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Dynamic Systematic Benefit Risk Analysis of Antiviral Drug Combination of Lopinavir - Ritonavir for Covid-19 Patient

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Abstract: *High-risk patients with early symptomatic COVID-19 in an outpatient setting. Lopinavir/ritonavir and arbidol have been previously used to treat acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) replication in clinical practice; nevertheless, their effectiveness remains controversial. In this study, we evaluated the antiviral effects and safety of lopinavir/ritonavir and arbidol in patients with the 2019-nCoV disease (COVID-19). Fifty patients with laboratory-confirmed COVID-19 were divided into two groups: including lopinavir/ritonavir group (34 cases) and arbidol group (16 cases). Lopinavir/ritonavir group received 400 mg/100mg of Lopinavir/ritonavir, twice a day for a week, while the arbidol group was given 0.2 g arbidol, three times a day. Data from these patients were retrospectively analyzed. The cycle threshold values of open reading frame 1ab and nucleocapsid genes by RT-PCR assay were monitored during antiviral therapy. None of the patients developed severe pneumonia or ARDS. There was no difference in fever duration between the two groups (P=0.61). On day 14 after the admission, no viral load was detected in arbidol group, but the viral load was found in 15(44.1%) patients treated with lopinavir/ritonavir. Patients in the arbidol group had a shorter duration of positive RNA test compared to those in the lopinavir/ritonavir group (P<0.01). Moreover, no apparent side effects were found in both groups. In conclusion, our data indicate that arbidol monotherapy may be superior to lopinavir/ritonavir in treating COVID-19.*

Objective: In this study, we review the evidence of the use of lopinavir/ritonavir as a potential treatment candidate against COVID-19.

Keywords: Lopinavir; Ritonavir; COVID-19; SARS; MERS

I. INTRODUCTION

1.1 Lopinavir-Ritonavir

Lopinavir-Ritonaviris the most common reported antiviral in this review. Lopinavir is a Protease inhibitor used for treatment of HIV infection with ritonavir as a booster (35). Protease is the key enzyme in CoV polypeptide processing and controlling coronavirus replication (36). Consequently, LPV/RTN showed in vitro activity against MERS and SARS-CoV with mean 50% effective concentrations (EC50) ranged from 6.6–17.1 μM (37). Furthermore, in vitro study of LPV/RTN showed antiviral activity against SARS-CoV-2 with EC50 at 26.1 μM (38). The clinical dose of lopinavir/ritonavir 400/100 mg twice daily may reach a minimum inhibitory concentration of 9.4 μM, which is lower than EC50 against SARS-CoV-2 9(39). Higher doses are generally avoided due to severe gastrointestinal adverse events of Lopinavir/ritonavir. Altogether, 19 trials reported in this study used LPV/RTN in COVID-19 patients including 2 randomized control trials (25,31), 5 retrospective cohort trials (24,26,29,30,33). and 4 case series and case reports (27,28,32,34). A randomized control trial including 199 severe COVID-19 patients revealed that lopinavir group had significantly shorter time for clinical improvement compared to standard therapy. Moreover, 28-day mortality was

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numerically lower without significant difference. Hospital stay and duration of mechanical ventilation were not significantly different between both groups (31). Moreover, a prospective cohort study of 47 mild COVID-19 patients enrolled to receive LPV/RTN + adjunctive therapy or adjunctive therapy alone. Results showed LPV/RTN group had a shorter time in returning to normal temperature and negative PCR conversion time compared to the control group. However, a small sample size, non-blinded design, and including mild COVID-19 cases, limits its clinical usefulness. Moreover, 8 trials failed to prove efficacy of LPV/RTN in treating COVID-19 patients(33).

Lopinavir is ineffective to inhibit SARS-CoV-2 Mpro. (A) Chemical structure of lopinavir and ritonavir. (B) Purification of SARS-CoV-2 Mpro. Cell lysate and purified Mpro protein were subject to SDS-PAGE. (C) Measurement of the relative Mpro activity over time. Activity is measured relative to maximal activity at 5 hr. (D) Lopinavir did not inhibit Mpro. Indicated concentrations of lopinavir were incubated with Mpro and the relative protease activity was determined. The Mpro activity was measured in quadruple and the mean and standard deviation are shown. NS, not significant. (E) Mixtures of lopinavir and ritonavir at a weight ratio of 4:1 were incubated with Mpro, and the relative protease activity was determined. (F) EGCG was incubated with Mpro, and the protease activity was examined as a positive control(1,2)

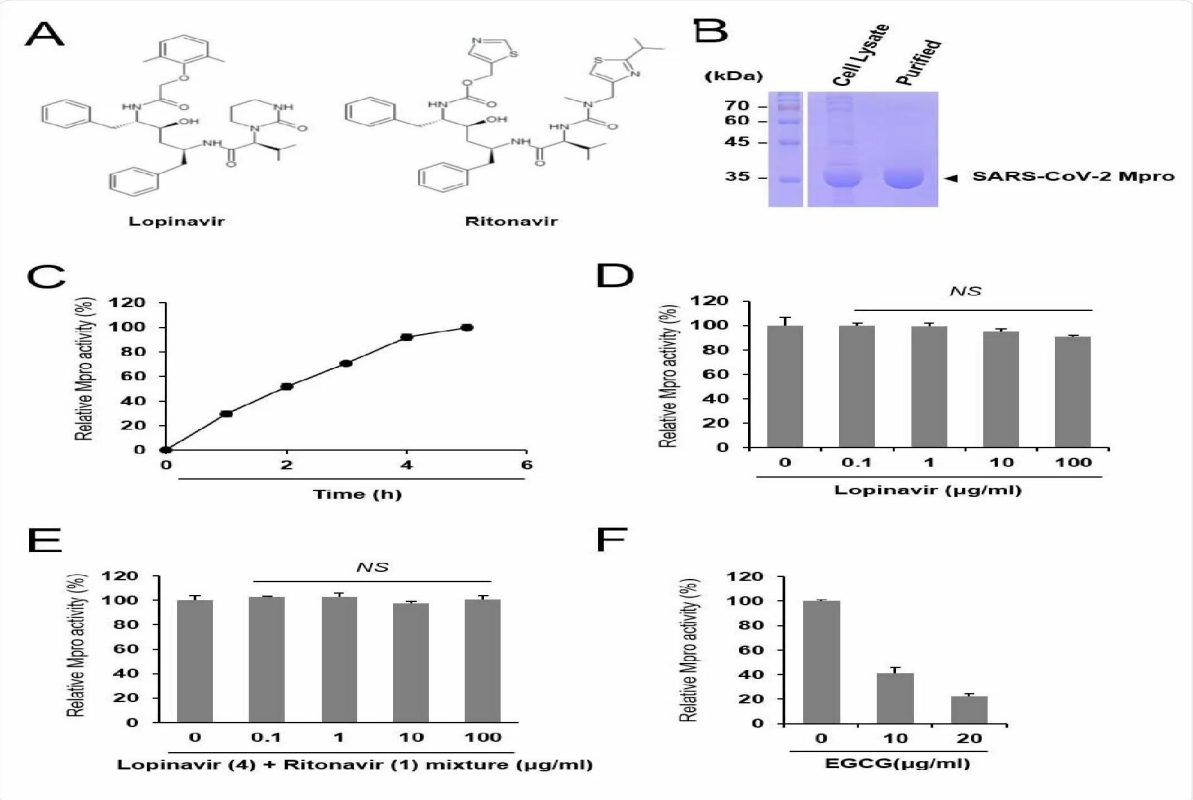

Fig 1: Lopinavir is ineffective to inhibit SARS-CoV-2 Mpro.

1.2 Information

Lopinavir is a novel protease inhibitor (PI) developed from ritonavir. Co-administration with low-dose ritonavir significantly improves the pharmacokinetic properties and hence the activity of lopinavir against HIV-1 protease . lopinavir/ritonavir was diarrhea, followed by other gastrointestinal disturbances, asthenia, headache and skin rash. Coformulated lopinavir/ritonavir (Kaletra®) is a boosted protease inhibitor (PI) containing lopinavir and low-dose ritonavir. It is approved for use in combination with other antiretroviral drugs for the treatment of HIV infection in adults, adolescents and children aged ≥6 months (in the US) or ≥2 years (in the EU). Lopinavir/ritonavir is one of the preferred PIs for first-line treatment of HIV infection in adults, adolescents and children, according to US and British guidelines, reflecting its comparatively better virological efficacy than nelfinavir and low incidence of de novo resistance during long-term treatment(3).

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Combination of the two approved drugs for HIV infection, lopinavir and ritonavir (KALETRA), has been reported to be active toward SARS and MERS. (14,19) Both anti-HIV drugs were initially purposed to inhibit 3CLpro of SARS-CoV and MERS-CoV, and they appeared to be related to clinical benefits of patients with SARS in a nonrandomized open-label trial. (17) Although ritonavir is a protease inhibitor, it is generally used to inhibit cytochrome P450 3A4 and markedly increases the plasma concentrations of other protease inhibitors. (20) Nevertheless, whether HIV protease inhibitors could effectively target SARS-CoV-2 3CLpro is under debate. This is based on the fact that HIV protease is from the aspartic protease family, whereas SARS-CoV-2 3CLpro belongs to the cysteine protease family. Previously, a theoretical study of the molecular interaction of lopinavir and ritonavir with 3CLpro of SARS-CoV suggested that these two drugs could bind well at the substrate-binding pocket of SARS-CoV 3CLpro. (15) To date, the three-dimensional structure of SARS-CoV-2 3CLpro in a complex with lopinavir and ritonavir has not been reported. Thus, in our study, we aimed to investigate the binding interactions of lopinavir and ritonavir with the SARS-CoV-2 proteinase using both molecular modeling and quantum chemical methods. It is our hope that this information can be useful for the future design or development of more specific inhibitors for the treatment of human coronaviruses .Coronaviruses have risen as a global threat to public health. Currently, the outbreak of coronavirus disease-19 (COVID-19) from Wuhan caused a worldwide panic. There are no specific antiviral therapies for COVID-19. However, there are agents that were used during the severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) epidemics. We could learn from SARS and MERS. Lopinavir (LPV) is an effective agent that inhibits the protease activity of coronavirus. In this review, we discuss the literature on the efficacy of LPV in vitro and in vivo, especially in patients with SARS and MERS, so that we might clarify the potential for the use of LPV in patients with COVID-19.

Based on previous experiences (SARS outbreak in 2003), lopinavir/ritonavir might be used for treating SARS-CoV2 replication; however, its effectiveness remains controversial(4,5). To date, clinical evidence on lopinavir/ritonavir and arbidol monotherapy in patients with COVID-19 is limited. Herein, we evaluated the antiviral effects and safety of lopinavir/ritonavir and arbidol in patients with COVID-19. Lopinavir / Ritonavir as a single medication was approved for used in the United State in 2000.(7).

Lopinavir/ Ritonavir is available in three dosage forms

- lopinavir 200 mg / Ritonavir 50 mg formulated tablet.
- lopinavir 100 mg / Ritonavir 25 mg formulated tablet.
- lopinavir 400 mg / Ritonavir 100 mg per 10 ml oral solution.

Lopinavir / Ritonavir tablet may be taken with or without food; the oral solution must be taken with food.

Adult dosage is lopinavir / Ritonavir 400 mg /100 mg, twice daily or lopinavir / Ritonavir 800mg / 200 mg once daily.

A combination of the approved drug for HIV infection, lopinavir and Ritonavir (KALETRA) ,has been reported to be active toward SARS and MERS.(6)

Since the emergence of a novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndromecoronavirus 2 (SARS-CoV-2) was first reported from Wuhan, China, neither a specific vaccine nor an antiviral drug against SARS-CoV-2 has become available. However, a combination of two HIV-1 protease inhibitors, lopinavir and ritonavir, has been found to be effective against SARS-CoV, and both drugs could bind well to the SARS-CoV 3C-like protease (SARS-CoV 3CLpro). In this work, molecular complexation between each inhibitor and SARS-CoV-2 3CLpro was studied using all-atom molecular dynamics simulations, free energy calculations, and pair interaction energy analyses based on MM/PB(GB)SA and FMO-MP2/PCM/6-31G* methods. Both anti-HIV drugs interacted well with the residues at the active site of SARS-CoV-2 3CLpro. Ritonavir showed a somewhat higher number atomic contacts, a somewhat higher binding efficiency, and a somewhat higher number of key binding residues compared to lopinavir, which correspond with the slightly lower water accessibility at the 3CLpro active site. In addition, only ritonavir could interact with the oxyanion hole residues N142 and G143 via the formation of two hydrogen bonds. The interactions in terms of electrostatics, dispersion, and charge transfer played an important role in the drug binding. The obtained results demonstrated how repurposed anti-HIV drugs could be used to combat COVID-19

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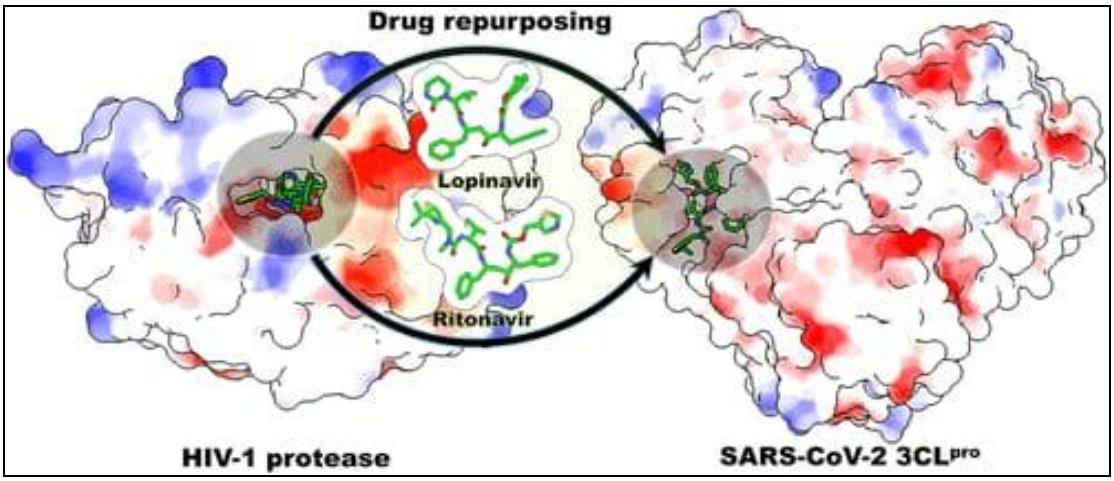

Fig. 2: Combination of HIV-1 Protease inhibitor &SARS-CoV-2 3CLpro.

II. METHODS

2.1 Literature Search

We systematically searched PubMed, medRXiv, Web of Science, and Scopus databases from May 2020-July 2020 using the following search string: '(lopinavir/ritonavir) AND (randomized OR trial OR observational OR comparative OR mortality OR PCR OR adverse) AND(COVID-19)'. For medRXiv database, we used 'lopinavir/ritonavir COVID-19' as a search string. Additionally, we reviewed the bibliographies of included studies to retrieve relevant studies not found during our initial electronic database search and contacted experts in the field for relevant articles. This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines(8).

2.2 Study Search, Selection, and Quality Assessment

All original research studies that reported the use of LPV/r for the treatment of patients with COVID-19 were included in this review. We excluded in vitro and animal studies, reviews, case reports, abstract-only research articles, single-armed studies (with no comparison group) and articles not written in English language. Retrieved studies were independently screened by at least two authors for inclusion-exclusion.

2.3 Data Extraction and Study Outcomes

Data were extracted by two authors (SK and MS) and checked for accuracy independently by two authors (JP and KW). When available, background characteristics were collected, including age, sex, body mass index (BMI), race, and comorbidities, such as hypertension, smoking, alcoholism, coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), and hyperlipidemia. Additionally, intervention-related information, such as dose and regimen, the period of follow-up, and concomitant medications were collected. The included outcomes were viral clearance measured by reverse-transcription polymerase chain reaction (RT-PCR) negativity and/or improvement on chest computed tomography (CT), mortality, and adverse events (AEs) (further categorized into cardiac, gastrointestinal, or respiratory)(8).

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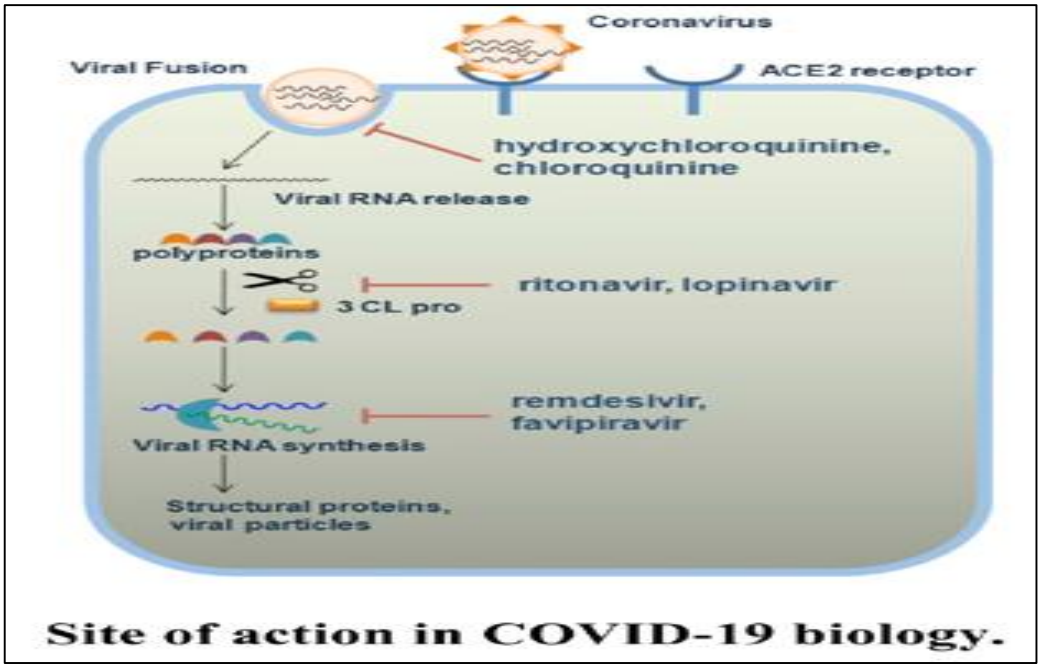
III. MECHANISM



Site of action in COVID-19 biology.

3.1 Benefits

Key benefits have been listed in the value tree in descending order of perceived clinical importance. At the current time, only one clinical trial was identified that provided empirical data for any of the clinical endpoints listed in the value tree (18) Whilst the primary objective of this clinical trial was time to clinical improvement, additional data were provided for various endpoints including mortality risk, risk and duration of invasive mechanical ventilation, risk of non-invasive ventilation and oxygen requirement.

3.2 RISKS

Key risks were identified for LPVr based on the current available evidence. It is acknowledged that this product is not licensed for use in the treatment of COVID-19 disease, and whilst safety data are available for its licenced use in HIV type 1, its safety profile in the context of COVID-19 is largely unknown. Furthermore, for the limited safety data that are available for its use in COVID-19, it is often unclear whether the reported adverse event is due to the use of LPVr, or attributable to the underlying disease. Potentially serious risks that are likely to still pose a risk with the proposed short-term use of LPVr for COVID-19 have been summarised in the value tree and ranked according to perceived seriousness.

One of the most serious risks is prolongation of the QT interval, and the subsequent increased risk of sudden cardiac death (19,20,21,22). Patients with COVID-19 are already predisposed to the development of cardiac arrhythmia owing to the effect of the virus on metabolic dysfunction, myocardial inflammation and the sympathetic nervous system (20). Additionally, it is important to note that LPVr is an inhibitor of cytochrome P450 3A4, and therefore it cannot be used with other medicines that are substrates of this enzyme, such as chloroquine, which itself can cause QT prolongation (21). In addition to the effects on QT prolongation, LPVr has also been shown to cause modest asymptomatic prolongation of the PR interval in some healthy adult subjects, with rare reports of second- or third-degree atrioventricular block in patients with underlying structural heart disease and pre-existing conduction system abnormalities or in patients receiving drugs known to prolong the PR interval (such as verapamil or atazanavir), and therefore LPVr should be used with caution (23) in such patients.

Lopinavir/ritonavir are both inhibitors of the cytochrome P450 3A isoform, and therefore treatment is likely to increase plasma concentrations of concomitant medicinal products that are primarily metabolized by cytochrome P450 3A. Clinically significant drug interactions have been observed with LPVr use during treatment for COVID-19, including increased plasma concentrations of direct oral anticoagulants, and increased plasma concentrations of

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immunosuppressant in organ transplant recipients (9).

Certain risks factors and clinical characteristics have been associated with the development of acute respiratory distress syndrome (ARDS) amongst patients with COVID-19. Patients who developed COVID-19-related ARDS were likely to require admission to the intensive care unit. In the study by Cao et al., respiratory failure/ARDS was reported as a serious adverse event in both treatment groups (18). Whilst causality in these cases is not known, it would seem likely that these cases were attributable to progression of the underlying COVID-19 disease.

Hypersensitivity reactions such as urticarial and angioedema are reported to occur commonly with the use of LPVr for the treatment of HIV, and rarely serious skin reactions such as Stevens–Johnson syndrome and erythema multiform have been reported with its use in this treatment population. Gastrointestinal side effects of LPVr are well recognized, and diarrhea and nausea are very common. Serious gastrointestinal adverse effects included in the key risks for this assessment include pancreatitis, which has been associated with the use of LPVr (10,11). most patients who developed pancreatitis during treatment for HIV had a prior history of this condition. Treatment with LPVr has been associated with an increase in triglycerides in patients treated for HIV, and amongst patients treated for COVID-19 (16), which is likely to be another contributory factor in the development of pancreatitis.

In the context of treatment for HIV, LPVr has been uncommonly associated with certain adverse renal outcomes, including a reduction in creatine clearance, nephritis and hematuria. Cases of acute kidney injury have been reported in patients taking LPVr in COVID-19; however, it is unclear whether there is any association, as this outcome was reported more frequently amongst patients in the standard of care comparator group(12,13). in addition to overall limited safety data availability. Elevations of liver enzymes have also been commonly reported with the use of LPVr in the treatment of HIV and liver injury has been reported in patients treated with LPVr for COVID-19. Blood dyscrasias have also been associated with the use of LPVr during HIV treatment with reports of severe anemia amongst patients treated for COVID-19(18).

IV. DISCUSSION

The study aim was to examine the benefit-risk profile of LPVr in COVID-19 patients compared to standard of care, placebo or other treatments. A key objective of this study was to provide a platform for a dynamic systematic benefit-risk evaluation; although initially this evaluation is likely to contain limited information, it is required because of the urgent unmet public need. Importantly, it allows additional data to be incorporated as they become available, and re-evaluation of the benefit-risk profile. This paper provides a systematic benefit-risk assessment using the BRAT methodology and is inclusive of the available literature up to and including 13 May, 2020. Therefore, this represents a snapshot of the data available to date and outlines a clear and transparent framework into which subsequent clinical trial and observational study data can be incorporated, and the benefit-risk profile re-assessed.

V. HIGHLIGHTS

- LPV is an effective agent inhibiting coronavirus in vitro and animal studies.
- The treatment of LPV improved outcomes of SARS and MERS patients.
- LPV may be a potential treatment option for COVID-19.
- On day 14 after the admission, no viral load was detected in arbidol group.
- 44.1% of patients in lopinavir/ritonavir group had positive RNA test on day 14.
- Patients in the arbidol group had a shorter duration of positive RNA test.
- No apparent side effects were found in both groups.
- Arbidol monotherapy may be superior to lopinavir/ritonavir in treating COVID-19.

VI. RESULTS

A total of 1,965 articles were screened, from which 6 articles were selected. Of 6 articles that were included in this study, 4 reported no significant benefit in clinical improvement with lopinavir/ ritonavir when compared to standard care of treatment, while 2 studies reported otherwise. Lopinavir/ritonavir was also not associated with a reduction of 28-day mortality rate as reported by 1 included study. Most included studies reported gastrointestinal symptoms as side effects from lopinavir/ritonavir therapy.

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VII. CONCLUSION

There is not yet enough evidence to support the regular use of lopinavir/ritonavir in the treatment of COVID-19. Further clinical trials are needed to evaluate lopinavir/ritonavir's efficacy in treatment. Based on currently available data, there was no clear benefit for use of LPVr compared to standard of care in severe COVID-19. Risk data suggested a possible decrease in serious adverse events. There was a reduction in ARDS with LPVr in one study. Overall, the benefit-risk profile for LPVr in severe COVID-19 cannot be considered positive until further efficacy and effectiveness data become available.

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