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Original Research Article

Lopinavir/ritonavir: is early administration better in Covid-19?

Sudhir Bhandari, Shrikant Sharma, Vishal Gupta, Abhishek Bhargava*, Govind Rankawat

Department of Medicine, SMS Medical College, Jaipur, Rajasthan, India

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***Correspondence:**
Dr. Abhishek Bhargava,
E-mail: bhargava_abhishek7a@yahoo.co.in

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ABSTRACT

Background: To share the data of coronavirus 2019 (Covid-19) patients started on lopinavir-ritonavir (lopi/r) in relation to time period from the onset of symptoms.
Method: Observational descriptive study of 23 Covid-19 patients admitted in a tertiary care center in India from March 2020 to May 2020. Patients categorized into 2 groups based on the timing of initiation of lopi/r from the onset of symptoms. Group 1 were given the drug early (≤7 days) and group 2 late (>7 days). The clinical events (oxygen requirement days and ICU stay) and outcomes of hospital stay between the two groups were evaluated.
Results: Patients were started on lopi/r for a period of 14 days on admission, out of which 12 patients were in group 1 and 11 patients in group 2. Underlying co-morbidities were present in 15 patients (65.21%). The mean duration from onset of symptoms to lopi/r initiation was 4 days and 11.1 days in Group 1 and 2 respectively. Requirement for oxygen support (2.16 versus 6.54 days), mean duration of hospitalization (8.58 versus 11.54 days) and mean duration of obtaining first Covid-19 negative report from the onset of symptoms (10.5 versus 19.57 days) were all significantly lesser in group 1 ($p<0.05$). All patients belonging to Group 1 and eight patients of group 2 recovered completely and were discharged whereas 3 patients of group 2 expired. Diarrhea was the most commonly observed adverse effect of lopi/r in our patients.
Conclusion: With no approved weapon to tackle the Covid-19 pandemic, we should keep lopi/r in our armamentarium of drugs and use it at the earliest. More clinical trials are needed in future to ascertain if lopi/r can reduce hospital stay, prompt faster recovery and result in better clinical outcome.

Keywords: Covid-19 pneumonia, Lopinavir, QTc interval, Ritonavir

INTRODUCTION

A novel coronavirus which originated from China in the November 2019 has brought our world to a standstill, forcing the longest lockdown in the history of mankind. Coronavirus 2019 (Covid-19) has infected more than 4 million people across the globe and more than 0.2 million people have succumbed to the illness with a case fatality ratio of 3.85%.[1,2]

Till now the World Health Organization (WHO) has not released standard drug guidelines which should be used for treatment of Covid-19 infection and the results of the solidarity trial of WHO are still awaited.[3] The clinical spectrum of Covid-19 varies from asymptomatic illness to full blown acute respiratory distress syndrome. The virus which mainly spreads through air droplets, aerosols and fomites predominantly infects the respiratory tract epithelium. The virus has binding affinity to Angiotensin converting enzyme-2 (ACE-2) receptors abundantly found in the lungs, intestine and kidney.[4] This virus is an error prone single stranded RNA virus and its immune-pathogenic effects consists of two phases.[5] The initial phase consists of virus replication in which the virus enters the human cells with the help of ACE-2 receptors and replicates with the help of cell machinery resulting in the release of new viruses that further infect other cells. Drugs such as ribavarin, lopinavir, remdesvir can have beneficial effect during this phase as they can inhibit virus replication.[6] The second phase consists of body's immune

system mounting a hyper immune response in the form of cytokine storm in response to the virus, which can lead to rapid deterioration of patient's condition. Immuno-suppressants like corticosteroids, tocilizumab, hydroxychloroquine may have a role in this phase. The time period of about 10 days between the replication and pathogenic phase provides us a window of opportunity for anti-replicative drugs like ribavarin, lopinavir and remdesvir to inhibit further virus production and prevent severe Covid-19 infection to develop.[5]

Lopinavir plus ritonavir combination is readily available in the market and is used in the treatment regimen of Human immunodeficiency virus (HIV) patients. Lopinavir is an HIV protease inhibitor that prevents the cleavage of gag-pol polyprotein resulting in the production of immature non-infectious virus particles. Ritonavir does not inhibit the viral activity directly but increases the plasma levels of lopinavir by inhibiting its metabolism as ritonavir is a potent cytochrome P3A (CYP3A) enzyme inhibitor. Though lopinavir + ritonavir can be used to inhibit the initial replication phase of Covid-19, its use is not without adverse effects such as anemia, pancreatitis, hyperglycemia, new-onset diabetes mellitus, hepatoxicity, hyperlipidemia, immune reconstitution syndrome, drug interactions, PR interval and QT interval prolongation which can result into serious cardiac arrhythmias.

The objective of this article is to share our experience of administering lopinavir-ritonavir combination in 23 patients with severe covid-19 infection at our tertiary care center in North India.

METHODS

History, diagnosis and standard treatment protocol

During the pandemic, all acute lung injury and suspected Covid-19 patients were admitted as a policy in converted dedicated Covid-19 SMS hospital, the largest tertiary care hospital in North India. Patient's oropharyngeal/ nasopharyngeal swab specimens were collected for reverse transcriptase polymerase chain reaction (RT-PCR) assay for Covid-19 confirmation. Patients with Covid-19 positive status were transferred to the separate building of Infectious Disease Hospital in the same campus with well-ventilated wards and a dedicated Covid-19 intensive care unit. Patients who were asymptomatic or had only mild symptoms been shifted to other wards. A detailed history of the patient was taken, and other relevant clinical information was collected from documents and electronic records. Important data was compiled for all patients and it included dates of chief events such as onset of symptoms including fever, dates of positive Covid-19 report, initiation of lopi/r, admission and discharge/death. Past-history of other diseases like diabetes mellitus, chronic liver and kidney disease, cerebrovascular disease, ischemic heart disease, cancer and lung diseases like asthma and chronic obstructive pulmonary disease were noted.

Laboratory investigations including hemogram, lactate dehydrogenase (LDH), liver function tests, serum amylase, serum ferritin, serum procalcitonin (PCT), Fibrin degradation Product (FDP), D dimer and electrocardiogram (ECG) findings were recorded. Radiological investigations included chest X-ray posteroanterior (PA) view, High resolution computed tomography (HRCT) chest scan and Computed tomography (CT) and pulmonary angiography.

Patients were given oxygen support to keep oxygen saturation ≥96% if they had increasing shortness of breath and not maintained by intermittent prone positioning.[7] Mode of oxygen support included low/high flow masks, non-invasive ventilation (NIV) and mechanical ventilation with intubation.

Besides supportive care they were given trial of beta-lactam with macrolide according to the recent recommendations.[8]

Lopinavir/Ritonavir protocol

Lopinavir 400 mg/ritonavir 100 mg was added to standard care as discussed above as per protocol issued by Indian Council of Medical Research (ICMR) orally every 12 hours. Patient eligibility criteria for administration of lopinavir+ ritonavir combination was as follows:[9]

Inclusion criteria

Inclusion criteria of this study were adult over 18 years of age. Laboratory confirmation of COVID-19 infection by RT-PCR from recommended sample. Symptomatic patients with any one of the following: respiratory distress with RR ≥22/min or SpO_2 of < 94%. Lung parenchymal infiltrates on X-ray chest or CT scan. Hypotension as defined as systolic blood pressure <90 mmHg or need for vasopressor/inotropic medication. New onset organ dysfunction (one or more). Increase in creatinine by 50% from baseline, glomerular filtration rate (GFR) reduction by >25% from baseline or urine output of <0.5 ml/kg for 6 hours. Reduction of Glasgow coma scale (GCS) by 2 or more. Any other organ dysfunction. High risk groups. Age >60 years. Diabetes mellitus, renal failure, chronic lung disease and immunocompromised persons. Informed consent from patient and caretaker. Consent from legally authorized representative in case the patient is not able to provide the same due to his/her medical condition.

Exclusion criteria

A patient with hepatic impairment (Child Pugh C or alanine transaminase (ALT) over 5 times the upper limit of normal). Use of medications that are contraindicated with lopinavir/ritonavir and that cannot be replaced or stopped. e.g. Rifampicin, benzodiazepines, simvastatin, voriconazole, sildenafil etc. Known HIV infected individual receiving other protease inhibitors containing regimen that cannot be replaced by lopinavir-ritonavir.

Baseline QTc >0.50 seconds were excluded from this study.

Statistical analysis

Data was incorporated in Microsoft excel sheets and analyzed with the help of statistical package for the social sciences (SPSS) software. Kaplan Meier survival analysis was done, and p value was calculated by mantel cox test and a value of <0.05 was considered significant. The mean difference of hospital duration for group 1 and group 2 patients was calculated and p value was obtained by using the Annova independent t-test.

Patient and public involvement (PPI)

This is an observational descriptive study and effect of lopinavir/ritonavir therapy was assessed in patients. Patients were divided into 2 groups based on onset of symptoms to admission. Group 1 (lopi/r started within 7 days of onset of symptoms) and group 2 (lopi/r was started >7 days after onset of symptoms). This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. There were no funds or time allocated for patient and public involvement (PPI) so we were unable to involve patients. We have invited patients to help us develop our dissemination strategy. We have requested patients who survived Covid-19 infection and those who were given lopinavir/ritonavir combination to help us in spreading awareness of early reporting to hospital so that lopinavir/ritonavir can be started at the earliest and have maximum benefits of this drug therapy.

RESULTS

Between March and May 2020, a total of 23 Covid-19 patients were given lopi/r combination after they had fulfilled the inclusion criteria and had no exclusion criteria according to ICMR guidelines.

All 23 patients were started on lopi/r therapy on admission out of which 12 patients were in Group 1 (lopi/r started within 7 days of onset of symptoms) and 11 patients in group 2 (lopi/r was started >7 days after onset of symptoms) because these patients either did not consult or were not declared Covid-19 positive with RT-PCR.

The median age of patients in group 1 was 49 years and was 56 years in patients in group 2, while the overall median age was 52 years (Table 1). Male patients comprised 56.53% of the total patients. 15 (65.21%) patients had underlying co-morbidities with the prevalence of hypertension being most common (43.37%) followed by diabetes mellitus. Co-morbidities were more common (90.90%) in group 2 patients (Table 1). Fever was the most common symptom and was found in 78.26% patients followed by cough (60.87%) and shortness of breath (56.52%), (Table 1). Diarrhea and anosmia were seen in only 2 patients.

On hemogram it was found that lymphopenia was observed in 18 (78.26%) patients and was more commonly present in group 2 patients (Table 1). Leukocytosis was present in 8 (34.78%) patients while thrombocytopenia was present in only 1 patient. In laboratory examination it was found that lactate dehydrogenase (LDH) was elevated in 14 patients (60.86%) while other markers of inflammation like fibrin degeneration products (FDP) and D-dimer were elevated in 9 patients (39.13%) (Table 1). It was observed that these inflammatory markers were more commonly elevated in group 2 patients.

A total 19 patients had consolidation patch on their chest X-rays which was also evident on HRCT chest scan. Most common CT scan findings were multifocal patchy areas of consolidation bilaterally with surrounding ground glass opacities and interstitial pneumonitis (Table 1). In one patient the diagnosis of pulmonary artery thrombosis was also found on CT pulmonary angiography. He was given low molecular weight heparin and low dose aspirin for its treatment. Patients were started on lopi/r based on the guidelines prescribed by the ICMR. 19 patients had chest infiltrates out of which 6 patients had respiratory rate above 22 per min and 13 patients needed oxygen support while 3 patients had organ dysfunction and 1 patient had hypotension at the time of admission (Table 2).

The mean duration of starting lopi/r therapy in patients in group 1 was 4 days and 11.1 days in group 2. Overall mean duration of starting lopi/r combination in our patients was 7.17 days (Table 2).

Along with lopi/r combination all patients were given hydroxychloroquine 400 mg twice a day on day 1 followed by 200 mg twice daily for the next 4 days (Table 2). 6 patients were also given oseltamivir due to concomitant H1N1 season during that time on empirical basis which was further stopped on confirmation of diagnosis. All patients were given empirical antibiotics which were substituted if necessary, according to culture and sensitivity. 4 patients in group 2 needed pulse of steroids for exacerbation of chronic obstructive pulmonary disease (COPD) to decrease the inflammation within airways and controlling excessive wheezing. Non-invasive ventilation (NIV) in the form of low flow and high flow oxygen masks was required in 13 patients, while 4 patients also required Bilevel Positive Airway Pressure (BiPaP) support (Table 2).

Requirement for oxygen support was comparatively lesser in group 1 (2.16 days) than in group 2 (6.54 days) patients and this reduction in duration of requirement for oxygen support was found to be significant ($p<0.05$) (Table 3). Unfortunately, 3 patients (13.04%) of group 2 who could not maintain oxygen saturation with the help of NIV were put on invasive ventilation later. Clinical improvement was assessed by monitoring decrease in fever, respiratory

rate /minute (resolution of tachypnoea), resolution of tachycardia, maintenance of oxygen saturation at room air/lower fraction of inspired oxygen (FiO2) and improvement in consciousness. Clinical improvement occurred in 20 patients out of which 12 were in group 1 and 8 patients in group 2.

Table 1: Demographic, clinical, laboratory and radiological profile of Patients at admission.

Characteristic (%)	Total (n=23)	Group 1 (n= 12)	Group 2 (n= 11)
Age (median-years)	52 (22-90)	49 (24-74)	56 (22-90)
Male/female	13 (56.53)/10 (43.47)	7 (58.33) / 5 (41.67)	6 (54.55)/5 (45.45)
Comorbidity	15 (65.21)	5 (41.67)	10 (90.90)
Diabetes mellitus	6 (26.08)	2 (16.67)	4 (36.36)
Hypertension	10 (43.47)	3 (25.0)	7 (63.63)
Others	9 (39.13)	2 (16.67)	7 (63.63)
History of fever/cough	18 (78.26) / 14 (60.87)	8 (75.0) / 5 (41.67)	10 (90.90)/9 (81.81)
History of dyspnoea	13 (56.52)	5 (41.66)	8 (72.72)
Abnormal hemogram			
Lymphopenia - (lymphocytes <1.5 × 109/l)	18 (78.26)	8 (66.67)	10 (90.90)
Leucocytosis- (leucocytes >11.0×109/l)	8 (34.78)	2 (16.67)	6 (54.54)
Thrombocytopenia- (platelets <1.2×109/l)	4 (17.39)	0	4 (36.36)
ALT (U/l)- median (range)	44 (22-92)	43 (22-64)	45 (22-92)
≤50 U/l	15 (65.21)	9 (75.0)	6 (54.54)
>50 U/l	8 (34.78)	3 (25.0)	5 (45.45)
LDH (U/l)- median (range)	569 (134-1478)	306 (134-982)	707 (256-1478)
≤460 U/l	9 (39.13)	7 (58.33)	2 (18.18)
>460 U/l	14 (60.86)	5 (41.66)	9 (81.81)
Procalcitonin (PCT) (ng/ml)- median (range)	0.21 (0.05-1.20)	0.08 (0.05-0.90)	0.23 (0.12-1.20)
≤0.50 ng/ml	14 (60.86)	8 (66.67)	6 (54.54)
>0.50 ng/ml	9 (39.13)	4 (33.33)	5 (45.45)
FDP (ug/ml)- median (range)	1.6 (1.4-32)	1.5 (1.4-16)	1.8 (1.4-32)
≤4 ug/ml	14 (60.86)	9 (75.0)	5 (45.45)
> 4ug/ml	9 (39.13)	3 (25.0)	6 (54.54)
D - dimer (ug/l)- median (range)	487 (112-33300)	222 (112-1564)	657 (340 - 33300)
≤583 ug/l	14 (60.86)	9 (75.0)	5 (45.45)
>583 ug/l	9 (39.13)	3 (25.0)	6 (54.54)
Patients with pneumonitis patch on chest X-ray	19 (82.60)	9 (75.0)	10 (90.90)
Patients with abnormal HRCT chest	19 (82.60)	9 (75.0)	10 (90.90)
Patients with abnormal CT pulmonary angiography	1 (4.34)	0	1 (9.09)

Table 2: Treatment and radiological profile of patients.

Characteristic (%)	Total (n=23)	Group 1 (n=12)	Group 2 (n=11)
Inclusion criteria for starting Lopi/r *			
Patients who had hypotension at the time of admission	1 (4.34)	1 (8.33)	0
Patients who had organ dysfunction present at the time of admission	3 (13.04)	2 (16.67)	1 (9.09)
Respiratory Rate >22 /min	13 (56.52)	5 (41.66)	8 (72.72)
Patients with lung infiltrates on chest X-ray	19 (82.60)	9 (75.0)	10 (90.90)
More than 1 criteria	13 (56.52)	5 (41.66)	8 (72.72)
Days from symptom onset to start of Lopi/r therapy (mean)	7.17	4	11.1

Continued.

Characteristic (%)	Total (n=23)	Group 1 (n=12)	Group 2 (n=11)
Completed full course of Lopi/r (14 days)	18 (78.26)	10 (83.33)	8 (72.72)
Treatment during hospital stay			
Hydroxychloroquine	22 (95.65)	11 (91.66)	11 (100.0)
Oseltamivir	6 (26.08)	4 (33.33)	2 (18.18)
Antibiotic	23 (100.0)	12 (100.0)	11 (100.0)
Steroid therapy	4 (17.39)	0	4 (36.36)
Non-invasive ventilation	13 (56.52)	5 (41.66)	8 (72.72)
Mechanical ventilation	3 (13.04)	0	3 (27.27)
Ionotropic support	1 (4.34)	1 (8.33)	0

*Inclusion criteria besides adult over 18 years of age, high risk groups with age > 60 years and those with comorbidities and patients from whom written consent was taken.

Table 3: Clinical outcome of patients.

Characteristic (%)	Total (n=23)	Group 1 (n= 12)	Group 2 (n= 11)	P value
Clinical improvement (from symptom onset)	20 (86.95)	12 (100.0)	8 (72.72)	
Day 7	10 (43.47)	7 (58.33)	3 (27.27)	0.64
Day 14	18 (78.26)	11 (91.67)	7 (63.63)	0.005
Day 28	20 (86.95)	12 (100.0)	8 (72.72)	0.093
Oxygen support (mean)	4.26	2.16	6.54	0.018
Duration of mechanical ventilation (mean)	1	No patient needed mechanical ventilation	1	
Time to 1st COVID-19 negative report after onset of symptoms (mean)	14.57	10.5	19.57	0.001
Time to 1st COVID-19 negative report after admission (start of Lopi/r and other medications) (mean)	7.79	7.16	10.28	0.06
ICU length of stay (mean)	8.33	6.66	9.16	
Of survivors	8	6.66	9.33	
Of non-survivors	9	All patients survived	9	
Hospital stay (mean)	9.82	8.58	11.54	0.044
Patients discharged	20 (86.95))	12 (100.0)	8 (72.72)	
Within 10 days of admission	14 (60.86)	11 (91.67)	3 (27.27)	
After 10 days of admission	6 (26.08)	1 (8.33)	5 (45.45)	0.06
Death	3 (13.04)	0	3 (27.27)	

Clinical improvement was faster in patients of group 1 than group 2 as by day 7 and day 14, 58.33% and 91.67% patients of group 1 showed improvement while only 27.27% and 63.63% patients of group 2 showed improvement at day 7 and day 14. Though clinical improvement was faster in group 1 patients than group 2 patients at day 7 but the results were insignificant but were significant at day 14, $p<0.05$ (Table 3). The mean duration of hospital stay was 8.58 days in group 1 patients while it was 11.54 days in group 2 patients and this reduction in mean duration of hospital stay in group 1 patients was found to be significant ($p<0.05$) (Table 3). The mean duration of intensive care unit (ICU) stay was also longer in group 2 (9.16 days) as compared to the former (6.66 days). The mean duration of obtaining first Covid-19 report negative from 1st positive Covid-19 report at the time of admission, was 7.16 days in group 1 patients and 10.28 days in group 2 patients and the results were significant ($p<0.05$) (Table 3).

Kaplan Meier test was done to analyze the hospital stay duration between group 1 and group 2 patients and graphs were plotted (Figure1). It was observed that in patients with equal chances of survivability (i.e. 80%) - the hospital stay duration was longer in patients who were treated with lopi/r therapy after 7 days of onset of symptoms (group 2) than in patients where lopi/r combination was started within 7 days (group 1). 3 patients were censored out from group 2 as they expired during the course of treatment. This data was analyzed by log proportional cox test and Mantel cox test and a p value of 0.008 was obtained indicating that induction of lopi/r therapy within 7 days of onset of symptoms reduced hospital stay duration significantly (by approximately 3 days). Similarly Hazard

function was plotted against hospital duration (Figure 2) and it was observed that at equal cumulative hazard ratio the hospital duration was longer in group 2 patients as compared to group 1 patients. Diarrhea/abdominal discomfort (7 patients) were the most common adverse events seen in patients after initiation of lopi/r therapy (Table 4). 18 patients were able to complete full 14-day course of lopi/r therapy. One patient developed excessive diarrhea and refused to take further medication besides standard care and one patient had an episode of hypotension during which Tall T-waves were seen. lopi/r was discontinued in this patient even though Troponin-T and pro-Brain derived Natriuretic Peptide (pro-BNP) levels were normal. One patient suffered with aggravation of his pre-existing psoriatic rash, which was controlled over years, but its cause cannot be attributed to medications alone as the patient also suffered with severe stress. Overall, 20 patients (86.95%) recovered completely out of which 12 patients were from group 1 and 8 from group 2. They were discharged after obtaining 2 consecutive Covid-19 oropharyngeal/ nasopharyngeal swabs negative with a mean duration of hospital stay of 9.82 days. More number of patients (91.67%) belonging to group 1 were discharged within 10 days of admission as compared to group 2 in which only 3 patients (27.27%) could be discharged within 10 days. Deterioration occurred in 3 patients as they landed in Acute Respiratory Distress Syndrome (ARDS) and later expired before completing 14 days course of lopi/r. All these 3 patients belonged to the group 2.

Table 4: Summary of adverse events.

Characteristic	Total (n=23)	Group 1 (n=12)	Group 2 (n=11)
Any adverse event - no. (%)			
Abnormal hemogram	2	1	1
Rash/rash aggravation	1	1	0
Loss of appetite	4	2	2
Vomiting	3	1	2
Diarrhoea/abdominal discomfort	7	4	3
Hypoalbuminemia	3	1	2
Hyperglycemia	3	2	1
Hyperlipidemia	4	2	2
ECG changes			
Prolongation of PR interval	0	0	0
Prolongation of QTc interval (>0.50s)	0	0	0
ST/T wave changes	2	2	0
Serious adverse events			
ARDS	3	0	3
Acute kidney injury	5	1	4
Sepsis	4	1	3

*Increase in amylase >3 times, Increase in ALT >5 times, increase in CPK >3 times was not found in any patient during the course of treatment.

DISCUSSION

In this observational study of 23 patients it was observed lopi/r in group 1 had better results than group 2 in terms of clinical improvement, decreased mean duration of ICU and hospital stay, less time to obtain first Covid-19 sample negative (marker of reduced viral load) and decrease in time for discharge.

A total 13 patients (56.52%) needed oxygen support in the form of non-invasive or invasive ventilation. The mean duration of requiring oxygen support was also lesser in group 1 (5.2 days) as compared group 2 (9 days).

Despite the concern for major side effects with lopi/r no major adverse events were observed out of which diarrhoea/abdominal discomfort were most common and were mostly self-limiting and mild. 3 patients could not recover and landed in ARDS and later expired and all these patients belonged to the group 2. Studies conducted by Chu and Cheng et al on the role of lopinavir-ritonavir in the treatment of SARS have concluded with a reduction in steroid usage and nosocomial infections in patients initially treated with lopinavir-ritonavir and these patients had a decrease in viral load, rising peripheral lymphocyte count and was associated with a better clinical outcome when compared to standard therapy.[10]

Another study conducted by Cao B, Wang Y et al although suggested that no benefit was observed with lopi/r treatment beyond standard care in hospitalized adult patients with severe Covid-19, but median duration of start of lopi/r therapy of 13 days after onset of symptoms and

may be limitation of study.[11] This is supported by the fact that when we see modified intention –to-treat analysis, after exclusion of 3 patients who didn't complete course due to very early death in 24 hours of enrolment, the time to clinical improvement was 1 day shorter with lopi/r group. Study conducted by Xiatong Ye, Yunling Luo et al states that addition of lopi/r combination to standard care of therapy helped in achieving better responses in remission of fever and subsiding ongoing inflammation with minimal side effects and concluded that that the use of lopi/r combined with pneumonia associated adjuvant drugs should be promoted.[12]

Recent study conducted by Hung et al states that early triple antiviral therapy comprising of interferon beta-1b, lopinavir-ritonavir and ribavarin was safe and shortened the duration of viral shedding and hospital stay in patients with mild to moderate Covid-19.[13] Till now the beneficial role of lopinavir-ritonavir in severe Covid-19 infection remains inconclusive and further trials are needed in future for definitive evidence. Considering the disease progression study by Hsu et al there is sequential rise in viral replicative phase up to day 10.[14] Thereafter, the disease progresses to ARDS and severe organ damage in some patients. This favours the fact that any factor which reduces the viral load, reduces the need of salvage therapy with immune-suppressants and thus decreasing risk of nosocomial infections in this window period of 10 days can have substantial benefits in treatment of coronavirus infection.[15] Suggestion of early use of lopi/r by above studies are similar to our study with results of reduced ICU and hospital stay if we go by the hypothesis of acting early before peak viral replication (at day 10).

The solidarity trial of WHO is still underway and till no specific guidelines with respect to treatment of Covid-19 patients is available and our centre is fortunate enough to be a part for contribution in it. Keeping in mind that few antiviral medications like lopi/r have shown antiviral action against severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS) in the past, we decided to use this drug combination according to ICMR guidelines.[16,17]

Limitations of this study includes small sample size and and patients were not randomly assigned to treatment and control group. Although both groups matched to most of known prognostic factors for lopi/r treated subgroups, however existing co-morbidities may have confounded results.

CONCLUSION

Supplementation of lopi/r to a standard protocol for Covid-19 care at early stage appears to be beneficial in terms of reduction in ICU and hospital stay. Early initiation also results in decrease in duration of oxygen support. Patients who were given lopi/r within 7 days of onset of symptoms also had decrease in time period to obtain first negative Covid-19 report. Larger double blinded trials are needed for timing of initiation of antiviral agents for evaluation of this fact.

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