What Medicines are Under Consideration for Treatment of COVID-19?

INTRODUCTION

Most individuals with COVID-19 remain asymptomatic or develop mild symptoms. However, approximately 14% develop severe disease that requires hospitalization and oxygen support, and 5% require intensive care[1]. These proportions are likely to be different in African population because of differences in population age structures and other vulnerabilities (such as the prevalence of non-communicable diseases, HIV/AIDS, TB, malnutrition). Current management of COVID-19 revolves around the supportive management of the most common complications of severe COVID-19 such as pneumonia and acute respiratory distress syndrome (ARDS)[2]. Treatment of patients that are critically ill with these conditions is difficult as no specific treatment is currently available. Several therapeutic candidates—some previously used against SARS-CoV and MERS-CoV—are undergoing investigation as potential COVID-19 treatment options. In some countries such as the United States and China, medications such as Hydroxychloroquine have been recommended for use. However, due to lack of sufficient evidence, we should be cautious about proposed treatments until appropriately designed clinical trials that determine safety and efficacy are reported.

KEY MESSAGES

1. There is currently no recommended treatment for COVID-19. Only supportive management is available.
2. Given the available knowledge on their action and safety profiles, and in some cases efficacy against closely related coronaviruses, using existing antiviral agents is a potentially important strategy to manage the disease.
3. Laboratory studies have suggested that Chloroquine, Hydroxychloroquine, Remdesivir, Favipiravir, and Tocilizumab demonstrate antiviral activity against COVID-19.
4. Some of these agents, such as Hydroxychloroquine are already recommended for use in countries such as China, the United States and Italy.
5. However, none of these agents have strong evidence to support their use as COVID-19 treatment. Better, properly powered, randomized controlled trials of these agents are needed to support clinical use

This brief provides an overview of medications that have been considered for repurposing for COVID-19 treatment and summarizes the studies testing their effectiveness.

THERAPEUTIC OPTIONS UNDER INVESTIGATION

Many drugs approved for other diseases as well as several new drugs are being studied in clinical trials as potential therapeutic options for COVID-19 (Table 1). As the safety profile of these drugs are already known, repurposing them for COVID-19 can expedite options for control of the pandemic. Some of these agents have already demonstrated preliminary efficacy against SARS-CoV-2 in laboratory (but not yet in clinical) studies.

Table 1: Compounds currently under clinical trials for the treatment and prevention of COVID-19

Antibodies	Adalimumab Camrelizumab Eculizumab Meplazumab Tocilizumab		Antimalarial	Chloroquine & hydroxychloroquine Dihydroartemisinin
Miscellaneous	Acetylcysteine Angiotensin receptor blockers Angiotensin converting enzyme (ACE) inhibitors Bismuth potassium citrate Bromhexine hydrochloride Diammonium glycyrrhizinate	rhG-CSF Thymosin Tranilast Pirfenidone Polyinosinic-Polycytidylic acid	Antibiotics & Antiparasitic	Carriomycin Suramin sodium
Antiviral	Favipiravir Triazavirin Umifenovir ASC09 Azvudine Danoprevir	Darunavir Lopinavir + ritonavir Remdesivir Baloxavir marboxil Interferon Interleukin 2	Anti-inflammatory /immunosuppressive	Corticosteroids Fingolimod Leflunomide Thalidomide

CURRENT EVIDENCE ON THE EFFECTIVENESS OF SOME COVID-19 THERAPEUTIC COMPOUNDS

Chloroquine (CQ) and hydroxychloroquine (HCQ) are used for the treatment of malaria and the management of certain autoimmune diseases. These compounds have both demonstrated inhibitory activity against SARS-CoV-2 when tested in the laboratory[3,4]. Furthermore, efficacy studies in humans have been carried out in China and France. In a Chinese randomized trial, patients with mild symptoms received either HCQ plus standard care or standard care only. Patients in the HCQ group experienced relief from fever and cough a day sooner than those receiving standard care only[5]. However, the findings of this study are yet to be peer-reviewed. Furthermore, an initial report from a small randomized trial of HCQ in China reported that there was no difference in the rates of recovery, time to discharge, time to fever resolution or incidence of severe disease in the patients receiving HCQ plus standard of care and those receiving standard care only[6]. In addition, a French non-randomized trial on asymptomatic patients, patients with upper respiratory tract infection, and those with lower respiratory tract infection showed that patients on HCQ, and those on a combination of HCQ and azithromycin were more likely to test negative for COVID-19 on day 6 compared to those who received standard care only[7]. In contrast, another French study reported that 8 out of 10 hospitalized patients treated with HCQ and azithromycin still tested positive for COVID-19 at days 5-6 after treatment[8]. Studies on CQ and HCQ have so far been conflicting and casts doubts on the effectiveness of these candidates. Concerns about study design and sample sizes means that these results should be interpreted cautiously. Nevertheless, findings from some of these studies led to countries such as China and Italy recommending treatment with Chloroquine and/or hydroxychloroquine in their guidelines[9]. Larger, better designed trials are needed to inform evidence. Thus, several clinical trials on the effectiveness of Chloroquine and hydroxychloroquine as treatment or prophylaxis are currently underway in several countries[10].

Remdesivir is a novel drug with broad antiviral activity. Laboratory studies indicate that Remdesivir can inhibit SARS-CoV-2[11]. Additionally, the first COVID-19 patient in the United States showed improved oxygen saturation and regression of chest abnormalities after treatment with Remdesivir [12]. Report from a second study on compassionate use of

Remdesivir on patients who required oxygen support showed that after treatment, oxygen support requirements of 68% of these patients were lower compared to before treatment[13]. Data from several randomized control trials will provide more evidence on the effectiveness and safety of Remdesivir in COVID-19 patients (NCT04292730, NCT04292899).

Lopinavir-ritonavir is a licensed HIV drug combination that initially showed inhibitory activity against SARS-CoV-1 and MERS-CoV[14,15]. However, a trial in China reported that there was no benefit to time to clinical improvement after treatment with Lopinavir-ritonavir in hospitalized COVID-19 patients beyond the standard of care[16]. However, patients who received Lopinavir-ritonavir had shorter stays in intensive care units and a fewer number developed severe complications compared to those who received standard care only. In a single-blind randomized controlled trial in China, patients with mild or moderate symptoms received either lopinavir/ritonavir plus standard care or Umifenovir plus standard care or standard care only. The authors reported that there was no difference in time to a negative COVID-19 test between the three groups. There was also no difference in time to relief of fever, cough or chest imaging findings. 38% of the patients who received Lopinavir/ritonavir advanced to critical disease compared to 12% in the Umifenovir arm and 14% in the standard care group[17]. Further studies on Lopinavir-ritonavir in combination with other compounds are ongoing (NCT04328012, NCT04330690, NCT04307693).

Favipiravir was first approved for treatment of novel influenza. A clinical trial on favipiravir for the treatment of COVID-19 conducted in China indicated that favipiravir had more potent antiviral activity than that of lopinavir/ritonavir[17]. In a second open label, randomized Chinese trial, favipiravir demonstrated a shorter time to relief for fever and cough in hospitalized COVID-19 patients compared to another influenza drug, Umifenovir[18].

Ribavirin, in combination with interferon-alpha is used to treat hepatitis C and has been considered as a treatment for COVID-19. However, in laboratory studies, only high concentrations of ribavirin were effective against SARS-CoV-2[11]. A clinical trial evaluating the safety and efficacy of a combination of ribavirin and interferon-alpha and ribavirin with Lopinavir-ritonavir is currently underway in China (ChiCTR2000029387).

Tocilizumab is a monoclonal antibody used for the treatment of rheumatoid arthritis. A study in China reported resolution of fever and improved oxygen saturation after treatment with tocilizumab for COVID-19[19]. In two separate case reports, a patient in China and another in France showed improvement of chest abnormalities and improved oxygen saturation and relief from fever respectively, after treatment with Tocilizumab. However, both patients had cancer therefore these results cannot be generalized for non-cancer populations[20,21]. More clinical trials evaluating the effectiveness of tocilizumab in hospitalized COVID-19 patients has been recently approved (NCT04317092, NCT04331795, NCT04330638).

Conclusion

At present, there is no treatment specific to COVID-19. However, different agents are under investigation as potential options. Some of these candidates have demonstrated clinical benefit in preliminary studies and have been recommended for use in various countries. However, there is limited evidence to support their safety and effectiveness and these findings should be interpreted cautiously. Appropriately designed randomized controlled clinical trials are needed. Fortunately, numerous trials have been registered to achieve this goal. Findings from these studies will help inform suitable treatment for COVID-19.

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