Effects of Treatment of Coronavirus Disease 2019 With Convalescent Plasma in 25 B-Cell–Depleted Patients

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Twenty-five B-cell–depleted patients (24 following anti-CD19/20 therapy) diagnosed with coronavirus disease 2019 had been symptomatic for a median of 26 days but remained antibody negative. All were treated with convalescent plasma with high neutralizing antibody titers. Twenty-one (84%) recovered, indicating the potential therapeutic effects of this therapy in this particular population.

Keywords. COVID-19; SARS-CoV-2; immunodeficiency; B-cell depletion; convalescent plasma.

B-cell–depleting therapy is used to treat hematological and autoimmune diseases and as a result of this treatment, an impaired antibody response is observed upon severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Patients who received this type of therapy are at risk for a more severe and protracted course of coronavirus disease 2019 (COVID-19) [1]. While the overall net therapeutic value of convalescent plasma (ConvP) for hospitalized COVID-19 patients is probably limited, B-cell–depleted patients may benefit from exogenous SARS-CoV-2 antibodies [2]. We conducted a prospective cohort study on the effect of treatment with ConvP on the outcome of B-cell–depleted patients with COVID-19.

METHODS

Setting

The Dutch Blood Bank (Sanquin) made ConvP available for immunocompromised COVID-19 patients as part of a compassionate use program. The study protocol was approved by the Erasmus Medical Center Institutional Review Board (MEC-2021–0309). Consent was obtained from patients or legal representatives for the use of data available in their health records.

Patients, Intervention, and Outcomes

ConvP was donated by patients recovered for at least 14 days from polymerase chain reaction (PCR)–confirmed SARS-CoV-2 infection and met standard Dutch donor selection criteria. Plasma was collected according to standard procedures and available in 300-mL units. Eligible patients for ConvP therapy had B-cell depletion or dysfunction and were under care for PCR-confirmed symptomatic COVID-19. All had undetectable SARS-CoV-2 receptor-binding domain (RBD) antibodies. The treating physician decided on the number of ABO-compatible plasma units used in 1 transfusion episode. A second transfusion episode was allowed in the absence of clinical response. The primary endpoint was survival after ConvP administration. Secondary outcomes were serological and inflammatory responses, time to lifting of isolation, and possible treatment-related adverse events. Isolation was lifted when symptoms had improved and SARS-CoV-2 genome in nasopharyngeal swabs was undetectable or detected at a cycle threshold (Ct) value of >34 by PCR, a Ct value that correlates well with replication-incompetent virus with the PCR assay that was used [3].

Serological Assays

An anti–SARS-CoV-2 RBD enzyme-linked immunosorbent assay (ELISA) developed by Sanquin Blood Supply or the Euroimmune SARS-CoV2 ELISA was used to select ConvP donors. A cutoff value of >60 arbitrary units/mL was used for the in-house ELISA while an optical density (OD) value ≥7 was used for the Euroimmune ELISA. Both correlate well with a SARS-CoV-2 neutralization antibody titer of ≥1:160, although outliers do occur [4]. For a few plasma units with a 50% plaque reduction neutralization test ($PRNT_{50}$) titer of ≥1:160, the $PRNT_{50}$ was performed and the plasma used before the ELISA had been performed [5]. In patients, SARS-CoV-2

RBD total immunoglobulin and immunoglobulin M antibody tests were measured preceding and following transfusion by ELISA (Wantai Biological, Beijing), and OD ratios are reported. An OD above a ratio of 10 has been shown to correspond to virus neutralization and both serological assays have been shown to be highly sensitive for the detection of anti-RBD antibodies. When stored serum samples were available, a PRNT was performed as well, following the methods previously described [6].

RESULTS

Primary Endpoint, Survival After ConvP Administration

One patient was diagnosed with X-linked agammaglobulinemia and 24 patients had received a B-cell–depleting therapy (21 rituximab, 1 blinatumomab, 1 obinituzumab, and 1 ocrelizumab) for either a hematological (n = 15) or autoimmune disorder (n = 9) (Supplementary Table 1). Fifteen (60%) patients were male and the median age was 53 years (interquartile range [IQR], 44–66 years). ConvP transfusion was given at a median of 26 days (IQR, 15–34 days) after COVID-19 symptom onset. Six patients were treated as outpatients and 19 were admitted to the hospital, of whom 7 were in the intensive care unit at the time of transfusion. SARS-CoV-2 viral genome was detectable at the time of transfusion in all patients, but RBD antibodies could not be detected in any of the patients.

Twenty-one of 25 patients recovered from COVID-19 after transfusion and 4 patients died. Twenty-one patients underwent 1 transfusion episode and 4 underwent a second transfusion episode at the time when the treating physician concluded that there was no clinical response. The first ConvP transfusion episode consisted of 1 unit (n = 6), 2 units (n = 18), or 3 units (n = 1). The second transfusion episode consisted of 2 units (n = 2) or 1 unit (n = 2) (Supplementary Table 2).

Two of 4 patients who died were already at the intensive care unit when they received their ConvP transfusion, and the other 2 were admitted to the general COVID-19 ward. The patients who died received ConvP on day 26, 18, 17, and 12 since their COVID-19 diagnosis. More details about the patients are available in the Supplementary Materials.

Secondary Endpoints, Serological and Inflammatory Responses, Time to Lifting Isolation, and Adverse Events

In 16 patients from whom we had stored serum samples available, we tested the presence and titer of antibodies against RBD preceding and on several occasions after transfusion. All patients seroconverted immediately after transfusion, but the height and duration of seropositivity varied substantially (Figure 1). In 11 patients, the PRNT$_{50}$ could be measured as well and was >1:20 (median, 1:40 [IQR, 1:20–1:40]) in all 10 patients who recovered. In the patient who died, the PRNT$_{50}$ titers did not increase upon transfusion despite the seroconversion as measured with the RBD antibody test (Figure 1).

Inflammatory markers (C-reactive protein [CRP] and ferritin) decreased in those who recovered compared with those who died (Supplementary Figure 1).

Possible treatment-related adverse events were observed in 5 patients. One patient had an anaphylactic reaction, while 2 patients experienced worsening of hypoxemia. Furthermore, a skin rash and an alanine aminotransferase increase to a peak of 526 U/L were observed in 2 other patients. All patients eventually recovered from their possible related adverse event.

In the 21 patients that survived, isolation could be lifted at a median of 11 days (IQR, 6–17.5 days) after transfusion. In 2 clinically recovered patients, SARS-CoV-2 genome was still detected by PCR, with Ct values <34 for 40 and 68 days, respectively, while in all 19 other patients the SARS-CoV-2 genome was no longer detectable by PCR at day 23.

DISCUSSION

We describe the largest case series of B-cell–depleted COVID-19 patients treated with ConvP. All were antibody negative at the time of transfusion despite their prolonged symptomatic COVID-19 course, and all seroconverted after transfusion with virus neutralizing antibody titers detectable as well in all but 1 patient. Twenty-one of the 25 patients recovered. Very recent additional observational as well as clinical trial data on the value of antibody-based therapy in certain patient populations further support our findings. In particular, the Randomised Evaluation of COVID-19 Therapy (RECOVERY) investigators describe the effects of therapy with casirivimab and imdevimab for hospitalized COVID-19 patients. Although this study did not focus on immunocompromised patients in particular, it showed a significant and substantial reduction in overall mortality in the subgroup of SARS-CoV-2 antibody–negative patients [7]. Additionally, in a case-control study, Thompson et al observed a reduced overall mortality in patients with hematological malignancies treated with ConvP [8]. Our findings are also in line with other smaller case series [9, 10]. Taken together, B-cell–depleted patients with COVID-19 without serological evidence of an autologous anti–SARS-CoV-2 antibody response seem to be a distinct subpopulation where ConvP therapy has a potential benefit, and this benefit may be present regardless of symptom duration.

Our study has limitations. Without a control group, a causal relationship between transfusion and recovery cannot be proven. However, the recovery was typically prompt and in sharp contrast with the symptom duration of a median of 26 days at the time of ConvP transfusion. The hypothesized mechanism of action through viral neutralization as well as the fact that seroconversion coincided with clinical recovery and decrease in inflammatory markers suggests a causal effect. Second, neither the dose of plasma nor the dose of antibodies that the patients received was standardized. Therefore, a firm
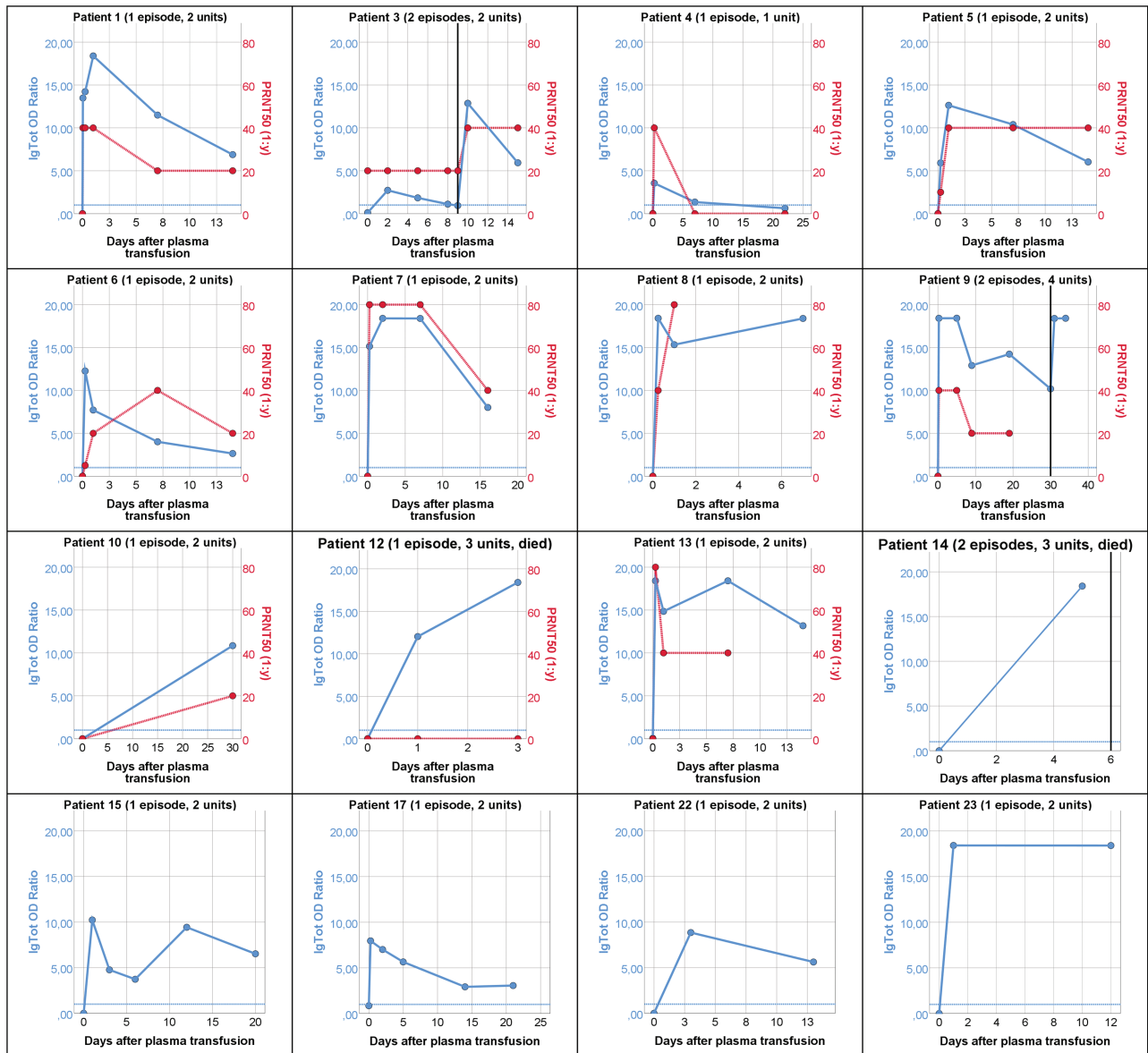
Figure 1. Enzyme-linked immunosorbent assay (ELISA) severe acute respiratory syndrome coronavirus 2 total immunoglobulin (IgTot) optical density (OD) ratios and 50% plaque reduction neutralization test ($PRNT_{50}$) titer after transfusion in 16 evaluable patients. Blue line represents the total Ig OD ratio. Red line represents the $PRNT_{50}$. The vertical black line represents when the second transfusion was given.

recommendation on the appropriate dose cannot be made. Last, the role of SARS-CoV-2 T-cell response in these patients is likely relevant as well but remains to be studied.

Although ConvP is generally considered safe, 5 patients had an adverse event possibly related to ConvP. Temporary worsening of hypoxemia might be related to binding of virus-neutralizing antibodies to virus particles and the resulting antibody-dependent enhancement of the inflammatory response in the lungs. Antibody-naive individuals might be more at risk for this phenomenon of antibody-dependent enhancement, also reported by others [10]. However, in the majority of patients there was no increase in the inflammatory marker

CRP after infusion of ConvP, as might have been expected when immune complexes would have activated macrophages to produce interleukin 6 [11]. Outside of the context of a randomized trial we can only speculate whether the progressive hypoxemia observed after transfusion in 2 patients was related to ConvP administration instead of progression of COVID-19.

A recent report described an immunocompromised patient who was treated with ConvP on 3 occasions over a 32-day period. In this patient, viral genome remained detectable and the ConvP treatment was associated with the occurrence and persistence of mutations in the spike gene. The patient eventually died [12]. This case led to the hypothesis that the use of

ConvP for immunocompromised patients may result in SARS-CoV-2 mutants and their potential spread. In our case series, SARS-CoV-2 genome remained detectable in 2 individuals after ConvP treatment for 40 and 68 days, respectively, but both patients eventually cleared the virus and recovered from prolonged COVID-19. In the other 19 individuals, SARS-CoV-2 viral genome became undetectable soon after transfusion (median 10 days), which indicates a rapid response to ConvP, and suggests that prolonged viral escape during ConvP is rare.

In conclusion, B-cell–depleted patients may benefit from antibody-based therapy. Ideally, our observation should be confirmed in randomized clinical trials. These trials are ongoing in hospitalized patients (Compromise study, EudraCT 2020–006075–15) as well as outpatients (CoV-Early study, NCT04375098) in the Netherlands.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

References

1. Sormani MP, De Rossi N, Schiavetti I, et al. Disease-modifying therapies and coronavirus disease 2019 severity in multiple sclerosis. Ann Neurol **2021**; 89:780–9.
2. Abani O, Abbas A, Abbas F, et al. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial. Lancet **2021**; 397:2049–59.
3. van Kampen JJA, van de Vijver DAMC, Fraaij PLA, et al. Duration and key determinants of infectious virus shedding in hospitalized patients with coronavirus disease-2019 (COVID-19). Nat Commun **2021**; 12:267.
4. Steenhuis M, van Mierlo G, Derksen NIL, et al. Dynamics of antibodies to SARS-CoV-2 in convalescent plasma donors. Clin Transl Immunology **2021**; 10:e1285.
5. GeurtsvanKessel CH, Okba NMA, Igloi Z, et al. An evaluation of COVID-19 serological assays informs future diagnostics and exposure assessment. Nat Commun **2020**; 11:3436.
6. Okba NMA, Müller MA, Li W, et al. Severe acute respiratory syndrome coronavirus 2-specific antibody responses in coronavirus disease patients. Emerg Infect Dis **2020**; 26:1478–88.
7. Horby PW, Mafham M, Peto L, et al. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. medRxiv [Preprint]. Posted online 16 June **2021**. doi:10.1101/2021.06.15.21258542.
8. Thompson MA, Henderson JP, Shah PK, et al. Association of convalescent plasma therapy with survival in patients with hematologic cancers and COVID-19 [manuscript published online ahead of print 17 June 2021]. JAMA Oncology **2021**. doi:10.1001/jamaoncol.2021.1799.
9. Hueso T, Pouderoux C, Péré H, et al. Convalescent plasma therapy for B-cell-depleted patients with protracted COVID-19. Blood **2020**; 136:2290–5.
10. Delgado-Fernández M, García-Gemar GM, Fuentes-López A, et al. Treatment of COVID-19 with convalescent plasma in patients with humoral immunodeficiency—three consecutive cases and review of the literature [manuscript published online ahead of print 11 February 2021]. Enferm Infecc Microbiol Clin (Engl Ed) **2021**. doi:10.1016/j.eimc.2021.01.013.
11. Larsen MD, de Graaf EL, Sonneveld ME, et al. Afucosylated IgG characterizes enveloped viral responses and correlates with COVID-19 severity. Science **2021**; 371:eabc8378.
12. Kemp SA, Collier DA, Datir RP, et al. SARS-CoV-2 evolution during treatment of chronic infection. Nature **2021**; 592:277–82.