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A Randomized Controlled Study Assessing Convalescent Immunoglobulins vs Convalescent Plasma for Hospitalized Patients With Coronavirus 2019

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Background. It is unknown whether convalescent immunoglobulins (cIgGs) are better than convalescent plasma (CP) for patients with coronavirus 2019 (COVID-19).

Methods. In this randomized controlled trial, we assigned high risk COVID-19 patients with ≤10 days of symptoms, to receive cIgGs or CP. The primary endpoint was improvement on day 14 according to the World Health Organization scale. Secondary endpoints were survival on day 14, and improvement, survival, and percent of ventilated patients on day 28, and treatment response in unvaccinated and vaccinated patients.

Results. A total of 319 patients were included: 166 received cIgGs and 153 CP. Median age was 64 to 66 years. A total of 112 patients (67.5%) in the cIgG group and 103 patients (67.3%) in the CP group reached the primary endpoint. Difference between groups was 0.1 (95% confidence interval, −10.1 to 10.4; $P = .026$), failing to reach noninferiority. More patients receiving cIgG improved by day 28 (136 patients [81.9%] and 108 patients [70.6%], respectively; 95% confidence interval, 1.9–20.7; $P < .001$; for superiority $P = .018$). Seventeen patients in the cIgG group (10.2%) and 25 patients (16.3%) in the CP group required mechanical ventilation ($P = .136$). Sixteen (9.6%) and 23 (15%) patients, respectively, died ($P = .172$). More unvaccinated patients improved by day 28 in the cIgG group (84.1% vs 66.1%; $P = .024$), and survival was better in the cIgG group (89.9% vs 77.4%; $P = .066$).

Conclusions. cIgGs failed to reach the primary noninferiority endpoint on day 14 but was superior to CP on day 28. Survival and improvement by day 28 in unvaccinated patients treated with cIgGs were better. In the face of new variants, cIgGs are a viable option for treating COVID-19.

Trial registration number. My Trials MOH_2021-01-14_009667.

Keywords. immunoglobulins; plasma; COVID-19.

Coronavirus disease 2019 (COVID-19) is a highly infectious pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Until November 2022, SARS-CoV-2 infected more than 640 million people and caused more than 6.5 million deaths worldwide [1, 2].

One of the cornerstones of COVID-19 treatment is antibodies against SARS-CoV-2. Publications regarding use of convalescent high titer plasma in patients with COVID-19 in the first 7 to 10 days of their illness have shown conflicting results. Some demonstrated improved outcomes and reduced mortality [3–6], whereas others failed to do so [7–9]. The efficacy of plasma is correlated with the levels of antibodies administered [10]. Administering antibodies for prophylaxis or in the first few days of illness produces better results than late administration [10]. Differences in patient allocation for treatment may affect the results [11].

As the pandemic evolved, antibody treatment transitioned from convalescent plasma (CP) to monoclonal antibody preparations [12, 13]. Commercial antibodies are easier to administer and do not require blood typing, as CP does, and are administered subcutaneously or intramuscularly and thus are easily administered in the community at the start of symptoms. The main limitation of predefined antibodies is the emergence of new variants that may escape neutralization [14, 15]. These antibodies are costly, which limits their use, especially in low-income settings [14].

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An additional method for administering antibodies is by purifying them from CP, producing a convalescent intravenous immunoglobulin (cIgG) preparation. Administration of cIgG does not require blood matching. The concentration of antibodies in cIgG is high. cIgG is derived from many plasma donors; thus, antibody diversity is higher than CP, decreasing the chances of escape of variants.

To assess the efficacy and safety of cIgG, we performed a study comparing cIgG vs 2 doses of high-titer CP in high-risk hospitalized patients with COVID-19. The primary objectives were to evaluate the safety and noninferiority of cIgG compared with 2 high-titer CP units administered for 2 consecutive days, as assessed by the proportion of patients who improve by ≥2 points on the World Health Organization (WHO) 8-scale clinical score on day 14.

PATIENTS AND METHODS

Trial Design

This was a randomized controlled, open-label, phase II, noninferiority multicenter study coordinated by Wolfson Medical Center. Eligible participants were randomly assigned in a 1:1 ratio to receive either cIgG or high-titer CP. The trial was conducted between 14 January 2021 and 12 November 2021. The trial was approved by the institutional review boards of all the clinical sites and by the Central Israeli Ethics Committee (0303-20-WOMC).

Written informed consent was obtained from all participants, and the trial was conducted in accordance with the principles stated in the Declaration of Helsinki and Good Clinical Practice guidelines.

Inclusion and Exclusion Criteria

Hospitalized adults aged ≥18 years at each participating site were screened for enrollment if they had a positive reverse-transcriptase–polymerase-chain-reaction assay. Additional inclusion criteria were lung infiltrates in a chest radiograph or computed tomography scan, up to 4 days from hospitalization at screening and up to 10 days from symptom onset, and oxygen saturation at room air <95% at screening. Patients with oxygen saturation at room air ≥95% were enrolled if they had one of the following risk factors for deterioration from COVID-19 infection: age ≥70 years, ages 50 to 69 years and 2 risk factors, or age <50 years and 4 risk factors. Risk factors were body mass index ≥30 kg/m^2; diabetes mellitus; cardiovascular disease; chronic lung disease, a cumulative ≥10 years of smoking; chronic renal insufficiency; chronic liver disease; neurological disease; active malignancy; immunosuppression, and organ implantation. Exclusion criteria were: mechanical ventilation; neutropenia (<500 neutrophils/μL); blood cultures positive for a pathogen (except contaminants as defined by the Centers for Disease Control and Prevention); failure of ≥3 organ systems; cirrhosis of the liver with Child-Pugh classification of class C; cardiac insufficiency with New York Heart Association classification ≥II; chronic lung disease requiring continuous use of oxygen; known immunoglobulin A deficiency; known sensitivity to blood products; underlying disease or any condition limiting life expectancy to <6 months; the existence of a do-not-resuscitate order.

Y. M. and O. Z. evaluated all inclusion and exclusion criteria before enrollment and authorized enrollment within 6 hours. All patients signed an informed consent form.

In the first stage of the study, treatments were given through a compassionate use emergency program authorized by the Israeli Ministry of Health (n = 61) and later after receiving all study approvals as a regular study. Randomization, informed consent, all inclusion and exclusion criteria, and all other procedures were similar in the 2 phases. The protocol can be seen in the supplement.

Intervention

Eligible patients underwent treatment randomized centrally at a of 1:1 ratio through a random number assignment to receive a 4-g dose of cIgG administered intravenously or 2 high-titer CP units, 200 mL each, administered on 2 consecutive days, in addition to standard treatment.

Anti-SARS-CoV-2 IgG Product Preparation

Human CP used for the cIgG was collected from volunteer donors of Magen David Adom National Blood Services between September 2020 and December 2020 (Supplementary Table 1). During plasma donation, a satellite sample was withdrawn and the level of anti-SARS-CoV-2 spike IgG was evaluated by semiquantitative enzyme-linked immunosorbent assay (Euroimmune GmbH). Anti-SARS-CoV-2 IgG was purified from CP using Kamada's Food and Drug Administration (FDA)-approved IgG technology, which includes 4 chromatography steps and at least 2 viral elimination/inactivation steps. The final product is at a concentration of 50 mg/mL IgG, aliquoted into 10 mL/vial. Anti-SARS-CoV-2 IgG concentration was analyzed by anti-SARS-CoV-2 QuantiVac enzyme-linked immunosorbent assay (Euroimmun Italia Diagnostica Medica Srl, Padova, Italy). The SARS-CoV-2 neutralization activity was characterized by a microneutralization assay (Viroclinic, Rotterdam, Netherlands). The final anti-SARS-CoV-2 IgG product exhibited neutralization activity 10-fold higher than the pooled CP used as the starting material. The geometric mean titer for the final product was 3051 binding antibody units (BAU)/mL, which equals 433 AU/mL (Supplementary Table 2). The geometric mean neutralizing antibody titers were 553 IU/mL (20).

CP Product Preparation

CP was prepared as previously described [3, 16]. Specific SARS-CoV-2 IgG antibody titer was measured in each CP

donation before transfusion. In CP donated from 21 May 2020 to 20 February 2021, a quantitative test for IgG anti-N SARS-CoV-2 antibody was performed. From 21 February 2021 onward, IgG anti-S was measured. Antibodies were determined by chemiluminescent microparticle immunoassay performed on the Architect i2000SR (Abbot, Green Oaks, MI, USA) automated immunoassay analyzer. A positive anti-N result was defined as S/CO ≥1.4 [17, 18]. Anti-S antibody levels ≥50 arbitrary units per milliliter (AU/mL) were considered positive [19]. Two CP units, collected from different convalescent donors, were used for every patient with COVID-19 to increase antibody diversity. We used only units with high anti-N or anti-S antibody levels. In CP units with anti-N, one CP unit had an antibody level of S/CO ≥7.0 and the other S/CO ≥4.0, the average antibody level was S/CO ≥4.5 [16]. In CP units with known anti-S, a level of ≥1050 AU/mL was considered high. Based on the WHO international standard study, there is a strong correlation between AU/mL units and WHO units (BAU/mL). The equation for the correlating the units is BAU/mL = 0.142 × AU/mL [20]. Thus, two CP units contained 25% to 50% of the antibodies administered by cIgG.

Clinical Outcomes

The primary efficacy endpoint was the proportion of patients with an improvement of ≥2 points on day 14 compared with baseline as evaluated by the WHO 8-point ordinal scale [21]. The WHO ordinal clinical severity scale was collected after signing the informed consent form, when the patient received the first dose of treatment, and on days 7, 14, and 28 (Supplementary Table 1).

We assessed the number and percent of patients who died on day 14.

Secondary efficacy endpoints were the proportion of patients with an improvement of 1 and 2 points on days 7 and 28, the proportion of patients ventilated, and the survival rate in in both groups.

We also assessed response rate and survival of cIgG and CP treatment in unvaccinated and vaccinated patients. Vaccination was defined as receiving ≥1 vaccine dose.

To further assess bias related to using anti-N and anti-S antibody measurements titer in CP, we performed a sensitivity analysis of the response rate between the groups according to the time these tests were used (Supplementary Table 3).

Secondary safety endpoints were treatment emergent adverse events of special interest (anaphylaxis, serious allergic responses) and treatment-emergent serious adverse events.

Statistical Analyses

The sample size was calculated assuming 75% of the patients treated with CP and that 80% of the patients treated with cIgG will improve by ≥2 points in the WHO 8-point ordinal scale on day 14. This yielded 270 patients to demonstrate noninferiority of cIgG.

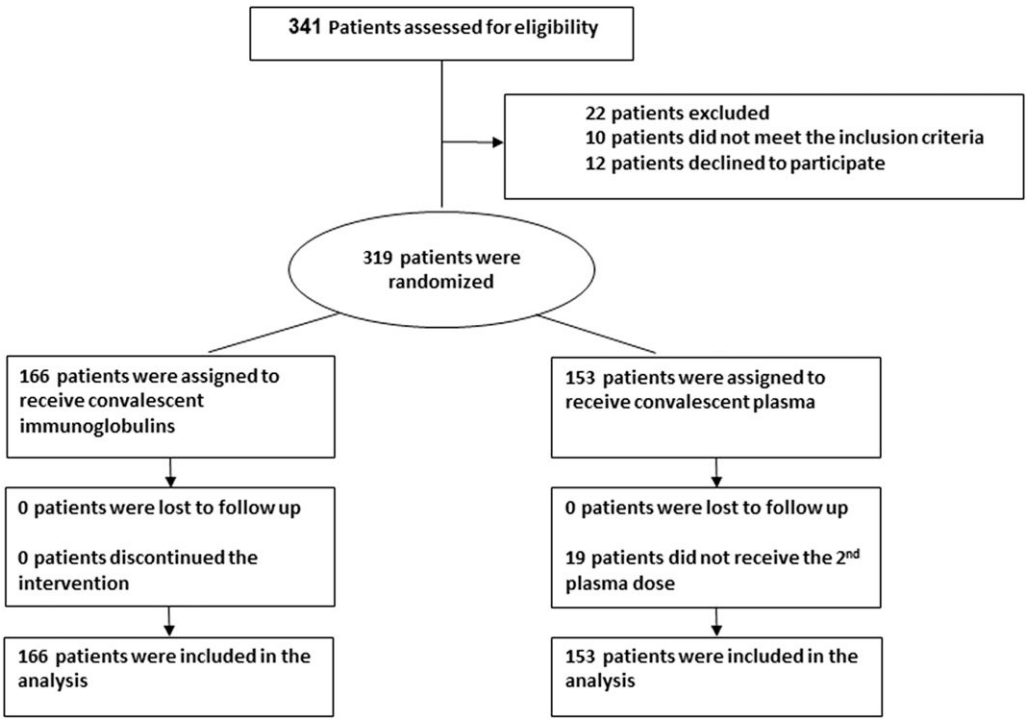

Figure 1. Flow chart of recruitment and randomization.

We first calculated noninferiority using a margin of 10%, at 80% power using the Farrington–Manning method with 1-sided alpha = 0.025. If the null hypothesis was rejected, the superiority of the cIgG treatment over CP was tested using Fisher exact test with 2-sided alpha = 0.05 when the lower bound of the confidence interval (CI) was >0.1 (10%). A 95% Clopper–Pearson CI was constructed for all secondary endpoints.

Safety endpoints were summarized descriptively by the treatment group. All statistical analyses were performed using SAS Version 9.4 or higher under Windows 2016 Terminal. The statistical analysis plan can be seen in the supplement.

RESULTS

Between 1 January 2021 and 19 October 2021, 341 patients were recruited at 6 participating centers (Wolfson Medical Center, Kaplan Medical Center, Sheba Medical Center, Samson Assuta University Hospital, Hadassah Ein Kerem Medical Center, and Shamir [Assaf Harofeh] Medical Center). Twenty-two patients were excluded (Figure 1). Consequently, 319 patients were included in the study:166 randomized to receive cIgG and 153 to receive CP. In the analysis, we included all patients that were randomized and received at least 1 dose of the treatment.

Patients' characteristics are presented in Table 1. There were no statistically significant differences between patients receiving cIgG and CP.

A total of 112 patients (67.5%) in the cIgG group and 103 patients (67.3%) in the CP group reached the primary efficacy endpoint. The difference between the groups was 0.1 (95% CI: −10.1 to 10.4; $P = .026$), thus failing to reach the noninferiority margin. The 8-point ordinal clinical status change was 2.1 ± 2.2 in the cIgG group and 1.9 ± 2.4 in the CP group.

Improvement by ≥1 point on day 14, ≥2 points on day 7, ≥1 point on day 7, and ≥2 points and ≥1 point on day 28 were better in the cIgG group vs the CP group in all comparisons, as can be seen in Table 2, and reached significance at 28 days. By day 28, improvement by ≥2 points in the WHO ordinal scale reached superiority for cIgG over CP (difference [%] 11.3; 95% CI: 1.9–20.7; $P = .026$; P for superiority 0.018). Seventeen patients (10.2%) required mechanical ventilation in the cIgG group vs 25 patients (16.3%) in the CP group ($P = .136$). Median time to discharge from the hospital was similar in both groups (7 days; CI: 6–8 days; $P = .309$).

Sixteen patients (9.6%) in the cIgG group and 23 patients (15%) in the CP group died within 14 days ($P = .172$). The Kaplan–Meier curve of survival by treatment group is presented in Figure 2. None of the deaths was linked to the treatment received.

To further analyze the effect of the interventions, we analyzed separately patients who received treatment ≤7 days and >7 days from symptom onset (Table 3). Time from treatment onset did not affect the response rate to the treatments.

We also assessed response to treatment in unvaccinated patients and patients who received ≥1 dose of COVID-19 vaccine (Table 3). In unvaccinated patients the effect of cIgG was better compared with CP. At day 14, more patients in the cIgG group responded than in the CP group but this did not reach superiority. By day 28, cIgG was superior to plasma in unvaccinated patients. Survival by day 28 in patients treated with cIgG was significantly higher in unvaccinated patients compared with CP (Table 3). As expected, differences between the treatments were less pronounced in vaccinated patients and cIgG did reach superiority in this group. There was no survival benefit of cIgG compared with CP in vaccinated patients.

The distribution of treatment-emergent serious adverse events by severity is presented in Table 4. Two patients in the

Table 1. Characteristics of the Patients at Baseline

Clinical Values	Convalescent IgG N = 166	Convalescent Plasma N = 153	*P* Value
Median age (range), y	64 (20.0–95.0)	66 (28.0–97.0)	.324
Female sex, no. (%)	78 (46.9)	60 (39.2)	.176
Patients with severe disability and dependency, no. (%)	12 (7.2)	19 (12.4)	.135
Coexisting conditions			
Body mass index, kg/m^2	29.6 (6.5)	29.8 (7.4)	.748
Hypertension	101 (60.8)	81 (53.3)	.212
Ischemic heart disease	22 (13.4)	29 (19.0)	.221
Congestive heart failure	21 (12.7)	12 (7.8)	.198
Diabetes	64 (38.6)	57 (37.5)	.908
Chronic lung disease	28 (17.0)	26 (17.2)	1.000
Chronic renal failure	31 (18.8)	25 (16.6)	.659
Dialysis	5 (3.0)	4 (2)	1.000
Neurological disease	11 (6.7)	9 (5.9)	.821
Chronic liver disease	4 (2.6)	4 (2.6)	1.000
Malignant disease	24 (14.5)	32 (20.9)	.142
Chronic steroid treatment	10 (6.1)	16 (10.6)	.156
Human immunodeficiency virus infection	0	1 (0.7)	.481
Immunodeficiency	17 (10.3)	23 (15.2)	.236
Vaccination status[a]			.805
Vaccinated at least once	66 (39.8)	64 (41.8)	
Not vaccinated	69 (41.6)	62 (40.5)	
Median time from symptom onset to treatment (range), d	7 (0–11)	6 (0–11)	
8-point Ordinal Clinical Status Score at baseline	5 (0.7)	5.1 (0.7)	.457
Baseline laboratory results			
Creatinine, mg/dL	1.4 (1.7)	1.2 (1.2)	.668
Lactate dehydrogenase, U/L	574.6 (445.4)	577 (382.0)	.816
C-reactive protein, mg/dL	11.6 (9.4)	14.8 (16.6)	.069
Lymphocytes, 10^3/μL	1.5 (3.7)	2.1 (8.3)	.716

Data are presented as median (range) or number of patients (%).

[a]Missing vaccination data for 58 patients (18.2%).

Table 2. Primary and Secondary Efficacy Endpoints, Responders Rate According to the 8-Point Ordinal Clinical Status Score

Treatment Group	N	Responders Rate, n (%)	95% CI	Noninferiority *P* Value	Superiority *P* Value [a]
Improvement of ≥2 points on day 14					
Convalescent IgG	166	112 (67.5%)	59.7–74.6		
Convalescent plasma	153	103 (67.3%)	59.2–74.7		
Difference (%)		0.1	−10.1 to 10.4	.026	1.000
Improvement of ≥1 point on day 14					
Convalescent IgG	166	126 (75.9)	68.6–82.2		
Convalescent plasma	153	112 (73.2)	65.4–80.1		
Difference (%)		2.7	−6.8 to 12.2	.005	.608
Improvement of ≥2 points on day 7					
Convalescent IgG	166	84 (50.6)	42.7–58.5		
Convalescent plasma	153	76 (49.7)	41.4–57.9		
Difference (%)		0.9	−10.0 to 11.9	.025	.911
Improvement of ≥1 point on day 7					
Convalescent IgG	166	95 (57.2)	49.3–64.9		
Convalescent plasma	153	87 (56.9)	48.6–64.9		
Difference (%)		0.4	−10.4 to 11.2	.030	1.000
Improvement of ≥2 points on day 28					
Convalescent IgG	166	136 (81.9)	75.2–87.5		
Convalescent plasma	153	108 (70.6)	62.6–77.7		
Difference (%)		11.3	1.9–20.7	<.001	.018
Improvement of ≥1 point on day 28					
Convalescent IgG	166	140 (84.3)	77.8–89.6		
Convalescent plasma	153	116 (75.8)	68.2–82.4		
Difference (%)		8.5	−.4 to 17.4	<.001	.067

[a]We first calculated noninferiority using the Farrington–Manning method with 1-sided alpha = 0.025 and a noninferiority margin of 10%. If this null hypothesis was rejected, the superiority of cIgG treatment over CP was tested using the Fisher exact test with 2-sided alpha = 0.05. A 95% Clopper–Pearson CI was constructed for all secondary endpoints.

Abbreviations: CI, confidence interval; cIgG, convalescent immunoglobulin; CP, convalescent plasma.

CP group developed mild urticaria after plasma administration. There were no reports of anaphylaxis.

DISCUSSION

This is the first randomized controlled study to report outcomes related to the administration of cIgG compared with high-titer CP for hospitalized patients with COVID-19. Our results did not reach the predefined noninferiority margin for cIgG compared with CP on day 14. However, treatment outcomes on day 28 were better in patients treated with cIgG. In addition, there was a trend toward fewer patients in the cIgG group requiring mechanical ventilation vs the CP group (10.2% vs 16.3%, respectively; $P = .136$) and a trend toward less mortality in the cIgG group compared with the CP group (9.6% vs 15%, respectively; $P = .172$). Of note was the significant beneficial effect of cIgG vs CP in unvaccinated patients. In this group, cIgG reached superiority regrading clinical benefit and survival. Both treatments had a good safety profile, and all the serious adverse events were linked to SARS-CoV-2 infection rather than the treatment administered.

In contrast to our beneficial results regarding cIgG, a recent Cochrane review summarizing the effect of cIgG from different sources (human and animal) demonstrated mixed results and could not reach a conclusion regarding the benefit of cIgG [22].

cIgG and CP are expected to control COVID-19 using multiple mechanisms, including SARS-CoV-2 neutralization, immunomodulation, and prevention of superimposed bacterial infections because the presence of polyclonal antibodies against other pathogens [23, 24]. Additional benefits include the higher dose of antibodies in cIgG and the greater antibody diversity of preparations derived from multiple plasma donors. The treatment is easily adaptable to new variants and is easy to administer because it does not require blood typing. Currently, data regarding the use of cIgG are limited [22]. In a small, randomized study including 50 patients that compared cIgG with the standard of care in patients with severe and critical COVID-19, administration of cIgG reduced mortality (25% in the intervention group vs 60% in the standard of care group) and was safe. Results did not reach significance, perhaps due to the small number of patients included [25]. Mortality in this study was assessed on day 28 after treatment. Our primary endpoint was improvement on day 14; at this time, we failed to reach noninferiority. In accordance with this publication, cIgG seemed to perform better than plasma on day 28, particularly in unvaccinated patients.

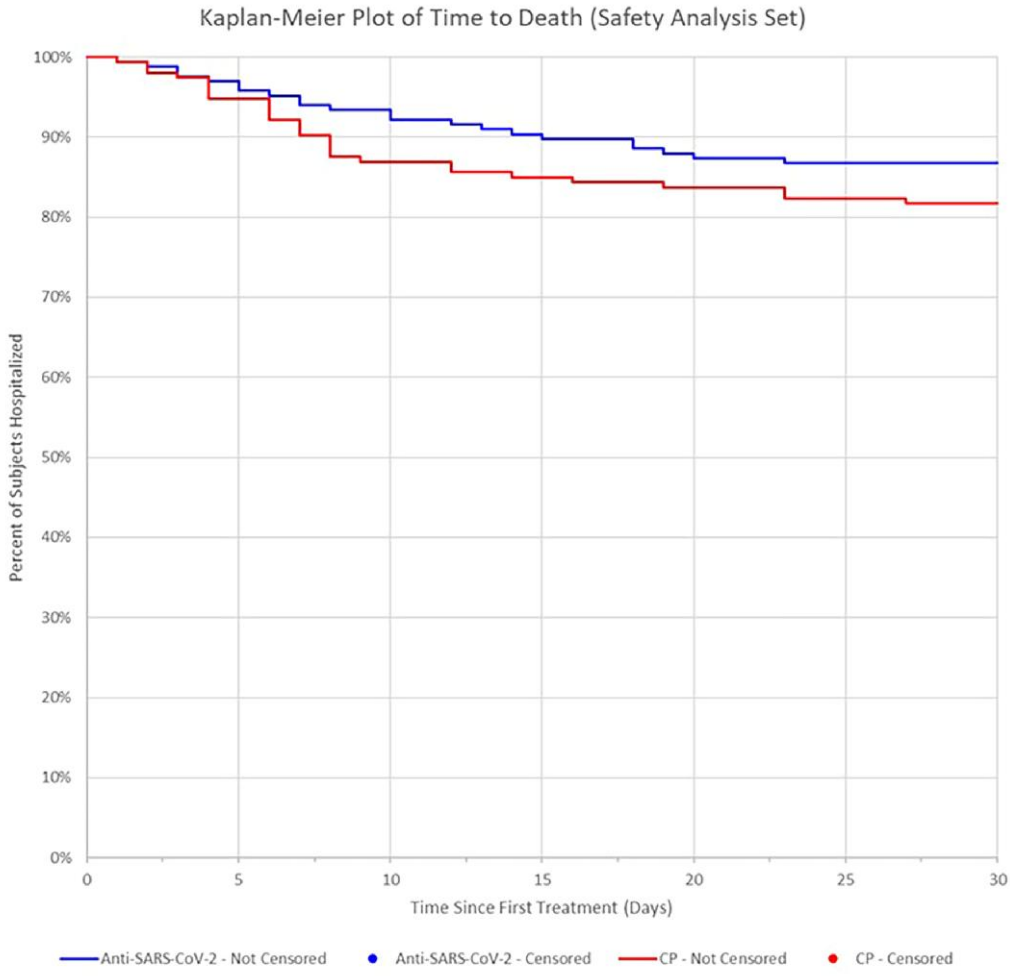

Figure 2. Kaplan–Meier curve of survival by treatment group. Kaplan–Meier plot depicts the survival rate of patients in the cIgG group and CP group from randomization to 28 d after randomization. cIgG, convalescent immunoglobulin; CP, convalescent plasma.

Results regarding CP are contradictory with some publications supporting the benefit of CP, whereas others failed to do so [3–9]. A key factor in the efficacy of CP treatment is the level of antibodies administered because higher antibody titers produce better outcomes [10]. The level of antibodies in both treatment arms in our study were high, approximately 2400 BAU/mL in cIgG, which is equivalent to 16 900 AU/mL for anti-S IgG, a higher level than that administered by 2 CP units [20]. The minimal anti-S antibodies administered to patients was 2 CP units with an anti-S level ≥1050 AU/mL. At the beginning of the study, we measured anti-N antibodies; later, as more test platforms became available, measurements transitioned into anti-S antibodies. Although we cannot directly compare the levels of anti-N antibodies and anti-S antibodies, data demonstrate that in people previously infected with COVID-19, there is a strong correlation between the level of both antibodies, so we are quite confident that all CP units indeed contained high antibody titers against COVID-19 [26]. In a sensitivity analysis, we could not demonstrate a specific effect of the different measurements used on outcomes. The minimal antibody levels administered in our study were higher than the FDA recommendations regarding the minimal level of antibodies required for CP [27]. We did not have the exact measurements of the antibody titer in the plasma units given. On average, CP contained 25% to 50% of the antibody titer in cIgG. To compare the antibody dose in CP with cIgG, we would have to administer 4 high-titer CP units in a limited time frame. Most patients who need CP are elderly with cardiovascular and renal comorbidities and would not be able to handle this volume overload without an increase in adverse events. Our results suggest that the higher antibody titer in cIgG were related to improved outcomes.

Our study has some caveats. Treatment was administered up to 4 days from hospitalization and up to 10 days from the beginning of symptoms. This time frame may have been too

Table 3. Improvement According to the 8-Point Ordinal Clinical Status Score in Subgroups

Subgroup	Treatment Group	N	Responders Rate, n (%)	95% CI	Noninferiority *P* Value	Superiority *P* Value[a]
Patients with ≥2 change from baseline to day 14 in the 8-point ordinal scale						
Time from symptom onset ≤7 d	Convalescent IgG	104	66 (63.5)	53.4–72.7	.742	
	Convalescent plasma	100	64 (64.0)	53.7–73.4		
Time from symptom onset >7 d	Convalescent IgG	61	46 (75.4)	62.7–85.6		
	Convalescent plasma	51	37 (72.5)	58.2–84.2		
Patients with ≥2 change from baseline to day 14 in the 8-point ordinal scale						
Not vaccinated	Convalescent IgG	69	52 (75.4)	65.4–83.7	.003	.1333
	Convalescent plasma	62	39 (62.9)	51.7–73.2		
Vaccinated at least once	Convalescent IgG	66	40 (60.6)	49.7–70.7	.770	1.000
	Convalescent plasma	64	49 (76.6)	66.2–85.0		
Patients with ≥2 change from baseline to day 28 in the 8-point ordinal scale						
Not vaccinated	Convalescent IgG	69	58 (84.1)	75.0–90.8	<.001	.024
	Convalescent plasma	62	41 (66.1)	55.0–76.1		
Vaccinated at least once	Convalescent IgG	66	56 (84.8)	75.7–91.5	.008	.371
	Convalescent plasma	64	50 (78.1)	67.9–86.3		
Survival after 28 d by subgroup						
Not vaccinated	Convalescent IgG	69	62 (89.9)	81.8–95.1	<.001	.066
	Convalescent plasma	62	48 (77.4)	67.9–85.8		
Vaccinated at least once	Convalescent IgG	66	57 (86.4)	77.4–92.7	.047	1.000
	Convalescent plasma	64	55 (85.9)	76.7–92.5		

[a]We first calculated non-inferiority using the Farrington–Manning method with one-sided alpha = 0.025 and a non-inferiority margin of 10%. If this null hypothesis was rejected, the superiority of cIgG treatment over CP was tested using Fisher's exact test with two-sided alpha = 0.05. A 95% Clopper–Pearson CI was constructed for all secondary endpoints.

Abbreviations: CI, confidence interval; cIgG, convalescent immunoglobulin; IgG, immunoglobulin G.

Table 4. Distribution of Treatment-Emergent Serious Adverse Events by Severity

Severity	CIgG N = 166 n; n1 (%)	CCP N = 153 n; n1 (%)	Total N = 319 n; n1 (%)
Any	23; 22 (13.3)	31; 31 (20.3)	54; 53 (16.6)
Mild	0; 0 (0.0)	1; 1 (0.7)	1; 1 (0.3)
Moderate	0; 0 (0.0)	0; 0 (0.0)	0; 0 (0.0)
Severe	22; 21 (12.7)	28; 28 (18.3)	50; 49 (15.4)

Adverse events were presented in the following scheme: number of events (number of patients, % of patients).

Abbreviations: cIgG, convalescent immunoglobulin; CP, convalescent plasma.

lenient; a better approach would have been to administer the treatment in the first few days of illness. Studies have demonstrated that earlier administration of CP is associated with better outcomes [5, 6].

Further study is warranted to assess cIgG efficacy when administered in the community before hospitalization. To be included in our study, patients without risk factors had to have a decline in O_2 saturation. This represents a more advanced SARS-CoV-2 infection, and it is plausible that some of these patients were in the inflammatory state of the SARS-CoV infection [28]. Antibodies are less efficacious in advanced stages of COVID-19 infection and perhaps a better strategy would have been to exclude these patients from the study.

Despite these limitations the results are essential, particularly in the face of loss of effectiveness of the current monoclonal antibodies used to treat COVID-19 [28, 29]. To date, there are no approved monoclonal antibodies that remain effective against new variants.

To conclude, the results did not reach the predefined noninferiority margin for cIgG compared with CP at day 14, but cIgG was superior to CP when assessing the number of patients that responded to treatment at 28 days. cIgG elicited better outcomes and better survival in unvaccinated patients. Treatment of both arms had a good safety profile. Thus, in the face of new variants cIgG is a viable option for treating patients with COVID-19. Further studies are warranted to assess cIgG earlier in the course of disease.

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

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet **2020**; 395:497–506.
2. Worldometer. COVID-19 coronavirus pandemic. Available at: https://www.worldometers.info/coronavirus/. Accessed 12 November 2022.
3. Maor Y, Cohen D, Paran N, et al. Compassionate use of convalescent plasma for treatment of moderate and severe pneumonia in COVID-19 patients and association with IgG antibody levels in donated plasma. EClinicalMedicine **2020**; 26: 100525.
4. Simonovich VA, Burgos Pratx LD, Scibona P, et al. A randomized trial of convalescent plasma in COVID-19 severe pneumonia. N Engl J Med **2021**; 384: 619–29.
5. Libster R, Pérez Marc G, Wappner D, et al. Early high-titer plasma therapy to prevent severe COVID-19 in older adults. N Engl J Med **2021**; 384:610–8.
6. Joyner MJ, Carter RE, Senefeld JW, et al. Convalescent plasma antibody levels and the risk of death from COVID-19. N Engl J Med **2021**; 384:1015–27.
7. Self WH, Wheeler AP, Stewart TG, et al. Neutralizing COVID-19 convalescent plasma in adults hospitalized with COVID-19: a blinded, randomized, placebo-controlled trial. Chest **2022**; 162:982–94.
8. Bégin 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.
9. Korley FK, Durkalski-Mauldin V, Yeatts SD, et al. Early convalescent plasma for high-risk outpatients with COVID-19. N Engl J Med **2021**; 385:1951–60.
10. Focosi D, Franchini M, Pirofski LA, et al. COVID-19 convalescent plasma and clinical trials: understanding conflicting outcomes. Clin Microbiol Rev **2022**; 35:e0020021.
11. Estcourt L, Callum J. Convalescent plasma for COVID-19—making sense of the inconsistencies. N Engl J Med **2022**; 386:1753–4.
12. Montgomery H, Hobbs FDR, Padilla F, et al. Efficacy and safety of intramuscular administration of tixagevimab-cilgavimab for early outpatient treatment of COVID-19 (TACKLE): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet Respir Med **2022**; 10:985–96.
13. O'Brien MP, Forleo-Neto E, Sarkar N, et al. Effect of subcutaneous casirivimab and imdevimab antibody combination versus placebo on development of symptomatic COVID-19 in early asymptomatic SARS-CoV-2 infection: a randomized clinical trial. JAMA **2022**; 327:432–41.
14. Choudhary MC, Chew KW, Deo R, et al. Emergence of SARS-CoV-2 escape mutations during Bamlanivimab therapy in a phase II randomized clinical trial. Nat Microbiol **2022**; 7:1906–17.
15. Marovich M, Mascola JR, Cohen MS. Monoclonal antibodies for prevention and treatment of COVID-19. JAMA **2020**; 324:131–2.
16. Izak M, Gendelman V, Bransburg-Zabary S, et al. Qualifying coronavirus disease 2019 convalescent plasma donors in Israel. Vox Sang **2022**; 117:185–92.
17. Manalac J, Yee J, Calayag K, et al. Evaluation of Abbott anti-SARS-CoV-2 CMIA IgG and Euroimmun ELISA IgG/IgA assays in a clinical lab. Clin Chim Acta **2020**; 510:687–90.
18. Meschi S, Colavita F, Bordi L, et al. Performance evaluation of Abbott ARCHITECT SARS-CoV-2 IgG immunoassay in comparison with indirect immunofluorescence and virus microneutralization test. J Clin Virol **2020**; 129:104539.
19. Abbot SARS-CoV-2 IgG II Quant assay reagent instruction for use. Available at: https://www.corelaboratory.abbott/int/en/offerings/segments/infectious-disease/sars-cov-2. Accecced 31 May 2023.
20. Mattiuzzo G, Bentley EM, Hassall M, et al. Establishment of the WHO International Standard and Reference Panel for anti-SARS-CoV-2 antibody (WHO/BS/2020/2403). Geneva, Switzerland: World Health Organization 2020.
21. WHO R&D Blueprint Novel Coronavirus COVID-19 Therapeutic Trial Synopsis. Available at: https://www.who.int/publications/i/item/covid-19-therapeutic-trial-synopsis.
22. Kimber C, Valk SJ, Chai KL, et al. Hyperimmune immunoglobulin for people with COVID-19. Cochrane Database Syst Rev **2023**; 1:CD015167.
23. Jawhara S. Could intravenous immunoglobulin collected from recovered coronavirus patients protect against COVID-19 and strengthen the immune system of new patients? Int J Mol Sci **2020**; 21:2272.
24. de Alwis R, Chen S, Gan ES, Ooi EE. Impact of immune enhancement on COVID-19 polyclonal hyperimmune globulin therapy and vaccine development. EBioMedicine **2020**; 16:102768.
25. Ali S, Uddin SM, Shalim E, et al. Hyperimmune anti-COVID-19 IVIG (C-IVIG) treatment in severe and critical COVID-19 patients: a phase I/II randomized control trial. EClinicalMedicine **2021**; 36:100926.
26. Lee N, Jeong S, Lee SK, et al. Quantitative analysis of anti-N and anti-S antibody titers of SARS-CoV-2 infection after the third dose of COVID-19 vaccination. Vaccines (Basel) **2022**; 10:1143.
27. US Food and Drug Administration. COVID-19 convalescent plasma EUA decision memo 02052021. Available at: https://www.fda.gov/media/141480/download. Accessed 29 May 2023.
28. Rovito R, Bono V, Augello M, et al. Association between SARS-CoV-2 RNAemia and dysregulated immune response in acutely ill hospitalized COVID-19 patients. Sci Rep **2022**; 12:19658.
29. Planas D, Bruel T, Staropoli I, et al. Resistance of omicron subvariants BA.2.75.2, BA.4.6 and BQ.1.1 to neutralizing antibodies. bioRxiv 516888 [Preprint]. November 17, 2022. Available at: https://doi.org/10.1101/2022.11.17.516888.