Hyperimmune globulin for severely immunocompromised patients hospitalized with COVID-19: a randomized, controlled trial

Running title: Hyperimmune globulin in COVID-19 patient

Sammy Huygens, MD[#1]; Quincy Hofsink, MD[#2]; Inger S Nijhof, MD, PhD[3,4]; Abraham Goorhuis, MD, PhD[5]; Arnon P Kater, MD, PhD[2]; Peter AW te Boekhorst, MD, PhD[6]; Francis Swaneveld, MD, PhD[7]; Věra MJ Novotný, MD, PhD[7]; Susanne Bogers, MSc[8]; Matthijs RA Welkers, MD, PhD[9]; Grigorios Papageorgiou, PhD[10]; Bart J Rijnders, MD, PhD[+1]; Jarom Heijmans, MD, PhD[+2,11]

1. Department of Internal Medicine, Section of Infectious Diseases, and Department of Medical Microbiology and Infectious Diseases, Erasmus University Medical Center, 3015 GD Rotterdam, The Netherlands.
2. Department of Hematology, Amsterdam UMC location University of Amsterdam, 1105 AZ Amsterdam, The Netherlands.
3. Department of Hematology, Amsterdam UMC location Vrije Universiteit Amsterdam, 1081 HV Amsterdam, The Netherlands.
4. Department of Internal Medicine-Hematology, St. Antonius Hospital, 3435 CM Nieuwegein, The Netherlands.
5. Department of Infectious Diseases, Amsterdam UMC location University of Amsterdam, 1105 AZ Amsterdam, The Netherlands.

6. Department of Hematology, Erasmus University Medical Center, 3015 GD Rotterdam, The Netherlands.
7. Unit of Transfusion Medicine, Sanquin Blood Supply Foundation, 1066 CX Amsterdam, The Netherlands.
8. Department of Viroscience, Erasmus University Medical Center, 3015 GD Rotterdam, The Netherlands.
9. Department of Medical Microbiology & Infection Prevention, Amsterdam UMC location University of Amsterdam, 1105 AZ Amsterdam, The Netherlands.
10. Department of Biostatistics, Erasmus University Medical Center, 3015 GD Rotterdam, The Netherlands.
11. Department of Internal Medicine, Amsterdam UMC location University of Amsterdam, 1105 AZ Amsterdam, The Netherlands.

[#+]: *These authors contributed equally*

Abstract

The aim of this randomized, controlled trial is to determine whether anti-SARS-CoV-2 hyperimmune globulin protects against severe COVID-19 in severely immunocompromised, hospitalized, COVID-19 patients. Patients were randomly assigned to receive anti-SARS-CoV-2 hyperimmune globulin (COVIG) or intravenous immunoglobulin without SARS-CoV-2 antibodies. Severe COVID-19 was observed in two out of ten (20%) patients treated with COVIG compared to seven out of eight (88%) in the IVIG control group (p=0.015, Fisher's exact test). COVIG may be a valuable treatment in severely immunocompromised, hospitalized, COVID-19 patients and should be considered when no monoclonal antibody therapies are available. The trial was registered at www.trialregister.nl (#NL9436).

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

Background

Severely immunocompromised patients, such as organ transplant recipients and patients with hematologic malignancies, are at risk for a severe course of 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 COVID-19 patients are likely to benefit most from such interventions and we set out to examine effects of anti-SARS-CoV-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 PCR-confirmed, symptomatic SARS-CoV-2 infection within 72 hours after admission. Patients that had received prior treatment with convalescent plasma or 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 intravenous immunoglobulin (IVIG, control). COVIG was derived from a single batch, containing a neutralizing titer of 900 IU/ml (VNT50) against SARS-CoV-2 wild-type.(12) The aim of this dose was to achieve equipotency to convalescent plasma treatment as was used in large randomized studies.(5-10) IVIG was derived from a single batch generated prior to December 2019 and, thus, did not contain SARS-CoV-2 antibodies. COVIG and IVIG production were similar, except that for COVIG production

convalescent plasma was derived from donors that had a history of symptomatic COVID-19 and had recovered from COVID-19 for at least 14 days prior to plasma donation. All convalescent plasma units were tested by a quantitative IgG ELISA test that correlated with virus neutralizing antibodies. Both COVIG and IVIG were produced by Prothya, the Netherlands, and labelled 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 following 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) ICU admission for respiratory deterioration, (3) lack of clinical improvement from day seven (no improvement in oxygen requirement or, in patients not requiring oxygen, in disease burden and fever), or (4) readmission 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 four 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 hypothesized a reduction to 30% with COVIG treatment. With a power of 90%, a two-sided alpha of 5% and a single pre-planned 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, as it was ethically inacceptable to withhold casirivimab/imdevimab therapy for patients in the trial.(13)

Intention-to-treat analysis was performed after enrolment of 21% of the target population. Continuous variables were described as medians with interquartile ranges (IQR). 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 two-sided p-value <0.05.

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.

Results

From April, 2021, to July, 2021, a total of 37 patients was screened of which 18 were enrolled at three sites in the Netherlands. Enrolled patients included six B cell-depleted patients with hematologic malignancies, nine solid organ transplant recipients, one B cell-depleted patient with auto-immune disease, one patient with congenital B cell deficiency, and one patient with acquired B cell deficiency. Ten patients were randomly allocated to receive COVIG and eight to IVIG (Supplemental figure 1). At baseline, median age of the patients was 58 years (IQR 35 – 66) and symptoms had been present for

nine days (IQR 7 – 21). The median Charlson Comorbidity Index was 3 (IQR 2 – 5) and oxygen supplementation was 3 L/min (IQR 0 – 5). 13 patients had received at least one SARS-CoV-2 vaccine (72%) and 11 patients (61%) were fully vaccinated. 16 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 Supplemental figure 2). Severe COVID-19 occurred in two (20%) patients in the COVIG arm compared to seven (88%) patients in the IVIG ($p = 0.015$). Among all 16 seronegative patients, 13% developed severe COVID-19 in the COVIG arm compared to 88% in the IVIG arm ($p = 0.010$). Both seropositive patients were randomized to the COVIG arm. Of these patients, one developed severe COVID-19 (a renal transplant recipient who was admitted to the ICU within hours after COVIG treatment and discharged one day later), and one 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, nine patients (50%) had a severe adverse event of which eight were related to COVID-19. There were three 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 ten days. No infusion-related serious adverse events were observed.

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 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 while three of eight 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 (Supplemental table 1). The protective effect we observed in immunocompromised patients specifically is in line with two 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, AIDS, and non-specified immunosuppressive therapy, a trend was reported towards increased organ support-free days.(7) The CORIPLASM study, that 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 immunosupressionwas not given.(14) Currently, two 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.

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.

Acknowledgments

The authors thank the patients who participated in the trial and research staff. The authors would also like to thank the Amsterdam UMC location University of Amsterdam, Amsterdam UMC location Vrije Universiteit Amsterdam, Erasmus University Medical Center, and St. Antonius Hospital.

Funding

This work was funded by The Netherlands Organisation for Health Research and Development and an unrestricted grant from Sanquin Blood Supply Foundation. COVIG was provided by the Dutch Ministry of Public Health, Welfare, and Sport. Funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Authorship

Contribution: J.H. initiated the study; F.S. and V.N. were involved in technical advice regarding the use of COVIG; S.H., Q.H., S.B., M.W., and G.P. were involved in data collection/acquisition and/or analysis; S.H., Q.H., B.R., and J.H. were involved in clinical data interpretation; S.H. and Q.H. wrote the first version of the manuscript; and I.N., A.G., A.K., P.B., M.W., G.P., B.R., and J.H. reviewed the manuscript.

Conflicts of Interest

F.S. and V.N. work at Sanquin Blood Supply Foundation. The remaining authors declare no competing financial interests.

Corresponding author

Jarom Heijmans
Meibergdreef 9
1105 AZ Amsterdam
j.heijmans@amsterdamumc.nl
+3120 566 9111

Alternate corresponding author

Quincy Hofsink
Meibergdreef 9
1105 AZ Amsterdam
q.hofsink@amsterdamumc.nl
+3120 566 9111

References

1. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020;584(7821):430-6. Epub 2020/07/09. doi: 10.1038/s41586-020-2521-4. PubMed PMID: 32640463; PubMed Central PMCID: PMCPMC7611074.
2. Vijenthira A, Gong IY, Fox TA, Booth S, Cook G, Fattizzo B, et al. Outcomes of patients with hematologic malignancies and COVID-19: a systematic review and meta-analysis of 3377 patients. Blood. 2020;136(25):2881-92. Epub 2020/10/29. doi: 10.1182/blood.2020008824. PubMed PMID: 33113551; PubMed Central PMCID: PMCPMC7746126.
3. Boyarsky BJ, Werbel WA, Avery RK, Tobian AAR, Massie AB, Segev DL, et al. Antibody Response to 2-Dose SARS-CoV-2 mRNA Vaccine Series in Solid Organ Transplant Recipients. JAMA. 2021;325(21):2204-6. Epub 2021/05/06. doi: 2779852 [pii]

10.1001/jama.2021.7489. PubMed PMID: 33950155; PubMed Central PMCID: PMC8100911.
4. Haggenburg S, Lissenberg-Witte BI, van Binnendijk RS, den Hartog G, Bhoekhan MS, Haverkate NJE, et al. Quantitative analysis of mRNA-1273 COVID-19 vaccination response in immunocompromised adult hematology patients. Blood Adv. 2022;6(5):1537-46. Epub 2022/02/04. doi: 10.1182/bloodadvances.2021006917. PubMed PMID: 35114690; PubMed Central PMCID: PMCPMC8816838.
5. Abani O, Abbas A, Abbas F, Abbas M, Abbasi S, Abbass H, et al. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial. Lancet. 2021;397(10289):2049-59. doi: 10.1016/S0140-6736(21)00897-7.
6. Polizzotto MN, Nordwall J, Babiker AG, Phillips A, Vock DM, Eriobu N, et al. Hyperimmune immunoglobulin for hospitalised patients with COVID-19 (ITAC): a double-blind, placebo-controlled, phase 3, randomised trial. Lancet. 2022;399(10324):530-40. doi: https://doi.org/10.1016/S0140-6736(22)00101-5.
7. Writing Committee for the R-CAPI, Estcourt LJ, Turgeon AF, McQuilten ZK, McVerry BJ, Al-Beidh F, 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(17):1690-702. Epub 2021/10/05. doi: 10.1001/jama.2021.18178. PubMed PMID: 34606578; PubMed Central PMCID: PMCPMC8491132.
8. Gharbharan A, Jordans CCE, GeurtsvanKessel C, den Hollander JG, Karim F, Mollema FPN, et al. Effects of potent neutralizing antibodies from convalescent plasma in patients hospitalized for severe SARS-CoV-2 infection. Nat Commun. 2021;12(1):3189. doi: 10.1038/s41467-021-23469-2.
9. Begin P, Callum J, Jamula E, Cook R, Heddle NM, Tinmouth A, et al. Convalescent plasma for hospitalized patients with COVID-19: an open-label, randomized controlled trial. Nat Med. 2021;27(11):2012-24. Epub 2021/09/11. doi: 10.1038/s41591-021-01488-2. PubMed PMID: 34504336; PubMed Central PMCID: PMCPMC8604729.
10. Simonovich VA, Burgos Pratx LD, Scibona P, Beruto MV, Vallone MG, Vazquez C, et al. A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia. N Engl J Med. 2021;384(7):619-29. Epub 2020/11/25. doi: 10.1056/NEJMoa2031304. PubMed PMID: 33232588; PubMed Central PMCID: PMCPMC7722692.
11. Piechotta V, Iannizzi C, Chai KL, Valk SJ, Kimber C, Dorando E, et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. Cochrane Database Syst Rev. 2021;5:CD013600. Epub 2021/05/21. doi: 10.1002/14651858.CD013600.pub4. PubMed PMID: 34013969; PubMed Central PMCID: PMCPMC8135693.
12. Nguyen D, Simmonds P, Steenhuis M, Wouters E, Desmecht D, Garigliany 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(27):2100568. doi: doi:https://doi.org/10.2807/1560-7917.ES.2021.26.27.2100568.
13. Abani O, Abbas A, Abbas F, Abbas M, Abbasi S, Abbass H, et al. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2022;399(10325):665-76. doi: 10.1016/S0140-6736(22)00163-5.
14. Lacombe K, Hueso T, Porcher R, Mekinian A, Chiarabini T, Georgin-Lavialle S, et al. COVID-19 convalescent plasma for hospitalized COVID-19 patients not requiring assisted ventilation. A randomized controlled trial [abstract PA28-L02]. Abstracts of the 37th International Congress of the ISBT, Virtual meeting, 4–8 June 2022. 2022.
15. CORONAVIRUS ANTIVIRAL & RESISTANCE DATABASE: Stanford University. Available from: https://covdb.stanford.edu/susceptibility-data/table-mab-susc/.

Table 1. Demographic and baseline characteristics

	COVIG group (n = 10)	IVIG group (n = 8)
Age (yr) – median (IQR)	48 (27 – 61)	63 (41 – 72)
Male gender – no. (%)	6 (60)	4 (50)
BMI[i] (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 auto-immune 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[ii]	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[iii] – 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[iv] – 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 µL)[v] – median (IQR)	12 (0 – 144)	20 (0 – 40)
CD4 T-cell count[v]	111 (65 – 257)	147 (53 – 298)
CD8 T-cell count[v]	140 (71 – 227)	180 (140 – 245)
NK-cell count[v]	60 (41 – 90)	90 (50 – 176)

Table 2. Primary and secondary outcomes[vi]

	COVIG group (n = 10)	IVIG group (n = 8)	RR (95% CI)	Fisher's exact test (*p*)
Severe course of COVID-19	2 (20)	7 (88)	*0.23 (0.06 – 0.81)*	*0.015*
Severe course of COVID-19 in seronegative patients	1/8 (13)	7/8 (88)	*0.14 (0.02 – 0.91)*	*0.010*
Mortality at 28 days	0 (0)	3 (38)		
Median duration of hospitalization[vii]	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)		

Figure legends

Supplemental figure 1: Trial profile. COVIG: anti-SARS-CoV-2 hyperimmune intravenous globulin; IVIG: intravenous immunoglobulin without SARS-CoV-2 antibodies; ITT: intention-to-treat. *Organ transplant recipients requiring immunosuppressive medication from two pharmacological classes could be included when seronegative only.

Supplemental figure 2: Cumulative incidence of severe COVID-19 per treatment group. Occurrence of severe COVID-19 was evaluated up until day 28 after treatment, defined as any of the following conditions: (1) respiratory deterioration requiring high-flow nasal oxygen or mechanical ventilation, (2) ICU admission for respiratory deterioration, (3) lack of clinical improvement from day seven (no improvement in oxygen requirement or, in patients not requiring oxygen, in disease burden and fever), or (4) readmission for COVID-19.

[i] BMI was not available for 1 patient in both groups.

[ii] Patient was considered as fully vaccinated 7 days after a 2nd vaccination with Moderna or BioNTech/Pfizer COVID-19 vaccine, 14 days after Janssen COVID-19 vaccine or after one Moderna or BioNTech/Pfizer COVID-19 vaccine in combination with prior SARS-CoV-2 infection.

[iii] All patients that required supplemental oxygen received corticosteroid therapy per standard of care.

[iv] Oxygen supplementation via nasal cannula.

[v] Counts were not available for 3 patients in COVIG group.

[vi] Data are n (%), median (IQR) or n/N (%).

[vii] Analyses exclude those who died during hospitalization.