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Role of adjunctive treatment strategies in COVID-19 and a review of international and national clinical guidelines

Abstract

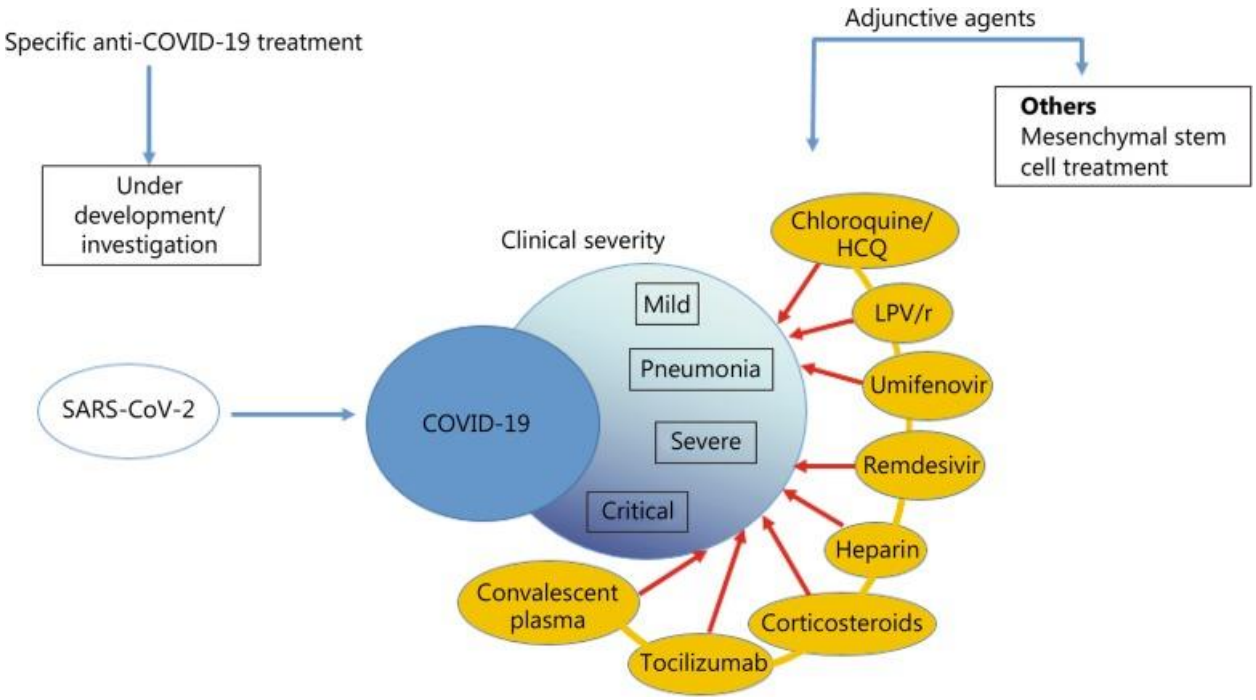
The coronavirus disease (COVID-19) pandemic has led to a global struggle to cope with the sheer numbers of infected persons, many of whom require intensive care support or eventually succumb to the illness.

The outbreak is managed by a combination of disease containment via public health measures and supportive care for those who are affected. To date, there is no specific anti-COVID-19 treatment. However, the urgency to identify treatments that could turn the tide has led to the emergence of several investigational drugs as potential candidates to improve outcome, especially in the severe to critically ill. While many of these adjunctive drugs are being investigated in clinical trials, professional bodies have attempted to clarify the setting where the use of these drugs may be considered as off-label or compassionate use.

This review summarizes the clinical evidence of investigational adjunctive treatments used in COVID-19 patients as well as the recommendations of their use

from guidelines issued by international and national organizations in healthcare.

Keywords: COVID-19, Adjunctive treatment, Chloroquine, Lopinavir-ritonavir, Remdesivir, Corticosteroids, Umifenovir, Convalescent plasma



INTRODUCTION

In recent years, novel coronavirus infections have emerged periodically in various countries around the world. Severe acute respiratory syndrome coronavirus (SARS-CoV) occurred in 2002, infecting 8422 people and

causing 916 deaths during the epidemic.1 Middle East respiratory syndrome coronavirus (MERS-CoV) was first identified in 2012.2 At the end of December 2019, a total of 2499 laboratory-confirmed cases of Middle East respiratory syndrome (MERS), including 861 associated deaths were reported globally.3 At the end of 2019, novel coronavirus pneumonia (NCP) emerged in Wuhan and had spread rapidly. The pathogen was confirmed new coronavirus, which was officially named coronavirus disease-19 (COVID-19) by the World Health Organization (WHO). As of February 21, 2020, a total of 76 395 confirmed cases have been reported, and 2 348 patients are reported to have died. Currently, there is no specific antiviral treatment for COVID-19. Therefore, identifying drug treatment options as soon as possible is critical for the response to the COVID-19 outbreak

Chloroquine/Hydroxychloroquine

Chloroquine is used in both treatment and chemoprophylaxis against malaria. HCQ, an analogue of chloroquine, is used in autoimmune conditions such assystemic lupus erythematosus and rheumatoid arthritis.

Both drugs have shown in-vitro activity against SARSCoV-2, with HCQ possibly being the more potent of the two（Savarino）

Hydroxychloroquine was found to be more potent than chloroquine to inhibit SARS-CoV-2 in vitro.

Their anti-viral mechanisms of action are not clear, but have been postulated to include inhibition of the pH-dependent steps of viral replication and immunomodulation via inhibition of tumor necrosis factor-alpha and interleukin-6 (IL-6) .

Given that both drugs have been around for decades, they are generally affordable and their safety profiles are well-established, they are attractive candidates as potential anti-COVID-19 treatments.

How we can prove that In December 2019 the outbreak of a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 or COVID-2019), was first reported in Wuhan, China. The outbreak has since rapidly spread to other provinces in mainland China, as well as other countries around the world. Currently, the number of people diagnosed with SARS-CoV-2 infection is increasing by approximately 1000 cases per day. Unfortunately, to date, no drugs have

been approved by regulatory agencies for the treatment of SARS-CoV-2 infection. Chloroquine is a widely used antimalarial with immunomodulatory effects (Romanelli F). In a recent in vitro study chloroquine was found to inhibit the growth of SARS-CoV-2 in vitro (Wang M)

Hydroxychloroquine and chloroquine are relatively safe drugs. Their most common side effects include gastrointestinal symptoms, pruritus and dermatological changes that can occur in up to 10% of the patients Abdulaziz

Lopinavir-ritonavir

Lopinavir is a human immunodeficiency virus (HIV) type-1 aspartate protease inhibitor.

Ritonavir inhibits CYP3A-mediated metabolism of lopinavir, thereby increasing the serum concentration of the latter and is therefore often given in combination.

Lopinavir-ritonavir has been used off-label during SARS and MERS outbreaks.

A systematic review of lopinavir-ritonavir use in SARS and MERS coronaviruses reported two retrospective matched cohort studies showing that lopinavir ritonavir

improved clinical outcome when given early in SARS patients, and lopinavir-ritonavir alone or given in combination with interferon improved clinical outcome of some MERS patients Kaplan

A literature search revealed 5 in-vivo studies of lopinavir-ritonavir use in COVID-19 patients. The only RCT was an open-label study in China by Cao et al cohort study comparing standard treatment (n = 100) versus standard treatment together with lopinavir-ritonavir (n = 99).

The study population was patients with arterial oxygen saturation (SaO2) ≤94% on room air or a ratio of partial pressure of arterial oxygen (PaO2) to fraction of inspired oxygen (FiO2) < 300 mmHg, which was close to NHC's definition of severe COVID-19.

The Authors did not observe significantly improved clinical outcomes in the lopinavir-ritonavir group.

The time to clinical improvement, mortality at 28 days and viral RNA load or detectability of viral RNA at various time points was not significantly different between the 2 groups.

The lopinavir-ritonavir group reported 4 serious adverse events (2 acute gastritis, 2 haemorrhage of the lower digestive tract); 13 patients were unable to complete the full course due to anorexia, nausea, abdominal discomfort, or diarrhea. Two patients had self-limited skin eruptions. The high overall mortality rate (22.1%) in this trial was noted to be a potential confounder, as patients may have been too ill to respond to the drug.

Umifenovir

Umifenovir is small indole-derivative molecule that has broad-spectrum antiviral properties, including Influenza A and B Blaising J

It blocks viral fusion with the target membrane, thus providing viral entry into target

cells. It is approved for prophylaxis and treatment of influenza in Russia and China.

Deng et al. performed a retrospective non-randomized cohort study of 33 patients in China, stratified into 16 patients who received oral umifenovir and lopinavirritonavir versus 17 patients who received

lopinavirritonavir without umifenovir Deng L. At day 7 of treatment, 75% in the combination group tested negative for the virus, compared with 35% in the lopinavir-ritonavir-only group (P < 0·05).

CT findings improved for 69% in the combination group compared with 29% patients in the lopinavir-ritonavir-only group (P < 0·05). At day 14, 94% in the combination group tested negative compared to 53% in the lopinavir-ritonavir-only group (P < 0·05). None of the patients developed acute respiratory failure, required invasive ventilation or vasopressor therapy during the treatment.

Adverse effects recorded included hyperbilirubinemia (68.7%) and mild gastrointestinal symptoms (43.7%) such as diarrhoea and nausea. The authors concluded that combination therapy might decrease the viral load of COVID-19 and delay progression of lung lesions. Potential confounders included the use of other drugs in patients in both groups (immunoglobulin therapy, corticosteroids, non-specified antivirals).

Remdesivir

Remdesivir is a novel nucleotide analogue prodrug which is incorporated into nascent viral RNA chains, causing premature termination of RNA transcription Warren TK. It was developed for use against the Ebola virus, an epidemic RNA virus Mulangu S

However, its use was suspended after a RCT evaluating the safety and efficacy of 3 monoclonal antibodies and remdesivir) terminated random assignment to remdesivir due to a clear reduction in survival in this treatment group Mulangu S.

In-vitro studies had shown that remdesivir effectively inhibited the replication of SARS-CoV and MERS-CoV Sheahan TP, and appeared to have effect on SARS-CoV-2 replication as well in non-human cells Wang M.

Remdesivir is not approved to treat any condition by regulatory agencies including the US FDA or the European Medicines Agency.

Grein et al. Grein J reported the outcome of an openlabel cohort study of 61 COVID-19 patients from 9 countries who received remdesivir on a compassionateuse basis.

The inclusion criteria were hospitalized COVID-19 with SpO2≤ 94% on ambient air or supplemental oxygen, creatinine clearance > 30 ml/min, serum aminotransferases less than 5 times the upper limit of normal and not on ,other investigational drugs for COVID-19. Eight patients were excluded due to missing or erroneous data.

The study population included 34 (64%) patients on invasive ventilation and 4 (8%) patients on ECMO. Over 18 days, 36 of 53 patients (68%) showed an improvement in the category of oxygen support, including 17 (57%) of 30 patients who were extubated. Eight of 53 patients (15%) showed worsening. The mortality rate of the cohort was 13%, including 6 of 34 patients on invasive ventilation and 1 of 19 patients on non-invasive oxygen support.

Adverse events were reported in 60% of the study population and were generally more common in patients on invasive ventilation. The most common adverse events were increased hepatic enzymes, diarrhea, rash, renal impairment and hypotension. Serious adverse events included multipleorgan-dysfunction syndrome, septic shock, acute kidney injury, and hypotension.

Four (8%) patients discontinued remdesivir treatment due to worsening pre-existing renal failure, multiple organ failure, elevated aminotransferases and maculopapular rash. Some limitations of the study were the lack of pre-defined sample size, short duration of follow-up, lack of data on viral load to determine anti-viral effects and lack of control group.

Systemic corticosteroids (against routine use)

A search of the literature uncovered 3 articles examining the role of corticosteroids in patients with COVID-19.

In a meta-analysis of systemic corticosteroid use in COVID-19 patients by Lu et al. Lu S, Zhou Q, the pooled results from 5 cohort studies found that corticosteroids did not reduce the risk of mortality (relative risk (RR) = 2.0, 95% CI: 0.7–5.8, I2 = 90.9%), shorten the duration of pneumonia (weighted mean difference (WMD) = − 1.0 day, 95% CI: − 2.9 – 0.9), or shorten hospital stay (WMD = 2.4 days, 95% CI: 1.4–3.4, I2 = 0.0%) in COVID-19 patients.

However, the duration of fever was significantly lower in COVID-19 patients who received corticosteroids than

patients who did not receive corticosteroids (WMD = − 3.2 days, 95% CI: − 3.6 to – 2.9).

The authors concluded that the evidence did not support routine use of systemic corticosteroids in COVID-19.

Two other studies were identified that were not included in the above meta-analysis. Zhou et al. Zhou W described the efficacy of corticosteroids in a cohort of 15 critical COVID-19 patients (NHC criteria) with moderate to severe ARDS. All had received anti-virals and/or antibiotics without improvement.

Corticosteroids (median hydrocortisone-equivalent dose of 400 mg/d) were initiated upon ICU admission for an average of 9.5 days. The authors observed that while corticosteroids improved arterial oxygenation (SaO2) and PaO2/FiO2 ratio in the first 3 to 5 days which could theoretically be further augmented with invasive ventilation, overall survival was not improved. The mortality rate of the study was 46.7%, compared with the 57.6% mortality rate of MERS ICU patients who did not receive corticosteroids.

Corticosteroids did not exert a survival advantage in 7 patients with concomitant ARDS, shock or multi-organ failure, who all eventually expired.

Liu et al. Liu K described their cohort of 137 COVID-19 patients, of whom 24.8% required non-invasive ventilation. None of the patients required invasive ventilation or ICU management. The mortality rate of this cohort was 11.7%. Forty (29.2%) patients who had persistently high fever or significant short-term disease progression on chest imaging were administered intravenous methylprednisolone (30–80 mg/d, for 3 to 5 days), with a view to inhibit cytokine storm and promote resorption of exudates. The authors observed that low dose, short course of intravenous methylprednisolone (30–80 mg/d, for 3 to 5 days) did not appear to improve patient outcomes. Potential confounders included the use of other drugs such as antivirals (not specified) and gamma-immunoglobulin.

Low molecular weight heparin

Severe to critically-ill patients can be complicated by sepsis-induced coagulopathy, disseminated intravascular

coagulation or venous thromboembolism from prolonged bedrest.

However, critically-ill COVID-19 patients appear to be particularly predisposed towards thrombotic complications.

A Dutch study of 184 critically-ill COVID-19 patients in ICU noted a 31% incidence of thrombotic complications including ischaemic stroke, systemic arterial embolism and myocardial infarction Magro C,. Similarly, a study of 81 critically-ill COVID-19 patients in ICU in China observed a 25% incidence of venous thromboembolic events Wang F.

Indicators of pro-coagulation state such as elevated D-dimer, fibrin degradation product levels, inflammatory markers, and prolonged prothrombin time and activated partial thromboplastin time in this population are associated with increased risk of mortality [12, 63, 64].

Convalescent plasma

Convalescent plasma is blood plasma from a person who has recovered from an infection and contains neutralizing antibodies against the offending agent.

It is considered a form of passive immunotherapy. Convalescent plasma has been explored as a treatment option in SARS and severe influenza; a meta-analysis noted it may reduce mortality, although many studies were of low quality and lacked control groups Mair-Jenkins. Currently, the only guideline that includes the use of convalescent plasma in its algorithm is from the NHC National Health Commission (NHC).

A literature search found 3 articles examining the use of convalescent plasma in COVID-19 patients. Duan et al. Duan reported on 10 patients with severe COVID-19 (NHC criteria) in China who received one dose of 200 ml convalescent plasma from recovered donors with neutralizing antibody titres above 1:640.

Patients additionally received various treatments including umifenovir, remdesivir, ribavirin, peramivir and methylprednisolone. Clinical symptoms improved within 3 days, and general improvements in chest CT appearance and lymphocyte counts were noted. The viral load became undetectable within 6 days of transfusion in

7 patients with pre-transfusion viraemia. Compared to 10 controls, the treatment group had greater proportions of patients discharged, improved and no deaths. No adverse events were reported.

Interleukin-6 inhibitors (Tocilizumab)

Tocilizumab is a humanized immunoglobulin that blocks the IL-6 receptor. It is licensed in the US and Europe for chimeric antigen receptor T-cell-induced severe or life-threatening cytokine release syndrome. It is hypothesized to be effective in suppressing the cytokine storm syndrome associated with severe or critical COVID-19 Mehta

Conclusion

The global scale of the COVID-19 outbreak has brought about much interest in identifying treatments that could potentially turn the tide. However, medical professionals are bound by the time-honored dictum to first do no harm. The current evidence of adjunctive treatments in COVID-19 does not support their routine use over standard care outside clinical trials. We eagerly await the results of quality, rigorous clinical trials that may shed light on effective and safe therapies that

improve outcome especially in the severe to critically ill patient population.

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