ORIGINAL ARTICLE

Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults

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ABSTRACT

BACKGROUND

Therapies to interrupt the progression of early coronavirus disease 2019 (Covid-19) remain elusive. Among them, convalescent plasma administered to hospitalized patients has been unsuccessful, perhaps because antibodies should be administered earlier in the course of illness.

METHODS

We conducted a randomized, double-blind, placebo-controlled trial of convalescent plasma with high IgG titers against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in older adult patients within 72 hours after the onset of mild Covid-19 symptoms. The primary end point was severe respiratory disease, defined as a respiratory rate of 30 breaths per minute or more, an oxygen saturation of less than 93% while the patient was breathing ambient air, or both. The trial was stopped early at 76% of its projected sample size because cases of Covid-19 in the trial region decreased considerably and steady enrollment of trial patients became virtually impossible.

RESULTS

A total of 160 patients underwent randomization. In the intention-to-treat population, severe respiratory disease developed in 13 of 80 patients (16%) who received convalescent plasma and 25 of 80 patients (31%) who received placebo (relative risk, 0.52; 95% confidence interval [CI], 0.29 to 0.94; P=0.03), with a relative risk reduction of 48%. A modified intention-to-treat analysis that excluded 6 patients who had a primary end-point event before infusion of convalescent plasma or placebo showed a larger effect size (relative risk, 0.40; 95% CI, 0.20 to 0.81). No solicited adverse events were observed.

CONCLUSIONS

Early administration of high-titer convalescent plasma against SARS-CoV-2 to mildly ill infected older adults reduced the progression of Covid-19. (Funded by the Bill and Melinda Gates Foundation and the Fundación INFANT Pandemic Fund; Dirección de Sangre y Medicina Transfusional del Ministerio de Salud number, PAEPCC19, Plataforma de Registro Informatizado de Investigaciones en Salud number, 1421, and ClinicalTrials.gov number, NCT04479163.)

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiologic agent of coronavirus disease 2019 (Covid-19), causes a particularly severe illness in older adults. The percentage of these patients who are hospitalized is high, and most deaths from Covid-19 worldwide occur in this age group.[1,2] Various coexisting conditions adversely affect the prognosis in patients with Covid-19, regardless of age. These conditions include hypertension, diabetes, cardiovascular disease, obesity, chronic renal failure, and chronic obstructive pulmonary disease (COPD).[1,2]

Treatments for Covid-19 in the early stages of the disease remain elusive. Few strategies provide benefit, several have failed, and others are being evaluated.[3-12] Among the strategies under investigation is the infusion of specific antibodies that are present in the plasma of convalescent patients.[7-12] Plasma infusions have not been commonly associated with adverse events[13] and have been associated with improved outcomes in patients who have had other diseases.[14-16] However, antibodies in plasma must be administered soon after infection in order to be effective.[14-16]

In hospitalized patients with Covid-19, the infusion of convalescent plasma against SARS-CoV-2 late in the course of illness has not shown clear benefits and, consequently, the most appropriate antibody concentrations for effective treatment are unclear.[7-12] We evaluated whether convalescent plasma with high SARS-CoV-2 antibody titers, administered within 72 hours after the onset of mild symptoms, would be efficacious in preventing progression to severe disease in older adult patients with Covid-19.

Methods

Trial Design and Oversight

We conducted a randomized, double-blind, placebo-controlled trial between June 4, 2020, and October 25, 2020 (when the last patient completed follow-up), at clinical sites and geriatric units in Argentina. The trial was approved by the institutional review boards of the participating institutions and the state of Buenos Aires and was supervised by an independent data and safety monitoring board. The authors who designed the trial and wrote the manuscript are listed in Table S15 in the Supplementary Appendix, available with the full text of this article at NEJM.org. All the authors compiled the data and vouch for the accuracy and completeness of the data and the adherence of the trial to the protocol, available at NEJM.org. Three of the authors analyzed the data. The last author wrote the first draft of the manuscript. No one who is not an author contributed to the writing of the manuscript. No confidentiality agreements related to the data are in place between the sponsors and the authors or their institutions.

Trial Patients

Patients who were 75 years of age or older, irrespective of current coexisting conditions, or between 65 and 74 years of age with at least one coexisting condition were identified and assessed for eligibility. Coexisting conditions, which are defined in Table S1, included hypertension or diabetes for which the patient was currently receiving pharmacologic treatment, obesity, chronic renal failure, cardiovascular disease, and COPD. At the time of screening for SARS-CoV-2 by reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay, eligible patients had had at least one of each sign or symptom in the following two categories for less than 48 hours: a temperature of at least 37.5°C, unexplained sweating, or chills; and dry cough, dyspnea, fatigue, myalgia, anorexia, sore throat, dysgeusia, anosmia, or rhinorrhea. Exclusion criteria included severe respiratory disease (the primary end point), any disease listed in Table S5, or both.

Patients who provided consent to undergo screening received home visits, and samples of nasopharyngeal and oropharyngeal secretions were obtained for testing with an RT-PCR assay (iAMP COVID-19, Atila BioSystems) to detect SARS-CoV-2. Patients with detectable SARS-CoV-2 RNA were transported to trial hospitals and invited to sign the informed-consent form. After July 22, 2020, legal guardians provided consent for patients who had cognitive impairment. Starting on July 27, 2020, since several geriatric institutions with SARS-CoV-2 outbreaks were transformed into low-complexity inpatient units for mildly ill residents infected with SARS-CoV-2, we screened and invited residents who met the trial criteria to participate in the trial on-site.

Randomization and Intervention

Eligible patients who provided written informed consent were randomly assigned to receive either

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250 ml of convalescent plasma with an IgG titer greater than 1:1000 against SARS-CoV-2 spike (S) protein (COVIDAR IgG, Instituto Leloir, Argentina) or 250 ml of placebo (0.9% normal saline). The convalescent plasma was arbitrarily defined as "high-titer" and included antibody concentrations in the upper 28th percentile. A computer-generated randomization sequence with a balanced permuted block design (block size 2) was prepared at the data center.

Convalescent plasma or placebo was administered less than 72 hours after the onset of symptoms, and the infusions were given over a period of 1.5 to 2.0 hours. Both the convalescent plasma and placebo were concealed with opaque bags and tape to cover the infusion catheter. Patients were monitored for adverse events until 12 hours after the intervention.

A total of 479 potential plasma donors who had had SARS-CoV-2 infection for a minimum of 10 days and who had been asymptomatic for 3 days or longer and had two negative RT-PCR tests[17] were identified through hospital lists and an online campaign. Potential donors who provided written informed consent were visited at home and screened for SARS-CoV-2 S IgG at a titer greater than 1:1000 in serum. Each of the 135 candidates (28%) with adequate titers donated 750 ml of plasma (see Fig. S6).

CLINICAL AND LABORATORY MONITORING

A total of 24 hours after the end of the infusion, a sample of venous blood (5 ml) was obtained from the patients. Serum samples were preserved at −20°C until completion of the trial. We assayed anti–S IgG SARS-CoV-2 using the COVIDAR IgG test. In addition, we assayed samples using the SARS-CoV-2 Spike S1-RBD IgG enzyme-linked immunosorbent assay detection kit (GenScript) and the SARS-CoV-2 surrogate virus neutralization test kit (GenScript).

The patients' clinical status was monitored daily by trial physicians until day 15 to assess for primary end-point events that occurred in the hospital, in participating geriatric institutions, or at home if the patients had been discharged (Figs. S7 and S8). Patients who had persistent symptoms for which medical care was warranted were followed until the resolution of symptoms or for a maximum of 25 days to assess for secondary end-point events. The trial physicians used predesigned questionnaires to collect clinical information. None of the patients received any experimental therapy for Covid-19 besides convalescent plasma. Data were recorded on paper forms and then double-entered into an electronic database.

TRIAL END POINTS

The primary end point of the trial was the development of severe respiratory disease, defined as a respiratory rate of 30 breaths per minute or more, an oxygen saturation of less than 93% while the patient was breathing ambient air, or both. Patients were assessed for this end-point event between 12 hours after the infusion of convalescent plasma or placebo and day 15 of trial participation.

Prespecified secondary clinical end points were life-threatening respiratory disease (defined as oxygen supplementation at a fraction of inspired oxygen [FIO_2] of 100%, noninvasive or invasive ventilation, admission to an intensive care unit, or any combination of these), critical systemic illness (respiratory failure with a ratio of the partial pressure of oxygen to FIO_2 ≤200 mm Hg, shock, multiple organ dysfunction syndrome, or any combination of these), and death associated with Covid-19. Patients in whom the illness had not resolved were assessed for these end-point events until day 25 of trial participation. On July 22, 2020, we amended the protocol to include a fourth secondary end point that included any of the three secondary end points described above, alone or in combination.

EARLY TRIAL TERMINATION

The trial was initiated when the number of cases of Covid-19 in Buenos Aires was high. However, as the number of cases decreased, it became clear that it would take approximately 5 months to reach the enrollment goal. Consequently, after discussions with the data and safety monitoring board and enrollment of 76% of the target population, we decided that it would be logistically impossible and ethically questionable, given the daily cost of the pandemic in lives and illness, to continue the trial, and we stopped to examine the results.

STATISTICAL ANALYSIS

Given the complexity of implementing this intervention, the minimal clinically important difference was set at a 40% relative reduction for an

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expected 50% of the patients in the placebo group and 30% of the patients in the convalescent plasma group who would have a primary end-point event. We estimated that a total sample size of 210 patients (105 per trial group) would provide the trial with 80% power to detect a between-group difference, at a significance level of α=0.05. We used a two-sided z-test of proportions with continuity correction and one planned interim analysis with the O'Brien–Fleming spending function to determine the test boundaries.

In the intention-to-treat analysis, the end points were assessed from the time of randomization. Continuous variables are presented as means and standard deviations or medians and interquartile ranges, as appropriate, and categorical variables are presented as percentages.

In the primary analysis strategy, we used the Kaplan–Meier product limit estimates to compare the time to reach the primary end point in the trial groups. An estimate of the relative risk and 95% confidence interval was also reported. A modified intention-to-treat analysis excluded patients who became ineligible between randomization and the administration of convalescent plasma or placebo.

The protocol prespecified an evaluation of IgG protection correlates and a subgroup analysis that was suggested by the data and safety monitoring board and approved by the institutional review boards on November 2, 2020. This analysis included an evaluation of end-point events in patients who were 75 years of age or older, irrespective of coexisting conditions, and in those between 65 and 74 years of age who had at least one coexisting condition.

RESULTS

TRIAL POPULATION

A total of 165 patients presented with symptoms that met the eligibility criteria and tested positive for SARS-CoV-2 RNA (Fig. S1). Four of these patients became ineligible before enrollment, and one did not provide consent to participate in the trial. Therefore, 160 patients with SARS-CoV-2 infection underwent randomization; 80 were assigned to receive convalescent plasma and 80 were assigned to receive placebo. Five of 160 patients (3%; 3 patients who were assigned to receive convalescent plasma and 2 who were assigned to receive placebo) received convalescent plasma or placebo after they had a primary end-point event. Hypoxemia developed before the infusion in an additional patient who had been assigned to receive convalescent plasma, and that patient did not receive convalescent plasma but was included in the analysis.

A total of 160 patients were included in the intention-to-treat analysis. One patient voluntarily left the trial on day 9 of follow-up. After day 15, a total of 38 of 160 patients (24%) continued to have Covid-19 symptoms for which hospitalization was warranted, and they were followed for 16 to 25 days, until recovery or death. By day 25 of follow-up, only 2 patients were receiving oxygen support. Both recovered by day 27.

The mean (±SD) age of the patients was 77.2±8.6 years, and 100 patients (62%) were women (Table 1). A total of 72 patients (45%) were 65 to 74 years of age and 88 (55%) were 75 years of age or older. There were no clinically significant imbalances in baseline characteristics between the convalescent plasma and placebo groups. Most patients had prespecified coexisting conditions at enrollment (Table 1). The administration of convalescent plasma was not associated with any solicited adverse events (Table S6).

PRIMARY END POINT

In the intention-to-treat population, severe respiratory disease developed in 13 of 80 patients (16%) who received convalescent plasma and in 25 of 80 patients (31%) who received placebo (relative risk, 0.52; 95% confidence interval [CI], 0.29 to 0.94; P=0.03) (Table 2). As shown in Figure 1, in the time-to-event analysis, the median time to the development of severe respiratory disease in the convalescent plasma group (15 days; interquartile range, 15 to 15) was longer than that in the placebo group (15 days; interquartile range, 9 to 15) (P=0.03). The relative risk reduction with convalescent plasma was 48%, and the number needed to treat to avert an episode of severe respiratory disease was 7 (95% CI, 4 to 50).

Four patients in the convalescent plasma group and 2 patients in the placebo group became ineligible because they had a primary end-point event before they received convalescent plasma or placebo (one of them, who was assigned to receive convalescent plasma, did not receive a transfusion). A modified intention-to-treat population that excluded these patients showed a larger intervention effect size; severe respiratory

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Table 1. Baseline Characteristics of the Patients in the Intention-to-Treat Population.*

Variable	Convalescent Plasma (N=80)	Placebo (N=80)
Demographic characteristics		
Age — yr	76.4±8.7	77.9±8.4
Age category — no./total no. (%)		
65–74 yr	40/80 (50)	32/80 (40)
≥75 yr	40/80 (50)	48/80 (60)
Sex — no./total no. (%)		
Female	54/80 (68)	46/80 (58)
Male	26/80 (32)	34/80 (42)
Vital signs		
Axillary temperature — °C	36.5±0.7	36.8±0.8
Heart rate — beats/min	79.8±13.4	78.6±14.1
Blood pressure — mm Hg		
Systolic	124.8±15.6	125.4±15.3
Diastolic	75.1±11.2	75±10.9
Respiratory rate — breaths/min	17±2.8	17.3±3.0
Oxygen saturation while breathing ambient air — %	96.1±1.6	96.1±1.7
Time since onset of symptoms — hr	39.6±13.9	38.3±14.3
Primary coexisting conditions — no./total no. (%)		
Hypertension for which treatment was being received	62/80 (78)	52/80 (65)
Diabetes for which treatment was being received	23/80 (29)	13/79 (16)
Obesity	4/80 (5)	8/79 (10)
COPD for which treatment was being received	2/80 (2)	5/79 (6)
Cardiovascular disease	14/80 (18)	7/79 (9)
Chronic renal failure	1/80 (1)	3/79 (4)
At least one primary coexisting condition	69/80 (86)	62/80 (78)
Secondary coexisting conditions — no./total no. (%)		
Asthma or other respiratory disease	3/80 (4)	3/80 (4)
Noncirrhotic liver disease	0/80	0/80
Cancer in remission	4/80 (5)	2/80 (2)
Neurologic disease	11/80 (14)	9/80 (11)
History of smoking	13/80 (16)	10/80 (12)
Use of medication		
Regular use	76/80 (95)	73/80 (91)
Use in past 15 days	71/80 (89)	64/80 (80)
SARS-CoV-2 cycle-threshold value — cycles	16.4±7.4	16.0±7.9

* Plus–minus values are means ±SD. COPD denotes chronic obstructive pulmonary disease, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.

disease developed in 9 of 76 patients (12%) in the convalescent plasma group and 23 of 78 patients (29%) in the placebo group (relative risk, 0.40; 95% CI, 0.20 to 0.81). In the modified intention-to-treat population, patients in the convalescent plasma group also had a longer time to the development of severe respiratory disease than those in the placebo group (see Fig. S2).

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Table 2. Trial End Points in the Intention-to-Treat Population.*

End Point	Convalescent Plasma (N=80)	Placebo (N=80)	Relative Risk (95% CI)
	no./total no. (%)		
Primary end point: severe respiratory disease	13/80 (16)	25/80 (31)	0.52 (0.29–0.94)
Secondary end points			
Life-threatening respiratory disease	4/80 (5)	10/80 (12)	0.40 (0.13–1.22)
Oxygen supplementation at an F_{IO_2} of 100%	4/80 (5)	6/80 (8)	0.67 (0.20–2.27)
Noninvasive ventilation	1/80 (1)	6/80 (8)	0.17 (0.02–1.35)
Admission to intensive care unit	2/80 (2)	6/80 (8)	0.33 (0.07–1.60)
Mechanical ventilation	2/80 (2)	4/80 (5)	0.50 (0.09–2.65)
Critical systemic illness	5/80 (6)	6/80 (8)	0.83 (0.27–2.62)
Acute respiratory failure	2/80 (2)	5/80 (6)	0.40 (0.08–2.00)
Shock	2/80 (2)	1/80 (1)	2.00 (0.19–21.6)
Multiple organ dysfunction syndrome	3/80 (4)	5/80 (6)	0.60 (0.15–2.43)
Death from Covid-19	2/80 (2)	4/80 (5)	0.50 (0.09–2.65)
Life-threatening respiratory disease, critical systemic illness, or death, alone or in combination	7/80 (9)	12/80 (15)	0.58 (0.24–1.41)

* CI denotes confidence interval, and F_{IO_2} fraction of inspired oxygen.

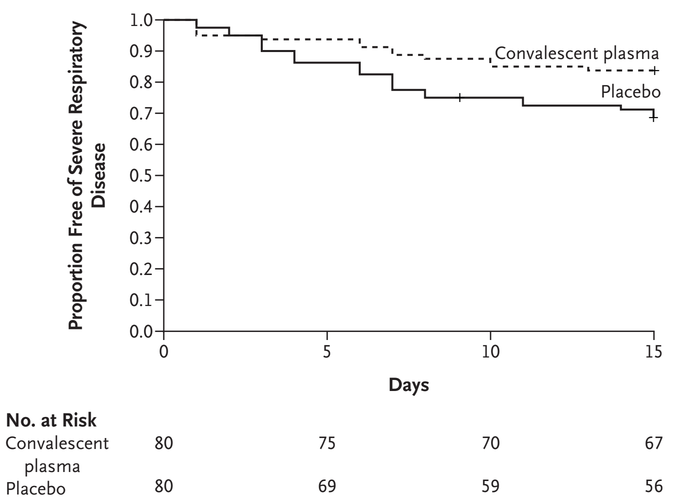

Figure 1. Time to the Development of Severe Respiratory Disease Due to Coronavirus Disease 2019, According to Trial Group in the Intention-to-Treat Analysis.

Shown are Kaplan–Meier estimates of the time from the intervention (administration of convalescent plasma or placebo) to the development of severe respiratory disease. The tick marks on the curves represent the interquartile range in the Kaplan–Meier time-to-event analysis in the convalescent plasma and placebo groups.

SECONDARY END POINTS

Secondary end-point results are provided in Table 2. Four convalescent plasma recipients (5%) and 10 placebo recipients (12%) had life-threatening respiratory disease, and 5 (6%) and 6 (8%), respectively, had a critical systemic illness. Two patients in the convalescent plasma group and 4 patients in the placebo group died. A combined secondary end-point event (life-threatening respiratory disease, critical systemic illness, and death, or any of these outcomes) occurred in 7 patients (9%) who received convalescent plasma and 12 patients (15%) who received placebo. Secondary end-point results in the modified intention-to-treat analysis are presented in Table S10.

ANTIBODY TITERS

The distribution of anti–SARS-CoV-2 serum S IgG titers 24 hours after infusion differed significantly in the two groups, with higher concentrations in patients in the convalescent plasma group (median log anti–SARS-CoV-2 S IgG titer, 5.7; interquartile range, 4.9 to 6.3) than in those in the placebo group (median log anti–SARS-CoV-2 S IgG titer, 3.9; interquartile range, 3.9 to 4.7)

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Table 3. Primary End Point, According to Donor SARS-CoV-2 S IgG Titer.

Patient Group	Patients with Severe Respiratory Disease	Relative Risk (95% CI)	Relative Risk Reduction
	no./total no. (%)		*percent*
Placebo group	25/80 (31)	1.00	
Recipient of SARS-CoV-2 S IgG in donor plasma*			
At a titer at or above median concentration	3/36 (8)	0.27 (0.08–0.68)	73.3
At a titer below median concentration	9/42 (21)	0.69 (0.34–1.31)	31.4

* The median concentration is a SARS-CoV-2 S IgG titer of 1:3200.

(Fig. 2). A comparison between severe and mild cases of illness showed no IgG correlate of protection for antibodies against SARS-CoV-2 in the serum samples of convalescent plasma recipients (Fig. S5B).

Conversely, a dose-dependent effect was observed for SARS-CoV-2 S IgG titers in plasma bags (Table 3). Donor titers selected on the basis of a median titer of 1:3200 showed a relative risk reduction of 73.3%, with a number needed to treat of 4 (range, 3 to 11) to avoid a worsening of Covid-19 in recipients of antibody concentrations above the median concentration (Table 3). The SARS-CoV-2 S IgG results were replicated with the use of a different SARS-CoV-2 spike S1-RBD IgG commercial assay; this assay provides a potential alternative tool for donor selection (r=0.7; 95% CI, 0.6 to 0.8) (see Fig. S3).

DISCUSSION

We report the use of convalescent plasma in older adult patients early in the course of Covid-19. The administration of convalescent plasma with high titers of antibodies against SARS-CoV-2 to infected patients within 72 hours after the onset of symptoms reduced the risk of progression to severe respiratory disease by 48%. Although our trial lacked the statistical power to discern long-term outcomes, the convalescent plasma group appeared to have better outcomes than the placebo group with respect to all secondary end points. Our findings underscore the need to return to the classic approach of treating acute viral infections early, and they define IgG targets that facilitate donor selection.

Our trial has fundamental differences in design from previous randomized trials of convalescent plasma therapy in patients with Covid-19 (see Table S14).[7-11] For example, we focused on older adults because they are most affected by the Covid-19 pandemic.[1,2] Previous trials involved adults who were 18 years of age or older.[7-11] In addition, we aimed to stop disease progression early and at a mild stage. Our primary end point was an enrollment criterion in previous studies. Consequently, our patients had had symptoms for less than 3 days at enrollment, whereas the median duration of symptoms ranged from 8 to 30 days in other trials.[7-11]

Studies have suggested that antibody interventions against Covid-19 work better when administered early in the course of the illness. In one study involving patients in Houston, mortality decreased only among patients who received convalescent plasma within 72 hours after admission,[8] and in a large U.S. multicenter study, mortality at 7 days was lower among hospitalized

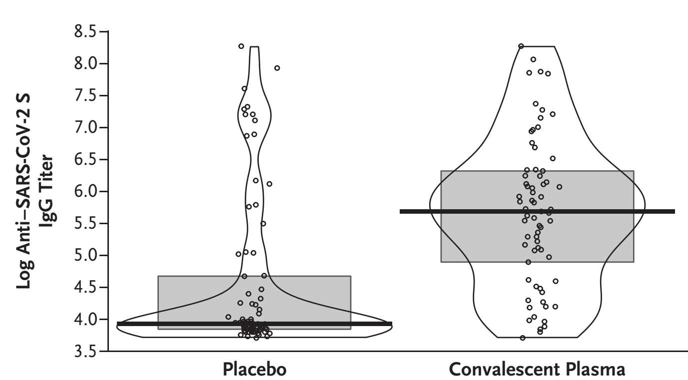

Figure 2. SARS-CoV-2 Serum Titers, According to Trial Group.
Shown are IgG antibody titers against SARS-CoV-2 spike (S) protein in the convalescent plasma and placebo groups 24 hours after infusion. The horizontal bars indicate medians, and the shaded gray areas interquartile ranges. Each circle represents one patient.

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patients who received transfusions within 72 hours after diagnosis than among those who received transfusions later.[12] Recently, on the basis of clinical benefits that were prespecified in the secondary end points of the Blocking Viral Attachment and Cell Entry with SARS-CoV-2 Neutralizing Antibodies (BLAZE-1) trial, the Food and Drug Administration granted emergency use authorization for monoclonal antibodies to treat outpatients with mild-to-moderate Covid-19.[18,19] Access to convalescent plasma can be rapid in many low- and middle-income countries, and at a per-patient cost of $186.25 (U.S. dollars) for plasma infusion in Buenos Aires (Table S13), it is a potentially inexpensive alternative to monoclonal antibodies. The early administration of convalescent plasma in our small randomized clinical trial, which had a wide 95% confidence interval for the primary end point, was not associated with any serious side effects.

In order to provide convalescent plasma of all blood types to 15 institutions, two infusion teams with persons who were aware of the trial-group assignments drove from a central hemotherapy station where the convalescent plasma was stored to all the trial hospitals after randomization. The trial region was more than 100 square miles, and security challenges precluded access to several hospitals after 8 p.m. Consequently, six patients had a primary end-point event before they received convalescent plasma or placebo. The exclusion of these patients in the modified intention-to-treat analysis increased the efficacy to 60%. Again, this finding suggests that early intervention is critical for efficacy.

Our trial showed a dose-dependent IgG effect in convalescent plasma infusions. Plasma with IgG titers of 1:3200 or higher reduced the risk of severe respiratory disease by 73%; this exploratory result directly implicates antibodies as the active therapeutic ingredient in convalescent plasma. “Super donors” with IgG titers of 1:12,800 or higher and perhaps immunized persons in the future could contribute to build a therapeutic arsenal. Among the plasma donors in our trial, 71% of those with titers of 1:3200 or higher had been hospitalized. Since high IgG titers can be maintained for months, hospitalized patients with high titers should be identified for future plasma donations.[20]

In our randomized, controlled trial, the administration of high-titer convalescent plasma against SARS-CoV-2 to infected older adults within 72 hours after the onset of mild symptoms reduced the progression of Covid-19 to severe illness. This simple and inexpensive intervention can reduce demands on the health care system and may save lives. Early infusions of convalescent plasma can provide a bridge to recovery for at-risk patients until vaccines become widely available.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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