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Statistical review of *Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial*

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Brennan Kahan - Senior Research Fellow, MRC Clinical Trials Unit at UCL.

Darren Dahly, PhD - Principal Statistician, HRB Clinical Research Facility - Cork. Senior Lecturer in Research Methods, School of Public Health, University College Cork.

Kerry Hood, PhD - Professor of Trials, Centre for Trials Research, Cardiff University.

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 *Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial*, by Hung *et al* [2], published in the Lancet on the 8th May.

Overall, this was a well-conducted randomised controlled trial with a few deficiencies in how it was reported and analysed, though none of these were disqualifying. The observed outcomes were consistently in favor of the group receiving triple therapy that included interferon beta-1b, ribavirin, and lopinavir–ritonavir (compared to the group that only received lopinavir–ritonavir), though, as pointed out by the authors, this was in patients with mild to moderate COVID-19, and so the results may not be generalisable to patients with more severe illness.

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Study Summary

The paper reports a two-arm parallel randomised controlled trial in patients hospitalized with rt-PCT confirmed COVID-19. The study aimed to recruit 35 patients per group and was conducted in six major public health hospitals in Hong Kong, between February 10 and March 20, 2020. Patients were randomised using a 2:1 allocation ratio to receive either oral lopinavir–ritonavir (400 mg / 100 mg, every 12 h) for 14 days, or to a triple combination of ribavirin (400 mg, every 12 h), interferon beta-1b (1 mL 8 million IU on alternate days via subcutaneous injection of one to three doses), and oral lopinavir–ritonavir.

The primary outcome was time to a negative rt-PCR for SARS-CoV-2. Key secondary outcomes were time to resolution of symptoms measured by NEWS2 and sequential organ failure assessment (SOFA) score; length of hospital stay; and 30-day mortality. Safety endpoints were the frequencies and durations of adverse events.

A total of 127 patients were recruited and randomised (86:41). The time to a negative rt-PCR for SARS-CoV-2 in the combination group (7 days [IQR 5 to 11]) was significantly less than that in the the control group (12 days [8 to 15]; HR 4.37 [95% CI 1.86 to 10.24]). Results for the secondary outcomes were also in favor of the combination group, who had a shorter time to a NEWS2 of 0 (4 days [IQR 3 to 8] vs 8 days [7 to 9] in the control group; HR 3.92 [95% CI 1.66 to 9.23]); and a shorter time to a SOFA score of 0 (3.0 days [1.0 to 8.0] vs 8.0 days [6.5 to 9.0] in the control group; HR 1.89 [1.03 to 3.49]). The better clinical and virological response was also reflected in the shorter median hospital stay in the combination group (9.0 days [7.0 to 13.0]) vs 14.5 days (9.3 to 16.0) in the control group (HR 2.72 [1.2 to 6.13]). There were no differences in adverse events or durations of nausea or diarrhoea between the treatment groups.

Based on these findings, the authors appropriately concluded that “Triple antiviral therapy with interferon beta-1b, lopinavir–ritonavir, and ribavirin were safe and superior to lopinavir–ritonavir alone in shortening virus shedding, alleviating symptoms, and facilitating discharge of patients with mild to moderate 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.

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Major comments

The sample size calculation was inconsistent with what took place for the actual trial.

The sample size calculation was based on mortality, which was not the primary outcome of this trial (which was instead time to negative rt-PCR for SARS-Cov-2). Further, the reported sample size calculation implied a 2 arm trial with 35 patients per arm (a figure we were able to replicate based on the details they reported) indicating a 1:1 allocation ratio, whereas the trial recruited in a 2:1 allocation ratio. Further, if we assume a 2:1 ratio was planned, this would indicate a recruitment target of 105, but the trial actually recruited 127 patients. Finally, there was also no information reported on why the trial ended at 127 patients.

Recommendations:
For future studies

- Ensure the study is appropriately powered for the primary outcome.

For this study

- Please clarify the discrepancies, and comment on why the trial ended and whether there were any interim looks at the data.

The methods around the key subgroup analysis were suboptimal.

Treatment in the combination arm actually varied depending on how many days of symptoms patients experienced prior to study enrollment. Those who had symptoms for 7 or more days did *not* receive interferon beta-1b. It thus makes sense to consider a subgroup analysis based on this distinction. However, the subgroup analysis was not prespecified in the registry or protocol, nor was it conducted using a multivariable model with an interaction term, but was instead based on estimating treatment effects within each subgroup using stratified models.

Recommendations:
For future studies

- When testing for subgroup effects, ensure that they are specified in a pre-registered protocol (or clearly label them as *post-hoc* if they weren't pre-registered) and estimated using a multivariable model with the relevant treatment by subgroup interaction term.

For this study

- Include correctly estimated subgroup effects based on a multivariable model with the relevant treatment by subgroup interaction term.

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The context of this trial was atypical, which may limit the generalisability of the result.

Like other trials of potential COVID-19 treatments, this study recruited hospitalised patients. However, unlike in most other settings globally, in Hong Kong all patients who test positive for COVID-19 are admitted to hospital. Therefore the patients in this trial are much healthier overall than we would expect to see in hospitalised patients in other countries. This is reflected in the fact that there were zero deaths in this trial. It is unclear whether the results from this trial would translate to hospitalised patients in other settings who are generally much sicker than those seen in this trial. This of course is not a critique of the trial itself, but it is an important factor to consider when interpreting the results of the trial.

Recommendations:
For the reader

- Pay close attention to how this study population compares to the context you are interested in.

Minor points

- For the control group, the authors used lopinavir and ritonavir, instead of standard of care. Importantly, lopinavir and ritonavir have not been established as efficacious treatments in COVID-19, but were chosen based on apparent efficacy in SARS (though this was in a trial with historical controls). They justified this by saying that placebo groups were generally not accepted in Chinese culture. However this seems at odds with other trials coming out of China which have used standard of care as a control, e.g. Cao *et al*[3]. Regardless, use of an additional, unproven treatment to the standard-of-care control group can cloud the interpretation of the trial's results.

- Patients and clinicians in the study were not blinded to treatment allocation, and it was unclear whether assessment/data collection (e.g. for adverse events) was done by blinded personnel or not. The authors note that there was consecutive enrollment, and while that might help to reassure that there was no selection bias in patients enrolling onto the study, it doesn't address the lack of blinding.

- The authors added a number of endpoints which were not listed in the protocol/trial registry, including daily NEWS2 and SOFA scores. No justification or explanation was provided. Time to negativity across all swabs (in addition to each individual one) which was also added, prior to the trial closing.

- Several of the outcomes were measured longitudinally, but then analysed as if they were independent cross-sections. It would have been more appropriate to employ explicitly longitudinal models (e.g. multilevel models) to appropriately account for correlation between outcomes on different days.

- Interpretation of results is challenging for most outcomes as they haven't presented treatment effect estimates, but have instead only presented p-values. This challenge is exacerbated by the plots showing outcomes in each treatment group (with group-specific confidence intervals) instead of showing outcome differences between the groups (with a single confidence interval for the difference).

- Patients were allocated in a 2:1 ratio, 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 not stratified, but those who are recruited who have had symptoms for 7 or more days were given an amended intervention, and a subgroup was conducted to accommodate this (see major comments above). This would have been a good opportunity to stratify by this subgroup (<7 vs ≥ 7 days of symptoms) to improve the efficiency (i.e. power, precision) of the analysis.

- The paper only reports unadjusted treatment effects, whereas adjustment for important prognostic factors measured at baseline (factors which should be pre-registered, prior to data collection) would have led to more precisely estimated treatment effects [4].

- There was only a limited description of the process used to maintain allocation concealment.

- There were variables measured at baseline (IL-6, TNFα) and concomitant treatments that were reported in the main results tables, which confused the presentation.

- The key outcomes were based on time to event analyses, but none of them were summarised using survival plots, and the paper didn't comment on the presence of any censoring.

- There was no clear purpose to their use of multivariable models to identify significant correlates of outcomes. Covariates so identified are not guaranteed to have a causal interpretation, nor are they likely to be useful predictors of outcomes.

- A number of baseline variables have been compared using p-values which is counter to expert advice[5] since any differences would be down to chance.

Open Data

No.

Open Analysis Code

No.

Pre-registered study design

A protocol is included with the published paper, though it was not to our knowledge formally pre-registered.

PubPeer

There may be comments on the PubPeer page for the published version of this paper.
https://pubpeer.com/publications/2FFA2B5F4FFE470FF551E805AE198C

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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)	Yes
Methods	
Participants: Eligibility criteria for participants and the settings where the data were collected	No
Interventions: Interventions intended for each group	Yes
Objective: Specific objective or hypothesis	Yes
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	No
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

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Introduction

Background and objectives

2a Scientific background and explanation of rationale

Yes

2b Specific objectives or hypotheses

Therefore, we did this phase 2 randomised trial to establish whether a combination of three modestly active drugs against SARS-CoV-2 can improve the viral load profile and clinical parameters in adults with COVID-19 requiring hospital admission.

Methods

Trial design

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

This was a phase 2, multicentre, open-label, randomised trial.

Patients were randomly assigned to either the triple combination lopinavir–ritonavir, ribavirin, and interferon beta-1b group or the control group (lopinavir–ritonavir only), in the ratio of 2:1, by simple randomisation with no stratification.

3b Important changes to methods after trial commencement (such as eligibility criteria), with reasons

None given.

Participants

4a Eligibility criteria for participants

Eligibility criteria for the study were age at least 18 years, a national early warning score 2 (NEWS2) of at least 1, and symptom duration of 14 days or less upon recruitment (appendix pp 9–10). [**from the paper**]

[**from the registry**]
Inclusion Criteria:

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- *Recruited subjects include all adult patients ≥18 years hospitalised for virologically confirmed 2019-n-CoV infection.*
- *NEWS of ≥1 upon recruitment*
- *Auditory temperature ≥38°C with at least one of the following symptoms (cough, sputum production, sore-throat, nasal discharge, myalgia, headache or fatigue) upon admission Symptom duration ≤10 days*
- *All subjects give written informed consent.*
- *Subjects must be available to complete the study and comply with study procedures.*
- *Willingness to allow for serum samples to be stored beyond the study period, for potential additional future testing to better characterize immune response.*

Exclusion Criteria:

- *Inability to comprehend and to follow all required study procedures.*
- *Allergy or severe reactions to the study drugs*
- *Patients with known prolonged QT or PR interval, second- or third-degree heart block, or ventricular cardiac arrhythmias, including torsade de pointes*
- *Patients taking medication that will potentially interact with lopinavir/ ritonavir, ribavirin or interferon-beta1b*
- *Patients with known history of severe depression*
- *Pregnant or lactation women*
- *Inability to comprehend and to follow all required study procedures*
- *Received an experimental agent (vaccine, drug, biologic, device, blood product, or medication) within 1 month prior to recruitment in this study or expect to receive an experimental agent during this study.*
- *Unwilling to refuse participation in another clinical study through the end of this study.*
- *Have a history of alcohol or drug abuse in the last 5 years.*
- *Have any condition that the investigator believes may interfere with successful completion of the study.*

[**from the protocol**]
3.2 Selection of Study population 3.2.1
Inclusion criteria
1. Recruited subjects include all adult patients ≥18 years hospitalised for virologically confirmed SARS-CoV-2 infection.
2. NEWS of ≥1 upon recruitment
3. Auditory temperature ≥38°C or other symptoms including cough, sputum
10 production, sore-throat, nasal discharge, myalgia, headache, fatigue or diarrhoea upon admission
4. Symptom duration ≤14 days

5.All subjects give written informed consent. For patients who are critically ill,requiring ICU, ventilation or confused, informed consent will be obtained from spouse, next-of-kin or legal guardians.
6. Subjects must be available to complete the study and comply with study procedures. Willingness to allow for serum samples to be stored beyond the study period, for potential additional future testing to better characterize immune response.

3.2.2 Exclusion criteria
1. Inability to comprehend and to follow all required study procedures.
2.Allergy or severe reactions to the study drugs
3. Patients with known prolonged QTc syndrome, ventricular cardiac arrhythmias,including torsade de pointes, second or third degree heart block, QTc interval≥480ms
4. Patients taking medication that will potentially interact with lopinavir/ ritonavir,ribavirin or interferon b-1b
5. Patients with known history of severe depression
6. Pregnant or lactating women
7. Received an experimental agent (vaccine, drug, biologic, device, blood product,or medication) within 1 month prior to recruitment in this study or expect to receive an experimental agent during this study.
8. To participate in an unrelated trial during the current clinical trial. Nevertheless,the patients have the right to withdraw from the current clinical trial to join another clinical trial.
9. Have a history of alcohol or drug abuse in the last 5 years.10. Have any condition that the investigator believes may interfere with successful completion of the study.

4b Settings and locations where the data were collected

Adult patients aged at least 18 years admitted to hospital from Feb 10, 2020, for virologically confirmed COVID-19, were recruited from the Queen Mary Hospital, Pamela Youde Nethersole Hospital, Ruttonjee Hospital, United Christian Hospital, Queen Elizabeth Hospital, and Tuen Mun Hospital in Hong Kong. These six major public hospitals are positioned across five of the seven hospital clusters, and serve 75% of the 7·5 million population.

Interventions

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

In the combination group, patients who were recruited and treated less than 7 days from symptom onset received a triple combination of 14 days of oral lopinavir–ritonavir (lopinavir 400

mg and ritonavir 100 mg) every 12 h (via nasogastric tube to intubated patients), ribavirin 400 mg every 12 h, and subcutaneous injection of one to three doses of interferon beta-1b 1 mL (8 million international units [IU]) on alternate days depending on the day of drug commencement (if commenced on day 1–2 from symptom onset, the patient received all three doses of interferon beta-1b; if commenced on day 3–4, the patient received two doses; if commenced on day 5–6, the patient received one dose). For those recruited and treated between days 7 and 14, interferon beta-1b injection was omitted to avoid its proinflammatory effects. Patients assigned to the control group received only oral lopinavir–ritonavir (lopinavir 400 mg and ritonavir 100 mg) every 12 h for 14 days. For patients who had no history of prolonged QTc syndrome, but were found to have prolonged QTc less than 480 ms, first-degree heart block or bundle branch block, or bradycardia upon ECG examination, and those who developed increased alanine transaminase of three times the upper limit of normal (ULN), the lopinavir–ritonavir treatment was reduced to once per day. Lopinavir–ritonavir would be stopped if alanine transaminase levels exceeded six times the ULN. The randomisation window from symptom onset was extended from 10 to 14 days after trial commencement after knowing that the incubation period could go beyond 14 days. Because a placebo group was generally not accepted in Chinese culture, and our previous study showed that interferon beta-1b and lopinavir–ritonavir are active against SARS-CoV and MERS-CoV, lopinavir–ritonavir was used in the control group whereas interferon beta-1b, lopinavir–ritonavir, and ribavirin were used in the combination group for patients admitted less than 7 days from symptom onset.
The intervention treatment had to be started within 48 h after hospital admission. Standard of care included oxygen, non-invasive and invasive ventilatory support, extracorporeal membrane oxygenation support, dialysis support, and antimicrobial treatment for secondary bacterial infection as indicated clinically. Stress doses of corticosteroid (50 mg hydrocortisone every 8 h intravenously, tapering over 7 days) were given to patients who developed oxygen desaturation and required oxygen support. Non-invasive or invasive ventilatory support beyond day 7 from symptom onset was at the discretion of the consultants.

Outcomes

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

The primary endpoint was time to achieve a negative RT-PCR result for SARS-CoV-2 in a nasopharyngeal swab sample.

Secondary clinical endpoints were time to resolution of symptoms defined as a NEWS2 of 0 maintained for 24 h; daily NEWS2 and sequential organ failure assessment (SOFA) score; length of hospital stay; and 30-day mortality.

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Other virological endpoints included the time to achieve negative SARS-CoV-2 RT-PCR in all clinical samples, including nasopharyngeal swab, posterior oropharyngeal saliva, throat swab, stool, and urine; daily viral load changes in the first 7 days; and emergence of amino acid mutations in the nsp5 gene encoding a 3C-like protease. The serum cytokine response was also measured.

Safety endpoints were the frequencies and duration of adverse events. [**From the paper**]

[**From the registry**] *Primary outcome: Time to negative nasopharyngeal swab (NPS) 2019-n-CoV coronavirus viral RT-PCR*

Secondary outcome:

1. *Time to negative saliva 2019-n-CoV coronavirus viral RT-PCR*
2. *Time to clinical improvement of NEWS2 (National Early Warning Score 2) of 0 maintained for 24 hours*
3. *Length of hospitalisation*
4. *Adverse events during treatment*
5. *30-day mortality*
6. *Cytokine/ chemokine changes*

[**From the protocol**] *3.4 Outcome measurements*

3.4.1Primary outcome measurement

Time to negative nasopharyngeal swab (NPS) SARS-CoV-2viral RT-PCR

3.4.2Secondary outcome measurements

1.Time to resolution of symptoms as defined by NEWS of 0 maintained for 24hours

2.Length of hospitalization

3.30-day mortality

4.Time to negative SARS-CoV-2 RT-PCR for all samples including NPS, throat saliva, throat swab, urine and stool

5.All samples SARS-CoV-2 viral load changes post treatment

6.Cytokine/ chemokine changes

7.Adverse events during treatment

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

Sample size

7a How sample size was determined

It is important to note that COVID-19 is a new disease caused by SARS-CoV-2, which is phylogenetically closest to the 2003 SARS-CoV. At the time of study design in mid-January, 2020, there was insufficient information on the mortality of COVID-19. Thus, we based our sample size calculation on our own findings of lopinavir–ritonavir treatment in a trial on the 2003 SARS-CoV.-The current study was designed on the basis of an estimated difference of 26·4% in the 21-day mortality or acute respiratory distress syndrome rate in patients with severe SARS-CoV-2 infection, when treated with lopinavir–ritonavir (2·4%) versus historical controls without antiviral treatment (28·8%). The necessary sample size had been calculated to be 30 patients per group to detect such a difference at a two-sided α level of 0·05, with 80% power. The protocol proposed recruiting at least 35 patients per group to allow for a 17% dropout rate.

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

None described.

Randomisation

Sequence generation

8a Method used to generate the random allocation sequence

Each serial number was linked to a computer-generated randomisation list assigning the antiviral treatment regimens.

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

Patients were randomly assigned to either the triple combination lopinavir–ritonavir, ribavirin, and interferon beta-1b group or the control group (lopinavir–ritonavir only), in the ratio of 2:1, by simple randomisation with no stratification.

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

None described.

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Implementation

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

Patients were assigned to a serial number by the study coordinator. Each serial number was linked to a computer-generated randomisation list assigning the antiviral treatment regimens. The study medications were dispensed by the hospital pharmacy and then to the patients by the medical ward nurses.

Blinding

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

Randomised treatment was open-label.

11b If relevant, description of the similarity of interventions

Statistical methods

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

The primary endpoint was assessed in the intention-to-treat population of all randomised patients. Safety was assessed in all patients who received at least one dose of their assigned drug. Categorical variables were compared using the χ^2 test and continuous variables were compared using the Mann-Whitney U test, for both intention-to-treat and subgroup analyses. For viral load, specimens with undetectable viral load were assigned a value of 1 $\log_{10}$ copies per mL for the purpose of statistical analysis. Hazard ratios (HRs) with 95% CIs were calculated by Cox proportional hazards model. Factors significant at univariable analysis (p<0·10) were further assessed by means of a multivariable analysis by Cox proportional hazards model to identify the independent factors for negative nasopharyngeal swab RT-PCR on day 7 after treatment. A p value of less than 0·05 was considered statistically significant. Statistical analysis was performed using SPSS, version 26.0 and PRISM, version 8.

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

Results

Participant flow (a diagram is strongly recommended)

13a For each group, the numbers of participants who were randomly assigned, received

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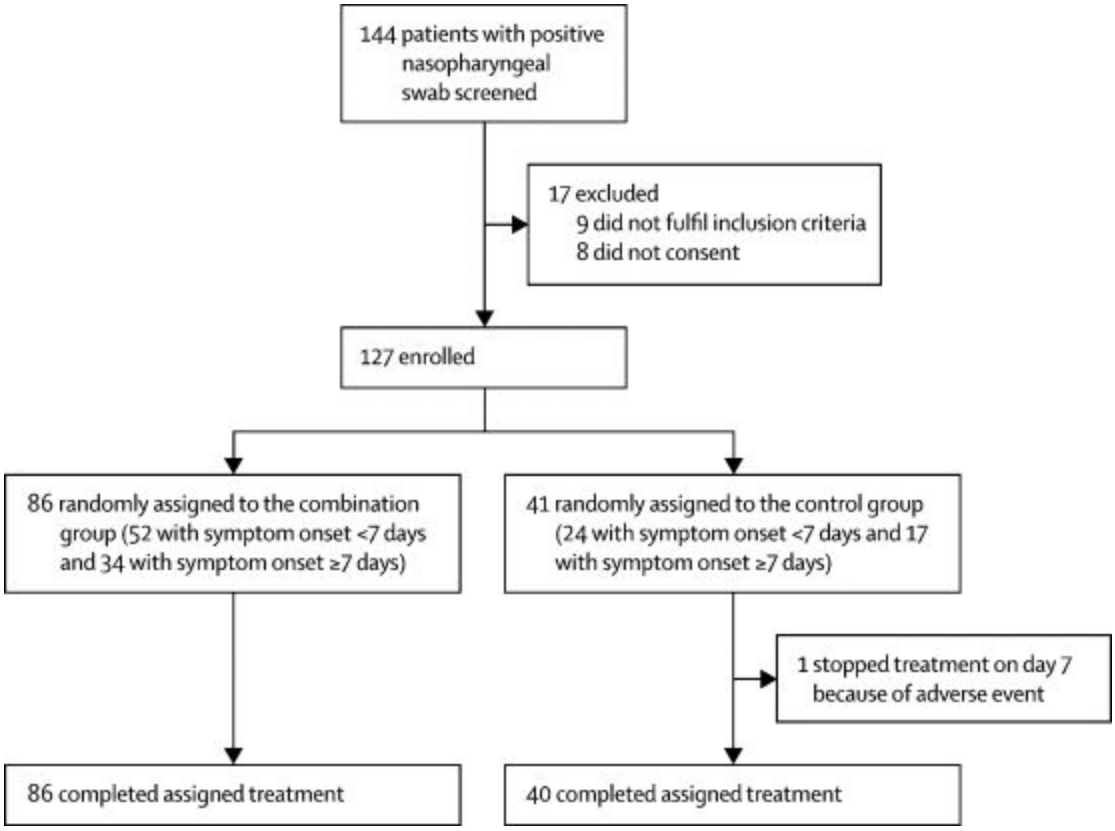
intended treatment, and were analysed for the primary outcome

Between Feb 10 and March 20, 2020, 144 patients were screened, and 127 patients were recruited (figure 1). The number of patients screened accounted for 80% of the confirmed COVID-19 cases in Hong Kong during this period. Nine patients did not fulfil the inclusion criteria (four with second-degree and third-degree cardiac arrhythmia, two with severe depression, and three because of pregnancy) and eight patients declined the treatment regimen. One patient in the control group required discontinuation of lopinavir–ritonavir because of alanine transaminase six times greater than the ULN after 1 week of treatment.

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



Recruitment

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

Between Feb 10 and March 20, 2020, 144 patients were screened, and 127 patients were recruited.

14b Why the trial ended or was stopped

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Baseline data

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

The median age was 52 years (IQR 32–62); 68 (54%) patients were men versus 59 (46%) women (table 1). 51 (40%) patients had underlying diseases. The median time to hospital admission from symptom onset was 5 days (IQR 3–7)

Numbers analysed

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

Among the 127 patients, 86 were randomly assigned to the combination group and 41 patients were assigned to the control group. Within the combination group, 52 patients were admitted to hospital less than 7 days from symptom onset and received the lopinavir–ritonavir, ribavirin, and interferon beta-1b regimen, and 34 patients who were admitted 7 days or more after symptom onset received the lopinavir–ritonavir and ribavirin only regimen.

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)

For the primary endpoint of time from start of study treatment to negative nasopharyngeal swab, the combination group had a significantly shorter median time (7 days [IQR 5–11]) than the control group (12 days [8–15]; HR 4·37 [95% CI 1·86–10·24], p=0·0010; table 2).

Clinical improvement was significantly better in the combination group, with a significantly shorter time to complete alleviation of symptoms, defined as a NEWS2 of 0 (4 days [IQR 3–8] in the combination group vs 8 days [7–9] in the control group; HR 3·92 [95% CI 1·66–9·23], p<0·0001) and SOFA score of 0 (3·0 days [1·0–8·0] vs 8·0 days [6·5–9·0]; HR 1·89 [1·03–3·49], p=0·041; table 2). A similar pattern was observed on the daily NEWS2 (all p<0·0001; figure 2A) and daily SOFA score after treatment (all p<0·05 except day 1 [p=0·21]; table 2). The significantly better clinical and virological response is also reflected in the shorter median hospital stay in the combination group than in the control group (9·0 days [7·0–13·0] vs 14·5 days [9·3–16·0]; HR 2·72 [1·2–6·13], p=0·016).

For the virological outcome, the combination treatment was associated with significantly shorter time to negative viral load in all specimens when assessed individually (nasopharyngeal swab, posterior oropharyngeal saliva, throat swab, and stool samples) as well as in all specimens combined (table 2). All urine samples tested negative for viral load.

All patients had a SARS-CoV-2 positive baseline nasopharyngeal swab. With regards to the other clinical samples, 108 (85%) patients provided posterior oropharyngeal saliva samples, 99 (78%) provided throat swabs, 36 (28%) provided stool samples, and 83 (65%) provided urine samples. The baseline viral loads for all specimens were similar between the combination group and control group (table 2). The nasopharyngeal swab viral load was significantly lower in the combination group than in the control group from day 1 to day 7 after treatment (figure 2B). Similar results were found in the posterior oropharyngeal saliva, throat swab, and stool specimens after treatment (figure 2C–E).

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

Ancillary analyses

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

Post-hoc subgroup comparison of the 76 patients who started treatment less than 7 days after onset of symptoms showed better clinical and virological outcomes in the combination group (52 patients, receiving lopinavir–ritonavir, ribavirin, and interferon beta-1b) than in the control group (24 patients; table 3) across all measured variables except stool samples. However, no significant differences between the treatment groups were measured in these outcomes in the 51 patients who were treated 7 days or more after symptom onset (34 in the combination group [receiving lopinavir–ritonavir and ribavirin only] and 17 in the control group; appendix p 31).

Harms

19 All important harms or unintended effects in each group (for specific guidance see CONSORT for harms42)

Adverse events were reported by 41 (48%) of 86 patients in the combination group and 20 (49%) of 41 patients in the control group. The most common adverse events were diarrhoea (52 [41%] of 127 patients), fever (48 [38%] patients), nausea (43 [34%]) and raised alanine transaminase level (18 [14%]; table 4). These side-effects mostly resolved within 3 days after drug initiation. Sinus bradycardia was reported by four (3%) patients. There were no differences between incidence of any of the adverse events or durations of nausea or diarrhoea between the treatment groups. The peak median alanine transaminase concentration was 38·0 units per L (24·5–62·5) and peak median bilirubin was 22·0 μmol/L (17·0–32·5), in all patients. No serious adverse events were reported in the combination group. One patient in the control group had a serious adverse event of impaired hepatic enzymes requiring discontinuation of treatment. No patients died during the study.

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Discussion

Limitations

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

Our study had several limitations. This trial was open label, without a placebo group, and confounded by a subgroup omitting interferon beta-1b within the combination group, depending on time from symptom onset. A subsequent phase 3 trial with interferon beta-1b as a backbone treatment with a placebo control group should be considered, because subgroup comparison suggested that interferon beta-1b appears to be a key component of our combination treatment. Our absence of critically ill patients did not allow the generalisation of our findings to severe cases.

Generalisability

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

Our absence of critically ill patients did not allow the generalisation of our findings to severe cases.

Interpretation

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

Triple antiviral therapy with interferon beta-1b, lopinavir–ritonavir, and ribavirin were safe and superior to lopinavir–ritonavir alone in shortening virus shedding, alleviating symptoms, and facilitating discharge of patients with mild to moderate COVID-19.

Other information

Registration

23 Registration number and name of trial registry

The study is registered with ClinicalTrials.gov, NCT04276688.

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Protocol

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

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31042-4/fulltext#seccestitle190

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

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