ORIGINAL ARTICLE

Early Convalescent Plasma for High-Risk Outpatients with Covid-19

F.K. Korley, V. Durkalski-Mauldin, S.D. Yeatts, K. Schulman, R.D. Davenport, L.J. Dumont, N. El Kassar, L.D. Foster, J.M. Hah, S. Jaiswal, A. Kaplan, E. Lowell, J.F. McDyer, J. Quinn, D.J. Triulzi, C. Van Huysen, V.L.W. Stevenson, K. Yadav, C.W. Jones, B. Kea, A. Burnett, J.C. Reynolds, C.F. Greineder, N.L. Haas, D.G. Beiser, R. Silbergleit, W. Barsan, and C.W. Callaway, for the SIREN-C3PO Investigators*

ABSTRACT

BACKGROUND

Early administration of convalescent plasma obtained from blood donors who have recovered from coronavirus disease 2019 (Covid-19) may prevent disease progression in acutely ill, high-risk patients with Covid-19.

METHODS

In this randomized, multicenter, single-blind trial, we assigned patients who were being treated in an emergency department for Covid-19 symptoms to receive either one unit of convalescent plasma with a high titer of antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or placebo. All the patients were either 50 years of age or older or had one or more risk factors for disease progression. In addition, all the patients presented to the emergency department within 7 days after symptom onset and were in stable condition for outpatient management. The primary outcome was disease progression within 15 days after randomization, which was a composite of hospital admission for any reason, seeking emergency or urgent care, or death without hospitalization. Secondary outcomes included the worst severity of illness on an 8-category ordinal scale, hospital-free days within 30 days after randomization, and death from any cause.

RESULTS

A total of 511 patients were enrolled in the trial (257 in the convalescent-plasma group and 254 in the placebo group). The median age of the patients was 54 years; the median symptom duration was 4 days. In the donor plasma samples, the median titer of SARS-CoV-2 neutralizing antibodies was 1:641. Disease progression occurred in 77 patients (30.0%) in the convalescent-plasma group and in 81 patients (31.9%) in the placebo group (risk difference, 1.9 percentage points; 95% credible interval, −6.0 to 9.8; posterior probability of superiority of convalescent plasma, 0.68). Five patients in the plasma group and 1 patient in the placebo group died. Outcomes regarding worst illness severity and hospital-free days were similar in the two groups.

CONCLUSIONS

The administration of Covid-19 convalescent plasma to high-risk outpatients within 1 week after the onset of symptoms of Covid-19 did not prevent disease progression. (SIREN-C3PO ClinicalTrials.gov number, NCT04355767.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Callaway at the University of Pittsburgh, 400A Iroquois, 3600 Forbes Ave., Pittsburgh, PA 15260, or at callawaycw@upmc.edu.

*A list of the SIREN-C3PO investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on August 18, 2021, at NEJM.org.

N Engl J Med 2021;385:1951-60.
DOI: 10.1056/NEJMoa2103784

A Quick Take is available at NEJM.org

In elderly patients and in those with certain coexisting medical conditions, there is an increased risk that coronavirus disease 2019 (Covid-19) will cause respiratory or systemic illness that becomes very severe or fatal.[1] Several vaccines reduce the likelihood of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), but few treatments have shown efficacy.

Passive immunization by the infusion of convalescent plasma obtained from patients who have recently recovered from Covid-19 and have antibodies to SARS-CoV-2 is one potential strategy to reduce the severity of illness.[2] Plasma from recovered patients has also been the most readily available source of antibodies early in epidemics or in emerging infections. Although this strategy has been used for more than a century, few randomized, controlled trials have evaluated whether Covid-19 convalescent plasma improves clinical outcomes.

Administration of convalescent plasma to hospitalized patients with Covid-19 late in the course of illness has not increased clinical recovery,[3,4] but such use in older adults in outpatient settings within 72 hours after symptom onset has been shown to reduce disease progression.[5] Thus, members of the Strategies to Innovate Emergency Care Clinical Trials Network (SIREN) performed the Covid-19 Convalescent Plasma in Outpatients (C3PO) trial involving patients at high risk for severe Covid-19 who presented to the emergency department within 7 days after symptom onset to determine whether the infusion of convalescent plasma containing high titers of neutralizing antibodies would prevent progression to severe Covid-19.

Methods

Trial Design and Oversight

The C3PO clinical trial was a phase 3, multicenter, randomized, placebo-controlled trial that was designed and performed by the SIREN members. The trial was supported (including funding and material support in the form of plasma and testing supplies) by the National Heart, Lung, and Blood Institute and the National Institute of Neurological Disorders and Stroke of the National Institutes of Health and by the Biomedical Advanced Research and Development Authority and the Operation Warp Speed interagency program. A complete list of enrolling sites and investigators is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org. The trial protocol containing the statistical analysis plan is also available at NEJM.org.

The Food and Drug Administration (FDA) approved an Investigational New Drug application for the trial. A central institutional review board (Advarra) reviewed and approved the trial protocol for all participating sites. An independent medical safety monitor reviewed and adjudicated all serious adverse events, and the National Heart, Lung, and Blood Institute appointed the independent data and safety monitoring board.

The authors were responsible for the trial design, data collection, analysis, and writing of the manuscript. All the authors vouch for the completeness and accuracy of the data and the analyses and for the fidelity of the trial to the protocol.

Patients

At 48 hospital emergency departments in 21 states, we enrolled patients with SARS-CoV-2 infection as confirmed by nucleic acid assay, with an onset of symptoms within 7 days before enrollment. All the trial patients were either 50 years of age or older or had one or more risk factors for disease progression, as detailed in the Supplementary Appendix. Before enrolling a patient, the clinical team determined that the patient's condition was stable for outpatient treatment without new supplemental oxygen; the trial team confirmed that ABO-compatible Covid-19 convalescent plasma was available. We excluded patients who were younger than 18 years of age, prisoners or wards of the state, patients who were deemed to have an inability to complete follow-up assessments, those who had a history of adverse reactions from blood-product transfusion, those who had received any blood product within the past 120 days, those who were not eligible to receive up to 250 ml of fluid, and those who had received another investigational treatment for Covid-19, including anti–SARS-CoV-2 monoclonal antibodies or vaccination. All the trial patients provided written informed consent.

Trial Randomization and Intervention

Patients were randomized in a 1:1 ratio to receive an infusion of either one unit of ABO-compatible Covid-19 convalescent plasma or 250 ml of normal saline (placebo) that was colored with a parenteral multivitamin concentrate to resemble plasma. Both convalescent plasma and placebo were

covered with light-resistant bags to preserve the blinded group assignment. Intravenous infusions were given over a period of at least 30 minutes, and patients were observed for at least 60 minutes to monitor for adverse reactions.

Convalescent plasma was collected from donors at least 14 days after clinical recovery from Covid-19, according to FDA guidance for donor eligibility.[6] Convalescent plasma units were qualified for use on the basis of SARS-CoV-2 neutralizing antibody titers. Initially, we used the SARS-CoV-2 pseudovirus reporter viral particle neutralization (RVPN) assay of the Vitalant Research Institute to assess antibody titers, with the threshold for use being a 50% neutralization titer (NT_{50}) of 1:160 or more. In August 2020, the FDA Emergency Use Authorization 26382 defined high-titer convalescent plasma on the basis of the live-virus, five-dilution plaque reduction neutralization test (PRNT) as a 50% inhibitory dilution (ID_{50}) of 1:250 or more, as described by the Broad Institute. Thus, convalescent plasma samples that had previously been issued on the basis of the RVPN titer were reassayed with the Broad PRNT; we subsequently issued qualifying convalescent plasma that also had an ID_{50} of 1:250 or more. Both neutralization assays have been described previously.[6]

OUTCOMES

The primary outcome was disease progression within 15 days after randomization, which was a composite of hospital admission for any reason, seeking emergency or urgent care, or death without hospitalization. Prespecified secondary outcomes were the worst rating on an 8-category ordinal scale of illness severity within 30 days after randomization, the time until a worsening of symptoms on the 5-category Covid-19 Outpatient Ordinal Outcome Scale within 15 days after randomization, the number of hospital-free days within 30 days after randomization, and death from any cause within 30 days. Adverse events were evaluated throughout the follow-up period. In order to reduce variability in reporting of respiratory adverse events, specific definitions were adopted early in the trial, as described in the Supplementary Appendix.

PROCEDURES

Patients were asked to complete a symptom inventory every other day for 14 days after randomization by means of either email or telephone. Patients were also evaluated in person or by telephone and by chart review on days 15 and 30 to identify subsequent medical care and adverse events and to repeat a symptom inventory. The 8-category ordinal scale of illness severity, which was modified from the Covid-19 Ordinal Scale for Clinical Improvement of the World Health Organization,[7] and the 5-category Covid-19 Outpatient Ordinal Outcome Scale were derived from symptom inventories and subsequent medical care. The 8-category illness severity scale ranges from 1 (indicating that the patient is not hospitalized and has no limitation in activity) to 8 (indicating death). The 5-category outpatient scale ranges from 1 (indicating hospital admission) to 5 (indicating usual state of health). (Details regarding these instruments are provided in the Supplementary Appendix.) To assess the adequacy of blinding of trial-group assignments, patients reported their best guess of treatment assignment on day 15, along with a confidence level for their guess from 1 (not at all confident) to 5 (extremely confident).

STATISTICAL ANALYSIS

At the time the trial was initiated, we estimated that the primary outcome would occur in 20% of the patients in the placebo group. The trial required a sample size of 600 patients to detect an absolute between-group difference of 10 percentage points (the minimum difference that we considered to be clinically important) with a power of 85%. The trial plan included a prespecified blinded review of the sample size that was based on the observed percentage of patients who had disease progression before the first interim analysis. The reestimated maximum sample size was 900 patients.

The primary analysis was performed in the intention-to-treat population, which included all the patients who had undergone randomization, and was specified in a Bayesian framework. The prior probability of outcome for each treatment group was assumed to follow a noninformative beta distribution, which yielded a beta distribution for the posterior probability when a binomial likelihood was assumed for the outcome. After drawing 10,000 samples from each posterior distribution, we calculated the posterior probability of the superiority of convalescent plasma as the percentage of the 10,000 samples for which the value for the placebo group exceeded the value for the convalescent-plasma group. Efficacy

was defined as a posterior probability of 0.975 or more that the proportion of patients with outcome events was higher in the placebo group.

Three interim analyses were planned for a determination of overwhelming efficacy or futility after 33%, 50%, and 75% of the patients had completed the primary follow-up. A posterior probability of more than 0.999 was considered to be evidence of the superiority of convalescent plasma; a value of less than 0.2 for the predictive probability of success (i.e., declaring the superiority of convalescent plasma with the maximum sample size) was considered to be evidence of futility.

We performed a sensitivity analysis of data obtained in the per-protocol population, which excluded patients who had not received the assigned trial product, had an identified eligibility violation, or met the primary outcome event before infusion initiation. Summary measures with 95% confidence intervals for the secondary efficacy outcomes included the Hodges–Lehmann estimate of the difference between the medians of the two distributions from the rank-sum test for the 8-category ordinal scale, the difference in means for hospital-free days, and a hazard ratio for the time until symptom worsening. Because of the small number of deaths, the risk difference with a 95% exact confidence interval is reported for death from any cause.

A secondary analysis examined the association of the primary outcome with trial-group assignment, after adjustment for age, sex, symptom duration, and trial site. A separate analysis examined the relationship between the neutralizing antibody titer of the donor convalescent plasma and the primary outcome in the group that received convalescent plasma.

Statistical analyses were performed with the use of R software, version 4.0.4, and SAS software, version 9.4 or higher (SAS Institute).

RESULTS

PATIENTS

From August 2020 through February 2021, a total of 511 patients underwent randomization (257 to the convalescent-plasma group and 254 to the placebo group) (Fig. 1). The baseline features of the patients and their coexisting illnesses were similar in the two groups (Table 1). The median age of the patients was 54 (interquartile range, 41 to 62; simple range, 18 to 93); 54% of the patients were women.

On February 25, 2021, trial enrollment was halted after the second planned interim analysis of the primary outcome indicated that the a priori stopping threshold for futility had been reached on the basis of a posterior predictive probability of success of 0.042. The mean (±SD) time from symptom onset until enrollment was 3.7±2.1 days (median, 4 days). The dates and geographic sources of donation of convalescent plasma are provided in Table S1 in the Supplementary Appendix.

PRIMARY OUTCOME

The composite outcome of disease progression occurred in 77 of 257 patients (30.0%) in the convalescent-plasma group and in 81 of 254 (31.9%) in the placebo group within 15 days after randomization (risk difference, 1.9 percentage points; 95% credible interval, −6.0 to 9.8; posterior probability of superiority, 0.68). Results were similar for individual components of the outcome, in the per-protocol analysis, and after adjustment for age, sex, symptom duration, and enrollment site (Table 2).

Although eligibility to participate in the trial required an intent to discharge patients home from the emergency department, 25 patients (19 in the convalescent-plasma group and 6 in the placebo group) were ultimately admitted to the hospital during the index visit. In a post hoc sensitivity analysis that excluded these patients, the posterior probability of superiority of convalescent plasma was 0.93 in the intention-to-treat population and 0.94 in the per-protocol population, with credible intervals for both the risk differences that included zero (indicating uncertainty about any between-group difference) (Table S2). In a post hoc analysis of subgroups according to demographic characteristics, the duration of symptoms before randomization, and eligibility risk factors, the incidence of the primary outcome within 15 days after randomization was also similar in the two groups (Fig. 2).

Of the units of convalescent plasma that were transfused, 96.4% had a SARS-CoV-2 neutralizing ID_{50} of 1:250 or more. The median ID_{50} was 641 (interquartile range, 468 to 1702). There was no association between the antibody titer and disease progression (Fig. S1).

ADDITIONAL ANALYSES

Within 30 days after randomization, death was reported in 5 patients (1.9%) in the convalescent-

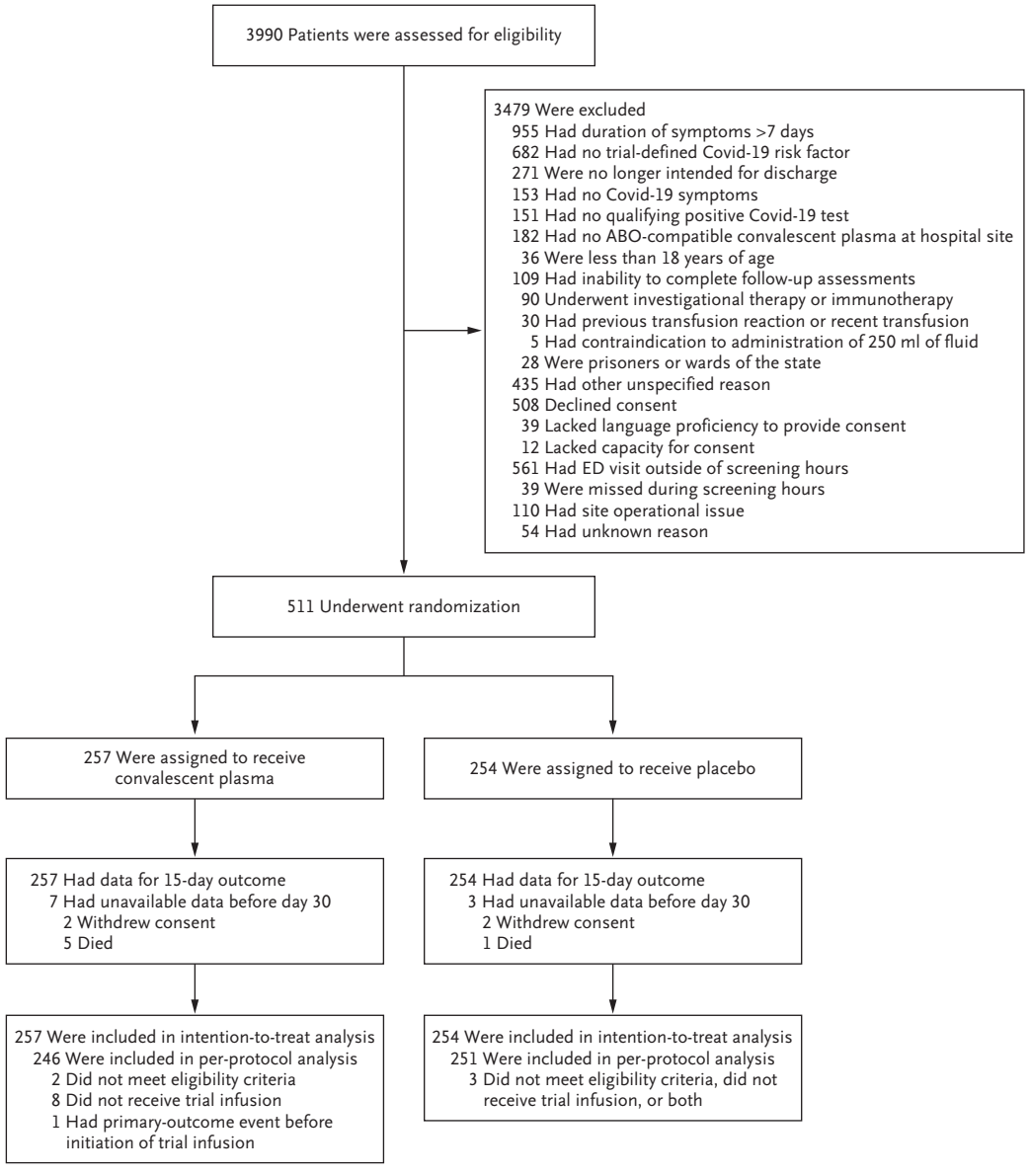

Figure 1. Enrollment, Randomization, and Analysis Populations.

Patients who presented to the emergency department (ED) because they had symptoms of coronavirus disease 2019 (Covid-19) were assessed for eligibility. After evaluating the patients, ED personnel determined whether they were good candidates for outpatient management. Patients may have had more than one reason for exclusion from the trial. The intention-to-treat population included all the patients who had undergone randomization. The per-protocol population excluded patients who had undergone randomization but had not received the assigned trial product, had an identified eligibility violation, or had a disease-progression event before the initiation of treatment. In the placebo group, one of the patients who was excluded from the per-protocol analysis did not receive placebo and was later found not to have met the trial eligibility criteria.

plasma group and in 1 (0.4%) in the placebo group (risk difference, −1.6 percentage point; exact 95% confidence interval [CI], −4.2 to 0.50); causes of death were pneumonia (in 2 patients) and hypoxia, respiratory failure, and pulmonary embolism in 1 patient each in the convalescent-plasma group and pneumonia in the placebo group; none of the deaths were considered to be related to a trial product (Table S3). The worst score on the 8-category illness severity scale

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Convalescent Plasma (N=257)	Placebo (N=254)
Median age (IQR) — yr	54 (42–62)	54 (40–62)
Female sex — no. (%)	135 (52.5)	139 (54.7)
Race — no. (%)†		
Asian	8 (3.1)	10 (3.9)
Black	49 (19.1)	54 (21.3)
Other	28 (10.9)	25 (9.8)
White	172 (66.9)	165 (65.0)
Ethnic group — no. (%)†		
Hispanic or Latino	83 (32.3)	73 (28.7)
Not Hispanic or Latino	170 (66.1)	179 (70.5)
Unknown	4 (1.6)	2 (0.8)
Eligibility risk factor — no. (%)		
Age ≥50 yr	155 (60.3)	155 (61.0)
Body-mass index ≥30‡	152 (59.1)	150 (59.1)
Hypertension	105 (40.9)	111 (43.7)
Current or former tobacco use	81 (31.5)	71 (28.0)
Diabetes mellitus	76 (29.6)	66 (26.0)
COPD or asthma	56 (21.8)	68 (26.8)
Coronary artery disease	28 (10.9)	23 (9.1)
Immunosuppression	33 (12.8)	17 (6.7)
Chronic lung disease	16 (6.2)	15 (5.9)
Chronic kidney disease	16 (6.2)	12 (4.7)
Congestive heart disease	9 (3.5)	11 (4.3)
Currently pregnant	3 (1.2)	3 (1.2)
Organ transplant recipient	5 (1.9)	0
Active cancer	2 (0.8)	2 (0.8)
Sickle-cell disease	1 (0.4)	0
Number of eligibility risk factors — no. (%)		
1	51 (19.8)	66 (26.0)
2	65 (25.3)	65 (25.6)
≥3	141 (54.9)	123 (48.4)
Other coexisting illness — no. (%)		
Current or former alcohol abuse	20 (7.8)	16 (6.3)
Current or former drug abuse	18 (7.0)	17 (6.7)
Thromboembolic disorder	15 (5.8)	10 (3.9)
Liver disease	12 (4.7)	6 (2.4)
Other hematologic disorder	9 (3.5)	8 (3.1)
Median symptom duration before randomization (IQR) — days	4 (2–5)	3 (2–5)
Median interval between randomization and infusion (IQR) — min	92 (76–128)	69 (48–96)

* COPD denotes chronic obstructive pulmonary disease, and IQR interquartile range.
† Race or ethnic group was reported by the patients or obtained from the medical record.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

Table 2. Primary Composite Outcome of Disease Progression within 15 Days after Randomization.*

Outcome	Intention-to-Treat Population (N = 511)				Per-Protocol Population (N = 497)†			
	Convalescent Plasma (N = 257)	Placebo (N = 254)	Risk Difference (95% Credible Interval)‡	Posterior Probability of Superiority of Convalescent Plasma	Convalescent Plasma (N = 246)	Placebo (N = 251)	Risk Difference (95% Credible Interval)‡	Posterior Probability of Superiority of Convalescent Plasma
			percentage points				*percentage points*	
Patients with a disease-progression event — no. (%)	77 (30.0)	81 (31.9)	1.9 (−6.0 to 9.8)	0.68	71 (28.9)	80 (31.9)	3.0 (−4.9 to 10.8)	0.76
Hospital admission for any reason	51 (19.8)	56 (22.0)			47 (19.1)	55 (21.9)		
Seeking emergency or urgent care	25 (9.7)	25 (9.8)			24 (9.8)	25 (10.0)		
Death without hospitalization	1 (0.4)	0			0	0		

* The primary outcome was disease progression within 15 days, which was a composite of hospital admission for any reason, seeking emergency or urgent care, or death without hospitalization.
† The per-protocol population included all the patients who had undergone randomization after the exclusion of those who did not receive the assigned trial product, had an identified eligibility violation, or had a disease-progression event before the initiation of treatment.
‡ The risk difference is for the placebo group minus the convalescent-plasma group. In the intention-to-treat population, the risk difference after adjustment for age, sex, symptom duration, and enrollment site was 2.2 percentage points (95% confidence interval, −5.9 to 10.4).

within 30 days after randomization was similar in the two groups (Fig. 3). The mean number of hospital-free days during the trial period was 28.3 in the convalescent-plasma group and 28.6 in the placebo group (mean difference, 0.3; 95% CI, −0.4 to 1.1) (Fig. S2). Within the 15 days after randomization, 107 of 257 patients (41.6%) in the convalescent-plasma group and 116 of 254 patients (45.7%) in the placebo group had worsening of symptoms based on the 5-category outpatient scale. The time until worsening of symptoms was similar in the two groups (hazard ratio, 0.90; 95% CI, 0.69 to 1.17).

Adverse events occurred with similar frequency in the two groups except for dyspnea, which occurred more often in the placebo group, and infusion-related reactions, which occurred more often in the convalescent-plasma group (Fig. S4 and Table S4). Three patients in the convalescent-plasma group had serious infusion reactions resulting in the administration of glucocorticoids or epinephrine or admission to the hospital. Patients' best guesses of which treatment they received were collected on day 15 from 87.5% of the patients, who more often concluded that they had been assigned to receive convalescent plasma (73% in the convalescent-plasma group and 60% in the placebo group). Of these patients, 180 of 447 patients (40.3%) reported being extremely or considerably confident in their guess; of these patients, 62.2% were accurate.

DISCUSSION

In our trial, high-risk patients who presented to the emergency department within 7 days after the onset of Covid-19 symptoms and were treated with convalescent plasma containing high titers of neutralizing antibodies against SARS-CoV-2 did not have a lower incidence of disease progression than those who received placebo. The receipt of convalescent plasma also did not influence clinically important secondary outcomes. The rationale for administering convalescent plasma is to increase levels of neutralizing antibodies in the recipient, and this is most likely to be effective before the development of the patient's own antibody response. Since we tested the administration of convalescent plasma during the first 7 days after symptom onset, antibody levels were still increasing in most patients infected with SARS-CoV-2.[8]

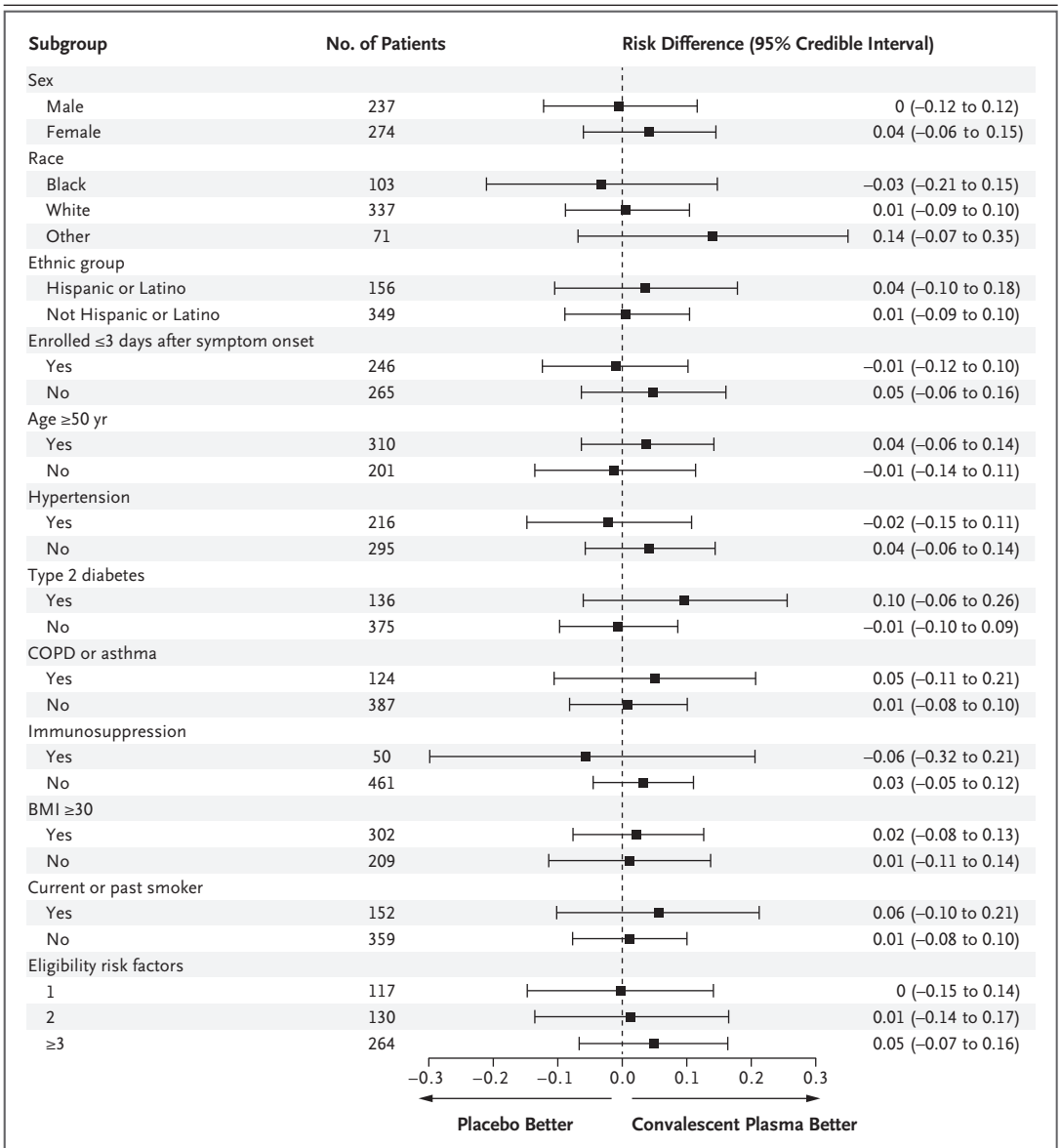

Figure 2. Primary Outcome, According to Subgroup.

Shown are data from the post hoc subgroup analysis comparing the primary outcome of disease-progression events at 15 days in the intention-to-treat population between the patients in the convalescent-plasma group and those in the placebo group. Data are shown as the absolute risk difference and 95% credible interval, as calculated by Bayesian analysis; these data have been carried to 2 decimal places to clarify small differences between groups. The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters. COPD denotes chronic obstructive pulmonary disease.

Most data on convalescent plasma for Covid-19 come from case series or uncontrolled cohort studies.[9] In a large observational study involving hospitalized patients with Covid-19, in a subgroup of patients who were not undergoing mechanical ventilation, the absolute risk of death was 7 percentage points lower among those who received a high-titer infusion of convalescent plasma than among those who received a low-titer infusion.[10] This finding led the FDA to authorize the use of high-titer Covid-19 convalescent plasma for the treatment of hospitalized patients.

Our results are similar to those from three randomized, controlled trials involving hospitalized patients that showed no improvement in

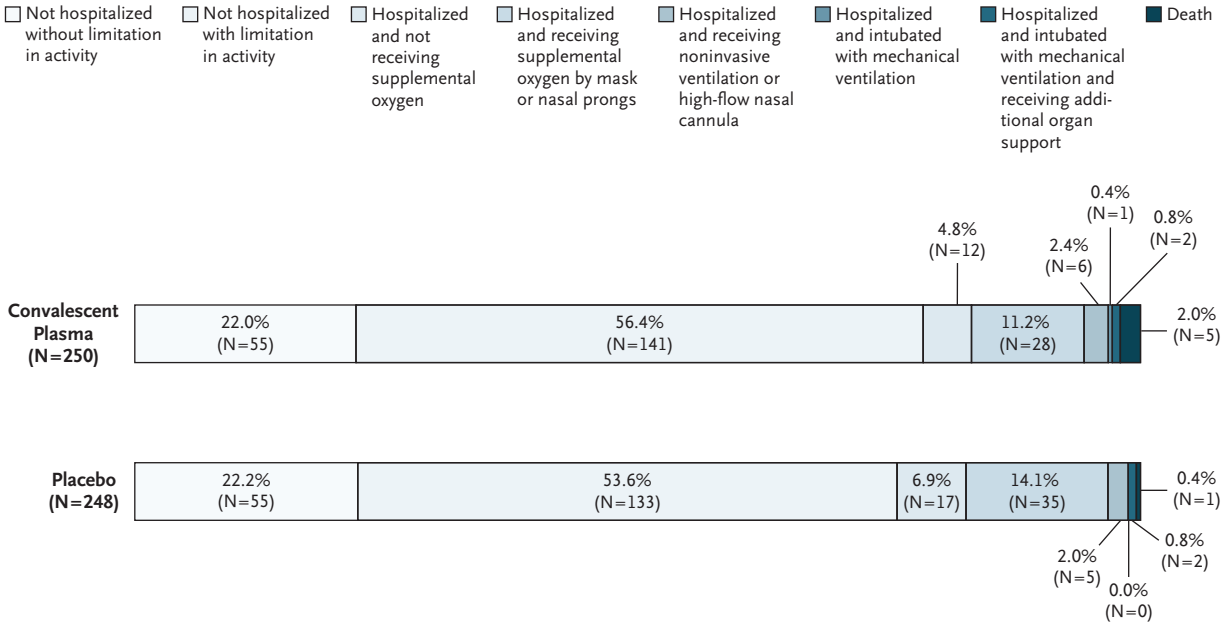

Figure 3. Worst Scores for Covid-19 Severity at 30 Days.

Shown is the distribution of scores for worst-illness severity within 30 days after randomization (a secondary efficacy outcome), according to the 8-category ordinal scale used by the World Health Organization. Moving from lighter to darker shading represents increasing scores on the severity scale. Data for this outcome were missing for seven patients in the convalescent-plasma group and for six in the placebo group.

clinical outcome in those who received convalescent plasma.[3,4,11] A recent systematic review of published and preprint trials involving patients with Covid-19 did not identify any benefit from convalescent plasma on clinical outcomes.[12] Our results differ from the findings of a randomized, controlled trial involving 160 older outpatients with mild symptoms in Argentina, in which patients received high-titer convalescent plasma or placebo within 72 hours after the onset of symptoms. Among these patients, the risk of severe respiratory disease was 15 percentage points lower in the convalescent-plasma group than in the placebo group.[5] Patients in that trial were older than those in our trial (mean age, 77.2 years vs. 51.6 years), convalescent plasma was administered earlier (median time from symptom onset, 39.6 hours vs. 4 days), and different titers and assays were used in the screening of donor convalescent plasma.

The lack of efficacy of convalescent plasma in our trial could have resulted from insufficient doses of plasma or titers of neutralizing antibodies, the timing of administration, the selection of patients, or the presence of potentially harmful components in the convalescent plasma that was administered. To avoid subjectivity and given the uncertainty about the possible manifestations of disease progression at the time the trial was designed, the primary outcome included all emergency or urgent care visits, hospitalizations, or deaths without hospitalization. Because the primary outcome was not adjudicated, some treatment failures may have resulted from conditions other than the progression of Covid-19. However, we did not observe differences between groups in the progression of respiratory symptoms or respiratory failure on the 8-category Covid-19 ordinal outcome scale. Our data do not directly address whether passive immunization with monoclonal antibodies would have had different effects on clinically important outcomes.

Convalescent plasma may still play a role if it is administered before the development of native antibodies. The treatment may also be efficacious in preventing symptomatic Covid-19 after exposure. This trial was designed to detect an absolute risk difference of 10 percentage points in disease progression. However, we cannot exclude smaller effect sizes with less clinical importance. Data regarding viral genotypes were not collected during this trial, and new variants

emerged during the period of enrollment. Future studies may also consider whether convalescent plasma that is collected during different epochs and from different geographic locations during a pandemic will have different therapeutic potentials. Donations that are temporally and geographically proximate to their point of use may be more effective. Since convalescent plasma may be the only available therapeutic agent during the early phases of a pandemic, understanding how and when it is useful is important for public health. It is also important to consider that host factors and other aspects of the host response to the infection may be more important than humoral immunity for determining the natural history of the illness.

In this randomized, controlled trial, infusion of high-titer Covid-19 convalescent plasma within 7 days after symptom onset did not prevent the progression of Covid-19 in patients at high risk for severe disease.

The views expressed in this article are those of the authors and do not necessarily represent the views of the National Institutes of Health or the Department of Health and Human Services.

Supported by awards (1OT2HL156812-01, U24NS100659, and U24NS100655) from the National Heart, Lung, and Blood Institute (NHLBI) and the National Institute of Neurological Disorders and Stroke of the National Institutes of Health and by a contract (75A50120C00094) with the Biomedical Advanced Research and Development Authority (BARDA) through the Department of Health and Human Services and the Operation Warp Speed interagency program. Support included funding and material support in the form of plasma and testing supplies.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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

We thank the patients and their families for their participation in the trial; the emergency department nurses, pharmacists, transfusion medicine colleagues, and members of the clinical care team; Dr. Michael A. Puskarich of the Hennepin County Medical Center for serving as the independent medical safety monitor for the trial; the members of the data and safety monitoring board (Drs. Naomi Luban [chair], Eldad Hod, Charles Cairns, Terry Gernsheimer, KyungMann Kim, John Roback, Darby Thompson, and Katheryn Weise and Ms. Erin Smith [liaison officer with the NHLBI]); the members of the steering committee of the NHLBI Collaborating Network of Networks for Evaluating Covid-19 and Therapeutic Strategies (CONNECTS) for their coordination and advice; Dr. Simone Glynn of the NHLBI and Dr. Mary Homer of BARDA for their outstanding problem solving; other members of the NHLBI leadership (Drs. Keith Hoots, Antonello Punturieri, James Troendle, and Amy Patterson); and Dr. Gilbert L. Marks of BARDA.

APPENDIX

The authors' full names and academic degrees are as follows: Frederick K. Korley, M.D., Ph.D., Valerie Durkalski-Mauldin, Ph.D., Sharon D. Yeatts, Ph.D., Kevin Schulman, M.D., Robertson D. Davenport, M.D., Larry J. Dumont, Ph.D., Nahed El Kassar, M.D., Ph.D., Lydia D. Foster, M.S., Jennifer M. Hah, M.D., Siddartha Jaiswal, M.D., Ph.D., Alesia Kaplan, M.D., Ezekiel Lowell, B.S., John F. McDyer, M.D., James Quinn, M.D., Darrell J. Triulzi, M.D., Carol Van Huysen, B.S., Valerie L.W. Stevenson, B.A.S., R.R.T., Kabir Yadav, M.D.C.M., Christopher W. Jones, M.D., Bory Kea, M.D., Aaron Burnett, M.D., Joshua C. Reynolds, M.D., Colin F. Greineder, M.D., Ph.D., Nathan L. Haas, M.D., David G. Beiser, M.D., Robert Silbergleit, M.D., William Barsan, M.D., and Clifton W. Callaway, M.D., Ph.D.

The authors' affiliations are as follows: the University of Michigan, Ann Arbor (F.K.K., R.D.D., C.V.H., V.L.W.S., C.F.G., N.L.H., R.S., W.B.), Spectrum Health, Grand Rapids (J.C.R.), and Michigan State University, East Lansing (J.C.R.) — all in Michigan; the Medical University of South Carolina, Charleston (V.D.-M., S.D.Y., L.D.F., E.L.); Stanford University, Palo Alto, CA (K.S., J.M.H., S.J., J.Q.); Vitalant Research Institute, Scottsdale, AZ (L.J.D.); the National Heart, Lung, and Blood Institute, Bethesda, MD (N.E.K.); the University of Pittsburgh, Pittsburgh (A.K., J.F.M., D.J.T., C.W.C.); Harbor–UCLA Medical Center, Los Angeles (K.Y.); Cooper University Hospital, Camden, NJ (C.W.J.); Oregon Health and Science University, Portland (B.K.); Health Partners Methodist Hospital, St. Louis Park, MN (A.B.); and the University of Chicago, Chicago (D.G.B.).

REFERENCES

1. Ko JY, Danielson ML, Town M, et al. Risk factors for coronavirus disease 2019 (COVID-19)-associated hospitalization: COVID-19-Associated Hospitalization Surveillance Network and Behavioral Risk Factor Surveillance System. Clin Infect Dis 2021;72(11):e695-e703.
2. Ripoll JG, van Helmond N, Senefeld JW, et al. Convalescent plasma for infectious diseases: historical framework and use in COVID-19. Clin Microbiol Newsl 2021;43(4):23-32.
3. Li L, Zhang W, Hu Y, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. JAMA 2020;324:460-70.
4. Agarwal A, Mukherjee A, Kumar G, Chatterjee P, Bhatnagar T, Malhotra P. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). BMJ 2020;371:m3939.
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. Di Germanio C, Simmons G, Kelly K, et al. SARS-CoV-2 antibody persistence in COVID-19 convalescent plasma donors. March 26, 2021 (https://www.medrxiv.org/content/10.1101/2021.03.24.21254260v1). preprint.
7. WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research. Lancet Infect Dis 2020;20(8):e192-e197.
8. Long Q-X, Liu B-Z, Deng H-J, et al. Antibody responses to SARS-CoV-2 in patients with COVID-19. Nat Med 2020;26:845-8.
9. Peng HT, Rhind SG, Beckett A. Convalescent plasma for the prevention and treatment of COVID-19: a systematic review and quantitative analysis. JMIR Public Health Surveill 2021;7(4):e25500.
10. 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.
11. 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.
12. Janiaud P, Axfors C, Schmitt AM, et al. Association of convalescent plasma treatment with clinical outcomes in patients with COVID-19: a systematic review and meta-analysis. JAMA 2021;325:1185-95.