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Baricitinib versus dexamethasone for adults hospitalised with COVID-19 (ACTT-4): a randomised, double-blind, double placebo-controlled trial

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Summary

Background Baricitinib and dexamethasone have randomised trials supporting their use for the treatment of patients with COVID-19. We assessed the combination of baricitinib plus remdesivir versus dexamethasone plus remdesivir in preventing progression to mechanical ventilation or death in hospitalised patients with COVID-19.

Methods In this randomised, double-blind, double placebo-controlled trial, patients were enrolled at 67 trial sites in the USA (60 sites), South Korea (two sites), Mexico (two sites), Singapore (two sites), and Japan (one site). Hospitalised adults (≥18 years) with COVID-19 who required supplemental oxygen administered by low-flow (≤15 L/min), high-flow (>15 L/min), or non-invasive mechanical ventilation modalities who met the study eligibility criteria (male or non-pregnant female adults ≥18 years old with laboratory-confirmed SARS-CoV-2 infection) were enrolled in the study. Patients were randomly assigned (1:1) to receive either baricitinib, remdesivir, and placebo, or dexamethasone, remdesivir, and placebo using a permuted block design. Randomisation was stratified by study site and baseline ordinal score at enrolment. All patients received remdesivir (≤10 days) and either baricitinib (or matching oral placebo) for a maximum of 14 days or dexamethasone (or matching intravenous placebo) for a maximum of 10 days. The primary outcome was the difference in mechanical ventilation-free survival by day 29 between the two treatment groups in the modified intention-to-treat population. Safety analyses were done in the as-treated population, comprising all participants who received one dose of the study drug. The trial is registered with ClinicalTrials.gov, NCT04640168.

Findings Between Dec 1, 2020, and April 13, 2021, 1047 patients were assessed for eligibility. 1010 patients were enrolled and randomly assigned, 516 (51%) to baricitinib plus remdesivir plus placebo and 494 (49%) to dexamethasone plus remdesivir plus placebo. The mean age of the patients was 58·3 years (SD 14·0) and 590 (58%) of 1010 patients were male. 588 (58%) of 1010 patients were White, 188 (19%) were Black, 70 (7%) were Asian, and 18 (2%) were American Indian or Alaska Native. 347 (34%) of 1010 patients were Hispanic or Latino. Mechanical ventilation-free survival by day 29 was similar between the study groups (Kaplan-Meier estimates of 87·0% [95% CI 83·7 to 89·6] in the baricitinib plus remdesivir plus placebo group and 87·6% [84·2 to 90·3] in the dexamethasone plus remdesivir plus placebo group; risk difference 0·6 [95% CI −3·6 to 4·8]; p=0·91). The odds ratio for improved status in the dexamethasone plus remdesivir plus placebo group compared with the baricitinib plus remdesivir plus placebo group was 1·01 (95% CI 0·80 to 1·27). At least one adverse event occurred in 149 (30%) of 503 patients in the baricitinib plus remdesivir plus placebo group and 179 (37%) of 482 patients in the dexamethasone plus remdesivir plus placebo group (risk difference 7·5% [1·6 to 13·3]; p=0·014). 21 (4%) of 503 patients in the baricitinib plus remdesivir plus placebo group had at least one treatment-related adverse event versus 49 (10%) of 482 patients in the dexamethasone plus remdesivir plus placebo group (risk difference 6·0% [2·8 to 9·3]; p=0·00041). Severe or life-threatening grade 3 or 4 adverse events occurred in 143 (28%) of 503 patients in the baricitinib plus remdesivir plus placebo group and 174 (36%) of 482 patients in the dexamethasone plus remdesivir plus placebo group (risk difference 7·7% [1·8 to 13·4]; p=0·012).

Interpretation In hospitalised patients with COVID-19 requiring supplemental oxygen by low-flow, high-flow, or non-invasive ventilation, baricitinib plus remdesivir and dexamethasone plus remdesivir resulted in similar mechanical ventilation-free survival by day 29, but dexamethasone was associated with significantly more adverse events, treatment-related adverse events, and severe or life-threatening adverse events. A more individually tailored choice of immunomodulation now appears possible, where side-effect profile, ease of administration, cost, and patient comorbidities can all be considered.

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Introduction

The disease course of patients hospitalised with severe COVID-19 is notable for a dysregulated inflammatory response, which can culminate in progressive respiratory failure and death.[1] Use of immunomodulatory agents such as baricitinib[2] and dexamethasone[3] has been shown to improve outcomes in the treatment of hospitalised patients with COVID-19.

In a double-blind, placebo-controlled, randomised trial, baricitinib, a selective Janus kinase (JAK)1/2 inhibitor, shortened the time to recovery and reduced progression to mechanical ventilation or death compared with placebo plus remdesivir.[2] A second double-blind, randomised trial of baricitinib versus placebo in hospitalised patients with COVID-19 showed a significant reduction in mortality with baricitinib compared with placebo.[4] In an open-label, randomised trial, dexamethasone decreased the mortality rate in hospitalised patients on oxygen and mechanical ventilation compared with the standard of care.[3] These three trials supported the use of baricitinib and dexamethasone, but were different in terms of their study population, baseline characteristics, mortality rates, and safety assessments. Consequently, direct comparisons to ascertain the relative value of each drug in patients with COVID-19 were not possible.

ACTT-4 was a randomised trial of immunomodulation as treatment for hospitalised adults with COVID-19 who required supplemental oxygen by low-flow, high-flow, or non-invasive ventilation to compare baricitinib in combination with remdesivir versus dexamethasone with remdesivir at preventing progression to mechanical ventilation or death.

Methods

Study design and participants

In this randomised, double-blind, double placebo-controlled trial, patients were enrolled at 67 trial sites in the USA (60 sites), South Korea (two sites), Mexico (two sites), Singapore (two sites), and Japan (one site). Hospitalised adults (≥18 years) with COVID-19 who required supplemental oxygen administered by low-flow (≤15 L/min), high-flow (>15 L/min), or non-invasive mechanical ventilation modalities who met the study eligibility criteria were enrolled in the study. Full inclusion criteria are listed in the appendix (p 19).

The trial protocol was approved by the institutional review board at each site (or a centralised institutional review board as applicable). Informed consent was obtained from each patient or from the patient's legally authorised representative if the patient was unable to provide consent. Full details of the trial design, conduct, oversight, and analyses were made public on Oct 23, 2020, and can be found in the protocol and statistical analysis plan.

Randomisation and masking

Patients were randomly assigned (1:1) to receive either baricitinib, remdesivir, and placebo or dexamethasone, remdesivir, and placebo using a permuted block design. The treatment allocation table was generated using SAS version 9.4. Randomisation was stratified by study site and baseline ordinal score at enrolment.

An independent unmasked statistical group generated the treatment sequence and was not involved with operation of the trial other than reporting unblinded

Research in context

Evidence before this study

Previous studies have shown improved outcomes from baricitinib or dexamethasone in hospitalised patients with COVID-19. We searched PubMed using the terms "baricitinib", "dexamethasone", "COVID-19", "SARS-CoV-2", "treatment", and "trials" for articles published in English between database inception and Dec 21, 2021. In patients hospitalised with COVID-19, our search identified one randomised placebo-controlled trial of baricitinib 4 mg (ACTT-2) and one randomised open-label trial of dexamethasone 6 mg (RECOVERY). Compared with placebo, baricitinib accelerated clinical recovery of patients with COVID-19 and prevented progression to invasive mechanical ventilation or death. Compared with usual care, dexamethasone reduced death in patients hospitalised with COVID-19.

Added value of the study

To our knowledge, this is the first double placebo-controlled, double-blind, randomised head-to-head trial comparing different immunomodulator therapies—baricitinib versus dexamethasone—both in combination with remdesivir, for efficacy and clinically impactful safety events in adults hospitalised with COVID-19.

Implications of all the available evidence

We showed that baricitinib and dexamethasone have similar efficacy in preventing progression to invasive mechanical ventilation or death, but dexamethasone causes significantly more drug-related adverse events. The number needed to harm for one additional severe or life-threatening adverse event with dexamethasone is 12·5. A more tailored treatment approach can now be used based on patients' individual risks for immunomodulatory-related side-effects.

information to the data and safety monitoring board (DSMB). All treatment assignments were stored in a secure area of a server with restricted access.

Only the unmasked group at the Emmes company (Rockville, MA, USA; the statistical and data coordinating centre) and the site unmasked pharmacist were aware of treatment assignment. All other trial staff and participants were masked. Tablets and intravenous injections had identical appearance. Remdesivir was given to all participants so no masking was necessary.

Procedures

All enrolled patients received remdesivir intravenously as a 200-mg loading dose and 100-mg maintenance dose administered daily for up to 10 days or until hospital discharge or death. A 4-mg daily dose of baricitinib (or placebo) was administered orally or by nasogastric tube for up to 14 days or until hospital discharge or death; the dose was reduced for patients with an estimated glomerular filtration rate less than 60 mL/min. A 6-mg daily dose of dexamethasone (or placebo) was administered intravenously for up to 10 days or until hospital discharge or death. All patients received standard supportive care from the trial site hospital. Venous thromboembolism prophylaxis was recommended unless there was a contraindication. Concomitant use of experimental treatment or off-label use of marketed medications intended as treatment for COVID-19 was prohibited unless specified in the local hospital policy or National Institutes of Health COVID-19 treatment guidelines. More than one dose of 6-mg of dexamethasone (or equivalent steroid) given before enrolment was prohibited. Off-study baricitinib, dexamethasone, and other glucocorticoids during the study were prohibited unless patient clinical status worsened to require invasive mechanical ventilation. In addition, if oral study product was held for more than 2 days and the clinical condition required an open-label (off-study) anti-inflammatory agent, including dexamethasone, it could be given while the oral study product was held. Mineralocorticoids for standard indications such as adrenal insufficiency and shock were allowed as was low-dose prednisone administered as part of an immunosuppression regimen for underlying medical conditions such as solid-organ transplant.

All patients were evaluated daily during hospitalisation from day 1 up to day 29. After hospital discharge, patients had study visits at days 15, 22, 29, and 60. Patients' clinical status was captured daily while hospitalised using an eight-category ordinal scale, defined as follows: not hospitalised and no limitations of activities; not hospitalised, with limitation of activities, home oxygen requirement, or both; hospitalised, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalisation was extended for infection control or other non-medical reasons); hospitalised, not requiring supplemental oxygen but requiring ongoing medical care (related to COVID-19 or other medical conditions); hospitalised, requiring any supplemental oxygen; hospitalised, requiring non-invasive ventilation or use of high-flow oxygen devices; hospitalised, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); and death. The ordinal scale was also used to access clinical status at all the follow-up visits. Blood samples for safety laboratory tests (white blood cell count with differential, haemoglobin, platelet count, creatinine, glucose, total bilirubin, alanine aminotransferase, aspartate aminotransferase, and international normalised ratio), oropharyngeal swab samples (nasopharyngeal swab samples could be substituted), and serum for exploratory and secondary research were collected on days 1 (before initial dosing), 3, 5, 8, and 11 while hospitalised, and on days 15 and 29 for participants who were able to attend an in-person visit or who remained hospitalised. Blood plasma for cytokines, inflammatory markers, and SARS-CoV-2 PCR testing were collected on the same schedule except for day 15 (see the full description of procedures in the appendix p 20).

Outcomes

The primary outcome was the difference in mechanical ventilation-free survival by day 29 between the two treatment groups in the modified intention-to-treat population. Outcomes were assessed locally at each trial site using standard definitions contained in the study protocol. An endpoint review committee further reviewed the data in a masked fashion.

The key secondary outcome measure was clinical status at day 15, based on an eight-category ordinal scale.[5] Other secondary outcomes were the proportion of patients not progressing to ordinal score 6, 7, or 8 at any time by day 29; 14-day, 29-day, and 60-day mortality; time to recovery by day 29 (defined as the first day the patient reached an ordinal score of 1, 2, or 3); time to improvement by one or two categories from baseline ordinal score; clinical status using the ordinal scale at days 3, 5, 8, 11, 15, 22, and 29; desirability of outcome ranking (DOOR) at day 15 and day 29 (appendix p 33);[6] days of supplemental oxygen, non-invasive ventilation, or high-flow oxygen, and invasive ventilation or ECMO up to day 29; incidence and duration of non-invasive ventilation or high-flow oxygen and invasive ventilation or ECMO; and duration of hospitalisation up to day 29.

Secondary safety outcome measures included grade 3 and 4 adverse events and serious adverse events that occurred up to day 29; discontinuation or temporary suspension of study product for any reason; and changes in assessed laboratory values over time. Adverse events were graded using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events version 2.1 (July, 2017), coded in accordance with the Medical Dictionary for Regulatory Activities

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See **Online** for appendix

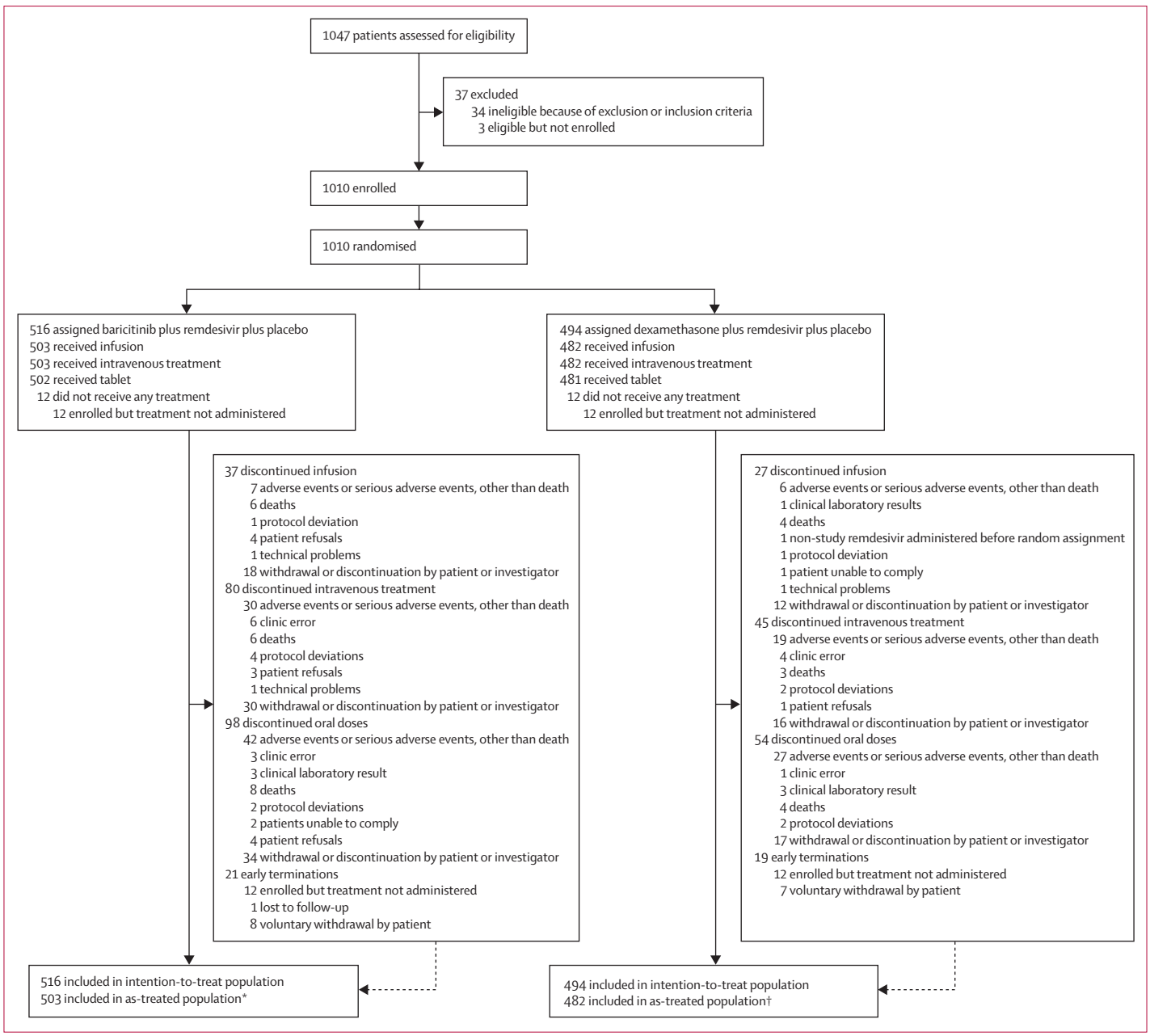

Figure 1: **Trial profile**
*13 patients excluded from as-treated population as they did not receive at least one dose of baricitinib plus remdesivir plus placebo. †12 patients excluded from as-treated population as they did not receive at least one dose of dexamethasone plus remdesivir plus placebo.

(version 23.0), and their relationship to study product, severity, and outcome were documented.

Statistical analysis

The target sample size to achieve 80% power was 1382 subjects (1500 after assuming 8% loss to follow-up) and was calculated using estimates for the per-arm proportions surviving without requiring invasive mechanical ventilation by day 29. Power was calculated using an exact score test assuming the power using Kaplan-Meier estimates with Greenwood's formula would have equal or greater power.

The primary analysis was a test of the difference in 28-day probability of mechanical ventilation-free survival using the Kaplan-Meier estimator with Greenwood's variance formula in the modified intention-to-treat population. Patients in the intention-to-treat population were classified by their random treatment assignment

	Baricitinib plus remdesivir plus placebo (n=516)	Dexamethasone plus remdesivir plus placebo (n=494)
Sex		
Male	300 (58%)	290 (59%)
Female	216 (42%)	204 (41%)
Ethnicity		
Not Hispanic or Latino	318 (62%)	318 (64%)
Hispanic or Latino	188 (36%)	159 (32%)
Not reported or unknown	10 (2%)	17 (3%)
Race		
American Indian or Alaska Native	8 (2%)	10 (2%)
Asian	35 (7%)	35 (7%)
Native Hawaiian or Other Pacific Islander	1 (<1%)	4 (1%)
Black or African American	94 (18%)	94 (19%)
White	307 (59%)	281 (57%)
Multi-racial	3 (1%)	2 (<1%)
Unknown	68 (13%)	68 (14%)
Geographical region		
North America	501 (97%)	478 (97%)
Asia	15 (3%)	16 (3%)
Age, years	58·2 (14·3)	58·5 (13·7)
Age group, years		
<40	57 (11%)	43 (9%)
40–64	288 (56%)	287 (58%)
≥65	171 (33%)	164 (33%)
Duration of Symptoms before enrolment, days*	8·3 (4·3)	7·9 (4·1)
Number of comorbidities at baseline†		
No comorbidities	44/504 (9%)	52/478 (11%)
One comorbidity	107/504 (21%)	92/478 (19%)
Two or more comorbidities	353/504 (70%)	334/478 (70%)
(Continued from previous column)		
Comorbidities at baseline‡		
Asthma	58/504 (12%)	50/481 (10%)
Autoimmune hepatitis	2/504 (<1%)	1/481 (<1%)
Cancer	22/503 (4%)	33/481 (7%)
Cardiac arrhythmia	42/504 (8%)	34/481 (7%)
Cardiac valvular disease	11/504 (2%)	8/480 (2%)
Chronic kidney disease	49/504 (10%)	43/480 (9%)
Chronic respiratory disease	45/504 (9%)	44/480 (9%)
Coagulopathy	6/504 (1%)	10/481 (2%)
Congestive heart failure	33/504 (7%)	24/481 (5%)
Coronary artery disease	56/502 (11%)	38/481 (8%)
Depression or psychotic disorder	95/504 (19%)	81/480 (17%)
Epilepsy or history of seizures	10/504 (2%)	5/481 (1%)
Hypertension	298/504 (59%)	285/480 (59%)
Immune deficiency	16/504 (3%)	17/481 (4%)
Obesity	307/503 (61%)	302/481 (63%)
Other autoimmune disease	14/504 (3%)	11/481 (2%)
Systemic lupus erythematosus	1/504 (<1%)	4/481 (1%)
Thyroid disease	53/504 (11%)	53/480 (11%)
Type 1 diabetes	4/504 (1%)	5/481 (1%)
Type 2 diabetes	198/504 (39%)	183/481 (38%)
History of deep vein thrombosis or pulmonary embolism	18/504 (4%)	20/480 (4%)
Body-mass index, kg/m²	32·9 (8·6)	33·6 (9·0)
C-reactive protein	123·4 (121·3)	120·0 (97·8)
D-dimer	1·4 (2·2)	1·3 (2·3)
Previous dexamethasone use		
Yes	383 (74%)	361 (73%)
No	133 (26%)	133 (27%)
Baseline ordinal score		
4	1 (<1%)	0
5	432 (84%)	424 (86%)
6	83 (16%)	70 (14%)

Data are n (%), mean (SD), or n/N (%). *Duration of symptoms before enrolment data were missing for 24 participants. †Number of comorbidities at baseline data were missing for 28 participants. ‡Percentages are based on the number of participants with data available for the individual comorbidity.

Table 1: **Baseline characteristics**

and randomly assigned disease severity stratum (ie, the stratum to which the patient was randomly assigned at enrolment, which was not necessarily equivalent to their baseline ordinal score).

Safety analyses were done in the as-treated population, comprising all participants who received at least one dose of study drug.

Prespecified subgroups were defined according to sex, age (18–39 years, 40–64 years, or ≥65 years), race, ethnicity, duration of symptoms before randomisation (≤10 days or >10 days, quartiles, and median), ordinal score used for randomisation, geographical region, previous dexamethasone use, and presence of comorbidities.

The DSMB overseeing the trial met on April 13, 2021, for a preplanned review for futility. The futility analysis evaluated the conditional power to declare a statistically significant result assuming that future observations followed the protocol-assumed alternative of 85% of patients on dexamethasone and 90% of patients on baricitinib being mechanical ventilation-free and alive by day 29. The DSMB determined that it was unlikely that the study would show a significant difference between the two study groups if the trial continued to complete

enrolment of 1500 patients. As such, the trial was closed on April 13, 2021, with 1010 enrolled patients.

Analyses were done using SAS version 9.4 and R version 4.0.2. The trial is registered with ClinicalTrials.gov, NCT04640168.

Role of the funding source

The ACTT-4 protocol was designed and written by the ACTT investigators and the study sponsor (the National Institute of Allergy and Infectious Diseases [NIAID]). Input from the manufacturer of baricitinib, Eli Lilly, Indianapolis, IN, USA, was considered by the investigators. Principal investigators and staff at participating sites gathered the data, which were then analysed by statisticians at the statistical and data coordinating centre (The Emmes Company) and NIAID. The funder, NIAID, participated in the writing of the manuscript, and the decision to submit for publication.

Results

Between Dec 1, 2020, and April 13, 2021, 1047 patients were assessed for eligibility. 1010 patients were enrolled and randomly assigned, 516 (51%) to baricitinib plus remdesivir plus placebo and 494 (49%) to dexamethasone plus remdesivir plus placebo (the intention-to-treat population; figure 1). 856 (85%) patients had a baseline ordinal score of 5 (low-flow oxygen) and 153 (15%) had an ordinal score of 6 (high-flow oxygen or non-invasive mechanical ventilation). One participant had a baseline ordinal score of 4 and was only included in analyses for all subjects.

The modified intention-to-treat population included 516 (51%) patients in the baricitinib plus remdesivir plus placebo group (432 [84%] ordinal score 5 and 83 [16%] ordinal score 6) and 494 (49%) patients in the dexamethasone plus remdesivir plus placebo group (424 [86%] ordinal score 5 and 70 [14%] ordinal score 6). 503 (97%) of 516 patients in the baricitinib plus remdesivir plus placebo group received treatment as assigned, and 482 (98%) of 494 patients in the dexamethasone plus remdesivir plus placebo group received treatment as assigned. The mean age of the patients was 58·3 years (SD 14·0) and 590 (58%) of 1010 patients were male (table 1). 588 (58%) of 1010 patients were White, 188 (19%) were Black, 70 (7%) were Asian, and 18 (2%) were American Indian or Alaska Native (table 1). 347 (34%) of 1010 patients were Hispanic or Latino (table 1).

Mechanical ventilation-free survival by day 29 was similar between the study groups (Kaplan-Meier estimates of 87·0% [95% CI 83·7 to 89·6] in the baricitinib plus remdesivir plus placebo group and 87·6% [84·2 to 90·3] in the dexamethasone plus remdesivir plus placebo group; risk difference 0·6 [95% CI −3·6 to 4·8]; p=0·91; table 2). The results did not differ when analysed by previous corticosteroid use (no prior corticosteroid risk difference 0·1 [−6·3 to 6·5]; previous corticosteroid use 0·6 [−4·1 to 5·3]). Of those enrolled with baseline ordinal score 5, mechanical ventilation-free survival by day 29 was

	Overall*		Ordinal score 5		Ordinal score 6	
	Baricitinib plus remdesivir plus placebo (n=516)	Dexamethasone plus remdesivir plus placebo (n=494)	Baricitinib plus remdesivir plus placebo (n=432)	Dexamethasone plus remdesivir plus placebo (n=424)	Baricitinib plus remdesivir plus placebo (n=83)	Dexamethasone plus remdesivir plus placebo (n=70)
Mechanical ventilation-free survival						
Number of events	65	58	32	37	33	21
Kaplan-Meier estimate of ventilation-free survival by day 29, % (95% CI)	87·0% (83·7 to 89·6)	87·6% (84·2 to 90·3)	92·4% (89·4 to 94·6)	90·7% (87·3 to 93·2)	57·9% (46·1 to 67·9)	67·4% (54·4 to 77·3)
Difference in Kaplan-Meier estimates at day 29 (95% CI)†	0·6 (−3·6 to 4·8); p=0·91	..	−1·7 (−5·5 to 2·2)	..	9·5 (−6·4 to 25·4)	..
Mortality by day 29‡						
HR (95% CI) for data up to day 29	1·21 (0·72 to 2·04)	..	1·62 (0·79 to 3·34)	..	0·86 (0·40 to 1·88)	..
Number of deaths by day 29	27	30	12	19	15	11
Kaplan-Meier estimate of mortality by day 29, % (95% CI)	5·5% (3·8 to 7·9)	6·4% (4·5 to 9·0)	2·9% (1·6 to 5·0)	4·7% (3·0 to 7·3)	19·5% (12·3 to 30·3)	17·4% (10·0 to 29·1)
Mortality over the entire study period§						
HR (95% CI) over the entire study period	1·23 (0·77 to 1·96)	..	1·39 (0·74 to 2·61)	..	1·03 (0·50 to 2·12)	..
Number of deaths by day 60	33	37	17	23	16	14
Kaplan-Meier estimate of mortality by day 60, % (95% CI)	6·8% (4·9 to 9·4)	8·0% (5·9 to 10·9)	4·2% (2·6 to 6·6)	5·7% (3·9 to 8·5)	20·9% (13·3 to 31·8)	22·5% (13·9 to 35·0)

HR=hazard ratio. CIs have not been adjusted for multiple comparisons. HRs were calculated from the stratified Cox model for overall and Cox model for individual baseline ordinal scores. *One participant who was enrolled with a baseline ordinal score of 4 is excluded from the overall column. †The difference in day 29 mechanical ventilation-free survival is dexamethasone plus remdesivir plus placebo minus baricitinib plus remdesivir plus placebo; the difference does not use the complementary log transformation and might not correspond directly to the p-value, which was calculated using a weighted stratified χ^2 test modified from Klein and colleagues.[7] ‡Mortality over the first 28 days treats all patients who were still alive up to 28 days after enrolment as censored on day 28, as if 28 days was the maximum follow-up time; HRs greater than 1 indicate a benefit for baricitinib plus remdesivir plus placebo. §Mortality over the entire study period censors patients who completed follow-up alive at 60 days after enrolment or at their last visit if before day 60; HRs greater than 1 indicate a benefit for baricitinib plus remdesivir plus placebo.

Table 2: **Recovery and mortality outcomes overall and according to ordinal score at baseline in the modified intention-to-treat population**

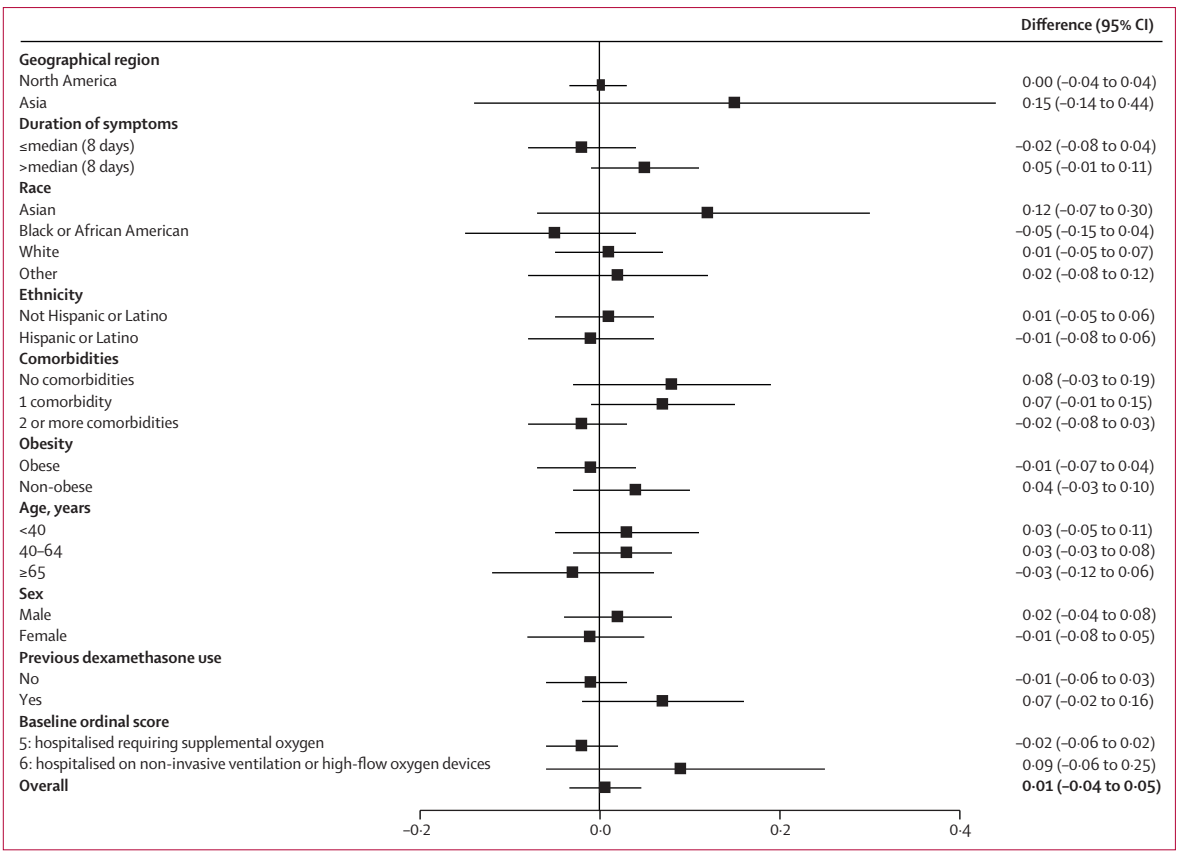

Figure 2: **Mechanical ventilation-free survival at day 29 by subgroup**
Each datapoint represents the difference in mechanical ventilation-free survival at day 29 between groups and 95% CI.

92·4% (89·4 to 94·6) in the baricitinib plus remdesivir plus placebo group and 90·7% (87·3 to 93·2) in the dexamethasone plus remdesivir plus placebo group (risk difference –1·7 [–5·5 to 2·2]; table 2). In those enrolled with baseline ordinal score 6, mechanical ventilation-free survival by day 29 was 57·9% (46·1 to 67·9) in the baricitinib plus remdesivir plus placebo group and 67·4% (54·4 to 77·3) in the dexamethasone plus remdesivir plus placebo group (risk difference 9·5 [–6·4 to 25·4]; table 2). Figure 2 shows the primary outcome in different subgroups. In general, the 95% CIs for all subgroups include 0, with differences ranging from 0·15 in Asia to –0·05 in participants who were Black or African American.

Clinical status at day 15 was similar between study groups. The odds ratio (OR) for improved status in the dexamethasone plus remdesivir plus placebo group compared with the baricitinib plus remdesivir plus placebo group was 1·01 (95% CI 0·80–1·27). Among patients with baseline ordinal score 5, the OR was 0·91 (0·70–1·17) and in patients with baseline ordinal score 6 the OR was 1·64 (0·92–2·90; table 3).

Kaplan-Meier estimates of the proportion of patients with baseline ordinal score 5 not progressing to a worse ordinal score at any time by day 29 was 81% (0·77 to 0·85) in the baricitinib plus remdesivir plus placebo group and 78% (0·74 to 0·82) in the dexamethasone plus remdesivir plus placebo group (risk difference –3% [95% CI –0·09 to 0·02]; table 3). The median time to recovery was 6 days (95% CI 5·0 to 6·0) for the baricitinib plus remdesivir plus placebo group and 5 days (5·0 to 6·0) for the dexamethasone plus remdesivir plus placebo group (rate ratio [RR] 1·04 [95% CI 0·91 to 1·19]). Median time to recovery among patients with baseline ordinal score 5 was 5 days in both groups (95% CI not estimable for the baricitinib plus remdesivir plus placebo group; 4 to 5 days for the dexamethasone plus remdesivir plus placebo group; RR 1·00 [95% CI 0·87 to 1·15]). For patients with baseline ordinal score 6, median time to recovery was 16 days (95% CI 13 to not estimable) for the baricitinib plus remdesivir plus placebo group versus 10 days (8 to 14) for the dexamethasone plus remdesivir plus placebo group (1·53 [1·01 to 2·31]). A treatment group assessed by a continuous baseline ordinal score interaction model (appendix p 32) showed no differences ($p_{interaction}$ 0·10) in time to recovery between the two subgroups (baseline ordinal score 5, RR 0·99 [0·86 to 1·14]; baseline ordinal score 6, 1·44 [0·95 to 2·17]).

The median time to a one category ordinal score improvement was 5 days (4–5) for the baricitinib plus

	Overall			Ordinal score 5			Ordinal score 6		
	Baricitinib plus remdesivir plus placebo (n=516)	Dexamethasone plus remdesivir plus placebo (n=494)	Effect size or difference* (95% CI)	Baricitinib plus remdesivir plus placebo (n=432)	Dexamethasone plus remdesivir plus placebo (n=424)	Effect size or difference* (95% CI)	Baricitinib plus remdesivir plus placebo (n=83)	Dexamethasone plus remdesivir plus placebo (n=70)	Effect size or difference* (95% CI)
Ordinal scale at day 15 (±2 days)*									
OR (95% CI)	..	..	1·01 (0·80 to 1·27)	..	..	0·91 (0·70 to 1·17)	..	..	1·64 (0·92 to 2·90)
Time to recovery									
Median days (95% CI)†	6·0 (5·0 to 6·0)	5·0 (5·0 to 6·0)	1·04 (0·91 to 1·19)‡	5·0 (NE)	5·0 (4·0 to 5·0)	1·00 (0·87 to 1·15)‡	16·0 (13·0 to NE)	10·0 (8·0 to 14·0)	1·53 (1·01 to 2·31)‡
Time to clinical improvement									
Median time to one-category improvement, days (95% CI)†	5·0 (4·0 to 5·0)	4·0 (4·0 to 5·0)	1·03 (0·90 to 1·18)‡	4·0 (4·0 to 5·0)	4·0 (4·0 to 5·0)	0·99 (0·86 to 1·14)‡	10·0 (8·0 to 16·0)	7·0 (4·0 to 9·0)	1·44 (0·98 to 2·13)‡
Median yime to two-category improvement, days (95% CI)†	6·0 (5·0 to 6·0)	5·0 (5·0 to 6·0)	1·04 (0·91 to 1·19)‡	5·0 (NE)	5·0 (4·0 to 5·0)	1·00 (0·87 to 1·15)‡	15·0 (12·0 to NE)	10·0 (8·0 to 14·0)	1·49 (0·99 to 2·24)‡
Proportion of patients with ordinal score 5 not progressing to ordinal score 6, 7, or 8‡									
Proportion of patients (95% CI)	81% (0·77 to 0·85)	78% (0·74 to 0·82)	–0·03 (–0·09 to 0·02)§	81% (0·77 to 0·85)	78% (0·74 to 0·82)	–0·03 (–0·09 to 0·02)§	..	..	..
Hospitalisation¶									
Median duration of initial hospitalisation, days|| (IQR)	7 (4 to 12)	6 (4 to 11)	–1·0 (–1·8 to –0·2)§	6 (4 to 9)	6 (4 to 9)	0·0 (–0·7 to 0·7)§	16 (8 to 28)	12 (7 to 28)	–4·0 (–11·2 to 3·2)§
Median duration of initial hospitalisation among those who did not die, days (IQR)	6 (4 to 10)	6 (4 to 9)	0·0 (–0·6 to 0·6)§	6 (4 to 9)	5 (4 to 8)	–1·0 (–1·7 to –0·3)§	13 (8 to 27)	9 (7 to 15)	–4·0 (–8·4 to 0·4)§
Oxygen¶									
Median days on oxygen, (IQR)||	10 (4 to 28)	11 (4 to 28)	0·0 (–3·2 to 3·2)§	8 (4 to 26)	8 (4 to 28)	0·0 (–2·6 to 2·6)§	28 (13 to 28)	28 (10 to 28)	0·0 (–5·4 to 5·4)§
Non-invasive ventilation or high-flow oxygen¶									
Median days of non-invasive ventilation or high-flow oxygen use during the study (if on these interventions at baseline; IQR)||	8 (4 to 21)	6 (3 to 13)	–2·0 (–4·6 to 0·6)§	..	..	..	8 (4 to 21)	6 (3 to 13)	–2·0 (–4·6 to 0·6)§
Incidence of new non-invasive ventilation or high-flow oxygen use during the study, proportion of patients (95% CI)	16% (13 to 20)	21% (17 to 25)	4·8 (–0·4 to 10·0)§	16% (13 to 20)	21% (17 to 25)	4·8 (–0·4 to 10·0)§	..	..	..
Median days of non-invasive ventilation or high-flow oxygen use during the study (if new use of these interventions; IQR)||	5 (3 to 9)	8 (4 to 28)	3·0 (–0·2 to 6·2)§	5 (3 to 9)	8 (4 to 28)	3·0 (–0·2 to 6·2)§	..	..	..
Mechanical ventilation or ECMO¶									
Incidence of new mechanical ventilation or ECMO use during study, proportion of patients (95% CI)	11% (8 to 14)	10% (7 to 12)	–1·1 (–4·9 to 2·6)§	6% (4 to 8)	7% (5 to 9)	1·0 (–2·2 to 4·4)§	37% (28 to 48)	27% (18 to 39)	–10·2 (–24·2 to 4·7)§
Median days of mechanical ventilation or ECMO use during study (if new use of these interventions; IQR)||	27 (14 to 28)	28 (18 to 28)	1·0 (–3·3 to 5·3)§	25 (11 to 28)	28 (15 to 28)	2·0 (–5·7 to 9·7) §	28 (19 to 28)	28 (24 to 28)	0·0 (–4·0 to 4·0)§

Differences and 95% CIs of difference are estimated using quantile regression and might not match differences in raw medians in small sample sizes. ECMO=extracorporeal membrane oxygenation. NE=not evaluable. OR=odds ratio. RR=rate ratio. *The difference in day 29 mechanical ventilation-free survival is dexamethasone plus remdesivir plus placebo minus baricitinib plus remdesivir plus placebo. ORs were calculated with a proportional odds model. RRs (equivalent to hazard ratios but for a positive outcome) were calculated with the use of a Cox model. Overall models were adjusted for actual baseline ordinal score. †RR (95% CI). ‡Median days and 95% CI were calculated using Kaplan-Meier methodology. §Difference (95% CI). ¶One patient enrolled not on oxygen (ordinal score 4) was not included in the hospitalisation and oxygen use data. ||Includes imputations for participants who died.

Table 3: **Secondary outcomes overall and according to score on the ordinal scale in the modified intention-to-treat population**

	Baricitinib plus remdesivir plus placebo (n=503)	Dexamethasone plus remdesivir plus placebo (n=482)	Risk difference* (of totals), % (95% CI)	Baricitinib plus remdesivir plus placebo (n=423)	Dexamethasone plus remdesivir plus placebo (n=417)	Baricitinib plus remdesivir plus placebo (n=80)	Dexamethasone plus remdesivir plus placebo (n=65)
At least one adverse event	149 (30%)	179 (37%)	7·5% (1·6 to 13·3)	100 (24%)	143 (34%)	49 (61%)	36 (55%)
At least one severe or life-threatening (grade 3 or 4) adverse event	143 (28%)	174 (36%)	7·7% (1·8 to 13·4)	96 (23%)	140 (34%)	47 (59%)	34 (52%)
At least one treatment-related adverse event	21 (4%)	49 (10%)	6·0% (2·8 to 9·3)	15 (4%)	39 (9%)	6 (8%)	10 (15%)
Severe (grade 3)	14 (3%)	37 (8%)	4·9% (2·1 to 7·8)	11 (3%)	30 (7%)	3 (4%)	7 (11%)
Life-threatening (grade 4)	8 (2%)	17 (4%)	1·9% (–0·1 to 4·1)	6 (1%)	12 (3%)	2 (3%)	5 (8%)
Severe or life-threatening (grade 3 or 4)	20 (4%)	49 (10%)	6·2% (3·0 to 9·5)	15 (4%)	39 (9%)	5 (6%)	10 (15%)
At least one serious adverse event	95 (19%)	94 (20%)	0·6% (–4·3 to 5·5)	56 (13%)	68 (16%)	39 (49%)	26 (40%)
At least one related serious adverse event	7 (1%)	8 (2%)	0·3% (–1·4 to 2·0)	6 (1%)	7 (2%)	1 (1%)	1 (2%)
At least one serious adverse event with fatal outcome	28 (6%)	34 (7%)	1·5% (–1·6 to 4·6)	12 (3%)	21 (5%)	16 (20%)	13 (20%)
Most common serious adverse events (≥4 total)							
Respiratory AE	71 (14%)	71 (15%)	0·6% (–3·8 to 5·0)	35 (8%)	50 (12%)	36 (45%)	21 (32%)
Pulmonary embolism	10 (2%)	8 (2%)	–0·3% (–2·2 to 1·5)	6 (1%)	7 (2%)	4 (5%)	1 (2%)
Increased creatinine	11 (2%)	6 (1%)	–0·9% (–2·8 to 0·8)	6 (1%)	3 (1%)	5 (6%)	3 (5%)
Pneumonia	8 (2%)	3 (1%)	–1·0% (–2·5 to 0·5)	5 (1%)	3 (1%)	3 (4%)	0
Multiple organ dysfunction syndrome	2 (<1%)	7 (1%)	1·1% (–0·2 to 2·6)	0	4 (1%)	2 (3%)	3 (5%)
Septic shock	6 (1%)	2 (<1%)	–0·8% (–2·2 to 0·5)	3 (1%)	2 (<1%)	3 (4%)	0
Sepsis	3 (1%)	4 (1%)	0·2% (–1·0 to 1·6)	2 (<1%)	4 (1%)	1 (1%)	0
Bacterial pneumonia	3 (1%)	3 (1%)	0·0% (–1·2 to 1·3)	2 (<1%)	3 (1%)	1 (1%)	0
Failure to thrive	2 (<1%)	3 (1%)	0·2% (–0·9 to 1·5)	1 (<1%)	3 (1%)	1 (1%)	0
Decreased lymphocyte count	2 (<1%)	3 (1%)	0·2% (–0·9 to 1·5)	1 (<1%)	3 (1%)	1 (1%)	0
Cardiac arrest	2 (<1%)	2 (<1%)	0·0% (–1·1 to 1·1)	1 (<1%)	2 (<1%)	1 (1%)	0
New infections (≥4 total)							
Any new infection	32 (6%)	31 (6%)	0·1% (–3·0 to 3·2)	17 (4%)	23 (6%)	15 (19%)	8 (12%)
Pneumonia	11 (2%)	13 (3%)	0·5% (–1·5 to 2·6)	6 (1%)	8 (2%)	5 (6%)	5 (8%)
Pneumonia bacterial	7 (1%)	7 (1%)	0·1% (–1·6 to 1·7)	5 (1%)	6 (1%)	2 (3%)	1 (2%)
Sepsis	5 (1%)	5 (1%)	0·0% (–1·4 to 1·5)	2 (<1%)	3 (1%)	3 (4%)	2 (3%)
Urinary tract infection	4 (1%)	6 (1%)	0·4% (–1·0 to 2·0)	2 (<1%)	6 (1%)	2 (3%)	0
Septic shock	4 (1%)	1 (<1%)	–0·6% (–1·8 to 0·5)	2 (<1%)	1 (<1%)	2 (3%)	0
Venous thromboembolism (≥4 total)							
Any venous thromboembolism	22 (4%)	21 (4%)	0·0% (–2·6 to 2·6)	11 (3%)	15 (4%)	11 (14%)	6 (9%)
Pulmonary embolism	12 (2%)	13 (3%)	0·3% (–1·8 to 2·4)	6 (1%)	11 (3%)	6 (8%)	2 (3%)
Deep vein thrombosis	9 (2%)	7 (1%)	–0·3% (–2·1 to 1·4)	4 (1%)	3 (1%)	5 (6%)	4 (6%)

Data are n (%), unless otherwise indicated. Data include treatment-emergent adverse events and fatal adverse events before treatment start. *The difference is calculated as Dexamethasone plus remdesivir plus placebo minus baricitinib plus remdesivir plus placebo.

Table 4: **Adverse events in the as-treated population**

remdesivir plus placebo group versus 4 days (4–5) for the dexamethasone plus remdesivir plus placebo group (RR 1·03 [95% CI 0·90–1·18]), and 6 days (95% CI 5–6) versus 5 days (5–6), respectively, for a two category improvement (1·04 [0·91–1·19]; table 3). The DOORs at day 15 and day 29 were similar between the study groups (appendix pp 33–34). Days on oxygen, days on non-invasive ventilation or high-flow oxygen, and days on invasive mechanical ventilation or ECMO were similar between the study groups (table 3). Days on oxygen, days on non-invasive ventilation or high-flow oxygen, incidence of new non-invasive ventilation, incidence of invasive mechanical ventilation or ECMO, and days on invasive mechanical ventilation or ECMO were similar between the study groups (table 3).

Patients who progressed to invasive mechanical ventilation could be unmasked, permitting open label use of dexamethasone or alteration of immune modulatory treatment. Only one patient was unmasked during this trial, in the dexamethasone plus remdesivir plus placebo group.

Kaplan-Meier estimates of overall mortality by day 29 were 5·5% (95% CI 3·8–7·9) in the baricitinib plus remdesivir plus placebo group and 6·4% (4·5–9·0) in the dexamethasone plus remdesivir plus placebo group (table 2). Mortality by day 29 was 2·9% (1·6–5·0) in the

baricitinib plus remdesivir plus placebo group and 4·7% (3·0–7·3) in the dexamethasone plus remdesivir plus placebo group among patients with baseline ordinal score 5, and 19·5% (12·3–30·3) and 17·4% (10·0–29·1), respectively, for patients with baseline ordinal score 6 (table 2). The overall 60-day mortality was 6·8% (4·9–9·4) in the baricitinib plus remdesivir plus placebo group and 8·0% (5·9–10·9) in the dexamethasone plus remdesivir plus placebo group (table 2). Among patients with a baseline ordinal score 5, the 60-day mortality was 4·2% (2·6–6·6) in the baricitinib plus remdesivir plus placebo group and 5·7% (3·9–8·5) in the dexamethasone plus remdesivir plus placebo group, and in those with a baseline ordinal score of 6, the 60-day mortality was 20·9% (13·3–31·8) and 22·5% (13·9–35·0), respectively (table 2). Day 14 mortality is summarised in the appendix (p 55).

At least one adverse event occurred in 149 (30%) of 503 patients in the baricitinib plus remdesivir plus placebo group and 179 (37%) of 482 patients in the dexamethasone plus remdesivir plus placebo group (risk difference 7·5% [95% CI 1·6–13·3]; p=0·014; table 4). The number needed to harm for one additional adverse event with dexamethasone was 13·3. 21 (4%) of 503 patients in the baricitinib plus remdesivir plus placebo group had at least one treatment-related adverse event versus 49 (10%) of 482 patients in the dexamethasone plus remdesivir plus placebo group (risk difference 6·0% [2·8–9·3]; p=0·00041; table 4). The number needed to harm for one additional treatment-related adverse event with dexamethasone was 16·7. Severe or life-threatening grade 3 or 4 adverse events occurred in 143 (28%) of 503 patients in the baricitinib plus remdesivir plus placebo group and 174 (36%) of 482 patients in the dexamethasone plus remdesivir plus placebo group (risk difference 7·7% [1·8–13·4]; p=0·012; table 4). The number needed to harm for one additional severe or life-threatening grade 3 or 4 adverse event with dexamethasone was 12·5.

Serious adverse events occurred in 95 (19%) of 503 patients in the baricitinib plus remdesivir plus placebo group and seven (1%) of these events were related to study drug (table 4). Serious adverse events occurred in 94 (20%) of 482 patients in the dexamethasone plus remdesivir plus placebo group and eight (2%) were related to study drug (table 4). The number of new infections was 32 (6%) in the baricitinib plus remdesivir plus placebo group and 31 (6%) in the dexamethasone plus remdesivir plus placebo group. The number of venous thromboembolism events was 22 (4%) in the baricitinib plus remdesivir plus placebo group and 21 (4%) in the dexamethasone plus remdesivir plus placebo group.

Discussion

In this double-blind, double placebo-controlled, randomised trial comparing the combination of baricitinib plus remdesivir versus dexamethasone plus remdesivir in hospitalised patients with COVID-19 requiring low-flow or high-flow oxygen, or non-invasive ventilation, outcomes were similar for mechanical ventilation-free survival by day 29, clinical status on day 15, mortality, and other efficacy measures, but the baricitinib plus remdesivir plus placebo group showed a significantly better safety profile compared with the dexamethasone plus remdesivir plus placebo group.

Outcomes were consistently similar among different geographical regions, gender, race, and ethnicity and were independent of the duration of symptoms. We found no significant 29-day or 60-day mortality difference between the treatment groups when stratified by ordinal score at enrolment, nor were there statistical interactions detected between ordinal score 5 and ordinal score 6, which indicates that the treatment effect was not dependent on the ordinal score. Notably, this study was not powered to analyse differences in outcomes between ordinal score subgroups and only 153 (15%) of 1010 enrolled patients required high-flow oxygen or non-invasive ventilation (ordinal score 6), limiting any reliable subgroup interpretation.

Particularly relevant to clinical practice is the higher rate of severe or life-threatening adverse events detected in patients receiving dexamethasone in this double-blind, double placebo-controlled, randomised trial. We found no differences in rates of venous thromboembolism or new infections, but there were significantly higher rates of treatment-related adverse events with dexamethasone. The difference in the safety profile for dexamethasone suggests that clinicians need to weigh up the potential benefits in each patient to decide if the higher rate of dexamethasone adverse events is acceptable.[8–10] The adverse events in patients who received dexamethasone did not affect the efficacy comparison (primary outcome) because this trial was neither designed nor powered for that. Patients with adverse events during hospitalisations have higher hospitalisation costs[11] and quality-adjusted life year losses.[12] The implications of our results for clinical practice are that despite similar prevention of intubation or death, baricitinib causes less adverse events than does dexamethasone, and this will directly aid clinicians in deciding which immunomodulatory drug to use according to patients' individual risks for dexamethasone-related side-effects.

Previous randomised trials have shown benefits with both baricitinib[2,4,13] and dexamethasone[3] in the treatment of patients hospitalised with COVID-19, but differences in methodology and study populations precluded comparison of the two therapies. The fact that all patients in the ACTT-4 trial received the same antiviral—remdesivir—provides further assurance that the primary aim to compare baricitinib versus dexamethasone was not affected by imbalanced use of an antiviral therapy by trial participants. To our knowledge, ACTT-4 is the first head-to-head trial comparing immunomodulators for the treatment of COVID-19, and suggests that baricitinib and

dexamethasone, when combined with remdesivir, provide similar rates of progression to invasive mechanical ventilation or death, but differ regarding safety. Our study was double placebo-controlled and double-blind, with a randomisation process stratified by disease severity and hospital site. Thus, this study has a very low risk of bias.

A limitation of this study is related to the low event rate of mechanical ventilation and death, potentially resulting in a low outcome event rate that might have decreased the power to detect potential differences between the study groups. The use of remdesivir in both study groups might have reduced the progression of the clinical disease, as shown in the ACTT-1 trial,[5] potentially making it more difficult to detect a differential effect between the two immunomodulators. We understand that remdesivir is not the standard of care for COVID-19 in all countries; however, independent of the magnitude of the remdesivir benefit, both study groups receiving remdesivir could not have affected the outcomes of the trial and therefore would not change the interpretation of the findings. Nevertheless, the systematic and comprehensive safety data collection in a double-blind manner is an important strength of our trial, enabling the detection of clinically relevant safety differences between immunomodulators, which were not previously noted.

With two similar regimens, the choice of baricitinib plus remdesivir or dexamethasone plus remdesivir might be informed by the nuances and trends in our trial. For the bedside clinician, a more individually tailored choice of immunomodulation now appears possible, where side-effect profile, ease of administration, cost, and patient comorbidities can all be considered.

In conclusion, in hospitalised patients with COVID-19 requiring supplemental oxygen by low-flow, high-flow, or non-invasive ventilation, baricitinib plus remdesivir and dexamethasone plus remdesivir resulted in similar mechanical ventilation-free survival by day 29, but dexamethasone was associated with significantly more adverse events, treatment-related adverse events, and severe or life-threatening adverse events.

Contributors

The ACTT-4 protocol was designed and written by the ACTT investigators and NIAID study staff. All investigators and staff at participating sites enrolled the participants and gathered study data. JLF, MM, TBo, and LED did the statistical analyses. The first draft of the manuscript was written by ACK, KMT, CRW, JHB, LED, and TBe. All authors were given the opportunity to review, comment, and edit the manuscript. All authors wrote the final manuscript, and, on behalf of the ACTT-4 Study Group, vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. LED, TBo, MM and JLF had access to the data. All authors had access to the analysis reports.

Declaration of interests

We declare no competing interests.

Data sharing

A dataset including deidentified individual patient data to reproduce the findings in this manuscript and a data dictionary can be requested at https://accessclinicaldata.niaid.nih.gov/. The datasets will be available within 4 months after publication of the Article.

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