

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.

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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 beyond physical and geopolitical boundaries reaching far-flung countries and taking its toll. What is more terrifying is that we are ill 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 (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-proofs of the accepted article, pre-prints, case reports or

case series, and letter to the editor published until May 10, 2020, which investigated or discussed the role of different therapeutic agents in COVID-19 infection. We searched the reference lists of identified articles to identify further relevant articles. We used systematic reviews as a point of reference. We excluded *in-vitro* studies and studies published in languages other than English.

Data extraction

The data from selected articles were studied independently by two investigators (SMB and MJ), and the consensus was achieved with mutual discussion. The data extracted from full-length articles wherever available. We included abstracts only when they had sufficient data. We extracted the following information from the included studies: Year of study, the country where the study was conducted, study population, intervention, comparisons (if applicable), study designs, sample size, the study objective/s, duration of the study, primary endpoints and outcomes in terms of virological load, disease progression, radiological progression, intensive care units (ICU) admission, mean length of hospital stay, and mortality. We present the findings in the form of a table and narrative summaries.

RESULTS

At present, no therapeutic drugs are available that are directly active against SARS-CoV-2. Antimalarials such as CQ, HCQ, and several antivirals such as lopinavir/ritonavir (LPVr), remdesivir, FPV, and biologics (convalescent plasma and monoclonal antibodies) have emerged as potential therapies.

Table 1 summarizes the mechanism of action and major pharmacologic parameters of select proposed treatments or adjunctive therapies for 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

HCQ and CQ

Some preliminary studies have shown that HCQ 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, HCQ to be more potent against SARS-CoV-2 than CQ [17]. In our review, we found ten studies using HCQ 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 HCQ 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 HCQ 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 HCQ

Table 1: Pharmacologic therapies considered for the treatment of COVID-19

Drug class	Mechanism of action	Adverse effects	Current recommendations
Chloroquine hydroxychloroquine [5-8]	Blocks viral entry into cells by inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification. Immunomodulatory effects are through attenuation of cytokine production and inhibition of autophagy in host cells.	Risk of cardiac arrhythmias (e.g., QTc prolongation) Risk of retinal damage on long-term use Caution in patients with G6PD deficiency, diabetics, and neuropsychiatric disorders	On March 28, 2020, the US FDA approved CQ and HCQ for emergency use in hospitalized COVID-19 patients
Lopinavir/Ritonavir [9,10]	Ritonavir act as a pharmacokinetic booster for Lopinavir. Both drugs bind and inhibit SARS-CoV main protease (Mpro), also called 3-chymotrypsin-like protease (3CLpro) which plays a crucial role in processing the viral RNA	Risk of cardiac arrhythmias (QTc prolongation), especially along with CQ, azithromycin, etc. Gastrointestinal disturbances (diarrhea, pancreatitis), hepatotoxicity. Significant drug-drug interaction (CYP450 enzyme inhibitor)	US FDA approved drug, but not for COVID-19
Remdesivir [5]	Investigational nucleoside analog and prodrug of remdesivir triphosphate. It acts as an inhibitor of RNA-dependent RNA polymerases and incorporated into the viral RNA at the position I, terminates RNA synthesis at position i+3	Nausea, vomiting, gastroparesis, hematochezia, elevation in hepatic aminotransferase	On May 1, 2020, the US FDA granted emergency use authorization of remdesivir for the treatment of confirmed COVID-19
Favipiravir [11,12]	Investigational agent Favipiravir converted into an active phosphoribosylated form in cells and inhibits viral RNA-dependent RNA polymerase, causing chain termination and preventing RNA elongation	Mild GI intolerance, hyperuricemia, liver injury	Not approved by the US FDA.
Tocilizumab [13,14]	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	Risk of GI perforation Increase in hepatic transaminase levels Caution in patients with thrombocytopenia and neutropenia Infusion-related reactions	Not approved by the US FDA.
Convalescent plasma (hyperimmune immunoglobulins) [15]	Antibodies from recovered COVID-19 patients may help with both free virus and infected cell immune clearance. Earlier used as salvage therapy in SARS and MERS	Inadvertent infection with another infectious pathogen Transfusion-associated circulatory overload, and transfusion-associated acute lung injury Potential worsening of immune-mediated tissue damage	Not approved by US FDA

G6PD: Glucose 6 phosphate deficiency, CQ: Chloroquine, HCQ: Hydroxychloroquine, IL: Interleukin, SARS: Severe acute respiratory syndrome, MERS: Middle East respiratory syndrome

Table 2: Clinical studies of HCQ and CQ in patients with COVID-19

Author/country/ sample size	Study design/intervention	Results
Gautret <i>et al.</i> France n=36 [18]	Prospective open label, non-randomized trial HCQ (n=14), HCQ + azithromycin (n=6) versus control group (n=20)	Virological clearance (day 6): 70.0% (HCQ) versus 12.5% (control) (p=0.001) Virological clearance (day 6): HCQ plus azithromycin (100%), HCQ monotherapy (57.1%), and control arm (12.5%) (p<0.001)
Chen <i>et al.</i> China n=30 [20]	Randomized control trial HCQ + standard of care (n=15) versus control group (n=15)	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) Fever recovery time: 1 (0–2) (HCQ) versus 1 (0–3) (control) (p>0.05) Mild adverse events reported in 4/15 (26.7%) of HCQ group and 3/15 (20%) of control group
Chen <i>et al.</i> China n=62 [21]	Randomized control trial HCQ+standard of care (n=31) versus control group (n=31)	Fever recovery time: 2.2 (0.4) days (HCQ) versus 3.2 (1.3) days (control) (p<0.05) Cough recovery time: 2 days (HCQ) versus 3.1 days (control) (p<0.05) Chest CT improvement: 80.6% (HCQ) versus 54.8% (control) (p<0.05) Mild adverse events reported in 2/31 patients who received HCQ.
Tang <i>et al.</i> China n=150 [22]	An open-label randomized control trial HCQ+standard of care (n=75) Control (standard of care) (n=75)	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) CRP (milligram/liter) reduction: 6.986 (HCQ) versus 2.723 (control), p=0.045 Adverse events: 8.8% in the control group and 30% in the HCQ group, with 2 serious adverse events
Gautret <i>et al.</i> France n=80 [19]	Prospective observational study HCQ and azithromycin No comparator	Virological clearance (day 7): 83% and 93% at Day8 Mortality – 1/80; ICU patients – 3/80 Mean length of hospital stay – 5 days
Molina <i>et al.</i> France n=11 [23]	Prospective observational study HCQ and azithromycin No comparator	Nasopharyngeal swab positive: 8/10 patients 5–6 days after treatment initiation Mortality 1/11; ICU admission: 2/11 Therapy discontinued in 1 patient due to QT prolongation
Million <i>et al.</i> France n=1061 [24]	Observational study HCQ and azithromycin No comparator	Virological clearance (day 10): 91.7% Poor clinical outcome: 46/1061 (4.3%) patients Mortality: 8/1061 (0.75%) The poor clinical outcome associated with -Older age (OR 1.11) -Initial higher severity (OR 10.05) -Low HCQ serum concentration. No cardiac toxicity observed.
Mahevas <i>et al.</i> France n=84 [25]	Observational study (routine care data) HCQ (n=84) Comparator (non HCQ group) (n=97)	ICU admission (within 7 days) : 20.2% (HCQ group) versus 22.1% (no-HCQ group) (relative risk [RR] 0.91, 95% CI: 0.47–1.80) Mortality (within 7 days): 2.8% (HCQ group) versus 4.6% (no-HCQ group) (RR 0.61, 95% CI: 0.13–2.89) ARDS (within 7 days): 27.4% (HCQ group) versus 24.1% (no-HCQ group) (RR 1.14, 95% CI: 0.65–2.00) Adverse events: 9.5% experienced electrocardiogram modifications requiring HCQ discontinuation
Magagnoli <i>et al.</i> United States n=368 [26]	Retrospective study HCQ (n=97), HCQ+azithromycin (n=113), no HCQ (n=158)	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) Rates of ventilation: HCQ (13.3%), HCQ+azithromycin (6.9%), and no HCQ groups (14.1%) (adjusted hazard ratio, 1.43; 95% CI, 0.53 to 3.79; p=0.48)
Geleris <i>et al.</i> United States n=1446 1376 assessed [27]	Observational study HCQ (n=811) non HCQ (n=565)	Composite 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 <i>et al.</i> China n=100 [28]	Randomized control trial CQ versus control	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 <i>et al.</i> China n=22 [29]	Randomized control trial CQ (n=10) versus LPVr (n=12)	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 <i>et al.</i> Brazil n= 81 [30]	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. 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 [28,29]. 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 μ M [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 they 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 a more evident clinical improvement with no evident toxic side effects compared with adjuvant 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 speedy 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 remdesivir initiation all patients improved, even though they had transient gastrointestinal symptoms [46]. In a cohort [47], of patients hospitalized for severe COVID-19 treated with 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/favilavir

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 <i>et al</i> China n=199 [34]	Randomized, controlled, open-label trial (LOTUS Trial) LPVr + standard care (n=99) standard-care alone (n=100)	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) Mortality at 28 days: 19.2% (LPVr) versus 25% (control) (difference, -5.8 percentage points; 95% CI, -17.3–5.7) Patients with detectable viral RNA at various time points were similar in both groups Gastrointestinal adverse events were more common in the LPVr group and treatment discontinued in 13 patients (13.8%) because of adverse events
Li <i>et al</i> China n=86 [35]	Exploratory randomized (2:2:1) controlled trial (ELACOI trial) LPVr group (n= 34) Arbidol group (n= 35) Control group with no antiviral medication (n= 17)	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) The rates of antipyresis, cough alleviation, or improvement of chest CT at days 7 or 14: all p>0.05 Deterioration in clinical status from moderate to severe/critical: At day 7, eight (23.5%) patients in the LPVr group, three (8.6%) in arbidol group, and two (11.8%) in the control group with p=0.206 Safety outcome: 12 (35.3%) patients in the LPVr group and five (14.3%) in the arbidol group
Yan <i>et al</i> 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 LPVr treatment (\leq 10 days from symptom onset) could shorten the duration of viral shedding
Ye <i>et al</i> 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 \pm 1.94 days versus control group: 7.3 \pm 1.53 days, p=0.0364 Virological clearance: Test group: 7.8 \pm 3.09 days versus control group: 12.0 \pm 0.82 days, p=0.0219
Deng <i>et al</i> China n = 33 [38]	Observational study Arbidol+LPVr combination group (n=16) LPVr monotherapy group (n=16)	Virological clearance: Negative in 12 (75%) of 16 in the combination group after 7 days, compared with 6 (35%) of 17 in the monotherapy group (p<0.05). After 14 days, 15 (94%) of 16 and 9 (52.9%) of 17, respectively, with p<0.05. Radiological improvement: 11 (69%) of 16 patients in the combination group after 7 days, compared with 5 (29%) of 17 in the monotherapy group (p<0.05)
Remdesivir Yeming <i>et al</i> China n=236 [48]	Randomized, double-blind, placebo-controlled, multicentre trial (2:1) 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) Hazard ratio 1.23 (95% CI 0.87–1.75) 28-day mortality: (22 [14%] (remdesivir) versus 10 [13%] (placebo) difference 1.1% [95% CI 8.1–10.3]). Virological clearance (day 28): 153 (78%) of 196 patients and the negative proportion was similar among patients receiving remdesivir and placebo Adverse events: 102 (66%) of 155 remdesivir recipients versus 50 (64%) of 78 placebo recipients. Treatment discontinued: Remdesivir in 18 (12%) patients versus four (5%) in placebo
Favipiravir Chen <i>et al</i> China n=240 [50]	Prospective, randomized, controlled, open-label multicenter trial FPV group (n=120), 116 assessed Arbidol group (n=120)	Clinical improvement: FPV group versus arbidol group-71/116 versus 62/120 (p=0.1396, difference of recovery rate: 0.0954; 95% CI: -0.0305–0.2213) 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: 5.52, p=0.0014)
Cai <i>et al</i> 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 14 th 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 (<0.001)

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 (LPVr) 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 seen 63 hospitalized adult patients with severe COVID-19. The overall mortality was 11% and TCZ administration within 6 days from admission in the hospital was 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 immunomodulatory agents and no *in vitro* studies were found on the cytopathic 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, CQ 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 part, 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 FFPV are limited and inconclusive with

one trial establishing no superiority over comparator. Other antiviral drugs do not earn a recommendation for monotherapy other than empirical or combination treatment.

The limited sample size and study design preclude a definitive statement about the potential effectiveness of convalescent plasma transfusion. It may be helpful in the treatment of critically ill patients with COVID-19 and ARDS. The optimal dose and time point, as well as the clinical benefit of convalescent plasma therapy, need further investigation in larger well-controlled trials. Although TCZ is not FDA-approved for the treatment of COVID-19, the established efficacy with the treatment of cytokine release syndrome has provided a rationale for its use in the treatment of COVID-19 as adjunctive therapy. Current phase III trials will be crucial in understanding the place in therapy of TCZ as a supportive care option in alleviating the severe respiratory symptoms associated with COVID-19 [77]. ECMO could be considered as effective rescue therapy for the patients having respiratory distress [78]. Regarding the anti-parasitic drugs as well as ACEIs and ARBs, more controlled studies are needed to arrive at a conclusive point.

According to the Indian council for medical research (ICMR) guidelines [79], HCQ in combination with azithromycin is recommended in patients with severe disease and patients requiring ICU management, under close medical supervision with monitoring side effects. Depending on local epidemiological data and risk factors empirical therapy with a neuraminidase inhibitor is suggested, provided de-escalation of treatment on microbiology results. Routine use of corticosteroids is not recommended outside clinical trials unless they are indicated for other reasons. Recently, ICMR researchers published a protocol restricted use of LPVr in symptomatic COVID-19 patients [80]. The apex body also approved a clinical trial of convalescent plasma for COVID-19 in multiple centers.

Limitations

Our review is not short on limitations. Newer evidence is flooding on a day-to-day basis owing that the views and recommendations can be changing. This review is based on available case reports, series, retrospective observational studies, and very few clinical trials. In addition, we only selected articles written in English because we did not have the resources available to translate potential articles written in various other languages.

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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