Clinical Infectious Diseases

MAJOR ARTICLE

Early Treatment of High-Risk Hospitalized Coronavirus Disease 2019 (COVID-19) Patients With a Combination of Interferon Beta-1b and Remdesivir: A Phase 2 Open-label Randomized Controlled Trial

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Background. Early antiviral therapy was effective in the treatment of coronavirus disease 2019 (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 200 mg loading on day 1 followed by 100 mg daily on day 2 to 5 (combination group), or to remdesivir only of similar regimen (control group) (1:1). The primary endpoint 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 vs 6.5 days; hazard ratio [HR], 6.59; 95% confidence interval [CI], 6.1–7.09; $P < .0001$) when compared to the control group. For the secondary endpoints, the combination group was quicker to negative nasopharyngeal swab (NPS) viral load (VL) (6 vs 8 days; HR, 8.16; 95% CI, 7.79–8.52; $P < .0001$) and to develop seropositive immunoglobulin G (IgG) (8 vs 10 days; HR, 10.78; 95% CI, 9.98–11.58; $P < .0001$). All adverse events resolved upon follow-up. Combination group (HR, 4.1 95% CI, 1.9–8.6, $P < .0001$) 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, and in shortening viral shedding and hospitalization with earlier seropositivity in high-risk COVID-19 patients.

Keywords. early; high-risk; COVID-19; interferon beta-1b; remdesivir.

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 the 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

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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 multicenter 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, multicenter 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 the 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 (Supplementary Appendix 1). 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, hematological diseases, rheumatological diseases, immunocompromised hosts, and obesity (body mass index [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 1 of 2 groups, the combination group or the control group, in the ratio of 1:1, by simple randomization with no stratification. In the combination group, the patients received a 5-day course of subcutaneous injection of daily dose of interferon beta-1b 2 mL (16 million IU) consecutively and intravenous infusion of remdesivir 200 mg loading on day 1 followed by 100 mg daily on days 2–5. Patients randomized to the control group received intravenous infusion of remdesivir 200 mg loading on day 1 followed by 100 mg daily on days 2–5.

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, extracorporeal membrane oxygenation (ECMO) support, dialysis support, and antimicrobial treatment for secondary bacterial infection as indicated clinically. Stress dose of intravenous corticosteroids (6 mg dexamethasone daily or 50 mg hydrocortisone every 8 hours, tapering over 7 days) were given to patients, who developed oxygen desaturation and required oxygen support, noninvasive 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 (Supplementary Appendix 1). 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 immunoglobulin G (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 Supplementary Appendixes.

Outcomes

The primary endpoint was the time to complete alleviation of symptoms as defined by the National Early Warning Score 2

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(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 (ICU) admission, requirement of oxygen, noninvasive and invasive ventilation, 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, <20 mm; grade 2, 20–50 mm; grade 3, >50 mm.

Randomization

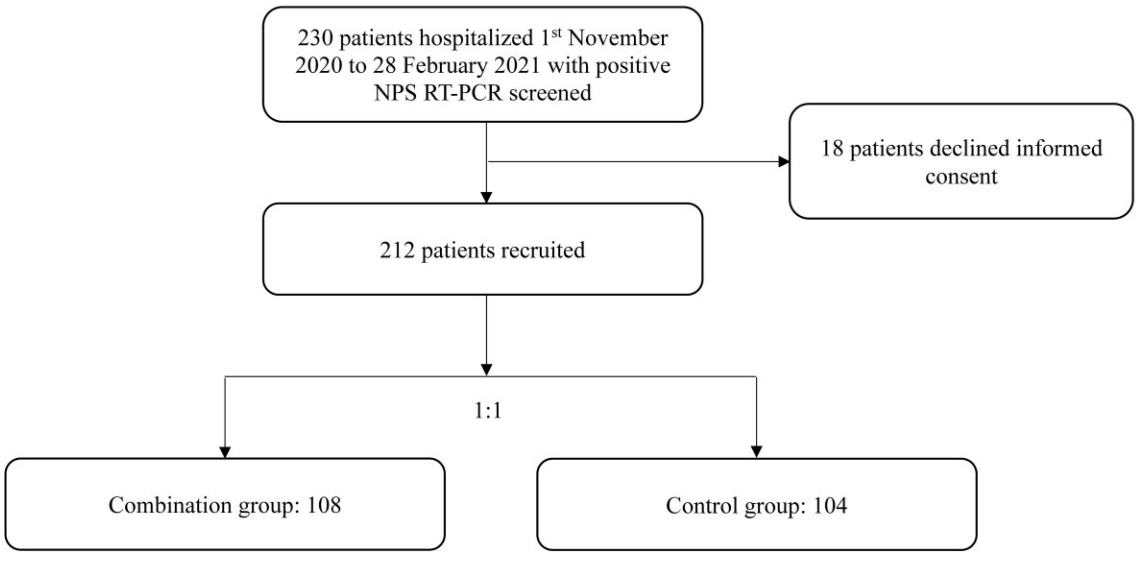
Randomized treatment was open label. Patients were assigned to a serial number by the study coordinator. Each serial number was linked to a computer-generated randomization list assigning the antiviral treatment regimens. The study medications was dispensed by the hospital pharmacy and then to the patients 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 2-sided alpha level of 0.05, with 80% 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 χ^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 ($P < .10$) 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 <.05 was considered to be statistically significant.



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

Figure 1. Recruitment flowchart of the 212 patients. Abbreviations: NPS, nasopharyngeal swab; RT-PCR, reverse-transcription polymerase chain reaction.

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Table 1. Baseline Demographics of 212 Patients

	IFN beta-1b + Remdesivir (n = 108)	Remdesivir (n = 104)	*P* Value
Age; median (IQR)	64 (55–72)	65 (52–71.8)	.94
Male sex (%)	52 (48.1)	60 (57.7)	.16
Days of starting treatment from symptoms onset; median (IQR)	2.5 (2–4)	3 (2–3)	.84
Oxygen saturation <94% on room air	10 (9.3)	11 (10.6)	.75
Underlying diseases (%)			
Charlson comorbidity index	2 (1–3)	2 (1–3)	.61
Chronic disease (overall)	80 (74.1)	79 (76)	.75
Diabetes mellitus	21 (19.4)	27 (26)	.26
Hypertension	45 (41.7)	45 (43.3)	.81
Coronary artery disease	9 (8.3)	11 (10.6)	.58
Hyperlipidemia	26 (24.1)	24 (23.1)	.86
Chronic renal disease	4 (3.7)	5 (4.8)	.69
Asthma	2 (1.9)	6 (5.8)	.14
Chronic hepatitis B	2 (1.9)	5 (4.8)	.23
Cerebrovascular disease	2 (1.9)	3 (2.9)	.62
Malignancy	11 (10.2)	7 (6.7)	.37
Obesity (BMI ≥30)	6 (5.6)	4 (3.8)	.56
Symptoms (%)			
Asymptomatic	13 (12)	15 (14.4)	.61
Fever	55 (50.9)	56 (53.8)	.72
Cough	53 (49.1)	51 (49)	1.00
Sputum	13 (12)	16 (15.4)	.48
Shortness of breath	16 (14.8)	16 (15.4)	.91
Sore throat	23 (21.3)	22 (21.2)	.98
Myalgia	5 (4.6)	11 (10.6)	.10
Malaise	10 (9.3)	14 (13.5)	.33
Dizziness	6 (5.6)	4 (3.8)	.56
Diarrhoea	9 (8.3)	9 (8.7)	.93
Rhinorrhoea	11 (10.2)	13 (12.5)	.60
Anosmia	4 (3.7)	6 (5.8)	.48
Headache	8 (7.4)	8 (7.7)	.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)	.23
White cell count (3.89–9.93 × 10^9/L)	4.9 (3.9–6.4)	5.2 (4.3–6.3)	.12
Neutrophil (2.01–7.42 × 10^9/L)	3.1 (2.4–4.4)	3.7 (2.7–4.3)	.15
Lymphocyte (1.06–3.61 × 10^9/L)	1 (0.7–1.3)	1.1 (0.8–1.3)	.43
Platelet (154–371 × 10^9/L)	185 (170–243)	187 (164–238)	.63
ALT (8–45 U/L)	26 (18.5–41.5)	26 (19–41)	.89
ALP (42–110 U/L)	62 (52.5–76.5)	59 (52–67)	.07
LDH (143–280 U/L)	247 (193–298)	246.5 (202.5–309.3)	.67
Creatinine (49–82 µmol/L)	72 (63–88)	74.5 (62–89.8)	.51
Urea (2.9–8 mmol/L)	4.3 (3.6–5.2)	4.2 (3.3–5.3)	.61
CRP (<.76 mg/dL)	2.1 (0.8–6.5)	2.3 (0.8–6)	.83
Concomitant treatment before study entry (%)			
Oxygen therapy	10 (9.3)	11 (10.6)	.75
Concomitant treatment post study entry (%)			
Oxygen therapy	28 (25.9)	47 (45.2)	**.003**
Time of starting oxygen therapy (median (IQR) days from study entry)	2 (1–2)	2 (2-2)	.06
ICU admission	4 (3.7)	12 (11.5)	**.031**
Time of ICU admission (median (IQR) days from study entry)	2.5 (2–3)	3 (2–3)	.78
High-flow oxygen or NIV support	4 (3.7)	6 (5.8)	.48
Ventilator support	1 (1)	7 (6.7)	**.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)	.31
Antibiotics	12 (11.1)	14 (13.5)	.37
Corticosteroid (stress dose)[a]	24 (22.2)	38 (36.5)	**.022**
Time of starting corticosteroid (median (IQR) days from study entry)	3 (2–5)	3 (2–4)	.5

Bold if *P* value <.5.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; CRP, C-reactive protein; ECMO, extracorporeal membrane oxygenation; ESR, erythrocyte sedimentation rate; ICU, intensive care unit; IFN beta-1b, interferon beta-1b; IQR, interquartile range; LDH, lactate dehydrogenase; NIV, non-invasive ventilation.

[a]Stress dose steroid: hydrocortisone 50 mg q8h IV or dexamethasone 6 mg q24h IV tapered over 5–7 days.

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 were ≥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

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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)	.54
Day 1	1 (1–2)	1 (1–2)	.07
Day 2	1 (0–1.3)	2 (1–4)	**<.0001**
Day 3	1 (0–1.3)	2 (1–5)	**<.0001**
Day 4	1 (0–1.8)	2 (1–4)	**<.0001**
Day 5	1 (0–2)	1 (1–4)	**.01**
Day 6	1 (0–1)	1 (0–4)	.16
Day 7	.5 (0–1)	2 (1–5)	**.006**
Day 8	1 (0–1.3)	2 (1–4)	.06
Day 9	0 (0–.5)	2 (0–4)	**.02**
Time to NEWS = 0; median days (IQR)	4 (3–6)	6.5 (4.3–9)	**<.0001**
WHO Clinical Progression Scale; median (IQR)			
Baseline	3 (3–4)	3 (3–4)	.67
Day 1	4 (4–4)	4 (4–5)	.07
Day 2	4 (3–4)	4 (4–5)	**<.0001**
Day 3	3 (1–4)	4 (4–5)	**<.0001**
Day 4	1 (1–3)	4 (1–5)	**<.0001**
Day 5	1 (1–3)	3 (1–5)	**<.001**
Day 6	1 (1–4)	3 (1–4)	**.048**
Day 7	1 (1–2)	1 (1–4)	.08
Day 8	1 (1–2)	1 (1–3)	.11
Day 9	1 (1–1.8)	3 (2–4)	**.02**
Time to WHO Clinical Progression Scale = 1; median days (IQR)	5 (5–6)	8 (6–9.8)	**<.0001**
Time to negative VL; median days (IQR)			
NPS	6 (5–8)	8 (7–10)	**<.0001**
POS	8 (6–9)	9 (7–10)	**<.0001**
NPS virologic findings (RT-PCR [log_{10} copies/mL]; median (IQR)			
Baseline	7 (5.3–8.4)	7.4 (5.7–8.7)	.25
Day 1	6.1 (4.7–7.6)	6.8 (5.1–7.9)	.07
Day 2	5.4 (4.2–6.4)	5.9 (4.4–7.4)	**.02**
Day 3	4.1 (3.1–5.5)	5.5 (4.3–6.9)	**<.0001**
Day 4	3.4 (2.1–4.8)	5.3 (3.7–6.4)	**<.0001**
Day 5	3 (1–4.1)	4.7 (3.9–6)	**<.0001**
Day 6	2.2 (1–3.5)	4.7 (1–6.5)	**<.0001**
Day 7	1 (1–2.5)	3.5 (1–6)	**.02**
Day 8	1 (1–2.4)	1.7 (1–3.8)	.11
Day 9	1 (1–1)	1 (1–2.8)	.10
POS Virologic findings (RT-PCR [log_{10} copies/mL]; median (IQR)			
Baseline	6.3 (5.1–8)	6.5 (4.8–8)	.50
Day 1	5.2 (4–6.7)	5.8 (4.4–7.4)	.07
Day 2	4.8 (3.8–6.3)	4.8 (3.7–6.4)	.83
Day 3	4.2 (3.2–5.3)	4.7 (4–5.9)	**.04**
Day 4	3.7 (2.5–4.7)	4.5 (3.7–5.9)	**<.0001**
Day 5	3.3 (1.4–4.3)	4.7 (4.2–5.9)	**<.0001**
Day 6	2 (1–3.8)	4 (1–5.8)	**.006**
Day 7	1 (1–3.3)	3.6 (1–6.3)	**<.0001**
Day 8	1 (1–1.6)	1 (1–6.3)	**.004**
Day 9	1 (1–1)	1 (1–5)	**.013**
Radiological findings (%)			
Abnormal CXR	72 (66.7)	59 (56.7)	.14
Multilobar infiltrate	53 (49.1)	34 (32.7)	**.02**
Length of hospitalization by clinical criteria (WHO Progression Scale <4); median days (IQR)	5 (4–6)	7 (5.3–8)	**<.0001**
Length of oxygen therapy; median days (IQR)	4 (3–9.8)	7 (4–10)	**.002**
Length of ICU care; median days (IQR)	8 (4.5–13)	11 (8.3–13.5)	**.028**
Length of ventilator support; median days (IQR)	4 (4–4)	5 (4–6)	**.012**
Length of high-flow oxygen or NIV support; median days (IQR)	5.5 (3.3–7.8)	7 (4.3–8.8)	**.029**
Length of ECMO support; median days (IQR)	0 (0–0)	8 (8–8)	.31
IgG positive; median days (IQR)	8 (6–11)	10 (8–14)	**<.0001**
Microneutralization antibody titer; median (IQR)			
Baseline	1 (1–1)	1 (1–1)	1.00
Day 3	5 (5–10)	5 (5–5)	**.003**
Day 5	10 (5–40)	5 (5–10)	**<.0001**
Day 7	20 (5–160)	5 (5–20)	**<.0001**
Day 9	40 (5–160)	5 (5–40)	**.001**
30-day mortality	0 (0)	0 (0)	1.00

Bold if *P* value <.5.

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

randomized to the control group. The median days of starting treatment from symptom onset were 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 (Tables 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 vs 6.5 days; HR,6.59; 95% CI, 6.1–7.09; $P < .0001$). Similarly, the combination group was significantly quicker to achieve WCPS = 1 (5 vs 8 days; HR,7.1; 95% CI, 7.29–8.11; $P < .0001$).

For the secondary endpoints, the combination group was quicker to negative NPS VL (6 vs 8 days; HR,8.16; 95% CI,

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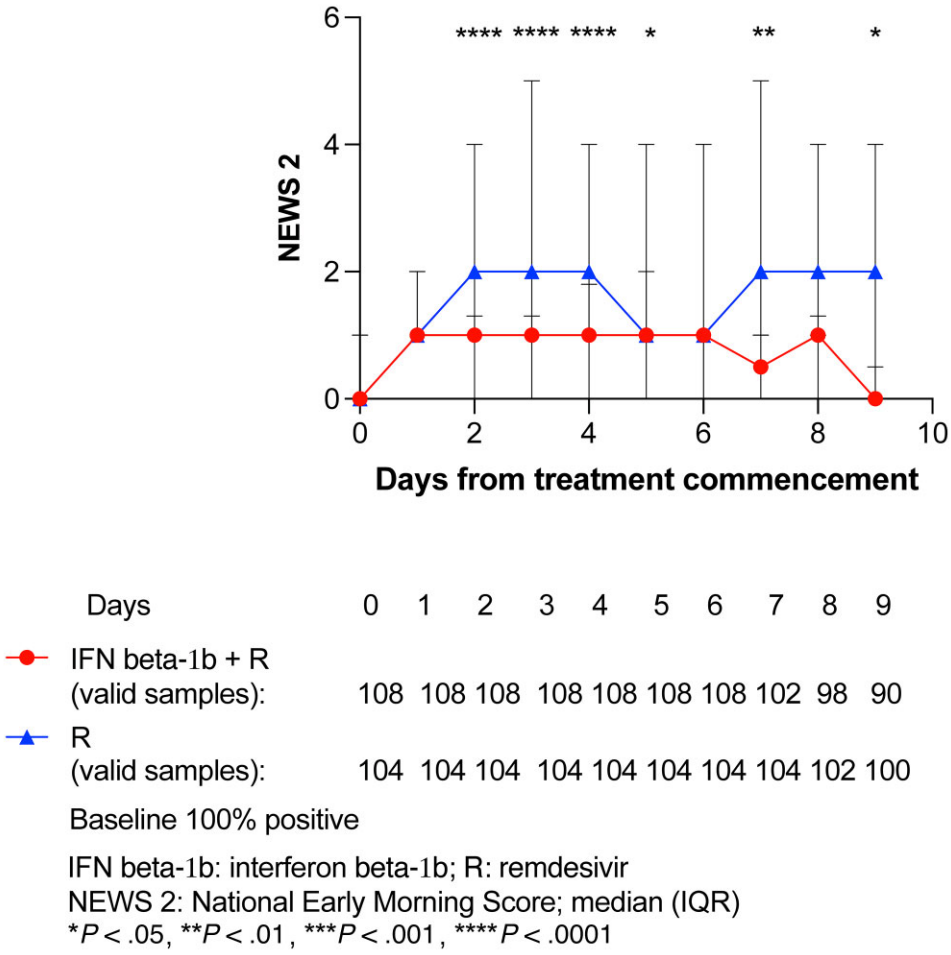

Figure 2. Profile of the National Early Warning Score 2 (NEWS2) with respect to days from treatment commencement. Abbreviation: IQR, interquartile range.

7.79–8.52; $P < .0001$), and to negative POS VL (8 vs 9 days; HR, 8.25; 95% CI, 7.81–8.69; $P < .0001$) (Table 2, Figures 3 and 4). The combination group was also associated with shorter hospital stays according to the clinical criteria (5 vs 7 days; HR, 7.38; 95% CI, 6.88–7.87; $P < .0001$) and shorter ICU stay (8 vs 11 days; HR, 11.06; 95% CI, 8.54–13.63; $P < .001$) (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 ($P = .003$), ICU admission ($P = .031$), ventilator support ($P = .027$), and corticosteroid treatment ($P = .022$) post study entry (Table 1). The median time of starting corticosteroid was 5 (IQR 4–9) days after admission. The length of oxygen therapy ($P = .002$), ventilator support ($P = .012$), and high-flow oxygen or NIV support ($P = .029$) 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 vs 10 days; HR, 10.78; 95% CI, 9.98–11.58; $P < .0001$). The microneutralization antibody titer was significantly higher in the combination group than the control group from day 3 onward after treatment commencement (Figure 5). The day 9 microneutralization antibody titer was significantly higher in the combination group than the control group (1:40 vs 1:5; $P < .0001$).

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

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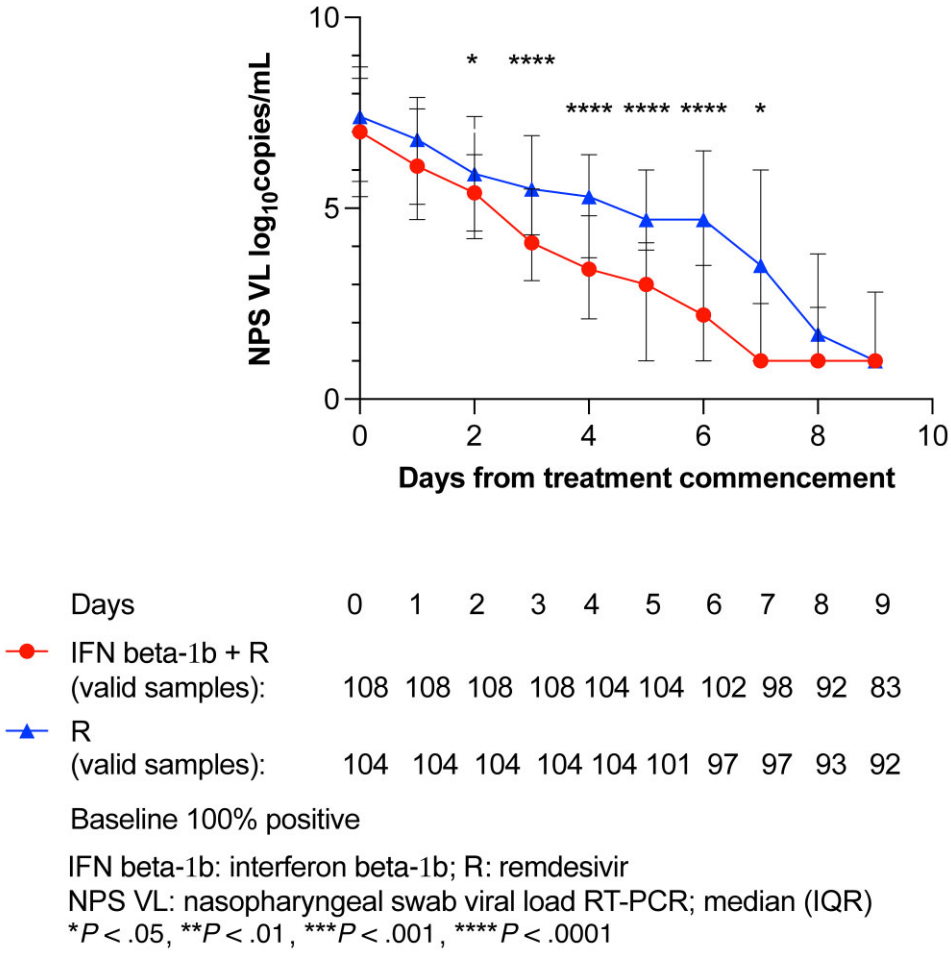

Figure 3. Profile of the nasopharyngeal swab (NPS) viral load (VL) with respect to days from treatment commencement. Abbreviations: IQR, interquartile range; RT-PCR, reverse transcription polymerase chain reaction.

oxygen, high-flow oxygen or NIV support, ventilator support, corticosteroid treatment, baseline

NPS or POS VL, baseline lymphocyte count, LDH and CRP, and abnormal CXR were further assessed by the multivariable analysis. Combination group (HR, 4.1, 95% CI, 1.9–8.6; $P <$ .0001), no oxygen therapy during hospitalization (HR, 7.5, 95% CI, 2.4–23.5; $P = .001$), and low baseline POS VL (HR, 1.4, 95% CI, 1.1–1.8; $P = .003$) 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%; $P < .0001$) and induration (6.5%; $P = .008$) at the interferon beta-1b injection site in the combination group. Only 1 patient (.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 2 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 MN antibody titer 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

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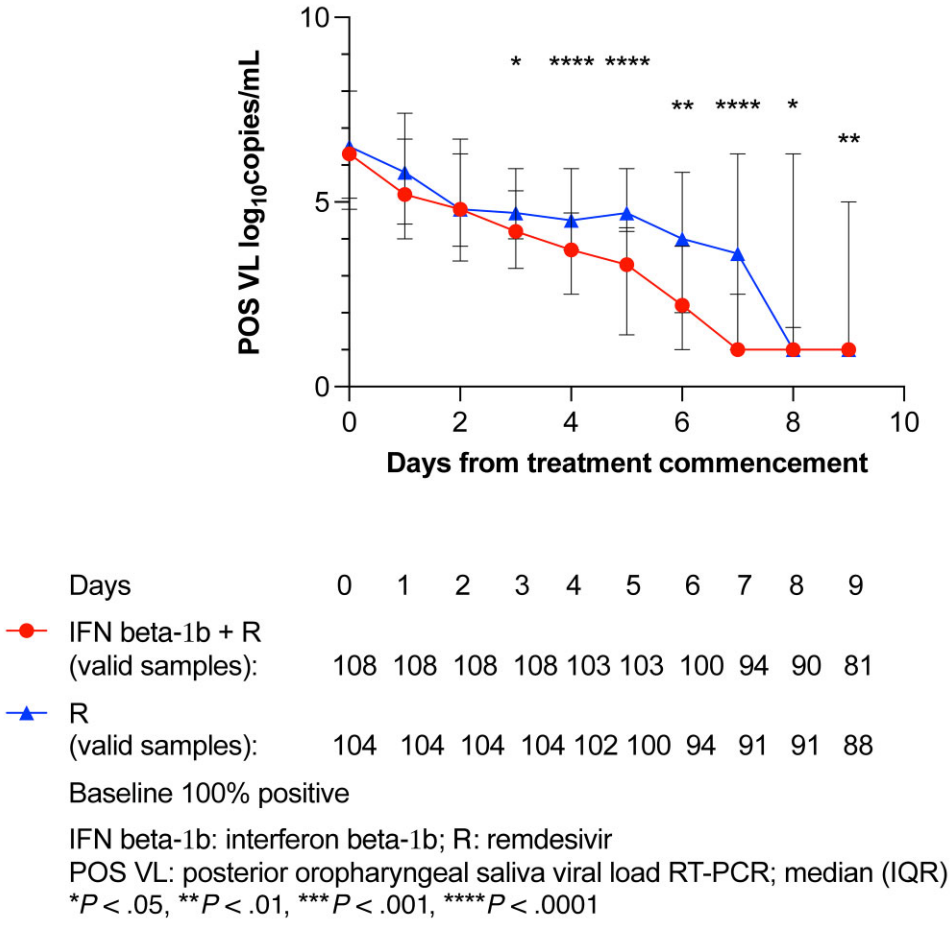

Figure 4. Profile of the posterior oropharyngeal saliva viral load (VL) with respect to days from treatment commencement. Abbreviation: IQR, interquartile range.

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 US 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

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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)	**<.0001**
Time to WHO Clinical Progression Scale = 1; median days (IQR)	6 (5–8)	9 (9–11)	**<.0001**
Time to negative VL; median days (IQR)			
NPS	7 (6–8)	9 (7–11)	**<.0001**
POS	8 (6–9)	9 (7–11)	**.027**
Length of hospitalization by clinical criteria (WHO Clinical Progression Scale <4); median days (IQR)	6 (5–7)	8 (7–10)	**<.0001**
Length of oxygen therapy; median days (IQR)	4 (4–12)	7 (4–12)	**.001**
Length of ICU care; median days (IQR)	10 (6–14)	11 (8–14)	**.016**
Length of ventilator support; median days (IQR)	4 (4–4)	5 (4–6)	**.023**

Bold if *P* value <.5.

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

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-α^2 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 ICU admission in patients with COVID-19 [30]. Therefore, early replacement of interferon might counteract

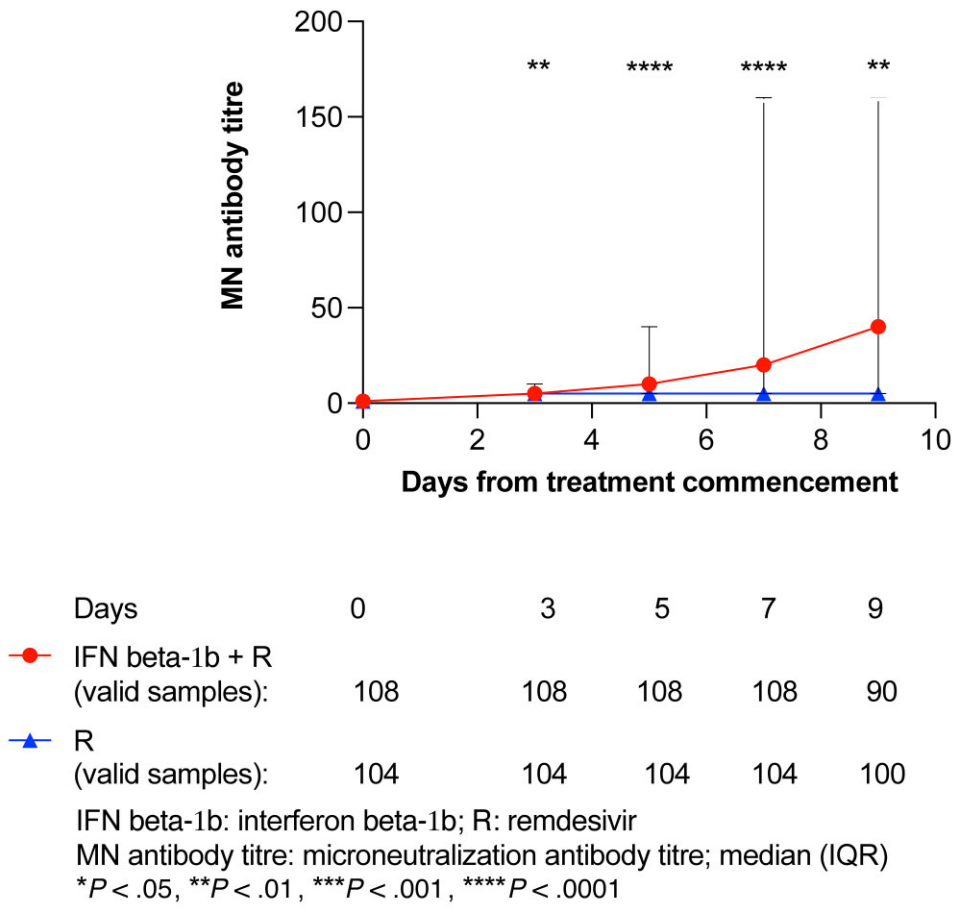

Figure 5. Profile of the microneutralization (MN) antibody titer with respect to days from treatment commencement. Abbreviation: IQR, interquartile range.

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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)	**.06**
Sex (male) %	44 (50.6)	68 (54.4)	.58
Days of starting treatment from symptoms onset; median (IQR)	3 (2–4)	2 (2–4)	.44
Combination group (%)	61 (77)	47 (37.6)	**<.0001**
Underlying diseases	58 (66.7)	101 (80.8)	**.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)	.22
Lymphocyte (1.06–3.61 $\times 10^9$/L)	1.1 (0.8–1.4)	1 (0.7–1.2)	**.002**
ALT (8–45 U/L)	28 (22–44)	23 (15–34.8)	.15
LDH (143–280 U/L)	247 (196–298)	247 (199.5–316.8)	**.001**
Creatinine (49–82 μmol/L)	69 (58.5–86.3)	76 (63–91.5)	**.02**
CRP (<0.76 mg/dL)	1.8 (0.9–5.9)	2.2 (0.8–6.6)	.71
Abnormal CXR	44 (50.6)	87 (69.6)	**.005**
Concomitant treatments (%)			
Oxygen therapy during hospitalization	10 (11.5)	65 (52)	**<.0001**
High-flow oxygen or NIV support	1 (1.1)	15 (12)	**.003**
Ventilator support	0 (0)	8 (6.4)	**.016**
ECMO support	0 (0)	1 (1)	.40
Antibiotics	7 (8)	19 (15.2)	.12
Corticosteroid (stress dose)[a]	11 (12.6)	51 (40.8)	**<.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)	**.04**
POS VL (baseline)[a]	5.6 (4.6–7.1)	7 (5.2–8.4)	**.006**

Bold if *P* value <.1 were significant for multivariable analysis.

Abbreviations: ALT, alanine transaminase; CRP, C reactive protein; CXR, chest radiograph; ECMO, extracorporeal membrane oxygenation; IQR, interquartile range; LDH, lactate dehydrogenase; NEWS, National Early Warning Score; NIV, non-invasive ventilation; NPS, nasopharyngeal swab; POS, posterior oropharyngeal saliva; RT-PCR, reverse transcription polymerase chain reaction; VL, viral load.

[a]Stress dose steroid: hydrocortisone 50 mg q8h IV or dexamethasone 6 mg q24h IV tapered over 5–7 days.

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)	**<.0001**
No oxygen therapy during hospitalization	7.5 (2.4–23.5)	**.001**
Low baseline POS VL	1.4 (1.1–1.8)	**.003**

Bold if *P* value <.5.

Abbreviations: CI, confidence interval; HR, hazard ratio; POS, posterior oropharyngeal saliva; VL, viral load.

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)	.73
Raised ALT	33 (30.6)	18 (17.3)	**.022**
Fever	45 (41.7)	46 (44.2)	.82
Skin erythema (injection site)	12 (11.1)	0	**<.0001**
Skin induration (injection site)	7 (6.5)	0	**.008**
Serious adverse events	0 (0)	0 (0)	1.00

Bold if *P* value <.5. Abbreviations: ALT, alanine transaminase; IFN beta-1b, interferon beta-1b.

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.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Notes

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Potential conflicts of interest. I. F. H received honoraria as speaker from MSD for COVID-19 Regional Expert Input Forum 2021 and Herpes Zoster lecture 2021 and was a member of the Advisory Board for Pfizer on COVID-19 Management 2022 and Gilead on Evolving Treatment Landscape in COVID-19 2021. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. WHO Coronavirus (COVID-19) Dashboard. Available at: https://covid19.who.int. Accessed 25 April 2022.
2. Chan JF, Yuan S, Kok KH, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet **2020**; 395:514–23. doi:10.1016/S0140-6736(20)30154-9.
3. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet **2020**; 395:1054–62. doi:10.1016/S0140-6736(20)30566-3.
4. Bhatraju PK, Ghassemieh BJ, Nichols M, et al. Covid-19 in critically ill patients in the Seattle Region—case series. N Engl J Med **2020**; 382:2012–22. doi:10.1056/NEJMoa2004500.
5. Leisman DE, Ronner L, Pinotti R, et al. Cytokine elevation in severe and critical COVID-19: a rapid systemic review, meta-analysis, and comparison with other inflammatory syndromes. Lancet Respir Med **2020**; 8:1233–44. doi:10.1016/S2213-2600(20)30404-5.
6. Mahamat-Saleh Y, Fiolet T, Rebeaud ME, et al. Diabetes, hypertension, body mass index, smoking and COVID-19 related mortality: a systematic review and meta-analysis of observational studies. BMJ Open **2021**; 11:e052777. doi:10.1136/bmjopen-2021-052777.
7. Hung IF, Lung KC, Tso EY, et al. 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. Lancet **2020**; 395:1695–704. doi:10.1016/S0140-6736(20)31042-4.
8. Feld JJ, Kandel C, Biondi MJ, et al. Peginterferon lambda for the treatment of outpatients with COVID-19: a phase 2, placebo-controlled randomised trial. Lancet Respir Med **2021**; 9:498–510. doi:10.1016/S2213-2600(20)30566-X.
9. Monk PD, Marsden RJ, Tear VJ, et al. Safety and efficacy of inhaled nebulized interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Respir Med **2021**; 9:196–206. doi:10.1016/S2213-2600(20)30511-7.
10. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19—final report. N Engl J Med **2020**; 383:1813–26. doi:10.1056/NEJMoa2007764.
11. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of remdesivir vs. standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. JAMA **2020**; 324:1048–57. doi:10.1001/jama.2020.16349.
12. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus remdesivir for hospitalized adults with Covid-19. N Engl J Med **2021**; 384:795–807. doi:10.1056/NEJMoa2031994.
13. WHO Solidarity trial Consortium, Pan H, Peto R, et al. Repurposed antiviral drugs for Covid-19—interim WHO solidarity trial results. N Engl J Med **2021**; 384:497–511.
14. Charlson ME, Carrozzino D, Guidi J, et al. Charlson comorbidity index: a critical review of clinimetric properties. Psychother Psychosom **2022**; 91:8–35. doi:10.1159/000521288.
15. To KK, Tsang OT, Leung WS, et al. Temporal profiles of viral load and antibody response during COVID-19 infection by SARS-CoV-2. Lancet Infect Dis **2020**; 20:565–74. doi:10.1016/S1473-3099(20)30196-1.
16. William B. The National Early Warning Score 2 (NEWS2) in patients with hypercapnic respiratory failure. Clin Med **2019**; 19:94–5. doi:10.7861/clinmedicine.19-1-94.
17. Scott LJ, Tavare A, Hill EM, et al. Prognostic value of National Early Warning Scores (NEWS2) and component physiology in hospitalised patients with COVID-19: a multicentre study. Emerg Med J **2022**. doi:10.1136/emermed-2020-210624.
18. WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research. Lancet Infect Dis **2020**; 20:e192–97. doi:10.1016/S1473-3099(20)30483-7.
19. Liu H, Chen S, Liu M, et al. Comorbid chronic diseases are strongly correlated with disease severity among COVID-19 patients: a systematic review and meta-analysis. Aging Dis **2020**; 11:668–78. doi:10.14336/AD.2020.0502.
20. Coronaviruses (COVID-19) update: FDA authorizes first oral antiviral for treatment of COVID-19. Available at: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-oral-antiviral-treatment-covid-19. Accessed 14 June 2022.
21. Arabi YM, Asiri AY, Assiri AM, et al. Interferon beta-1b and lopinavir-ritonavir for Middle East Respiratory Syndrome. N Engl J Med **2020**; 383:1645–56. doi:10.1056/NEJMoa2015294.
22. Gottlieb RL, Vaca CE, Paredes R, et al. Early remdesivir to prevent progression to severe Covid-19 in outpatients. N Engl J Med **2022**; 386:305–15. doi:10.1056/NEJMoa2116846.
23. Kalil AC, Mehta AK, Patterson TF, et al. Efficacy of interferon beta-1a plus remdesivir compared with remdesivir alone in hospitalized adults with COVID-19: a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Respir Med **2021**; 9:1365–76. doi:10.1016/S2213-2600(21)00384-2.
24. Weinreich DM, Sivapalasingam S, Norton T, et al. REGN-COV2, a neutralizing antibody cocktail, in outpatients with Covid-19. N Engl J Med **2021**; 384:238–51. doi:10.1056/NEJMoa2035002.
25. Fischer W, Eron JJ, Homan W, et al. A phase 2a clinical trial of molnupiravir in patients with COVID-19 shows accelerated SARS-CoV-2 RNA clearance and elimination of infectious virus. Sci Transl Med **2002**; 14:eabl7430. doi:10.1126/scitranslmed.abl7430.
26. Yuan S, Chan CC, Chik KK, et al. Broad-spectrum host-based antivirals targeting the interferon and lipogenesis pathways as potential treatment options for the pandemic coronavirus disease 2019 (COVID-19). Viruses **2020**; 12: 628. doi:10.3390/v12060628.
27. Blanco-Melo D, Nilsson-Payant BE, Liu WC, et al. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. Cell **2020**; 181:1036–45. doi:10.1016/j.cell.2020.04.026.
28. Bastard P, Rosen LB, Zhang Q. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. Science **2020**; 370:eebd4585. doi:10.1126/science.abd4585.
29. Bastard P, Gervais A, Le Voyer T, et al. Autoantibodies neutralizing type 1 IFNs are present in ~4% of uninfected individuals over 70 years old and account for ~20% of COVID-19 deaths. Sci Immunol **2021**; 6:eabl4340. doi:10.1126/sciimmunol.abl4340.
30. Abers MS, Rosen LB, Delmonte OM, et al. Neutralizing type-I autoantibodies are associated with delayed viral clearance and intensive care unit admission in patients with COVID-19. Immunol Cell Biol **2021**; 99:917–21. doi:10.1111/imcb.12495.
31. The Lancet Infectious Diseases. Unmet need for COVID-19 therapies in community settings. Lancet Infect Dis **2021**; 21:1471. doi:10.1016/S1473-3099(21)00633-2.
32. Fedson DS, Opal SM, Rordam OM. Hiding in plain sight: an approach to treating patients with severe COVID-19 infection. mBio **2020**; 11:e00398-20. doi:10.1128/mBio.00398-20.

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