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REVIEW

Treatment modalities for coronavirus disease 2019 (COVID-19)

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Abstract

Management of coronavirus disease 2019 (COVID-19) infection is based on limited data and keeps changing rapidly as new clinical data emerge. Remdesivir has shown to reduce duration of hospital stay and has been approved for treatment. In RECOVERY trial, corticosteroids lowered 28-day mortality in patients requiring oxygen supplementation or mechanical ventilation. Convalescent plasma did not live up to its initial promise and is not the standard of care for treatment at present. There's not enough evidence for use of Hydroxychloroquine, Interleukin-6 inhibitors and many other investigational drugs. Bamlanivimab, casirivimab- imdevimab combo, all monoclonal antibodies, have recently been approved for use in mild to moderate COVIID-19, when there's a high risk of progression to severe disease. Treatment of COVID-19 depends on stage and severity of disease. Antiviral medications are likely to be most effective when used early. Later in the disease, anti-inflammatory medications, anticoagulants and immunomodulators may be more effective. The world is waiting and hoping for a safe and effective vaccine which can put an end to this worldwide pandemic.

Keywords: COVID-19; treatment; coronavirus disease; remdesivir; favipravir; hydroxychloroquine; COVID antibody therapies

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Introduction

Coronavirus disease 2019 (COVID-19) is a multi-system disease caused by severe acute respiratory syndrome (SARS-CoV-2) and the pandemic has caused devastation and death around the world.

Approach to hospital management is based on limited data and keeps changing rapidly as new clinical data emerge. Interim guidance has been issued by Center for Disease Control and Prevention (CDC), USA [1], World Health Organization (WHO) and Indian Council for Medical Research (ICMR). In this article, we review drugs commonly considered for treatment of COVID-19 infection and proposed treatment protocol.

Remdesivir

Remdesivir is an intravenous investigational nucleotide prodrug of an adenosine analog. It binds to the viral RNA dependent RNA polymerase, inhibiting viral replication through premature termination of RNA transcription.

ACTT-1 trial [2] was a double-blind, randomized, placebo-controlled trial of intravenous remdesivir in adults who were hospitalized with COVID-19 and had evidence of lower respiratory tract infection. Patients were randomly assigned to receive either remdesivir (200 mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days) or placebo for up to 10 days. The primary outcome was the time to recovery, defined by either discharge from the hospital or hospitalization for infection-control purposes only. A total of 1062 patients underwent randomization (with 541 assigned to remdesivir and 521 to placebo). Those who received remdesivir had a median recovery time of 10 days as compared with 15 days among those who received placebo (P<0.001). The patients who received remdesivir were found to be more likely than those who received placebo to have clinical improvement at day 15 (odds ratio, 1.5). It was concluded that remdesivir was superior to placebo in shortening the time to recovery in adults who were hospitalized with COVID-19 and had evidence of lower respiratory tract infection.

The benefit of remdesivir was most apparent in patients receiving low flow oxygen. The suggested adult dose is 200 mg intravenously on day 1 followed by 100 mg daily for 5 days total (with extension to 10 days if there is no clinical improvement and in patients on mechanical ventilation or ECMO). If a patient is otherwise ready for discharge prior to completion of the course, remdesivir can be discontinued.

Just when there was wide acceptance of the benefits of remdesivir, came an interim report of SOLIDARITY trial [3] which again created confusion regarding this drug. Solidarity trial is an international clinical trial to help find effective treatment for COVID-19, launched by WHO and is one of the largest international randomized trials for COVID-19 treatments, enrolling almost 12000 patients in 500 hospital sites in over 30 countries. The interim results released on 15 Oct, 2020 found that all 4 treatments evaluated (Remdesivir, HCQS, Lopinavir/ Ritonavir and Interferon) had little or no effect on overall mortality, initiation of ventilation and duration of hospital stay in hospitalized patients.

In the midst of the controversy, FDA approved remdesivir [4] for use on 22 Oct, 2020 for the treatment of COVID-19 requiring hospitalization. This drug is at present time widely used in almost all patients requiring hospitalization. The last word on this drug is still awaited.

Corticosteroids

Systemic inflammatory response seen in severe COVID-19 leads to lung injury and multi system organ dysfunction. Corticosteroids have potent anti-inflammatory properties and can prevent or reduce these harmful effects.

RECOVERY trial [5] was a controlled, open-label trial comparing a range of possible treatments in patients who were hospitalized with COVID-19. Patients were randomly assigned to receive oral or intravenous dexamethasone (at a dose of 6 mg once daily) for up to 10 days or to receive usual care alone. The primary outcome was 28-day mortality. A total of 2104 patients were assigned to receive dexamethasone and 4321 to receive usual care. Overall, 482 patients (22.9%) in the dexamethasone group and 1110 patients (25.7%) in the usual care group died within 28 days after randomization (P<0.001). In the dexamethasone group, the incidence of death was lower than that in the usual care group among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%) and among those receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%); but not among those who were receiving no respiratory support at randomization (17.8% vs. 14.0%). It was concluded that in patients hospitalized with COVID-19, the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support.

There is widespread misuse of steroids. Indiscriminate use at an early stage or in mild cases may be harmful and can exaggerate the infection and may increase the severity of the disease. Steroids should be started only when patients require

oxygen therapy and preferably after admission to the hospital under the supervision of experienced doctors.

Convalescent plasma therapy (CPT)

Convalescent plasma from patients who have recovered from COVID-19 has been under evaluation and used for therapy of SARS CoV-2 infection in hospitalized patients. Small randomized trials of convalescent plasma have not shown a clear benefit. It may provide clinical benefit when it contains high neutralizing antibody titers and given early in the course of disease when virus replication is greatest [6, 7]. It may not be useful in patients who are intubated.

The NIH panel and the FDA, emphasize that convalescent plasma is not the standard of care for the treatment of COVID-19.

Recently ICMR conducted PLACID trial [8] which was the world's largest pragmatic trial on CPT conducted in 464 moderately ill COVID-19 patients in real world setting wherein no benefit of use of CPT could be established. It concluded that it did not lead to reduction in progression to severe COVID-19 or all-cause mortality in the group that received CPT as compared to the group that did not receive CPT. ICMR advised against indiscriminate use of CPT. ICMR advisory (on 17 Nov, 2020) also embraced the principle that a potential donor should have sufficient antibody working against COVID-19. It also highlighted that presence of antibody in a potential recipient makes transfusing a futile intervention.

Many clinical trials with plasma are still going on around the world.

Interleukin-6 pathway inhibitors

Markedly elevated inflammatory markers (including IL-6) are associated with critical and fatal COVID-19. Several agents that target the IL-6 pathway have been evaluated, including Tocilizumab, Sarilumab and Siltuximab. One study suggested earlier use of Tocilizumab associated with lower mortality [9]. However other studies, including CONVACTA trial [10], failed to show benefit. Further studies are under way. One significant drawback of the CONVACTA trial was the selection of patients as well as the initiation time of the medication.

Favipravir

Favipravir is an RNA polymerase inhibitor available in some Asian countries for treatment of Influenza and was approved in India by Drug Controller General of India (DCGI) for 'restricted emergency use' in mild to moderate COVID-19 cases. Although it is widely used in India, it is not included in ICMR guidelines for COVID-19. Clear evidence is so far lacking and is still being evaluated in clinical trials.

Hydroxychloroquine/ chloroquine

There has been a lot of controversy regarding use of HCQS but now the consensus is against the use of HCQS either alone or in combination with azithromycin. Many health care workers working with COVID-19 patients take it as prophylaxis although there is no clear evidence. Although it's a fairly safe drug when used in regular doses in low risk patients, risk of QT prolongation is higher in patients with history of cardiovascular disease and with higher doses or when combined with azithromycin.

The Recovery Collaborative Group Trial [11] showed that those COVID-19 patients who received HCQS did not have a lower incidence of death at 28 days than those who received usual care. The World Health Organization also terminated the hydroxychloroquine arm of its large SOLIDARITY trial [12], and the United States National Institutes of Health terminated its trial of hydroxychloroquine [13] in hospitalized patients; each cited a lack of benefit based on preliminary data from the trials.

COVID-19 antibody therapies

One way to transfer antibodies is through convalescent plasma, but another is to manufacture and mass produce specific antibodies against the viral spike protein that could supplement body's immune system. The main hope is that antibody therapies can stop mild COVID-19 from becoming severe [14].

The US-FDA issued an emergency use authorization (EUA) recently for the investigational monoclonal antibody therapy bamlanivimab (Eli Lilly) to treat adults and children >12-years old with mild to moderate COVID-19. Casirivimab and imdevimab, a monoclonal antibody combo developed by Regeneron Pharmaceuticals, Inc. for treatment of mild to moderate COVID-19, received an emergency

use authorization (EUA) from the FDA on Nov 21, 2020. These are recommended for patients who are considered to be at high risk for progression to severe COVID-19 or hospitalization. Patients older than 65, on immunosuppression or chronic kidney and heart disease are considered high risk group. These are not authorized for use in patients who are hospitalized or who require oxygen therapy. These antibody therapies are shown to decrease viral load, shorten the duration of symptoms and decrease the emergency room visits and hospitalizations.

Others

Other agents have been proposed including azithromycin, lopinavir-ritonavir, interferon, colchicine, vitamin D, zinc, famotidine, ivermectin, doxycycline etc., but there is no evidence of their benefit as of now and many of them are still undergoing trials. Many of these proposed drugs are from observational studies and not well-designed randomized trials, and definitive evidence is lacking for any of these drugs.

Defining disease severity [15]

Mild disease: Mild disease is characterized by fever, cough, upper respiratory symptoms and malaise, but there is no dyspnea and these patients do not need hospitalization. However, some patients who have mild symptoms initially may have sudden clinical worsening that occurs approximately 1 week after onset of symptoms [16]. In patients with risk factors for severe disease (Table 1) and those who develop worsening symptoms (e.g., dyspnea), close monitoring and evaluation for clinical progression is required. Physical examination should be performed to assess for tachypnea, hypoxemia, and abnormal lung findings.

Moderate disease: Moderate disease is characterized by the presence of clinical (dyspnea) or radiological evidence of lower respiratory tract disease with a blood oxygen saturation of 94% or higher on room air. They usually need hospitalization.

Severe disease: Severe disease indicators include severe tachypnea (respiratory rate > 30 breaths per min), hypoxemia (oxygen saturation, </= 93%); ratio of partial pressure of arterial oxygen (PaO_2) to fraction of inspired oxygen (FiO2) < 300; and lung infiltrates (>50% of the lung field involved within 24 – 48 hrs) [17].

Table 1: Risk factors for severe COVID-19 [18].

- Older age
- Chronic obstructive pulmonary disease
- Cardiovascular disease (e.g., heart failure, coronary artery disease, or cardiomyopathy)
- Type 2 diabetes mellitus
- Obesity (body-mass index, ≥30)
- Sickle cell disease
- Chronic kidney disease
- Immunocompromised state from solid-organ transplantation
- Cancer

Table 2: Laboratory features in severe COVID-19 [16, 19].

Abnormality	*Possible threshold*
Elevations in	
D-dimer	>1000 ng/mL (normal range: <500 ng/mL)
CRP	>100 mg/L (normal range: <8.0 mg/L)
LDH	>245 units/L (normal range: 110 to 210 units/L)
Troponin	>2× the upper limit of normal (normal range for troponin T high sensitivity: females 0 to 9 ng/L; males 0 to 14 ng/L)
Ferritin	>500 mcg/L (normal range: females 10 to 200 mcg/L; males 30 to 300 mcg/L)
CPK	>2× the upper limit of normal (normal range: 40 to 150 units/L)
Decrease in	
Absolute lymphocyte count	<800/microL (normal range for age ≥21 years: 1800 to 7700/microL)

Proposed treatment protocol

Treatment depends on the stage and severity of disease [20]. Because SARS-CoV-2 replication is greatest just before or soon after symptom onset, antiviral medications (e.g., remdesivir and antibody-based treatments) are likely to be most effective when used early. Later in the disease, a hyperinflammatory state and coagulopathy are thought to lead to clinical complications; in this stage, anti-inflammatory medications, anticoagulants, immunomodulators, or a combination of these treatments may be more effective than antiviral agents.

Management

Guidelines from NIH and CDC, USA [1] (Figure 1)

Figure 1: Recommendations for pharmacologic management of patients with COVID-19 based on disease severity.

Proposed treatment protocol is listed here

Fordoses or therapies that have no clear evidence from randomized trials, have been marked "consider". Regular monitoring of labs to be done including inflammatory markers: D-dimer, ferritin, CRP etc. Infection control measures are to be followed [21].

- Home isolation
- Symptomatic treatment and monitoring of oxygen saturation with pulse oximeter (should be > 94% on room air).

Cases with moderate disease

- Remdesivir (total 5 days)
- Dexamethasone (low dose) - only for patients requiring oxygen supplementation
- Prophylactic anticoagulation with LMWH (low molecular weight heparin) or UFH (unfractionated heparin)
- Antibiotics if bacterial pneumonia can't be ruled out
- Awake proning
- Low flow oxygen supplementation to keep oxygen saturations > 94%

Cases with severe disease

- Remdesivir (consider extending up to 10 days)

- Dexamethasone or equivalent steroid (consider higher dose)
- Anticoagulation (consider higher dose of LMWH). Therapeutic dose required for those with evidence of DVT or PE.
- Antibiotics if bacterial pneumonia can't be ruled out
- Consider convalescent plasma transfusion (may be repeated once). Donor should have high titers and recipient should be negative for antibody.
- High flow oxygen supplementation with Non-Rebreather Mask (with reservoir) / HFNC (high flow nasal cannula) / NIV (non-invasive positive pressure ventilation).
- Critical patients - Mechanical ventilation / ECMO
- Prone ventilation and Lung protective ventilation (ARDSnet protocol) - for patients requiring mechanical ventilation

Conclusion

Among the available treatments, only remdesivir has shown clinical benefit and steroids has shown survival benefit. Antibody therapies hold some promise. Treatment depends on the stage and severity of disease. As results from clinical trials keep coming in, our management protocols are going to keep getting updated. The only constant is 'change' and this has proven true for COVID-19 therapies. The world is waiting and hoping for a safe and effective vaccine which can put an end to this worldwide pandemic.

Conflicts of interest

Author declares no conflicts of interest.

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