CASE REPORT

A Trial of Lopinavir–Ritonavir in 11 Adults Hospitalized patients with Covid-19 Pneumonia: A Case Series Report

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ABSTRACT

As an emerging disease, COVID-19 has turned itself into a pandemic in no time due to rapid transmission with no effective antiviral agent to combat its growth and replication. However, lopinavir-ritonavir, a protease inhibitor originally designed against HIV, is now a subject nominated to be the potentially efficacious antiviral agent. In this case series, we will report administration results of lopinavir-ritonavir on 11 distinct patients admitted to Udayana University Hospital. Subjects included had a median age of 36 years, four of them also suffer different forms of comorbidities such as hypertension, chronic heart disease, and type 1 or 2 diabetes mellitus. Median duration of treatment were 9 days; and in cases requiring hospitalization the treatment duration was 16 days. Patients also displayed a median of 3 days of viral shedding since initiation of treatment, or around 9 days post-onset of symptoms. These results were in alignment with previous studies regarding administration of lopinavir-ritonavir treatment in COVID-19 patients. While our study does not conclusively prove the effectiveness of lopinavir-ritonavir administration in COVID-19 patients, it also does not disprove its potential. More investigations are needed to find a conclusive answer.

Keywords: COVID-19, Pneumonia, Lopinavir-Ritonavir, Efficacy

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INTRODUCTION

In late 2019, early reports of a locally-transmitted pneumonia of unknown etiology clustered around a live animal market in Wuhan, Hubei in People's Republic of China. The subsequently isolated pathogen was later identified as SARS-CoV-2, a coronavirus related to SARS-CoV and MERS-CoV (1). Eight months since its first appearance, the world has suffered over 17 million confirmed SARS-CoV-2 infections, resulting in over than 680 thousand deaths (1).

Initial finding estimated COVID-19's case fatality rate (CFR) ranging around 3% to 4%. However, later reviews found COVID-19's CFR lower than initial estimations, ranging around 1% to 2% (1,2). Although its CFR is comparably lower than that of previous coronaviruses, namely SARS and MERS, this still translate to hundreds of thousands, or even millions, of potential deaths due to the global spread of the disease (2).

Currently, there still hasn't been a proven efficacious antiviral therapy to treat COVID-19. Searches for an effective antiviral compound branches from antivirals previously given to SARS-CoV and MERS-CoV patients, where those patients exhibited improvement in clinical parameters, thereby reducing mortality and intubation rate (2). Early experimental administrations of lopinavir-ritonavir has shown to be exceptionally effective to combat COVID-19 when compared to other drugs, further confirmed in later clinical trials (3).

If proven effective, this drug could be a game-changer due to its already known safety parameters and approval by US Food and Drugs Administration (FDA). Regardless, further rigorous investigations on administration of lopinavir-ritonavir on COVID-19 patients are necessary to conclusively establish the efficacy of this drug combination to treat SARS-CoV-2 infection. In this case series, we will report the development of 11 COVID-19 patients receiving lopinavir–ritonavir as the main antiviral agent in Udayana University Hospital, Bali.

CASE REPORT

All subjects included in this study were positive COVID-19 cases confirmed by RT-PCR, with a spectrum of clinical manifestations ranging from mild, moderate, to severe. Detailed breakdown of cases can be seen in Table I. Seven cases were female while the rest were male. These patients had a median age of 36 years old,

ranging from 22 to 65 years. Six suffered mild symptoms, two suffered moderate symptoms, while the later three in the more severe end of the spectrum.

Seven patients suffered no comorbidity while the remainder suffered one or more. The rest consists of one hypertensive patient, one hypertensive with chronic heart disease, and two diabetic patients, one case each for type 1 and type 2 diabetes mellitus. All patients received antibiotics treatment, with lighter cases receiving 500 mg of azithromycin daily while severe cases receiving 750 mg of levofloxacin daily (table I).

Patients began their lopinavir-ritonavir treatment at different stages of their disease. With a median of 9 days, treatment initiation may be as early as day one of hospitalization up to as late as a month post-admission. Patients had a median duration of lopinavir-ritonavir treatment of 9 days, ranging from 4 to 14 days (full regiment). All patients achieved full recovery and were eventually discharged from hospital. These patients had a median hospitalization duration of 16 days, ranging from 4 to 53 days.

Median duration of viral shedding from initiation of lopinavir-ritonavir was 8 days, ranging from 6 to 27 days. Meanwhile, the median duration of viral shedding since onset of symptoms stood at 18 days, ranging from 11 to 56 days. Adverse effect was observed in one case, in which the patient suffered transaminitis, halting the regiment after 8 days.

DISCUSSION

Even though our cases showed unequal sex distribution, which is different from how COVID-19 tend to be distributed evenly, distribution based on clinical spectrum was more in line with current evidence. In our case, 8 out of 11 cases were mild or moderate while only 3 were severe (2). Distribution of severity by sex is also in line with current evidence, where male were at more risk of severe infection (1,3). In our case series, 3 out of 4 male showed severe forms of symptoms while only one was moderate. Hospitalization stay in Udayana University Hospital is comparable with previous studies in China which shows hospitalization period ranging from 4 to 53 days and 4 to 21 days in other affected countries (3). Median viral shedding duration of 8 days since initiation of lopinavir-ritonavir regiment and 18 days since onset is higher, which showed median viral shedding under standard of care treatment of 11 days since onset with an interquartile range from 8 to 14 days (4,5).

Lopinavir-ritonavir combination is a potent peptidomimetic protease inhibitor initially designed as an anti-HIV-1 agent and approved by FDA to be used for that purpose in clinical practice. It mainly acts by preventing budding of immature virion from already infected cells, preventing further infection of other non-infected susceptible cells (5).

Coronaviruses, including preceding SARS-CoV and MERS-CoV, were also single-strand RNA viruses that replicates in a similar way to HIV (5). Thus, it is rational to nominate lopinavir-ritonavir as potential antiviral agent to combat SARS-CoV-2. Initial screening for the potential of this combination to treat COVID-19 were noted during clinical experimental administrations (5).

Further trials showed promising results. One case report began regiments of lopinavir-ritonavir on day 4 of illness. The disease subsequently subsided on day 14 since onset of symptoms or day 10 since administration

Table I: Demographic, Clinical Characteristics, and The Course of Treatment of Patients Receiving Lopinavir-Ritonavir Regiments at Udayana University Hospital (n=11)

No.	Age (years)	Sex	Severity	Comorbidity	Antibiotics	Treatment Duration (Days)	Hospital-ization Duration (Days)	Duration Until Negative RT-PCR		Adverse Effect
								Since Treat-ment (Days)	**Since Onset (Days)**	
1	22	F	Mild	None	Azithromycin 500 mg @24 hour	8	9	6	15	None
2	28	F	Mild	None		8	10	6	11	None
3	30	F	Mild	None		9	10	6	12	None
4	36	F	Mild	None		14	35	27	30	None
5	47	F	Mild	None		10	11	7	14	None
6	64	F	Mild	Type 2 Diabetes		10	53	8	56	None
7	36	M	Moderate	None		10	11	8	18	None
8	52	F	Moderate	Hypertension		12	20	10	22	None
9	32	M	Severe	None	Levofloxacin 750 mg @24 hour	8	16	13	17	Transaminitis (increase AST-ALT)
10	24	M	Severe	Type 1 Diabetes		14	30	21	32	None
11	65	M	Severe	Hypertension, Chronic Heart Failure		21	26	25	30	None

of lopinavir-ritonavir regiment (5). Another case report added that RT-PCR showed negative results immediately following initiation of lopinavir-ritonavir regiments (4). However, both case reports stated that improvement of clinical condition could not be definitively linked to administration of lopinavir-ritonavir regiments, therefore may have been a natural part of the disease progression. However, other studies showed that there is no clinical improvement observed on COVID-19 patients receiving lopinavir-ritonavir regiments. A case series of five patients, two receiving lopinavir-ritonavir regiments while three did not, showed that the regiment did not reduce viral shedding duration. All five cases showed sustained viral shedding in both sputum and oropharyngeal swab until up to day 24 days of illness. First negative RT-PCR results were found on day 6 to 19 days since the observation began (5). However, it must be noted that a sample size of five cases is inadequate for a true comparative cohort study. Another study conducted an open-label randomized controlled trial design also found little to no clinical benefit of lopinavir-ritonavir administration on COVID-19 patients. With a sample size of 199 subjects, 99 on treatment and 100 on control, both arms showed similar rate of improvement with a median of 16 days for both arms. However, the study showed that treatment arm had a shorter stay in ICU (6 days compared to 11 days, with a mean difference of 5 days and CI 95% 9 to 0 days). Patients receiving the regiment also showed higher clinical improvement within 14 days after regiment administration (45.5% compared to 30.0%, with a difference of 15.5% and CI 95%, 2.2% to 28.8%) (3).

In our study, we compare the viral shedding duration (8 days since treatment, 18 days since onset) of patients receiving lopinavir-ritonavir regiment with those receiving standard treatments (11 days) (3). Our result can also be compared to the viral shedding duration ranges from 6 to 19 days since observation or another study which observed immediate reduction of viral load based on RT-PCR results (1,4). Due to a difference in sample size and the frequency of RT-PCR tests, our patients showed a longer median viral shedding period (1). Limited resources allowed us to conduct RT-PCR test only every 2 to 4 days for each patient. As such, it may take longer in our setting to reach two consecutive negative results, thereby confirming the patient is no longer shedding SARS-CoV-2.

In our study, only one patient finished the whole 14 days regiment of lopinavir-ritonavir, two patients had less than 7 days of treatment, while other cases had between 7 to 13 days of treatment. Incomplete treatment were substantially higher compared to the open-label randomized trial which observed 22.2% incomplete treatment rate from 199 samples (3). In our study, we observed zero mortality, lower than the 19.2% observed in other treatment group. This may be explained by the fact that our sample size was statistically too small when the estimated mortality rate is 1% to 2% (3). We also observed the difference in gap between the onset of symptoms to treatment initiation, which means we cannot exclude the possibility that the clinical improvement and cessation of viral shedding is a natural part of the infection. Lack of control group also contributes to the inconclusiveness of these results.

CONCLUSION

Our uncontrolled case series observed clinical improvement and eventual discharge of all 11 hospitalized COVID-19 patients. We observed that the median duration of viral shedding is 8 days post-treatment initiation and 18 days since the onset of symptoms, which is comparable to previous studies among patients receiving standard of care. Our study observed that the median duration of hospitalization is 16 days, which was also comparable with previous studies where patients were receiving standard COVID-19 care. Caveats in our study, such as lack of control group, gap variation between onset and treatment initiation, and lower frequency of RT-PCR tests conducted should be noted when interpreting these results. In the end, further investigations are needed to be performed, especially to test the effect of lopinavir-ritonavir on the cessation of viral shedding among COVID-19 patients.

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