Monotherapy with Lopinavir/Ritonavir or in Combination with Interferon Beta-1b in Patients with Non-severe COVID-19 Disease: A Clinical Case Series

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ABSTRACT

The outbreak of Coronavirus Disease 2019 (COVID-19), caused by severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV-2), has infected and killed millions of people worldwide. It has substantially increased the burden on healthcare system. However, the optimal approach to treatment of COVID-19 is uncertain. “Off-label” use of lopinavir/ritonavir (LPV/r) and interferons, particularly interferon beta (IFN- β), were the most suggested at the early stage. Although the United States National Institutes of Health’s (NIH) COVID-19 guidelines do not recommend the use of both medications for the treatment of COVID-19 in hospitalized patients, their roles in patients with non-severe disease are still unclear. Macau, a famous city for tourism, had 46 COVID-19 confirmed cases as of 2020. In this retrospective review, we summarized clinical and laboratory features of 39 COVID-19 patients admitted in the Centro Hospitalar Conde de São Januário (CHCSJ), of whom all did not receive oxygen therapy or ventilatory support during hospitalization. Of note, 12 (30.8%) of them were asymptomatic. The most common symptoms were fever and cough upon admission. They were all treated with LPV/r $\pm$ IFN- β -1b plus supportive care. The mean length of hospitalization was 26.6 (SD $\pm$ 12.6) days with LPV/r monotherapy, whereas 27.8 (SD $\pm$ 10.1) days with LPV/r/IFN- β -1b combination therapy ($p=0.65$). The percentage of 28-day negative results for polymerase chain reaction (PCR) test were 67.9% (19 of 28) with monotherapy and 63.6% (7 of 11) with combination therapy ($p=0.80$). No fatal case was reported and all patients discharged successfully. No beneficial clinical outcome was observed with the addition of IFN- β -1b to LPV/r-based therapy. Further studies are warranted to confirm these findings.

INTRODUCTION

At the end of 2019, a novel coronavirus was identified as the cause of atypical pneumonia in Wuhan, a city in the Hubei Province of China and quickly spread in a number of countries. In February 2020, the World Health Organization (WHO) named the disease COVID-19, which stands for coronavirus disease 2019 [1]. The virus that causes COVID-19 is called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of Dec, 2020, it has infected more than 79 million patients with over 1.7 million deaths globally [2]. Moreover, healthcare professionals are now facing a big challenge, in

particular on the treatment and the burden on the health care system. However, the optimal approach to treatment of COVID-19 remains uncertain. Lopinavir/ritonavir (LPV/r) and interferon beta (IFN- β), in particular interferon beta-1b were the most proposed treatment options in off-label use at the early stage of pandemic due to modest activity in vitro against SARS-CoV and Middle East respiratory syndrome (MERS)-CoV. Although the United States National Institutes of Health’s (NIH) COVID-19 guidelines in Oct, 2020 [3] did not recommend the use of both medications for treating COVID-19 in hospitalized patients, their roles in patients with non-severe disease are still unclear. Macau, a Special

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Administrative Region of the People's Republic of China reported a total of 46 COVID-19 cases in 2020. Among them, over 80 % were non-severe meaning that they did not need oxygenation or mechanical ventilatory support during hospitalization. In this retrospective study, we collected data from 39 patients with COVID-19 admitted to the Centro Hospitalar Conde de São Januário (CHCSJ), which is the designated hospital for managing all COVID-19 patients in Macau SAR, China. All patients were treated with LPV/r monotherapy or in combination with IFN- β -1b plus supportive care. This study was to observe whether any clinical benefit exists by adding IFN- β -1b to LPV/r-based therapy compared with LPV/r monotherapy.

METHOD

Study design and participants

Ethical approval (document no. 0067/DAH/N/2020) was obtained from the ethical committee of Centro Hospitalar Conde de São Januário, Macau Health Bureau, Macau SAR, China. Eligibility criteria for this study were patients with confirmed COVID-19 disease and hospitalized at CHCSJ, while fulfilled the below clinical classification of non-severe disease, and received LPV/r for a median of 21 days $\pm$ IFN- β -1b for a median of 14 days plus supportive care (i.e. symptomatic drug treatment as well as general inpatient care including daily vital signs monitoring and regular biochemistry tests). We reviewed the details from medical records including demographics, past medical history, laboratory results, radiological findings, clinical management, length of hospitalization and time to completed negative result for polymerase chain reaction (PCR) test.

PCR assay for SARS-CoV-2

Samples were mainly taken from nasopharyngeal swabs (NPS) in all patients. The extraction of nucleic acid from samples was performed using EasyMag in accordance with the manufacturer's instructions (bioMerieux, France). Extracted nucleic acid samples were tested for SARS-CoV-2 with qRT-PCR using a commercial SARS-CoV-2 (previously known as 2019-nCoV) ORF1ab/N Gene Nucleic acid detection kit (BioGerm, China) and the LightCycler 480 real-time PCR system (Roche, Switzerland) in accordance with manufacturer's instructions.

Definitions for clinical classification

According to the United States National Institutes of Health's (NIH) COVID-19 guidelines [3], severe illness is defined as individuals who have SpO₂ <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO₂/FiO₂) <300 mm Hg, respiratory frequency >30

breaths/min, or lung infiltrates >50%. Whereas critical illness refers to individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction. In this study, we defined non-severe COVID-19 disease patients as those who were asymptomatic or presymptomatic, mild illness with signs and symptoms compatible with upper respiratory tract infection (e.g. isolated low-grade fever, cough, rhinorrhea or myalgia), moderate illness that exhibited lower respiratory tract infection (e.g. pneumonia or bronchitis) but did not present with hypoxia (oxygen saturation $\leq$ 94 percent on room air) or need for oxygenation or mechanical ventilatory support during hospitalization.

COVID treatments

All included patients with no contraindications received LPV/r (400 mg/100 mg) twice daily for a median of 21 days. Besides, they were given either azithromycin 500mg daily or levofloxacin 500-750mg daily as prophylactic agent for secondary bacterial infection. Patients with an early onset of illness (within 7 days) were given interferon beta-1b 250mcg (8 million IU) subcutaneously every other day for a median of 14 days when the drug was available in Macau. Symptomatic treatments (e.g. antipyretics, antihistamines and expectorants, etc.) were given when required. The standard biochemistry, imaging tests were systematically performed upon admission.

Criteria for discharge

Patients with completed negative result for PCR assay (i.e. two consecutive negative nasopharyngeal samples) were transferred to other units for medical observation then discharged in the absence of relapse.

Measured Outcomes

We interpreted the collected data including the length of hospitalization and the percentage of 28-day negative result for PCR test via nasopharyngeal swabs.

Data and statistical analyses

Patients' data are presented as absolute value, percentage, mean $\pm$ SD or median ((interquartile range (IQR))). Continuous variables and categorical variables were compared using the Mann-Whitney U test and χ^2 test, respectively; P value of less than 0.05 was considered statistically significant. All tables were generated by JASP 0.14.1.

Table I Demographic and clinical characteristics of the patients at admission

Characteristics	Lopinavir + ritonavir (n=28)	Lopinavir + ritonavir + interferon beta-1b (n=11)
Age, median (IQR) — yr	24.5 (18.5)	44.0 (20.0)
<18y — no. (%)	6 (21.4)	0 (0.0)
18 to 59 y — no. (%)	21 (75.0)	11 (100.0)
≥60 y — no. (%)	1 (3.6)	0 (0.0)
Male — no. (%)	16 (57.1)	8 (72.7)
Comorbidity — no. (%)		
Diabetes mellitus	0 (0.0)	2 (18.2)
Hypertension	2 (7.1)	4 (36.4)
Cardiovascular disease	1 (3.6)	0 (0.0)
Current smoker — no. (%)	2 (7.1)	2 (18.2)
Ex-smoker — no. (%)	4 (14.3)	3 (27.3)
Time between onset of symptoms and hospitalization, median (IQR) — days	1.5 (8.0)	1.0 (5.5)
Signs and symptoms — no. (%)		
Fever,		
Body temperature ≥37.5°C (%)	10 (35.7)	3 (27.3)
Body temperature, median (IQR) — °C	37.0 (0.9)	37.3 (1.2)
Cough	8 (28.6)	4 (36.4)
Sore throat	3 (10.7)	6 (54.5)
Myalgia	3 (10.7)	1 (9.1)
Diarrhea, ≥3 times/day	3 (10.7)	0 (0.0)
Headache	3 (10.7)	0 (0.0)
Rhinorrhea	3 (10.7)	1 (9.1)
Dizziness	2 (7.1)	1 (9.1)
Abdominal pain	0 (0.0)	1 (9.1)
Loss of smell	1 (3.6)	0 (0.0)
Respiratory rate ≥ 24/min (%)	0 (0.0)	0 (0.0)
Serum creatinine, median (IQR) — umol/L	67.5 (22.3)	77.0 (14.0)
White cell count, median (IQR) — x109/L	5.4 (3.6)	5.2 (3.8)
Lymphocyte count, median (IQR) — x109/L	1.6 (0.9)	1.3 (0.6)
Aspartate transaminase, median (IQR) — U/L	20.0 (6.0)	33.0 (11.5)
Alanine transaminase, median (IQR) — U/L	15.0 (25.0)	26.0 (38.0)
Lactate dehydrogenase, median (IQR) — U/L	166.5 (53.3)	176.0 (88.0)
C-reactive protein, median (IQR) — mg/dL	0.1 (0.3)	0.3 (0.5)

Table II Treatment and outcome

Outcomes	Lopinavir + ritonavir (n=28)	Lopinavir + ritonavir + interferon beta-1b (n=11)
Death, no. (%)	0 (0.0)	0 (0.0)
Discharged, no. (%)	28 (100.0)	11 (100.0)
28-day negative result for PCR assay, no. (%)	19 (67.9)	7 (63.6)
Time for completed negative PCR result, days		
Mean ± SD	25.7 ± 14.5	25.5 ± 5.4
Min – Max	6 - 63	18 - 33
Length of stay in hospital, days		
Mean ± SD	26.6 ± 12.6	27.8 ± 10.1
Min - Max	6 - 61	12 - 47
Possible adverse events, no. (%)		
Dermatologic	2 (7.1)	4 (36.4)
Gastrointestinal	19 (67.9)	8 (72.7)
Endocrine and metabolic	3 (10.7)	2 (18.2)
Hepatic	1 (3.6)	0 (0.0)
Central nervous system	4 (14.3)	0 (0.0)
Neuromuscular and skeletal	0 (0.0)	1 (9.1)

RESULT

A total of 46 patients were reviewed, seven patients did not fulfil the inclusion criteria. Therefore, 39 patients were lastly recruited which accounted for 85% of the confirmed COVID-19 cases in Macau in 2020. Of note, 12 (30.8%) of them were asymptomatic. 28 patients were treated with LPV/r monotherapy and 11 patients were treated with LPV/r/IFN- β -1b combination therapy. All patients received treatment on the day of admission, and successfully discharged in the end. The median age of patients was 24.5 years old (IQR 18.5) for the LPV/r monotherapy group; 44 years old (IQR 20.0) for the LPV/r/IFN- β -1b combination group. The most common symptoms were fever and cough (with the exception of sore throat in the combination group) in both groups at admission. The median time between onset of symptoms and hospitalization was 1.5 day (IQR 8.0) for the monotherapy group and 1.0 day (IQR 5.5) for the combination group (Table I). The mean length of hospitalization was 26.6 (SD $\pm$ 12.6) days with LPV/r monotherapy whereas 27.8 (SD $\pm$ 10.1) days with LPV/r/IFN- β -1b combination therapy ($p=0.65$). The percentage of 28-day negative results for PCR test were 67.9% (19 of 28) with monotherapy and 63.6% (7 of 11) with combination therapy ($p=0.80$). The most common adverse events possibly related to medications include diarrhea and skin rash. Those were minor and treated accordingly (Table II). There was a potential risk of interaction with the disease and other drugs.

DISCUSSION

In this retrospective review, no beneficial clinical effect was observed in hospitalized patients with COVID-19 with the addition of injectable IFN- β -1b (given within 7 days of symptom onset) to oral protease inhibitor (LPV/r)-based therapy. On the contrary, a multicenter, open-label, randomized, phase 2 trial conducted in Hong Kong, over 80% included patients with mild to moderate disease, compared 14 days of triple antiviral therapy ($n = 86$) (LPV/r [400 mg/100 mg q12h], ribavirin [400 mg q12h], IFN- β -1b [8 million IU x 3 doses q48h]) with LPV/r alone ($n = 41$). Results showed that triple therapy significantly shortened the duration of viral shedding and hospital stay in patients with mild-to-moderate COVID-19, the median time of combination therapy from the beginning of study treatment to negative nasopharyngeal swab (7 days [IQR 5–11]) than the control group (12 days [IQR 8–15]; hazard ratio 4.37 [95% CI 1.86–10.24], $p=0.0010$) [4]. Another retrospective cohort study demonstrated that ribavirin therapy compared with supportive therapy in severe COVID-19, was not associated with improved negative conversion time for SARS-CoV-2 test and was not associated with an improved mortality rate⁵. Compared with our findings without ribavirin, the mean time to negative result was approximately 25 days between the two groups. Owing to small sample size and lack

of control group, the results of our study could not draw a conclusion on how effective is LPV/r in non-severe COVID-19 patients. It is worth noting that the patients' age in the combination group ranged from 18-59 years old. We postulated that these patients may have better immune response so that the results may be affected. In addition, most cases were imported from different parts of the world, the genotype or phenotype of different viral variants they carried might interfere with the findings.

At present, the COVID-19 pandemic has caused a huge burden to the economy and healthcare system around the world. Healthcare professionals work under stress every day. In Macau, CHCSJ, the designated hospital for treating COVID-19 offered adequate resources for in-hospital care and isolation wards throughout the outbreak even for asymptomatic patients. As a matter of fact, there are no clear criteria for hospital admission with COVID-19. The criteria may vary with the availability of hospital resources. Nonetheless, according to the US National Institutes of Health (NIH) COVID-19 Treatment Guidelines Panel3, most patients with mild illness can be managed in an ambulatory care setting or at home. Therefore, we believed that some of our non-severe cases may be treated in the outpatient setting in principle. Although several international guidelines against the use of LPV/r in hospitalized patient based on the results from multiple clinical trials [6-8], its role in the outpatient setting is being investigated. Therefore, our findings may provide an important reference for future investigation in such situation.

CONCLUSION

This series illustrated that no clinical benefit was observed with the addition of IFN- β -1b to LPV/r-based therapy plus general supportive care in hospitalized COVID-19 patient. In addition, it may also provide important information for the use of LPV/r in outpatient settings. In fact, more powerful evidences are warranted to confirm these findings.

CONFLICT OF INTEREST

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