Therapies for COVID-19 Treatment

Subjects: Others

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The virus SARS-CoV-2, the etiological agent of COVID-19, is responsible for more than 400,000 deaths worldwide as of June 10, 2020. As a result of its recent appearance (December 2019), an efficacious treatment is not yet available. Although considered a lung infection since its emergence, COVID-19 is now causing multiple organ failure, requiring a continuous adjustment in the procedures. In this review, we summarized the current literature surrounding unproven therapies for COVID-19. Analyses of the clinical trials were grouped as chemo-, sero-, anticoagulant, and the use of human recombinant soluble ACE2 therapies. We conclude that while no agent has hit the threshold for quality of evidence to demonstrate efficacy and safety, preliminary data show potential benefits. Moreover, there is a possibility for harm with these unproven therapies, and the decision to treat should be based on a comprehensive risk-benefit analysis.

Keywords: COVID-19 ; SARS-CoV-2 ; SARS-CoV ; MERS ; therapies ; antivirals ; clinical trials

1. Antiviral Therapies

1.1. Lopinavir/Ritonivir

Lopinavir is used as a retroviral therapy to exert an anti-HIV effect through HIV-1 viral protease inhibition, whereas ritonavir boosts the effects of lopinavir [1]. In the context of coronaviruses, the 3CL protease has been a target of interest due to its function in liberating individual proteins from the unprocessed polyprotein. Lopinavir is known to cause gastrointestinal discomfort, serum lipid elevations, and has many drug–drug interactions that may result in hepatotoxicity, hemophilia, metabolic derangement, and heart block [2][3][4]. Adverse effects of ritonavir include paresthesia, hepatitis, diarrhea, and nausea. The combination has been used for the treatment of MERS through its activity on the 3CL protease in SARS-CoV, but no high-quality data on its efficacy have been published [5]. The following studies have been published (Table 1).

Table 1. Description of the studies using different types of therapeutic agents.

Therapeutic Agent	Methodology	Key Findings	Reference
Chemotherapy			
Hydroxychloroquine +/− Azithromycin	***n* = 64** **Study: double blind randomized control trial** **Treatment: HCQ 400 mg/day × 5 days**	**Improved total time to recovery, resolution of fever, cough remission, and pneumonia severity**	**[6]**
	***n* = 36** **Study: preliminary trial** **Treatment: HCQ 200 mg TID for 10 days**	**Showed large reduction in viral carriage following treatment with HCQ and HCQ + Az**	**[7]**
	***n* = 80** **Study: single hospital in-patients, non-randomized, no control, no blinding** **Treatment: HCQ 200 mg TID for 10 days Az 500 mg OD (Day 1), 250 mg OD (Days 2–5)**	**93% patients negative viral RNA PCR by day 8. 97.5% negative viral cultures by Day 5. 81% of patients had mild disease; initiation to discharged mean 4.1 days**	**[8]**
	***n* = 11** **Numerous comorbidities** **Treatment: HCQ 600 mg/day for 10 days, Az 500 mg OD (Day 1), 250 mg OD (Days 2–5)**	**5–6 days post treatment, 8/10 nasal swabs positive. One patient death, two transferred to ICU. Discontinuation due to QTc prolongation in 1 patient**	**[9]**

Therapeutic Agent	Methodology	Key Findings	Reference
	n = 84 Consecutive admissions, retrospective trial	11% of patients developed a QTc >500 (high risk for arrhythmia). 30% demonstrated a QTc increase > 40 ms	[10]
Antivirals			
Lopinavir/Ritonavir (LPV/R)	*n* = 199 Study: open label randomized control trial LPV: 400 mg/day R: 100 mg/day × 14 days	No significant improvement in mortality or viral load. No benefit compared to standard care	[11]
	n = 120 Study: Retrospective trial of admitted patients in Wuhan LP: 400 mg/day R: 100 mg/day	Lack of treatment with LPV/R is associated with an increase in duration of viral shedding vs. control. Old age is associated with an increase. Benefits of LPV/R present when treated <10 days after symptom onset	[12]
+Abridol	*n* = 44 Study: exploratory randomized control trial LPV: 400 mg/day R: 100 mg/day Arbidol: 600 mg/day × 7–14 days	No significant difference in time to viral conversion from positive to negative. 24% of LPV/R group experienced adverse effects	[13]
Remdesivir	Study: Investigation of in vitro activity of chloroquine and remdesivir	Remdesivir: 1.76 μmol/L for EC90 in nonhuman primates Chloroquine: 6.09 μmol/L for EC90 in non-human primates	[14]
	n = 18 Study: Rhesus macaques drug vehicle control, prophylactic vs. therapeutic. Inoculated with MERS-CoV	When given prophylactically, prevents infection. When given therapeutically, leads to clinical improvement. Decreased number and severity of lung lesions, reduced viral replication in the lungs	[15]
	Single case study	Patient showed improvement within a day of remdesivir treatment. Oropharyngeal swab converted to negative, nasopharyngeal remained positive	[16]
	n = 12 Study: 3/12 patients received remdesivir under compassionate use. Treatment: 200 mg IV first day, then 100 mg IV once daily	Mild GI symptoms, transient aminotransferase elevations. One episode of bloody stool	[17]
Clinical trial in progressPhase 3	*n* = 1063 Study: multi-center randomized control trial	Improved time to recovery (11 vs. 15 days, $p < 0.001$), mortality (8% vs. 11.6, $p = 0.059$). Modest effect size	[18]
Oseltamivir/Amantadine	In vitro investigation of the anti-SARS-CoV activity of numerous approved drugs	No inhibition of SARS-CoV-2 cytopathic effect with use of oseltamivir or amantadine in vitro	[19]
Colchicine			
Clinical trial in progressPhase 3	*n* = 6000 Study: Multi center, double blinded randomized control trial	N/A	[20]
Glucocorticoids			
	n = 46 Study: retrospective review, methylprednisolone 1–2 mg/kg/day 5–7 days	Improvement in time to resolution of fever, duration of supplemental oxygen use, and CT absorption degree of focus	[21]
	Review of literature surrounding corticosteroid use during SARS and MERS	Corticosteroids use for SARS and MERS showed no benefit, but harming in some cases	[22]

Therapeutic Agent	Methodology	Key Findings	Reference
Recovery Trial	*n* = 2104 (dexamethasone) Study: open-label randomized controlled trial	In patients with mechanical ventilation, dexamethasone reduced mortality by 1/3, and by 1/5 in those receiving oxygen alone. No survival benefit for those not requiring respiratory support	[23]
Convalescent plasma			
	n = 10 severely ill patients Treatment: 200 mL IV	In all 10 patients, fever, cough, shortness of breath, and chest pain disappeared or largely improved within 1–3 days of therapy initiation	[24]
	In vitro study determining the activity of convalescent plasma from a recovered SARS-1 patient against SARS-CoV-2	Demonstrates conserved epitope in SARS-1 and SARS CoV-2. Viral inhibition of SARS-CoV-2 with specific biochemical configuration	[25]
	Study: Randomized control trial	Trial halted early due to 53/66 patients having anti SARS-CoV-2 antibodies at baseline. No difference in mortality, severity, or duration of hospital stay was observed over 15 days	[26]
Anticoagulants			
Heparin	In vitro study exploring pathophysiology of SARS-CoV-2 infection. Human blood vessel and kidney cell organoids	Demonstrates ability for SARS-CoV-2 to infect blood vessel and kidney organoids	[27]
	n = 449 Study: stratification based on risk level for coagulopathy. *n* = 94 enoxaparin 40–60 mg/day, *n* = 5 unfractionated heparin 10,000 U/day	Demonstrates benefit for those with sepsis induced coagulopathy scores ≥4 or D-dimer >6 × ULN	[28]
Recombinant Human Soluble Angiotensin Converting Enzyme 2 (rhsACE2)			
	In vitro study exploring pathophysiology of SARS-CoV-2 infection. Human blood vessel and kidney cell organoids	Rates of infection of blood vessel and kidney organoids were reduced compared to controls in the presence of recombinant human serum ACE2	[27]
Biological Treatment-Tocilizumab			
TOCIVID-19	*n* = 301 Study: a multicenter, single arm trial Hypothesis driven – null = 20 and 35% lethality rate at 14 and 30 days	Tocilizumab reduced lethality rate at the 30-day interval (22.4%), rejected null hypothesis (35%). $p \leq 0.001$. Null hypothesis not rejected for 14-day interval. Suggest use of tocilizumab awaiting phase 3 trials	[29]
	n= 154 Study: single center observational cohort study	45% reduction in hazard of death in those who received tocilizumab vs. untreated. Increased risk of superinfection with tocilizumab (54% vs. 26%), but no difference in case fatality due to superinfection	[30]
	n= 3098 Study: retrospective analysis of health records. COVID-19 hospitalizations with cytokine storm over a month and a half period	The use of corticosteroids alone, or in conjunction with tocilizumab improved hospital survival compared to standard care (no immunomodulatory medication) alone	[31]

HCQ, hydroxychloroquine; Az, azithromycin; QTc, corrected QT interval; LPV, lopinavir; R, ritonavir; ULN, upper limit of normal.

1.1.1. A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe COVID-19

This randomized control trial [32] of 199 patients explored the efficacy of lopinavir–ritonavir in hospitalized COVID-19 patients with relatively mild respiratory illness. The authors demonstrated that there is no significant improvement in time to clinical improvement or mortality compared to patients who received standard care. There was also no significant difference in detectable viral RNA between the groups. Adverse effects were noted in the lopinavir–ritonavir group (13.8%

stopped early), although serious adverse events were frequent in the standard care group. The authors concluded that there was no benefit to the use of lopinavir/ritonavir beyond standard care. While this is one of the more extensive studies of COVID-19 therapies, the sample size is not ideal. Further, little or no information was given on patient comorbidities.

1.1.2. An Exploratory Randomized, Controlled Study on the Efficacy and Safety of Lopinavir/Ritonavir or Arbidol Treating Adult Patients Hospitalized with Mild/Moderate COVID-19 (ELACOI)

This exploratory randomized control trial included 44 patients (21 lopinavir/ritonavir, 16 arbidol, and 7 neither). Similar baseline characteristics were observed in patients. There was no statistical difference found in time for positive to negative conversion of the viral RNA test between treatment groups. Five (23.8%) patients from the lopinavir/ritonavir group experienced adverse events. No adverse events were reported in the other groups. Limitations include the small sample size and imbalanced groups. The study had intended to recruit more patients but was unable to.

1.1.3. Factors Associated with Prolonged Viral Shedding and Impact of Lopinavir/Ritonavir Treatment in Patients with SARS-CoV-2 Infection

This retrospective study included all test-positive cases (n = 120) at a single site in Wuhan, China [33]. Seventy-eight patients received lopinavir/ritonavir, and 42 did not. The authors demonstrated a significant increase in the duration of viral shedding in those who did not receive lopinavir/ritonavir (OR 2.42; 1.10–5.36). There was a positive correlation between age and length of viral shedding. Comorbidities or systemic corticosteroid use were not associated with changes in the duration of viral shedding. Limitations include retrospective design and small sample size.

1.2. Remdesivir

Remdesivir is an adenosine nucleotide analog that interferes with the function of the viral RNA dependent RNA polymerase [34]. The drug is still in its experimental stage, and a robust side effect profile has not been published. The following studies were published (Table 1).

1.2.1. Remdesivir and Chloroquine Effectively Inhibit the Recently Emerged Novel Coronavirus (2019-nCoV) in Vitro

An in vitro study demonstrated inhibition of SARS-CoV-2 with the use of remdesivir and chloroquine [35]. The results of the study suggest a recommendation for human trials using these agents. For example, the effective concentrations (EC) were 1.76 µmol/L for EC_{90} in non-human primates for remdesivir and 6.09 µmol/L for EC_{90} in non-human primates for chloroquine.

1.2.2. Prophylactic and Therapeutic Remdesivir (GS-5734) Treatment in the Rhesus Macaque Model of MERS-CoV Infection

This study is shown here because remdesivir was used with success in the treatment of MERS-CoV infection [36]. The possible prophylactic and therapeutic efficacy of remdesivir was established in this controlled trial through the inoculation of 18 Rhesus macaques. Remdesivir administration 24 h before the inoculation of the virus led to complete prevention of infection. In addition, remdesivir administration 12 h post-inoculation demonstrated a clear clinical benefit, including a reduction in clinical signs, reduced viral replication in the lungs, and decreased number and severity of lung lesions. Further clinical studies are necessary to demonstrate the efficacy of the drug as a therapy in COVID-19.

1.2.3. First Case of 2019 Novel Coronavirus in the United States

This case report demonstrates the potential role that remdesivir may have played in the improvement of clinical status. The condition of the patient in question declined for seven days in the hospital, and remdesivir was used as a therapy [37]. The following day, the patient's condition improved; supplemental oxygen was discontinued, and oxygen saturation rose to 94–96%. Rales were no longer heard; the patient became afebrile and had an improvement in cough. It is not reasonable to make conclusions from a single case, but further investigation is warranted.

1.2.4. First 12 Patients with Coronavirus Disease 2019 (COVID-19) in the United States

In this study, 3 of 12 patients received remdesivir under compassionate use [38]. Mild GI symptoms were noted, as well as transient aminotransferase elevation. One episode of bloody stool was noted. All patients recovered or improved. The authors could not comment on efficacy, as this was not a randomized control trial to investigate the drug.

1.2.5. Adaptive COVID-19 Treatment Trial (ACTT)

There is currently a lack of randomized controlled trials on the therapeutic effects of remdesivir for coronavirus and coronavirus-like illnesses. ACTT is a multi-center, randomized, double blind, placebo-control trial that is setting out to evaluate the efficacy and safety of remdesivir [18]. The estimated enrollment is 440 participants, and the study has posted an estimated completion date of April 2023.

1.3. Oseltamivir and Amantadine

Oseltamivir is an anti-influenza drug that exerts its effect through neuraminidase inhibition [39]. Adverse effects of oseltamivir include nausea, vomiting, and abdominal pain. Amantadine is active against influenza A and exerts its effect through blockade of the viral M2 proton ion channel [40]. Adverse effects of amantadine include nausea, anorexia, and CNS toxicity (nervousness, insomnia, and light-headedness).

1.4. Inhibition of SARS Coronavirus Infection in Vitro with Clinically Approved Antiviral Drugs

Currently, there is no evidence of in vitro inhibition of SARS-CoV-2 with oseltamivir and amantadine. The inhibition of the cytopathic effects of SARS-CoV-2 was observed when combined interferons (Wellferon, Alferon, and Betaferon) and ribavirin were administered [41]. This work warrants further in vivo investigation of the mentioned therapeutic agents.

2. Other therapies

2.1. Colchicine

Colchicine is an anti-inflammatory drug that exerts its effects by preventing microtubule polymerization [42], inhibiting leukocyte migration, and phagocytosis. Common adverse effects include diarrhea, nausea, vomiting, and abdominal pain. More rarely, it can cause hepatic necrosis, renal failure, disseminated intravascular coagulation, hair loss, bone marrow suppression, peripheral neuritis, and death [43].

COLCORONA Trial

The Montreal Health Institute is carrying out a large multi-center randomized controlled trial to investigate the role of colchicine in the treatment of COVID-19. The study estimates enrollment of 60,000 subjects, and a completion date of September 2020 has been suggested [20].

2.2. Glucocorticoids

Glucocorticoids act on glucocorticoid receptor elements (GRE) to exert their anti-inflammatory effects. They have a wide range of effects including but not limited to decreased production of inflammatory mediators, inhibition of the arachidonic acid pathway, and reduced migration of immune cells to the site of insult. Adverse side effects are numerous, including osteoporosis, avascular necrosis, weight gain, hypothalamic pituitary adrenal axis dysfunction, increased incidence of opportunistic infections, and psychosis.

2.2.1. Early, Low-Dose and Short-Term Application of Corticosteroid Treatment in Patients with Severe COVID-19 Pneumonia: Single-Center Experience from Wuhan, China

This retrospective review of 46 patients included 26 patients who received intravenous methylprednisolone [21], as detailed in Table 1. There were no other notable differences in patient parameters. Clinical symptoms and CT chest results were compared before and after therapy. Of 46 patients, 27 (59%) were febrile and 15 (33%) received the drug.

For the methylprednisolone group, patients showed fever resolution at 2 ± 0.28 days, whereas, for the control group, the resolution of fever was at 4.39 ± 0.70 days. All 46 patients received oxygen therapy. Those who received methylprednisolone required supplemental oxygen for 8.2 (7–10.3) days, whereas the control group needed it for 13.5 (10.3–16) days. In patients who received methylprednisolone, an improvement in the absorption degree of focus was observed on CT. This trial's limitations include its retrospective design, small sample size, and absence of mid- to long-term outcome measures.

2.2.2. Clinical Evidence Does Not Support Corticosteroid Treatment for 2019-nCoV Lung Injury

In this review, the author provided a summary of the clinical data to this point on corticosteroid use in the treatment of SARS and MERS [22]. They suggested that the use of corticosteroids for SARS and MERS likely led to no benefit with evidence of definite harm in some cases. In the SARS case, there was a delayed clearance of viral RNA from blood,

increased incidence of psychosis, diabetes, avascular necrosis, and osteoporosis associated with corticosteroid use. The authors concluded that COVID-19 is not likely to differ from MERS and SARS as far as response to corticosteroids. The decision to use glucocorticoids should be made after reviewing each patient's situation's risks and benefits.

2.2.3. Effect of Dexamethasone in Hospitalized Patients with COVID-19-Preliminary Report (RECOVERY Trial)

The preliminary results of the dexamethasone arm of the RECOVERY trial were released due to clear benefits in the treatment. In this trial, 2104 patients were randomly allocated to the dexamethasone arm and 4321 patients to the usual care arm. In those who required mechanical ventilation or supplemental oxygen, a 28-day survival benefit was observed (35%, $p < 0.001$, and 20%, $p < 0.002$, respectively). No such benefit was observed in patients who did not require respiratory support. Given the wide accessibility of dexamethasone globally, this trial is promising that it shows a clear benefit to patients with the most severe illness [23].

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