CURRENT THERAPEUTIC OPTIONS FOR CORONAVIRUS DISEASE-2019 – A PHARMACOLOGICAL REVIEW

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ABSTRACT

Objectives: Coronavirus pandemic is currently a global public health emergency. With expanding knowledge of the virus and the disease, new therapeutic targets are emerging widely. There is limited evidence about the use of different treatment options in coronavirus disease-2019 (COVID-19). This review aims to summarize the available evidence regarding therapeutic options in treating coronavirus infection.

Methods: We searched PubMed, Google Scholar, and Cochrane library using pre-specified Medical Subject Headings terms about the role of therapeutic options in COVID-19 patients.

Results: The majority of the published evidence is either case reports or small observational studies. Antimalarial like hydroxychloroquine reported equivocal results with five studies got positive results and five without any added benefit compared with standard of care. Lopinavir/ritonavir monotherapy does not show any significant role except in combination with other antiviral drugs but encouraging results are emerging with remdesivir. Studies with favipiravir are inconclusive with some exhibit benefit and others not. Limited case series have shown that tocilizumab and convalescent plasma to be useful as adjuvant therapy in critically ill patients.

Conclusion: There is currently no strong evidence for the efficacy of different therapeutic agents in the treatment of COVID-19. More data from ongoing and future trials will add more insight into the role of various drugs.

Keywords: Coronavirus disease-2019, Severe acute respiratory syndrome-coronavirus-2, Coronavirus, Drug treatment.

INTRODUCTION

We all came across firstly a severe acute respiratory syndrome (SARS)-like flu or influenza spreading across China in numbers, which was monumental. What started from a wet market from Wuhan China, soon spread across physical and geopolitical boundaries reaching far-flung countries and taking its toll. What is more terrifying is that we are still whipped both materialistically and scientifically to combat this pandemic. As per the WHO coronavirus situation reports on May 10, globally there are 4,179,479 confirmed cases of coronavirus disease-2019 (COVID-19) and 287,525 deaths [1]. In India, the toll remains as 74,281 confirmed cases and 2415 deaths so far [1].

Scientists identified 2019 novel coronavirus (2019-nCoV) in samples of bronchoalveolar lavage fluid from a patient in Wuhan. The WHO named the disease officially as COVID-19 on February 11, 2020. COVID-19 characterized by respiratory syndrome with a variable degree of severity, ranging from a mild upper respiratory tract illness to severe interstitial pneumonia and acute respiratory distress syndrome (ARDS) [2,3]. 2019-nCoV (also called SARS-CoV-2) is a single-stranded RNA virus coming under the same genus beta coronavirus as SARS coronavirus 1 (SARS-CoV-1) and Middle East respiratory syndrome coronavirus (MERS-CoV) [4]. SARS-CoV-2 binds angiotensin-converting enzyme 2 (ACE2), which is an ectoenzyme anchored to the plasma membrane of the cells of several tissues like respiratory cells. SARS-induced down-regulation of ACE2 receptors in lung epithelium contributes to the pathogenesis of acute lung injury and subsequent ARDS.

There is no specific antiviral treatment recommended for COVID-19, and no vaccine is currently available. The treatment is symptomatic, and oxygen therapy represents the major treatment intervention for patients with severe infection. Mechanical ventilation, high-flow nasal oxygen or non-invasive ventilation, and extracorporeal membrane oxygenation (ECMO) are among other strategies, which vary on case to case. There have been few studies on coronaviruses and the effective antiviral therapies that the world at large is ignorant and at an emergent time to scuttle all the available research to battle up on coronavirus.

With expanding knowledge of the virus and the disease, new therapeutic targets are emerging day by day. However, so far, published evidence is less. Many clinical trials are also ongoing worldwide. In this review, we tried to combine all the available evidence in literature and researches to get an overall knowledge of the current therapeutic options for COVID-19.

METHODS

We prepared a study protocol and predefined the data sources, search strategy, study eligibility criteria, and data extraction of the studies.

Data sources and search strategies

We searched for clinical studies providing data on the efficacy of different therapeutic agents COVID-19 infection, restricting the search to English articles. We searched PubMed, Google Scholar, and Cochrane library using the Medical Subject Headings terms: "Chloroquine (CQ)," "Hydroxychloroquine (HCQ)," "Lopinavir," "Ritonavir," "Remdesivir," "Favipiravir (FPV)" “immunoglobulins or Convalescent plasma or hyperimmune immunoglobulins” “Tocilizumab (TCZ)” and “COVID-19,” “SARS-CoV-2,” and “treatment” published through May 10, 2020.

Study selection

Two independent reviewers systematically searched the literature using the pre-specified strategy. We included the abstracts, original articles, pre-prints of the accepted article, pre-prints, case reports or...
Mechanism of action
Investigational agent

Current
A monoclonal antibody that inhibits IL-6-mediated signaling
IL-6 is a pro-inflammatory cytokine
Cytokine release syndrome may be a component of severe disease in COVID-19

Agents previously used to treat similar respiratory viruses; SARS-CoV and MERS-CoV are potential candidates to treat COVID-19. We summarize clinical experiences of some of the most promising repurposed drugs we reviewed for COVID-19 by drug-class.

Antimalarials
HQQ and CQ
Some preliminary studies have shown that HQQ has significant in vitro activity against SARS-CoV-2, providing the rationale for its use in the treatment and prevention of COVID-19 infection [16]. Studies have shown, HQQ to be more potent against SARS-CoV-2 than CQ [17]. In our review, we found ten studies using HQQ and three studies using CQ (Table 2).

The study by Gautret et al. [18] showed significantly higher virus clearance rate at 6-day post-inclusion in HQQ group compared with standard-of-care with added benefit on the addition of azithromycin. This same group from France reported results from an observational study that reported good clinical outcomes, but there was no comparison group and most patients had a low National Early Warning Score [19]. In contrast, a randomized study [20] showed no impact of HQQ on virological clearance and clinical resolution in patients with mild to moderate COVID-19 infection. In another randomized trial [21] published as preprint version (not peer-reviewed), the patients on HQQ...
Table 2: Clinical studies of HCQ and CQ in patients with COVID-19

| Author/country/sample size | Study design/intervention | Results |
|---------------------------|---------------------------|---------|
| **Gautret et al. France** | Prospective open label, non-randomized trial | HCQ(n=14), HCQ + azithromycin (n=6) versus control group (n=20) |
| n=36 [18] | Virological clearance (day 6): 70.0% (HCQ) versus 12.5% (control) (p=0.001) | Cough recovery time: 2 days (HCQ) versus 3.1 days (control) (p=0.05) |
| **Chen et al. China** | Randomized control trial | HCQ + standard of care (n=15) versus control group (n=15) |
| n=30 [20] | Virological clearance (day 7): 86.7% (HCQ) versus 93.3% (control) (p=0.05) | Median time for virological clearance: 4 [1–9] days (HCQ) versus 2 [1–4] days (control) (p=0.05) |
| **Chen et al. China** | Randomized control trial | HCQ+standard of care (n=31) versus control group (n=31) |
| n=62 [21] | Fever recovery time: 2.2 (0.4) days (HCQ) versus 3.2 [1.3] days (control) (p=0.05) | Chest CT improvement: 80.6% (HCQ) versus 54.8% (control) (p<0.05) |
| **Tang et al. China** | An open-label randomized control trial | HCQ+standard of care (n=75) Control (standard of care) (n=75) |
| n=150 [22] | Virological clearance (28-day PCR): 85.4% (HCQ) versus 81.3% (control) (p=0.341) | Post-hoc analysis: HCQ was better in symptom resolution when the effects of anti-viral agents were removed (Hazard ratio, 8.83, 95% CI: 1.09–71.3) |
| **Molina et al. France** | Prospective observational study | HCQ and azithromycin |
| n=11 [23] | Mortality 1/10; ICU admission: 2/11 | Therapy discontinued in 1 patient due to QT prolongation |
| **Millien et al. France** | Observational study | HCQ and azithromycin |
| n=1061 [24] | Mortality: 8/1061 (0.75%) | No significant association between HCQ use and intubation or death (hazard ratio, 2.61; 95% CI, 1.10 to 6.17; p=0.03) |
| **Mahevas et al. France** | Observational study (routine care data) | HCQ (n=84) Comparator (non HCQ group) (n=97) |
| n=84 [25] | Virological clearance (day 7): 83% and 93% at Day8 | No cardiac toxicity observed. |
| **Magagnoli et al. United States** | Retrospective study | HCQ (n=97), HCQ+azithromycin (n=113), no HCQ (n=158) |
| n=368 [26] | Rates of death: HCQ (27.8%), HCQ+azithromycin (22.1%), no HCQ groups (11.4%) (adjusted hazard ratio, 2.61; 95% CI: 1.10 to 6.17; p<0.03) | No significant association between HCQ use and intubation or death (hazard ratio, 1.04, 95% confidence interval, 0.82 to 1.32) |
| **Geleris et al. United States** | Observational study | HCQ (n=811), non HCQ (n=565) |
| n=1446 [27] | Compose the endpoint of intubation or death: 25.1% in HCQ group | No significant association between HCQ use and intubation or death (hazard ratio, 1.04, 95% confidence interval, 0.82 to 1.32) |
| **Gao et al. China** | Randomized control trial | CQ versus control |
| n=100 [28] | CQ found to be superior in reducing symptom duration, exacerbation of pneumonia, and promoting virus-negative seroconversion without any severe side effects (details not yet published) |
| **Huang et al. China** | Randomized control trial | CQ (n=10) versus LPVr (n=12) |
| n=22 [29] | CQ was slightly superior to LPVr in terms of virological clearance on day 7, day 10, and day 14 post-treatment. CQ improved the radiological appearance of the lungs (by day 14, the rate ratio was 2.21, 95% CI: 0.81–6.62) and decreased the hospital stay |
| **Borba et al. Brazil** | Double-blinded, randomized, phase IIb clinical trial two arms: high dose CQ (600 mg twice daily for 10 days) and low dose CQ (450 mg for 5 days) All received azithromycin and ceftriaxone | High dosage CQ arm: 18.9% had QTc >500 ms and the trend toward higher lethality (39%) than the lower dosage arm |
| n=81 [30] | Fatality rate until day 13–27% (95% CI: 17.9–38.2%) in high dose arm |

n: Total number of patients, p: Significant level, CI: Confidence interval, CRP: C reactive protein, CQ: Chloroquine, HCQ: Hydroxychloroquine, LPVr: Lopinavir/ritonavir
improved clinically in terms of fever recovery time, cough remission time, and radiological improvement. In another open-label, randomized, and controlled trial from China [22] (released as a preprint), the patients on HCQ had a slight benefit in resolution in symptoms, when controlling for receipt of antivirals, but no benefit was seen in virological clearance.

A study by Molina et al. [23] reported persistence of SARS-CoV-2 in the nasopharyngeal swab in 8 of 10 patients who had other significant co-morbidities. In an observational study in 1061 patients [24], the majority obtained virological clearance by day 10 and poor clinical outcome was associated with older age, initial higher severity, and low HCQ serum concentration. Results from another study (also from France) [25] released as a preprint, do not support the use of HCQ in patients hospitalized with SARS-CoV-2 positive hypoxic pneumonia, and noted that seven (out of 84) patients developed QTc prolongation. A retrospective analysis done in the United States [26], the risk for death was higher in the HCQ group than in the non-HCQ group (adjusted hazard ratio with HCQ versus without, 2.6). A recent observational study from the US involving hospitalized COVID-19 patients concluded that HCQ administration was not associated with either a greatly lowered or an increased risk of the composite endpoint of intubation or death [27].

CQ was superior in reducing symptom duration, exacerbation of pneumonia, and promoting virus-negative seroconversion without any severe side effects in two randomized trials from China [26,29]. In a double-blind, randomized trial from Brazil [30], the higher-dose CQ arm discontinued as per a data safety monitoring board for increased mortality. A Cochrane review protocol to evaluate the effect of CQ and HCQ on the treatment of COVID-19 had published and results are awaiting [31].

**Antivirals (Table 3)**

**LPVr**

LPVr is an FDA approved fixed-dose combination used for the treatment of human immunodeficiency virus (HIV). Preliminary studies demonstrated *in vitro* activity against SARS-CoV-1 and MERS-CoV; both are closely related to SARS-CoV-2 [32]. A recent study reported that LPVr inhibits SARS-CoV-2 replication in Vero E6 cells with half-maximal effective concentration (EC50) under 100 μM [33]. Earlier *in vivo*, human evidence published were mainly individual case reports and clinical series. Many clinical trials are ongoing, with results expected in near future.

LOTUS trial (Table 3), which compared LPVr with standard-of-care, no benefit seen with LPVr treatment beyond standard care in terms of clinical improvement or viral load [34]. In ELACOI Trial [35], (released as pre-print) LPVr and arbidol monotherapy compared with the control group and found little benefit for improving the clinical outcome or in virological conversion over supportive care. In both these trials, severely or critically affected patients were not included in the study.

Yan et al. [36] found that virological clearance is more in LPVr treated patients and Ye et al. [37] demonstrated LPVr combination treatment has more evident clinical improvement with no evident toxic side effects compared with adjunctive drugs alone. Deng et al. [38] also compared arbidol and LPVr combination with LPVr monotherapy and found the apparent favorable clinical response and virological clearance with arbidol and LPVr combination over LPVr monotherapy.

In two published clinical series [39,40] from China reported clinical improvement and speed virological clearance in COVID-19 pneumonia after administration of LPVr. Another case series from Singapore [41] reported only an equivocal clinical benefit with supportive care. Two different case reports from Korea and China [42,43] reported significantly decreased viral load and clinical as well as a radiological improvement after the administration of LPVr.

**Remdesivir**

Remdesivir is an investigational nucleoside analog, developed for the treatment of Ebola. As an experimental drug, remdesivir will not be available for treating a large population and obtained only via compassionate use, expanded access, or enrolment in a clinical trial. *In vitro* data found that remdesivir exerts potent antiviral activity against a clinical isolate of SARS-CoV-2 (EC50=0.77 mcg, half-cytotoxic concentration (CC50) >100 mcg, selective index [SI] >129.87). Data suggest remdesivir inhibits the activity of 2002 SARS-CoV, MERS-CoV, and bat CoV strains that can replicate in human epithelial cells and mediate entry through human CoV receptors. Remdesivir has shown prophylactic and therapeutic efficacy against 2002 SARS-CoV in a mouse model [5,44].

In the United States, the first patient with COVID-19 has shown significant improvement in clinical symptoms within 24 h of treatment with remdesivir [45]. In a Clinical series by Kujawski et al. following receipt of compassionate-use remdesivir, 36 of 53 patients (68%) showed clinical improvement.

A multicentre trial carried out at ten hospitals in Hubei China [48] compared the effects of remdesivir with placebo in severe COVID-19. Patients permitted for concomitant use of other antiviral drugs also. They concluded that remdesivir was not associated with statistically significant clinical benefits or antiviral effects. Clinical trials [49] are ongoing to evaluate the safety and antiviral activity of remdesivir in patients with mild to moderate or severe COVID-19.

**FPV/favipiravir**

FPV is an investigational nucleoside analog licensed in Japan and China for the treatment of influenza. FPV effectively inhibits the SARS-CoV-2 infection in Vero E6 cells [5].

A multicentre trial [50] conducted to compare the efficacy of FPV and arbidol, another anti-influenza drug approved in China and Russia. They observed that FPV associated with significantly shortened latency to relief for pyrexia and cough, it does not significantly improve clinical recovery. Cai et al. [51] compared the clinical outcomes between patients who treated with FPV and LPVr and reported that FPV showed better treatment outcomes in COVID-19 patients in terms of their disease progression and viral clearance than LPVr.

**Other antiviral agents**

**Interferon (IFN)**

IFN-α is a broad-spectrum antiviral agent that is usually used to treat hepatitis and it is reported to inhibit SARS-CoV reproduction *in vitro*. Antiviral effects had demonstrated in animal models also [52]. Even though *in vitro* activity against SARS-CoV2 has been reported [53], human data are limited as IFN often evaluated in combination with other drugs and make it difficult to decipher whether the effect is due to IFN alone. Various combinations of ribavirin, IFN, and other antiviral agents are currently studying in several clinical trials.

**Ribavirin**

Ribavirin is a nucleoside analog with broad-spectrum antiviral effects. The synergistic antiviral effect between ribavirin and IFN was also described [52]. However, *in vitro* activity [5] against SARS-CoV-2 is far less, along with a lack of human data apart from combination therapy and high toxicity makes ribavirin a less promising agent in the treatment of COVID-19.

**Oseltamivir**

Oseltamivir is a neuraminidase inhibitor approved for the treatment of influenza. There is no documented data suggesting *in vitro* activity against SARS-CoV-2. In the early phases of the COVID-19 outbreaks in China oseltamivir have been widely used as empirical treatment [54], but to date, there is no evidence for its effectiveness.
Table 3: Clinical studies of antiviral drugs in patients with COVID-19

| Author/country/sample size | Study design/intervention | Result |
|----------------------------|---------------------------|--------|
| **Lopinavir/Ritonavir**    |                           |        |
| Cao et al China n=199 [34] | Randomized, controlled, open-label trial (LOTUS Trial) | Time to clinical improvement between the two arms [16 days in both groups; hazard ratio 1.31; 95% CI: 0.95–1.85; p=0.09] |
|                           | LPVr + standard care (n=99) standard-care alone (n=100) |        |
| Li et al China n=86 [35]  | Exploratory randomized (2:1:1) controlled trial (ELACOI trial) | Meantime for the positive-to-negative conversion of SARS-CoV-2 nucleic acid: 9.0 days (SD 5.0) in the LPVr group, 9.1 (SD 4.4) in the arbidol group, and 9.3 (SD 5.2) in the control group (p=0.981) |
|                           | LPVr group (n=34) Arbidol group (n=35) Control group with no antiviral medication (n=17) |        |
| Yan et al China n=120 [36] | Observational study LPVr treatment group (n=78) Control group not treated with LPVr (n=42) | Virological clearance: The median duration of viral shedding the LPV/r treatment group versus control group- median, 22 days versus 28.5 days, (p=0.02) Only earlier administration of LPV/r treatment (≤10 days from symptom onset) could shorten the duration of viral shedding |
| Ye et al China n=47 [37]   | Observational study Test group treated with LPVr + adjuvant medicines (n=42) Control group, only adjuvant medicine (n=5) | Fever recovery: Test group: 4.8±1.94 days versus control group: 7.3±1.53 days, p=0.0364 |
| Deng et al China n=33 [38] | Observational study Arbidol+LPVr combination group (n=16) LPVr monotherapy group (n=16) | Virological clearance: Test group: 7.8±3.09 days versus control group: 12.0±0.82 days, p=0.0219 |
| Remdesivir Yeming et al China n=236 [48] | Randomized, double-blind, placebo-controlled, multicentre trial (2:1:1) Remdesivir group (n=158) Placebo group (n=78) | The time to clinical improvement: 21.0 days (interquartile range, IQR 13.0–28.0) (remdesivir) versus 23.0 days (15.0–28.0) (control) |
| Favipiravir Chen et al China n=240 [50] | Prospective, randomized, controlled, open-label multicenter trial | Clinical improvement: FPV group versus arbidol group-71/116 versus 62/120 (p=0.1396, difference of recovery rate: 0.0954; 95% CI: −0.305–0.2213) Fever recovery and cough relief: FPV led to shorter latencies to relief for both pyrexia (difference: 1.70 days, p=0.0001) and cough (difference: 1.75 days, p=0.0001). No difference was observed of AOT or NMV rate (both p>0.05) Safety outcome: FPV-associated adverse event was raised serum uric acid (16/116, OR: 1.31; 95% CI: 0.87–1.75) |
|                           | FPV group (n=120), 116 assessed Arbidol group (n=120) |        |
| Cai et al China n=80 [51]  | Open label non randomized controlled study FPV group (n=35) LPVr group (n=45) | Virological clearance: The FPV arm versus the control arm – median (interquartile range, IQR), 4 (2.5–9) days versus 11 (8–13) days, p<0.001 Radiological improvement after 14th day: The FPV arm versus the control arm, 91.43% versus 62.22% (p=0.004) The total number of adverse events in the FPV arm versus control arm – 4 (11.43%) versus 25 (55.56%) with (p<0.001) |

**Note:** n: Total number of patients, LPVr: Lopinavir/Ritonavir; CI: Confidence interval; SD: Standard deviation, p: Significant level, FPV: Favipiravir; AOT: Auxiliary oxygen therapy, NMV: Noninvasive mechanical ventilation

**Arbidol/umifenovir**

Arbidol is a broad-spectrum antiviral drug act by inhibiting cell entry of enveloped viruses by blocking viral fusion with the host cell membrane and approved in China and Russia for the treatment of influenza [55]. Even though it is shown in vitro activity against many DNA and RNA viruses, there is no data to support in vitro activity against SARS-CoV-2. Many trials and observational studies compared arbidol and other antiviral drugs with hopeful results [35,38,50]. However, published data for monotherapy as well as availability are limited.
**Biologics**

**Immunoglobulins/convalescent plasma/hyperimmune immunoglobulins**

The rationale to use convalescent COVID-19 antibody-positive plasma to treat persons with active COVID-19 is based on the prior experience treating SARS-CoV-1 and MERS-CoV. A systematic review by Mair-Jenkins et al. of eight observational studies including 714 patients with SARS showed administration of convalescent plasma was associated with a reduction in mortality (odds ratio, 0.25 [95% CI, 0.14–0.45]) with relatively few harms [15]. In theory, the benefits of this therapy would occur primarily within the first 7–10 days of infection, when viremia is at its peak and the primary immune response has not yet occurred. Limited data are available from five small case series (combined 28 patients) [56-60] reported from China have provided initial encouraging results. These patients were critically ill patients with ARDS or at an early stage of clinical deterioration or in ventilators. Clinical symptoms and paraclinical criteria improved shortly after the administration of plasma. No obvious adverse effects observed during the treatment of these patients. The use of convalescent plasma had not studied in pregnancy, though one of the patients in a small case series of four critically ill patients was pregnant [60].

**TCZ**

A subset of persons with COVID-19 develops a massive inflammatory response that can result in ARDS, multi-organ failure, and potentially death [14]. This massive systemic inflammatory response is characterized as a cytokine storm and with very high levels of IL-6, thereby suggesting IL-6 may play a central role in the acute clinical decompensation. TCZ by competitive inhibition of IL-6 could potentially diminish this massive systemic inflammatory response in these patients. There are limited data from uncontrolled studies about the potential benefit of TCZ in patients with COVID-19.

In a prospective observational study in China [61], TCZ was added to standard care in 21 patients with severe COVID-19. Patients who received TCZ had reduced oxygen requirement, normalization of the C-reactive protein (CRP), and decreased lymphocytopenia. All these patients were also treated with an antiviral (LFPV) and methylprednisolone. A retrospective study from China [62], involving 15 moderate to critically ill COVID-19 patients, TCZ improved CRP in all patients, but 3 of 4 critically ill patients died despite therapy. These four critically ill patients experienced persistent elevations in IL-6 levels. A prospective, single-arm multicenter study [63] on off-label use of TCZ, a significant improvement in the levels of ferritin, CRP, and D-dimer has been seen 36 hospitalized adult patients with severe COVID-19. The overall mortality was 11% and TCZ administration within 6 days from admission in the hospitalized patients associated with an increased likelihood of survival (hazard ratio 2.2 [95% CI 1.3–6.7, p=0.05]). Many case reports show improvement with a single dose of TCZ in critically ill patients with comorbidities such as liver transplant, sickle cell disease, hemodialysis, systemic sclerosis, and multiple myeloma [64-69]. In a case series of two patients with COVID-19 induced cytokine release syndrome and elevated IL-6 levels progressed to secondary hemophagocytic lymphohistiocytosis despite treatment with TCZ and one developed viral myocarditis challenging the safety and clinical utility of the drug [70].

**Miscellaneous drugs**

**Corticosteroids**

Corticosteroids act as immuno modulatory agents and no in vitro studies were found on the cytotoxic effect of corticosteroids alone against SARS-CoV. The data assessing the role of corticosteroids as adjunctive care for severe coronavirus (SARS-CoV-1, MERS-CoV, and SARS-CoV-2) pneumonia is difficult to interpret because of significant heterogeneity about the timing of administration and dose of steroids use [52]. Potential side effects such as delayed viral clearance and secondary infections warrant the use of steroids on a risk-benefit assessment in individual patients. Russell et al. [71] recommend that corticosteroids should not be used in 2019-nCoV-induced lung injury or shock, except in the setting of a clinical trial.

**Ivermectin and nitazoxanide**

Both agents are FDA-approved commercial antiparasitic drugs which shown to have in vitro activity against SARS-CoV-2 [5,72]. However, published evidence is limited and clinical trials need to be conducted to confirm the effectiveness in humans with COVID-19.

**Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs)**

As coronaviruses bind to their target cells through ACE2, ACEIs or ARBs may have a protective effect in COVID-19. Initial speculation was that ACEIs or ARBs may increase ACE2 expression and this will be harmful in SARS-CoV-2 infection, while recent studies [73,74] shown that the use of ARBs or ACEs is not associated with an increased risk of acquiring SARS-CoV-2 infection. Data are insufficient to evaluate the effects of ACEis or ARBs in COVID-19. Multiple trials are underway on this purpose, including recombinant human ACE2 and the ARB losartan in COVID-19.

**DISCUSSION**

Considering antimalarials, five studies showed positive results in terms of virological clearance and resolution of clinical symptoms whereas five studies showed no added benefit in the HCQ group compared with standard of care. These studies have significant limitations. The study by Gautret et al. [18] had a small sample size and was nonrandomized. Moreover, their evaluation was purely microbiological and not clinical. In the trial conducted by Chen et al. [20], concomitant antivirals were given to the patients, which might have served as confounders when interpreting the results some studies only included patients with mild disease and so it is not possible to extrapolate these results to critically ill patients [21]. Beyond these concerns about efficacy, QP and HCQ are not without toxicity, of particular concern is QTc prolongation due to these agents. One meta-analysis [75] done on treatment effects of HCQ in COVID-19 infection showed treatment with HCQ resulted in less number of cases showing the radiological progression of lung disease (odds ratio 0.31, 0.11–0.9) whereas no difference was observed in virological cure (odds ratio 2.37, 0.13–44.53) when compared to the control/conventional treatment.

Among the direct antiviral drugs, LPVr was used very widely in China during the early phase of the outbreak, and many cases reports shown encouraging results. The two clinical trials conducted on LPVr depicted that LPVr is not superior to the standard treatments. The LOTUS trial was non-blinded as well as they did not take account of concurrent pharmacological treatment [34] Even though some of the observational studies yield positive results [36-38], it is difficult to generalize the results of these studies as the sample size is too small and their endpoints are narrow and limited. Their retrospective nature also contributes to the chance of missing many details, which hinders the generalization. Extrapolation of results to critically ill patients is also difficult as different hospitals differently classified the patients based on the evidence. LPVr monotherapy does not show any significant role in the treatment of COVID-19 except in combination with other antiviral drugs and leads to minimal use in many countries. It is too early to disregard the drug as a potential target. In all of the existing case-series and case-reports, antiviral agents were used in combination with other medications, and therefore the observed outcomes cannot be solely attributed to antiviral therapy.

On the other hand, remdesivir is emerging as a promising agent in COVID-19 treatment due to its potent in vitro activity and favorable case reports. It has been administered to 700 patients with confirmed, severe SARS-CoV-2 infections in the United States, Europe, and Japan through Expanded Access or Compassionate Use programs and yielding encouraging results [76]. The small size of the cohort and the relatively short follow-up period, limit the interpretation of the study. Even though the only clinical trial published establishes no significant benefit for remdesivir over placebo, there are more trials ongoing and expecting breakthrough results. Studies on FPV are limited and inconclusive with...
CONCLUSIONS

There is currently no strong evidence for the efficacy of different therapeutic agents in the treatment of COVID-19. Overall, the limited studies identified were subject to methodological flaws and some available in only non-peer-reviewed preprints. The majority of the existing articles have used concurrent treatments such as antibiotics, immunoglobulin, IFN, and glucocorticoids in their studies. Hence, the reports presented cannot be attributed solely to targeted drugs.

AUTHORS’ CONTRIBUTIONS

All the authors have contributed to the collection of articles, preparation, and editing of the manuscript.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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