Review Article
Advancements in Life Sciences – International Quarterly Journal of Biological Sciences

ARTICLE INFO

Date Received: 19/08/2021;
Date Revised: 25/07/2022;
Date Published Online: 31/10/2022;

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How to Cite:
Pantsari T, Ali MM, Ghouri MH, Alharbi AM, Alfahemi H, (2022). Role of Antiviral Drugs in Management of Mild and Moderate Coronavirus Disease-19: A Systematic Review. Adv. Life Sci. 9(3): 270-276.

Keywords:
COVID-19; SARS-CoV-2; Mild disease; Antivirals; Lopinavir/ritonavir; Remdesivir; Critical Care; Coronavirus Disease

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Role of Antiviral Drugs in Management of Mild and Moderate Coronavirus Disease-19: A Systematic Review

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Abstract

This study was conducted to determine the objective role of antiviral drugs such as arbidol, lopinavir/ritonavir, and others in improving clinical symptoms, decreasing duration of hospitalization, and decreasing duration of viral shedding in patients with mild and moderate COVID-19 infection. A systematic literature search was carried out on Google Scholar and PubMed databases, using the keywords "COVID-19", "Antiviral", "Treatment", and "Symptomatic" in various combinations. Observational studies, cohort and case control studies, and clinical trials published in English with full-text available were included in the study. Data extraction was carried out from selected studies, and all statistical analysis for the study was carried out using Microsoft Excel. The key outcomes studied were time to negative PCR, duration of clinical stay, time to clinical improvement, and occurrence of adverse events. Seven studies were selected for final review after rigorous selection process. Data of total 4734 participants was analyzed, the majority of which were females (n=2810, 59.3%). The majority of participants had mild disease (n=4197, 88.65%). Average time for negative RT-PCR in the included treatment groups was 13.5 days, whereas the average duration of hospitalization was 14.9 days for the treatment groups. Adverse reactions such as ECG changes, gastrointestinal symptoms, secondary bacterial infections, and hepatic and renal dysfunction were scarcely reported in the included studies. There is no clear benefit in terms of duration of hospitalization and time to negative PCR with the use of various antiviral regimens in mild disease; however, these drugs did play a role in limiting disease progression in the participant population. Pending further evidence, the use of these drugs for the management of COVID-19 is not recommend in patients with mild disease.

Introduction

Although coronavirus disease (COVID-19) is no longer 'novel', having afflicted more than 142,557,268 people globally since its appearance in December 2019; only a limited number of treatments have been shown to be conclusively beneficial in halting disease progression or limiting mortality [1]. With the availability of multiple vaccines across the globe, the focus has shifted from treating severe coronavirus disease, to preventing its occurrence in the first place. However, global vaccine availability and universal vaccination are somewhat idealistic goals in the presence of cost restraints, vaccine hesitancy, poor accessibility, and the highlighted emergence of vaccine side effects and limited vaccine efficacy that are dissuading people from getting vaccinated [2]. In this context, exploring the role of various treatments for COVID-19, especially those that influence disease progression, becomes even more important to ensure that prevention and cure are discovered side by side.

Currently, guidelines for COVID-19 treatment differ among outpatient and hospitalized individuals. For outpatients with asymptomatic or symptomatic mild disease, treatment is usually tailored according to presentation: symptomatic management includes antipyretics such as acetaminophen and NSAIDs, self-proning and Cardiopulmonary Physical Therapy, adequate hydration, over-the-counter cough medication, and adequate rest [3]; advanced treatments, such as monoclonal antibody therapy with Bamlanivimab/etesevimab, and Casirivimab-imdevimab [4,5], as well as high-titer convalescent plasma [6] have also been authorized for use in high risk outpatient populations with mild disease [7]. For hospitalized individuals, management is multimodal, revolving around infection prevention, anticoagulation, specific treatments for COVID, and assisted ventilation either by invasive or non-invasive means [8]. Figure 1 presents a simplified approach for the management of hospitalized adults with COVID-19, based on current recommendations.

Antiviral therapy for COVID-19 is based on targets derived from models on viral replication and synthesis in host cells. SARS-CoV-2, an enveloped, single stranded RNA virus, targets host cells via combination of viral spike proteins and angiotensin-converting enzyme 2 (ACE2) receptors on the host cells, especially lung and small intestinal epithelial cells [10,11]; TMPRSS2, a host cell protease, can also promote viral entry via the spike protein [10]. Various non-structural proteins for viral replication are then produced, including 3-chymotrypsin-like protease, papain-like protease, helicase and RNA-dependent RNA polymerase [12]; all of these can be potential targets for antiviral therapy. This knowledge of viral pathogenesis has been used during the current pandemic to explore existing medications with a possible role in COVID-19 disease; a key example of this is Remdesevir, which acts on papain-like protease as well as RNA dependent RNA polymerase to prevent viral replication, and which has been widely supported by clinical trials for use in hospitalized patients with COVID-19 [13].

The objective of the current review is to summarize the role of antiviral medications in COVID-19, with special focus on mild and moderately symptomatic disease; the focus will be on reviewing antiviral treatments that can be used for prevention of disease progression as well as limitation of disease transmission.

Figure 1: Approach for managing COVID-19 in hospitalized adults

Methods

Literature Search and Selection Criteria

A systematic literature search was carried out on Google Scholar and PubMed databases, using the keywords "COVID-19", "Antiviral", "Treatment", and "Symptomatic" in various combinations. After initial data search, references of articles were cross-searched to expand the bibliography; a simultaneous search was also carried out on the preprint server medRxiv, to identify any potential publications on the subject topic. Observational studies, cohort and case control studies, and clinical trials published in English with full-text available were included in the study; studies which dealt with the role of antiviral treatments in patients with severe disease (as specified in the study protocol) were excluded. Editorials, case studies, in vitro studies, animal studies, guidelines, and review articles were also excluded from the final analysis.

Initially, two researchers carried out the data search, and reviewed titles and abstracts of records obtained by searching databases. Selected full texts were then reviewed and screened on the basis of inclusion/exclusion criteria. Data extraction was carried out from selected studies, and all statistical analysis for

the study was carried out using Microsoft Excel. The key outcomes studied were time to negative PCR, duration of clinical stay, time to clinical improvement, and occurrence of adverse events. The study selection process according to PRISMA guidelines is detailed in figure 2.

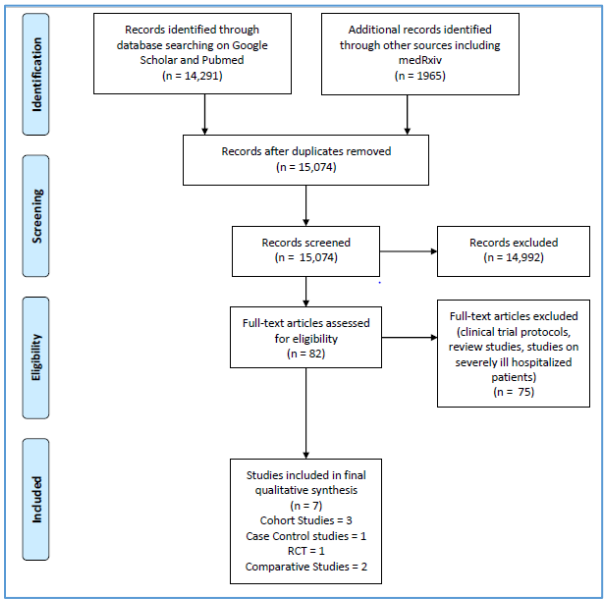

Figure 2: PRISMA flowchart describing study selection process

Discussion

Following initial database searching and screening, 8 studies which met the inclusion criteria were finally analyzed for the review. Ultimately, 7 studies were identified which dealt with antiviral treatment in mild and moderate COVID-19 disease; however, 2 of these also included data on patients with severe disease, while 1 dealt with lopinavir/ritonavir in pediatric population [14-20]. Due to paucity of available literature, studies which included patients with severe disease alongside mild and moderate were included as well, and this is specified in table 1, which highlights the key demographic characteristics of the study populations and the study outcomes in the included studies. One study [20] only reported the safety profile of lopinavir/ritonavir compared to darunavir/ritonavir with no relevant information regarding study outcomes of present study. Another study [16] compared the effectiveness of various regimens of lopinavir/ritonavir in treatment of COVID-19. Table 2 presents the results of the studies in terms of the study outcomes, as well as possible limitations if any, where specified.

Data of total 4734 participants was analyzed in our review, the majority of which were females (n=2810, 59.3%); participants were predominantly from Asian countries, with only one study reporting participants from France. The majority of participants had mild disease (n=4197, 88.65%); moderate (n=440, 9.29%) disease was less common, and only 24 participants (0.5%) with severe disease were included in the review. The predominant method of diagnosing COVID-19 was RT-PCR from nasopharyngeal or oropharyngeal swabs; CT findings were used as an alternative means of diagnosis in 2/7 studies. Average time for negative RT-PCR in the included treatment groups was 13.5 days, whereas the average duration of hospitalization was 14.9 days for the treatment groups.

Only a few major adverse reactions were reported among the study participants; 4 deaths were reported in one study, which were attributed to the severity of disease as well as complications from co-existing morbidities. Lymphopenia elevated or deranged liver function tests, and GI abnormalities were the most common reported side effects, mostly with mild severity. Regarding the efficacy of the various antiviral treatments, no benefit of antiviral treatment was demonstrated over standard of care in the majority of the studies. However, different regimens of antivirals i.e. lopinavir/ritonavir with interferon, danoprevir/ritonavir, and arbidol monotherapy were found to be relatively superior in terms of clinical improvement and decreased length of hospital stay compared to lopinavir/ritonavir alone or hydroxychloroquine as well.

The role of antivirals in COVID-19 has been debatable; the evidence from randomized trials has not been forthcoming in this regard. A previous systematic review on the role of antivirals included just one clinical trial and found disappointing results by the addition of lopinavir/ritonavir to the standard of care in management of severe COVID-19 [21]. It has been postulated that the addition of antivirals late in the disease course is less beneficial as compared to their early use, especially since in severe disease aggravation can occur despite provision of standard of care, due to hospital acquired complications [18].

This systematic review was undertaken to study the role of antiviral drugs in mild and moderate COVID-19 infections. Evidence for the role of these drugs in less severe infections has been lacking, with different randomized trials failing to show a superiority of these drugs over standard supportive care. In an exploratory RCT which studied the role of lopinavir/ritonavir and arbidol vs standard of care in mild and moderate COVID-19, the mean time for negative conversion of NAT was comparable among the different drug groups (9 days in LPV/R, 9.1 days in Arbidol and 9.3 days in standard care; p=0.981); the rate of alleviation of symptoms and resolution of CT findings did not differ significantly among the groups as well on days 7 and 14 [22]. Although a benefit has been reported with the use of Arbidol (Umifenovir), a broad spectrum antiviral in two

randomized trials, the sample size of the Arbidol group in one trial was too small to report any statistical significance [23]; whereas arbidol was used as a second line of management in the second trial following hydroxychloroquine, thereby limiting any potential role as a first-line therapy for mild to moderate COVID-19 [17,21]. Favipiravir, a purine analogue which inhibits viral replication, was also purported as a potential treatment for mild and moderate COVID-19; in a multicenter randomized trial with 96 patients randomized to either chloroquine or favipiravir, there was a lower duration of hospital stay (13.29 ± 5.86 days vs 15.89 ± 4.75 days), and zero requirement for invasive mechanical ventilation compared to chloroquine, although these differences were statistically insignificant [24]. Another recent open-label multicenter RCT found that the median time to clinical cure in mild and moderate COVID-19 was decreased by favipiravir from 5 to 3 days compared to standard of care; while this association was statistically significant, the concomitant rate of cessation of viral shedding was not, with a higher rate of adverse events being reported in the favipiravir group [25]. Similarly, a randomized trial in moderate and severe COVID-19 patients comparing favipiravir followed by inhaled interferon versus hydroxychloroquine failed to demonstrate a clinical benefit in terms of duration of recovery, improvement in oxygenation, levels of inflammatory markers, level of hospital stay and mortality [26].

Various case series and retrospective studies have also failed to demonstrate a benefit of antivirals on mortality rate, need for invasive mechanical ventilation, and clinical improvement [27-29]. Remdesevir, a nucleotide analogue which inhibits viral RNA-dependent RNA polymerase, was shown to improve clinical status after five days of administration compared with standard of care in moderate COVID patients in a multicenter RCT; however, no clear mortality benefit was observed, and the rate of adverse reactions was more frequent in Remdesevir-treated patients [30]. Although a systematic review and meta-analysis has reported efficacy of a five-day Remdesevir regimen in increasing clinical improvement while reducing mortality and need of ICU admission, this effect is difficult to generalize because of varying disease severity among the spectrum of patients studied [31]. Clinical data on the role of Remdesevir in mild COVID-19 continues to be scarce as well, and reported gastrointestinal, hepatic, and cardiopulmonary adverse events prompted stopping its administration in another randomized controlled trial [32].

In our review, only a modest benefit was shown by the use of danoprevir/ritonavir, arbidol, and lopinavir/ritonavir with novaferon in patients with mild and moderate disease; in the largest propensity matched cohort study included, lopinavir/ritonavir had no supremacy over hydroxychloroquine in terms of decreasing duration of viral shedding [18]. Our study mainly dealt with patients with mild disease, and the lack of antiviral benefit in this population, especially in terms of decreased viral shedding, supplements the current guidelines that propose standard symptomatic management in these patients.

There are certain limitations in our review. Due to the paucity as well as variability of clinical data, a meta-analysis could not be conducted. A risk-benefit analysis could not be carried out; moreover, the beneficial effects of certain antivirals is biased due to a small sample size and other concurrent first line therapies being used in the included studies. We are also forced to include two studies with severe disease patients, even though the effect size of this on the overall review was negligible.

Conclusion

In mild and moderate COVID-19, antiviral therapy with lopinavir/ritonavir based regimens or with arbidol based regimens offers little benefit in terms of decreasing length of hospital stay, time to negative PCR conversion, and resolution of clinical symptoms. Even though the risk of adverse reactions of these drugs is relatively low, the lack of a clear benefit precludes that such drugs should not be used outside of a clinical trial to routinely treat COVID patients, especially with mild disease.

Competing Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Authors' Contribution

Tanapong Pantasri: Contributed to research idea, study design, literature search, literature synthesis, data screening, article selection, and writing of manuscript.
Muhammad Mohsin Ali: Contributed to study design, literature search, literature review and synthesis, data screening, article selection, writing and editing of manuscript.
Muhammad Hashim Ghouri: Contributed to literature search and literature review, data screening, article selection, writing of manuscript and final drafting of manuscript.
Ahmad M. Alharbi: Contributed to literature search, data screening, and writing of manuscript.
Hasan Alfahemi: Contributed to literature search, data screening, and writing of manuscript.

Serial No.	Author, Year	Number of Participants	Reported Country (s)	Study Design	Treatment Group (n)	Control Group (n)	M:F	Age (years) in treatment group	Age (years) in control group	Antiviral Treatment Given (Name, dose, duration, route)	Placebo/ Comparator	Study Outcomes	Enrollment Criteria	Disease Severity in Participant population
1	Ji-Won Kim, 2021 [14]	65	Korea	Retrospective Cohort Study	31	34	25:40:00	Mean ± SD= 64.3 ± 14.6	Mean ± SD= 64.3 ± 16.3	Lopinavir-Ritonavir (400-100 mg) twice daily for median 11 (IQR 10-14) days orally	Hydroxychloroquine 400mg once daily for median 10 days (IQR 10-13) orally	Time to negative conversion of viral RNA in nasopharyngeal and oropharyngeal swabs (Primary) Time to clinical improvement i.e., cessation of O2 support, normalized body temperature <37.5 °C, resolution of respiratory symptoms (Secondary)	All hospitalized patients with COVID-19 who were treated with lopinavir-ritonavir or hydroxychloroquine at Daegu Catholic University Medical Center in South Korea from February 17 to March 31, 2020 were eligible	Mild (n=39) and moderate (n=26) severity
2	Zhicheng Zhang, 2020 [15]	33	China	Comparative Study	28	5	11:22	Median 43	Median 44	Lopinavir/Ritonavir Oral Solution (80 mg/20 mg), adult, 5 ml (400/100 mg) twice daily or 10 ml (800/200 mg) once daily, with meal, duration till patient discharge	Danoprevir sodium tablets, 100mg twice daily orally, duration till patient discharge	Hospital stays, time to achieve 2 negative Nucleic Acid Testing (NAT) tests	A total of 33 COVID-19 patients in the nineth hospital of Nanchang from January 27 to February 24, 2020, were involved in this study, after confirmation of COVID-19 by positive NAT PCR	Mild (10); Moderate (n=22); Severe (n=1)
3	Jian Qu, 2020 [16]	170	China	Retrospective Case Control Study	97		44:53:00	In Median (IQR) LPV/r alone= 45 (34-55); LPV/r + Interferon=37.5 (29.75-49.25) ; LPV/r + Novaferon= 43.5 (40-57); LPV/r + interferon + arbidol = 45 (37.5-61.5); LPV/r + interferon + novaferon= 45.5 (36.5-53.5)		LPV/r alone; LPV/r + Interferon; LPV/r + Novaferon; LPV/r + interferon + arbidol; LPV/r + interferon + novaferon; medication regimens of these drugs followed the instructions [LPV/r: per oral 500 mg (400 mg Lopinavir + 100 mg Ritonavir) twice daily; Novaferon: Aerosol 20 μg twice daily; Arbidol: per oral 0.2 g thrice daily; IFN: Aerosol 500 × 10^4 IU twice daily.]		Primary outcome: time of negative nucleic acid conversion. The secondary indicators: length of hospitalization, rate of adverse reaction, transferring to ICU and mechanical therapy.	(a) Confirmed COVID-19 patients who were tested positive for novel coronavirus nucleic acid for two respiratory specimens; (b) Mild and moderate patients in line with the diagnostic criteria in the 'novel coronavirus infected pneumonia treatment scheme; (c) Patients who have experienced antiviral treatment due to novel coronavirus nucleic acid infection.	Mild severity (n= 97)
4	Marzieh Nojomi, 2020 [17]	100	Iran	Open Label Randomized Controlled Trial	50	50	60:40:00	Mean (SD)= 56.2 (14.8)	Mean (SD)= 56.6 (17.8)	Hydroxychloroquine 400 mg on first day only, followed by 400 mg KALETRA (lopinavir/ritonavir) per oral for 7-14 days	Hydroxychloroquine 400mg twice daily on first day, followed by arbidol 200 mg thrice daily for 7-14 days	Duration of hospitalization, clinical improvement 7 days after admission (relief of cough, dyspnea and fever)—Primary/Secondary outcomes were death during 30 days of treatment, duration of hospitalization, changing of laboratory tests and CT findings in 30 days and need for invasive mechanical ventilation (IMV)	Non-pregnant women and men aged 18 years or older with definite diagnosis of COVID19 by RT-PCR or CT scan imaging (pneumonia), and oxygen saturation of 94% or less. Patients were enrolled into the study from hospitalized patients who were admitted to the infectious diseases ward of Firoozgar teaching hospital.	Mild (n=19); Moderate (n=58); Severe (n=23)
5	Min Joo Choi, 2020 [18]	4197	Korea	Propensity Score-matched Cohort Study	1268 for Lopinavir/ ritonavir group, 801 for HCQ group	2128	1694:2503	Mean (SD)= 49.78 (17.01) for LPV/r; 51.86 (17.71) for HCQ	Mean (SD)= 39.32 (16.01)	Lopinavir/ritonavir OR HCQ	Standard symptomatic treatment	Length of hospitalization (in terms of duration of viral shedding)	Patients with laboratory-confirmed COVID-19 diagnoses who were discharged during the study period from January 12, 2020 to May 15, 2020. Inclusion Criteria: (i) adults aged >19 years and (ii) hospitalization within 1 week after laboratory diagnosis for COVID-19.	Mild (n=3909) and moderate (n=288) severity
6	Jinmiao Lu, 2021 [19]	123	China	Retrospective multicenter comparative analysis	31	92	65:58:00	Median (IQR)= 8.66 (2.44, 11.90)	Median (IQR)= 8.85 (2.00, 11.60)	Lopinavir/ritonavir 12 mg/kg for 7-15 kg; 10 mg/kg for 15-40 kg; maximum dose 400/100 mg; twice a day, for at least five days	Standard symptomatic treatment	Mean nasopharyngeal swab negative time, time to hospital discharge, adverse drug reactions	all patients consecutively admitted to 13 hospitals in China with a diagnosis of mild COVID-19 from January 1, 2020, until June 1, 2020.	Mild severity (n= 123)
7	Etienne Meriglier, 2020 [20]	46	France	Observational Cohort Study	21	25	25:21:00	Median (IQR)= 68 (54–81)	Median (IQR)= 71 (61–80)	Hydroxychloroquine 200 mg, two tablets twice daily on day 1, then two tablets in the morning and one tablet in the evening if weight 60 kg from day 2 to 7; or one tablet in the morning and one in the evening if weight <60 kg plus lopinavir/ritonavir 200 mg/50 mg twice daily from day 1-7	Hydroxychloroquine 200 mg, two tablets twice daily on day 1, then two tablets in the morning and one tablet in the evening if weight 60 kg from day 2 to 7; or one tablet in the morning and one in the evening if weight <60 kg plus darunavir/ritonavir (800 mg/100 mg) once daily from days 1-7	Clinical evaluation, electrocardiogram changes before treatment and from days 1-7 and residual plasma levels of hydroxychloroquine, darunavir and lopinavir on days 3 and 7	Patients with confirmed COVID-19 infection; hospitalized with pneumonia and a need for oxygen support; or patients with at least one of the following risk factors for developing severe COVID-19: age >70 years, BMI >25 kg/m2, diabetes, chronic respiratory disease, any cardiovascular history, chronic kidney failure, Child cirrhosis B, HIV infection with CD4 <200 cells/mm3 and immunosuppressive treatment.	Moderate (n=46) severity

Table 1: Details of included studies and summary of findings.

Serial No.	Author, Year	COVID19 Diagnostic Criteria	Clinical Improvement Time in treatment group	Clinical Improvement Time in control group	Duration of hospitalization in treatment group (days)	Duration of hospitalization in control group (days)	Time to negative RT-PCR/NAT in treatment group (days)	Time to negative RT-PCR/NAT in control group (days)	Adverse Drug Reactions	Conclusion based on results
1	Ji-Won Kim, 2021 [14]	RT-PCR from nasopharyngeal/ oropharyngeal swabs and/or sputum	Median 18 days	Median 21 days	-	-	Median 21 days	Median 28 days	Lymphopenia, anemia, elevated liver function tests and bilirubin--detected more in lopinavir/ritonavir group but not clinically significant; ARDS in one patient in LPV/r group, and ARDS and shock in 2 patients in HCQ group	Lopinavir-ritonavir was associated with better outcomes in terms of viral clearance; clinical response was similar for LPV/r versus HCQ
2	Zhicheng Zhang, 2020 [15]	NAT by quantitative PCR	-	-	Median 17 days	Median 9 days	Median 12 days	Median 7 days	-	Efficacy of danoprevir was greater compared to LPV/r in terms of viral clearance defined by negative PCR as well as duration of hospital stay
3	Jian Qu, 2020 [16]	NAT	-	-	In Median (IQR): LPV/r alone= 12.00 (11.00–15.00); LPV/r + Interferon= 12.00 (10.00–13.50); LPV/r + Novaferon= 7.50 (5.00–10.00); LPV/r + interferon + arbidol= 19.50 (13.25–24.00); LPV/r + interferon + novaferon= 13.50 (11.50–17.00)	-	In Median (IQR): LPV/r alone= 9.00 (5.00–12.00); LPV/r + Interferon= 9.00 (7.25–11.00); LPV/r + Novaferon= 6.00 (4.00–8.00); LPV/r + interferon + arbidol= 14.00 (9.75–19.00); LPV/r + interferon + novaferon= 10.00 (8.00–11.25)	-	In n (%): LPV/r alone= 1 (4.8)% renal dysfunction, 1 (4.8%) secondary bacterial infection; LPV/r + Interferon= 1 (3.3%) renal dysfunction, 1 (3.3%) secondary bacterial infection; LPV/r + Novaferon= none; LPV/r + interferon + arbidol= 2 (10%) renal and 2 (10%) liver dysfunction, 1 (5%) secondary bacterial infection; LPV/r + interferon + novaferon= 2 (14.3%) liver dysfunction, 1 (7.1%) secondary bacterial infection; overall ICU stay in 10/97 participants	Combination of LPV/r with Novaferon has better efficacy in terms of shortening length of hospitalization and time to negative NAT; addition of arbidol or interferon did not confer any additional benefit
4	Marzieh Nojomi, 2020 [17]	RT-PCR or CT findings(s bilateral lung opacities and lobular and sub segmental areas of consolidation)	Median 3.1 days	Median 2.7 days	Median 9.6 days	Median 7.2 days	-	-	Nausea/vomiting in 8/100 participants overall; dizziness in 3/100 participants overall; need for intubation and invasive mechanical ventilation in 5/100 participants overall	Arbidol monotherapy is superior to KALETRA in terms of clinical and laboratory improvement, oxygen saturation improvement, duration of hospital stay, need for ICU admission and progression of CT findings
5	Min Joo Choi, 2020 [18]	RT-PCR	-	-	Median (IQR) = 23 (17–32) in the LPV/r-group' 23 (16–32) in the HCQ-group	Median (IQR)= 18 (12–25)	Median (IQR) = 23 (17–32) in the LPV/r-group' 23 (16–32) in the HCQ-group	Median (IQR)= 18 (12–25)	-	Similar viral shedding duration between HCQ and LPV/r groups; monotherapy did not show benefit compared to control after propensity score matching
6	Jinmiao Lu, 2021 [19]	RT-PCR on rhino-pharyngeal swab	-	-	Median (IQR)= 12.21 (10.00,14.00)	Median (IQR)= 8.05 (4.00,12.00)	Median (IQR)= 8.39 (4.50,12.00)	Median (IQR)= 4.34 (1.50,5.50)	16 cases of GI complications, mild and self-limiting: reported in 23 patients (69.6%) in treatment group	No benefit of lopinavir/ritonavir in reducing viral shedding time and total hospitalization duration.
7	Etienne Meriglier, 2020 [20]	RT-PCR on nasopharyngeal swab or typical CT findings	-	-	-	-	-	-	ECG abnormalities (17.4%) of participants; death in 4 participants	Combination of hydroxychloroquine with protease inhibitor and ritonavir is associated with ECG abnormalities especially in population >70 years old

Table 2: Outcomes associated with antiviral treatment

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