



Review Article

An insight to pharmacological modalities for COVID-19: Rationale and recommendations

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ABSTRACT

The recent outbreak of COVID-19 pandemic has caused a havoc worldwide leading to high morbidity and mortality. A very high transmission rates and limited data available on the pathophysiology of the virus, poses a big challenge in the development of effective treatment options for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The purpose of this article is to provide a short and crisp review of the rationalia and recommendations on the use of multiple therapeutic options available at different scenarios of the disease development and progression. The treatment options approved by the USFDA and CDSCO are being discussed to be used in specific population set and disease severity. Furthermore, drugs authorized as EUA but not as standard treatment of care such as monoclonal antibodies are also discussed in the article. The future of the global pandemic depends on adequacy of the treatments options for all population groups in a cost-effective manner to minimize the mortality associated with the disease.

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1. Introduction

The first incident of coronavirus disease 2019 generally called as COVID-19 was reported in Wuhan city of China in December 2019 and since then the pandemic has burst out rapidly across the globe. According to the WHO recent estimates as of January 2021, there were more than 98.2 million reported cases with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection with over 2.1 million deaths worldwide since the beginning of the pandemic.¹

The SARS-CoV-2 infection has become a global public health hazard owing to its high transmission potential and unpredictable nature of disease progression.² Contrary to the severe acute respiratory syndrome, COVID -19 patients show the highest viral load near presentation, which contributes to the rapid-transmission nature of this pandemic. An early therapeutic management of the infected patients might be beneficial since viral load already peaks around the time of hospitalization.³ However; currently

standard treatment approach against COVID-19 is missing. The present review provides an insight to the rationale and recommendations for clinical use of some antiviral agents, corticosteroids, and monoclonal/polyclonal antibodies in fighting SARS-CoV-2 infection.

The therapeutic options currently approved and/or under clinical evaluation for COVID-19 can be classified broadly into the following classes:^{4,5}

- 1. RNA-dependent RNA polymerase inhibitors:** Remdesivir and Favipiravir.^{4,5}
- 2. Protease inhibitors:** Chloroquine, hydroxychloroquine, and azithromycin, Lopinavir/ritonavir.
- 3. Immunomodulators:** Corticosteroids (dexamethasone, hydrocortisone, methylprednisolone)^{4,5}
- 4. Monoclonal antibodies:** Bamlanivimab Plus Etesevimab Combination, Casirivimab Plus Imdevimab Combination.

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2. RNA-dependent RNA polymerase inhibitors

2.1. (Remdesivir (GS-5734))

2.1.1. Mechanism of action

Remdesivir is an intravenous phosphoramidate prodrug of an adenosine analog⁴ with a broad spectrum of antiviral activity. It inhibits the viral replication through early termination of RNA transcription by binding to the viral RNA-dependent RNA polymerase (RdRp) while avoiding proofreading by viral exoribonuclease. *In vitro* activity of remdesivir has been reported in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).⁶

2.1.2. Indications and posology

Remdesivir is approved by the US FDA (United States Food and Drug Administration) on October 22, 2020; the populations are hospitalized adult and pediatric patients (≥ 12 years of age and weight of ≥ 40 kg). The agency has additionally approved its Emergency Use Authorization (EUA) in hospitalized pediatric patients aged less than 12 years and weighing ≥ 3.5 kg or weighing 3.5 kg to less than 40 kg.^{5,7} The recommended dosage for adults and pediatric patients ≥ 12 years of age and weighing at least 40 kg is a single loading dose of 200 mg on day 1 via intravenous (IV) infusion; and subsequently once-daily maintenance doses of 100 mg IV infusion starting from day 2 used over 30 to 120 minutes.⁷

2.1.3. Clinical evidence

Two phase 3 human trials GS-US-540-5773 for severe adult SARS-CoV-2 cases⁸ (ClinicalTrials.gov Identifier: NCT04292899) and GS-US-540-5774 for moderate adult SARS-CoV-2 cases⁹ (ClinicalTrials.gov Identifier: NCT04292730) have shown the efficacy of remdesivir in the treatment of COVID-19.^{8,9} The Adaptive COVID-19 Treatment Trial (ACTT-1) (ClinicalTrials.gov Identifier: NCT04280705)¹⁰ is a multinational, double-blind, randomized, placebo-controlled trial to assess the efficacy of remdesivir vs. placebo in adults hospitalized with COVID-19 and had evidence of lower respiratory tract infection. The primary outcome was time to recovery and recovery was defined as either being hospitalized for infection-control purposes only or discharged from the hospital without requirement of supplemental oxygen and no longer needed ongoing medical care. The median time to recovery in severe cases was lesser in the remdesivir group than placebo.¹⁰

2.2. Favipiravir

2.2.1. Mechanism of action

Favipiravir is considered as a repurposed drug for COVID-19.¹¹ It is another RdRp inhibitor, which acts as a substrate of viral RNA polymerase in many RNA viruses on its

conversion into an active phosphoribosylated form.⁴

2.2.2. Indications and posology

The Indian drug regulatory agency, the Central Drugs Standard Control Organization (CDSCO), granted fast-tracked approval to Glenmark Pharmaceuticals, Mumbai to market it in mild-to-moderate cases of COVID-19 on June 19, 2020, for restricted use.¹² The current recommended dosage of favipiravir is loading dose of 1800 mg twice-a-day (BID) on day 1 and subsequently 800 mg BID from day 2 to maximum of day 14.¹¹

2.2.3. Clinical evidence

Theoretically, if a drug does not show improvement in clinical outcomes even though having excellent viral clearance potential, may not be approved for COVID-19. However, in the three clinical trials, conducted in India to evaluate the efficacy of favipiravir, two trials had viral clearance as the primary efficacy outcome and the third one had time to clinical cure as the primary outcome.¹² Of these three trials two were conducted by Glenmark Pharmaceuticals (CTRI/2020/05/025114 and CTRI/2020/06/025957) and one was conducted by Cipla Pharmaceuticals (CTRI/2020/06/025799). The trial with the registration number CTRI/2020/05/025114 was a multicenter, randomized, comparative, open-label, parallel-arm, phase 3 clinical trial conducted to assess the efficacy and safety of favipiravir in adults with mild-to-moderate cases of COVID-19. The patients were randomized 1:1 to oral favipiravir (N=75) 1800 mg twice-a-day (BID) on day 1 and subsequently 800 mg BID from day 2 to maximum of day 14 combined with standard supportive care versus supportive care alone (N=75). The findings of the study indicated a significant improvement in time to clinical cure compared to the control group (3 days versus 5 days; $P = 0.030$) suggestive of potential benefits of favipiravir in mild-to-moderate cases of COVID-19. The median time to the cessation of viral shedding, though non-significant, was also lesser in the treatment group compared to the control group; 5 days versus 7 days ($P = 0.129$).¹³ The other two trials are still ongoing and the findings from these trials are awaited.

3. Protease Inhibitors

3.1. Chloroquine or hydroxychloroquine as monotherapy or combination therapy with azithromycin

Chloroquine is an antimalarial drug and hydroxychloroquine is an analogue of chloroquine. Hydroxychloroquine is also used to treat rheumatoid arthritis and systemic lupus erythematosus (SLE) (autoimmune diseases), in addition to malaria.^{4,5}

3.1.1. Mechanism of action

The mode of action of both chloroquine and hydroxychloroquine entails the inhibition of the fusion of SARS-CoV-2 and the host cell membranes by increasing the endosomal pH (intracellular vacuoles).¹⁴ Chloroquine might restrict the binding of SARS-CoV to the cell receptor by obstructing the glycosylation of the cellular angiotensin-converting enzyme 2 receptor.¹⁵

3.1.2. Clinical evidence

A plethora of clinical trials has been conducted to evaluate the efficacy of chloroquine or hydroxychloroquine as monotherapy or combination therapy with azithromycin in COVID-19. The Randomised Evaluation of COVID-19 therapy (RECOVERY) trial (Clinicaltrials.gov NCT04381936, ISRCTN number, 50189673) was a randomized, controlled, open-label, trial that compared an array of possible treatments with usual care in hospitalized COVID-19 patients. Patients in the hydroxychloroquine treatment arm were administered a loading dose of hydroxychloroquine 800 mg at admission and post 6 hours, followed by hydroxychloroquine 400 mg every 12 hours for the next 9 days or until discharge. The results of the trial were negative and not promising. The treatment with hydroxychloroquine did not reduced 28-day mortality but, on the contrary, an increased length of hospital stay and increased risk of the need of invasive mechanical ventilation or death was observed.¹⁶

Several other trials assessing the efficacy of monotherapy and combination therapy (hydroxychloroquine alone and hydroxychloroquine azithromycin combination) in hospitalized adults, hydroxychloroquine versus standard of care in mild or moderate cases of COVID-19, high-dose versus low-dose chloroquine treatment, and hydroxychloroquine in non-hospitalized adults with early COVID-19 have been conducted but no significant improvements were observed in the patients in all these trials with different scenarios.⁵

3.2. Lopinavir/Ritonavir

3.2.1. Mechanism of action

The replication of SARS-CoV-2 depends on the cleavage of polyproteins into an RdRp and a helicase. This cleavage is carried out by two proteases namely 3-chymotrypsin-like protease (3CLpro) and papain-like protease (PLpro). *In vitro* lopinavir/ritonavir has been reported to inhibit SARS-CoV 3CLpro, and this protease seems to be highly conserved in SARS-CoV-2.⁵ Even though lopinavir/ritonavir has favourable results *in vitro* against SARS-CoV, achieving significant inhibition *in vivo* might require higher than tolerable drug levels due to the poor selectivity index of the drug.¹⁷

3.2.2. Clinical evidence

The clinical trials comparing lopinavir/ritonavir with the standard of care have been conducted but there was no significant difference observed between the two arms. This was an open-label, phase 2 clinical trial that compared a combination therapy of lopinavir/ritonavir (400 mg/100 mg every 12 hours) plus interferon beta-1b (subcutaneous administration of 8 million international units) plus ribavirin (400 mg orally every 12 hours) with lopinavir/ritonavir alone (400 mg/100 mg q12H) in patients with COVID-19. A faster viral clearance and more prompt clinical improvement with the combination therapy than with lopinavir/ritonavir alone was observed.⁵

4. Immunomodulators

A systemic inflammatory response seen in patients with severe COVID-19 can cause lung injury and multiorgan dysfunction. The corticosteroids might alleviate these harmful effects by their potent anti-inflammatory effects. The important drugs of this category are dexamethasone, prednisone, methylprednisolone and hydrocortisone.⁵

4.1. Mechanism of action of dexamethasone

A cytokine storm (hyperinflammatory state) is the presentation in the sickest patients with COVID-19. This cytokine storm has common features with a rare haematological condition called haemophagocytic lymphohistiocytosis. The immune suppression can be a useful treatment strategy in such patients. The blockade of the transport of histone deacetylase 2(HDAC2) into the nucleus by 3C-like proteinase on SARS-CoV-2 nonstructural protein 5 (nsp5) weakens the capability of HDAC2 in mediating inflammation and cytokine responses, and dexamethasone by activating the histone deacetylase might directly compete with the action of SARS-CoV-2.¹⁸

4.2. Indications and Posology of corticosteroids

The recommended dosage of dexamethasone is 6 mg (oral dose or intravenous [IV] dose for ten days).¹⁹ Other corticosteroids which provide dose equivalencies of 6 mg dexamethasone are prednisone, methylprednisolone and hydrocortisone at the dosage of 40mg, 32mg and 160 mg respectively. In the situation of septic shock, hydrocortisone is a usual option. Contrary to the corticosteroids used earlier in acute respiratory distress syndrome (ARDS), the mineralocorticoid activity is absent with dexamethasone and therefore only slight effect on sodium balance and fluid volume.⁵

4.3. Clinical evidence

The findings of the RECOVERY trial showed that COVID-19 related mortality at 28 days was lesser in patients

administered with dexamethasone compared to those received the standard of care. A significant reduction in deaths was observed with dexamethasone than standard of care; by $1/3^{rd}$ in the invasive mechanical ventilation requiring patients (29.0% vs. 40.7%; $p < 0.001$) and by $1/5^{th}$ in those receiving oxygen without invasive mechanical ventilation (21.5% vs. 25.0%; $p = 0.002$).²⁰ Similarly, the results of a meta-analysis conducted on seven randomized controlled trials showed that a decrease in 28-day mortality with systemic corticosteroids decrease with well tolerated safety profile. This meta-analysis was conducted on the majority of patients of RECOVERY trial so there is a probability that the beneficial outcomes were from dexamethasone, the intervention drug used in the RECOVERY trial. The use of methylprednisolone and hydrocortisone did not prove beneficial in the COVID-19 treatment as documented in several other clinical trials.⁵

4.4. Other immunomodulators

The classes of immunomodulators such as interferons, interleukin-1 inhibitors, interleukin-6 inhibitors and kinase inhibitors have not been reported to show any clinically meaningful results until recently and there is no recommendation on the use of these agents for the treatment of COVID-19.⁵

5. Recombinant Human Monoclonal Antibodies

The FDA has issued EUA for two monoclonal antibody combinations for COVID-19 treatment. The EUA does not establish FDA approval of a product for standard care of treatment.

5.1. Casirivimab and Imdevimab Combination

The FDA issued EUA on November 21, 2020 for casirivimab and imdevimab combination for the treatment of non-hospitalized adults and pediatric patients with mild to moderate COVID-19 with ≥ 12 years of age and weight at least 40 Kg (including adults of age 65 years or older); SARS-CoV-2 viral test positive, and if there is high risk of progressing of disease to severe COVID-19 and/or hospitalization. The EUA authorized dosage casirivimab and imdevimab (each 1,200 mg) administered in combination as a single dose IV infusion shortly after positive viral testing for SARS-CoV-2 and within 10 days of the symptom onset.²¹

5.1.1. Mechanism of action: Casirivimab (formerly REGN10933) and Imdevimab (formerly REGN10987)

The mode of action of these two recombinant human monoclonal antibodies includes binding to the nonoverlapping epitopes of the spike protein receptor-binding domain (RBD) of SARS-CoV-2 and thus blocking RBD binding to the host cell receptor.⁵

5.1.2. Clinical evidence

The supportive clinical data for EUA for casirivimab and imdevimab combination are based on a randomized, double-blind, placebo-controlled clinical trial conducted on 799 non-hospitalized patients with mild to moderate COVID-19. The patients were randomized into three groups: 1) a single IV dose casirivimab and imdevimab (2400mg: 1,200 mg of each; $N=266$), 2) a dose of 8,000 mg casirivimab and imdevimab (4,000 mg of each; $N=267$); 3) placebo ($N=266$) within three days of positive SARS-CoV-2 viral test. The primary outcome was time-weighted average change in viral load from baseline values. A larger reduction in the viral load was observed in patients treated with casirivimab and imdevimab compared to placebo at day seven. The hospitalizations and emergency room visits reduced in the treatment group compared to placebo (3% vs.9%) in patients who were at high risk for disease progression.²¹

5.2. Bamlanivimab and Etesevimab Combination

On February 9, 2021, the FDA issued an EUA for bamlanivimab and etesevimab combination for mild to moderate COVID-19 in adults and pediatric patients aged ≥ 12 years and weight at least 40 kg), positive on SARS-CoV-2 viral testing, and at high risk of disease progression to severe COVID-19.²²

5.2.1. Mechanism of action: Bamlanivimab and etesevimab

Bamlanivimab and etesevimab act as neutralizing Immunoglobulin G1 (IgG1) monoclonal antibodies and the mode of action entails the binding to the overlapping epitopes within the RBD of the spike protein of SARS-CoV-2.²³ The EUA authorized dosage is bamlanivimab 700mg and etesevimab 1400 mg administered together.²²

5.2.2. Clinical evidence

The interim data from two ongoing randomized, double-blind, placebo-controlled clinical trial; Phase 2/3 Blocking Viral Attachment and Cell Entry with SARS-CoV-2 Neutralizing Antibodies-1 (BLAZE-1) trial (NCT04427501) and the Phase 2 BLAZE-4 trial (NCT04634409), has provided satisfactory of efficacy of bamlanivimab plus etesevimab in the treatment of COVID-19.²⁴

The supportive clinical data for EUA for bamlanivimab and etesevimab combination are based on a randomized, double-blind, placebo-controlled clinical trial conducted on 1,035 adults who were non-hospitalized with mild to moderate COVID-19 and with a high risk of progression to severe disease. The patients were randomized to receive a single infusion of bamlanivimab and etesevimab 2,800 mg each administered together ($N=518$), and placebo ($N=517$). The primary endpoint was COVID-19 associated

Table 1: Recommendations from National Institutes of Health (2021) on the use of different drugs for the treatment of COVID-19⁵

Drug	Recommendations
Antiviral Therapy Remdesivir (RDV) ⁵	Administration is recommended in a hospital or a health care setting providing a comparable level of care to an inpatient hospital. In India, CDSCO approved lyophilised powder of remdesivir for injection 100 mg/vial for restricted emergency use on July 7, 2020. Source: https://www.europeanpharmaceuticalreview.com/news/123045/india-approves-remdesivir-for-restricted-emergency-use-in-covid-19-patients/ (Accessed on February 1, 2021)
Favipiravir	In India, CDSCO has approved generics of Favipiravir for COVID-19 treatment on June 22, 2020. Source: https://www.pharmaceutical-business-review.com/news/covid-19-india-favipiravir-remdesivir/ (Accessed on February 1, 2021)
Chloroquine or Hydroxychloroquine alone or in combination with Azithromycin ⁵	The use of chloroquine or hydroxychloroquine as monotherapy or in combination with azithromycin for the treatment in hospitalized patients is not recommended. ⁵ In non-hospitalized patients: The use of chloroquine or hydroxychloroquine with or without azithromycin for treatment is not recommended, excluding in a clinical trial. ⁵ Use of high-dose chloroquine (600 mg BID for 10 days) is not recommended. ⁵ Adverse effects The hydroxychloroquine and azithromycin combination is associated with QTc prolongation (abnormal heart rhythm condition) in patients with COVID-19. Both hydroxychloroquine and azithromycin have long half-lives (up to 40 days and 72 hours respectively) so caution is necessary if sequential use is there rather than concomitant. Source: Institute for Safe Medication Practices. Special Edition: Medication Safety Alert! 2020. Available at: https://ismp.org/acute-care/special-edition-medication-safety-alert-april-9-2020/covid-19 (Accessed on February 1, 2021).
Lopinavir/Ritonavir ⁵	The use of lopinavir/ritonavir for treatment is not recommended except in a clinical trial.
Immunomodulators Dexamethasone ^{5,20}	Based on the findings of the RECOVERY trial, dexamethasone reduces 28-day mortality (dose 6 mg OD for up to 10 days) with COVID-19 for patients receiving respiratory support.
Interferons ⁵	The use of interferons for the treatment of patients with severe COVID-19 is not recommended, excluding in a clinical trial.
IL-1 inhibitors (Anakinra) ⁵	Inadequate data to recommend for in favour or against the use of IL-1 inhibitor for the treatment.
Anti-IL-6 monoclonal antibody (for example :siltuximab) Anti-IL-6 receptor monoclonal antibodies (for example: sarilumab, tocilizumab) ⁵	The use of these agents is not recommended for the treatment, except in a clinical trial.
Monoclonal antibodies	The combination is not recommended as the standard treatment.
Casirivimab and imdevimab combination ⁵	Hospitalized patients should not be administered with casirivimab and imdevimab combination excluding a clinical trial.
Bamlanivimab and Etesevimab combination ⁵	The combination is not recommended as the standard treatment. Hospitalized patients should not be administered with bamlanivimab and etesevimab combination excluding a clinical trial.

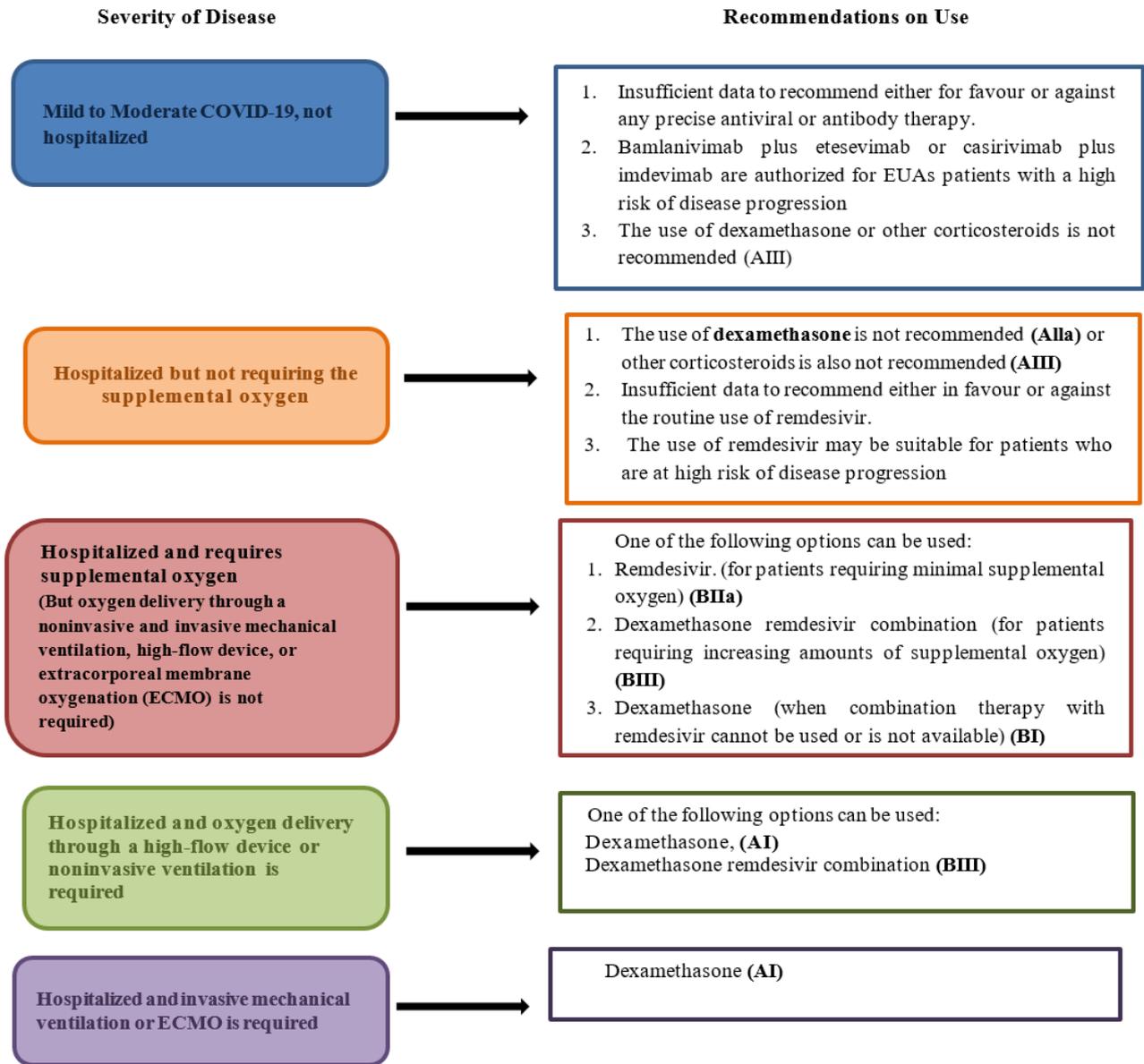


Fig. 1: Treatment algorithm for patients with COVID-19 based on disease severity (Adapted from therapeutic management of adults with COVID-19; 2021)²⁴

Recommendations Rating: A = Strong; B = Moderate, C = Optional

Evidence Levels: I = One or more randomized trials without any major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

hospitalizations or death by any cause during 29 days of follow-up. A 70% reduction was observed in the hospitalization or death with bamlanivimab and etesevimab together compared to placebo. Thus, death by any cause was significantly lower in the treatment group compared to the placebo group.²²

6. Conclusion

The pharmacological management of COVID-19 requires an in-depth understanding of drug targets and dynamics of the SARS-CoV-2 in human population. There is a huge necessity of large clinical trials to validate the drugs under investigation and revised recommendations based on this clinical data might aid in enlightening the path for this global pandemic. The role of repurposed drugs in COVID-19 treatment requires further research

and development. Moreover, the transition on the use of monoclonal antibodies from EUA to standard treatment will also require clinical evidences on efficacy and safety profile of these agents.

7. Source of Funding

None.

8. Conflict of Interest

The authors declare that there is no conflict of interest.

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