ORIGINAL ARTICLE

Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19

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ABSTRACT

BACKGROUND

Severe coronavirus disease 2019 (Covid-19) is associated with dysregulated inflammation. The effects of combination treatment with baricitinib, a Janus kinase inhibitor, plus remdesivir are not known.

METHODS

We conducted a double-blind, randomized, placebo-controlled trial evaluating baricitinib plus remdesivir in hospitalized adults with Covid-19. All the patients received remdesivir (≤10 days) and either baricitinib (≤14 days) or placebo (control). The primary outcome was the time to recovery. The key secondary outcome was clinical status at day 15.

RESULTS

A total of 1033 patients underwent randomization (with 515 assigned to combination treatment and 518 to control). Patients receiving baricitinib had a median time to recovery of 7 days (95% confidence interval [CI], 6 to 8), as compared with 8 days (95% CI, 7 to 9) with control (rate ratio for recovery, 1.16; 95% CI, 1.01 to 1.32; P=0.03), and a 30% higher odds of improvement in clinical status at day 15 (odds ratio, 1.3; 95% CI, 1.0 to 1.6). Patients receiving high-flow oxygen or noninvasive ventilation at enrollment had a time to recovery of 10 days with combination treatment and 18 days with control (rate ratio for recovery, 1.51; 95% CI, 1.10 to 2.08). The 28-day mortality was 5.1% in the combination group and 7.8% in the control group (hazard ratio for death, 0.65; 95% CI, 0.39 to 1.09). Serious adverse events were less frequent in the combination group than in the control group (16.0% vs. 21.0%; difference, −5.0 percentage points; 95% CI, −9.8 to −0.3; P=0.03), as were new infections (5.9% vs. 11.2%; difference, −5.3 percentage points; 95% CI, −8.7 to −1.9; P=0.003).

CONCLUSIONS

Baricitinib plus remdesivir was superior to remdesivir alone in reducing recovery time and accelerating improvement in clinical status among patients with Covid-19, notably among those receiving high-flow oxygen or noninvasive ventilation. The combination was associated with fewer serious adverse events. (Funded by the National Institute of Allergy and Infectious Diseases; ClinicalTrials.gov number, NCT04401579.)

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A complete list of members of the ACTT-2 Study Group is provided in the Supplementary Appendix, available at NEJM.org.

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In May 2020, the first stage of the Adaptive Covid-19 Treatment Trial (ACTT-1), a randomized, double-blind, placebo-controlled trial, showed that remdesivir is an effective treatment for hospitalized adult patients with coronavirus disease 2019 (Covid-19) pneumonia.[1] Despite the benefits of remdesivir, substantial morbidity and mortality due to Covid-19 remain. Emerging data suggest that disease severity may be due in part to a dysregulated inflammatory response.[2] It is postulated that mitigating the immune response and preventing a hyperinflammatory state may further improve clinical outcomes. Baricitinib, an orally administered, selective inhibitor of Janus kinase (JAK) 1 and 2, was predicted with the use of artificial intelligence algorithms to be a potential therapeutic against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[3,4] Baricitinib inhibits the intracellular signaling pathway of cytokines known to be elevated in severe Covid-19, including interleukin-2, interleukin-6, interleukin-10, interferon-γ, and granulocyte–macrophage colony-stimulating factor; acts against SARS-CoV-2 through the impairment of AP2-associated protein kinase 1 and the prevention of SARS-CoV-2 cellular entry and infectivity; and improves lymphocyte counts in patients with Covid-19.[3,5-8] In three case series of patients with Covid-19, baricitinib treatment was associated with both an improvement in oxygenation and a reduction in select inflammatory markers.[9-11] Randomized, controlled trials are needed to further understand the role of immunomodulation in patients with Covid-19.[12] After the successful completion of ACTT-1, we designed the next iteration of ACTT (ACTT-2) to evaluate whether the combination of baricitinib plus remdesivir was superior to remdesivir alone.

METHODS

DESIGN

The ACTT-2 protocol was designed and written by a working group of the ACTT investigators and the sponsor (the National Institute of Allergy and Infectious Diseases), with input from the manufacturer of baricitinib, Eli Lilly. Investigators and staff at participating sites gathered the data, which were then analyzed by statisticians at the statistical and data center (Emmes) and the sponsor. The authors wrote the manuscript, and, on behalf of the ACTT-2 Study Group, vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Enrollment into this double-blind, placebo-controlled trial began on May 8, 2020, and ended on July 1, 2020. There were 67 trial sites in 8 countries: the United States (55 sites), Singapore (4), South Korea (2), Mexico (2), Japan (1), Spain (1), the United Kingdom (1), and Denmark (1). Eligible patients were randomly assigned in a 1:1 ratio to receive either remdesivir and baricitinib or remdesivir and placebo. Randomization was stratified according to trial site and disease severity at enrollment (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Patients received remdesivir intravenously as a 200-mg loading dose on day 1, followed by a 100-mg maintenance dose administered daily on days 2 through 10 or until hospital discharge or death. Baricitinib was administered as a 4-mg daily dose (either orally [two 2-mg tablets] or through a nasogastric tube) for 14 days or until hospital discharge. Patients with an estimated glomerular filtration rate of less than 60 ml per minute received baricitinib at a dose of 2 mg once daily. A matching oral placebo was administered according to the same schedule as the active drug. All the patients received standard supportive care at the trial site hospital. Venous thromboembolism prophylaxis was recommended for all the patients without a major contraindication. If a hospital had a written policy for Covid-19 treatments, patients could receive those treatments. In the absence of a written policy, other experimental treatment and off-label use of marketed medications intended as specific treatment for Covid-19 were prohibited. This included glucocorticoids, which were permitted only for standard indications such as adrenal insufficiency, asthma exacerbation, laryngeal edema, septic shock, and acute respiratory distress syndrome.

The trial protocol was approved by the institutional review board at each site (or a centralized institutional review board as applicable) and was overseen by an independent data and safety monitoring board. Written informed consent was obtained from each patient or from the patient's legally authorized representative if the patient was unable to provide consent. Full details of the trial design, conduct, oversight, and analyses are provided in the protocol and statistical analysis plan (available at NEJM.org).

PROCEDURES

All patients were evaluated daily during their hospitalization, from day 1 through day 29. (See the full description of procedures in the Supplementary Appendix.) The trial team was unaware of the trial-group assignments until after all data queries were resolved and the database was locked. The first draft of the manuscript was written by the first author, and then all the authors contributed to the subsequent versions. No one who is not an author contributed to the writing of the manuscript.

OUTCOMES AND STATISTICAL ANALYSIS

The primary outcome measure was the time to recovery, with the day of recovery defined as the first day, during the 28 days after enrollment, on which a patient attained category 1, 2, or 3 on the eight-category ordinal scale. The competing event of death was handled in a manner similar to the Fine–Gray competing-risk approach.[13] The categories are the same as those used in ACTT-1[1] and are listed in Table S1 in the Supplementary Appendix. The primary analysis was a stratified log-rank test of the time to recovery with remdesivir plus baricitinib as compared with remdesivir plus placebo, stratified according to baseline disease severity (i.e., score on the ordinal scale of 4 or 5 vs. 6 or 7 at enrollment).

The key secondary outcome measure was clinical status at day 15, based on the eight-category ordinal scale. Other secondary outcome measures included the time to improvement by one or two categories from the ordinal score at baseline; clinical status, as assessed on the ordinal scale at days 3, 5, 8, 11, 15, 22, and 29; mean change in the ordinal score from day 1 to days 3, 5, 8, 11, 15, 22, and 29; time to discharge or to a National Early Warning Score of 2 or less (on a scale from 0 to 20, with higher scores indicating greater clinical risk) that was maintained for 24 hours, whichever occurred first; change in the National Early Warning Score from day 1 to days 3, 5, 8, 11, 15, 22, and 29; number of days of receipt of supplemental oxygen, noninvasive ventilation or high-flow oxygen, and invasive ventilation or extracorporeal membrane oxygenation (ECMO) up to day 29 (if these were being used at baseline); the incidence and duration of new use of oxygen, new use of noninvasive ventilation or high-flow oxygen, and new use of invasive ventilation or ECMO; duration of hospitalization up to day 29 (patients who remained hospitalized at day 29 had a value of 28 days); and mortality at 14 and 28 days after enrollment. Secondary safety outcomes included grade 3 and 4 adverse events and serious adverse events that occurred through day 29, discontinuation or temporary suspension of trial-product administration for any reason, and changes in assessed laboratory values over time. There was a single primary hypothesis test. For secondary outcomes, no adjustments for multiplicity were made.

Prespecified subgroups were defined according to sex, disease severity (as defined for stratification and by an ordinal score of 4, 5, 6, and 7 at enrollment), age (18 to 39 years, 40 to 64 years, or ≥65 years), race, ethnic group, duration of symptoms before randomization (measured as ≤10 days or >10 days, in quartiles, and as the median), site location, and presence of coexisting conditions.

RESULTS

PATIENTS

Of 1067 patients assessed for eligibility, 1033 underwent randomization; 515 were assigned to the combination group, and 518 to the control group (Fig. 1). The intention-to-treat population included 706 patients with moderate disease (ordinal score of 4 or 5 [not receiving ventilation]) and 327 with severe disease (ordinal score of 6 or 7 [receiving noninvasive or invasive ventilation]). Of those assigned to the combination group, 507 (98.4%) received treatment as assigned. Of those assigned to the control group, 509 (98.3%) received treatment as assigned. A total of 498 patients in the combination group and 495 in the control group completed the trial through day 29, recovered, or died. The mean age of the patients was 55.4 years, and 63.1% were male (Table 1). Overall, 48.0% of the patients were White, 15.1% were Black, 9.8% were Asian, and 1.0% were American Indian or Alaska Native; 51.4% were Hispanic or Latino (Table 1). The characteristics of the U.S. patients are shown in Table S4.

PRIMARY OUTCOME

Patients who received combination treatment with baricitinib plus remdesivir recovered a median of 1 day faster than patients who received remdesivir and placebo (median, 7 days vs. 8 days; rate ratio for recovery, 1.16; 95% confidence interval [CI], 1.01 to 1.32; P=0.03 by log-rank test

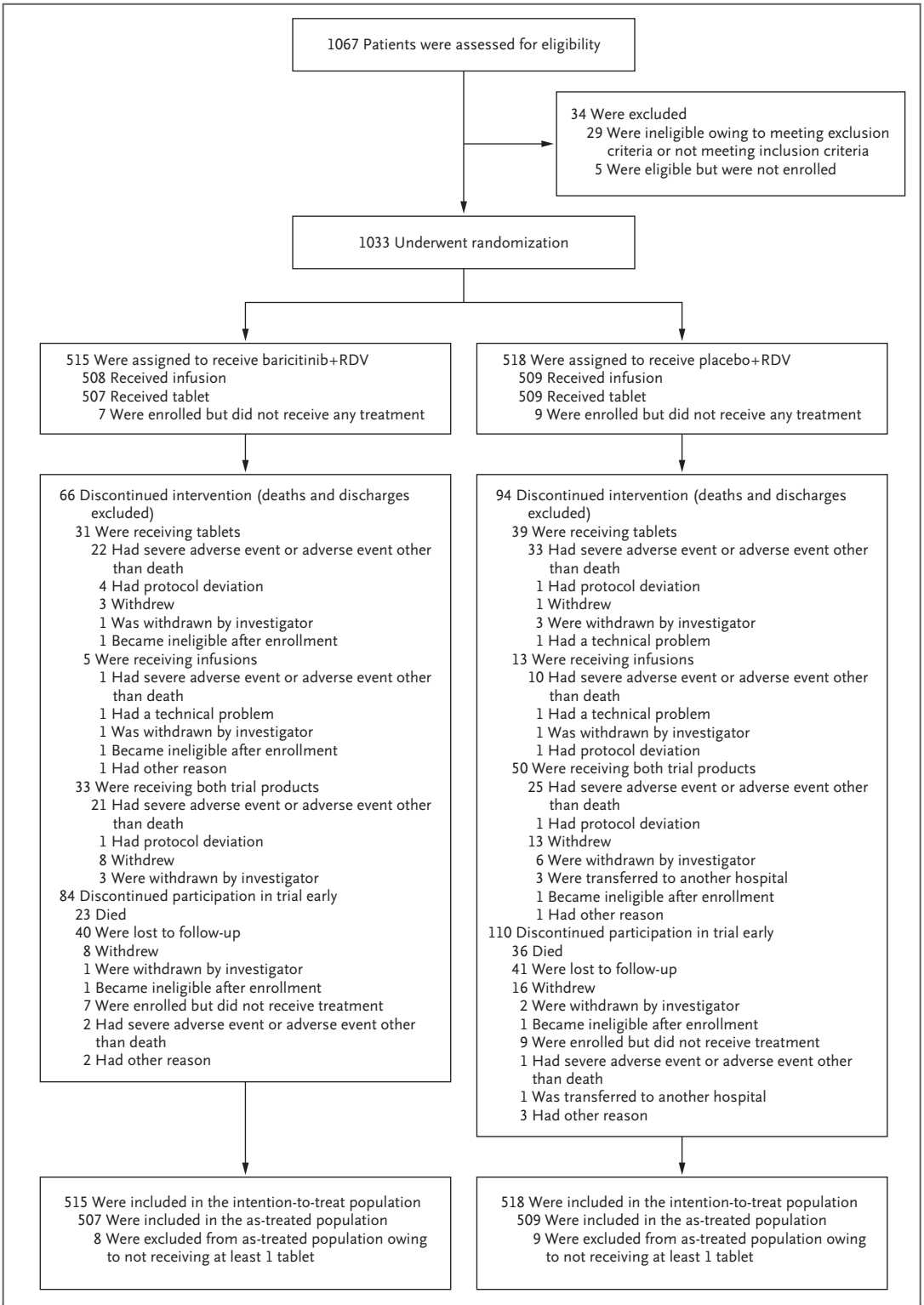

Figure 1. Enrollment and Randomization.

RDV denotes remdesivir.

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

Characteristic	All Patients (N=1033)	Baricitinib+RDV (N=515)	Placebo+RDV (N=518)
Age			
Mean — yr	55.4±15.7	55.0±15.4	55.8±16.0
Distribution — no. (%)			
<40 yr	173 (16.7)	87 (16.9)	86 (16.6)
40–64 yr	555 (53.7)	281 (54.6)	274 (52.9)
≥65 yr	305 (29.5)	147 (28.5)	158 (30.5)
Sex — no. (%)			
Female	381 (36.9)	196 (38.1)	185 (35.7)
Male	652 (63.1)	319 (61.9)	333 (64.3)
Race — no. (%)†			
Asian	101 (9.8)	49 (9.5)	52 (10.0)
Black	156 (15.1)	77 (15.0)	79 (15.3)
White	496 (48.0)	251 (48.7)	245 (47.3)
Other or unknown	280 (27.1)	138 (26.8)	142 (27.4)
Ethnic group — no. (%)†			
Hispanic or Latino	531 (51.4)	263 (51.1)	268 (51.7)
Not Hispanic or Latino	486 (47.0)	246 (47.8)	240 (46.3)
Not reported or unknown	16 (1.5)	6 (1.2)	10 (1.9)
Body-mass index‡	32.2±8.3	32.2±8.2	32.3±8.4
Median time (IQR) from symptom onset to randomization — days	8 (5–10)	8 (5–10)	8 (5–11)
Disease severity — no. (%)			
Moderate	706 (68.3)	358 (69.5)	348 (67.2)
Severe	327 (31.7)	157 (30.5)	170 (32.8)
Coexisting conditions — no./total no. (%)			
None	155/994 (15.6)	64/496 (12.9)	91/498 (18.3)
One	270/994 (27.2)	148/496 (29.8)	122/498 (24.5)
Two or more	569/994 (57.2)	284/496 (57.3)	285/498 (57.2)
Score on ordinal scale — no. (%)			
4. Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care (Covid-19–related or otherwise)	142 (13.7)	70 (13.6)	72 (13.9)
5. Hospitalized, requiring supplemental oxygen	564 (54.6)	288 (55.9)	276 (53.3)
6. Hospitalized, receiving noninvasive ventilation or high-flow oxygen devices	216 (20.9)	103 (20.0)	113 (21.8)
7. Hospitalized, receiving invasive mechanical ventilation or ECMO	111 (10.7)	54 (10.5)	57 (11.0)
Geographic region — no. (%)			
Asia	67 (6.5)	33 (6.4)	34 (6.6)
Europe	13 (1.3)	6 (1.2)	7 (1.4)
North America	953 (92.3)	476 (92.4)	477 (92.1)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. Covid-19 denotes coronavirus disease 2019, ECMO extracorporeal membrane oxygenation, IQR interquartile range, and RDV remdesivir.
† Race and ethnic group were reported by the patients. With respect to "other" race, the categories that were used when data on race were reported included American Indian or Alaska Native and Native Hawaiian or other Pacific Islander.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

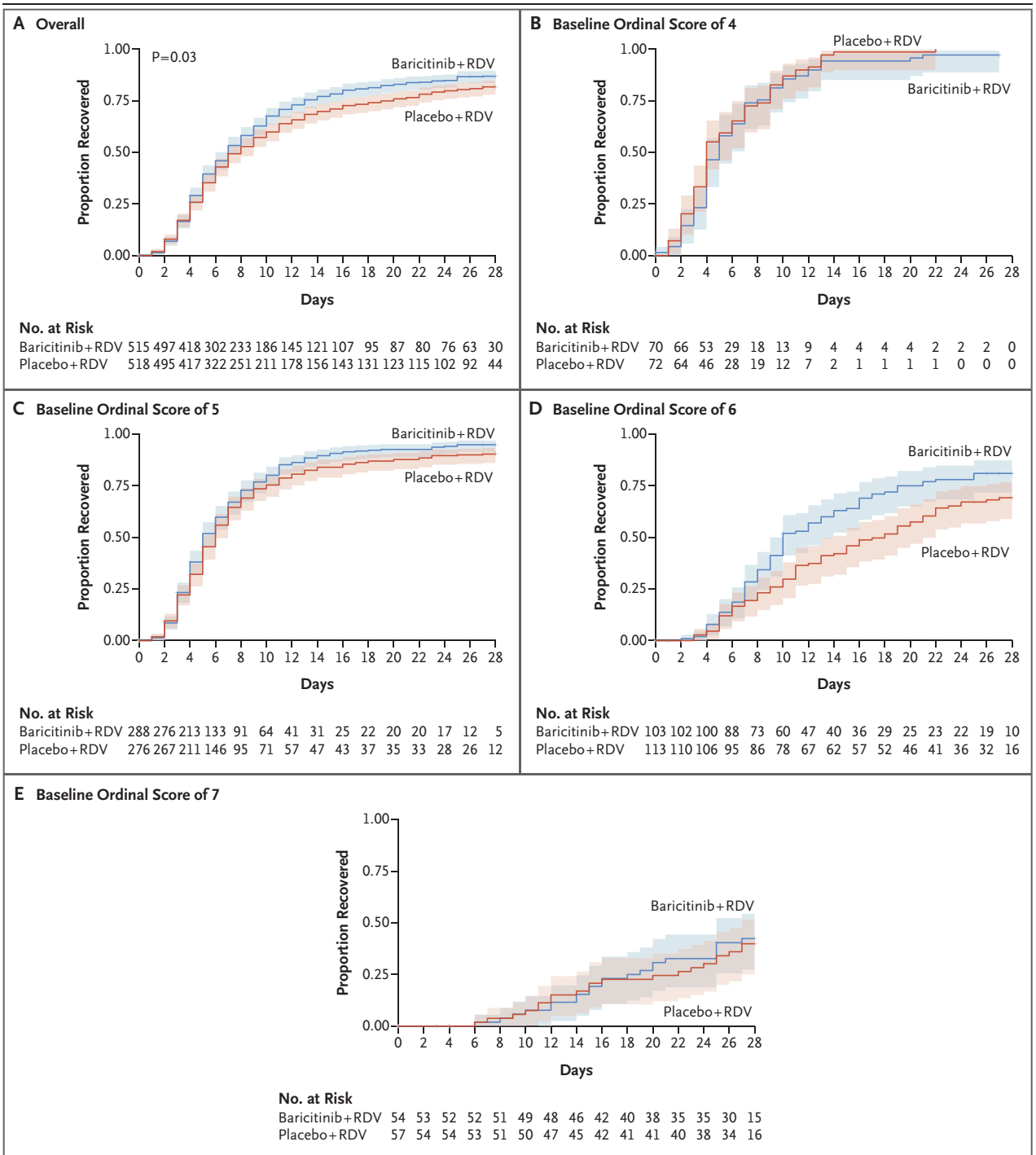

Figure 2. Kaplan–Meier Estimates of Cumulative Recoveries.

Cumulative recovery estimates are shown in the overall population (Panel A), in patients with a baseline score of 4 on the ordinal scale (not requiring oxygen; Panel B), in those with a baseline score of 5 (requiring oxygen; Panel C), in those with a baseline score of 6 (receiving high-flow oxygen or noninvasive mechanical ventilation; Panel D), and in those with a baseline score of 7 (receiving mechanical ventilation or extracorporeal membrane oxygenation [ECMO]; Panel E). Shaded areas indicate 95% confidence intervals.

stratified according to actual baseline severity) (Fig. 2 and Table 2). When analyzed according to the severity entered at the time of randomization (moderate vs. severe), the hazard ratio was 1.15 (95% CI, 1.00 to 1.31; P=0.047) (Table S6). The median time to recovery among patients receiving noninvasive ventilation or high-flow oxygen (baseline ordinal score of 6) was 10 days in the combination group and 18 days in the control group (rate ratio for recovery, 1.51; 95% CI, 1.10 to 2.08). Among patients with a baseline score of 4 (no oxygen) and 5 (supplemental oxygen), the rate ratio for recovery was 0.88 (95% CI, 0.63 to 1.23) and 1.17 (95% CI, 0.98 to 1.39), respectively. For those receiving mechanical ventilation or ECMO at enrollment (baseline ordinal score of 7), the rate ratio for recovery was 1.08 (95% CI, 0.59 to 1.97) (Table 2 and Fig. 3). The rate ratio for recovery among the 223 patients who received glucocorticoids for clinical indications during the trial was 1.06 (95% CI, 0.75 to 1.48). A sensitivity analysis with a random effect for hospital site yielded similar results (conditional random-effects estimate of rate ratio for recovery, 1.16; 95% CI, 1.01 to 1.33; restricted maximum likelihood–based random-effects estimate of variance, 0.0305) (Table S13).

KEY SECONDARY OUTCOME

The odds of improvement in clinical status at day 15 as assessed with the ordinal scale were greater in the combination group than in the control group (odds ratio for improvement, 1.3; 95% CI, 1.0 to 1.6). Patients with a baseline ordinal score of 6 who received combination treatment were most likely to have clinical improvement at day 15 (odds ratio, 2.2; 95% CI, 1.4 to 3.6) (Table 2 and Fig. S1).

MORTALITY

The Kaplan–Meier estimates of mortality at day 28 after randomization were 5.1% (95% CI, 3.5 to 7.6) in the combination group and 7.8% (95% CI, 5.7 to 10.6) in the control group (hazard ratio for death, 0.65; 95% CI, 0.39 to 1.09). The greatest numerical differences in mortality between patients in the combination group and those in the control group were observed among those with a baseline ordinal score of 5 (1.9% vs. 4.7%; hazard ratio, 0.40; 95% CI, 0.14 to 1.14) or 6 (7.5% vs. 12.9%; hazard ratio, 0.55; 95% CI, 0.22 to 1.38). The Kaplan–Meier estimates of mortality at 14 days after randomization were 1.6% in the combination group and 3.0% in the control group (hazard ratio, 0.54; 95% CI, 0.23 to 1.28) (Table 2 and Fig. S2).

ADDITIONAL SECONDARY OUTCOMES

The median time to an improvement by one category on the ordinal scale was 6 days in the combination group and 8 days in the control group (rate ratio, 1.21; 95% CI, 1.06 to 1.39), and the median time to discharge or a National Early Warning Score of 2 or less for 24 hours was 6 days and 7 days in the respective groups (rate ratio, 1.24; 95% CI, 1.07 to 1.44) (Table 3). The incidence of new use of oxygen was lower in the combination group than in the control group (22.9% vs. 40.3%; difference, –17.4 percentage points; 95% CI, –31.6 to –2.1), as was the incidence of new use of mechanical ventilation or ECMO (10.0% vs. 15.2%; difference, –5.2 percentage points; 95% CI, –9.5 to –0.9). The median number of days of receipt of mechanical ventilation or ECMO among the 128 patients in whom these interventions were started after enrollment or who died with no observed new use was 16 days in the combination group and 27 days in the control group (difference, –11.0; 95% CI, –18.3 to –3.7). The incidence of progression to death or noninvasive or invasive ventilation was lower in the combination group than in the control group (22.5% vs. 28.4%; rate ratio, 0.77; 95% CI, 0.60 to 0.98), as was the incidence of progression to death or invasive ventilation (12.2% vs. 17.2%; rate ratio, 0.69; 95% CI, 0.50 to 0.95).

SAFETY OUTCOMES

Grade 3 or 4 adverse events occurred in 207 patients (40.7%) in the combination group and 238 (46.8%) in the control group (Table S11). A total of 25 grade 3 or 4 adverse events were judged by the principal investigators to be related to combination treatment and 28 to control (Table S10). The most common grade 3 or 4 adverse events occurring in at least 5% of all patients were hyperglycemia, anemia, decreased lymphocyte count, and acute kidney injury (Table S10). The incidence of these adverse events was similar in the two treatment groups. The percentage of patients who were reported to have a serious or nonseri-

Table 2. Outcomes Overall and According to Score on the Ordinal Scale in the Intention-to-Treat Population.*

Outcome	Overall		Ordinal Score at Baseline							
			4		5		6		7	
	Baricitinib (N=515)	Placebo (N=518)	Baricitinib (N=70)	Placebo (N=72)	Baricitinib (N=288)	Placebo (N=276)	Baricitinib (N=103)	Placebo (N=113)	Baricitinib (N=54)	Placebo (N=57)
Recovery										
No. of recoveries	433	406	67	69	262	243	82	73	22	21
Median time to recovery (95% CI) — days	7 (6–8)	8 (7–9)	5 (4–6)	4 (4–6)	5 (5–6)	6 (5–6)	10 (9–13)	18 (13–21)	NE (25–NE)	NE (26–NE)
Rate ratio (95% CI)†	1.16 (1.01–1.32 [P=0.03])		0.88 (0.63–1.23)		1.17 (0.98–1.39)		1.51 (1.10–2.08)		1.08 (0.59–1.97)	
Mortality over first 14 days‡										
Hazard ratio (95% CI) for data through day 14	0.54 (0.23–1.28)		NE		0.73 (0.16–3.26)		0.21 (0.02–1.80)		0.69 (0.19–2.44)	
No. of deaths by day 14	8	15	0	0	3	4	1	5	4	6
Kaplan–Meier estimate of mortality by day 14 — % (95% CI)	1.6 (0.8–3.2)	3.0 (1.8–5.0)	0 (NE–NE)	0 (NE–NE)	1.1 (0.4–3.4)	1.5 (0.6–3.9)	1.0 (0.1–6.7)	4.6 (2.0–10.8)	7.6 (2.9–19.1)	11.3 (5.3–23.5)
Mortality over entire trial period‡										
Hazard ratio (95% CI)	0.65 (0.39–1.09)		NE		0.40 (0.14–1.14)		0.55 (0.22–1.38)		1.00 (0.45–2.22)	
No. of deaths by day 28	24	37	0	0	5	12	7	13	12	12
Kaplan–Meier estimate of mortality by day 28 — % (95% CI)	5.1 (3.5–7.6)	7.8 (5.7–10.6)	0 (NE–NE)	0 (NE–NE)	1.9 (0.8–4.4)	4.7 (2.7–8.1)	7.5 (3.6–15.2)	12.9 (7.7–21.3)	23.1 (13.8–37.1)	22.6 (13.5–36.4)
Ordinal score at day 15 (±2 days) — no. (%)§										
1	177 (34.4)	165 (31.9)	33 (47.1)	44 (61.1)	114 (39.6)	101 (36.6)	27 (26.2)	17 (15.0)	3 (5.6)	3 (5.3)
2	177 (34.4)	163 (31.5)	25 (35.7)	20 (27.8)	120 (41.7)	115 (41.7)	30 (29.1)	24 (21.2)	2 (3.7)	4 (7.0)
3	8 (1.6)	3 (0.6)	5 (7.1)	2 (2.8)	2 (0.7)	1 (0.4)	0	0	1 (1.9)	0
4	31 (6.0)	18 (3.5)	7 (10.0)	6 (8.3)	14 (4.9)	7 (2.5)	7 (6.8)	3 (2.7)	3 (5.6)	2 (3.5)
5	43 (8.3)	50 (9.7)	0	0	18 (6.2)	27 (9.8)	15 (14.6)	20 (17.7)	10 (18.5)	3 (5.3)
6	20 (3.9)	19 (3.7)	0	0	9 (3.1)	1 (0.4)	7 (6.8)	16 (14.2)	4 (7.4)	2 (3.5)
7	48 (9.3)	83 (16.0)	0	0	8 (2.8)	19 (6.9)	15 (14.6)	28 (24.8)	25 (46.3)	36 (63.2)
8	11 (2.1)	17 (3.3)	0	0	3 (1.0)	5 (1.8)	2 (1.9)	5 (4.4)	6 (11.1)	7 (12.3)
Odds ratio (95% CI)	1.3 (1.0–1.6)		0.6 (0.3–1.1)		1.2 (0.9–1.6)		2.2 (1.4–3.6)		1.7 (0.8–3.4)	

* Patients in both groups received RDV in addition to either baricitinib or placebo. Neither the P value nor any confidence intervals have not been adjusted for multiple comparisons. Percentages may not total 100 because of rounding. NE denotes not possible to estimate.

† Rate ratios for recovery and hazard ratios were calculated from the stratified Cox model. The P value for the primary outcome was calculated with the stratified log-rank test (overall model stratified according to actual disease severity). Rate ratios for recovery greater than 1 indicate a benefit with baricitinib plus RDV; hazard ratios less than 1 indicate a benefit with baricitinib plus RDV.

‡ Mortality over the first 14 days includes data from all patients who were still alive through 14 days after enrollment, with data censored on day 14, as if 14 days was the maximum follow-up time. Mortality over the entire trial period uses the totality of the trial data and censors data from patients who completed follow-up alive at 28 days after enrollment.

§ The ordinal score at day 15 (±2-day visit window) is the patient's worst score on the ordinal scale during the previous day. Scores on the ordinal scale are as follows: 1, not hospitalized, no limitations of activities; 2, not hospitalized, limitation of activities, home oxygen requirement, or both; 3, hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection-control reasons); 4, hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (Covid-19–related or other medical conditions); 5, hospitalized, requiring any supplemental oxygen; 6, hospitalized, receiving noninvasive ventilation or use of high-flow oxygen devices; 7, hospitalized, receiving invasive mechanical ventilation or ECMO; and 8, death. Five deaths (three in patients receiving baricitinib plus RDV and two in patients receiving placebo plus RDV) occurred within the day 15 visit window but after 14 days — these deaths are included in the outcome of the ordinal score at day 15 but not in the outcome of mortality over the first 14 days. Odds ratios were calculated with the use of a proportional odds model (overall model adjusted for actual disease severity). Odds ratios greater than 1 indicate a benefit with baricitinib plus RDV.

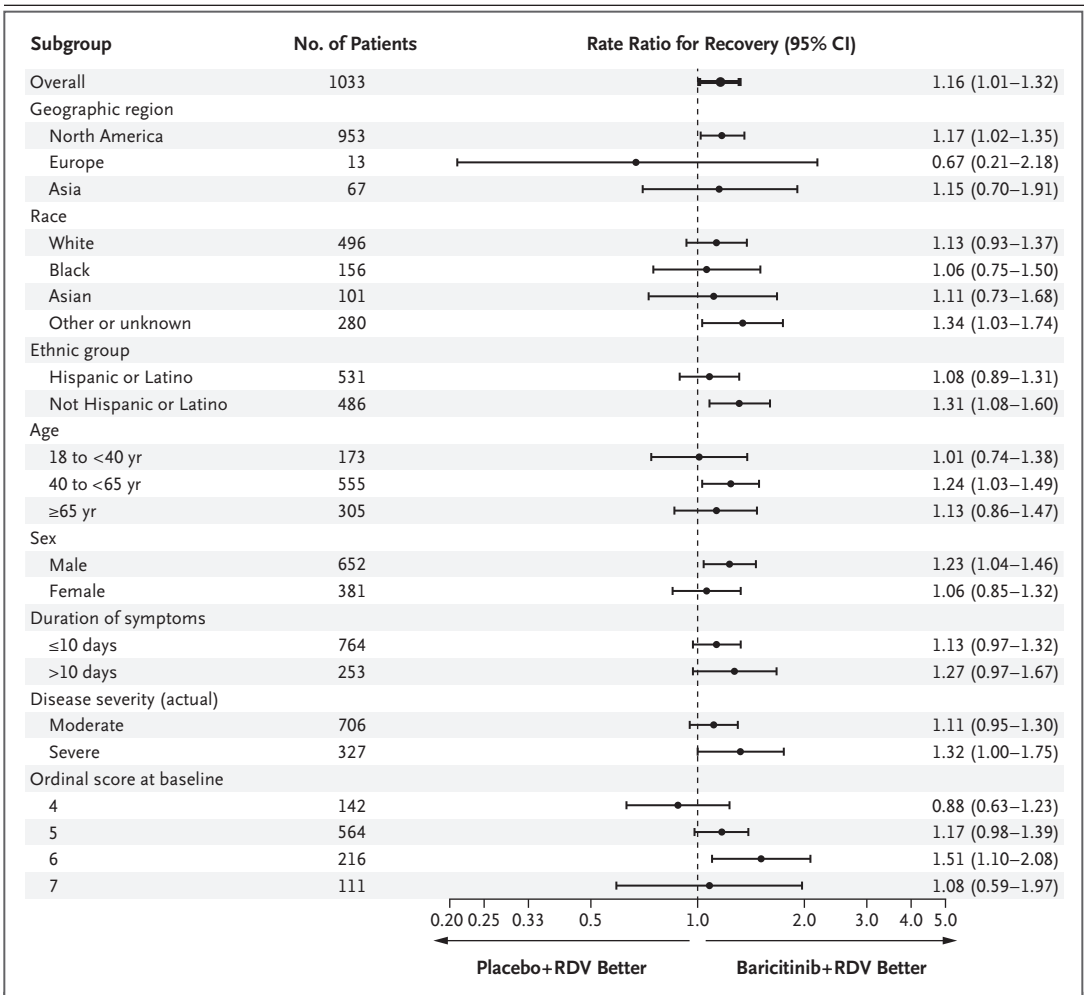

Figure 3. Time to Recovery According to Subgroup.

The widths of the confidence intervals have not been adjusted for multiplicity and therefore cannot be used to infer treatment effects. Race and ethnic group were reported by the patients. With respect to "other" race, the categories that were used when data on race were reported included American Indian or Alaska Native and Native Hawaiian or other Pacific Islander.

ous adverse event of venous thromboembolism was similar in the combination group and the control group (21 patients [4.1%] and 16 patients [3.1%], respectively; difference, 1.0 percentage points; 95% CI, –1.3 to 3.3).

Serious adverse events occurred in 81 patients (16.0%) in the combination group, and six of these events were thought to be related to the trial product (Table S7). Serious adverse events occurred in 107 patients (21.0%) in the control group, and five of these events were thought to be related to the trial product. The between-group difference was –5.0 percentage points (95% CI, –9.8 to –0.3; P=0.03). The incidences of all serious adverse events, all adverse events, serious adverse events with fatal outcome, and adverse events leading to discontinuation of the trial product were each lower in the combination group than in the control group. Overall, the incidence of serious or nonserious adverse events of new infection was lower in the combination group (30 patients [5.9%]) than in the control group (57 patients [11.2%]) (difference, –5.3 percentage points; 95% CI, –8.7 to –1.9; P=0.003). Patients who received glucocorticoids after randomization had a higher incidence of serious or nonserious new infection than those who did not (56 of 223 patients [25.1%] vs. 44 of 793 patients [5.5%]).

Table 3. Additional Secondary Outcomes.

Outcome	Baricitinib+RDV	Placebo+RDV	Rate Ratio (95% CI)
Median time to event (95% CI) — days			
Improvement by one category on ordinal scale	6.0 (5.0 to 7.0)	8.0 (7.0 to 9.0)	1.21 (1.06 to 1.39)
Improvement by two categories on ordinal scale	12.0 (12.0 to 13.0)	13.0 (NE)	1.20 (1.05 to 1.38)
Discharge or National Early Warning Score ≤2 for 24 hr*	6.0 (6.0 to 7.0)	7.0 (6.0 to 9.0)	1.24 (1.07 to 1.44)
Death or progression to noninvasive or invasive mechanical ventilation	NE	NE	0.77 (0.60 to 0.98)
Death or progression to invasive mechanical ventilation	NE	NE	0.69 (0.50 to 0.95)
New use of oxygen	NE	NE (3.0 to NE)	0.53 (0.29 to 0.98)
New use of invasive mechanical ventilation or ECMO	NE	NE	0.64 (0.44 to 0.93)
Use of noninvasive ventilation or high-flow oxygen	NE	NE	0.82 (0.60 to 1.13)
			Difference (95% CI)
Hospitalization			
Median duration of initial hospitalization (IQR) — days			
With imputation of data for those who died†	8 (5 to 15)	8 (5 to 20)	0.0 (–1.1 to 1.1)
Among those who did not die	8 (5 to 13)	8 (5 to 15)	0.0 (–1.0 to 1.0)
Patients rehospitalized — % (95% CI)	3 (2 to 5)	2 (1 to 4)	1.0 (–1.1 to 3.1)‡
Oxygen			
Median days receiving oxygen if receiving oxygen at baseline (IQR)			
With imputation of data for those who died†	10 (4 to 27)	12 (4 to 28)	–2.0 (–5.2 to 1.2)
Among those who did not die	9 (4 to 23)	10 (4 to 28)	–1.0 (–3.5 to 1.5)
New use of oxygen during trial			
No. of patients/total no.	16/70	29/72	
Percent of patients (95% CI)	23 (15 to 34)	40 (30 to 52)	–17.4 (–31.6 to –2.1)‡
Median days receiving oxygen (IQR)	3 (2 to 4)	3 (2 to 6)	0.0 (–2.2 to 2.2)
Noninvasive ventilation or high-flow oxygen			
Median days of noninvasive ventilation or high-flow oxygen use during trial if receiving these interventions at baseline (IQR)			
With imputation of data for those who died†	4 (3 to 9)	5 (2 to 12)	–1.0 (–2.9 to 0.9)
Among those who did not die	4 (3 to 6)	4 (2 to 9)	0.0 (–1.7 to 1.7)
New use of noninvasive ventilation or high-flow oxygen during trial			
No. of patients/total no.	70/358	82/348	
Percent of patients (95% CI)	20 (16 to 24)	24 (19 to 28)	–4.0 (–10.1 to 2.1)‡
Median days of use during trial (IQR)	6 (3 to 13)	4 (2 to 11)	2.0 (–0.4 to 4.4)
Mechanical ventilation or ECMO			
Median days of mechanical ventilation or ECMO during trial if receiving these interventions at baseline (IQR)			
With imputation of data for those who died†	20 (9 to 28)	25 (11 to 28)	–5.0 (–12.9 to 2.9)
Among those who did not die	13 (7 to 24)	16 (6 to 28)	–2.0 (–11.4 to 7.4)
New use of mechanical ventilation or ECMO during trial			
No. of patients/total no.	46/461	70/461	
Percent of patients (95% CI)	10 (8 to 13)	15 (12 to 19)	–5.2 (–9.5 to –0.9)‡
Median days of use during trial§	16 (7 to 28)	27 (12 to 28)	–11.0 (–18.3 to –3.7)

* The National Early Warning Score includes six physiological measures; total scores range from 0 to 20, with higher scores indicating greater clinical risk. Only patients with a score of more than 2 at baseline were included in this analysis.
† The value for patients who died was imputed as 28 days.
‡ Differences between percentages are given in percentage points.
§ This analysis includes imputation of data for patients who died with no observed new use. A total of 12 patients died without progression to ECMO. All the patients who died had other oxygen use.

DISCUSSION

The results of this randomized, double-blind, placebo-controlled trial show that combination treatment with the antiinflammatory drug baricitinib and the antiviral drug remdesivir was safe and superior to remdesivir alone for the treatment of hospitalized patients with Covid-19 pneumonia. The beneficial effects of the combination treatment were seen both in the primary outcome, with a 1-day shorter time to recovery, and in the key secondary outcome, with a greater improvement in clinical status as assessed on the ordinal scale. Although ACTT-2 was not powered to detect a difference in mortality between the two groups, both the survival rate and the time-to-death analyses favored combination treatment. These clinical benefits were observed across different age groups, sexes, ethnic groups, and races and were independent of symptom duration or disease severity at enrollment. The large proportion of Hispanic or Latino patients who were enrolled in the trial reflects the disproportionate effect of the pandemic on racial and ethnic minorities with respect to high incidences of hospitalization.[14]

The observed benefit of combination treatment was most evident in patients with a baseline ordinal score of 5 (supplemental oxygen) or 6 (high-flow oxygen or noninvasive ventilation), among whom the median time to recovery was, respectively, 1 and 8 days sooner with combination treatment than with placebo. Patients with a baseline ordinal score of 6 who received combination treatment were twice as likely as those in the control group to have improved clinical status at day 15 (odds ratio, 2.2; 95% CI, 1.4 to 3.6). The faster recovery in patients who received baricitinib plus remdesivir suggests that the combination treatment may have an effect in lowering the hospital-associated risk of nosocomial infections, thrombosis, and errors in hospital drug administration. Moreover, faster recovery also decreases the burden on the health care system, potentially increasing capacity, which is of critical importance during a surge of cases.

In addition, the combination treatment showed clinical benefits directly relevant to patient care, such as a difference of –17.4 percentage points in new use of oxygen (22.9% vs. 40.3%) and a difference of –5.2 percentage points in new use of mechanical ventilation or ECMO (10.0% vs. 15.2%). In fact, the odds of progression to death or invasive ventilation were 31% lower in the combination group than in the control group (hazard ratio, 0.69; 95% CI, 0.50 to 0.95), and patients in the combination group had 11 fewer days receiving new mechanical ventilation than those in the control group.

Despite concerns about immunosuppression, secondary infections, and thrombosis with use of JAK inhibitors, the addition of baricitinib was not associated with a significantly higher incidence of adverse events or thromboembolic events. In fact, patients receiving baricitinib plus remdesivir had a significantly lower incidence of adverse events, adverse events leading to discontinuation of the trial drug, serious adverse events, serious adverse events with a fatal outcome, and infection-related adverse events than patients who received remdesivir alone. The consistently lower incidence of adverse events with baricitinib may be related to its action in reducing inflammatory-mediated lung injury and improving lymphocyte counts, its antiviral properties, or its associated shorter recovery time and faster clinical improvement, all of which could have reduced the risk of nosocomial infection. Another ongoing trial may provide more information regarding the effects of baricitinib (ClinicalTrials.gov number, NCT04421027). In summary, our results and the characteristics of baricitinib, including the fact that it is an oral drug with few drug–drug interactions and a good safety profile, lend itself to use in low-to-middle-income countries.

The Randomized Evaluation of Covid-19 Therapy (RECOVERY) trial evaluated dexamethasone in patients with Covid-19[15] and showed a significant benefit in survival, most pronounced in patients receiving mechanical ventilation, and a 1-day shorter hospital stay. Baricitinib and dexamethasone have important biologic differences, and ACTT-2 and the RECOVERY trial have design differences. Dexamethasone has a long half-life, acts on glucocorticoid receptors, and reduces inflammation through a broad-pathway approach that has been associated with immunosuppression, hospital-acquired infections, gastrointestinal bleeding, hyperglycemia, and neuromuscular weakness, even with short courses.[16] Baricitinib has a short half-life, acts on targeted critical pathways to reduce inflammation while

minimizing biologic redundancy with less immunosuppression, and may have antiviral activity.[3] The two trials had different designs and cannot be compared directly. The high mortality in the control group of the RECOVERY trial and the low mortality in the control group of ACTT-2 suggest that these trials might not be generalizable to the same patient population. Only a randomized, double-blind, placebo-controlled, head-to-head comparison of baricitinib plus remdesivir with dexamethasone plus remdesivir will allow the efficacy and safety differences between these two approaches to be fully understood.

Baricitinib plus remdesivir was superior to remdesivir alone in reducing recovery time and accelerating improvement in clinical status, notably among patients receiving high-flow oxygen or noninvasive mechanical ventilation. The combination was associated with fewer serious adverse events.

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APPENDIX

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