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Effectiveness of Antiviral Therapies in COVID-19 Management

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ABSTRACT

Currently, there is not any specific effective antiviral treatment for COVID-19. Although most of the COVID-19 patients have mild or moderate courses, up to 5%–10% can have severe, potentially life threatening course, there is an urgent need for effective drugs. Optimized supportive care remains the mainstay of therapy. The purpose of this study was to review current evidence obtained from on the efficacy of antiviral for COVID-19 treatment. According to the reviewed articles it was found that antiviral drugs such as HCQ and CQ , LPV/r , Favipiravir, Remdesivir, Umifenovir, Oseltamivir have been used in the patients with Covid-19. Initial favorable reports on Remdesivir which is recommended as an effective antiviral treatment for COVID-19, as it reduces recovery time and mortality. Additionally, Favipiravir shows promise in reducing viral clearance time and improving clinical recovery.

Keywords: corona virus disease 2019, Hydroxychloroquine and Chloroquine, Lopinavir/ritonavir

INTRODUCTION

The global Corona virus disease (COVID 19) is a viral respiratory disease caused by severe acute respiratory syndrome corona virus 2(SARS-COVID-2) which emerged in China during December 2019. Subsequently, world health organization (WHO) declared COVID 19 as a pandemic in March 2020. 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[5].

Currently, there is not any specific effective antiviral treatment for COVID-19. At the moment, it is strongly recommended that patients be recruited into ongoing trials, which would provide much-needed evidence on the efficacy and safety of various therapies. Unless used in the context of randomized clinical trials, antiviral will not be proved to be efficacious or safe for the treatment of COVID-19.Combined usage of antiviral drugs for COVID-19 patients should be considered in the light of current knowledge and case by case; adverse drug reactions and drug-drug interactions should always be regarded. [1]

1. Hydroxychloroquine and Chloroquine

Chloroquine (CQ) and hydroxychloroquine (HCQ) are aminoquinolines, which have been used to treat malaria and autoimmune diseases for over 50 years.[1] Hydroxychloroquine acts on immune response through the interference with the macrophage antigen processing, and T-cells response, and in in vitro studies, hydroxychloroquine has been found to prevent the viral entry into the cells by inhibiting its binding with the ACE-2 receptor[3]. Chloroquine analogs are weak diprotic bases (can accept more two protons) and they can penetrate and concentrate within acidic organelles such as endosomes and lysosomes which leads to elevated intra-vesicular pH resulting in prevention of endosome trafficking and prevents viral fusion into the cell. This mechanism has translated to the potential role of these drugs in the treatment of COVID-19. Additionally, studies also revealed that these drugs interferes with the glycosylation of ACE-2 receptor which prevents SARS-CoV-2 receptor binding [1] An early report from China suggested that chloroquine usage was associated with reduced progression of the disease and decreased duration of symptoms[1].

Chloroquine phosphate and hydroxychloroquine were reported in this review and showed favorable outcomes in the recovery of patients with COVID-19. These two medications are likely to share the same mechanism of action. Chloroquine, an anti-malarial, has shown positive outcomes in patients with COVID-19. French open label, non- randomized clinical trial was promising and the first clinical trial of these medications in patients with COVID-19. The effect of hydroxychloroquine was significant because it

showed a reduction in the viral load compared with the control group.[7] There is also insufficient data to support this suggestion and these agents should not be used as prophylactic agents for SARS-CoV-2 except in the context of a clinical trial.

Limitation: The use of CQ or HCQ is included in COVID-19 treatment guidelines all over the world but data supporting this is quite scare. Other published clinical data on either of these agents are limited and have methodologic problems.There are insufficient data thus far to know whether HCQ or CQ has a role either in the treatment or in the prophylaxis of COVID-19. Beside anti-malarial drugs can cause ventricular arrhythmias, QT prolongation, and other cardiac toxicity, which may pose a particular risk to critically ill persons[1].

2. Lopinavir/ritonavir (LPV/r)

Lopinavir is a protease inhibitor used to treat HIV infection, with ritonavir as a booster[1]. It increase the plasma half-life by inhibiting cytochrome P450[4]. Most in vitro studies have shown that SARS- CoV could be inhibited by lopinavir and that the EC50 of lopinavir is acceptable. Lopinavir showed an antiviral effect against SARS-CoV-2 virus in Vero E6 cells with the estimated EC50 at 26.63 μM[1]. In the beginning of the pandemic, lopinavir/ritonavir was applied for the treatment of COVID-19 and showed promising results. In a clinical trial involving 47 patients with severe COVID-19 in China, the clinical effect in patients was accelerated elimination of the virus. Yet, further studies demonstrated the absence of clinical benefits. The RECOVERY trial was an open-label, platform trial conducted between March 19, 2020 and June 29, 2020 among 176 hospitals in the United Kingdom (UK). Patients were randomized to either standard of care alone or standard of care plus oral LPV/r for 10 days or until discharge. The primary outcome was 28-day all-cause mortality, which did not significantly difference between the intervention and control groups (rate ratio [RR] 1.03, 95% CI 0.91–1.17; P=0.60), and the results were consistent among all pre-specified subgroups. There was also no difference in the time until discharge alive or proportion of patients discharged alive within 28 days (RR 0.98, 95% CI 0.91–1.05; P=0.53).

In a study of 47 patients with COVID-19; compared with the standard of care (arbidol plus IFN-α inhaler) (SOC) (5 patients), the combination treatment with LPV/r plus SOC (42 patients) has resulted in a shorter time (test group: 4.8 ± 1.94 days vs. control group: 7.3 ± 1.53 days, P = 0.0364) to return normal body temperature and to be negative for SARS-CoV-2 test in clinical samples (7.8 ± 3.09 days vs. 12.0 ± 0.82 days, P = 0.0219)[1].Nine RCTs included LPV/r for COVID-19 therapy: two large trials (RECOVERY and TOGETHER), and seven relatively smaller trials (n=86–664). The trial conducted by Solaymani-Dodaran et al. compared LPV/r to favipiravir and found no significant differences. The TOGETHER trial was conducted between June 2, 2020 and September 20, 2020 in Brazil . The trial compared LPV/r to HCQ or placebo. The trial was discontinued early after finding no significant difference between the groups in COVID-19-associated hospitalization (LPV/r: HR, 1.16 [95% CI, 0.53–2.56]) or viral clearance at day 14 (LPV/r: odds ratio [OR], 1.04 [95% CI, 0.94–1.16]).

Nojomi et al. investigated the efficacy of umifenovir compared to LPV/r in COVID-19 patients. The patients were randomized to receive umifenovir or LPV/r for 7–14 days, based on disease severity, as well as HCQ on day 1. Patients that received umifenovir had a shorter duration of hospitalization (7.2 days) compared to patients that received LPV/r (9.6 days, P=0.02)[4].

3. Favipiravir

Favipiravir (T-705; 6-fluoro-3-hydroxy-2- pyrazinecarboxamide) is an antiviral agent that selectively and potently inhibits the RNA-dependent RNA polymerase (RdRp) of RNA viruses[1]. It is a purine analog that inhibits viral RNA-dependent RNA polymerase, blocking viral genome replication and transcription. Zhao et.al. conducted a multicentric open-label trial that compared favipiravir with a control group. Patients were randomly assigned to receive favipiravir treatments other than favipiravir, chosen at the discretion of the treating physician. Patients treated with favipiravir had a significantly shorter median time to positive-to-negative RT-PCR SARS-CoV-2 test conversion (17 days) compared to the control group (26 days; hazard ratio [HR]: 2.1 [95% confidence interval [CI] 1.1–4.0, p=0.038). The trial ended after 30 days, at which time the favipiravir group had a significantly higher incidence of conversion to negative RT-PCR tests (80.6%) compared to the control group (52.6% , p=0.030). Mortality did not occur in either group within the 30-day study period[4].

In a randomized, open-label trial of 236 patients, 116 allocated to favipiravir and 120 to umifenovir (another antiviral drug), the efficacy of favipiravir did not difference significantly from controls (p: 0.139)[3]. 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[5]. Chen et al. compared favipiravir with umifenovir in COVID-19 patients in a multicentric, open-label trial. Te primary outcome was rate of clinical recovery at day 7. Secondary outcomes were all-cause mortality, dyspnea, respiratory failure, auxiliary oxygen therapy or noninvasive mechanical ventilation (NMV), latency to pyrexia and cough relief, and need for intensive care.

While no differences were found in clinical recovery (favipiravir 61.2% ; umifenovir 51.7% ; P=0.1396) or in most secondary outcomes between treatments, favipiravir did shorten the latency of pyrexia and cough relief.

Dabbous et al. conducted a multicentric trial comparing favipiravir and chloroquine (CQ) in patients with confirmed cases of COVID-19 . There were no significant differences between the groups in mortality (p=1.00), duration of hospital stay (p=0.060), mechanical ventilation (p=0.118), or oxygen saturation (p=0.129). Bosaeed et al. also compared favipiravir (10 days) and HCQ . Nearly half of the favipiravir group discontinued therapy before the end of the trial due to pill burden or personal preference. This study found no significant difference in conversion to negative RT-PCR tests (p=0.73), time to clinical improvement (p=0.29), duration of hospital stay (p=0.42), 28-day mortality (p=0.45), and 90-day mortality (p=0.91). Solaymani-Dodaran et al. conducted a multicentric, open-label trial to compare favipiravir (in addition to HCQ) to LPV/r [44]. They found no significant differences between the groups for mortality (p=0.52), transfer to the ICU (p=0.47), time to clinical recovery (p=0.54), incidence of clinical recovery (HR: 0.94 [95% CI 0.75–1.17]), or change in oxygen saturation (p=0.46)[3].

4. Remdesivir

Remdesivir is a prodrug of a nucleotide analog[1]. Remdesivir is an analogue of adenosine, incorporating in the genomic RNA chain of the virus during its replication, which eventually leads to the so-called "breakage" of the synthesized chain, and as a consequence, to disruption of the reproduction process of the virus[8]. Remdesivir has broad-spectrum activity against members of several virus families, including filoviruses (e.g., Ebola) and corona viruses [e.g., SARSCoV and Middle East respiratory syndrome corona virus (MERSCoV)] and has shown prophylactic and therapeutic efficacy in nonclinical models of these corona viruses. Treatment with intravenous remdesivir showed significant improvement for the first COVID-19 case in US and then a trial has been initiated quickly to assess the efficacy and safety of remdesivir in patients hospitalized with 2019-nCoV infection.

In a cohort of patients hospitalized for severe Covid-19 who were treated with compassionate use remdesivir, clinical improvement was observed in 36 of 53 patients (68%) . As there was no placebo or active comparator in this study, it is hard to draw any concrete conclusions and measurement of efficacy will require results of ongoing randomized, placebo-controlled trials of remdesivir therapy.[1]

In a recent open-label, randomized trial , 312 patients receiving remdesivir added to the SOC for 5 or 10 days were compared with 818 matched controls treated with SOC therapy. The recovery rate was significantly higher in the remdesivir arm compared with controls (74.4% vs 59%; adjusted OR: 2.03; 95% CI 1.34–3.08; p =0.001). Data on safety were not available[3].

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. Based on this trial results, FDA authorized Remdesivir for emergency use for severe COVID-19 patients . Consequently, remdesivir showed clinical improvement of 68% in case series of 53 severe COVID-19 patients Interestingly, shorter duration of remdesivir was associated with less adverse events compared to longer duration . 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[5].

5. Umifenovir(Arbidol)

It 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 . In vitro, Arbidol shows effective antiviral activity against SARS COV-2 . Totally 9 clinical trials involving arbidol were included in this article. In retrospective cohort study for 504 patients, Arbidol was associated with reduction in mortality and faster lesion absorption compared to Ostalmovir and lopinavir groups. In another retrospective cohort study, arbidol was associated with higher negative PCR conversion rate, shorter viral shedding time and hospitalization stay compared with lopinavir . Consequently, addition of Arbidol to lopinavir were associated with positive outcomes in oxygen demand, viral shedding, clinical improvement, and reducing oxygen demand . Another cohort study showed superiority of Arbidol therapy over lopinavir in terms of viral shedding . On the other hand, 3 retrospective cohort studies failed to prove the antiviral efficacy of Arbidol against COVID-19 infection . 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[5]. Arbidol hydrochloride is used in Russia and China, but has not yet been approved for use in other countries. However, no conclusive evidence of its efficacy in patients with COVID-19 was reported. In this review, it was reported together with favipiravir, which was approved for the treatment of novel influenza on 15th February 2020 in China[7].

6. Oseltamivir

Oseltamivir (Table 5) is a Neuraminidase inhibitor with activity against influenzas viruses. There is no data for in-vitro activity of Oseltamivir against corona viruses. In retrospective study of 99 COVID-19 patients using antiviral therapy including Oseltamivir showed 31% of them only discharged and 11% of them died. 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 Oseltamivir [5]. A retrospective observational study reported the use of oseltamivir in 1099 patients with COVID-19; however, the study was not able to provide any solid data on the effectiveness of oseltamivir in the prevention or treatment of COVID-19. Study limitations included incomplete documentation of patient data and recall bias [7].

TABLE 1 Antivirals investigated for the treatment of COVID-19 in clinical trials[1]

Group	Drugs	Mechanism of action	Dosing
Inhibitors of viral RNA polymerase /RNA synthesis	Remdesivir (GS-5734)	Adenosine nucleotide analogue, prodrug, RdRp inhibitor	Day 1: 200mg, IV Day 2–5 (or 10): 100 mg/day, IV
	Favipiravir	Guanosinenucleotid analogue, prodrug, RdRp inhibitor	Day 1: 2X1600 mg Day 2–7 (or 10): 2 × 600 mg/day
Inhibitors of viral protein synthesis	Lopinavir/ritonavir	Protease inhibitor	Day 1–10 (or14): 400mg/100mg × 2/day, orally
Viral entry inhibitors	Hydroxychloroquine	Increasing endosomal pH required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV (ACE-2)	Day 1–5: 2 × 200 mg/day, orally
	Chloroquine		Day 1–5 (or 10): 2 × 500 mg/day, orally

CONCLUSION

Ongoing clinical trial for new antiviral drugs indicate that the effectiveness of Antiviral therapy for Covid-19 depends on several factors including the timing of treatment relative to symptom onset. According to the reviewed articles it was found that antiviral drugs such as Hydroxychloroquine and Chloroquine, Lopinavir/ritonavir, Favipiravir, Remdesivir, Umifenovir, Oseltamivir have been used in the patients with Covid-19.

Chloroquine (CQ) and hydroxychloroquine (HCQ) have shown potential in treating COVID-19, but further research is needed to confirm their efficacy and safety. Their use as prophylactic agents is not supported by current data. Lopinavir/ritonavir is not an effective treatment for COVID-19. Despite initial promising results, larger clinical trials have shown no significant benefit in reducing mortality, hospitalization, or viral clearance on the other hand Favipiravir may have some benefits in treating COVID-19, such as shortening the time to viral clearance and improving clinical recovery, but the evidence is not conclusive. More research is needed to fully understand its efficacy and optimal use in treating COVID-19.

Remdesivir is an effective antiviral treatment for COVID-19, with clinical trials demonstrating its ability to reduce recovery time, improve recovery rates, and lower mortality. While it has some adverse effects, such as gastrointestinal side effects and hepatic toxicity, the benefits of remdesivir in treating severe COVID-19 patients outweigh the risks. Arbidol may have potential as an antiviral treatment for COVID-19, but the current evidence is inconclusive and limited by small sample sizes and retrospective data analysis. Well-powered randomized controlled trials are needed to confirm its efficacy and safety. There is insufficient evidence to support the effectiveness of Ostalmovir (Oseltamivir) in treating or preventing COVID-19. Its use in COVID-19 patients may be due to co-infection with influenza, but more research is needed to determine its efficacy and safety in this context.

Overall context suggests that Remdesivir is recommended as an effective antiviral treatment for COVID-19, as it reduces recovery time and mortality. Additionally, Favipiravir shows promise in reducing viral clearance time and improving clinical recovery.

LIMITATION

The review highlights significant limitations in the evidence for various antiviral drugs, including small sample sizes and retrospective data analysis for Arbidol, which showed mixed results, lack of randomized controlled trials for Hydroxychloroquine and Chloroquine, which had uncertain efficacy, insufficient data for Oseltamivir, which had limited effectiveness, variable results for Lopinavir/Ritonavir, which showed no significant benefit in some trials, Favipiravir, which had inconsistent outcomes, and Remdesivir, which demonstrated promising results but requires further confirmation, emphasizing the need for well-designed, large-scale randomized controlled trials to establish the efficacy and safety of these drugs for COVID-19 treatment.

CONFLICT OF INTEREST

The Authors declare no competing interests.

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