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Statistical review of *Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial*

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The following review has been prepared in collaboration with members of the MRC-NIHR Trials Methodology Research Partnership[1]. The reviewers named above, and other, unnamed discussants of the paper, are all qualified statisticians with experience in clinical trials. Our objective is to provide a rapid review of publications, preprints and protocols from clinical trials of COVID-19 treatments, independent of journal specific review processes. We aim to provide timely, constructive, focused, clear advice aimed at improving both the research outputs under review, as well as future studies. Given our collective expertise (clinical trial statistics) our reviews focus on the designs of the trials and other statistical content (methods, presentation and accuracy of results, inferences). This review reflects the expert opinions of the named authors, and does not imply endorsement by the MRC-NIHR Trials Methodology Research Partnership, its wider membership, or any other organization.

Here we review *Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial* by Wang *et al* [2]*,* which was published in The Lancet, April 29, 2020.

Overall, this was a well-conducted, well-reported trial, which was faithful to a pre-registered, openly available study protocol. Our comments on the paper, detailed below, are all minor in nature. The trial ended early, roughly half-way to its planned sample size, once successful infection control efforts in the region made it difficult to recruit new patients. It is perhaps not surprising then that the study did not demonstrate any substantial effects of remdesivir, though the authors correctly noted that the study was too small to rule out potentially important effects. Regardless, it will be important for investigators and decision makers to take data from this study into account as our understanding of COVID-19 treatment grows.

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Study Summary

The paper reports a two-arm parallel randomized controlled trial planned in 453 patients hospitalized with rt-PCR confirmed COVID-19. The study was conducted in 10 COVID-19 treatment centers in Wuhan, China, between Feb 6 and March 12, 2020. Patients were randomized using a 2:1 allocation ratio to receive either standard-of-care plus intravenous remdesivir (200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions) or standard-of-care plus placebo. The primary outcome was the time to clinical improvement up to day-28 post-randomization, where clinical status was measured on a 6-category ordinal scale, ranging from *no longer hospitalized* to *death*, and improvement was then defined as moving down two or more categories (towards better outcomes) on this scale. Key secondary outcomes were clinical status at days 7, 14, and 28 (using the same ordinal measure); all-cause mortality at day-28; the frequency of invasive mechanical ventilation; the durations of oxygen therapy and hospital admission; and detection of viral RNA and viral load during the study period.

Recruitment to the study was stopped early (March 12), at the recommendation of the data safety and monitoring board, largely due to the success of infection control measures in Wuhan. This resulted in 236 patients in the intention-to-treat analysis sample (158:78). This timing also coincided with a planned interim analysis that was described in the pre-registered protocol and the paper. Overall, the results did not suggest any substantial differences in outcomes between the two study arms. The median time to clinical improvement in the remdesivir group was 21 days (IQR 13-28), vs 23 days (15-28) in the placebo arm (HR 1·23, 95% CI 0.87 to 1.75). Mortality at 28 days was also similar between the two groups (a risk difference of 1.1% favoring placebo; 95% CI −8.1 to 10.3). The authors reported no other meaningful differences between the two groups.

Based on these findings, the authors appropriately concluded that “this dose regimen of intravenous remdesivir was adequately tolerated but did not provide significant clinical or antiviral effects in seriously ill patients with COVID-19. However, we could not exclude clinically meaningful differences and saw numerical reductions in some clinical parameters. Ongoing studies with larger sample sizes will continue to inform our understanding of the effect of remdesivir on COVID-19.”

We sincerely thank the authors for their contribution to our collective understanding of COVID-19, for their commitment to the timely, clear, and complete dissemination of research results, and their transparency in pre-registering their full study protocol.

Minor points

- Similar to another COVID-19 trial we reviewed[3], this study used a 6-level ordinal endpoint for clinical status, ranging from *no longer hospitalized* to *death*. They then dichotomized this outcome, defining improved clinical status as moving down two or more categories (towards better outcomes) on this scale. This allowed the investigators to use a time-to-event analysis. In our previous review of the study with the same outcome, we commented that the dichotomization could lead to reduced power, which is a critique we still think has merit. However, in response[4], one of the statisticians on the previous paper we reviewed (Dr Thomas Jaki) made an important point, which was that the time spent utilizing hospital resources is an important outcome in the context of COVID-19, and that their dichotomization of the ordinal outcome was their approach to dealing with this important issue.

This ordinal outcome was previously proposed for use in influenza trials[5], seemingly to allow for a single, useful endpoint that could be used to accommodate multiple important outcomes observed in a patient population at various stages of disease. Its potential use in COVID-19 trials was noted in early reports from the WHO R&D Blueprint for COVID-19, but they have more recently suggested moving to a simpler endpoint[6]; and while a similar ordinal endpoint has been included in COVID-19 core outcome sets[7], the recommendation is to analyze it with ordinal models. Our own opinion is that studies should feel free to use multiple outcomes as needed if the goal is to understand a treatment's impact on both patient-focused outcomes, such as mortality and disability, where the element of timing is less pertinent, and resource usage outcomes, such as time spent in hospital or the ICU, where the element of timing is crucial[8]. Importantly, Wang *et al*, did exactly that, in addition to the dichotomized ordinal outcome, by including secondary outcomes such as mortality at 28 days and time spent on ECMO.

- The randomization was stratified, but the stratifier was not adjusted for in the reported analysis, meaning that the standard errors were not calculated correctly. Further, the analysis did not take advantage of prognostic covariates measured prior to randomization. Using multivariable models to adjust for these covariates would have led to more precise estimates of the treatment effects[9] and more appropriate conditional estimates of effects for non-linear models, and thus represents a missed opportunity to learn as much as possible with the data at hand.

- Patients were allocated in a 2:1 ratio (remdesivir vs placebo), but this choice wasn't justified in the paper. While there can be reasons for uneven allocation, it comes at a cost to the power and precision of the analysis, so it's important to balance any potential gains against this cost.

- The randomisation was well concealed with a central list created using random permuted blocks of 30 with a single two-level stratification factor. With this in mind, it was unusual that the actual allocation was exactly 2:1, given that there will have been at least one incomplete block.

- The timing for stopping the study early coincided with a planned interim analysis, which was noted in the pre-registered protocol. The authors, correctly in our opinion, decided to treat the reported analysis as final, rather than interim. This makes sense as there were no prior looks at the data, and the decision to stop the study when they did was not made in light of the data, but rather the impossibility for patient recruitment.

- The final follow-up was noted as April 10, but the analysis after early stopping was noted as taking place on March 29

- The majority of the secondary outcomes were reported as specified, though there were some omissions. The registration indicated analysis of clinical status at day 21, as well as days 7, 14 and 28, while the paper only reported the latter three. Similarly, the duration of ECMO was missing in the analysis and in general it is not clear how patients who started to receive mechanical ventilation after randomisation were dealt with in the analysis, which seems to presume they all were on it at the beginning. *Time to discharge* was analysed rather than *time to disease improvement*, as noted in the protocol, which was defined as discharge or a NEWS2 score ≤ 2, maintained for 24 hours. The text (but not the table) also presented time to improvement and time to deterioration based on a change of 1 point on the ordinal outcome, which was not prespecified.

- The subgroup analysis appears to have been prespecified, which is a positive, but it wasn't clear why *days of symptoms* was categorized, especially given the low power of the study. Further, the estimate appears to be based on a within-subgroup analysis, rather than the recommended approach of adding an interaction term in a multivariable model.

Open Data

No.

Open Analysis Code

No.

Pre-registered study design

Yes.

PubPeer

There may be comments on the PubPeer page for the published version of this paper.
https://pubpeer.com/publications/9C9A1AA1343F05CB5458B573C3694B

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CONSORT CHECKLIST

To support the review, we completed the CONSORT checklist [10] below. Material taken directly from the paper (or trial registry) is in *italics.* Our additional comments are in **bold**.

Title and abstract

1a Identification as a randomised trial in the title

Yes

1b Structured summary of trial design, methods, results, and conclusions.

Title: Identification of the study as randomised	Yes
Authors: Contact details for the corresponding author	Yes
Trial design: Description of the trial design (eg, parallel, cluster, non-inferiority)	No
Methods	
Participants: Eligibility criteria for participants and the settings where the data were collected	Yes
Interventions: Interventions intended for each group	Yes
Objective: Specific objective or hypothesis	No
Outcome: Clearly defined primary outcome for this report	Yes
Randomisation: How participants were allocated to interventions	Yes
Blinding (masking): Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	Yes
Results	
Numbers randomised: Number of participants randomised to each group	Yes
Recruitment: Trial status	Yes
Numbers analysed: Number of participants analysed in each group	Yes
Outcome: For the primary outcome, a result for each group and the estimated effect size and its precision	Yes
Harms: Important adverse events or side-effects	Yes
Conclusions: General interpretation of the results	Yes
Trial registration: Registration number and name of trial register	Yes
Funding: Source of funding	Yes

Introduction

Background and objectives

2a Scientific background and explanation of rationale

Yes, see introduction.

2b Specific objectives or hypotheses

However, the clinical and antiviral efficacy of remdesivir in COVID-19 remains to be established. Here, we report the results of a placebo-controlled randomised trial of remdesivir in patients with severe COVID-19.

Methods

Trial design

3a Description of trial design (such as parallel, factorial) including allocation ratio

This was an investigator-initiated, individually randomised, placebo-controlled, double-blind trial…

Eligible patients were randomly assigned (2:1) to either the remdesivir group or the placebo group.

Participants

4a Eligibility criteria for participants

Eligible patients were men and non-pregnant women with COVID-19 who were aged at least 18 years and were RT-PCR positive for SARS-CoV-2, had pneumonia confirmed by chest imaging, had oxygen saturation of 94% or lower on room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of 300 mm Hg or less, and were within 12 days of symptom onset. Eligible patients of child-bearing age (men and women) agreed to take effective contraceptive measures (including hormonal contraception, barrier methods, or abstinence) during the study period and for at least 7 days after the last study drug administration.

Exclusion criteria included pregnancy or breast feeding; hepatic cirrhosis; alanine aminotransferase or aspartate aminotransferase more than five times the upper limit of normal; known severe renal impairment (estimated glomerular filtration rate <30 mL/min per 1·73 m^2) or receipt of continuous renal replacement therapy, haemodialysis, or peritoneal dialysis; possibility of transfer to a non-study hospital within 72 h; and enrolment into an investigational

treatment study for COVID-19 in the 30 days before screening. The use of other treatments, including lopinavir–ritonavir, was permitted.

4b Settings and locations where the data were collected

The trial was done at ten hospitals in Wuhan, Hubei, China.

Interventions

5 The interventions for each group with sufficient details to allow replication, including how and when they were actually administered

Patients received either intravenous remdesivir (200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions) or the same volume of placebo infusions for a total of 10 days (both provided by Gilead Sciences, Foster City, CA, USA).

Outcomes

6a Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed

Patients were assessed once daily by trained nurses using diary cards that captured data on a six-category ordinal scale and safety from day 0 to 28 or death. Other clinical data were recorded using the WHO–International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) case record form.

The primary clinical endpoint was time to clinical improvement within 28 days after randomisation. Clinical improvement was defined as a two-point reduction in patients' admission status on a six-point ordinal scale, or live discharge from the hospital, whichever came first. The six-point scale was as follows: death=6; hospital admission for extracorporeal membrane oxygenation or mechanical ventilation=5; hospital admission for non-invasive ventilation or high-flow oxygen therapy=4; hospital admission for oxygen therapy (but not requiring high-flow or non-invasive ventilation)=3; hospital admission but not requiring oxygen therapy=2; and discharged or having reached discharge criteria (defined as clinical recovery—ie, normalisation of pyrexia, respiratory rate <24 breaths per minute, saturation of peripheral oxygen >94% on room air, and relief of cough, all maintained for at least 72 h)=1. The six-point scale was modified from the seven-point scale used in our previous COVID-19 lopinavir–ritonavir RCT by combining the two outpatient strata into one. [**paper**]

Time to Clinical Improvement (TTCI) [Censored at Day 28] [Time Frame: up to 28 days]
The primary endpoint is time to clinical improvement (censored at Day 28), defined as the time (in days) from randomization of study treatment (remdesivir or placebo) until a decline of two categories on a six-category ordinal scale of clinical status (1 = discharged; 6 = death) or live discharge from hospital.

Six-category ordinal scale:
6. Death; 5. ICU, requiring ECMO and/or IMV; 4. ICU/hospitalization, requiring NIV/ HFNC therapy; 3. Hospitalization, requiring supplemental oxygen (but not NIV/ HFNC); 2. Hospitalization, not requiring supplemental oxygen;
1. Hospital discharge or meet discharge criteria (discharge criteria are defined as clinical recovery, i.e. fever, respiratory rate, oxygen saturation return to normal, and cough relief).
Abbreviation: IMV, invasive mechanical ventilation; NIV, non-invasive mechanical ventilation; HFNC, High-flow nasal cannula. **[registry]**

Secondary outcomes were the proportions of patients in each category of the six-point scale at day 7, 14, and 28 after randomisation; all-cause mortality at day 28; frequency of invasive mechanical ventilation; duration of oxygen therapy; duration of hospital admission; and proportion of patients with nosocomial infection. Virological measures included the proportions of patients with viral RNA detected and viral RNA load (measured by quantitative RT-PCR). Safety outcomes included treatment-emergent adverse events, serious adverse events, and premature discontinuations of study drug. [**paper**]

- *Clinical status [Time Frame: days 7, 14, 21, and 28]*
- *Time to Hospital Discharge OR NEWS2 (National Early Warning Score 2) of ≤ 2 maintained for 24 hours. [Time Frame: up to 28 days]*
  All cause mortality [Time Frame: up to 28 days]
- *Duration (days) of mechanical ventilation [Time Frame: up to 28 days]*
- *Duration (days) of extracorporeal membrane oxygenation [Time Frame: up to 28 days]*
- *Duration (days) of supplemental oxygenation [Time Frame: up to 28 days]*
- *Length of hospital stay (days) [Time Frame: up to 28 days]*
- *Time to 2019-nCoV RT-PCR negativity in upper and lower respiratory tract specimens [Time Frame: up to 28 days]*
- *Change (reduction) in 2019-nCoV viral load in upper and lower respiratory tract specimens as assessed by area under viral load curve. [Time Frame: up to 28 days]*
- *Frequency of serious adverse drug events [Time Frame: up to 28 days]* **[registry]**

6b Any changes to trial outcomes after the trial commenced, with reasons

Sample size

7a How sample size was determined

The original design required a total of 325 events across both groups, which would provide 80% power under a one-sided type I error of 2·5% if the hazard ratio (HR) comparing remdesivir to placebo is 1·4, corresponding to a change in time to clinical improvement of 6 days assuming that time to clinical improvement is 21 days on placebo.

7b When applicable, explanation of any interim analyses and stopping guidelines

One interim analysis using triangular boundaries and a 2:1 allocation ratio between remdesivir and placebo had been accounted for in the original design. Assuming an 80% event rate within 28 days across both groups and a dropout rate of 10% implies that about 453 patients should be recruited for this trial (151 on placebo and 302 on remdesivir). The possibility for an interim analysis after enrolment of about 240 patients was included in the design if requested by the independent data safety and monitoring board. [**paper**]

One interim analysis for efficacy and futility will be conducted once half of the total number of events required had been observed...An interim analysis is planned for futility and efficacy using triangular boundaries. Additionally, sample size may be re-estimated at the interim analysis...The primary outcome is time to clinical improvement up to day 28. The total number of events required in this study is to be 325 events in total. [**protocol**]

Randomisation

Sequence generation

8a Method used to generate the random allocation sequence

The permuted block (30 patients per block) randomisation sequence, including stratification, was prepared by a statistician not involved in the trial using SAS software, version 9.4. [**paper**]

The allocation sequence is generated according to computer-generated random numbers. [**protocol**]

8b Type of randomisation; details of any restriction (such as blocking and block size)

Randomisation was stratified according to the level of respiratory support as follows: (1) no oxygen support or oxygen support with nasal duct or mask; or (2) high-flow oxygen, non-invasive ventilation, invasive ventilation, or extracorporeal membrane oxygenation.

The permuted block (30 patients per block) randomisation sequence, including stratification, was prepared by a statistician not involved in the trial using SAS software, version 9.4. [**paper**]

Patient randomisation is stratified based on respiratory support methods at the time of enrolment: (1) no oxygen support, oxygen support with nasal duct or mask; (2) high-flow oxygen, non-invasive ventilation, invasive ventilation/ECMO. [**protocol**]

Allocation concealment mechanism

9 Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned

Eligible patients were allocated to receive medication in individually numbered packs, according to the sequential order of the randomisation centre (Jin Yin-tan Hospital central pharmacy). Envelopes were prepared for emergency unmasking. [**paper**]

The allocation sequences are kept in sealed, opaque envelopes. Remdesivir and placebo are pre-blinded and stored in a secure area in the pharmacy at a temperature strictly controlled according to the protocol. An independent pharmacist is assigned to dispense the study drug in water-proof, sealed, opaque bags. [**protocol**]

Implementation

10 Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions

The allocation sequence was generated by the institutes of Materia Medica, CAMS & PUMC. Participants are enrolled by the investigators of each study site. A pharmacist in the central pharmacy assigns participants to interventions. [**protocol**]

Blinding

11a If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how

This is a double-blind trial. Trial participants, investigators, care providers, outcome assessors, and data analysts are all blinded. Treatment allocation will only be unblinded after database lock. [**protocol**]

11b If relevant, description of the similarity of interventions

Patients received either intravenous remdesivir (200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions) or the same volume of placebo infusions for a total of 10 days (both provided by Gilead Sciences, Foster City, CA, USA).

Statistical methods

12a Statistical methods used to compare groups for primary and secondary outcomes

Time to clinical improvement was portrayed by Kaplan-Meier plot and compared with a log-rank test. The HR and 95% CI for clinical improvement and HR with 95% CI for clinical deterioration were calculated by Cox proportional hazards model.

Other analyses include subgroup analyses for those receiving treatment 10 days or less vs more than 10 days after symptom onset, time to clinical deterioration (defined as one category increase or death), and for viral RNA load at entry.

The differences in continuous variables between the groups was calculated using Hodges-Lehmann estimation.

We present adverse event data on the patients' actual treatment exposure, coded using Medical Dictionary for Regulatory Activities.

Statistical analyses were done using SAS software, version 9.4.

12b Methods for additional analyses, such as subgroup analyses and adjusted analyses

Other analyses include subgroup analyses for those receiving treatment 10 days or less vs more than 10 days after symptom onset...

Results

Participant flow (a diagram is strongly recommended)

13a For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome

13b For each group, losses and exclusions after randomisation, together with reasons

Between Feb 6, 2020, and March 12, 2020, 255 patients were screened, of whom 237 were eligible (figure 1). 158 patients were assigned to receive remdesivir and 79 to receive placebo; one patient in the placebo group withdrew their previously written informed consent after randomisation, so 158 and 78 patients were included in the ITT population.

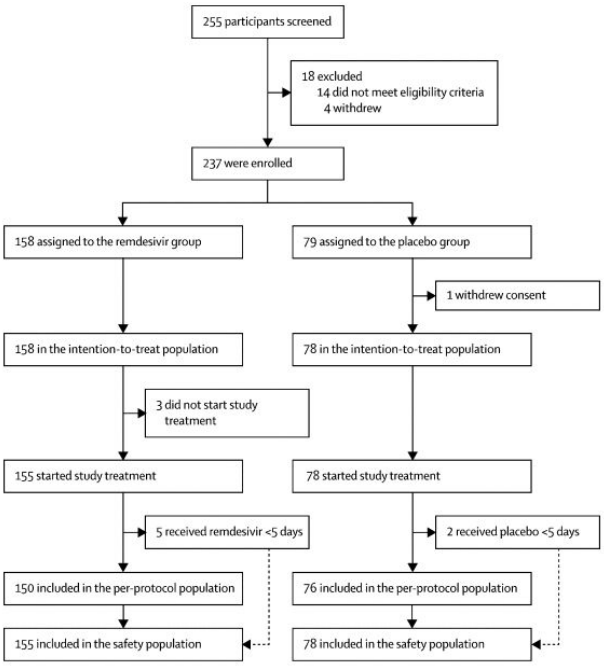

Figure 1 Trial profile

Recruitment

14a Dates defining the periods of recruitment and follow-up

Between Feb 6, 2020, and March 12, 2020, 255 patients were screened, of whom 237 were eligible.

14b Why the trial ended or was stopped

No patients were enrolled after March 12, because of the control of the outbreak in Wuhan and on the basis of the termination criteria specified in the protocol, the data safety and monitoring board recommended that the study be terminated and data analysed on March 29.

Baseline data

15 A table showing baseline demographic and clinical characteristics for each group

The median age of study patients was 65 years (IQR 56–71); sex distribution was 89 (56%) men versus 69 (44%) women in the remdesivir group and 51 (65%) versus 27 (35%) in the placebo group (table 1). The most common comorbidity was hypertension, followed by diabetes and coronary heart disease. Lopinavir–ritonavir was co-administered in 42 (18%) patients at baseline. Most patients were in category 3 of the six-point ordinal scale of clinical status at baseline. Some imbalances existed at enrolment between the groups, including more patients with hypertension, diabetes, or coronary artery disease in the remdesivir group than the placebo group. More patients in the control group than in the remdesivir group had been symptomatic for

10 days or less at the time of starting remdesivir or placebo treatment, and a higher proportion of remdesivir recipients had a respiratory rate of more than 24 breaths per min. No other major differences in symptoms, signs, laboratory results, disease severity, or treatments were observed between groups at baseline.

Median time from symptom onset to starting study treatment was 10 days (IQR 9–12). No important differences were apparent between the groups in other treatments received (including lopinavir–ritonavir or corticosteroids; table 2). During their hospital stay, 155 (66%) patients received corticosteroids, with a median time from symptom onset to corticosteroids therapy of 8·0 days (6·0–11·0); 91 (39%) patients received corticosteroids before enrolment.

	Remdesivir group (n=158)	Placebo group (n=78)
Age, years	66·0 (57·0-73·0)	64·0 (53·0-70·0)
Sex		
Men	89 (56%)	51 (65%)
Women	69 (44%)	27 (35%)
Any comorbidities	112 (71%)	55 (71%)
Hypertension	72 (46%)	30 (38%)
Diabetes	40 (25%)	16 (21%)
Coronary heart disease	15 (9%)	2 (3%)
Body temperature, °C	36·8 (36·5-37·2)	36·8 (36·5-37·2)
Fever	56 (35%)	31 (40%)
Respiratory rate >24 breaths per min	36 (23%)	11 (14%)
White blood cell count, × 10⁹ per L		
Median	6·2 (4·4-8·3)	6·4 (4·5-8·3)
4–10	108/155 (70%)	58 (74%)
<4	27/155 (17%)	12 (15%)
>10	20/155 (13%)	8 (10%)
lymphocyte count, × 10⁹ per L	0·8 (0·6-1·1)	0·7 (0·6-1·2)
≥1·0	49/155 (32%)	23 (29%)
<1·0	106/155 (68%)	55 (71%)
Platelet count, × 10⁹ per L	183·0 (144·0-235·0)	194·5 (141·0-266·0)
≥100	148/155 (95%)	75 (96%)
<100	7/155 (5%)	3 (4%)
Serum creatinine, μmol/L	68·0 (56·0-82·0)	71·3 (56·0-88·7)
≤133	151/154 (98%)	76 (97%)
>133	3/154 (2%)	2 (3%)
Aspartate aminotransferase, U/L	31·0 (22·0-44·0)	33·0 (24·0-48·0)
≤40	109/155 (70%)	49 (63%)
>40	46/155 (30%)	29 (37%)
Alanine aminotransferase, U/L	26·0 (18·0-42·0)	26·0 (20·0-43·0)
≤50	130/155 (84%)	66 (85%)
>50	25/155 (16%)	12 (15%)
Lactate dehydrogenase, U/L	339·0 (247·0-441·5)	329·0 (249·0-411·0)
≤245	36/148 (24%)	17//75 (23%)
>245	112/148 (76%)	58/75 (77%)
Creatine kinase, U/L	75·9 (47·0-131·1)	75·0 (47·0-158·0)
≤185	118/141 (84%)	54/67 (81%)
>185	23/141 (16%)	13/67 (19%)
National Early Warning Score 2 level at day 1	5·0 (3·0-7·0)	4·0 (3·0-6·0)
Stc-category scale at day 1		
2—hospital admission, not requiring supplemental oxygen	0	3 (4%)
3—hospital admission, requiring supplemental oxygen	129 (82%)	65 (83%)
4—hospital admission, requiring high-flow nasal cannula or non-invasive mechanical ventilation	28 (18%)	9 (12%)
5—hospital admission, requiring extracorporeal membrane oxygenation or invasive mechanical ventilation	0	1 (1%)

(Table 1 continues on next page)

Numbers analysed

16 For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups

The primary efficacy analysis was done on an intention-to-treat (ITT) basis with all randomly assigned patients. Time to clinical improvement was assessed after all patients had reached day 28; no clinical improvement at day 28 or death before day 28 were considered as right censored at day 28.

Outcomes and estimation

17a For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)

17b For binary outcomes, presentation of both absolute and relative effect sizes is recommended

Final follow-up was on April 10, 2020. In the ITT population, the time to clinical improvement in the remdesivir group was not significantly different to that of the control group (median 21·0 days [IQR 13·0–28·0] in the remdesivir group vs 23·0 days [15·0–28·0]; HR 1·23 [95% CI 0·87–1·75];

28-day mortality was similar between the two groups (22 [14%] died in the remdesivir group vs 10 (13%) in the placebo group; difference 1·1% [95% CI −8·1 to 10·3]).

Clinical improvement rates at days 14 and day 28 were also not significantly different between the groups, but numerically higher in the remdesivir group than the placebo group.

For patients assigned to the remdesivir group, duration of invasive mechanical ventilation was not significantly different, but numerically shorter than in those assigned to the control group; however, the number of patients with invasive mechanical ventilation was small.

No significant differences were observed between the two groups in length of oxygen support, hospital length of stay, days from randomisation to discharge, days from randomisation to death and distribution of six-category scale at day 7, day 14, and day 28 (table 3; appendix p 9).

Of 236 patients (158 in the remdesivir group and 78 in the placebo group) who were RT-PCR positive at enrolment, 37 (19%) of the 196 with data available had undetectable viral RNA on the nasopharyngeal and oropharyngeal swab taken at baseline. The mean baseline viral load of nasopharyngeal and oropharyngeal swabs was 4·7 log_{10} copies per mL (SE 0·3) in the remdesivir group and 4·7 log_{10} copies per mL (0·4) in the control group (table 1). Viral load decreased over time similarly in both groups (figure 3A).

The cumulative rate of undetectable viral RNA of nasopharyngeal and oropharyngeal swabs by day 28 was 153 (78%) of 196 patients, and the negative proportion was similar among patients receiving remdesivir and those receiving placebo (appendix p 4).

	Remdesivir group (n=158)	Placebo group (n=78)	Difference*
Time to clinical improvement	21·0 (13·0 to 28·0)	23·0 (15·0 to 28·0)	1·23 (0·87 to 1·75)†
Day 28 mortality	22 (14%)	10 (13%)	1·1% (−8·1 to 10·3)
Early (<10 days of symptom onset)	8/71 (11%)	7/47 (15%)	−3·6% (−16·2 to 8·9)
Late (>10 days of symptom onset)	12/84 (14%)	3/31 (10%)	4·6% (−8·2 to 17·4)
Clinical improvement rates			
Day 7	4 (3%)	2 (3%)	0·0% (−4·3 to 4·2)
Day 14	42 (27%)	18 (23%)	3·5% (−8·1 to 15·1)
Day 28	103 (65%)	45 (58%)	7·5% (−5·7 to 20·7)
Duration of invasive mechanical ventilation, days	7·0 (4·0 to 16·0)	15·5 (6·0 to 21·0)	−4·0 (−14·0 to 2·0)
Duration of invasive mechanical ventilation in survivors, days‡	19·0 (5·0 to 42·0)	42·0 (17·0 to 46·0)	−12·0 (−41·0 to 25·0)
Duration of invasive mechanical ventilation in non-survivors, days‡	7·0 (2·0 to 11·0)	8·0 (5·0 to 16·0)	−2·5 (−11·0 to 3·0)
Duration of oxygen support, days	19·0 (11·0 to 30·0)	21·0 (14·0 to 30·5)	−2·0 (−6·0 to 1·0)
Duration of hospital stay, days	25·0 (16·0 to 38·0)	24·0 (18·0 to 36·0)	0·0 (−4·0 to 4·0)
Time from random group assignment to discharge, days	21·0 (12·0 to 31·0)	21·0 (13·5 to 28·5)	0·0 (−3·0 to 3·0)
Time from random group assignment to death, days	9·5 (6·0 to 18·5)	11·0 (7·0 to 18·0)	−1·0 (−7·0 to 5·0)
Six-category scale at day 7			
1—discharge (alive)	4/154 (3%)	2/77 (3%)	OR 0·69 (0·41 to 1·17)§
2—hospital admission, not requiring supplemental oxygen	21/154 (14%)	16/77 (21%)	..
3—hospital admission, requiring supplemental oxygen	87/154 (56%)	43/77 (56%)	..
4—hospital admission, requiring high-flow nasal cannula or non-invasive mechanical ventilation	26/154 (17%)	8/77 (10%)	..
5—hospital admission, requiring extracorporeal membrane oxygenation or invasive mechanical ventilation	6/154 (4%)	4/77 (5%)	..
6—death	10/154 (6%)	4/77 (5%)	..
Six-category scale at day 14			
1—discharge (alive)	39/153 (25%)	18/78 (23%)	OR 1·25 (0·76 to 2·04)§
2—hospital admission, not requiring supplemental oxygen	21/153 (14%)	10/78 (13%)	..
3—hospital admission, requiring supplemental oxygen	61/153 (40%)	28/78 (36%)	..
4—hospital admission, requiring high-flow nasal cannula or non-invasive mechanical ventilation	13/153 (8%)	8/78 (10%)	..
5—hospital admission, requiring extracorporeal membrane oxygenation or invasive mechanical ventilation	4/153 (3%)	7/78 (9%)	..
6—death	15/153 (10%)	7/78 (9%)	..
Six-category scale at day 28			
1—discharge (alive)	92/150 (61%)	45/77 (58%)	OR 1·15 (0·67 to 1·96)§
2—hospital admission, not requiring supplemental oxygen	14/150 (9%)	4/77 (5%)	..
3—hospital admission, requiring supplemental oxygen	18/150 (12%)	13/77 (17%)	..
4—hospital admission, requiring high-flow nasal cannula or non-invasive mechanical ventilation	2/150 (1%)	2/77 (3%)	..
5—hospital admission, requiring extracorporeal membrane oxygenation or invasive mechanical ventilation	2/150 (1%)	3/77 (4%)	..
6—death	22/150 (15%)	10/77 (13%)	..

Data are median (IQR), n (%), or n/N (%). Clinical improvement (the event) was defined as a decline of two categories on the modified seven-category ordinal scale of clinical status, or hospital discharge. OR=odds ratio. *Differences are expressed as rate differences or Hodges-Lehmann estimator and 95% CI. †Hazard ratio and 95% CI estimated by Cox proportional risk model. ‡Three patients in each group were survivors and ten patients in the remdesivir group and seven patients in the placebo group were non-survivors. §Calculated by ordinal logistic regression model.

Table 3: **Outcomes in the intention-to-treat population**

Ancillary analyses

18 Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory

Results for time to clinical improvement were similar in the per-protocol population (median 21·0 days [IQR 13·0–28·0] in the remdesivir group vs 23·0 days [15·0–28·0] in the placebo group HR 1·27 [95% CI 0·89–1·80]; appendix pp 2–3, 5).

Although not statistically significant, in patients receiving remdesivir or placebo within 10 days of symptom onset in the ITT population, those receiving remdesivir had a numerically faster time to clinical improvement than those receiving placebo (median 18·0 days [IQR 12·0–28·0] vs 23·0 days [15·0–28·0]; HR 1·52 [0·95–2·43]; appendix p 6).

If clinical improvement was defined as a one, instead of two, category decline, the HR was 1·34 with a 95% CI of 0·96–1·86 (appendix p 7).

For time to clinical deterioration, defined as a one-category increase or death, the HR was 0·95 with a 95% CI of 0·55–1·64 (appendix p 8).

In patients with use of remdesivir within 10 days after symptom onset, 28-day mortality was not significantly different between the groups, although numerically higher in the placebo group; by contrast, in the group of patients with late use, remdesivir patients had numerically higher 28-day mortality, although there was no significant difference.

No differences in viral load were observed when stratified by interval from symptom onset to start of study treatment (appendix p 10). In the subset of patients from whom expectorated sputa could be obtained (103 patients), the mean viral RNA load at enrolment was nearly 1-log higher in the remdesivir group than the placebo group at enrolment (figure 3B). When adjusted for baseline sputum viral load at enrolment, the remdesivir group showed no significant difference at day 5 from placebo, but a slightly more rapid decline in load (p=0·0672).

Harms

19 All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)

The safety assessment included daily monitoring for adverse events, clinical laboratory testing (days 1, 3, 7, and 10), 12-lead electrocardiogram (days 1 and 14), and daily vital signs measurements.

We present adverse event data on the patients' actual treatment exposure, coded using Medical Dictionary for Regulatory Activities.

Adverse events were reported in 102 (66%) of 155 patients in the remdesivir group and 50 (64%) of 78 in the control group (table 4). The most common adverse events in the remdesivir group were constipation, hypoalbuminaemia, hypokalaemia, anaemia, thrombocytopenia, and increased total bilirubin; and in the placebo group, the most common were hypoalbuminaemia, constipation, anaemia, hypokalaemia, increased aspartate aminotransferase, increased blood lipids, and increased total bilirubin. 28 (18%) serious adverse events were reported in the remdesivir group and 20 (26%) were reported in the control group. More patients in the remdesivir group than the placebo group discontinued the study drug because of adverse events or serious adverse events (18 [12%] in the remdesivir group vs four [5%] in the placebo group), among whom seven (5%) were due to respiratory failure or acute respiratory distress syndrome in the remdesivir group. All deaths during the observation period were judged by the site investigators to be unrelated to the intervention).

Discussion

Limitations

20 Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses

Limitations of our study include insufficient power to detect assumed differences in clinical outcomes, initiation of treatment quite late in COVID-19, and the absence of data on infectious virus recovery or on possible emergence of reduced susceptibility to remdesivir. Of note, in non-human primates, the inhibitory effects of remdesivir on infectious SARS-CoV-2 recovery in bronchoalveolar lavages were much greater than in controls, but viral RNA detection in upper and lower respiratory tract specimens were not consistently decreased versus controls. Coronaviruses partially resistant to inhibition by remdesivir (about six-times increased EC_{50}) have been obtained after serial in vitro passage, but these viruses remain susceptible to higher remdesivir concentrations and show impaired fitness. The frequent use of corticosteroids in our patient group might have promoted viral replication, as observed in SARS and MERS, although these studies only reported prolongation of the detection of viral RNA, not infectious virus. Furthermore, we have no answer to whether longer treatment course and higher dose of remdesivir would be beneficial in patients with severe COVID-19.

Generalisability

21 Generalisability (external validity, applicability) of the trial findings

Interpretation

22 Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence

In summary, we found that this dose regimen of intravenous remdesivir was adequately tolerated but did not provide significant clinical or antiviral effects in seriously ill patients with COVID-19. However, we could not exclude clinically meaningful differences and saw numerical reductions in some clinical parameters. Ongoing studies with larger sample sizes will continue to inform our understanding of the effect of remdesivir on COVID-19. Furthermore, strategies to enhance the antiviral potency of remdesivir (eg, higher-dose regimens, combination with other antivirals, or SARS-CoV-2 neutralising antibodies) and to mitigate immunopathological host responses contributing to COVID-19 severity (eg, inhibitors of IL-6, IL-1, or TNFα) require rigorous study in patients with severe COVID-19.

Other information

Registration

23 Registration number and name of trial registry

https://clinicaltrials.gov/ct2/show/NCT04257656

Protocol

24 Where the full trial protocol can be accessed, if available

https://www.researchsquare.com/article/rs-14618/v1

Funding

25 Sources of funding and other support (such as supply of drugs), role of funders

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