Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review Article

Clinical efficacy of antivirals against novel coronavirus (COVID-19): A review

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ABSTRACT

The unprecedented challenge faced by mankind due to emergence of coronavirus 2019 (COVID-19) pandemic has obligated researchers across the globe to develop effective medicine for prevention and treatment of this deadly infection. The aim of this review is to compile recently published research articles on anti-COVID 19 management with their benefits and risk to facilitate decision making of the practitioners and policy makers. Unfortunately, clinical outcomes reported for antivirals are not consistent. Initial favorable reports on lopinavir/ritonavir contradicted by recent studies. Ostalmovir has conflicting reports. Short term therapy of remdesivir claimed to be beneficial. Favipiravir demonstrated good recovery in some of the cases of COVID-19. Umifenovir (Arbidol) was associated with reduction in mortality in few studies. Overall, until now, U.S. Food and Drug administration issued only emergency use authorization to remdesivir for the treatment of suspected or laboratory-confirmed COVID-19 in adults and children hospitalized with severe disease.

Contents

Introduction

The global Coronavirus disease (COVID 19) is a viral respiratory disease caused by severe acute respiratory syndrome coronavirus (SARS-COVID-2) which emerged in China during December 2019 [1]. Subsequently, world health organization (WHO) declared COVID 19 as a pandemic in March 2020. As of July 12, 2020, COVID 19 affected more than 227 countries worldwide and caused more than 12.5 million confirmed cases and 561,617 deaths [2]. SARS-COV-2 has phylogenetic similarity with SARS-associated coronavirus (SARS-COV) and Middle East respiratory syndrome-related coronavirus (MERS-COV), which also caused by Coronavirus [3–5].

COVID 19 is highly contiguous disease that spread through air droplets. Moreover, it is associated with a wide spectrum of illness ranging from asymptomatic/mild illness (majority of cases) to severe respiratory failure that lead to intensive care units (ICU) admission [2]. Multiple serious complications caused by cytokine release syndrome leading to severe inflammatory response were associated with COVID 19 including; acute respiratory distress syndrome, acute kidney injury, acute liver injury and cardiovascular complications. Elderly individuals and people of all ages with underlying medical conditions, including chronic respiratory

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disease (moderate to severe asthma, COPD), serious heart disease, immunocompromised, severe obesity (body mass index [BMI] higher than 40) and liver disease are at a high risk to develop severe illness of COVID-19 [2–6].

Since the onset of COVID-19 outbreak, several clinical and in vitro trials were done for agents that may have efficacy to treat COVID-19. Till date, U.S. Food and Drugs Administration (FDA) approved only remdesivir for emergency use authorization (https://www.fda.gov/media/137564/download) for the treatment of suspected or laboratory-confirmed COVID-19 in adults and children hospitalized with severe disease. There is still dearth of directions for the use of drugs in several countries for the prevention or treatment of COVID-19 [5]. Infection prevention and control standards as well as supportive care according to each patient situation, including supplemental oxygen, anticoagulants, antipyretics and mechanical ventilatory support when indicated, are core of management for COVID-19 [2]. However, several agents are included in Infectious Diseases Society of America (IDSA) Management Guidelines for treatment of COVID-19 patients; including antimalaria (chloroquine, hydroxychloroquine), antivirals (lopinavir/ritonavir), antibacterial (azithromycin, and immunomodulators (Tocilizumab) based on their beneficial role reported by practicing physicians or small scale clinical trials. The efficacy of these agents is still controversial due to limited randomized clinical trials proving their efficacy [7].

In recent past, out of the all drug therapies explored for combating COVID-19, antivirals exhibited promising results. Some of them are tested due to their earlier beneficial role against other coronaviruses such as MERS- CoV & SARS-CoV, while, others have shown favorable outcomes in in-vitro preclinical studies. However, majority of these agents possess significantly high proportion of adverse consequences in patients. The most extensively used therapy in SARS and MERS patients was ribavirin, but reports of hemolysis and bradycardia in large number of patients reduced its rampant use. Other antivirals includes, lopinavir ritonavir, ribavirin, remdesivir, arbidol, Ostalmovir, Favipiravir [8,9]. The purpose of this review is to compile most recently published studies on the role of antivirals including anti-retrovirals and anti-influenzas in management of patients with COVID-19 and analyze their outcomes and possible threats to the recipients.

Methodology

A comprehensive search of PubMed, Google Scholar and science direct was performed for studies involving COVID-19 management with antivirals during January 2020 through 12th July 2020. Preprint trials also retrieved from the websites MedRxiv. Key words “COVID-19”, “SARS-COV-2”, “coronavirus 19” extracted more than 6 thousand trials. Additional keywords such as treatment”, “antiviral”, “protease inhibitors”, “lopinavir ritonavir”, “ribavirin”, Ŗemdesivir”, “arbidol”, Östalmovir”, “Favipiravir”, human studies, randomized controlled trials (RCT), prospective or retrospective cohort designs, case-control designs, case series and case report, with COVID-19 produced more than 300 trails. Finally, 28 trials that have date of publication, place of research, study style, antiviral name, dose, duration, route of administration, number of patients and safety and efficacy outcomes were included in this review. Safety outcomes include adverse events while the efficacy outcomes include mortality, clinical improvement and time to negative PCR inversion.

Discussion

Information given in this review article is emerging and rapidly undergoing changes due to the ongoing research and is subject of discussion among the practitioners and policy makers to take most appropriate timely decision to provide adequate health care services to the patients.

Among several agents explored for possible anti-COVID 19 potency, antivirals investigated to a very large extent. Twenty eight articles, some of them published and others are still in preprint form, included in this study covers most pertinent antivirals that may eventually become major therapeutic approach in managing this pandemic. However, there is paucity of adequately powered and fully reported RCTs evaluating effects of antivirals.

Lopinavir/ritonavir (LPV/RTN) is the most common reported antiviral in this review. Lopinavir is a Protease inhibitor used for treatment of HIV infection with ritonavir as a booster (Table 1) [39]. Protease is the key enzyme in CoV polypeptide processing and controlling coronavirus replication [40]. 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 [41]. Furthermore, in vitro study of LPV/RTN showed antiviral activity against SARS-CoV-2 with EC50 at 26.1 μM [42]. 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 [43]. 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 [11,17], 5 retrospective cohort trials [10,12,15,16,19] and 4 case series and case reports [13,14,18,20]. 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 numerically lower without significant difference. Hospital stay and duration of mechanical ventilation were not significantly different between both groups [17]. 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.

Additionally, adverse effects including mild gastrointestinal side effects (diarrhea, loss of appetite, nausea, vomiting) and increase in alanine transferase (ALT) [11,17,19,29,31,32] dampen its beneficial impact. Also, therapy was discontinued in some of the studies due to serious side effects including severe gastrointestinal side effects, hypokalemia, and self-limited skin eruptions in some of the reported studies [14,18,17].

Remdesivir (Table 2) is a prodrug of adenosine analogue which inhibits viral RNA-dependent RNA polymerase of broad spectrum of RNA viruses; including SARS-CoV and MERS. In vitro, Remdesivir has shown antiviral efficacy against COVID-19 in human airway epithelial cells and clinical as well as virologic efficacy in a non-human primate model [44,45].

Our results included 5 clinical trials for antiviral efficacy of Remdesivir for treating COVID-19 patients. Preliminary results of a randomized double-blind control trial including 1063 advanced COVID-19 patients (538 received remdesivir and 521 received placebo) demonstrated that Remdesivir decrease the recovery time compared to placebo. Furthermore, Remdesivir group had numerically (non-significantly) lower mortality than placebo group [22]. Based on this trial results, FDA authorized Remdesivir for emergency use for severe COVID-19 patients [46]. Consequently, remdesivir showed clinical improvement of 68% in case series of 53 severe COVID-19 patients [25]. However, there was no comparison group, so it’s not possible to know if the Remdesivir lead to this improvement. Another RCT for 397 severe COVID-19 patients com-

Table 1
Trials/studies involving lopinavir/ lopinavir + ritonavir.

Study type	Trial outcome and design	Conclusion	Comments
Case series [10]	• Out of 10 COVID patients, 09 received LPV and interferon α2b atomization inhalation and one only LPV.	Recovery of eosinophil count in patients on LPV were associated with improvement in viral load	Role of prior azithromycin in recovery is possible.
Case report [11]	Five patients received antibiotics (azithromycin) therapy before the antiviral course. Out of 10, 7 patients discharged and three patients stopped LPV due to intolerable adverse effects, two of them deteriorated and transferred to other hospital. COVID-19 patient (43 year-old), received oxygen inhalation, LPV/RTN, recombinant human interferon a1b and ribavirin. On 7th day, clinical symptoms improved significantly. Discharged on day 13 and antiviral therapy discontinued. Three days later, her nucleic acid test reversed to positive, and chest CT scan showed completely absorbed lesion. Restarted with aerosol inhalation of recombinant human interferon a1b. • 7 days later, showed clinical improvement and thereafter discharged.	After discontinuation of antiviral drugs in some patients, the residual virus causes the pulmonary lesions to re-aggravate, resulting in subsequent positive viral nucleic acid test results.	Study based on single case, confounders are possible.
Analysis of five cases [12]	Two of the five cases received LPV/RTN along with supportive care, whereas, three cases were given only supportive care. Oropharyngeal swabs and sputum samples obtained daily from all cases. Upon follow up (10 days), there was no significant difference between treatment and control group in duration of illness and PCR negative conversion.	LPV/RTN didn't reduce the duration of illness in patients with COVID 19.	Small sample size
Randomized, controlled, open-label trial [13]	99 patients received LPV/RTN, in addition to standard care (supportive management), and 100 were assigned to receive to standard care (supportive management), alone. Tested group required shorter time to clinical improvement by 1 day than standard care. No significant difference was showed in other parameters.	No benefit of LPV/RTN over the standard care in clinical improvement and mortality.	Good number of patients in both group make this study more reliable.
Case report [14]	A 54-year-old Korean confirmed COVID 19 man with mild respiratory illness and small lung consolidation received LPV/RTN. β-coronavirus viral loads significantly decreased and no or little coronavirus titers were observed in daily reports.	LPV/RTN showed improvement in clinical symptoms and reduction of viral loads.	It is possible that the decreased load of SARS-CoV-2 resulted from the natural course of the healing process rather than administration of LPV/RTN,or both.
Pilot retrospective study [15]	Of 73 cases COVID-19, 34 cases received LPV/RTN and 39 cases given LPV/RTN with arbidol (ARB); for at least 3 days. No significant difference in the end points of COVID-19 patients including cure rate, hospitalization time, rate and the time of virus turning negative between both arms.	Reduced median hospital stay in group with addition of ARB.	Only few severe cases enrolled in this study. Small sample size.
Exploratory double blind randomized controlled trial [16]	Of 86 mild/moderate COVID-19 patients, 34 randomly assigned (2:2:1) to receive LPV/RTN, 35 to ARB and 17 with no antiviral medication as control. LPV/RTN or ARB neither shorten the time of negative PCR conversion nor improve the symptoms of COVID-19 or pneumonia on lung CT. On day 7, LPV/RTN group showed higher deterioration from moderate to severe/critical clinical status compared with the other two groups.	LPV/RTN or ARB monotherapy present little benefit for improving the clinical outcome of patients hospitalized with mild/moderate COVID-19 over supportive care	Retrospective study. Small sample size Didn't include severe/ critical cases patients.
Retrospective study [17]	In addition to the conventional therapy (oxygen inhalation and interferon-α2b Injection to total 50 COVID cases, 34 of them received LPV/RTN and 16 were given ARB. None of the patients developed severe pneumonia or ARDS, with no significant difference in fever duration between both groups.	ARB monotherapy may be superior to LPV/RTN in treating COVID-19.	Didn't mention the severity of the patients. Retrospective data subject to confounding.
Retrospective observational study [18]	53 COVID-19 patients (45 with mild illness and 8 with severe illness). Among mild illness; 17 patients received ARB, 17 received ARB + LPV/RTN, and five received LPV/RTN.	Early administration of antiviral drugs can be considered. ARB may benefit patients with mild symptoms, while LPV/RTN may benefit those with severe symptoms. Prophylactic administration of common antibiotics may reduce the risk of co infection.	Didn't mention the doses of antiviral been used. Most of the patients received antiviral therapy, thus there is absence of any control.

Table 1 (*Continued*)

Study type	Trial outcome and design	Conclusion	Comments
	Whereas, among severe patients 4 were treated with LPV/RTN, three with ARB + LPV/RTN, and one with ARB. 29 patients treated with antibiotics (moxifloxacin, linezolid). All patients recovered and achieve negative SARS-COVID-2 PCR.		All patients with severe symptoms received antibiotics, it is possible that antibiotics are more potent than LPV/RTN.
Prospective cohort study [19]	47 patients with confirmed cases of COVID 19 enrolled, 42 patients received LPV/RTN + adjuvant drugs (Interferon aerosol inhalation, ARB, Methoxyphenamine, eucalyptol limonene along with moxifloxacin) and 5 patients received adjuvant therapy alone. All patients evaluated daily for body temperature, CBC, biochemistry and days of nCov-RNA turning negative after treatment. Both groups returned to the normal therapeutic temperature, but LPV/RTN group returned to the normal body temperature with shorter time compared with the control group.	The combination treatment of LPV/RTN and routine adjuvant medicine against pneumonia could produce much better efficacy on patients with COVID-19 infection compared to treatment with adjuvant medicine alone.	Only mild cases were included in this study. Small number of cases in control group
Retrospective cohort study [20]	Out of 33 patients, 16 treated with LPV/RTN + ARB and 17 given LPV/RTN. At 7 days, SARS-CoV-2 could not be detected in 12/16 (75%) in combination group and in 6/17 (35%) in monotherapy group and significant improvement in chest scan in combination group (11/16-69%) compared to monotherapy group (5/17(29%)). After 14 days, SARS-CoV-2 could not be detected in 15/16 (94%) of LPV/RTN + ARB and 9/17 (52·9%) LPV/RTN.	Addition of ARB to LPV/RTN has beneficial impact.	Retrospective analysis, thus increase the risk of unmeasured confounding bias. Small sample size.

pared the efficacy of 10 days versus 5 days remdesivir dose regimen. Results shows that shorter duration significantly improved clinical recovery, ≥2-points improvement in ordinal scale, and duration of hospitalization. Moreover, 5-day group had numerically higher discharged rate and less mortality compared to 10-day group, with no significant difference found.[21] On the other hand, a randomized controlled trial of 237 severe COVID-19 patients (158 received Remdesivir and 97 received placebo) showed that Remdesivir was not associated with statistically significant clinical benefits with a numerical reduction in time to clinical improvement in those treated earlier. However, this study was terminated earlier due to small sample size because the outbreak of COVID-19 brought under control in China [24].

Interestingly, shorter duration of remdesivir was associated with less adverse events compared to longer duration [21]. Most common adverse events reported including gastrointestinal side effects (nausea, constipation, diarrhea) as well as a graded elevation in ALT and AST. Hepatic toxicity of remdesivir lead to discontinue therapy in 10% of patients in one randomized control trial [24]. However, there is a need to evaluate the pharmacokinetics of remdesivir in hepatic and impairment patients. Thus, FDA recommend to not use remdesivir in patients with eGFR less than 30

Table 2
Trials/studies involving Remdesivir.

Study type	Trial outcome and design	Conclusion	Comments
Case report [21]	A case of 40 years old critically ill man tested positive for COVID-19 and treated with chloroquine along with supportive therapy for 5 days, until remdesivir could be supplied on day 9 of hospitalization (days 13 of symptoms onset). 60 h later, patient was extubated and clinically improved and progressed for discharge.	Late initiation of remdesivir may still be effective in treating COVID-19 patient.	Remdesivir can provide effective improvement in COVID-19 patients based on this case report, a larger randomized control trial needed to prove it.
Randomized, double-blind, placebo-controlled [22]	237 patients with severe COVID 19 enrolled and randomly assigned (2:1 ratio) to a 158 receiving remdesivir and 79 to placebo. Clinical improvement results showed no significant difference between both groups and numerically shorter time in remdesivir group among patients with symptom duration of 10 days or less Remdesivir group was associated with higher adverse events compared to control (102/155 (66%), 50/78 (64%); respectively) and was stopped early in 18 (12%) compared to four (5%) patients who stopped placebo.	No statistically significant benefit of remdesivir treatment noted, however, numerically, reduction in time to clinical improvement found in remdesivir group.	Many adverse events reported in remdesivir group also found in placebo, hence it could be disease induced or any other common component of standard care.
Open-label, Phase 3 randomized controlled trial [23]	1063 patient with COVID-19 randomized to either receive remdesivir or placebo for the duration of hospitalization, up to total 10 days. Data suggest that the Remdesivir group were 65% more likely to have clinical improvement at Day 11 (median time to recover of 11 days vs 15 days). Mortality rate was numerically lower in remdesivir group without significant difference (8% vs 11.6%, $p = 0.059$).	Remdesivir was better than placebo from the perspective of the primary endpoint, time to recovery, a metric often used in influenza trials.	Preliminary report of results, more details about the results needed to confirm the clinical efficacy and safety of remdesivir for treating COVID-19 patients.

Table 2 (*Continued*)

Study type	Trial outcome and design	Conclusion	Comments
Open-label, Phase 3 randomized controlled trial [24]	397 severe COVID-19 patients were randomized in a 1:1 ratio to receive remdesivir 200 mg IV on the first day, followed by remdesivir 100 mg IV each day in addition to standard of care to evaluate the efficacy and safety of 5-day (n = 200) or 10-day dosing duration. Preliminary results show higher efficacy outcomes at day-14 were found in patients with 5-day duration with no significant difference were noticed between both groups in clinical recovery (129 (65%) vs 106 (54%)) and death (16 (8%) vs 21 (11%), p value = 0.70). More number of patients with 10-day duration discontinued the medications due to serious side effects.	Patients receiving a 10-day treatment course of remdesivir achieved similar improvement in clinical status compared with those taking a 5-day treatment course.	Data provided recently confirms efficacy and better tolerability of 5 days treatment than 10 days.
Retrospective cohort study [25]	53 patients with severe COVID 19 received 10-day course of Remdesivir. At baseline, 30/53 (57%) were receiving mechanical ventilation and 4/53 (8%) were receiving extracorporeal membrane oxygenation and followed up for any clinical improvement. Day 18 of follow up, 36/53 (68%) had an improvement in oxygen-support, including 17 /30 (57%) who were on mechanical ventilation were extubated. A total of 25/53 (47%) were discharged, and 7/53 (13%) died (18% (6 out of 34 among patients receiving invasive ventilation).	Remdesivir showed clinical improvement in 36/53(68%) severe COVID-19 patients.	Remdesivir showed improvement in 68% of patients and high mortality also in 13% of the patient. Thus using remdesivir for treating COVID-19 patients is controversial and need a larger randomized control trial.

Table 3
Trials/studies involving Favipiravir.

Study type	Trial outcome and design	Conclusion	Comments
Exploratory Randomized, Controlled Trial [26]	29 COVID-19 confirmed cases were randomized (1:1:1) to either receive Favipiravir for 14 days or Baloxavir Marboxil (80 mg once a day orally on Day 1 and Day 4) or control group. All patients received existing antiviral treatment including lopinavir/ritonavir (400 mg/100 mg, bid, orally) or darunavir/cobicistat (800 mg/150 mg, qd, orally) and arbidol (200 mg, tid, po.). All of them used in combination with interferon-α inhalation. On day 14, PCR was undetectable in all control group and 77% and 70 % in Baloxavir and Favipiravir groups, respectively. Furthermore, there was no significant difference between all groups in clinical improvement. One patient in the baloxavir marboxil group, and two patients in the favipiravir group transferred to ICU within seven days after trial initiation. Among all 29 patients, there was no death.	Findings do not support that adding either baloxavir or favipiravir under the trial dosages to the existing standard treatment benefit COVID-19 patients.	Small sample size, non-blinded trial. Concurrent use of other antivirals leads to misinterpretation of results.
Prospective, randomized, controlled, open-label multicenter trial [27]	236 moderate/severe confirmed COVID-19 cases randomized; 116 to receive Favipiravir for 10 days and 120 to receive Umifenovir (Arbidol) for 10 days and all patients received conventional therapy. Upon results, clinical improvement at day 7 (primary end point), did not significantly different between two groups. Whereas, in post-hoc analysis for moderate COVID-19 patients showed a significant higher clinical improvement in the Arbidol group (62/111, 55.86%) compared to Favipiravir group (70/98, 71.43%). Favipiravir led to shorter latencies to relief for both pyrexia and cough. Whereas, no significant differences were found between both groups in the rate of auxiliary oxygen therapy (AOT) or noninvasive mechanical ventilation (NMV).	Favipiravir, compared to Arbidol, did not significantly improve the clinically recovery rate at Day 7. Favipiravir significantly improved the latency to relief for pyrexia and cough.	Number of severe and critically ill patients were more in favipiravir that undermine the benefit of Arbidol.
Case report [28]	Two case reports with confirmed COVID-19. First case was young healthy male mild COVID-19 who received supportive care only and showed that supportive care alone with a tendency to gradually improve fever reduction and oxygenation and negative PCR found in day 20 of illness. Whereas, the second case showed 60 years old man with hypertension and diabetes mellitus admitted with severe case of COVID-19 received supportive care with Favipiravir. Since starting the drug, temperature decreased and improvement in oxygenation and dietary intake noted.	In COVID-19 patient with hypoxemia, Favipiravir showed as promising effect. Whereas, in healthy young patients, spontaneous remission in illness was observed only with supportive care.	Results based on two cases, larger studies needed to confirm these results.

Table 3 (*Continued*)

Study type	Trial outcome and design	Conclusion	Comments
Case report [29]	40 years old healthy female with severe COVID-19 received Ciclesonide and Favipiravir. Additionally, positive mycoplasma antigen was positive, thus levofloxacin started upon admission for 6 days. Upon follow up, fever and oxygenation didn't worsen and improvement in chest Ct scan showed on day 6. Day 10 of hospitalization, patient discharged with improvement in symptoms and negative PCR.	The administration of Favipiravir and ciclesonide in early onset was considered to be effective in improving symptoms.	Results based on single case, larger studies needed to confirm these results.
An Open-Label Control Study [30]	80 confirmed **mild to moderate** severity cases of COVID-19 were assigned to receive either Favipiravir (n = 35) or Lopinavir /ritonavir (n = 55) (control group) for 14 days and both groups received interferon (IFN)-a by aerosol inhalation. FPV arm showed preferable outcomes compared to control arm, including shorter viral clearance (4 (2.5–9) d *vs* 11 (8–13) d, $P < 0.001$) and significant improvement in chest imaging (improvement rate of 91.43% *vs* 62.22%, $P = 0.004$).	Favipiravir showed significantly better treatment effects on COVID-19 in terms of disease progression and viral clearance.	Only mild to moderate cases were included in the study.

Table 4
Trials/studies involving Umifenovir (Arbidol).

Study type	Trial outcome and design	Conclusion	Comments
Retrospective Multicenter Cohort Study [31]	141 non-advanced COVID-19 cases were included. 70 patients received IFN-α2b and 71 of them received Arbidol + IFN-α2b. All patients received appropriate supportive care as indicated. Upon results, there were no significant differences between both groups in hospitalization time. Subsequently, combination therapy group had numerically shorter time in PCR negative conversion without significant difference (23.8 days vs 27.4 days, respectively; P = 0.057).	Arbidol in combination with IFN-α2b has no significant effect in COVID-19 RNA clearance and hospitalization than IFN-α2b monotherapy.	Retrospective study which increase the risk for confounding factors. Severe and critically ill cases were not included in this study.
Retrospective Study [32]	Out of 81 COVID-19 patients included in the study, 45 received Umifenovir group, 18% received it for 5 days and 82% for 7–10 days and 36 in control group. Umifenovir group was found to have longer time in PCR negative conversion than control group (6 days vs 3 days, $p < 0.05$) and significantly had longer hospital stay (13 day vs 11 day, $p < 0.05$). No severe side effect found in umifenovir treatment.	Umifenovir treatment did not shorten the negativity time of SARS-CoV-2, or the length of hospital stay in non-ICU hospitalized patients with COVID-19.	Since Umifenovir showed lower recovery, it is vital to know control group treatment for correct interpretation.
Retrospective cohort study [33]	Of 27 patients, 10 received chloroquine phosphate, 11 received arbidol and 6 given lopinavir/ritonavir, for 10 days. As for the primary outcome, median viral shedding interval were shorter in Chloroquine (5.0 days, p = 0.003) and arbidol groups (8.0 days, p = 0.008). At 10 days, negative conversion of RT-PCR was higher in Chloroquine (9 patients, p = 0.001) and arbidol groups (8 patients p = 0.009) and no patient in lopinavir/ritonavir. Additionally, in 14 days, RT-PCR was found negative in all chloroquine and arbidol groups, while only 3 patients in lopinavir/ritonavir group. In secondary outcomes, length of hospitalization was significantly shorter in chloroquine and arbidol groups than lopinavir/ritonavir group (9.3 ± 1.8 days, 11.7 ± 3.7 days and 19.7 ± 4.4 days; respectively, p < 0.01) without significant difference between chloroquine and arbidol groups. Adverse events were not significantly difference between all three groups.	chloroquine and arbidol (Umifenovir) could not only shorten the viral shedding interval, but also decreased the hospitalization duration and hospitalization expenses of non-severe, COVID-19 patients.	Only non-severe cases included. Arbidol showed promising result. Small sample size. Retrospective study which increase the risk for confounding factors.
Retrospective, cohort study [34]	504 COVID-19 patients from three hospitals were included, Arbidol prescribed to 257 patients (51.0%); Oseltamivir prescribed to 66 patients (13.1%); and 259 given lopinavir/Ritonavir (51.4%). Overall mortality rate was 15.7% and arbidol shows to reduce mortality by 77% compared other groups (7% vs 24.7%). However, after adjusting age, sex, admission data and lesion size, all three antivirals showed reduction in mortality; by 93% in arbidol group (95% CI, 0.071 to 0.398), by 80% in Oseltamivir group (95% CI, 0.072 to 0.623) and by 64% in Lopinavir/Ritonavir (95% CI, 0.165 to 0.795).	Arbidol is able to substantially associated with a reduction in mortality among hospitalized COVID-19 patients.	The study is still under peer review. Retrospective analyzing patients, risk of confounding bias. Small sample size.

Table 4 (*Continued*)

Study type	Trial outcome and design	Conclusion	Comments
	Similarly, Arbidol is also associated with faster lesion absorption by 85.20% (P = 0.0203) after adjusting for patient's characteristics as well as Oseltamivir and Lopinavir/Ritonavir use.		
Retrospective cohort study [35]	280 confirmed COVID-19 cases were retrospectively analyzed including wide spectrum of illness ranging from asymptomatic (17), mild (22), moderate(199), serious(40), to critical (6) cases; including 36% patients with comorbidities Among them, 121 (43.2%) patient didn't receive antiviral. Whereas the other 159 patients received different antiviral regimens including chloroquine (n = 17), ostalmovir (n = 13), arbidol (n = 37), chloroquine + arbidol (n = 5), lopinavir/ritonavir (n = 60), lopinavir/ritonavir + Arbidol(n = 16), and oseltamivir + Arbidol (n = 11). Among all patients, viral RNA was cleared in 89% of the COVID-19 patients within 21 days after illness onset. However, usage of antiviral (as combination or as monotherapy) did not improve the clearance of viral RNA compared to those did not receive antiviral drugs. Whereas lopinavir/ritonavir delayed viral RNA clearance (HR; 0·62,95% CI (0·41–0·94), even after adjusting confounding variables.	The use of antiviral drugs (chloroquine, oseltamivir, arbidol, and lopinavir/ritonavir) did not improve viral RNA clearance.	Did not report the full dosage of antivirals. Preprint trial and not peer reviewed yet
Retrospective Cohort Study [36]	49 COVID 19 case were assigned to the empirical regimens supplemented with Arbidol group (group A + ER), and 62 patients were assigned to the empirical regimens group (group ER). Empirical regimen includes Interferon-α, lopinavir/ritonavir, favipiravir, Ribavirin, Darunavir/cobicistat (36 in group ER and 39 in group A + ER). Upon results, group A + ER had significantly higher virologic conversion comparing to group ER (59.2% vs 40.3%; P = 0.048) and numerically rate of stable virologic conversion without significant difference (2.46.9% vs. 30.6%, P = 0.079). Additionally, rate of radiologic recovery was higher in group A + ER compared to group ER (55.1% vs 32.2%, P = 0.016) and oxygen therapy was relatively fewer in group A + ER than in group ER (6.1% vs. 29%, P = 0.002.	Arbidol could accelerate and enhance the process of viral clearance, improve focal absorption on radiologic images, and reduce the demand for HFNC oxygen therapy in hospitalization.	Multiple antiviral medications used concurrently that makes interpretation a bit difficulty for specific antiviral. However, addition of arbidol was beneficial. This article is not peer reviewed yet.

mL/min or patients with hepatic impairment unless the potential benefit outweighs the potential risk [47].

Favipiravir (Table 3) is an RNA-dependent RNA polymerase inhibitor with antiviral activity against wide verities of RNA viruses [48]. In vitro, favipiravir showed antiviral efficacy at high concentration (EC50 = 61.88 μM) [49]. Whereas, in another study favipiravir showed antiviral property against SARS CoV-2 by less than 50% at concentrations up to 100 μM in vitro and achieved much lower concentration clinically (21 μM) in patients who received Favipiravir (first dose was 1600 mg or 2200 mg orally, followed by 600 mg each time TID) [26].

Five clinical trials for the efficacy of favipiravir are included in this study. One open labeled control study had mild/moderate and severity COVID-19 patients, where comparison made between efficacies of favipiravir vs lopinavir/ritonavir. Favipiravir group showed significant clinical outcomes including shorter viral clearance and improvement in chest imaging. However, due to small sample size, open labeled design, clinical decision making is difficult. On the other hand, two randomized clinical trials failed to prove the efficacy of favipiravir against COVID-19 [26.27]. Moreover, two case reports showed efficacy of favipiravir against COVID-19 that is not sufficient for medical practitioner to make prescription of favipiravir. More clinical trials are still continuing for the efficacy of favipiravir against COVID-19 infection [50].

Generally, favipiravir was well tolerated in all 5 trials. However, diarrhea, liver toxicity, hyperuricemia were reported in some patients [27,30]. Safety of favipiravir still under investigation, thus its safety in liver and renal impairment still unknown.

Umifenovir (Arbidol) (Table 4) is an indole derivative antiviral therapy approved in China and Russia for treatment of influenza A and B virus and shows activity against verities of enveloped and non-enveloped viruses [51]. In vitro, Arbidol shows effective antiviral activity against SARS COV-2 [52,53].

Totally 9 clinical trials involving arbidol were included in this article [12,15,19,31–36]. In retrospective cohort study for 504 patients, Arbidol was associated with reduction in mortality and faster lesion absorption compared to Ostalmovir and lopinavir groups [34]. In another retrospective cohort study, arbidol was associated with higher negative PCR conversion rate, shorter viral shedding time and hospitalization stay compared with lopinavir [33]. Consequently, addition of Arbidol to lopinavir were associated with positive outcomes in oxygen demand, viral shedding, clinical improvement, and reducing oxygen demand [19,36]. Another cohort study showed superiority of Arbidol therapy over lopinavir in terms of viral shedding [12]. On the other hand, 3 retrospective cohort studies failed to prove the antiviral efficacy of Arbidol against COVID-19 infection [31,32,35]. However, all trials included have small sample size and retrospective data analysis that may possess increase risk for confounding variables. A need for good powered randomized control trial needed to confirm the results.

Umifenovir was well tolerated and associated with mild gastrointestinal adverse events in some patients (including nausea,

Table 5
Trials/studies involving Ostalmovir.

Study type	Trial outcome and design	Conclusion	Comments
Case series [37]	Out of 115 COVID-19 confirmed case, 5 patients found co-infected with influenza virus and followed up. All patients received antiviral therapy (including Ostalmovir), antibacterial, and supportive therapy (when indicated). None of the patients taken to intensive care unit recovered and discharged from hospital with no death.	Patient with both COVID-19 and influenza virus co-infection did not appear to show a more severe condition.	Small sized case series. Multiple therapies used, thus cannot confirmed the efficacy of Ostalmovir against COVID-19.
Descriptive study [38]	Of 99 COVID-19 cases admitted to the hospital. 76% received antivirals (including Ostalmovir, ganciclovir, and lopinavir/ritonavir tablets. The duration of antiviral treatment was 3–14 days. While 70% of them treated with antibiotics. Upon results, 58% of patients remained hospitalized, 31% discharged, and 11% had died.	The infection of 2019-nCoV was of clustering onset, is more likely to infect older men with comorbidities, and can result in severe and even fatal respiratory diseases such as ARDS.	Retrospective case series with small sample size not enough to support clinical decision.

diarrhea, stomachache) as well as mild to moderate elevation in ALT and one case reported bradycardia [11,12,31,32,36].

Ostalmovir (Table 5) is a Neuraminidase inhibitor with activity against influenzas viruses. There is no data for in-vitro activity of Ostalmovir against coronaviruses. In retrospective study of 99 COVID-19 patients using antiviral therapy including Ostalmovir showed 31% of them only discharged and 11% of them died [37]. Another case series study for COVID-19 patients' coinfection with influenzae virus found in 5 cases out of 115 patients. All patients were discharged with no death or ICU admission. However, due to co-administration of other therapies including antibiotics, corticosteroids and other antivirals, results cannot confirm the effectiveness of Ostalmovir [38].

Conclusion

The COVID-19 pandemic present the greatest challenge to medical scientist. The scientist across the globe are working tirelessly to develop anti-COVID-19 therapy at the earliest possible date. Till date, several drugs have shown promising results. Among antivirals trials screened in the literature, remdesivir and arbidol demonstrated significant clinical improvement in several studies. However, the outcomes have to be refined with larger trails.

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Competing interests

None declared.

Ethical approval

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