The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics

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December 12, 2019
N Engl J Med 2019; 381:2293-2303
DOI: 10.1056/NEJMoa1910993

Abstract

BACKGROUND

Although several experimental therapeutics for Ebola virus disease (EVD) have been developed, the safety and efficacy of the most promising therapies need to be assessed in the context of a randomized, controlled trial.

METHODS

We conducted a trial of four investigational therapies for EVD in the Democratic Republic of Congo, where an outbreak began in August 2018. Patients of any age who had a positive result for Ebola virus RNA on reverse-transcriptase–polymerase-chain-reaction assay were enrolled. All patients received standard care and were randomly assigned in a 1:1:1:1 ratio to intravenous administration of the triple monoclonal antibody ZMapp (the control group), the antiviral agent remdesivir, the single monoclonal antibody MAb114, or the triple monoclonal antibody REGN-EB3. The REGN-EB3 group was added in a later version of the protocol, so data from these patients were compared with those of patients in the ZMapp group who were enrolled at or after the time the REGN-EB3 group was added (the ZMapp subgroup). The primary end point was death at 28 days.

RESULTS

A total of 681 patients were enrolled from November 20, 2018, to August 9, 2019, at which time the data and safety monitoring board recommended that patients be assigned only to the MAb114 and REGN-EB3 groups for the remainder of the trial; the recommendation was based on the results of an interim analysis that showed superiority of these groups to ZMapp and remdesivir with respect to mortality. At 28 days, death had occurred in 61 of 174 patients (35.1%) in the MAb114 group, as compared with 84 of 169 (49.7%) in the ZMapp group (P=0.007), and in 52 of 155 (33.5%) in the REGN-EB3 group, as compared with 79 of 154 (51.3%) in the ZMapp subgroup (P=0.002). A shorter duration of symptoms before admission and lower baseline values for viral load and for serum creatinine and aminotransferase levels each correlated with improved survival. Four serious adverse events were judged to be potentially related to the trial drugs.

CONCLUSIONS

Both MAb114 and REGN-EB3 were superior to ZMapp in reducing mortality from EVD. Scientifically and ethically sound clinical research can be conducted during disease outbreaks and can help inform the outbreak response. (Funded by the National Institute of Allergy and Infectious Diseases and others; PALM ClinicalTrials.gov number, NCT03719586.)

Introduction

QUICK TAKE

Ebola Virus Disease Therapeutics

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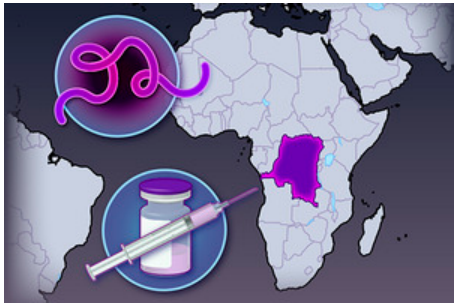


In August 2018, an outbreak of Ebola virus disease (EVD) began in the provinces of North Kivu and Ituri in the Democratic Republic of Congo (DRC); it was the tenth known outbreak of EVD in that country.[1,2] The outbreak became the second largest that has been recorded since the first description of *Zaire ebolavirus* infection in 1976, and it is surpassed only by the 2013–2016 outbreak in West Africa that resulted in more than 11,000 deaths.

After the end of the outbreak in West Africa, the World Health Organization (WHO) initiated a series of discussions to develop an R&D Blueprint for EVD research that included a working group focused on how experimental therapeutics should be assessed in the context of the next EVD outbreak.[3] These and other discussions led to a consensus that when a new outbreak occurred, the most promising experimental therapeutics should be studied in the context of a randomized, controlled trial, if possible.[4] This groundwork facilitated the uniting of the international community and DRC leadership to develop and implement the trial described in this report.

Methods

TRIAL DESIGN

The Pamoja Tulinde Maisha (PALM ["Together Save Lives" in the Kiswahili language]) trial compared ZMapp with three newer investigational agents.[5] Patients were assigned in a 1:1:1:1 ratio to receive ZMapp (a triple monoclonal antibody agent), remdesivir (a nucleotide analogue RNA polymerase inhibitor[6]), MAb114 (a single human monoclonal antibody derived from an Ebola survivor[7,8]), or REGN-EB3 (a coformulated mixture of three human IgG1 monoclonal antibodies[9,10]). ZMapp was chosen as the control on the basis of data from the Partnership for Research on Ebola Virus in Liberia II (PREVAIL II) trial.[11] The current trial was originally designed in November 2018 as a three-group trial, and the protocol was updated in January 2019 to add REGN-EB3 as a fourth group; data from this group were compared with those of patients in the ZMapp group who were enrolled on or after the time the REGN-EB3 group was added (the ZMapp subgroup). The primary end point was death at 28 days.

TRIAL OVERSIGHT

The trial was jointly approved by the ethics board at the University of Kinshasa and the institutional review board at the National Institute of Allergy and Infectious Diseases (NIAID) and was overseen by an independent data and safety monitoring board. Trial staff at participating Ebola treatment centers included staff from the Alliance for International Medical Action (ALIMA), International Medical Corps (IMC), Médecins sans Frontières (MSF), and the DRC Ministry of Health. Written informed consent was obtained from all patients or their legal guardians, and assent forms were obtained for children according to local standards and requirements. Full details about the trial design, conduct, oversight, and analyses are provided in the protocol and the Supplementary Appendix, both available with the full text of this article at NEJM.org. The PALM Writing Group performed the primary data analyses, wrote the manuscript, and, on behalf of the PALM Study Group, vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The Office of Clinical Research Policy and Regulatory Operations of the Division of Clinical Research of the NIAID is the holder of the Investigational New Drug application (125530) from the Food and Drug Administration. The Biomedical and Advanced Research and Development Authority of the U.S. Department of Health and Human Services provided financial support for the production of ZMapp and REGN-EB3. NIAID and the Defense Advanced Research Projects Agency of the U.S. Department of Defense provided financial support for the production and provision of MAb114.

SCREENING AND RANDOMIZATION

Patients were assessed for eligibility on the basis of a reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay to detect the RNA of the nucleoprotein of Ebola virus (EBOV). Patients of any age, including pregnant women, were eligible if they had a positive result on RT-PCR within 3 days before screening and if they had not received other investigational agents (except experimental vaccines) within the previous 30 days. Neonates who were 7 days of age or younger were eligible if the mother had documented EVD. Randomization was stratified according to baseline nucleoprotein cycle-threshold (Ct) value (≤22.0 or >22.0, corresponding to higher and lower viral loads, respectively, as determined by quantitative RT-PCR) and Ebola treatment center. Trial-group assignments were placed in sequentially numbered envelopes, which were distributed to trial sites to be opened at the time of enrollment. Data were recorded on bar-coded paper case-report forms that were transmitted from the site to a server, where they were digitally sorted into electronic patient folders with the use of software developed by the University of Minnesota and were then entered by trial staff at the Institut National de Recherche Biomédicale (INRB) Coordinating Center (Kinshasa, DRC) and NIAID (Bethesda, MD) into the Web-based REDCap database.

TRIAL PROCEDURES

All patients received standard care, which consisted of administration of intravenous fluids, daily clinical laboratory testing, correction of hypoglycemia and electrolyte imbalances, and administration of broad-spectrum antibiotic agents and antimalarial agents as indicated. All four trial agents were administered intravenously. Patients in the ZMapp group received a dose of 50 mg per kilogram of body weight every third day beginning on day 1 (for a total of three doses). Patients in the remdesivir group received a loading dose on day 1 (200 mg in adults, and adjusted for body weight in pediatric patients), followed by a daily maintenance dose (100 mg in adults) starting on day 2 and continuing for 9 to 13 days, depending on viral load. Patients in the MAb114 group received a dose of 50 mg per kilogram, administered as a single infusion on day 1. Patients in the REGN-EB3 group received a dose of 150 mg per kilogram, administered as a single infusion on day 1.

The Xpert Ebola Assay (Cepheid) was used for detection of the EBOV RNAs encoding surface glycoprotein and nucleoprotein.[12-14] Clinical chemical analyses of plasma samples that had been separated from whole blood were performed with the use of the Piccolo Xpress Chemistry Analyzer (Abbott).

STATISTICAL ANALYSIS

The primary end point (death at 28 days) was assessed with the use of a modified Boschloo's test for hypothesis testing.[15] We estimated that 145 patients would need to be enrolled in each group to give the trial approximately 80% power, at a type I error rate of 5%, to show that mortality would be 50% lower in each of the groups than in the ZMapp group (15% vs. 30%). Each of the primary comparisons of remdesivir, MAb114, and REGN-EB3 with ZMapp was tested at a two-sided type I error rate of 5%, without adjustment for multiplicity (as prespecified in the statistical analysis plan). After an assessment that was conducted in a blinded manner, the protocol was amended in July 2019 to increase the sample size to 725 to improve the power of the trial while taking into account the availability of ZMapp. The sample size was revised to 185 patients each in the ZMapp, remdesivir, and MAb114 groups and 170 in the REGN-EB3 group. Comparisons were restricted to patients who were enrolled in the trial concurrently.[15,16] Interim data and safety monitoring included four analyses of efficacy that were performed on the basis of prespecified enrollment targets (Table S1 in the Supplementary Appendix). Additional details are provided in the statistical analysis plan, which is included with the protocol.

Results

PATIENTS

From November 20, 2018, to August 9, 2019, a total of 681 patients were enrolled and underwent randomization at Ebola treatment centers in Beni (335 patients), Butembo (243 patients), Katwa (46 patients), and Mangina (57 patients). Eight patients were excluded from the final analysis: 1 patient was later found to have been ineligible because of a false positive EVD result on RT-PCR assay, and 7 patients underwent randomization during a 2-week period when ZMapp was unavailable because of compromised cold-chain conditions. Of the remaining 673 participants, 169 were assigned to receive ZMapp, 175 to receive remdesivir, 174 to receive MAb114, and 155 to receive REGN-EB3. A total of 154 patients were assigned to the ZMapp group after the REGN-EB3 group had been added (the ZMapp subgroup), and data from these patients were used in the comparison of REGN-EB3 with ZMapp (Fig. S1).

Table 1.

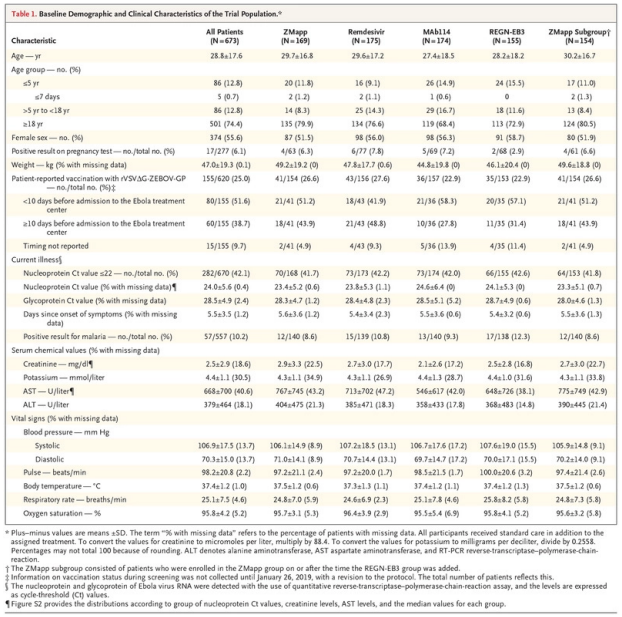


Table 1. Baseline Demographic and Clinical Characteristics of the Trial Population.*

Characteristic	All Patients (N=673)	ZMapp (N=169)	Remdesivir (N=175)	Mab114 (N=174)	REGN-EB3 (N=155)	ZMapp Subgroup† (N=154)
Age — yr	28.8±17.6	29.7±16.8	29.6±17.2	27.4±18.5	28.2±18.2	30.2±16.7
Age group — no. (%)						
≤5 yr	86 (12.8)	20 (11.8)	16 (9.1)	26 (14.9)	24 (15.5)	17 (11.0)
≤7 days	5 (0.7)	2 (1.2)	2 (1.1)	1 (0.6)	0	2 (1.3)
>5 yr to <18 yr	86 (12.8)	14 (8.3)	25 (14.3)	29 (16.7)	18 (11.6)	13 (8.4)
≥18 yr	501 (74.4)	135 (79.9)	134 (76.6)	119 (68.4)	113 (72.9)	124 (80.5)
Female sex — no. (%)	374 (55.6)	87 (51.5)	98 (56.0)	98 (56.3)	91 (58.7)	80 (51.9)
Positive result on pregnancy test — no./total no. (%)	17/277 (6.1)	4/63 (6.3)	6/77 (7.8)	5/69 (7.2)	2/68 (2.9)	4/61 (6.6)
Weight — kg (% with missing data)	47.0±19.3 (0.1)	49.2±19.2 (0)	47.8±17.7 (0.6)	44.8±19.8 (0)	46.1±20.4 (0)	49.6±18.8 (0)
Patient-reported vaccination with rVSVΔG-ZEBOV-GP — no./total no. (%)‡	155/620 (25.0)	41/154 (26.6)	43/156 (27.6)	36/157 (22.9)	35/153 (22.9)	41/154 (26.6)
<10 days before admission to the Ebola treatment center	80/155 (51.6)	21/41 (51.2)	18/43 (41.9)	21/36 (58.3)	20/35 (57.1)	21/41 (51.2)
≥10 days before admission to the Ebola treatment center	60/155 (38.7)	18/41 (43.9)	21/43 (48.8)	10/36 (27.8)	11/35 (31.4)	18/41 (43.9)
Timing not reported	15/155 (9.7)	2/41 (4.9)	4/43 (9.3)	5/36 (13.9)	4/35 (11.4)	2/41 (4.9)
Current illness§						
Nucleoprotein Ct value ≤22 — no./total no. (%)	282/670 (42.1)	70/168 (41.7)	73/173 (42.2)	73/174 (42.0)	66/155 (42.6)	64/153 (41.8)
Nucleoprotein Ct value (% with missing data)¶	24.0±5.6 (0.4)	23.4±5.2 (0.6)	23.8±5.3 (1.1)	24.6±6.4 (0)	24.1±5.3 (0)	23.3±5.1 (0.7)
Glycoprotein Ct value (% with missing data)	28.5±4.9 (2.4)	28.3±4.7 (1.2)	28.4±4.8 (2.3)	28.5±5.1 (5.2)	28.7±4.9 (0.6)	28.0±4.6 (1.3)
Days since onset of symptoms (% with missing data)	5.5±3.5 (1.2)	5.6±3.6 (1.2)	5.4±3.4 (2.3)	5.5±3.6 (0.6)	5.4±3.2 (0.6)	5.5±3.6 (1.3)
Positive result for malaria — no./total no. (%)	57/557 (10.2)	12/140 (8.6)	15/139 (10.8)	13/140 (9.3)	17/138 (12.3)	12/140 (8.6)
Serum chemical values (% with missing data)						
Creatinine — mg/dl¶	2.5±2.9 (18.6)	2.9±3.3 (22.5)	2.7±3.0 (17.7)	2.1±2.6 (17.2)	2.5±2.8 (16.8)	2.7±3.0 (22.7)
Potassium — mmol/liter	4.4±1.1 (30.5)	4.3±1.1 (34.9)	4.3±1.1 (26.9)	4.4±1.3 (28.7)	4.4±1.0 (31.6)	4.3±1.1 (33.8)
AST — U/liter¶	668±700 (40.6)	767±745 (43.2)	713±702 (47.2)	546±617 (42.0)	648±726 (38.1)	775±749 (42.9)
ALT — U/liter	379±464 (18.1)	404±475 (21.3)	385±471 (18.3)	358±433 (17.8)	368±483 (14.8)	390±445 (21.4)
Vital signs (% with missing data)						
Blood pressure — mm Hg						
Systolic	106.9±17.5 (13.7)	106.1±14.9 (8.9)	107.2±18.5 (13.1)	106.7±17.6 (17.2)	107.6±19.0 (15.5)	105.9±14.8 (9.1)
Diastolic	70.3±15.0 (13.7)	71.0±14.1 (8.9)	70.7±14.4 (13.1)	69.7±14.7 (17.2)	70.0±17.1 (15.5)	70.2±14.0 (9.1)
Pulse — beats/min	98.2±20.8 (2.2)	97.2±21.1 (2.4)	97.2±20.0 (1.7)	98.5±21.5 (1.7)	100.0±20.6 (3.2)	97.4±21.4 (2.6)
Body temperature — °C	37.4±1.2 (1.0)	37.5±1.2 (0.6)	37.3±1.3 (1.1)	37.4±1.2 (1.1)	37.4±1.2 (1.3)	37.5±1.2 (0.6)
Respiratory rate — breaths/min	25.1±7.5 (4.6)	24.8±7.0 (5.9)	24.6±6.9 (2.3)	25.1±7.8 (4.6)	25.8±8.2 (5.8)	24.8±7.3 (5.8)
Oxygen saturation — %	95.8±4.2 (5.2)	95.7±3.1 (5.3)	96.4±3.9 (2.9)	95.5±5.4 (6.9)	95.8±4.1 (5.2)	95.6±3.2 (5.8)

* Plus–minus values are means ±SD. The term "% with missing data" refers to the percentage of patients with missing data. All participants received standard care in addition to the assigned treatment. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for potassium to milligrams per deciliter, divide by 0.2558. Percentages may not total 100 because of rounding. ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and RT-PCR reverse-transcriptase–polymerase-chain-reaction.
† The ZMapp subgroup consisted of patients who were enrolled in the ZMapp group on or after the time the REGN-EB3 group was added.
‡ Information on vaccination status during screening was not collected until January 26, 2019, with a revision to the protocol. The total number of patients reflects this.
§ The nucleoprotein and glycoprotein of Ebola virus RNA were detected with the use of quantitative reverse-transcriptase–polymerase-chain-reaction assay, and the levels are expressed as cycle-threshold (Ct) values.
¶ Figure S2 provides the distributions according to group of nucleoprotein Ct values, creatinine levels, AST levels, and the median values for each group.

Baseline Demographic and Clinical Characteristics of the Trial Population.

Most patients (74.4%) were 18 years of age or older, 12.8% were 6 to 17 years of age, and 12.8% were 5 years of age or younger, of whom 0.7% were neonates (≤7 days old). A total of 55.6% patients were female, of whom 6.1% were pregnant at the time of EVD diagnosis (Table 1).

The mean (±SD) baseline nucleoprotein Ct value was 24.0±5.6, and 42.1% of patients had a baseline value of 22.0 or lower. Patients were enrolled within an average of 5.5 days after the onset of symptoms. The most commonly reported baseline symptoms were diarrhea (in 53.8% of the patients), fever (in 51.4%), abdominal pain (in 46.4%), headache (in 44.4%), and vomiting (in 39.4%) (Table S2). Malaria coinfection was identified in 57 of 557 patients (10.2%). Patient-reported information regarding vaccination status (i.e., whether the patient had received the rVSVΔG-ZEBOV-GP vaccine) was available for 620 patients; of these, 155 (25.0%) reported that they received the vaccine. Among patients who reported that they had been vaccinated, 38.7% reported that they had received the vaccination at least 10 days before enrollment.

The mean baseline serum creatinine level was 2.5±2.9 mg per deciliter (221±256 μmol per liter), the mean aspartate aminotransferase level was 668±700 U per liter, and the mean alanine aminotransferase level was 379±464 U per liter. The mean baseline creatinine and aspartate aminotransferase values were higher in the ZMapp and remdesivir groups than in the other two groups. However, the baseline creatinine level was not recorded in 18.6% of patients, aspartate aminotransferase level was not recorded in 40.6%, and alanine aminotransferase level was not recorded in 18.1%. In addition, 70.1% of the available baseline samples indicated some degree of hemolysis.

MORTALITY

On August 9, 2019, when 681 patients had been enrolled, the data and safety monitoring board conducted an interim analysis on data from 499 patients and, on the basis of two observations, recommended terminating random assignment to ZMapp and remdesivir. First, results in the REGN-EB3 group crossed an interim boundary for efficacy with respect to a surrogate end point for death at 28 days that took into account outcomes in all patients with at least 10 days of follow-up (Fig. S3). Second, an analysis of mortality showed that there was a clear separation between the MAb114 and REGN-EB3 groups and the ZMapp and remdesivir groups (Fig. S4).

Table 2.

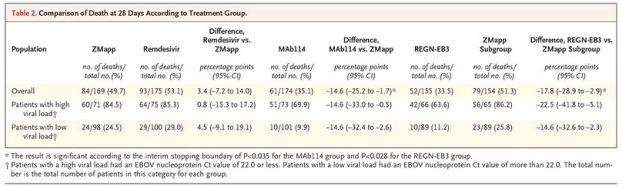


Table 2. Comparison of Death at 28 Days According to Treatment Group.

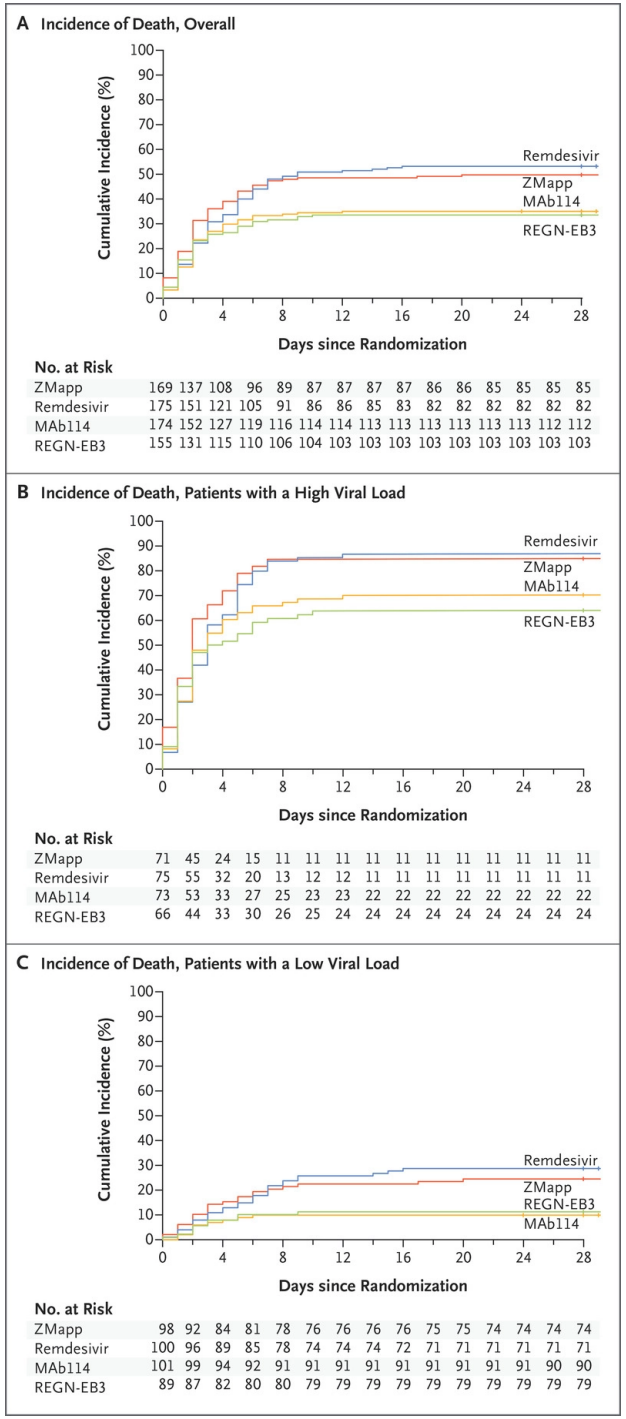
Population	ZMapp	Remdesivir	Difference, Remdesivir vs. ZMapp	MAb114	Difference, MAb114 vs. ZMapp	REGN-EB3	ZMapp Subgroup	Difference, REGN-EB3 vs. ZMapp Subgroup
	no. of deaths/ total no. (%)	*no. of deaths/ total no. (%)*	*percentage points (95% CI)*	*no. of deaths/ total no. (%)*	*percentage points (95% CI)*	*no. of deaths/ total no. (%)*	*no. of deaths/ total no. (%)*	*percentage points (95% CI)*
Overall	84/169 (49.7)	93/175 (53.1)	3.4 (−7.2 to 14.0)	61/174 (35.1)	−14.6 (−25.2 to −1.7)*	52/155 (33.5)	79/154 (51.3)	−17.8 (−28.9 to −2.9)*
Patients with high viral load†	60/71 (84.5)	64/75 (85.3)	0.8 (−15.3 to 17.2)	51/73 (69.9)	−14.6 (−33.0 to −0.5)	42/66 (63.6)	56/65 (86.2)	−22.5 (−41.8 to −5.1)
Patients with low viral load†	24/98 (24.5)	29/100 (29.0)	4.5 (−9.1 to 19.1)	10/101 (9.9)	−14.6 (−32.4 to −2.6)	10/89 (11.2)	23/89 (25.8)	−14.6 (−32.6 to −2.3)

* The result is significant according to the interim stopping boundary of P<0.035 for the MAb114 group and P<0.028 for the REGN-EB3 group.
† Patients with a high viral load had an EBOV nucleoprotein Ct value of 22.0 or less. Patients with a low viral load had an EBOV nucleoprotein Ct value of more than 22.0. The total number is the total number of patients in this category for each group.

Comparison of Death at 28 Days According to Treatment Group.

A total of 673 patients were included in the primary analyses. At 28 days, death had occurred in 290 patients (43.1%) overall, in 18.8% of patients with a low viral load (Ct value >22.0), and in 76.1% with a high viral load (Ct value ≤22.0) (Table 2).

Figure 1.



Cumulative Incidence of Death.

Table 3.

Table 3. Logistic-Regression Analyses for Death at 28 Days.

Variable	No. of Patients in Analysis*	Odds Ratio (95% confidence interval)†			
		For Each Variable	Remdesivir vs. ZMapp	MAb114 vs. ZMapp	REGN-EB3 vs. ZMapp
Duration of symptoms	615	1.11 (1.05–1.16) per day of symptoms‡	1.04 (0.66–1.64)	0.49 (0.31–0.78)	0.45 (0.28–0.73)
Nucleoprotein Ct value	620	0.66 (0.62–0.71) per 1 unit increase	1.29 (0.71–2.34)	0.39 (0.21–0.73)	0.37 (0.20–0.68)
Years of age	623	1.00 (1.00–1.01) per 1 yr increase	1.07 (0.68–1.66)	0.52 (0.33–0.82)	0.48 (0.31–0.77)
Creatinine level§	507	1.43 (1.31–1.56) per 1 mg/dl increase	0.93 (0.54–1.59)	0.48 (0.27–0.84)	0.38 (0.21–0.67)
AST level§	380	1.15 (1.11–1.20) per 100 U/liter increase	1.06 (0.54–2.05)	0.31 (0.14–0.67)	0.29 (0.14–0.63)
ALT level§	511	1.43 (1.33–1.54) per 100 U/liter increase	0.95 (0.54–1.68)	0.37 (0.20–0.69)	0.36 (0.20–0.66)
Patient-reported vaccination§	620	0.37 (0.24–0.55) yes vs. no	1.06 (0.67–1.68)	0.48 (0.30–0.77)	0.44 (0.28–0.71)

* Model estimates include data from patients who were enrolled after the REGN-EB3 group was added. The number of patients in the analysis reflects the number enrolled after the REGN-EB3 group was added for whom data were available for each variable.
† Each row shows the odds ratios derived from a multivariate logistic-regression model that included the variable listed plus the four treatment groups.
‡ The variable reflects each additional day of symptoms before admission to the treatment center.
§ Because of its clinical significance, the variable was added after the statistical analysis plan was finalized but before analysis of the data.

Logistic-Regression Analyses for Death at 28 Days.

Table 4.

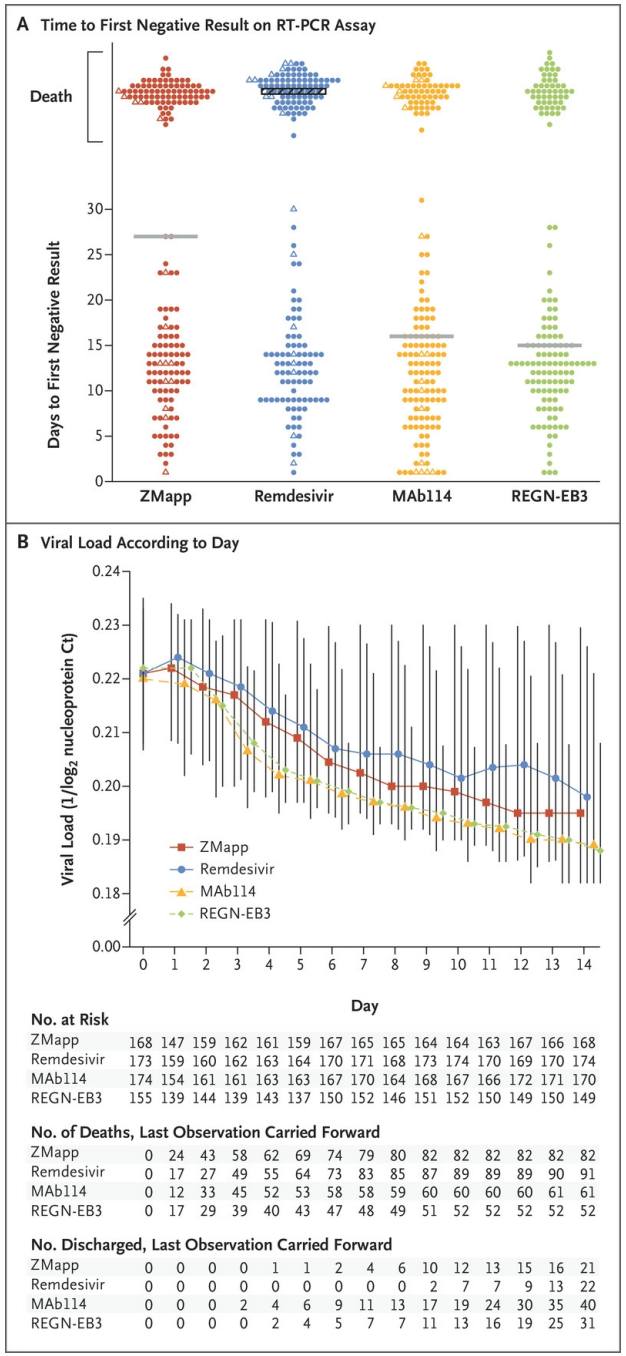
Table 4. Multivariate Logistic-Regression Analyses for Death at 28 Days in the 371 Patients Who Had Data Available for All Variables.

Variable	Odds Ratio (95% CI)
Assignment to remdesivir vs. ZMapp	0.99 (0.46–2.14)
Assignment to MAb114 vs. ZMapp	0.24 (0.10–0.61)
Assignment to REGN-EB3 vs. ZMapp	0.21 (0.08–0.53)
Duration of symptoms before admission to treatment center, per each additional day	1.12 (1.00–1.24)
Baseline nucleoprotein Ct value per 1-unit increase	0.67 (0.59–0.76)
Years of age per 1 yr increase	1.02 (1.00–1.04)
Creatinine level per 1 mg/dl increase	1.36 (1.18–1.58)
AST level per 100 U/liter increase	1.00 (0.92–1.07)
ALT level per 100 U/liter increase	0.96 (0.79–1.17)
Patient-reported vaccination, yes vs. no	0.47 (0.21–1.01)

Multivariate Logistic-Regression Analyses for Death at 28 Days in the 371 Patients Who Had Data Available for All Variables.

The percentage of patients who died was lower in the MAb114 group and in the REGN-EB3 group than in the ZMapp group (Figure 1 and Table 2). The difference between the MAb114 and the ZMapp groups was −14.6 percentage points (95% confidence interval [CI], −25.2 to −1.7; P=0.007); the difference between the REGN-EB3 group and the ZMapp subgroup was −17.8 percentage points (95% CI, −28.9 to −2.9; P=0.002); and the difference between the remdesivir and ZMapp groups was 3.4 percentage points (95% CI, −7.2 to 14.0). (Fig. S5 shows the differences in mortality in the remdesivir, MAb114, and REGN-EB3 groups relative to the ZMapp group according to Ct value, age, sex, and site.) The survival benefits seen in the MAb114 and REGN-EB3 groups were also seen in sensitivity analyses adjusted for potential baseline imbalances (Table 3 and Table 4 and Table S3).

Figure 2.



No. at Risk

ZMapp	168	147	159	162	161	159	167	165	165	164	164	163	167	166	168
Remdesivir	173	159	160	162	163	164	170	171	168	173	174	170	169	170	174
MAb114	174	154	161	161	163	163	167	170	164	168	167	166	172	171	170
REGN-EB3	155	139	144	139	143	137	150	152	146	151	152	150	149	150	149

No. of Deaths, Last Observation Carried Forward

ZMapp	0	24	43	58	62	69	74	79	80	82	82	82	82	82	82
Remdesivir	0	17	27	49	55	64	73	83	85	87	89	89	89	90	91
MAb114	0	12	33	45	52	53	58	58	59	60	60	60	60	61	61
REGN-EB3	0	17	29	39	40	43	47	48	49	51	52	52	52	52	52

No. Discharged, Last Observation Carried Forward

ZMapp	0	0	0	0	1	1	2	4	6	10	12	13	15	16	21
Remdesivir	0	0	0	0	0	0	0	0	0	2	7	7	9	13	22
MAb114	0	0	0	2	4	6	9	11	13	17	19	24	30	35	40
REGN-EB3	0	0	0	0	2	4	5	7	7	11	13	16	19	25	31

Time to Viral Clearance.

In an analysis of the time to the first negative result on RT-PCR assay for EBOV nucleoprotein, in which patients who had died were considered as not having had viral clearance, the time to the first negative result was shorter in the MAb114 and REGN-EB3 groups than in the ZMapp group (median in the MAb114 group, 16 days; median in the REGN-EB3 group, 15 days; median in the ZMapp group, 27 days) (Figure 2). Among patients in the remdesivir group, the estimated median time was more than 28 days because mortality exceeded 50%.

PROGNOSTIC VARIABLES

A longer duration of symptoms before treatment was associated with significantly worse outcomes. Of note, 19% of patients who arrived at the treatment center within 1 day after the reported onset of symptoms died, as compared with 47% of patients who arrived after they had had symptoms for 5 days (Table S4). The odds of death increased by 11% (95% CI, 5 to 16) for each day after the onset of symptoms that the patient did not present to the treatment center (Table 3).

The odds of death were lower among patients with lower viral loads (odds ratio per unit increase in Ct value, 0.66; 95% CI, 0.62 to 0.71) and higher among patients with higher levels of creatinine (odds ratio per 1 mg per deciliter increase, 1.43; 95% CI, 1.31 to 1.56), aspartate aminotransferase (odds ratio per 100 U per liter increase, 1.15; 95% CI, 1.11 to 1.20), and alanine aminotransferase (odds ratio per 100 U per liter increase, 1.43; 95% CI, 1.33 to 1.54). A multivariate logistic-regression analysis showed that the duration of symptoms at enrollment, baseline nucleoprotein Ct value, and serum creatinine level all remained significant prognostic indicators of death (Table 4). Across all models, the effect estimates of treatment with MAb114 and REGN-EB3 remained significant (Table 3 and Table 4).

The percentage of patients who died was lower among those who reported that they had received the rVSVΔG-ZEBOV-GP vaccine than among those who reported no vaccination (27.1% [42 of 155 patients] vs. 48.4% [225 of 465]). However, patients who reported vaccination were also more likely to have had fewer days of illness before enrollment, higher baseline nucleoprotein Ct values, and lower levels of alanine aminotransferase (Table S5).

SAFETY

At least 98% of the patients received the infusions according to protocol (Table S6). A total of 29 serious adverse events were determined by trial investigators to be potentially related to the trial drugs (Table S7). However, after adjudication by an independent pharmacovigilance committee, four events in three patients, all of which resulted in death, were determined to be possibly related to a trial drug: one patient in the ZMapp group had worsening of gastrointestinal symptoms; one patient in the ZMapp group had periinfusional hypotension and hypoxia that responded to resuscitation after treatment interruption but that resulted in death within 24 hours; and one patient in the remdesivir group had hypotension that resulted in cessation of a loading dose of remdesivir and that was followed rapidly by cardiac arrest. However, even in these cases, the deaths could not readily be distinguished from underlying fulminant EVD itself.

DELAYS IN TREATMENT ADMINISTRATION

The mean time from randomization to administration of the first infusion was somewhat longer in the ZMapp and remdesivir groups than in the MAb114 and REGN-EB3 groups. (Table S8 and Fig. S6 provide a summary of the time from randomization to the first infusion according to trial group and site, and Table S9 provides the results of a sensitivity analysis of outcomes that excluded data from patients with delays of more than 6 hours.) Twelve patients were enrolled but died before receiving the first infusion: one in the ZMapp group, three in the remdesivir group, three in the MAb114 group, and five in the REGN-EB3 group.

Discussion

In this trial of four promising experimental treatments against *Z. ebolavirus*, the combination of standard care plus either MAb114 or REGN-EB3 was superior to standard care plus ZMapp against the Ituri EBOV variant currently circulating in the DRC. Survival benefits were seen both in patients with high viral loads and in those with low viral loads at presentation. The reason that mortality among patients who received ZMapp was 22% in the PREVAIL II trial (conducted during the outbreak in West Africa) and 50% in our trial (conducted during the current outbreak in the DRC) is unclear. Potential differences in virulence, the relevant viral epitopes,[14] patient populations, duration of symptoms, and standard-of-care practices are being explored.

In addition to differential effects of the four trial agents with respect to mortality, the results showed the importance of early diagnosis and treatment. We observed an 11% increase in the odds of death for each day that symptoms persisted before enrollment. These data highlight the need for community awareness that earlier diagnosis and treatment are associated with increased survival. Similarly, there was an effect of baseline viral load with respect to death at 28 days with each trial drug: mortality among patients who had a nucleoprotein Ct value of 22 or less at screening (i.e., high viral load) was 4 times as high as mortality among patients with a nucleoprotein Ct value of greater than 22 (i.e., low viral load). As described previously, the degree of baseline renal dysfunction was also a strong adverse prognostic indicator of survival, despite the use of medical countermeasures,[17,18] with higher creatinine levels at presentation correlating with a higher risk of death.

Given that 97% of deaths in this trial occurred within 10 days after enrollment, the efficacy of MAb114 and REGN-EB3 as compared with that of ZMapp and remdesivir might be partly attributable to the fact that the full treatment courses of MAb114 and REGN-EB3 were administered in a single dose, whereas ZMapp and remdesivir were administered in multiple infusions. Differences in the time to appearance of the first negative nucleoprotein Ct result among trial groups support this observation; patients in the MAb114 and REGN-EB3 groups had faster rates of viral clearance than patients in the ZMapp and remdesivir groups. With ZMapp, the longer preparation time and the recommendation to allot up to 4 hours for the infusion of the first dose led to some delays in initiating therapy until the following day for patients who arrived later in the day to

their respective treatment centers. However, in a sensitivity analysis, mortality was only slightly lower when ZMapp recipients with delayed therapy were excluded.

Although most characteristics at baseline were balanced across the four groups, values for serum creatinine and aminotransferases were higher in the ZMapp and remdesivir groups than in the MAb114 and REGN-EB3 groups; patients in the latter groups had better outcomes, despite similar durations of illness before enrollment. This suggests that enrolled patients might, on average, have been somewhat sicker in the ZMapp and the remdesivir groups, which could potentially account for some of the differences in outcomes. A high percentage of missing baseline data complicates this analysis. Nevertheless, sensitivity analyses confirm the persistence of benefits of treatment with MAb114 and REGN-EB3 despite these potential imbalances.

Of the 620 patients for whom information on vaccination with rVSVΔG-ZEBOV-GP was available, 155 patients (25.0%) reported that they had received the vaccine; of these, 38.7% reported that they had received the vaccine at least 10 days before the onset of clinical symptoms. Patients who reported vaccination were more likely to enroll sooner after the onset of symptoms and generally had more favorable prognostic profiles at baseline, suggesting a possible relationship between vaccination and health-seeking behaviors associated with improved outcomes. Alternatively, the less severe clinical status of these persons at presentation could be the result of a direct effect of the vaccine on outcomes. A limitation of these results is that vaccination status was reported by the patient; efforts to confirm vaccination status are under way. Given that vaccination status was not a randomization factor in this trial, it is not possible to draw firm conclusions about its effect on mortality.

With few exceptions, the safety profiles of all four trial drugs were generally consistent with either their limited previous investigational use in EBOV-infected humans, published phase 1 data in healthy volunteers, or both. Twenty-nine serious adverse events were reported by the investigators as possibly related to the experimental treatments — not all of which occurred during the treatment period. On review, four were thought to be possibly related to the trial-drug infusions. It is difficult to distinguish adverse events associated with the trial drug from those related to underlying EVD, so the assessment of relatedness is challenging. These favorable safety profiles support the notion that relative efficacy rather than safety considerations will most likely provide the major rationale for the future use of these drugs.

Although the observed treatment benefits of MAb114 and REGN-EB3 were striking, 34% of all patients and 67% of patients who presented with higher viral loads died despite receiving one of these agents. Exploration of more efficacious interventions — such as further improvements in aggressive supportive-care measures and combination strategies that use agents with potentially complementary mechanisms of action — is needed. It is worth noting, however, that all the treatments chosen for this trial had shown comparatively high survival rates in nonhuman primate EBOV challenge models with the use of a non-Ituri EBOV variant (Kikwit), which illustrates a potential limitation of these models in evaluating single-drug and (future) combination-drug strategies.

We encountered numerous challenges in the performance of this trial. It was conducted in a region of the DRC in which there is regional violence, mistrust of government, mistrust of the Ebola response, an unstable electrical power grid, transportation difficulties, and a history of high morbidity from other infectious diseases. Missing results from laboratory tests make the logistic-regression analyses difficult to interpret. Continual oversight of staffing and supply-chain issues by the DRC Ministry of Health, the INRB, the WHO, ALIMA, IMC, and MSF was essential to maintaining an appropriate standard of supportive care in the trial centers. The trial was interrupted temporarily in two participating centers that had to be evacuated because of violence directed against those units by local community or paramilitary groups who were reportedly suspicious of the activities under way in those facilities.

Reaching a successful conclusion to this challenging trial required careful planning as well as the cooperation, support, and coordination of national and international health agencies, government leaders, pharmaceutical companies, dedicated oversight boards, scientists, and nongovernmental organizations. This trial showed that it is possible to conduct scientifically rigorous and ethically sound research during an outbreak, even in a conflict zone. Although it is important to recognize the collective strength of this partnership in ensuring the completion of the trial, the single greatest factor that ensured its success was the commitment of the staff in the field and at the sites (the physicians, nurses, pharmacists, hygienists, the *gardes-malades* [guardians of the sick], and the numerous other support staff) who worked under highly challenging circumstances at the front lines of this effort in the Ebola treatment centers, as well as that of the patients themselves.

Funding and Disclosures

Supported primarily by the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH). In-kind support and cosponsorship were provided by the national government of the Democratic Republic of Congo (DRC) and the African Coalition for Epidemic Research, Response, and Training. Logistic support was provided by the World Health Organization (WHO). Some funding for NIAID was provided by the National Cancer Institute through a contract (HHSN261200800001E) with Leidos Biomedical Research and subcontracts to the Mitchell Group. The Biomedical and Advanced Research and Development Authority of the U.S. Department of Health and Human Services provided financial support for the production of ZMapp (contract number, HHSO100201400009C) and REGN-EB3 (contract number, HHSO100201700016C). NIAID and the Defense Advanced Research Projects Agency of the U.S. Department of Defense provided financial support for the production and provision of MAb114. Mapp Biopharmaceutical provided ZMapp, Gilead Sciences provided remdesivir, and NIAID provided MAb114 to the project. Regeneron Pharmaceuticals provided financial support for the provision of REGN-EB3 to the project.

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

Drs. Mulangu, Dodd, and Davey and Drs. Lane and Muyembe-Tamfum contributed equally to this article.

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This article was published on November 27, 2019, 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 members of the PALM Consortium Study Team (see the Supplementary Appendix) for their many contributions in conducting the trial under very challenging field conditions, the members of the data and safety monitoring board (Lisa A. Cooper, M.D., M.P.H. [chair], Scott Hammer, M.D., Dave DeMets, Ph.D., M.Sc., Ann Sarah Walker, Ph.D., M.Sc., Mesia Kahunu, Pharm.D., Ph.D., Amadou Traore, M.D., M.Sc., Albert Faye, Ph.D., Salim Abdulla, Ph.D., M.Sc., and Rebecca DerSimonian, Sc.D., and Sally Hunsberger, Ph.D. [coexecutive secretaries]) for their oversight, the WHO and their coordinating committees (see Table S11), Anthony Fauci (NIAID), Robert Redfield (Centers for Disease Control and Prevention [CDC]), and Peter Salama and Michael Ryan (WHO) for leadership guidance, CDC staff (including Raimi Ewetola, Alstead Forbes, and Laetitia Vahaviraki) and the WHO staff (including the incident manager and field coordinators, supply and logistic teams, and Global Outbreak Alert and Response Network clinician experts) for in-country support, Raoul Kamanda and colleagues from the DRC Ministry of Health for invaluable support, and, most important, the patients themselves for their extraordinary bravery and altruism in participating in a trial of these experimental countermeasures.

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A complete list of members of the PALM Consortium Study Team is provided in the Supplementary Appendix, available at NEJM.org.

Supplementary Material

Protocol	PDF	2114KB
Supplementary Appendix	PDF	1552KB
Disclosure Forms	PDF	789KB
Data Sharing Statement	PDF	76KB

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Comments (2)

Dr. Prem raj P.
Dec 16, 2019

PALM Ebola Clinical Trial -- A Success Story
This protocol proved the greater efficacy and safety of combination of standard care plus Mab114 or REGN-EB3 over standard care plus ZMapp in terms of patients' survival. The study could be an eye opener for future better therapeutic options for Ebola infected patients. The statistical and molecular analysis were done precisely and is highly appreciable. Good article!!!

Diane HALLINEN
Dec 11, 2019

Appreciate the workers caring for the patients
Having worked in an ETU in Sierra Leone, I am so impressed that clinical trials were completed during this current epidemic. The bleach scented, sweat full boots on the ground deserve high praise. Thank you.

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Case Reports Int J Infect Dis. 2020 Sep;98:290-293. doi: 10.1016/j.ijid.2020.06.093.

Epub 2020 Jun 30.

Case report study of the first five COVID-19 patients treated with remdesivir in France

Marie Dubert [1], Benoit Visseaux [2], Valentina Isernia [3], Lila Bouadma [4], Laurène Deconinck [3], Juliette Patrier [4], Paul-Henri Wicky [4], Diane Le Pluart [3], Laura Kramer [5], Christophe Rioux [3], Quentin Le Hingrat [2], Nadhira Houhou-Fidouh [6], Yazdan Yazdanpanah [7], Jade Ghosn [7], Francois-Xavier Lescure [7]

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PMID: 32619764 PMCID: PMC7326458 DOI: 10.1016/j.ijid.2020.06.093

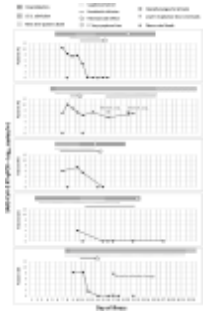
Free PMC article

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been identified as the virus responsible for the coronavirus disease 2019 (COVID-19) outbreak worldwide. Data on treatment are scare and parallels have been made between SARS-CoV-2 and other coronaviruses. Remdesivir is a broad-spectrum antiviral with efficient in vitro activity against SARS-CoV-2. Evidence of clinical improvement in patients with severe COVID-19 treated with remdesivir is controversial. The aim of this study was to describe the clinical outcomes and virological monitoring of the first five COVID-19 patients admitted to the intensive care unit of Bichat-Claude Bernard University Hospital, Paris, France, for severe pneumonia related to SARS-CoV-2 and treated with remdesivir. Quantitative reverse transcription PCR was used to monitor SARS-CoV-2 in blood plasma and the lower and upper respiratory tract. Among the five patients treated, two needed mechanical ventilation and one needed high-flow cannula oxygen. A significant decrease in SARS-CoV-2 viral load in the upper respiratory tract was observed in most cases, but two patients died with active SARS-CoV-2 replication in the lower respiratory tract. Plasma samples were positive for SARS-CoV-2 in only one patient. Remdesivir was interrupted before the initialy planned duration in four patients, two because of alanine aminotransferase elevations (3 to 5 normal range) and two because of renal failure requiring renal replacement. This case series of five COVID-19 patients requiring intensive care unit treatment for respiratory distress and treated with remdesivir, highlights the complexity of remdesivir use in such critically ill patients.

Keywords: Antiviral therapy; Case reports; Remdesivir; SARS-CoV-2 viral load; Viral pneumonia.

Figures



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Editor's Note: This article was published on April 10, 2020, at NEJM.org.

ORIGINAL ARTICLE

Compassionate Use of Remdesivir for Patients with Severe Covid-19

Jonathan Grein, M.D., Norio Ohmagari, M.D., Ph.D., Daniel Shin, M.D., George Diaz, M.D., Erika Asperges, M.D., Antonella Castagna, M.D., Torsten Feldt, M.D., Gary Green, M.D., Margaret L. Green, M.D., M.P.H., François-Xavier Lescure, M.D., Ph.D., Emanuele Nicastri, M.D., Rentaro Oda, M.D., Kikuo Yo, M.D., D.M.Sc., Eugenia Quiros-Roldan, M.D., Alex Studemeister, M.D., John Redinski, D.O., Seema Ahmed, M.D., Jorge Bernett, M.D., Daniel Chelliah, M.D., Danny Chen, M.D., Shingo Chihara, M.D., Stuart H. Cohen, M.D., Jennifer Cunningham, M.D., Antonella D'Arminio Monforte, M.D., Saad Ismail, M.D., Hideaki Kato, M.D., Giuseppe Lapadula, M.D., Erwan L'Her, M.D., Ph.D., Toshitaka Maeno, M.D., Sumit Majumder, M.D., Marco Massari, M.D., Marta Mora-Rillo, M.D., Yoshikazu Mutoh, M.D., Duc Nguyen, M.D., Pharm.D., Ewa Verweij, M.D., Alexander Zoufaly, M.D., Anu O. Osinusi, M.D., Adam DeZure, M.D., Yang Zhao, Ph.D., Lijie Zhong, Ph.D., Anand Chokkalingam, Ph.D., Emon Elboudwarej, Ph.D., Laura Telep, M.P.H., Leighann Timbs, B.A., Ilana Henne, M.S., Scott Sellers, Ph.D., Huyen Cao, M.D., Susanna K. Tan, M.D., Lucinda Winterbourne, B.A., Polly Desai, M.P.H., Robertino Mera, M.D., Ph.D., Anuj Gaggar, M.D., Ph.D., Robert P. Myers, M.D., Diana M. Brainard, M.D., Richard Childs, M.D., and Timothy Flanigan, M.D.et al.

June 11, 2020
N Engl J Med 2020; 382:2327-2336
DOI: 10.1056/NEJMoa2007016
Chinese Translation 中文翻译

Metrics

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Abstract

BACKGROUND

Remdesivir, a nucleotide analogue prodrug that inhibits viral RNA polymerases, has shown in vitro activity against SARS-CoV-2.

METHODS

We provided remdesivir on a compassionate-use basis to patients hospitalized with Covid-19, the illness caused by infection with SARS-CoV-2. Patients were those with confirmed SARS-CoV-2 infection who had an oxygen saturation of 94% or less while they were breathing ambient air or who were receiving oxygen support. Patients received a 10-day course of remdesivir, consisting of 200 mg administered intravenously on day 1, followed by 100 mg daily for the remaining 9 days of treatment. This report is based on data from patients who received remdesivir during the period from January 25, 2020, through March 7, 2020, and have clinical data for at least 1 subsequent day.

RESULTS

Of the 61 patients who received at least one dose of remdesivir, data from 8 could not be analyzed (including 7 patients with no post-treatment data and 1 with a dosing error). Of the 53 patients whose data were analyzed, 22 were in the United States, 22 in Europe or Canada, and 9 in Japan. At baseline, 30 patients (57%) were receiving mechanical ventilation and 4 (8%) were receiving extracorporeal membrane oxygenation. During a median follow-up of 18 days, 36 patients (68%) had an improvement in oxygen-support class, including 17 of 30 patients (57%) receiving mechanical ventilation who were extubated. A total of 25 patients (47%) were discharged, and 7 patients (13%) died; mortality was 18% (6 of 34) among patients receiving invasive ventilation and 5% (1 of 19) among those not receiving invasive ventilation.

CONCLUSIONS

In this cohort of patients hospitalized for severe Covid-19 who were treated with compassionate-use remdesivir, clinical improvement was observed in 36 of 53 patients (68%). Measurement of efficacy will require ongoing randomized, placebo-controlled trials of remdesivir therapy. (Funded by Gilead Sciences.)

Introduction

Since the first cases were reported in December 2019, infection with the severe acute respiratory coronavirus 2 (SARS-CoV-2) has become a worldwide pandemic.[1,2] Covid-19 — the illness caused by SARS-CoV-2 — is overwhelming health care systems globally.[3,4] The symptoms of SARS-CoV-2 infection vary widely, from asymptomatic disease to pneumonia and life-threatening complications, including acute respiratory distress syndrome, multisystem organ failure, and ultimately, death.[5-7] Older patients and those with preexisting respiratory or cardiovascular conditions appear to be at the greatest risk for severe complications.[6,7] In the absence of a proven effective therapy, current management consists of supportive care, including invasive and noninvasive oxygen support and treatment with antibiotics.[8,9] In addition, many patients have received off-label or compassionate-use therapies, including antiretrovirals, antiparasitic agents, antiinflammatory compounds, and convalescent plasma.[10-13]

Remdesivir is a prodrug of a nucleotide analogue that is intracellularly metabolized to an analogue of adenosine triphosphate that inhibits viral RNA polymerases. Remdesivir has broad-spectrum activity against members of several virus families, including filoviruses (e.g., Ebola) and coronaviruses (e.g., SARS-CoV and Middle East respiratory syndrome coronavirus [MERS-CoV]) and has shown prophylactic and therapeutic efficacy in nonclinical models of these coronaviruses.[14-17] In vitro testing has also shown that remdesivir has activity against SARS-CoV-2. Remdesivir appears to have a favorable clinical safety profile, as reported on the basis of experience in approximately 500 persons, including healthy volunteers and patients treated for acute Ebola virus infection,[18,19] and supported by our data (on file and shared with the World Health Organization [WHO]). In this report, we describe outcomes in a cohort of patients hospitalized for severe Covid-19 who were treated with remdesivir on a compassionate-use basis.

Methods

PATIENTS

Gilead Sciences began accepting requests from clinicians for compassionate use of remdesivir on January 25, 2020. To submit a request, clinicians completed an assessment form with demographic and disease-status information about their patient (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Approval of requests was reserved for hospitalized patients who had SARS-CoV-2 infection confirmed by reverse-transcriptase–polymerase-chain-reaction assay and either an oxygen saturation of 94% or less while the patient was breathing ambient air or a need for oxygen support. In addition, patients were required to have a creatinine clearance above 30 ml per minute and serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) less than five times the upper limit of the normal range, and they had to agree not to use other investigational agents for Covid-19.

In approved cases, the planned treatment was a 10-day course of remdesivir, consisting of a loading dose of 200 mg intravenously on day 1, plus 100 mg daily for the following 9 days. Supportive therapy was to be provided at the discretion of the clinicians. Follow-up was to continue through at least 28 days after the beginning of treatment with remdesivir or until discharge or death. Data that were collected through March 30, 2020, are reported here. This open-label program did not have a predetermined number of patients, number of sites, or duration. Data for some patients included in this analysis have been reported previously.[20-22] Details of the study design and conduct can be seen in the **protocol** (available at NEJM.org).

STUDY ASSESSMENTS

Data on patients' oxygen-support requirements, adverse events, and laboratory values, including serum creatinine, ALT, and AST, were to be reported daily, from day 1 through day 10, and additional follow-up information was solicited through day 28. Although there were no prespecified end points for this program, we quantified the incidence of key clinical events, including changes in oxygen-support requirements (ambient air, low-flow oxygen, nasal high-flow oxygen, noninvasive positive pressure ventilation [NIPPV], invasive mechanical ventilation, and extracorporeal membrane oxygenation [ECMO]), hospital discharge, and reported adverse events, including those leading to discontinuation of treatment, serious adverse events, and death. In addition, we evaluated the proportion of patients with clinical improvement, as defined by live discharge from the hospital, a decrease of at least 2 points from baseline on a modified ordinal scale (as recommended by the WHO R&D Blueprint Group), or both. The six-point scale consists of the following categories: 1, not hospitalized; 2, hospitalized, not requiring supplemental oxygen; 3, hospitalized, requiring supplemental oxygen; 4, hospitalized, requiring nasal high-flow oxygen therapy, noninvasive mechanical ventilation, or both; 5, hospitalized, requiring invasive mechanical ventilation, ECMO, or both; and 6, death.

PROGRAM OVERSIGHT

Regulatory and institutional review board or independent ethics committee approval was obtained for each patient treated with remdesivir, and consent was obtained for all patients in accordance with local regulations. The program was designed and conducted by the sponsor (Gilead Sciences), in accordance with the **protocol**. The sponsor collected the data, monitored conduct of the program, and performed the statistical analyses. All authors had access to the data and assume responsibility for the integrity and completeness of the reported data. The initial draft of the manuscript was prepared by a writer employed by Gilead Sciences along with one of the authors, with input from all the authors.

STATISTICAL ANALYSIS

No sample-size calculations were performed. The analysis population included all patients who received their first dose of remdesivir on or before March 7, 2020, and for whom clinical data for at least 1 subsequent day were available. Clinical improvement and mortality in the remdesivir compassionate-use cohort were described with the use of Kaplan–Meier analysis. Associations between pretreatment characteristics and these outcomes were evaluated with Cox proportional hazards regression. Because the analysis did not include a provision for correcting for multiple comparisons in tests for association between baseline variables and outcomes, results are reported as point estimates and 95% confidence

intervals. The widths of the confidence intervals have not been adjusted for multiple comparisons, so the intervals should not be used to infer definitive associations with outcomes. All analyses were conducted with SAS software, version 9.4 (SAS Institute).

Results

PATIENTS

In total, 61 patients received at least one dose of remdesivir on or before March 7, 2020; 8 of these patients were excluded because of missing postbaseline information (7 patients) and an erroneous remdesivir start date (1 patient) (Fig. S1 in the Supplementary Appendix). Of the 53 remaining patients included in this analysis, 40 (75%) received the full 10-day course of remdesivir, 10 (19%) received 5 to 9 days of treatment, and 3 (6%) fewer than 5 days of treatment.

BASELINE CHARACTERISTICS OF THE PATIENTS

Table 1.

Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*

Characteristic	Invasive Ventilation (N=34)	Noninvasive Oxygen Support (N=19)	Total (N=53)
Median age (IQR) — yr	67 (56–72)	53 (41–68)	64 (48–71)
Age category — no. (%)			
<50 yr	6 (18)	8 (42)	14 (26)
50 to <70 yr	14 (41)	7 (37)	21 (40)
≥70 yr	14 (41)	4 (21)	18 (34)
Male sex — no. (%)	27 (79)	13 (68)	40 (75)
Region — no. (%)			
United States	14 (41)	8 (42)	22 (42)
Japan	8 (24)	1 (5)	9 (17)
Europe or Canada	12 (35)	10 (53)	22 (42)
Oxygen-support category — no. (%)			
Invasive ventilation	34 (100)	—	34 (64)
Invasive mechanical ventilation	30 (88)	—	30 (57)
Extracorporeal membrane oxygenation	4 (12)	—	4 (8)
Noninvasive oxygen support	—	19 (100)	19 (36)
Noninvasive positive-pressure ventilation	—	2 (11)	2 (4)
High-flow oxygen	—	5 (26)	5 (9)
Low-flow oxygen	—	10 (53)	10 (19)
Ambient air	—	2 (11)	2 (4)
Median duration of symptoms before remdesivir therapy (IQR) — days	11 (8–15)	13 (10–14)	12 (9–15)
Coexisting conditions — no. (%)			
Any condition	25 (74)	11 (58)	36 (68)
Hypertension	9 (26)	4 (21)	13 (25)
Diabetes	8 (24)	1 (5)	9 (17)
Hyperlipidemia	6 (18)	0	6 (11)
Asthma	5 (15)	1 (5)	6 (11)
Median laboratory values (IQR)			
ALT — IU per liter	48 (31–79)	27 (20–45)	37 (25–61)
AST — IU per liter	39 (30–76)	35 (28–46)	36 (29–67)
Creatinine — mg per deciliter	0.90 (0.66–1.17)	0.79 (0.63–1.00)	0.89 (0.64–1.08)

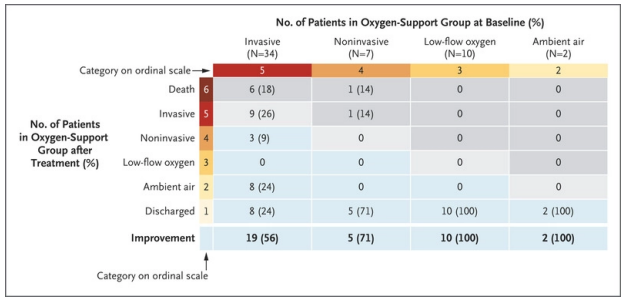
* ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and IQR interquartile range. To convert the values for creatinine to micromoles per liter, multiply by 88.4.

Baseline Demographic and Clinical Characteristics of the Patients.

Table 1 shows baseline demographic and clinical characteristics of the 53 patients in the compassionate-use cohort. Patients were enrolled in the United States (22 patients), Japan (9), Italy (12), Austria (1), France (4), Germany (2), Netherlands (1), Spain (1), and Canada (1). A total of 40 patients (75%) were men, the age range was 23 to 82 years, and the median age was 64 years (interquartile range, 48 to 71). At baseline, the majority of patients (34 [64%]) were receiving invasive ventilation, including 30 (57%) receiving mechanical ventilation and 4 (8%) receiving ECMO. The median duration of invasive mechanical ventilation before the initiation of remdesivir treatment was 2 days (interquartile range, 1 to 8). As compared with patients who were receiving noninvasive oxygen support at baseline, those receiving invasive ventilation tended to be older (median age, 67 years, vs. 53 years), were more likely to be male (79%, vs. 68%), had higher median serum ALT (48 U per liter, vs. 27) and creatinine (0.90 mg per deciliter, vs. 0.79 [79.6 µmol per liter, vs. 69.8]), and a higher prevalence of coexisting conditions, including hypertension (26%, vs. 21%), diabetes (24%, vs. 5%), hyperlipidemia (18%, vs. 0%), and asthma (15%, vs. 5%). The median duration of symptoms before the initiation of remdesivir treatment was 12 days (interquartile range, 9 to 15) and did not differ substantially between patients receiving invasive ventilation and those receiving noninvasive ventilation (Table 1).

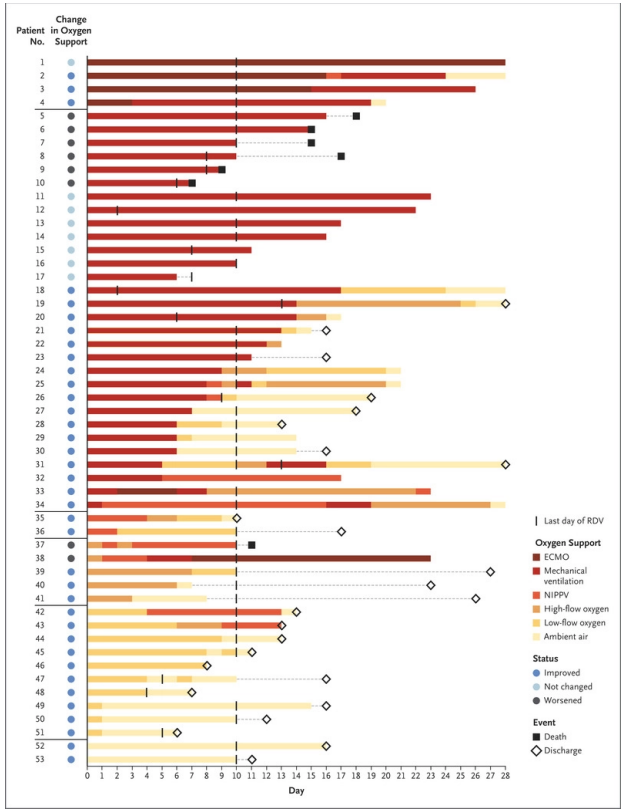
CLINICAL IMPROVEMENT DURING REMDESIVIR TREATMENT

Figure 1.



Oxygen-Support Status at Baseline and after Treatment.

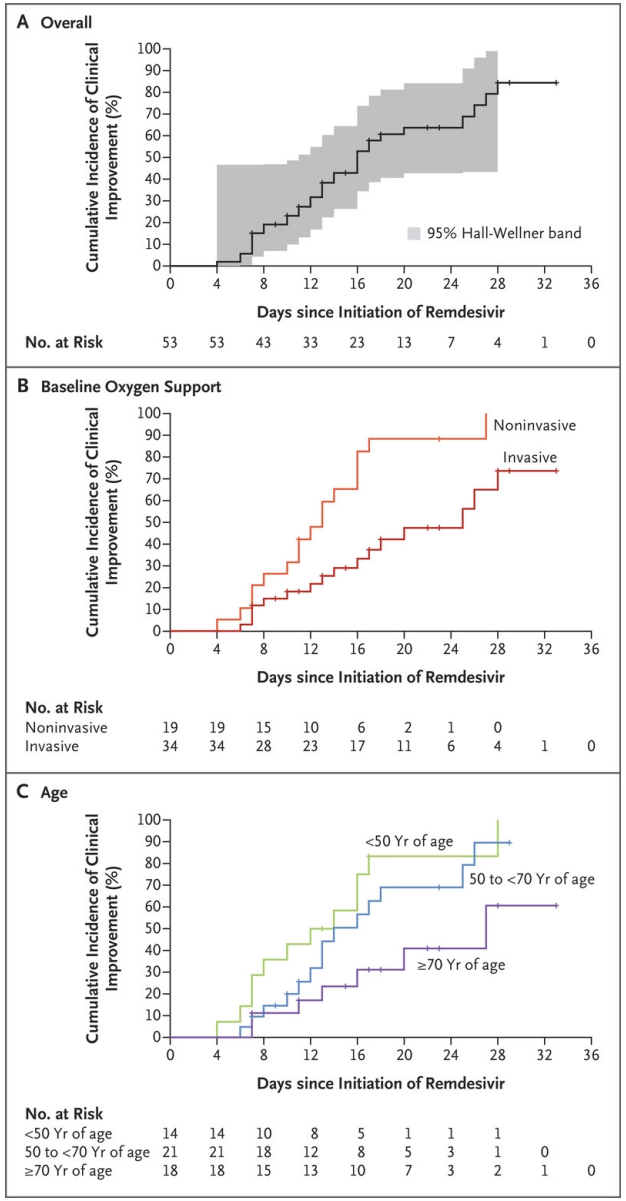
Figure 2.



Changes in Oxygen-Support Status from Baseline in Individual Patients.

Over a median follow-up of 18 days (interquartile range, 13 to 23) after receiving the first dose of remdesivir, 36 of 53 patients (68%) showed an improvement in the category of oxygen support, whereas 8 of 53 patients (15%) showed worsening (Figure 1). Improvement was observed in all 12 patients who were breathing ambient air or receiving low-flow supplemental oxygen and in 5 of 7 patients (71%) who were receiving noninvasive oxygen support (NIPPV or high-flow supplemental oxygen). It is notable that 17 of 30 patients (57%) who were receiving invasive mechanical ventilation were extubated, and 3 of 4 patients (75%) receiving ECMO stopped receiving it; all were alive at last follow-up. Individual patients' changes in the category of oxygen support are shown in Figure 2. By the date of the most recent follow-up, 25 of 53 patients (47%) had been discharged (24% receiving invasive ventilation [8 of 34 patients] and 89% [17 of 19 patients] receiving noninvasive oxygen support).

Figure 3.



Cumulative Incidence of Clinical Improvement from Baseline to Day 36.

By 28 days of follow-up, the cumulative incidence of clinical improvement, as defined by either a decrease of 2 points or more on the six-point ordinal scale or live discharge, was 84% (95% confidence interval [CI], 70 to 99) by Kaplan–Meier analysis (Figure 3A). Clinical improvement was less frequent among patients receiving invasive ventilation than among those receiving noninvasive ventilation (hazard ratio for improvement, 0.33; 95% CI, 0.16 to 0.68) (Figure 3B) and among patients 70 years of age or older (hazard ratio as compared with patients younger than 50 years,

0.29; 95% CI, 0.11 to 0.74) (Figure 3C). Sex, region of enrollment, coexisting conditions, and duration of symptoms before remdesivir treatment was initiated were not significantly associated with clinical improvement (Table S1).

MORTALITY

Seven of the 53 patients (13%) died after the completion of remdesivir treatment, including 6 of 34 patients (18%) who were receiving invasive ventilation and 1 of 19 (5%) who were receiving noninvasive oxygen support (see the Supplementary Appendix for case narratives). The median interval between remdesivir initiation and death was 15 days (interquartile range, 9 to 17). Overall mortality from the date of admission was 0.56 per 100 hospitalization days (95% CI, 0.14 to 0.97) and did not differ substantially among patients receiving invasive ventilation (0.57 per 100 hospitalization days; 95% CI, 0 to 1.2]) as compared with those receiving noninvasive ventilation (0.51 per 100 hospitalization days; 95% CI, 0.07 to 1.1]). Risk of death was greater among patients who were 70 years of age or older (hazard ratio as compared with patients younger than 70 years, 11.34; 95% CI, 1.36 to 94.17) and among those with higher serum creatinine at baseline (hazard ratio per milligram per deciliter, 1.91; 95% CI, 1.22 to 2.99). The hazard ratio for patients receiving invasive ventilation as compared with those receiving noninvasive oxygen support was 2.78 (95% CI, 0.33 to 23.19) (Table S2).

SAFETY

Table 2.

Table 2. Summary of Adverse Events.

Event	Invasive Ventilation (N=34)	Noninvasive Oxygen Support (N=19)	Total (N=53)
	number of patients (percent)		
Any adverse event	22 (65)	10 (53)	32 (60)
Adverse events occurring in 2 or more patients			
Hepatic enzyme increased*	8 (24)	4 (21)	12 (23)
Diarrhea	1 (3)	4 (21)	5 (9)
Rash	3 (9)	1 (5)	4 (8)
Renal impairment	4 (12)	0	4 (8)
Hypotension	3 (9)	1 (5)	4 (8)
Acute kidney injury	2 (6)	1 (5)	3 (6)
Atrial fibrillation	2 (6)	1 (5)	3 (6)
Multiple-organ-dysfunction syndrome	3 (9)	0	3 (6)
Hypernatremia	3 (9)	0	3 (6)
Deep-vein thrombosis	3 (9)	0	3 (6)
Acute respiratory distress syndrome	1 (3)	1 (5)	2 (4)
Pneumothorax	2 (6)	0	2 (4)
Hematuria	2 (6)	0	2 (4)
Delirium	1 (3)	1 (5)	2 (4)
Septic shock	2 (6)	0	2 (4)
Pyrexia	1 (3)	1 (5)	2 (4)
Any serious adverse event	9 (26)	3 (16)	12 (23)
Serious events occurring in 2 or more patients			
Multiple-organ-dysfunction syndrome	2 (6)	0	2 (4)
Septic shock	2 (6)	0	2 (4)
Acute kidney injury	2 (6)	0	2 (4)
Hypotension	2 (6)	0	2 (4)

* Adverse-event terms are based on the *Medical Dictionary for Regulatory Activities*, version 22.1. Hepatic enzyme increased includes the following terms: hepatic enzyme increased, alanine aminotransferase increased, aspartate aminotransferase increased, and transaminases increased. Elevated hepatic enzymes resulted in discontinuation of remdesivir therapy in 2 patients.

Summary of Adverse Events.

A total of 32 patients (60%) reported adverse events during follow-up (Table 2). The most common adverse events were increased hepatic enzymes, diarrhea, rash, renal impairment, and hypotension. In general, adverse events were more common in patients receiving invasive ventilation. A total of 12 patients (23%) had serious adverse events. The most common serious adverse events — multiple-organ-dysfunction syndrome, septic shock, acute kidney injury, and hypotension — were reported in patients who were receiving invasive ventilation at baseline.

Four patients (8%) discontinued remdesivir treatment prematurely: one because of worsening of preexisting renal failure, one because of multiple organ failure, and two because of elevated aminotransferases, including one patient with a maculopapular rash.

LABORATORY DATA

Given the nature of this compassionate-use program, data on a limited number of laboratory measures were collected. Median serum ALT, AST, and creatinine fluctuated during follow-up (Fig. S2).

Discussion

To date, no therapy has demonstrated efficacy for patients with Covid-19. This preliminary report describes the clinical outcomes in a small cohort of patients who were severely ill with Covid-19 and were treated with remdesivir. Although data from several ongoing randomized, controlled trials will soon provide more informative evidence regarding the safety and efficacy of remdesivir for Covid-19, the outcomes observed in this compassionate-use program are the best currently available data. Specifically, improvement in oxygen-support status was observed in 68% of patients, and overall mortality was 13% over a median follow-up of 18 days. In a recent randomized, controlled trial of lopinavir–ritonavir in patients hospitalized for Covid-19, the 28-day mortality was 22%.[10] It is important to note that only 1 of 199 patients in that trial were receiving invasive ventilation at baseline. In case series and cohort studies, largely from China, mortality rates of 17 to 78% have been reported in severe cases, defined by the need for admission to an intensive care unit, invasive ventilation, or both.[23-28] For example, among 201 patients hospitalized in Wuhan, China, mortality was 22% overall and 66% (44 of 67) among patients receiving invasive mechanical ventilation.[7] By way of comparison, the 13% mortality observed in this remdesivir compassionate-use cohort is noteworthy, considering the severity of disease in this patient population; however, the patients enrolled in this compassionate-treatment program are not directly comparable to those studied in these other reports. For example, 64% of remdesivir-treated patients were receiving invasive ventilation at baseline, including 8% who were receiving ECMO, and mortality in this subgroup was 18% (as compared with 5.3% in patients receiving noninvasive oxygen support), and the majority (75%) of patients were male, were over 60 years of age, and had coexisting conditions.

Unfortunately, our compassionate-use program did not collect viral load data to confirm the antiviral effects of remdesivir or any association between baseline viral load and viral suppression, if any, and clinical response. Moreover, the duration of remdesivir therapy was not entirely uniform in our study, largely because clinical improvement enabled discharge from the hospital. The effectiveness of a shorter duration of therapy (e.g., 5 days, as compared with 10 days), which would allow the treatment of more patients during the pandemic, is being assessed in ongoing randomized trials of this therapy.

No new safety signals were detected during short-term remdesivir therapy in this compassionate-use cohort. Nonclinical toxicology studies have shown renal abnormalities, but no clear evidence of nephrotoxicity due to remdesivir therapy was observed. As reported in studies in healthy volunteers and patients infected with Ebola virus, mild-to-moderate elevations in ALT, AST, or both were observed in this cohort of patients with severe Covid-19.[18,19] However, considering the frequency of liver dysfunction in patients with Covid-19, attribution of hepatotoxicity to either remdesivir or the underlying disease is challenging.[29] Nevertheless, the safety and side-effect profile of remdesivir in patients with Covid-19 require proper assessment in placebo-controlled trials.

Interpretation of the results of this study is limited by the small size of the cohort, the relatively short duration of follow-up, potential missing data owing to the nature of the program, the lack of information on 8 of the patients initially treated, and the lack of a randomized control group. Although the latter precludes definitive conclusions, comparisons with contemporaneous cohorts from the literature, in whom general care is expected to be consistent with that of our cohort, suggest that remdesivir may have clinical benefit in patients with severe Covid-19. Nevertheless, other factors may have contributed to differences in outcomes, including the type of supportive care (e.g., concomitant medications or variations in ventilatory practices) and differences in institutional treatment protocols and thresholds for hospitalization. Moreover, the use of invasive ventilation as a proxy for disease severity may be influenced by the availability of ventilators in a given location. The findings from these uncontrolled data will be informed by the ongoing randomized, placebo-controlled trials of remdesivir therapy for Covid-19.

Funding and Disclosures

Supported by Gilead Sciences.

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

This article was published on April 10, 2020, at NEJM.org.

We thank Sarah Tse, Deborah Ajayi, and Gretchen Schmelz of BioScience Communications for creating earlier versions of the figures. Writing and editorial assistance with earlier versions of the manuscript were provided by David McNeel and Sandra Chen, both of Gilead Sciences. The names of those who

assisted in the care of the patients in this program are listed in the Supplementary Appendix. We express our solidarity with those who are or have been ill with Covid-19, their families, and the health care workers on the front lines of this pandemic.

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Supplementary Material

Protocol	PDF	282KB
Supplementary Appendix	PDF	1576KB
Disclosure Forms	PDF	871KB

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Remdesivir and Acute Renal Failure: A Potential Safety Signal From Disproportionality Analysis of the WHO Safety Database

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PMID: 33340409 DOI: 10.1002/cpt.2145

Abstract

Remdesivir is approved for emergency use by the US Food and Drug Administration (FDA) and authorized conditionally by the European Medicines Agency (EMA) for patients with coronavirus disease 2019 (COVID-19). Its benefit-risk ratio is still being explored because data in the field are rather scant. A decrease of the creatinine clearance associated with remdesivir has been

inconstantly reported in clinical trials with unclear relevance. Despite these uncertainties, we searched for a potential signal of acute renal failure (ARF) in pharmacovigilance postmarketing data. An analysis of the international pharmacovigilance postmarketing databases (VigiBase) of the World Health Organization (WHO) was performed, using two disproportionality methods. Reporting odds ratio (ROR) compared the number of ARF cases reported with remdesivir, with those reported with other drugs prescribed in comparable situations of COVID-19 (hydroxychloroquine, tocilizumab, and lopinavir/ritonavir). The combination of the terms "acute renal failure" and "remdesivir" yielded a statistically significant disproportionality signal with 138 observed cases instead of the 9 expected. ROR of ARF with remdesivir was 20-fold (20.3; confidence interval 0.95 [15.7-26.3], P < 0.0001]) that of comparative drugs. Based on ARF cases reported in VigiBase, and despite the caveats inherent to COVID-19 circumstances, we detected a statistically significant pharmacovigilance signal of nephrotoxicity associated with remdesivir, deserving a thorough qualitative assessment of all available data. Meanwhile, as recommended in its Summary of Product Characteristics, assessment of patients with COVID-19 renal function should prevail before and during treatment with remdesivir in COVID-19.

Supplementary concepts

COVID-19 drug treatment

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