure 1. Individual longitudinal evolution before and after CPT. Individual longitudinal evolution of temperature (A), inflammation biomarkers [CRP (B), ferritin (C), IL-6 (D)], and SARS-CoV-2 RT-PCR (E) and viral load assessed using ddPCR (F). (D) IL-6 was assessed in 5 patients at days −5 and +7, considering days 0 and +1 the days of CPT. (F) ddPCR was assessed in 9 patients with a sensitivity threshold of 1.17 log (copies per milliliter), represented by the dashed line. (G) Lymphocyte immunophenotyping (T, natural killer [NK], and B lymphocytes) at baseline was assessed by flow cytometric analysis. The expression of CD3, CD19, and CD16/CD56 was used to quantify T cells, B cells, and natural killer cells, respectively. (H) Quantification of peripheral SARS-CoV-2–specific T lymphocytes in 3 patients (P1, P2, and P3) prior to plasma transfusion. Results are expressed as the number of spot-forming cells (SFC) per million circulating $CD3^+$ T lymphocytes. CFX1, positive control peptide pool; COV-S1, Spike glycoprotein S1; COV-S2, Spike glycoprotein S2; NCAP, nucleoprotein; PHA, phytohemagglutinin A (positive control mitogen); VME1, membrane protein.

In conclusion, passive transfer of COVID-19–neutralizing antibodies through CPT proved to be efficient and safe in patients with protracted COVID-19 diseases presenting with severe humoral immunity impairment. The benefit of an earlier administration of CPT in such patients remains unknown. However, we assume that, in this specific population, CPT should be considered before clinical worsening and the need for mechanical ventilation.

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Authorship

Contribution: T.H., C.P., A.-L.B., D.G., P.T., and K.L. designed the study and wrote the manuscript. T.H., C.P., L.-A.R., and A.-L.B. analyzed data; H.P. and D.V. performed ddPCR; L.C. and A.O. evaluated T-cell responses; and all authors contributed to data collection and critically revised the manuscript.

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Footnotes

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Data sharing requests should be sent to Thomas Hueso (hueso.th@gmail.com).

The online version of this article contains a data supplement.

There is a *Blood* Commentary on this article in this issue.

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