

Hyperimmune Globulin for Severely Immunocompromised Patients Hospitalized With Coronavirus Disease 2019: A Randomized, Controlled Trial

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Background. The aim of this randomized, controlled trial is to determine whether antisevere acute respiratory syndrome coronavirus 2 hyperimmune globulin (COVIG) protects against severe coronavirus disease 2019 (COVID-19) in severely immunocompromised, hospitalized, COVID-19 patients.

Methods. Patients were randomly assigned to receive COVIG or intravenous immunoglobulin (IVIG) without SARS-CoV-2 antibodies.

Results. Severe COVID-19 was observed in 2 of 10 (20%) patients treated with COVIG compared to 7 of 8 (88%) in the IVIG control group ($P = .015$, Fisher's exact test).

Conclusions. Antisevere acute respiratory syndrome coronavirus 2 hyperimmune globulin may be a valuable treatment in severely immunocompromised, hospitalized, COVID-19 patients and should be considered when no monoclonal antibody therapies are available.

Keywords. anti-SARS-CoV-2 hyperimmune globulin; B-cell dysfunction; COVID-19; plasma-derived antibody therapy; severely immunocompromised state.

Severely immunocompromised patients, such as organ transplant recipients and patients with hematologic malignancies, are at risk for a severe course of coronavirus disease 2019 (COVID-19) with increased mortality rates and may suffer reduced protection from vaccination [1–4]. An unprecedented number of randomized trials demonstrated that plasma-derived antibody treatment, such as convalescent plasma or hyperimmune globulin, does not improve outcome in hospitalized COVID-19 patients. However, severely immunocompromised patients are grossly underrepresented in these trials [5–11]. We hypothesized that severely immunocompromised patients with COVID-19 are likely to benefit most from such interventions, and we set out to examine the effects of antisevere acute respiratory syndrome coronavirus 2 hyperimmune intravenous globulin (COVIG) in this population in a double-blind, controlled, randomized fashion.

METHODS

The study included adult patients who were severely immunocompromised (as defined in the Study Protocol, which is included as a [Data Supplement](#) available with the online version of this article) and who were hospitalized with a polymerase chain reaction-confirmed, symptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection within 72 hours after admission. Patients that had received prior treatment with convalescent plasma or intravenous immunoglobulin (IVIG) with neutralizing SARS-CoV-2 antibodies, patients with hypersensitivity to IVIG, or patients that required respiratory support with endotracheal intubation or high-flow nasal oxygen were excluded.

Patients were randomly assigned in a 1:1 ratio to receive 150 mL:100 mg/mL COVIG or 150 mL:100 mg/mL of IVIG (control). Antisevere acute respiratory syndrome coronavirus 2 hyperimmune globulin was derived from a single batch, containing a neutralizing titer of 900 IU/mL (VNT50) against wild-type SARS-CoV-2 [12]. The aim of this dose was to achieve equipotency to convalescent plasma treatment as was used in large, randomized studies [5–10]. Intravenous immunoglobulin was derived from a single batch generated before December 2019 and, thus, did not contain SARS-CoV-2 antibodies. Antisevere acute respiratory syndrome coronavirus 2 hyperimmune globulin and IVIG production were similar, except that for COVIG production, convalescent plasma was

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derived from donors who had a history of symptomatic COVID-19 and had recovered from COVID-19 for at least 14 days before plasma donation. All convalescent plasma units were tested by a quantitative immunoglobulin G (IgG) enzyme-linked immunosorbent assay test that correlated with virus neutralizing antibodies. Both COVIG and IVIG were produced by Prothya (the Netherlands) and labeled similarly as Nanogam.

Randomization was performed by computer, stratified according to the origin of the immunocompromised state. All investigators, research staff, and participants were blinded to the allocated treatment until day 28, but unblinding was possible before day 28 when the primary endpoint was reached. Baseline data were collected using a web-based case report form. At baseline and after treatment, serum SARS-CoV-2 antibody measurements were performed using LIAISON SARS-CoV-2 TrimericS IgG assay (DiaSorin). Positivity was defined as anti-S IgG > 33.8 BAU/mL.

The primary endpoint of this study was the occurrence of severe COVID-19, evaluated up until day 28 after treatment, and defined as any of the following conditions: (1) respiratory deterioration requiring high-flow nasal oxygen or mechanical ventilation; (2) intensive care unit (ICU) admission for respiratory deterioration; (3) lack of clinical improvement from day 7 (no improvement in oxygen requirement or, in patients not requiring oxygen, in disease burden and fever); or (4) re-admission for COVID-19. Secondary endpoints included occurrence of severe COVID-19 in the subgroup of patients that had no SARS-CoV-2 antibodies upon inclusion, duration of hospitalization, 28-day mortality, the 4 individual endpoints that compose the primary endpoint, and serious adverse events.

We estimated that this high-risk patient group had a 70% chance of reaching the primary endpoint of severe COVID-19, and we hypothesized a reduction to 30% with COVIG treatment. With a power of 90%, a 2-sided alpha of 5%, and a single preplanned efficacy interim analysis, a sample size of 86 participants was required. However, the trial was terminated prematurely when, based on the results of the RECOVERY trial, monoclonal antibodies casirivimab/imdevimab became recommended for seronegative, hospitalized COVID-19 patients by the Dutch COVID-19 treatment guideline, because it was ethically unacceptable to withhold casirivimab/imdevimab therapy for patients in the trial [13].

Intention-to-treat analysis was performed after enrollment of 21% of the target population. Continuous variables were described as medians with interquartile ranges (IQRs). Categorical variables were described as proportions. In the primary endpoint analysis, proportions in both treatment groups were compared by a Fisher's exact test, given the small number of observations. Significance was defined as a 2-sided $P < .05$.

Patient Consent Statement

The protocol was approved by the medical ethics committees of all participating centers, and written informed consent was obtained from all patients.

Data Sharing Statement

For original data or deidentified individual participant data, please contact j.heijmans@amsterdamumc.nl. The study protocol is included as a [Data Supplement](#) available with the online version of this article. The trial was registered at the dutch trial register, accessible at the ICTRP search portal (trialsearch.who.int no. NL9436).

RESULTS

From April 2021 to July 2021, a total of 37 patients was screened, 18 of which were enrolled at 3 sites in the Netherlands. Enrolled patients included 6 B-cell-depleted patients with hematologic malignancies, 9 solid organ transplant recipients, 1 B-cell-depleted patient with autoimmune disease, 1 patient with congenital B-cell deficiency, and 1 patient with acquired B-cell deficiency. Ten patients were randomly allocated to receive COVIG, and 8 patients were randomly allocated to receive to IVIG ([Supplementary Figure 1](#)). At baseline, median age of the patients was 58 years (IQR, 35–66) and symptoms had been present for 9 days (IQR, 7–21). The median Charlson comorbidity index was 3 (IQR, 2–5) and oxygen supplementation was 3 L/min (IQR, 0–5). Thirteen patients had received at least 1 SARS-CoV-2 vaccine (72%) and 11 patients (61%) were fully vaccinated. Sixteen patients (89%) were seronegative for SARS-CoV-2 anti-spike IgG at baseline ([Table 1](#)).

The intention-to-treat analysis included data from 18 patients ([Table 2](#) and [Supplementary Figure 2](#)). Severe COVID-19 occurred in 2 (20%) patients in the COVIG arm compared to 7 (88%) patients in the IVIG ($P = .015$). Among all 16 seronegative patients, 13% developed severe COVID-19 in the COVIG arm compared to 88% in the IVIG arm ($P = .010$). Both seropositive patients were randomized to the COVIG arm. Of these patients, 1 developed severe COVID-19 (a renal transplant recipient who was admitted to the ICU within hours after COVIG treatment and discharged 1 day later), and 1 patient did not develop severe COVID-19 (a multiple sclerosis patient with uveitis on dual immunosuppression). All separate parameters that composed the primary endpoint were more frequent in the IVIG arm compared to the COVIG arm.

Of all 18 patients, 9 patients (50%) had a severe adverse event, 8 of which were related to COVID-19. There were 3 deaths due to COVID-19, all in the IVIG group. One patient was readmitted for treatment of a community-acquired bacterial pneumonia and after antibiotic treatment, the patient fully recovered within 10 days. No infusion-related serious adverse events were observed.

Table 1. Demographic and Baseline Characteristics

Characteristics	COVIG Group (n = 10)	IVIIG Group (n = 8)
Age (years)—median (IQR)	48 (27–61)	63 (41–72)
Male gender—no. (%)	6 (60)	4 (50)
BMI ^a (kg/m ²)—median (IQR)	26 (24–32)	29 (24–33)
Charlson comorbidity index, median (IQR)	2 (2–4)	5 (2–7)
Cause of Immunocompromised State, No. (%)
Immunosuppression for solid organ transplant	4 (40)	5 (63)
Recent use of anti-B-cell therapy for malignancy	3 (30)	3 (38)
Immunosuppression for autoimmune disease	1 (10)	0 (0)
Congenital hypogammaglobulinemia	1 (10)	0 (0)
Acquired hypogammaglobulinemia	1 (10)	0 (0)
Prior Vaccination Against SARS-CoV-2
One or more	5 (50)	8 (100)
Full schedule ^b	5 (50)	6 (75)
Number of days since symptom onset, median (IQR)	10 (8–22)	8 (6–26)
Number of days since admission to hospital, median (IQR)	2 (1–4)	1 (1–2)
Corticosteroid therapy for COVID-19 at baseline ^c , no. (%)	10 (100)	4 (50)
Tocilizumab therapy for COVID-19 at baseline, no. (%)	1 (10)	0 (0)
Respiratory Support
No oxygen supplementation, no. (%)	1 (10)	4 (50)
Simple oxygen supplementation ^d , no. (%)	9 (90)	4 (50)
Required oxygen dose (L/min), median (IQR)	3 (1–8)	1 (0–4)
SARS-CoV-2 Variant
Wild-type, no. (%)	1 (10)	1 (13)
Alpha, no. (%)	5 (50)	5 (63)
Unknown, no. (%)	4 (40)	2 (25)
Presence SARS-CoV-2 IgG, no. (%)	2 (20)	0 (0)
B cell count (per μ L) ^e , median (IQR)	12 (0–144)	20 (0–40)
CD4 T cell count ^e	111 (65–257)	147 (53–298)
CD8 T cell count ^e	140 (71–227)	180 (140–245)
NK cell count ^e	60 (41–90)	90 (50–176)

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; COVIG, antisevere acute respiratory syndrome coronavirus 2 hyperimmune intravenous globulin; IgG, immunoglobulin G; IQR, interquartile range; IVIG, intravenous immunoglobulin; NK, natural killer; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

^aBMI was not available for 1 patient in both groups.

^bPatient was considered as fully vaccinated 7 days after a second vaccination with Moderna or BioNTech/Pfizer COVID-19 vaccine, 14 days after Janssen COVID-19 vaccine, or after 1 Moderna or BioNTech/Pfizer COVID-19 vaccine in combination with prior SARS-CoV-2 infection.

^cAll patients that required supplemental oxygen received corticosteroid therapy per standard of care.

^dOxygen supplementation via nasal cannula.

^eCounts were not available for 3 patients in the COVIG group.

DISCUSSION

To date, data from large, randomized trials showed that treatment of hospitalized COVID-19 patients with plasma-derived antibody therapy does not improve outcome, but severely immunocompromised patients were grossly underrepresented in

Table 2. Primary and Secondary Outcomes^a

Outcome	COVIG Group (n = 10)	IVIIG Group (n = 8)	RR (95% CI)	Fisher's Exact Test (<i>P</i>)
Severe course of COVID-19	2 (20)	7 (88)	.23 (.06–.81)	.015
Severe course of COVID-19 in seronegative patients	1/8 (13)	7/8 (88)	.14 (.02–.91)	.010
Mortality at 28 days	0 (0)	3 (38)
Median duration of hospitalization ^b	9 (4 to 15)	9 (4 to 17)
Indication for adjunctive ventilator support	2 (20)	5 (63)
Admission to an intensive care unit due to respiratory insufficiency	1 (10)	3 (38)
Lack of clinical improvement at day 7 or any day thereafter	0 (0)	3 (38)
Readmission for COVID-19	0 (0)	2 (25)

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; COVIG, antisevere acute respiratory syndrome coronavirus 2 hyperimmune intravenous globulin; IVIG, intravenous immunoglobulin; RR, relative risk.

^aData are *n* (%), median (interquartile range), or *n*/*N* (%).

^bAnalyses exclude those who died during hospitalization.

these trials. These patients have a more severe course of disease and may suffer reduced protection from vaccination. This study shows that COVIG significantly reduces the incidence of severe COVID-19 in severely immunocompromised patients hospitalized with COVID-19. No patient died in the COVIG arm, whereas 3 of 8 patients in the control arm died. However, interpretation of the results is limited by the small sample size. In the IVIG arm, we observed higher age and increased comorbidity that may have confounded occurrence of severe COVID-19 in this group. On the other hand, in the COVIG arm, patients had a higher baseline oxygen requirement.

Nevertheless, the surprisingly strong effect of COVIG on COVID-19 severity in immunocompromised patients, compared to absent effects of equipotent or more potent doses of convalescent plasma or hyperimmune globulin given to immunocompetent, hospitalized patients with COVID-19, may demonstrate that dose and timing of antibody-based treatment is less critical in patients with hampered antibody production [5, 6]. However, comparison between studies may be challenging due to different methods used to assess neutralization (Supplementary Table 1). The protective effect we observed in immunocompromised patients specifically is in line with 2 recent trials. The REMAP-CAP trial compared convalescent plasma to usual care and reported results on critically ill

COVID-19 patients admitted to the ICU. In the subgroup of immunocompromised patients, including patients with solid malignancies, hematologic malignancies, acquired immune deficiency syndrome, and nonspecified immunosuppressive therapy, a trend was reported towards increased organ support-free days [7]. The CORIPLASM study, which has not yet been peer-reviewed, compared convalescent plasma to usual care in patients that were hospitalized but did not receive mechanical ventilation. In the published abstract, a significant survival benefit was described for the subgroup of immunocompromised patients, but a specification of the mechanism and severity of immunosuppression was not given [14]. Currently, 2 large trials are studying effects of high-titer convalescent plasma in immunocompromised patients either in the outpatient setting (COVIC19) or upon hospital admission (REMAP-CAP).

Large trials have confirmed efficacy of neutralizing monoclonal antibodies in treatment of patients with severe COVID-19, but resistance to these monoclonal antibodies has often occurred. Of note, most available monoclonal antibodies have limited activity to the currently dominant BA.4 variant [15]. Polyclonal plasma-derived antibody treatment can rapidly be generated with high neutralization titers against emerging variants.

CONCLUSIONS

Our findings indicate that plasma-derived antibody treatment, such as COVIG, may reduce the risk for severe COVID-19 in severely immunocompromised patients and should be considered when no monoclonal antibody therapies are available.

Supplementary Data

[Supplementary materials](#) are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copy-edited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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manuscript; and I. S. N., A. G., A. P. K., P. A. W. t. B., M. R. A. W., G. P., B. J. R., and J. H. reviewed the manuscript.

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References

- Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* **2020**; 584:430–6.
- Vijenthira A, Gong IY, Fox TA, et al. Outcomes of patients with hematologic malignancies and COVID-19: a systematic review and meta-analysis of 3377 patients. *Blood* **2020**; 136:2881–92.
- Boyarsky BJ, Werbel WA, Avery RK, et al. Antibody response to 2-dose SARS-CoV-2 mRNA vaccine series in solid organ transplant recipients. *JAMA* **2021**; 325:2204–6.
- Haggenburg S, Lissenberg-Witte BI, van Binnendijk RS et al. Quantitative analysis of mRNA-1273 COVID-19 vaccination response in immunocompromised adult hematology patients. *Blood Adv* **2022**; 6:1537–46.
- 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.
- Polizzotto MN, Nordwall J, Babiker AG, et al. Hyperimmune immunoglobulin for hospitalised patients with COVID-19 (ITAC): a double-blind, placebo-controlled, phase 3, randomised trial. *Lancet* **2022**; 399:530–40.
- Writing Committee for the R-CAPI, Estcourt LJ, Turgeon AF, et al. Effect of convalescent plasma on organ support-free days in critically ill patients with COVID-19: a randomized clinical trial. *JAMA* **2021**; 326:1690–702.
- Gharbharan A, Jordans CCE, GeurtsvanKessel C, et al. Effects of potent neutralizing antibodies from convalescent plasma in patients hospitalized for severe SARS-CoV-2 infection. *Nat Commun* **2021**; 12:3189.
- Begin P, Callum J, Jamula E, et al. Convalescent plasma for hospitalized patients with COVID-19: an open-label, randomized controlled trial. *Nat Med* **2021**; 27:2012–24.

10. Simonovich VA, Burgos Pratz LD, Scibona P et al. A randomized trial of convalescent plasma in covid-19 severe pneumonia. *N Engl J Med* **2021**; 384:619–29.
11. Piechotta V, Iannizzi C, Chai KL, et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. *Cochrane Database Syst Rev* **2021**; 5:CD013600.
12. Nguyen D, Simmonds P, Steenhuis M, et al. SARS-CoV-2 neutralising antibody testing in Europe: towards harmonisation of neutralising antibody titres for better use of convalescent plasma and comparability of trial data. *Euro Surveill* **2021**; 26:2100568.
13. Abani O, Abbas A, Abbas F, et al. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* **2022**; 399:665–76.
14. Lacombe K, Hueso T, Porcher R, et al. COVID-19 convalescent plasma for hospitalized COVID-19 patients not requiring assisted ventilation. A randomized controlled trial [abstract PA28-L02]. In: Abstracts of the 37th International Congress of the ISBT; June 4–8, 2022; Virtual Meeting.
15. Tzou PL, Tao K, Kosakovsky Pond SL, Shafer RW. Coronavirus Resistance Database (CoV-RDB): SARS-CoV-2 susceptibility to monoclonal antibodies, convalescent plasma, and plasma from vaccinated persons. *PLoS One* 2022; 9;17(3):e0261045. <https://doi.org/10.1371/journal.pone.0261045>. Available at: <https://covdb.stanford.edu/susceptibility-data/table-mab-susc/>. Accessed 1 May 2022.