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Efficacy of interferon beta-1a plus remdesivir compared with remdesivir alone in hospitalised adults with COVID-19: a double-bind, randomised, placebo-controlled, phase 3 trial

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Summary

Background Functional impairment of interferon, a natural antiviral component of the immune system, is associated with the pathogenesis and severity of COVID-19. We aimed to compare the efficacy of interferon beta-1a in combination with remdesivir compared with remdesivir alone in hospitalised patients with COVID-19.

Methods We did a double-blind, randomised, placebo-controlled trial at 63 hospitals across five countries (Japan, Mexico, Singapore, South Korea, and the USA). Eligible patients were hospitalised adults (aged ≥18 years) with SARS-CoV-2 infection, as confirmed by a positive RT-PCR test, and who met one of the following criteria suggestive of lower respiratory tract infection: the presence of radiographic infiltrates on imaging, a peripheral oxygen saturation on room air of 94% or less, or requiring supplemental oxygen. Patients were excluded if they had either an alanine aminotransferase or an aspartate aminotransferase concentration more than five times the upper limit of normal; had impaired renal function; were allergic to the study product; were pregnant or breast feeding; were already on mechanical ventilation; or were anticipating discharge from the hospital or transfer to another hospital within 72 h of enrolment. Patients were randomly assigned (1:1) to receive intravenous remdesivir as a 200 mg loading dose on day 1 followed by a 100 mg maintenance dose administered daily for up to 9 days and up to four doses of either 44 µg interferon beta-1a (interferon beta-1a group plus remdesivir group) or placebo (placebo plus remdesivir group) administered subcutaneously every other day. Randomisation was stratified by study site and disease severity at enrolment. Patients, investigators, and site staff were masked to interferon beta-1a and placebo treatment; remdesivir treatment was given to all patients without masking. The primary outcome was time to recovery, defined as the first day that a patient attained a category 1, 2, or 3 score on the eight-category ordinal scale within 28 days, assessed in the modified intention-to-treat population, defined as all randomised patients who were classified according to actual clinical severity. Safety was assessed in the as-treated population, defined as all patients who received at least one dose of the assigned treatment. This trial is registered with ClinicalTrials.gov, NCT04492475.

Findings Between Aug 5, 2020, and Nov 11, 2020, 969 patients were enrolled and randomly assigned to the interferon beta-1a plus remdesivir group (n=487) or to the placebo plus remdesivir group (n=482). The mean duration of symptoms before enrolment was 8·7 days (SD 4·4) in the interferon beta-1a plus remdesivir group and 8·5 days (SD 4·3) days in the placebo plus remdesivir group. Patients in both groups had a time to recovery of 5 days (95% CI not estimable) (rate ratio of interferon beta-1a plus remdesivir group *vs* placebo plus remdesivir 0·99 [95% CI 0·87–1·13]; p=0·88). The Kaplan-Meier estimate of mortality at 28 days was 5% (95% CI 3–7%) in the interferon beta-1a plus remdesivir group and 3% (2–6%) in the placebo plus remdesivir group (hazard ratio 1·33 [95% CI 0·69–2·55]; p=0·39). Patients who did not require high-flow oxygen at baseline were more likely to have at least one related adverse event in the interferon beta-1a plus remdesivir group (33 [7%] of 442 patients) than in the placebo plus remdesivir group (15 [3%] of 435). In patients who required high-flow oxygen at baseline, 24 (69%) of 35 had an adverse event and 21 (60%) had a serious adverse event in the interferon beta-1a plus remdesivir group compared with 13 (39%) of 33 who had an adverse event and eight (24%) who had a serious adverse event in the placebo plus remdesivir group.

Interpretation Interferon beta-1a plus remdesivir was not superior to remdesivir alone in hospitalised patients with COVID-19 pneumonia. Patients who required high-flow oxygen at baseline had worse outcomes after treatment with interferon beta-1a compared with those given placebo.

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*A complete list of the ACTT-3 study study group is provided in the appendix (pp 5–9)

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Introduction

Use of the antiviral remdesivir and anti-inflammatory agents, such as dexamethasone or baricitinib, have been shown to improve outcomes in hospitalised patients with COVID-19.[1–3] Despite these interventions, morbidity and mortality due to COVID-19 remain high. Interferons (IFNs) are naturally occurring proteins produced in response to pathogens that influence innate and adaptive immune responses. In-vitro studies have shown impaired induction of type 1 IFNs following SARS-CoV-2 infection.[4–9] Studies of hospitalised patients with COVID-19 have shown that these patients have a downregulated interferon response, which is associated with more severe disease compared with those without a downregulated interferon response.[10–12] Type 1 IFN can inhibit SARS-CoV-1, Middle East respiratory syndrome (MERS) coronavirus, and SARS-CoV-2 replication,[4,8,13,14] and recent data published in 2020 suggest that SARS-CoV-2 could be more sensitive to intrinsic IFN than SARS-CoV-1.[4,5]

Preliminary data from small studies suggest a potential benefit of interferon therapy for COVID-19. The combination of interferon beta-1b and lopinavir–ritonavir was shown to decrease mortality from 44% in the control group to 28% in the intervention group among patients hospitalised with laboratory-confirmed MERS.[15] In an open-label, randomised study, treatment of hospitalised adults with mild COVID-19 disease with the combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin within 7 days of symptom onset was associated with a significantly shorter median time from treatment initiation to a negative nasopharyngeal RT-PCR result (7 days *vs* 12 days), earlier resolution of symptoms (4 days *vs* 8 days), and a shorter hospital stay (9 days *vs* 15 days) compared with lopinavir–ritonavir alone.[16] In another open-label, randomised study in hospitalised adults with severe COVID-19, subcutaneous interferon beta-1a did not improve time to clinical response compared with standard of care (9·7 days *vs* 8·3 days), but did lead to a higher proportion (67% *vs* 44%) of patients discharged by day 14 (odds ratio 2·5 [95% CI 1·05–6·37]) and lower overall mortality at 28 days (19% *vs* 44%; p=0·015).[17] These preclinical and clinical data support the hypothesis that treatment with interferon could improve outcomes in patients with COVID-19. In this report, we present findings of the third stage of the Adaptive COVID-19 Treatment Trial (ACTT-3), in which we evaluated the efficacy of treatment with interferon beta-1a plus remdesivir (combination treatment) compared with remdesivir alone (control treatment) in adults hospitalised with COVID-19.

Methods

Study design and patients

This double-blind, randomised, placebo-controlled trial was done at 63 hospitals in Japan (one site), Mexico (two sites), Singapore (two sites), South Korea (two sites), and the USA (56 sites). Eligible patients were hospitalised adults (aged ≥18 years) with SARS-CoV-2 infection, as confirmed by a positive RT-PCR assay result from any respiratory specimen collected less than 72 h before randomisation, or collected 72 h or more before randomisation if the patient had progressive disease consistent with ongoing SARS-CoV-2 infection. Patients also had to meet one of the following criteria suggestive of lower respiratory tract infection at the time of

Research in context

Evidence before this study

Previous studies have shown an impaired induction of type 1 interferons (IFNs) following SARS-CoV-2 infection. Hospitalised patients with COVID-19 have shown a downregulated IFN response, which is associated with more severe disease. We searched PubMed using the search terms "COVID-19", "SARS-CoV-2", "interferon beta-1a", "interferon beta-1b", and "treatment". We searched for articles published in English between database inception and June 28, 2021. We evaluated clinical trials of investigational medications in COVID-19, as well as studies that evaluated interferon beta-1a and interferon beta-1b before this study. Four randomised, open-label trials have been previously published: two showed non-significant benefits of interferon beta-1b compared with controls, and two suggested significantly faster clinical resolution and higher rates of hospital discharge with interferon beta-1a compared with controls. We found no double-blind, randomised, placebo-controlled trials investigating interferon beta-1a in hospitalised patients with COVID-19 before this study.

Added value of the study

To our knowledge, this is the first double-blind, randomised, placebo-controlled trial to evaluate the efficacy of interferon beta-1a plus antiviral remdesivir treatment with remdesivir alone in adults hospitalised with COVID-19.

Implications of all the available evidence

We found that the subcutaneous administration of interferon beta-1a was not associated with clinical benefits in hospitalised patients with COVID-19. This implies that interferon beta-1a is not suitable for clinical practice in hospitalised patients with COVID-19.

enrolment: the presence of radiographic infiltrates on imaging; a peripheral oxygen saturation on room air of 94% or less; or requiring supplemental oxygen. Patients already on mechanical ventilation were excluded due to concerns of exacerbating the pulmonary inflammation. There was no limit to the duration of symptoms before enrolment. Patients were excluded if they had either an alanine aminotransferase or an aspartate aminotransferase concentration more than five times the upper limit of normal; had impaired renal function, as defined by an estimated glomerular filtration rate (eGFR) of less than 30 mL per min per 1·73 m² or the need for haemodialysis or haemofiltration (clinical trial sites were asked to calculate eGFR with the same formula, and the site hospital's clinical laboratory was asked to calculate eGFR automatically for all patients enrolled at the site for the duration of the study, including for the eGFR measurement used for screening and safety laboratory monitoring); were allergic to the study product; were pregnant or breast-feeding; and were anticipating discharge from the hospital or transfer to another hospital within 72 h of enrolment.

The trial protocol was approved by the institutional review board at each site (or by a centralised institutional review board, as applicable) and was overseen by an independent data and safety monitoring board (DSMB). Written or institutionally approved informed consent was obtained from each patient. Full details of the trial design, inclusion and exclusion criteria, conduct, oversight, and analyses can be found in the study protocol (appendix pp 111–271) and statistical analysis plan (appendix pp 272–435).

Randomisation and masking

Eligible patients were randomly assigned (1:1) to receive either interferon beta-1a plus remdesivir or placebo plus remdesivir. Randomisation was stratified by study site and disease severity at enrolment, and was done by use of the web-based data entry system Advantage eClinical (The Emmes Company, Rockville, MD, USA). Independent, unmasked statisticians at The Emmes Company generated the treatment table. Disease severity was defined according to the eight-category ordinal scale used in previous ACTT studies. Patients defined by a score of: 1 were not hospitalised and had no limitations to their activities; 2 were not hospitalised but had limitations to their activities or required home oxygen supplementation, or both; 3 were hospitalised but did not require supplemental oxygen and no longer required ongoing medical care; 4 were hospitalised and did not require supplemental oxygen but did require ongoing medical care; 5 were hospitalised and required any supplemental oxygen; 6 were hospitalised and required non-invasive ventilation or use of high-flow oxygen devices; 7 were hospitalised and receiving invasive mechanical ventilation or extracorporeal membrane oxygenation; and 8 were those who had died. Intravenous remdesivir was given to all patients without masking. Interferon beta-1a and placebo were administered subcutaneously by use of syringes with an identical appearance, and the investigational label covered the syringe barrel, thus obscuring the fluid within the syringe. The study team (ie, those giving the interventions, assessing the outcomes, and analysing the data) was masked to treatment assignment until the end of the trial, after all data queries were resolved and the database was locked. Unmasked statisticians analysed data for the interim analyses.

Procedures

Hospitalised patients received up to four doses of either 44 µg interferon beta-1a or matched normal saline placebo administered subcutaneously every other day. The dose chosen was based on the bioavailability of interferon beta-1a, which is approximately 30% after subcutaneous administration, with peak serum concentrations being reached within several hours of receiving a dose. Serum concentrations of interferon beta-1a typically peak 3–15 h after intramuscular administration. Interferon beta-1a is excreted by hepatic and renal pathways. All hospitalised patients also received intravenous remdesivir as a 200 mg loading dose on day 1 followed by a 100 mg maintenance dose administered daily for up to 9 days. All patients received standard supportive care by the trial site hospital, including glucocorticoids, but other experimental treatments for COVID-19 were prohibited. All patients were evaluated daily during their hospital stay, from day 1 to day 29. Patients who were discharged were contacted on days 15, 22, and 29 for follow-up assessments. Clinical status was captured at each visit using the eight-category ordinal scale and the National Early Warning Score (NEWS) at in-person visits. Blood samples for safety laboratory tests and oropharyngeal swab samples (nasopharyngeal could be substituted) were collected on days 1 (before initial infusion), 3, 5, 8, and 11 while hospitalised, and days 15 and 29 for participants able to attend an in-person visit or who were still hospitalised. Adverse events were assessed by review of the electronic medical record, physical examinations, vital signs, and laboratory studies from the time the informed consent form was signed up to day 29. Adverse events were classified in accordance with the Medical Dictionary for Regulatory Activities (version 23.0), and their relationship to the study product, severity, and outcome were documented. The full description of procedures used is provided in the study protocol (appendix 111–271).

Outcomes

The primary outcome was time to recovery, defined as the first day, during the 28 days after enrolment, on which a patient attained a score of 1, 2, or 3 on the ordinal scale. Blinded central assessment of ordinal score data was used to determine the recovery day.

The key secondary outcome measure was the odds of improved clinical status (defined by the ordinal scale

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See **Online** for appendix

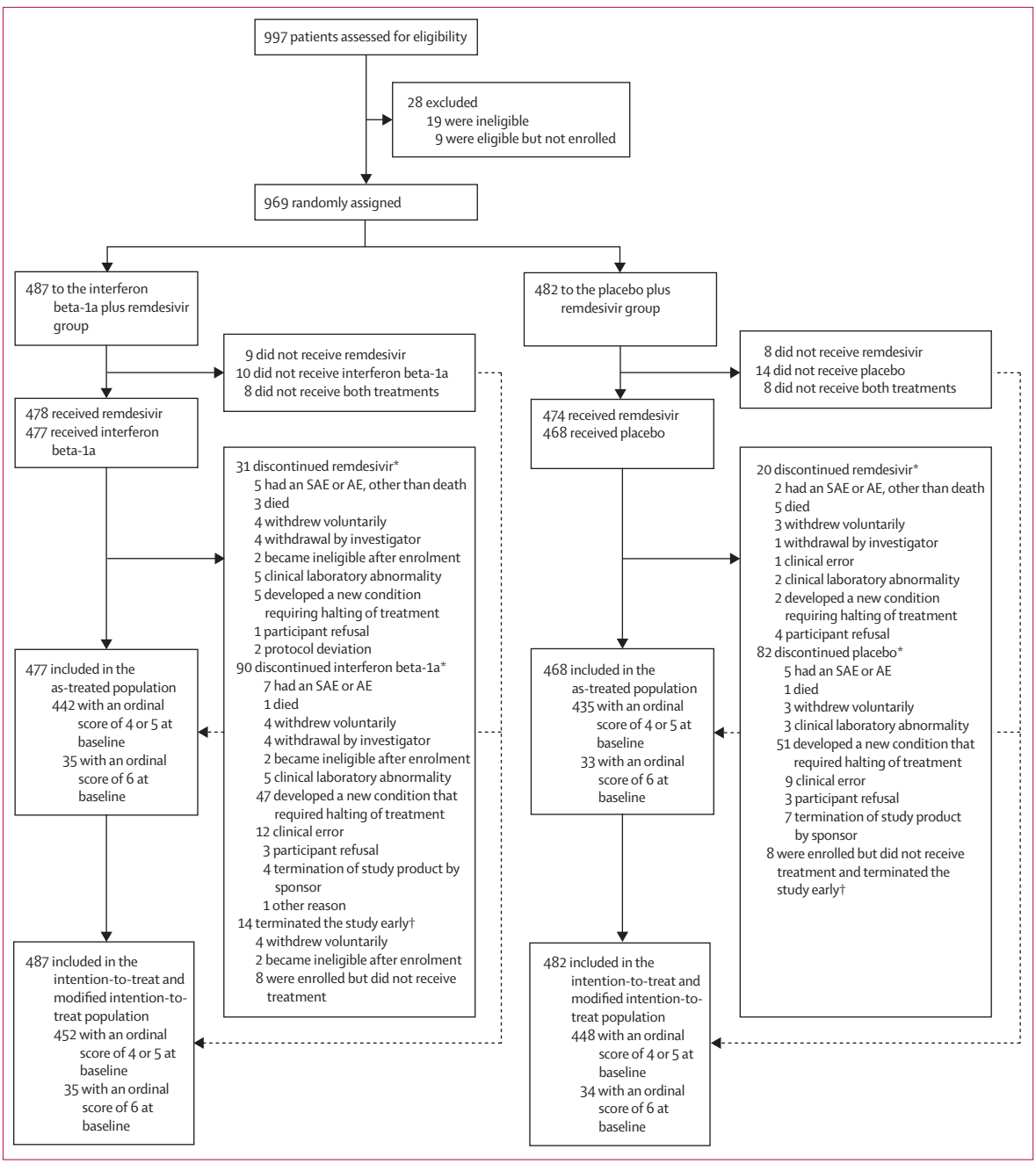

Figure 1: **Trial profile**
Definitions of ordinal scale scores are provided in the appendix (p 22). AE=adverse event. SAE=serious adverse event. *Discontinued for reasons other than hospital discharge. †Early termination numbers include only those patients who did not die or recover.

distribution of the study groups) at 14 days. Other secondary outcome measures were time to improvement by one or two categories from baseline ordinal score; clinical status according to the ordinal scale at days 3, 5, 8, 11, 15, 22, and 29; mean change in the ordinal scale from day 1 to days 3, 5, 8, 11, 15, 22, and 29; time to discharge or to a NEWS of 2 or less and maintained for 24 h, whichever occurred first; change in NEWS from day 1 to days 3, 5, 8, 11, 15, and 29; number of days of supplemental oxygen, and non-invasive ventilation or high-flow oxygen (if on these at baseline); incidence and duration of new supplemental oxygen use, non-invasive ventilation or high-flow oxygen, and invasive ventilation or extracorporeal membrane oxygenation; duration of hospitalisation up to day 29 (patients who remained hospitalised at day 29 were assigned value of 28 days);

mortality at 14 and 28 days after enrolment; and changes in laboratory values over time. Secondary safety outcome measures included the incidence of grade 3 and 4 adverse events and serious adverse events that occurred up to day 29, discontinuation or temporary suspension of study product administration for any reason, and changes in assessed laboratory values over time.

Statistical analysis

The primary analysis was a log-rank test of time to recovery between the interferon beta-1a plus remdesivir group and the placebo plus remdesivir group, stratified by disease severity. The population analysed was the modified intention-to-treat population. Both the intention-to-treat and modified intent-to-treat population include all randomised patients but the modified intention-to-treat population classifies patients according to actual baseline disease severity as opposed to the severity recorded at baseline. The recovery rate ratio (for the interferon beta-1a plus remdesivir group relative to the placebo plus remdesivir group) was reported for the primary outcome, with a recovery rate ratio greater than 1 indicating an improvement for the combination treatment. Analysis of the key secondary outcome tested the difference in the ordinal score distribution between the interferon beta-1a plus remdesivir group and the placebo plus remdesivir group at day 14 by use of the common odds ratio from a proportional odds model, stratifying by disease severity at baseline. The study was designed to have 85% power for detecting a recovery rate ratio of 1·25 with a two-sided type I error rate of 5%. In accordance with the protocol, an interim analysis was done at approximately 50% information (ie, information time was computed on the basis of the observed number of recoveries compared with the number of recoveries required to power the trial). Symmetric boundaries were derived from a Lan-DeMets spending function that corresponds closely to the O'Brien-Fleming boundaries. There was a single primary hypothesis test. For secondary outcomes, no multiplicity adjustments were made. Safety was assessed in the as-treated population, defined as all patients who had received at least one dose of the assigned treatment. All other analyses reported were done in the modified intention-to-treat population. Prespecified subgroup analyses included geographical region, duration of symptoms before randomisation, race, ethnicity, comorbidities, age, sex, and severity of disease. More details of the statistical analyses can be found in the appendix (pp 272–435).

Statistical analyses were done using SAS version 9.4 and R version 4.0.2. This study is registered with ClinicalTrials.gov, NCT04492475.

Role of the funding source

The ACTT-3 protocol was designed and written by the ACTT investigators and the study sponsor (the National Institute of Allergy and Infectious Diseases [NIAID]), with input from the manufacturer of interferon beta-1a, EMD Serono (Rockland, MA, USA). 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. The sponsor and staff from Emmes, which is funded by the sponsor, analysed the data.

Results

Between Aug 5, 2020, and Nov 11, 2020, 997 hospitalised patients were assessed for eligibility, of whom 969 were enrolled and randomly assigned to the interferon beta-1a plus remdesivir group (n=487) or to the placebo plus

	Interferon beta-1a plus remdesivir group (n=487)	Placebo plus remdesivir group (n=482)	All participants (n=969)
Sex			
Male	297 (61%)	266 (55%)	563 (58%)
Female	190 (39%)	216 (45%)	406 (42%)
Ethnicity			
Not Hispanic or Latino	323 (66%)	317 (66%)	640 (66%)
Hispanic or Latino	154 (32%)	157 (33%)	311 (32%)
Not reported or unknown	10 (2%)	8 (2%)	18 (2%)
Race			
American Indian or Alaska Native	8 (2%)	3 (1%)	11 (1%)
Asian	44 (9%)	39 (8%)	83 (9%)
Native Hawaiian or other Pacific Islander	4 (1%)	5 (1%)	9 (1%)
Black or African American	76 (16%)	84 (17%)	160 (17%)
White	299 (61%)	285 (59%)	584 (60%)
Multi-racial	2 (<1%)	3 (1%)	5 (1%)
Unknown or other	54 (11%)	63 (13%)	117 (12%)
Geographical region			
North America	460 (94%)	457 (95%)	917 (95%)
Asia	27 (6%)	25 (5%)	52 (5%)
Mean age, years	58·3 (15·8)	59·1 (16·1)	58·7 (15·9)
Age category, years			
<40	65 (13%)	59 (12%)	124 (13%)
40–64	236 (48%)	245 (51%)	481 (50%)
≥65	186 (38%)	178 (37%)	364 (38%)
Mean duration of symptoms before enrolment, days*	8·7 (4·4)	8·5 (4·3)	8·6 (4·3)
Ordinal score at enrolment			
4	84 (17%)	68 (14%)	152 (16%)
5	368 (76%)	380 (79%)	748 (77%)
6	35 (7%)	34 (7%)	69 (7%)
Number of comorbidities at baseline†			
Any	435 (89%)	434 (90%)	869 (90%)
None	45 (9%)	42 (9%)	87 (9%)
1	101 (21%)	104 (22%)	205 (21%)
≥2	333 (68%)	329 (68%)	662 (68%)
Unknown	8 (2%)	7 (1%)	15 (2%)

(Table 1 contines on next page)

	Interferon beta-1a plus remdesivir group (n=487)	Placebo plus remdesivir group (n=482)	All participants (n=969)
(Continued from previous page)			
Comorbidities at baseline‡			
Hypertension	282/481 (59%)	277/478 (58%)	559/959 (58%)
Obesity	285/480 (59%)	270/477 (57%)	555/957 (58%)
Type 2 diabetes	177/481 (37%)	175/478 (37%)	352/959 (37%)
Depression or psychotic disorder	80/479 (17%)	90/478 (19%)	170/957 (18%)
Coronary artery disease	60/479 (13%)	66/476 (14%)	126/955 (13%)
Asthma	64/481 (13%)	58/478 (12%)	122/959 (13%)
Chronic kidney disease	67/478 (14%)	45/478 (9%)	112/956 (12%)
Chronic respiratory disease	51/481 (11%)	54/478 (11%)	105/959 (11%)
Thyroid disease	52/481 (11%)	52/478 (11%)	104/959 (11%)
Mean BMI, kg/m²	32·8 (8·4)	33·2 (9·4)	33·0 (8·9)

Data are n (%), mean (SD), or n/N (%). Definitions of ordinal scale scores are provided in the appendix (p 20). *Data were missing for 15 participants. †Comorbidity counts include patients with asthma, cancer, cardiac arrhythmia, cardiac valvular disease, chronic kidney disease, chronic liver disease, chronic oxygen requirement, chronic respiratory disease, coagulopathy, congestive heart failure, coronary artery disease, deep vein thrombosis or pulmonary embolism, depression or psychotic disorder, type 1 diabetes, type 2 diabetes, epilepsy or a history of two or more seizures, hypertension, immune deficiency (acquired or innate), obesity, systemic lupus erythematosus, autoimmune hepatitis, other autoimmune diseases, or thyroid disease. ‡Percentages are based on the number of participants with data available for the individual comorbidity.

Table 1: **Baseline clinical and demographic characteristics of patients**

remdesivir group (n=482; figure 1). The trial initially enrolled patients with an ordinal score of 4, 5, or 6. On Sept 4, 2020, after 270 patients had been enrolled (138 in the placebo plus remdesivir group and 131 in the interferon beta-1a plus remdesivir group), the study was modified to no longer include patients with an ordinal score of 6 after a preplanned DSMB review noted an increase in severe adverse events in these patients. The study remained open to patients with an ordinal score of 4 and 5 at baseline after the DSMB confirmed no safety signal in these categories. The intention-to-treat population included 487 patients in the interferon beta-1a plus remdesivir group (452 with an ordinal score of 4 or 5 at baseline, and 35 with an ordinal score of 6 at baseline) and 482 patients in the placebo plus remdesivir group (448 with an ordinal score of 4 or 5 at baseline, and 34 with an ordinal score of 6 at baseline). Of all patients assigned to the interferon beta-1a plus remdesivir group, 477 (98%) received at least one dose of the assigned treatment, and of those assigned to the placebo plus remdesivir group, 468 (97%) received at least one dose of the assigned treatment. The mean age of all 969 patients was 58·7 years (SD 15·9), 563 (58%) were male, and 406 (42%) were female (table 1). Overall, 584 (60%) of patients were White, 160 (17%) were Black or African American, 83 (9%) were Asian, 11 (1%) were American Indian or Alaskan Native, and 311 (32%) were Hispanic or Latino. The number of patients with at least one comorbidity at baseline was similar between the two groups (435 [89%] in the interferon beta-1a plus remdesivir group *vs* 434 [90%] in the placebo plus remdesivir group).

There was no difference in time to recovery between patients in the interferon beta-1a plus remdesivir group and those in the placebo plus remdesivir group (median 5 days, 95% CI not estimable [NE]–NE *vs* median 5 days, NE–NE; recovery rate ratio 0·99, 95% CI 0·87–1·13; p=0·88; table 2). In a prespecified subgroup analysis of patients with an ordinal score of 6 at baseline, the median time to recovery was not estimable (95% CI 12–NE) in the interferon beta-1a group (ie, >28 days) and 9 days (6–13) in the placebo plus remdesivir group (rate ratio 0·40, 95% CI 0·22–0·75; table 2; figure 2). There were no subgroups in which interferon beta-1a appeared to have benefit over placebo (figure 3).

The odds of clinical improvement at 14 days after randomisation, as assessed with the ordinal scale, were not different between interferon beta-1a plus remdesivir and placebo plus remdesivir groups (odds ratio 1·01, 95% CI 0·79–1·28; table 2). In patients with an ordinal score of 6 at baseline, the odds of clinical improvement at 14 days in the interferon beta-1a plus remdesivir group versus the placebo plus remdesivir group was 0·35 (0·15–0·85; table 2).

There was no difference in time to improvement by one point or two points on the ordinal scale, time to discharge or to a NEWS of 2 or less and maintained for 24 h (whichever occurred first), the number of days of requiring supplemental oxygen (among patients on supplemental oxygen at baseline), the number of patients who started supplemental oxygen (among those who did not need supplemental oxygen at baseline), the number of days on high-flow oxygen or non-invasive ventilation, or the number of patients who started high-flow oxygen or non-invasive ventilation between the interferon beta-1a plus remdesivir and placebo plus remdesivir groups (table 3). There was also no difference between groups in the duration of initial hospitalisation or in the proportion of patients readmitted to hospital (table 3). Finally, no difference in the proportion of patients requiring mechanical ventilation among those with an ordinal scale 4 or 5 at baseline was observed between the two groups.

21 (4%) of 487 patients in the interferon beta-1a plus remdesivir group and 16 (3%) of 482 patients in the placebo plus remdesivir group died during the 28-day follow-up period. Kaplan-Meier estimates of mortality at 28 days after randomisation were 5% (95% CI 3–7) in the interferon beta-1a plus remdesivir group and 3% (2–6) in the placebo plus remdesivir group (hazard ratio 1·33, 95% CI 0·69–2·55; table 2). Among patients with an ordinal score of 6 at baseline, seven (20%) of 35 patients in the interferon beta-1a plus remdesivir group died (Kaplan-Meier estimate 21%, 95% CI 11–39) and four (12%) of 34 patients in the placebo plus remdesivir group died (12%, 5–30; hazard ratio 1·74, 95% CI 0·51–5·93).

Among patients with an ordinal score of 4 or 5 at baseline, grade 3 or 4 adverse events were reported in 172 (39%) of 442 patients in the interferon beta-1a plus remdesivir group and in 138 (32%) of 435 in the placebo plus remdesivir group (appendix p 29).

	Overall			Ordinal score 4			Ordinal score 5			Ordinal score 6		
	Interferon beta-1a plus remdesivir group (n=487)	Placebo plus remdesivir (n=482)	RRR, HR, or OR (95% CI); p value*	Interferon beta-1a plus remdesivir group (n=84)	Placebo plus remdesivir (n=68)	RRR, HR, or OR (95% CI); p value*	Interferon beta-1a plus remdesivir group (n=368)	Placebo plus remdesivir (n=380)	RRR, HR, or OR (95% CI); p value	Interferon beta-1a plus remdesivir group (n=35)	Placebo plus remdesivir (n=34)	RRR, HR, or OR (95% CI); p value*
Recovery	..	..	..	..	..	..	..	..	..	..	..	..
Number of patients who had recovered (%)	435 (89%)	450 (93%)	..	79 (94%)	67 (99%)	..	340 (92%)	356 (94%)	..	16 (46%)	27 (79%)	..
Median time to recovery (95% CI), days	5 (NE–NE)	5 (NE–NE)	RRR 0·99 (0·87–1·13); p=0·88	4 (4–5)	4 (3–5)	RRR 0·98 (0·70–1·36); p=0·89	5 (4–5)	5 (4–5)	RRR 1·05 (0·90–1·22); p=0·54	NE (12–NE)	9 (6–13)	RRR 0·40 (0·22–0·75); p=0·0031
Ordinal scale at 14 days†	..	..	OR 1·01 (0·79–1·28); p=0·95	..	..	OR 0·95 (0·52–1·74); p=0·87	..	..	OR 1·14 (0·87–1·50); p=0·35	..	..	OR 0·35 (0·15–0·85); p=0·020
Mortality over first 14 days‡	..	..	..	..	..	..	..	..	..	..	..	..
Number of deaths (%)§	8 (2%)	11 (2%)	..	1 (1%)	0	..	3 (1%)	9 (2%)	..	4 (11%)	2 (6%)	..
Kaplan-Meier estimate of mortality (95% CI)	2% (1–3)	2% (1–4)	HR 0·73 (0·30–1·83); p=0·50	1% (0–8)	NE	NE	1% (0–3)	2% (1–5)	HR 0·35 (0·09–1·28); p=0·11	12% (5–28)	6% (2–22)	HR 1·96 (0·36–10·70); p=0·44
Mortality over entire study period¶	..	..	..	..	..	..	..	..	..	..	..	..
Number of deaths (%)§	21 (4%)	16 (3%)	..	2 (2%)	0	..	12 (3%)	12 (3%)	..	7 (20%)	4 (12%)	..
Kaplan-Meier estimate of mortality (95% CI)	5% (3–7)	3% (2–6)	HR 1·33 (0·69–2·55); p=0·39	2% (1–9)	NE	NE	3% (2–6)	3% (2–6)	HR 1·04 (0·47–2·32); p=0·92	21% (11–39)	12% (5–30)	HR 1·74 (0·51–5·93); p=0·38

Definitions of ordinal scale scores are provided in the appendix (p 22). RRRs and ORs greater than 1 indicate a benefit for the interferon beta-1a plus remdesivir group, and HRs less than 1 indicate benefit for the interferon beta-1a plus remdesivir group. All p values and 95% CIs have not been adjusted for multiple comparisons. HR=hazard ratio. NE=not estimable. OR=odds ratio. RRR=recovery rate ratio. *RRRs and HRs were calculated by use of the stratified Cox model and p values were calculated with the stratified log-rank test (overall model stratified by actual disease severity) and the OR was calculated with a proportional odds model (overall model adjusted for actual baseline ordinal score). †The ordinal scale at 14 days after randomisation (visit window from 12 to 16 days after randomisation) is the patient's worst score on the ordinal scale during the 24-h assessment period. ‡Mortality over the first 14 days treats all patients who were still alive up to 14 days after enrolment as censored on day 14 (ie, considering 14 days as the maximum follow-up time). §Raw percentages might differ from the Kaplan-Meier estimates due to censoring. ¶Mortality over the entire study period uses all study data and censors patients who completed follow-up alive at 28 days after enrolment.

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

The most common non-serious grade 3 or 4 adverse event occurring in at least 5% of all patients was decreased lymphocyte count (33 [7%] of 477 patients in the interferon beta-1a plus remdesivir group *vs* 33 [7%] of 468 in the placebo plus remdesivir group; appendix p 30).

Among patients with an ordinal score of 4 or 5 at baseline, 65 (15%) of 442 patients in the interferon beta-1a plus remdesivir group had a serious adverse event compared with 58 (13%) of 435 in the placebo plus remdesivir group (appendix p 29). The most common serious adverse events were respiratory, thoracic, and mediastinal disorders. 37 (8%) patients in the interferon beta-1a plus remdesivir group and 34 (8%) patients in the placebo plus remdesivir group had a respiratory adverse event including respiratory failure, acute respiratory failure, hypoxia, dyspnoea, and respiratory distress (appendix pp 31–32).

Among patients with an ordinal score of 6 at baseline, grade 3 or 4 adverse events were reported in 21 (60%) of 35 in the interferon beta-1a plus remdesivir group and in 12 (36%) of 33 in the placebo plus remdesivir group (appendix p 33). The most common non-serious grade 3 or 4 adverse events occurring in at least 5% of patients with an ordinal score of 6 at baseline were decreased lymphocyte count (three [9%] in the interferon beta-1a plus remdesivir group *vs* six [18%] in the placebo plus remdesivir group); decreased haemoglobin concentrations (four [11%] *vs* two [6%]); a decrease in eGFR (four [11%] *vs* one [3%]); acute kidney injury (one [3%] *vs* four [12%]); deep vein thrombosis (three [9%] *vs* none); and decreased blood albumin concentrations (two [6%] *vs* none; appendix p 34).

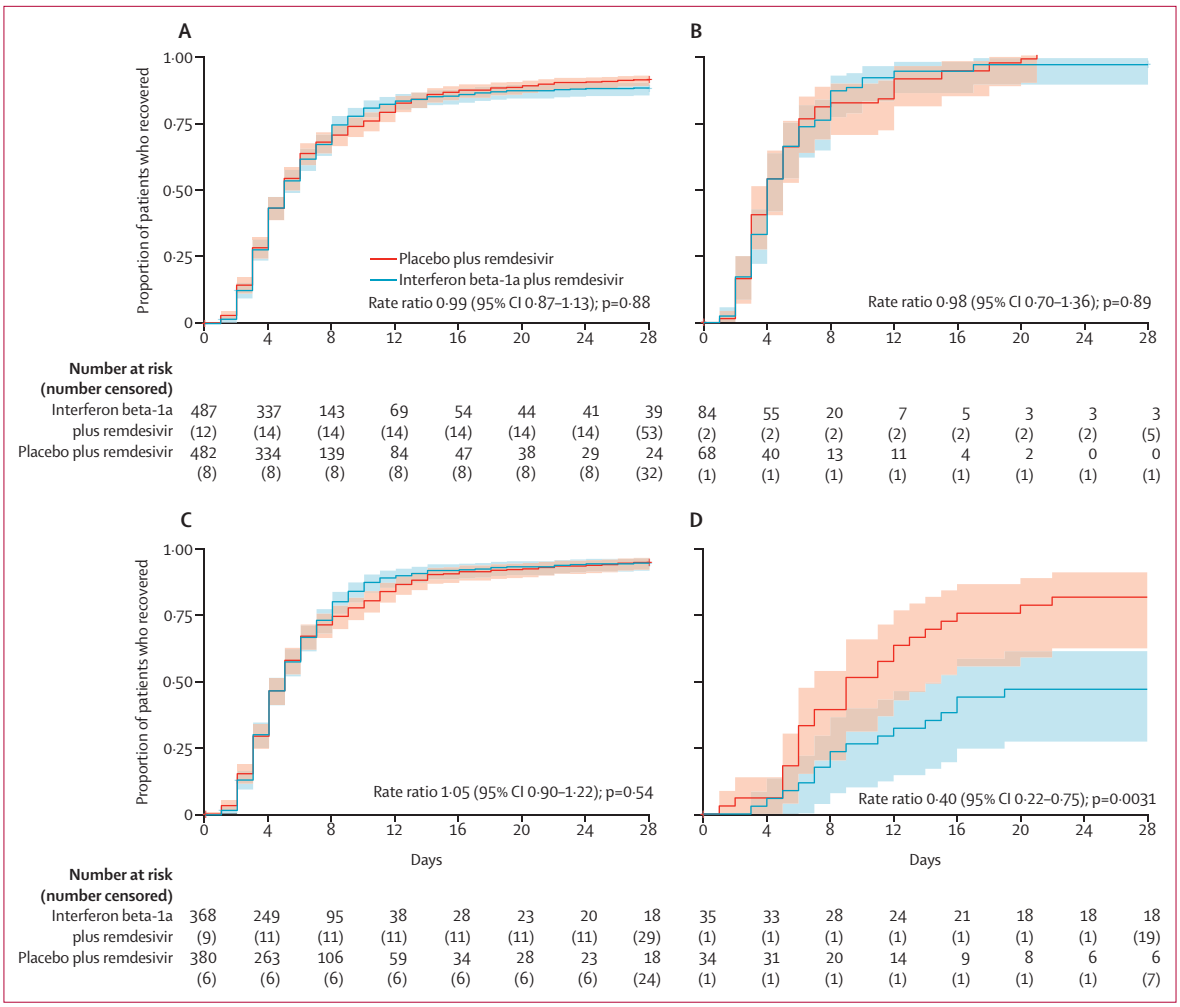

Figure 2: **Kaplan-Meier estimates of the cumulative proportion of patients who recovered overall (A) and with a baseline ordinal scale of 4 (B), 5 (C), and 6 (D)**
Shaded regions represent 95% CIs. Definitions of ordinal scale scores are provided in the appendix (p 22).

21 (60%) patients with an ordinal score of 6 at baseline in the interferon beta-1a plus remdesivir group and eight (24%) patients in the placebo plus remdesivir group had a serious adverse event; no serious adverse events were considered related to the investigational product. The most common serious adverse events in patients with a baseline ordinal score of 6 were respiratory, thoracic, and mediastinal disorders. 19 (54%) patients in the interferon beta-1a plus remdesivir group and seven (21%) patients in the placebo plus remdesivir group had a respiratory adverse event, including respiratory failure, acute respiratory failure, hypoxia, dyspnoea, and respiratory distress (appendix p 35). The small sample size of this cohort of patients with an ordinal score of 6 at baseline did not allow for a definitive conclusion on whether the outcomes were due to interferon beta-1a or not, but based on the potential safety issues, the DSMB decided to stop the enrolment of these patients.

Among the 69 patients with an ordinal score of 6 at baseline, those randomly assigned to the interferon beta-1a plus remdesivir group were more likely to be male (25 [71%] of 35 *vs* 19 [56%] of 34), present to hospital within 8 days of symptom onset (22 [63%] *vs* 15 [44%]), be older (median age 58·9 [SD 13·1] years *vs* 54·7 years [15·0]), have baseline D-dimer concentrations of ≥2·025 mg/L (eight [23%] *vs* six [18%]), and have baseline C-reactive protein concentrations of ≥100·0 mg/L (21 [60%] *vs* 16 [47%]) than those in the placebo plus remdesivir group (appendix pp 26–27, 44, 96). Additionally, patients randomly assigned to the interferon beta-1a plus remdesivir group were more likely than those in the placebo plus remdesivir group to have comorbidities shown in other studies to be associated with severe disease:[18,19,20] type 2 diabetes (19 [54%] *vs* 11 [32%]), coronary artery disease (20 [60%] *vs* two [6%]), hypertension 25 [71%] *vs* 19 [56%]), chronic kidney disease (eight [24%] *vs* three [9%]), and obesity (21 [60%] *vs* 22 [65%]; appendix pp 25, 97). Univariate and multivariate Cox proportional hazards models were created, adjusting for these baseline characteristics for

the primary endpoint, but all models yielded recovery rate ratios consistent with the estimated treatment effect in the primary unadjusted model, indicating worse outcomes with interferon beta-1a in those on high-flow oxygen at baseline (appendix pp 36–37).

Discussion

The results of our study suggest that interferon beta-1a plus remdesivir is not associated with clinical benefit compared with remdesivir alone in hospitalised patients with COVID-19. The primary outcome of time to recovery was 5 days in both treatment groups. Additionally, no difference in treatment effect was observed among any secondary outcomes. Five completed, open-label, randomised trials[16,17,21–23] evaluated the role of interferon beta in hospitalised adult patients with COVID-19, of which three suggested efficacy of interferon beta. There are several potential reasons for the results of these trials differing from those of ACTT-3. First, the mechanism of action of interferon is to decrease viral replication. ACTT-3 evaluated interferon beta-1a in combination with remdesivir, which is an effective antiviral; therefore, interferon might not have had additional antiviral effects. Second, there are fundamental differences in trial design between ACTT-3 and these previous trials. The trial by Hung and colleagues[16] showed a significant reduction in the time to a negative viral load in nasopharyngeal swabs and other respiratory samples, time to clinical improvement, and duration of hospital stay in patients who received interferon beta-1b compared with those who did not. Compared with the ACTT-3 trial, this previous trial enrolled patients with milder illness (only 17 [13%] of 127 patients required supplemental oxygen, the median NEWS among all patients was 2, and no deaths were reported) and patients received treatment earlier in the disease course (median duration of illness was 5 days in the study by Hung and colleagues[16] compared with 9 days in the ACTT-3 trial), which could explain the antiviral effects of interferon and the observed clinical benefit in this group. The trial by Davoudi-Monfared and colleagues[17] found a significant difference in the proportion of patients discharged by day 14 and 28-day mortality in patients who received interferon beta-1a compared with controls. The trial by Rahmani and colleagues[21] found that patients who received interferon beta-1b had a shorter time to clinical improvement, were more likely to be discharged by day 14, and were less likely to be admitted to the intensive care unit compared with controls. Finally, the Solidarity[22] and DisCoVeRy[23] trials, which primarily aimed to evaluate in-hospital mortality and clinical status at day 15, respectively, did not find differences between interferon beta-1a treatment and usual care. None of these trials were double-blinded, increasing the potential for bias in treatment selection, patient assessment, and patient enrolment.

The ACTT-3 trial used a placebo-controlled, double-blind design, stratified by balanced baseline disease severity. The trial measured clinically relevant primary and secondary outcomes, all indicating that treatment with interferon beta-1a does not add clinical benefit to hospitalised adult patients with COVID-19. Although our results contrast those of other observational studies and randomised trials, considering the size and design of ACTT-3, it is unlikely that subcutaneous interferon beta-1a shows efficacy in patients hospitalised with COVID-19.

Even though no efficacy or clinically significant differences in safety were observed between the interferon beta-1a plus remdesivir and placebo plus remdesivir groups overall, patients requiring high-flow supplemental oxygen or non-invasive ventilation (ie, those with an ordinal score of 6) at baseline who received interferon beta-1a appeared to have worse outcomes and more serious adverse events, particularly worsening of respiratory status, than those who received placebo. For this reason, although no definitive conclusions could be reached about whether these outcomes were due to

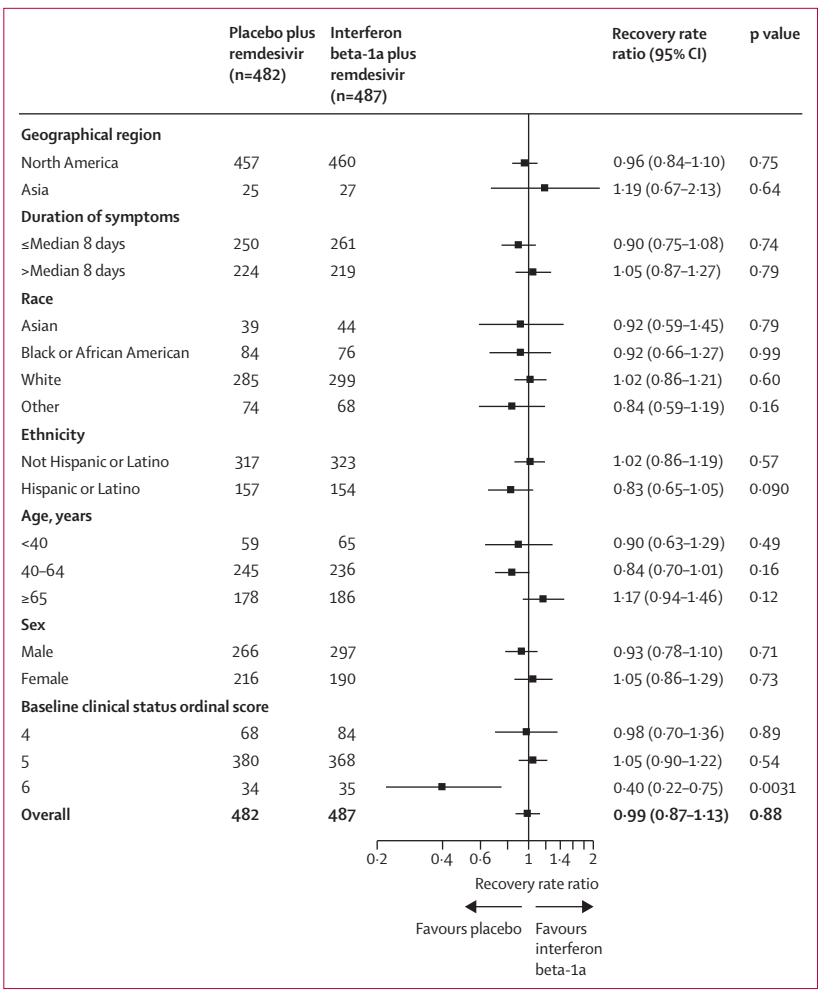

Figure 3: **Forest plot showing recovery rate ratios for time to recovery by subgroup in the modified intention-to-treat population**

Each point represents the recovery rate ratio estimate and 95% CIs.

	Ordinal score 4 or 5			Ordinal score 6		
	Interferon beta-1a plus remdesivir (n=452)	Placebo plus remdesivir (n=448)	Recovery rate ratio (95% CI) or difference (95% CI)*	Interferon beta-1a plus remdesivir (n=35)	Placebo plus remdesivir (n=34)	Recovery rate ratio (95% CI) or difference (95% CI)
Time to clinical improvement						
Median time to improvement by one category or discharge, days (95% CI)	4 (NE–NE)	4 (NE–NE)	Rate ratio 1·03 (0·90 to 1·17)	15 (7–NE)	5 (4–7)	Rate ratio 0·39 (0·22 to 0·70)
Median time to improvement by two categories or discharge, days (95% CI)	5 (4–5)	5 (4–5)	Rate ratio 1·04 (0·91 to 1·19)	NE (11–NE)	9 (6–13)	Rate ratio 0·42 (0·23 to 0·77)
Median time to discharge or a NEWS score of ≤2 for 24 h, days (95% CI)†	4 (4–5)	4 (4–5)	Rate ratio 1·08 (0·93 to 1·26)	NE (10–NE)	9 (6·0–11·0)	Rate ratio 0·39 (0·21 to 0·72)
Hospitalisation						
Median duration of initial hospitalisation, days (IQR)‡	6 (4–9)	6 (4–10)	Difference 0 (–0·6 to 0·6)	28 (9–28)	10 (7–17)	Difference 18·0 (10·7 to 25·3)
Median duration of initial hospitalisation among patients who survived, days (IQR)	6 (4–9)	6 (4–9)	Difference 0 (–0·5 to 0·5)	17 (9–28)	10 (7–14)	Difference 6·0 (–1·8 to 13·8)
Proportion of patients readmitted (95% CI)	0·06 (0·04–0·09)	0·05 (0·03–0·07)	Difference 0·01 (–0·02 to 0·05)	0·06 (0·01–0·28)	0·04 (0·01–0·18)	Difference 0·03 (–0·13 to 0·25)
Oxygen supplementation						
Median duration on oxygen supplementation (if on oxygen supplementation at baseline), days (IQR)‡	6 (3–23)	8 (3–24)	Difference –1·0 (–2·8 to 0·8)	28 (15–28)	22 (9–28)	Difference 6·0 (–1·3 to 13·3)
Proportion of patients on new oxygen supplementation during the study (95% CI)	0·51 (0·41–0·62)	0·57 (0·46–0·68)	Difference –0·1 (–0·2 to 0·1)	NA	NA	NA
Median duration of new oxygen supplementation, days (IQR)‡	3 (1–10)	3 (1–8)	Difference 0 (–3·2 to 3·2)	NA	NA	NA
Non-invasive ventilation or high-flow oxygen						
Median duration of non-invasive ventilation or high-flow oxygen use during the study (if on these interventions at baseline), days (IQR)‡	NA	NA	NA	6 (3–28)	6 (3–10)	Difference 0 (–3·5 to 3·5)
Proportion of patients on new non-invasive ventilation or high-flow oxygen during the study (95% CI)	0·15 (0·12–0·18)	0·15 (0·12–0·19)	Difference 0 (–0·05 to 0·05)	NA	NA	NA
Median duration of new non-invasive ventilation or high-flow oxygen use during the study, days (IQR)‡	5 (2–12)	6 (3–14)	Difference –1·0 (–3·7 to 1·7)	NA	NA	NA
Mechanical ventilation or ECMO						
Proportion of patients on new mechanical ventilation or ECMO during study (95% CI)	0·04 (0·03–0·07)	0·05 (0·03–0·07)	Difference 0 (–0·03 to 0·03)	0·54 (0·38–0·70)	0·15 (0·06–0·30)	Difference 0·4 (0·2 to 0·6),
Median duration of new mechanical ventilation or ECMO use during the study (IQR)‡	28 (15–28)	27 (12–28)	Difference 0 (–8·4 to 8·4)	23 (14–28)	28 (20–28)	Difference –5·0 (–13·2 to 3·2)

ECMO=extracorporeal membrane oxygenation. NA=not applicable. NE=not estimable. NEWS=National Early Warning Score. *Differences and the associated 95% CIs are estimated with quantile regression and might not match the difference in raw median values in small sample sizes. †Analysis was restricted to patients with a NEWS of greater than 2 at baseline. ‡Includes imputations for patients who had died.

Table 3: **Secondary outcomes according to ordinal score at baseline in the modified intention-to-treat population**

interferon beta-1a, the DSMB made the recommendation to stop enrolment in the ordinal score 6 group during a regularly scheduled DSMB review. It is possible that interferon beta-1a could have increased the inflammatory response, leading to more severe respiratory disease in these patients. However, it is also possible that this worse outcome was influenced by baseline imbalances between the interferon beta-1a plus remdesivir and placebo plus

remdesivir groups. None of the previous observational studies or randomised trials have observed safety issues with interferon. However, when adverse event reporting is limited to unexpected serious adverse reactions, signals of potential harm could be missed, attributing any worsening respiratory status in this population to COVID-19. ACTT-3 is the largest study thus far to collect comprehensive data on safety events.

Slight baseline imbalances in risk factors are expected given the sample size of this study. Post-hoc analyses suggested that the characteristics in which imbalances were observed were associated with a worse prognosis. However, univariate and multivariate Cox proportional hazards models adjusting for these baseline characteristics did not produce substantially different estimates of the treatment effect. Model limitations in small sample sizes make it difficult to fully assess the effect of baseline differences on the estimated treatment effect. Although, we cannot conclude that imbalances between the two groups are solely the cause of the worse outcomes observed in patients with an ordinal score of 6 at baseline who received interferon beta-1a compared with those who received placebo, we also cannot conclude that these imbalances do not play some role in explaining this difference.

As interferons are used routinely in the treatment of particular infections and other diseases, the results of this trial necessitate a nuanced interpretation. Our study does not inform on the efficacy of interferon beta-1a in patients with early-stage or mild disease, who do not require hospitalisation, nor on the effect of interferon beta-1a without concomitant use of steroids. IFN is suppressed early in SARS-CoV-2 infection, and early treatment could still be beneficial and needs to be evaluated in rigorous studies. Other routes of interferon administration, such as inhaled or intravenous, have been reported to have different mechanisms of action;[24,25] therefore, our findings should not be extrapolated beyond the subcutaneous route. Finally, this trial should not be interpreted as suggesting that chronic use of interferon is a risk factor for severe disease; our study was not designed to evaluate this outcome, and there have been no data to suggest an association between chronic interferon use and worse outcomes in COVID-19.

In conclusion, the combination of interferon beta-1a plus remdesivir was not superior to remdesivir alone in hospitalised patients with COVID-19 pneumonia. In the subgroup of patients who required high-flow oxygen at baseline, treatment with interferon beta-1a was associated with more adverse events and worse outcomes than placebo. Given the absence of benefit, subcutaneous interferon beta-1a treatment is not advised for patients hospitalised with COVID-19.

Contributors

The ACTT-3 protocol was designed and written by the ACTT investigators and NIAID study staff, with input from the manufacturer of interferon beta-1a, EMD Serono. All investigators and staff at participating sites enrolled the patients and collected the study data. JF, MM, TBo, and LD did the statistical analyses. The first draft of the manuscript was written by investigators at the top seven enrolling sites (ACK, AKM, TFP, NE, CAG, MKJ, and CRW) and NIAID study staff (LD, KMT, and JHB). All authors were given the opportunity to review, comment, and edit the manuscript. The authors, on behalf of the ACTT-3 study group (appendix pp 5-9), vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. All authors had full access to all data in the study and had final responsibility for the decision to submit for publication. ACK, LD, and JHB accessed and verified the data.

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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