Early treatment of high-risk hospitalized COVID-19 patients with a combination of interferon beta-1b and remdesivir: a phase 2 open-label randomized controlled trial

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Abstract

Background

Early antiviral therapy was effective in the treatment of COVID-19. We assessed the efficacy and safety of combined interferon beta-1b and remdesivir treatment in hospitalized COVID-19 patients.

Methods

We conducted a multicentre, prospective open-label, randomized-controlled trial involving high-risk adults hospitalized for COVID-19. Patients were randomly assigned to a 5-day interferon beta-1b 16 million units daily and remdesivir 200mg loading on day 1 followed by 100mg daily on day 2 to 5 (combination-group), or to remdesivir only of similar regimen (control-group) (1:1). The primary end-point was the time to complete alleviation of symptoms (NEWS2=0).

Results

Two-hundred and twelve patients were enrolled. The median days of starting treatment from symptom-onset was 3 days. The median age was 65 years and 159 patients (75%) had chronic disease. The baseline demographics were similar. There was no mortality. For the primary-endpoint, the combination-group was significantly quicker to NEWS2=0 (4 versus 6.5 days; hazard-ratio [HR],6.59; 95% confidence-interval [CI],6.1-7.09; p<0.0001) when compared to the control-group. For the secondary endpoints, the combination-group was quicker to negative NPS VL (6 versus 8 days; HR,8.16; 95% CI,7.79-8.52; p<0.0001) and develop seropositive IgG (8 versus 10 days; HR,10.78; 95% CI,9.98-11.58; p<0.0001). All adverse events resolved upon

follow-up. Combination group (HR,4.1 95%CI,1.9-8.6, p<0.0001), was the most significant independent factor associated with NEWS2=0 on day 4.

Conclusions

Early treatment with interferon beta-1b and remdesivir was safe and better than remdesivir only in alleviating symptoms, shorten viral shedding and hospitalization with earlier seropositivity in high-risk COVID-19 patients.

Keywords: early, high-risk, COVID-19, interferon beta-1b, remdesivir

Introduction

Since severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in Wuhan, China in December 2019, the Coronavirus Disease 2019 (COVID-19) pandemic has affected more than 500 million patients with over 6.2 million deaths [1]. Despite most patients recovered without sequelae, a significant proportion developed severe acute viral pneumonia leading to respiratory failure [2-4]. Patients who developed severe COVID-19 disease tend to have prolonged viral shedding in the first week, followed by a hyper-inflammatory phase associated with cytokine storm, pneumonia, and other systemic complications [4,5]. High-risk patients included the elderlies, history of chronic illnesses and obese [3-6].

Our previous randomized controlled trial of hospitalized COVID-19 patients demonstrated that early treatment started within the first week of symptoms onset with a triple combination of interferon beta-1b, lopinavir/ritonavir and ribavirin was highly effective in alleviating symptoms and shortening viral shedding [7]. Similar result was demonstrated in other studies using early peginterferon lambda [8] or inhaled interferon beta-1a [9]. Two clinical trials have demonstrated that remdesivir treatment was superior to placebo in shortening the time to recovery in hospitalized COVID-19 patients [10,11], with additional benefits when combined with baricitinib in the treatment of severe cases [12]. A large multicentre trial coordinated by the World Health Organization (WHO) however, failed to demonstrate any clinical benefits in 4 repurposed antivirals in hospitalized COVID-19 patients [13]. The lack of benefits in these agents could be explained by the delayed treatment. Therefore, we conducted this phase 2 randomized treatment trial to assess early treatment with a combination of interferon beta-1b and remdesivir could

improve the clinical outcome, viral load profile and immunological response in adult COVID-19 patients requiring hospitalization.

Methods

Study Participants

This was a phase 2, multicentre open-label randomized controlled clinical trial. Adult patients ≥18 years hospitalized from 1 November 2020, for virologically confirmed COVID-19, were recruited from the Queen Mary Hospital, Pamela Youde Nethersole Hospital and Ruttonjee Hospital under the Hospital Authority (HA) of the Hong Kong Special Administrative Region (HKSAR). These 3 major public hospitals covered the entire 1.27 million population residing on the Hong Kong Island. Public health ordinance in HKSAR required all patients tested positive for COVID-19 be hospitalized. Only high-risk patients for clinical deterioration, including age ≥65 years, history of chronic illnesses and patients with pneumonia would be managed in negative pressure facilities in the public hospitals. Low-risk patients including those <65 years old and without underlying diseases would be managed in the community treatment facilities in the AsiaWorld-Expo. Therefore, all patients recruited in this study were high-risk to progress to severe disease. Potential patients were screened according to the detail inclusion and exclusion criteria of our protocol (Appendix). All recruited patients fulfilled one of the following criteria associated with high-risk of clinical deterioration: age ≥65 years, radiological evidence of pneumonia, oxygen deterioration <94% on room air, comorbidity including hypertension, diabetes, cardiovascular diseases, chronic obstructive lung disease, chronic liver diseases, chronic kidney diseases, malignancy, haematological diseases, rheumatological diseases, immunocompromised hosts and obesity (BMI>30). The discharge criteria under the public health

ordinance required negative reverse transcription-polymerase chain reaction (RT-PCR) in the nasopharyngeal swab (NPS) and posterior oropharyngeal saliva (POS), on consecutive days 24 hours apart. The Institutional Review Board of the University of Hong Kong/HA approved this study (UW20-535). The study was registered at the clinicaltrial.gov (NCT04647695).

Study Design

Upon recruitment, patients were randomly assigned into one of two groups, the combination group or the control group, in the ratio of 1:1, by simple randomisation with no stratification. In the combination group, the patients received a 5-day course of subcutaneous injection of daily dose of interferon beta-1b 2mL (16 million IU) consecutively and intravenous infusion of remdesivir 200mg loading on day 1 followed by 100mg daily on day 2 to day 5. Patients randomized to the control group received intravenous infusion of remdesivir 200mg loading on day 1 followed by 100mg daily on day 2 to day 5.

Initiation of the interventional treatment had to be commenced within 48 hours after hospital admission. Standard of care included oxygen, non-invasive and invasive ventilatory support, ECMO support, dialysis support and antimicrobial treatment for secondary bacterial infection as indicated clinically. Stress dose of intravenous corticosteroids (6mg dexamethasone daily or 50mg hydrocortisone every 8 hours, tapering over 7 days) were given to patients, who developed oxygen desaturation and required oxygen support, non-invasive or invasive ventilatory support at the discretion of the attending consultants.

Clinical and laboratory monitoring

Clinical findings including history and physical examination, laboratory and radiological investigation results were entered into a predesigned database. Chest radiograph (CXR) and electrocardiogram were taken at baseline and at regular interval for monitoring of the progress. All patients were followed up at the infectious disease clinic within 30 days upon discharge. Patients' medical history of chronic disease were documented upon admission and retrieved from the Clinical Management System which was an electronic medical records management system of the HA. The Charlson comorbidity index (CMI) was recorded [14]. Obesity was defined as a BMI≥30.

Initial diagnosis of SARS-CoV-2 infection was made upon admission. All recruited patients must have confirmation of SARS-CoV-2 infection by RT-PCR in the NPS (Appendix). Daily NPS and POS were obtained for viral load quantification as in previous studies [7,15]. Complete blood count, liver and renal function tests, lactate dehydrogenase, C-reactive protein (CRP), serum anti-N SARS-CoV-2 IgG and live virus microneutralization assay (MN) were regularly checked until discharge. Blood and urine for bacterial culture was performed when clinically indicated. The NPS upon admission was also assessed by BioFire® FilmArray® Respiratory Panel 2 *plus* (bioMérieux, Marcy l'Etoile, France). The methodology for assays by RT-qPCR, serum anti-RBD IgG and MN can be found in the Appendices.

Outcomes

The primary endpoint was the time to complete alleviation of symptoms as defined by the National Early Warning Score 2 (NEWS2) =0 maintained for 24 hours [16,17]. Patients who

have a baseline NEWS2=0 would have reached the primary endpoint if the NEWS2=0 on the following day. The secondary end points were the time to WHO Clinical Progression Scale (WCPS) =1 maintained for 24 hours [18], the time to negative NPS and POS SARS-CoV-2-RT-PCR, length of hospitalization according to the clinical outcome (WCPS<4 for 24 hours), intensive care unit admission, requirement of oxygen, non-invasive and invasive ventilation, extracorporeal membrane oxygenation (ECMO) support, time of positive anti-N SARS-CoV-2 IgG and 30-day mortality. Other endpoints included the daily NEWS2, WCPS, VL and alternate day MN changes in the first 9 days post treatment. The safety endpoints included the frequencies of systemic and local adverse events. Fever was defined as body temperature ≥37.5°C. Erythema and induration were graded based on size: grade 1, <20mm; grade 2, 20-50mm; grade 3, >50mm.

Randomization

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

Sample size calculation

The sample size calculation is based on the finding of our previous clinical trial on using the combination therapy of interferon beta-1b, lopinavir/ ritonavir and ribavirin and the findings of the clinical trial by using remdesivir alone [7]. An estimated difference of 20% the patients in the treatment arm reaching NEWS2=0 on day 7, when treated with the combination of interferon

beta-1b and remdesivir (80%) vs. remdesivir (60%) alone. The necessary sample size has been calculated to be 82 patients per group to detect such a difference at a two-sided alpha level of 0.05, with 80 percent power. The protocol proposed recruiting at least 90 subjects per group to allow for a 12.5% drop out rate, due to adverse effects or premature termination of the trial.

Statistical analysis

Statistical analysis was performed using SPSS26.0 and PRISM8. Intention-to-treat analysis was performed by comparing the combination group with the control group. Categorical variables and continuous variables were compared using $\chi 2$ test and Mann-Whitney U test, respectively, for both intention-to-treat analyses. For VL, specimens with undetectable VL were assigned a value of 1 $\log_{10}$ copies/ml for the purpose of statistical analysis. Hazard ratios (HR) with 95% confidence interval (CI) were calculated by means of the 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 in reaching NEWS2=0. A p-value of <0.05 was considered to be statistically significant.**Results**

Between 1 November 2020 and 28 February 2021, 230 patients were screened, and 212 patients were recruited (Figure 1). Eighteen patients declined the treatment regimen. All recruited patients completed the treatment and follow-up. The median age was 65 years, interquartile range (IQR) 54-72 years and 107/212 (50.5%) patients was ≥65 years. The oldest patient recruited was 97 years old and 112 patients (52.8%) were male (Table 1). All recruited patients were age ≥65 years or with chronic illness. The median CMI of 2 (IQR 1-3). The median day of starting treatment from symptom onset was 3, IQR (2-4) days and 21 patients (9.9%) developed oxygen desaturation <94% on room air before study entry.

Treatment and clinical presentations

Among the 212 patients (Table 1), 108 patients were randomized to the combination group and 104 patients were randomized to the control group. The median days of starting treatment from symptom onset was 2.5 and 3 days for the combination group and control group respectively. The age, sex, baseline NEWS2 and demographics in each group were similar (Table 1 and 2).

Clinical outcomes and virologic efficacy

Upon completion of the study, there was no mortality (Table 2). One hundred and fifteen patients had a baseline NEWS2=0. For the primary endpoint, the combination group was significantly quicker to achieve a NEWS2=0 (4 versus 6.5 days; HR,6.59; 95%CI,6.1-7.09; p<0.0001). Similarly, the combination group was significantly quicker to achieve WCPS=1 (5 versus 8 days; HR,7.1;95%CI,7.29-8.11; p<0.0001).

For the secondary endpoints, the combination group was quicker to negative NPS VL (6 versus 8 days; HR,8.16; 95%CI,7.79-8.52; p<0.0001), and to negative POS VL (8 versus 9 days; HR,8.25; 95%CI,7.81-8.69; p<0.0001) (Table 2, Figure 3 and 4). The combination group was also associated with shorter hospital stays according to the clinical criteria (5 versus 7 days; HR,7.38; 95%CI,6.88-7.87; p<0.0001) and shorter ICU stay (8 versus 11 days; HR,11.06; 95%CI, 8.54-13.63; p<0.001) (Table 2). Both the serial NEWS2 and WCPS (Figure 2) were significantly lower in the combination group. In addition, we have performed subgroup analysis in patients with baseline WCPS≥4, excluding asymptomatic patients and those hospitalized initially for isolation. The result was similar (Table 3).

Concomitant treatment

Significantly fewer patients in the combination group required oxygen therapy (p=0.003), ICU admission (p=0.031), ventilator support (p=0.027) and corticosteroid treatment (p=0.022) post study entry (Table 1). The median time of starting corticosteroid was 5 (IQR 4-9) days after admission. The length of oxygen therapy (p=0.002), ventilator support (p=0.012), and high-flow O2 or NIV support (p=0.029) were significantly shorter in the combination group (Table 2).

Microneutralization and IgG antibody response

The time to onset of anti-N SARS-CoV-2 IgG seropositive was significantly shorter in the combination group (8 versus 10 days; HR,10.78; 95%CI,9.98-11.58; p<0.0001). The microneutralization antibody titre was significantly higher in the combination group than the control group from day 3 onwards after treatment commencement (Figure 5). The day 9 microneutralization antibody titre was significantly higher in the combination group than the control group (1:40 versus 1:5; p<0.0001).

Multivariable analysis

Significant factors associated with NEWS2=0 on day 4 after treatment in the univariable analysis (Table 4), including age, combination group, presence of underlying diseases, use of oxygen, high-flow oxygen or NIV support, ventilator support, corticosteroid treatment, baseline NPS or POS VL, baseline lymphocyte count, LDH and CRP, abnormal CXR were further assessed by the multivariable analysis. Combination group (HR,4.1, 95%CI,1.9-8.6; p<0.0001), no oxygen therapy during hospitalization (HR,7.5, 95%CI;2.4-23.5; p=0.001), and low baseline POS VL

(HR,1.4, 95%CI;1.1-1.8; p=0.003) were independent factors associated with NEWS2 = 0 on day 4 after treatment (Table 5).

Adverse Events

The most common adverse events were fever (42.9%) raised ALT level (24.1%) and nausea (12.3%) with no difference between the two groups (Table 6). There were significantly more patients who developed local skin erythema (11.1%; p<0.0001) and induration (6.5%; p=0.008) at the interferon beta-1b injection site in the combination group. Only one patient (0.9%) developed Grade 3 skin erythema and induration. Nevertheless, all adverse events resolved upon subsequent follow-up with no difference in serious adverse events between the two groups.

Discussion

In this multicenter open-label phase 2 randomized controlled treatment trial for COVID-19, we demonstrated that early treatment in the older or high-risk patients with chronic illness, with a combination of interferon beta-1b and remdesivir when given within 3 days from symptoms onset, could significantly shorten the time to complete alleviation of symptoms, to negative NPS and DTS VL, resulting in shorter hospital stay and duration of supportive care when compared to remdesivir alone. The onset time of anti-N SARS-CoV-2 IgG was earlier and the microneutralization antibody titre was also higher in the combination group. The findings in this study were consistent with our previous study on the triple combination therapy [7]. Although most patients had relatively mild disease upon enrolment and were in the early phase of their infection, all the patients recruited were high-risk aged ≥65 years or with chronic illness. These comorbid chronic diseases including hypertension, diabetes, coronary artery disease and chronic

pulmonary disease were associated with developing severe disease if left untreated [19], especially before COVID-19 vaccination and oral antiviral treatment became available. This was the rationale to commence early treatment with remdesivir and interferon beta-1b, and more recently with the oral antiviral treatment for COVID-19 in those aged ≥60 years or with prespecified chronic illness, as approved by the U.S. Food & Drug Administration, despite these patients had mild or asymptomatic disease upon recruitment [20]. In order to shorten the treatment duration from 2 weeks to 5 days and to optimize the effect of the interferon beta-1b at the initial phase of the infection, we have modified the dosage of the interferon beta-1b 8 million IU alternative day to 16 million IU daily. Such modification in the interferon beta-1b dosage did not result in an increase in adverse events when compared to the previous study.

Clinical trials studying inhaled nebulised interferon beta-1a and subcutaneous injection of interferon lambda in COVID-19 patients have demonstrated a significantly quicker clinical improvement and viral clearance than placebo [8,9]. Early treatment with interferon beta-1b and lopinavir-ritonavir in MERS patients have also demonstrated a reduction in the 28-day mortality [21]. A more recent study supported the use of early remdesivir to prevent progression to severe COVID-19 in high-risk patients at outpatients. In comparison to the current study, there was only 1.6% of the recruited patients required a COVID-19 related medically attended event. The difference in disease progression could be explained by the younger mean age of 50 years, comparing to 62 years in the current study. Besides, patients who were already receiving or were expected to receive supplemental oxygen at the time of screening were excluded from the redmesivir study [22].

On the contrary, the WHO Solidarity Trial which studied 4 repurposed antiviral drugs for COVID-19, including interferon beta-1a, remdesivir, hydroxychloroquine and lopinavir have failed to demonstrate additional benefit to supportive care [13]. A more recent study also failed to demonstrate additional benefit of interferon beta-1a to remdesivir [23]. Both studies were limited by the delay in treatment after symptom onset and the lack of viral load profile. Outpatient trials on the casirivimab and imdevimab convalescent antibody cocktail [24] and molnupiravir [25] have highlighted the importance of early treatment to the outcome. In-vitro study in cell culture-based assays showed a significant better selective index (CC_{50}/EC_{50}) for interferon beta-1b (>1602.6), when compared to interferon beta-1a (>706.2) and remdesivir (96.2) respectively [26]. Therefore, interferon beta-1b is likely to have a significantly better antiviral effect when compared to interferon beta-1a alone, or when combined with remdesivir, especially when started early in high-risk patients before they deteriorated.

Other in-vitro and in-vivo studies have suggested that SARS-CoV-2 infection induces low levels of interferon I and III response [27], and serum anti-interferon-α2 and anti-interferon-ω were found in life-threatening COVID-19 [28,29], whereas these antibodies were not found in asymptomatic infected or healthy controls. The presence of neutralizing type-I autoantibodies was also associated with delayed viral clearance and intensive care unit admission in patients with COVID-19 [30]. Therefore, early replacement of interferon might counteract the suppressive effect of SARS-CoV-2 on the innate immunity and also the effect of these interferon blocking antibodies which allowed an early and effective suppression of SARS-CoV-2 replication and expedited viral clearance.

It is important to identify patients who are at risk of complications and mortality and to commence early antiviral treatment in these cohort. These include elderly patients and those with chronic illness, especially the immunocompromised. These patients are likely to have persistently high viral load, poor antibody response and prolonged proinflammatory cytokine phase. Early treatment with antiviral in this high-risk cohort, regardless of their clinical presentation at that juncture will prevent subsequent deterioration and mortality. It is therefore important to identify safe, affordable and easily accessible generic repurposed medications for treatment and prevention of COVID-19 [24,31,32].

None of our study patients required early termination and withdrawal due to adverse events. Mild self-limiting liver dysfunction was observed in 24% of these patients. The skin erythema and induration at the interferon injection site on the abdomen were mostly mild and resolved upon further follow-up.

Our study had several limitations. This trial was open label and without a placebo group. The highly effective infection control and quarantine control measures limited the number of patients that we could enrol. We have also included asymptomatic and patients with mild disease upon enrolment.

The early use of a human antiviral cytokine, interferon beta-1b, appears safe and effective in alleviating symptoms, shortening viral shedding, reducing the need for respiratory support and duration of hospitalization, and accelerating the onset of serum antibody response due to infection by SARS-CoV-2.

NOTES

Disclaimer.

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Potential conflicts of interest.

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Figures Legend

Figure 1. Recruitment flowchart of the 212 patients

Figure 2. Profile of the National Early Warning Score 2 (NEWS2) with respect to days from treatment commencement

Figure 3. Profile of the nasopharyngeal swab (NPS) viral load (VL) with respect to days from treatment commencement

Figure 4. Profile of the posterior oropharyngeal saliva viral load (VL) with respect to days from treatment commencement

Figure 5. Profile of the microneutralization antibody titre with respect to days from treatment commencement

1 **Table 1 – Baseline demographics of 212 patients**
2

	IFN beta-1b + Remdesivir (n=108)	Remdesivir (n=104)	p-value
Age; median (IQR)	64 (55-72)	65 (52-71.8)	0.94
Male sex (%)	52 (48.1)	60 (57.7)	0.16
Days of starting treatment from symptoms onset; median (IQR)	2.5 (2-4)	3 (2-3)	0.84
Oxygen saturation <94% on room air	10 (9.3)	11 (10.6)	0.75
Underlying diseases (%)			
Charlson comorbidity index	2 (1-3)	2 (1-3)	0.61
Chronic disease (overall)	80 (74.1)	79 (76)	0.75
Diabetes mellitus	21 (19.4)	27 (26)	0.26
Hypertension	45 (41.7)	45 (43.3)	0.81
Coronary artery disease	9 (8.3)	11 (10.6)	0.58
Hyperlipidemia	26 (24.1)	24 (23.1)	0.86
Chronic renal disease	4 (3.7)	5 (4.8)	0.69
Asthma	2 (1.9)	6 (5.8)	0.14
Chronic hepatitis B	2 (1.9)	5 (4.8)	0.23
Cerebrovascular disease	2 (1.9)	3 (2.9)	0.62
Malignancy	11 (10.2)	7 (6.7)	0.37
Obesity (BMI ≥30)	6 (5.6)	4 (3.8)	0.56
Symptoms (%)			
Asymptomatic	13 (12)	15 (14.4)	0.61
Fever	55 (50.9)	56 (53.8)	0.72

Cough	53 (49.1)	51 (49)	1.00
Sputum	13 (12)	16 (15.4)	0.48
Shortness of breath	16 (14.8)	16 (15.4)	0.91
Sore throat	23 (21.3)	22 (21.2)	0.98
Myalgia	5 (4.6)	11 (10.6)	0.10
Malaise	10 (9.3)	14 (13.5)	0.33
Dizziness	6 (5.6)	4 (3.8)	0.56
Diarrhoea	9 (8.3)	9 (8.7)	0.93
Rhinorrhoea	11 (10.2)	13 (12.5)	0.60
Anosmia	4 (3.7)	6 (5.8)	0.48
Headache	8 (7.4)	8 (7.7)	0.94
Baseline laboratory findings *(normal range)*; median (IQR)			
Hemoglobin (11.5-14.8 g/dL)	13.3 (12.2-14.2)	13.4 (12.6-14.5)	0.23
White cell count (3.89-9.93 x 10^9/L)	4.9 (3.9-6.4)	5.2 (4.3-6.3)	0.12
Neutrophil (2.01-7.42 x 10^9/L)	3.1 (2.4-4.4)	3.7 (2.7-4.3)	0.15
Lymphocyte (1.06-3.61 x 10^9/L)	1 (0.7-1.3)	1.1 (0.8-1.3)	0.43
Platelet (154-371 x 10^9/L)	185 (170-243)	187 (164-238)	0.63
ALT (8-45 U/L)	26 (18.5-41.5)	26 (19-41)	0.89
ALP (42-110 U/L)	62 (52.5-76.5)	59 (52-67)	0.07
LDH (143-280 U/L)	247 (193-298)	246.5 (202.5-309.3)	0.67
Creatinine (49-82 µmol/L)	72 (63-88)	74.5 (62-89.8)	0.51
Urea (2.9-8 mmol/L)	4.3 (3.6-5.2)	4.2 (3.3-5.3)	0.61

CRP (<0.76 mg/dL)	2.1 (0.8-6.5)	2.3 (0.8-6)	0.83
Concomitant treatment before study entry (%)			
Oxygen therapy	10 (9.3)	11 (10.6)	0.75
Concomitant treatment post study entry (%)			
Oxygen therapy	28 (25.9)	47 (45.2)	**0.003**
Time of starting oxygen therapy (median (IQR) days from study entry)	2 (1-2)	2 (2-2)	0.06
ICU Admission	4 (3.7)	12 (11.5)	**0.031**
Time of ICU admission (median (IQR) days from study entry)	2.5 (2-3)	3 (2-3)	078
High-flow oxygen or NIV support	4 (3.7)	6 (5.8)	0.48
Ventilator support	1 (1)	7 (6.7)	**0.027**
Time of starting ventilator support (median (IQR) days from study entry)	3 (3-3)	3 (3-3)	1.00
ECMO support	0 (0)	1 (1)	0.31
Antibiotics	12 (11.1)	14 (13.5)	0.37
Corticosteroid (stress dose) *	24 (22.2)	38 (36.5)	**0.022**
Time of starting corticosteroid (median (IQR) days from study entry)	3 (2-5)	3 (2-4)	0.5

IFN beta-1b: interferon beta-1b; ALT: alanine transaminase; ALP: alkaline phosphatase; LDH lactate dehydrogenase; CRP: C reactive protein;
ESR: erythrocyte sedimentation rate; ICU: intensive care unit; NIV: non-invasive ventilation; ECMO: extracorporeal membrane oxygenation
*Stress dose steroid: hydrocortisone 50mg q8h IV or dexamethasone 6mg q24h IV tapered over 5-7 days, IQR: interquartile range; p-value <0.05

Table 2 – Clinical, virological and immunological outcome of 212 patients

	IFN beta-1b + Remdesivir (n=108)	Remdesivir (n=104)	p-value
NEWS median (IQR)			
Baseline	0 (0-1)	0 (0-1)	0.54
Day 1	1 (1-2)	1 (1-2)	0.07
Day 2	1 (0-1.3)	2 (1-4)	**<0.0001**
Day 3	1 (0-1.3)	2 (1-5)	**<0.0001**
Day 4	1 (0-1.8)	2 (1-4)	**<0.0001**
Day 5	1 (0-2)	1 (1-4)	**0.01**
Day 6	1 (0-1)	1 (0-4)	0.16
Day 7	0.5 (0-1)	2 (1-5)	**0.006**
Day 8	1 (0-1.3)	2 (1-4)	0.06
Day 9	0 (0-0.5)	2 (0-4)	**0.02**
Time to NEWS = 0; median days (IQR)	4 (3-6)	6.5 (4.3-9)	**<0.0001**
WHO Clinical Progression Scale; median (IQR)			
Baseline	3 (3-4)	3 (3-4)	0.67
Day 1	4 (4-4)	4 (4-5)	0.07
Day 2	4 (3-4)	4 (4-5)	**<0.0001**
Day 3	3 (1-4)	4 (4-5)	**<0.0001**
Day 4	1 (1-3)	4 (1-5)	**<0.0001**
Day 5	1 (1-3)	3 (1-5)	**<0.001**
Day 6	1 (1-4)	3 (1-4)	**0.048**

Day 7	1 (1-2)	1 (1-4)	0.08
Day 8	1 (1-2)	1 (1-3)	0.11
Day 9	1 (1-1.8)	3 (2-4)	**0.02**
Time to WHO Clinical Progression Scale = 1; median days (IQR)	5 (5-6)	8 (6-9.8)	**<0.0001**
Time to negative VL; median days (IQR)			
NPS	6 (5-8)	8 (7-10)	**<0.0001**
POS	8 (6-9)	9 (7-10)	**<0.0001**
NPS Virologic findings (RT-PCR [log_{10} copies/ml]; median (IQR)			
Baseline	7 (5.3-8.4)	7.4 (5.7-8.7)	0.25
Day 1	6.1 (4.7-7.6)	6.8 (5.1-7.9)	0.07
Day 2	5.4 (4.2-6.4)	5.9 (4.4-7.4)	**0.02**
Day 3	4.1 (3.1-5.5)	5.5 (4.3-6.9)	**<0.0001**
Day 4	3.4 (2.1-4.8)	5.3 (3.7-6.4)	**<0.0001**
Day 5	3 (1-4.1)	4.7 (3.9-6)	**<0.0001**
Day 6	2.2 (1-3.5)	4.7 (1-6.5)	**<0.0001**
Day 7	1 (1-2.5)	3.5 (1-6)	**0.02**
Day 8	1 (1-2.4)	1.7 (1-3.8)	0.11
Day 9	1 (1-1)	1 (1-2.8)	0.10
POS Virologic findings (RT-PCR [log_{10} copies/ml]; median (IQR)			
Baseline	6.3 (5.1-8)	6.5 (4.8-8)	0.50
Day 1	5.2 (4-6.7)	5.8 (4.4-7.4)	0.07
Day 2	4.8 (3.8-6.3)	4.8 (3.7-6.4)	0.83

Day 3	4.2 (3.2-5.3)	4.7 (4-5.9)	**0.04**
Day 4	3.7 (2.5-4.7)	4.5 (3.7-5.9)	**<0.0001**
Day 5	3.3 (1.4-4.3)	4.7 (4.2-5.9)	**<0.0001**
Day 6	2 (1-3.8)	4 (1-5.8)	**0.006**
Day 7	1 (1-3.3)	3.6 (1-6.3)	**<0.0001**
Day 8	1 (1-1.6)	1 (1-6.3)	**0.004**
Day 9	1 (1-1)	1 (1-5)	**0.013**
Radiological findings (%)			
Abnormal CXR	72 (66.7)	59 (56.7)	0.14
Multilobar infiltrate	53 (49.1)	34 (32.7)	**0.02**
Length of hospitalization by clinical criteria (WHO Progression Scale <4); median days (IQR)	5 (4-6)	7 (5.3-8)	**<0.0001**
Length of oxygen therapy; median days (IQR)	4 (3-9.8)	7 (4-10)	**0.002**
Length of ICU care; median days (IQR)	8 (4.5-13)	11 (8.3-13.5)	**0.028**
Length of ventilator support; median days (IQR)	4 (4-4)	5 (4-6)	**0.012**
Length of high-flow O2 or NIV support; median days (IQR)	5.5 (3.3-7.8)	7 (4.3-8.8)	**0.029**
Length of ECMO support; median days (IQR)	0 (0-0)	8 (8-8)	0.31
IgG positive; median days (IQR)	8 (6-11)	10 (8-14)	**<0.0001**
Microneutralization antibody titre; median (IQR)			

Baseline	1 (1-1)	1 (1-1)	1.00
Day 3	5 (5-10)	5 (5-5)	**0.003**
Day 5	10 (5-40)	5 (5-10)	**<0.0001**
Day 7	20 (5-160)	5 (5-20)	**<0.0001**
Day 9	40 (5-160)	5 (5-40)	**0.001**
30-day mortality	0 (0)	0 (0)	1.00

IFN beta-1b: interferon beta-1b; NEWS: National Early Warning Score; WHO: World Health Organization;
NPS: nasopharyngeal swab; POS: posterior oropharyngeal saliva; RT-PCR: reverse transcription polymerase chain reaction; VL: viral load;
CXR: chest radiograph; RUZ: right upper zone, RMZ: right middle zone; RLZ: right lower zone; RMZ: right middle zone, LUZ left upper zone;
LMZ: left middle zone; LLZ: left lower zone; IQR: interquartile range; p-value <0.05

Table 3 – Clinical and virological outcome in patients with baseline WHO Clinical Progression Scale ≥4

	IFN beta-1b + Remdesivir (n=51)	Remdesivir (n=49)	p-value
Time to NEWS = 0; median days (IQR)	5 (4-7)	9 (7-11)	**<0.0001**
Time to WHO Clinical Progression Scale = 1; median days (IQR)	6 (5-8)	9 (9-11)	**<0.0001**
Time to negative VL; median days (IQR)			
NPS	7 (6-8)	9 (7-11)	**<0.0001**
POS	8 (6-9)	9 (7-11)	**0.027**
Length of hospitalization by clinical criteria (WHO Clinical Progression Scale <4); median days (IQR)	6 (5-7)	8 (7-10)	**<0.0001**
Length of oxygen therapy; median days (IQR)	4 (4-12)	7 (4-12)	**0.001**
Length of ICU care; median days (IQR)	10 (6-14)	11 (8-14)	**0.016**
Length of ventilator support; median days (IQR)	4 (4-4)	5 (4-6)	**0.023**

IFN beta-1b: interferon beta-1b; NEWS: National Early Warning Score; WHO: World Health Organization
NPS: nasopharyngeal swab; POS: posterior oropharyngeal saliva; RT-PCR: reverse transcription polymerase chain reaction; VL: viral load

Table 4 – Univariable analysis for baseline factors associated with NEWS=0 on day 4 after treatment

	NEWS=0 (n=87)	**NEWS>0** (n=125)	**p-value**
Age; median (range)	64 (48-70)	65 (55-73)	**0.06**
Sex (male) %	44 (50.6)	68 (54.4)	0.58
Days of starting treatment from symptoms onset; median (IQR)	3 (2-4)	2 (2-4)	0.44
Combination group (%)	61 (77)	47 (37.6)	**<0.0001**
Underlying diseases	58 (66.7)	101 (80.8)	**0.02**
Baseline laboratory findings *(normal range)*			
Hemoglobin (11.5-14.8 g/dL)	13.6 (12.6-14.4)	13.4 (12.3-14.2)	0.22
Lymphocyte (1.06-3.61 x 10^9/L)	1.1 (0.8-1.4)	1 (0.7-1.2)	**0.002**
ALT (8-45 U/L)	28 (22-44)	23 (15-34.8)	0.15
LDH (143-280 U/L)	247 (196-298)	247 (199.5-316.8)	**0.001**
Creatinine (49-82 µmol/L)	69 (58.5-86.3)	76 (63-91.5)	**0.02**
CRP (<0.76 mg/dL)	1.8 (0.9-5.9)	2.2 (0.8-6.6)	0.71
Abnormal CXR	44 (50.6)	87 (69.6)	**0.005**
Concomitant treatments (%)			
Oxygen therapy during hospitalization	10 (11.5)	65 (52)	**<0.0001**
High-flow oxygen or NIV support	1 (1.1)	15 (12)	**0.003**
Ventilator support	0 (0)	8 (6.4)	**0.016**
ECMO support	0 (0)	1 (1)	0.40
Antibiotics	7 (8)	19 (15.2)	0.12

Corticosteroid (stress dose) *	11 (12.6)	51 (40.8)	**<0.0001**
Virologic findings [RT-PCR (log_{10} copies/ml)] median (IQR)			
NPS VL (baseline)	7 (5.2-8.1)	7.3 (5.9-8.8)	**0.04**
POS VL (baseline) *	5.6 (4.6-7.1)	7 (5.2-8.4)	**0.006**

ALT: alanine transaminase; LDH lactate dehydrogenase; CRP: C reactive protein; NIV: non-invasive ventilation; ECMO: extracorporeal membrane oxygenation;
*Stress dose steroid: hydrocortisone 50mg q8h IV or dexamethasone 6mg q24h IV tapered over 5-7 days; NEWS: National Early Warning Score;
NPS: nasopharyngeal swab; POS: posterior oropharyngeal saliva; RT-PCR: reverse transcription polymerase chain reaction; VL: viral load;
CXR: chest radiograph; IQR: interquartile range; p-value <0.1 were significant for multivariable analysis

Table 5 - Multivariable analysis of independent factors associated with NEWS = 0 on day 4 after treatment

Factors	HR (95% CI)	p-value
Combination group	4.1 (1.9-8.6)	**<0.0001**
No oxygen therapy during hospitalization	7.5 (2.4-23.5)	**0.001**
Low baseline POS VL	1.4 (1.1-1.8)	**0.003**

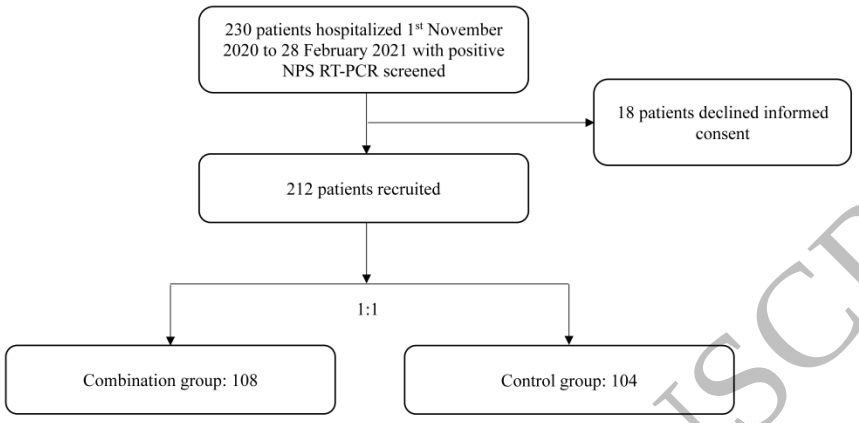
POS: posterior oropharyngeal saliva; VL: viral load; HR: hazard ratio; CI: confidence interval; p-value <0.05

Table 6 – Adverse Events of 212 patients

	IFN beta-1b + Remdesivir (n=108)	Remdesivir (n=104)	p-value
Adverse events %			
Nausea	12 (11.1)	14 (13.5)	0.73
Raised ALT	33 (30.6)	18 (17.3)	**0.022**
Fever	45 (41.7)	46 (44.2)	0.82
Skin erythema (injection site)	12 (11.1)	0	**<0.0001**
Skin induration (injection site)	7 (6.5)	0	**0.008**
Serious adverse events	0 (0)	0 (0)	1.00

IFN beta-1b: interferon beta-1b; ALT: alanine transaminase

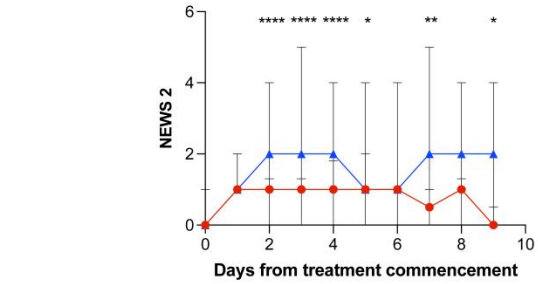
Figure 1



NPS: nasopharyngeal swab; RT-PCR: reverse transcription polymerase chain reaction
Combination group: 5 days of interferon beta-1b + remdesivir
Control group: 5 days of remedesivir

297x210 mm (40 x DPI)

Figure 2



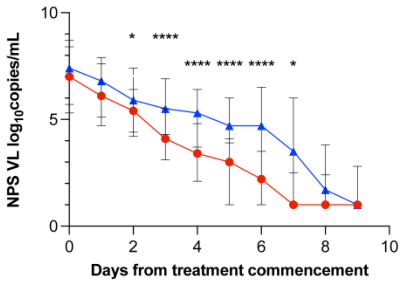
Days	0	1	2	3	4	5	6	7	8	9
IFN beta-1b + R (valid samples):	108	108	108	108	108	108	108	102	98	90
R (valid samples):	104	104	104	104	104	104	104	104	102	100

Baseline 100% positive

IFN beta-1b: interferon beta-1b; R: remdesivir
NEWS 2: National Early Morning Score; median (IQR)
*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001

297x210 mm (40 x DPI)

Figure 3



Days	0	1	2	3	4	5	6	7	8	9
IFN beta-1b + R (valid samples):	108	108	108	108	104	104	102	98	92	83
R (valid samples):	104	104	104	104	104	101	97	97	93	92

Baseline 100% positive

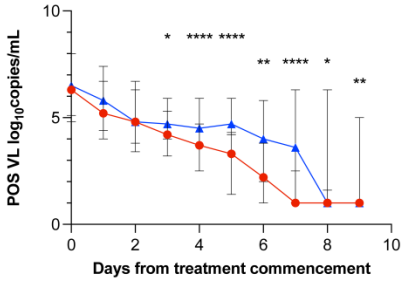
IFN beta-1b: interferon beta-1b; R: remdesivir
NPS VL: nasopharyngeal swab viral load RT-PCR; median (IQR)
*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001

1

2 **297x210 mm (40 x DPI)**

3

Figure 4



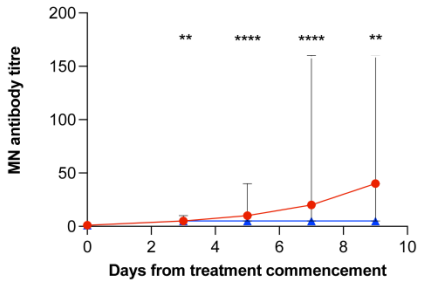
Days	0	1	2	3	4	5	6	7	8	9
IFN beta-1b + R (valid samples):	108	108	108	108	103	103	100	94	90	81
R (valid samples):	104	104	104	104	102	100	94	91	91	88

Baseline 100% positive

IFN beta-1b: interferon beta-1b; R: remdesivir
POS VL: posterior oropharyngeal saliva viral load RT-PCR; median (IQR)
*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001

297x210 mm (40 x DPI)

Figure 5



Days	0	3	5	7	9
IFN beta-1b + R (valid samples):	108	108	108	108	90
R (valid samples):	104	104	104	104	100

IFN beta-1b: interferon beta-1b; R: remdesivir
MN antibody titre: microneutralization antibody titre; median (IQR)
*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001

1

2 **297x210 mm (40 x DPI)**