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Fighting COVID-19: What Are the Available Options?

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the novel coronavirus, and its infection, coronavirus disease 2019 (COVID-19), have quickly become a worldwide threat. It is essential for clinicians to learn about this pandemic to manage patients. Among different aspects of the condition, is the treatment of this disease. Unfortunately, currently there is no effective treatment option that can be supported by evidence-based medicine. This review analyzes information from literature on treatments.

Key words: Antiviral Agents; COVID-19; COVID-19 drug treatment

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CONTEXT

In December 2019, a novel coronavirus was identified as the causative agent for outbreak of pneumonia. The virus was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the disease was subsequently termed COVID-19. The World Health Organization (WHO) declared the disease a pandemic, with 4 million infected people and about 300 thousand deaths worldwide. Currently, there is no consistent evidence from randomized clinical trials for any potential therapy. There is no data available for any prophylactic therapy. While there are many clinical trials under way, this narrative review summarizes proposed treatment options for COVID-19.

Anti-viral agents

- **Atazanavir**

Atazanavir is an antiretroviral protease inhibitor, which is used for the treatment of human immunodeficiency virus 1 (HIV-1) infection. Atazanavir can cause transient and usually asymptomatic elevation in serum liver enzymes, mild elevation in indirect bilirubin level and, rarely, clinically apparent, acute liver injury. The antiviral medicine is available as 100 and 300 mg capsules. Atazanavir was proposed to exert an inhibitory effect on SARS-CoV-2 by its antiretroviral protease. An artificial intelligence model showed that atazanavir has a potential binding affinity to multiple components of the coronavirus (e.g. RNA polymerase, helicase), suggesting that replication of many subunits of the virus may be inhibited by atazanavir [(1)]. It should be noted that, this medication has binding affinity for some proteins of SARS-CoV-2 (e.g. 3C-like proteinase) and the replication complex components [(1)]. The data suggest that atazanavir and atazanavir/ritonavir could be considered as an option to fight against COVID-19 [(2)].

- **Lopinavir/ritonavir**

Lopinavir/ritonavir (400 mg and 100 mg, respectively), known as Kaletra, is an HIV-1 aspartate protease inhibitor, which is used in combination with other antiretroviral medicines to treat HIV-1 infection in patients older than 14 days. Lopinavir/ritonavir could create pancreatitis and liver problems. Healthcare providers should monitor the liver function using tests before and during treatment. Lopinavir/ritonavir is shown to have in vitro inhibitory activity against SARS virus and Middle East respiratory syndrome coronavirus (MERS-CoV), and case reports have suggested that its combination with ribavirin and interferon alfa results in virologic clearance and survival. The

results are not consistent regarding the treatment of COVID-19. While a systematic review showed that use of lopinavir/ritonavir has some effects in the early phase of the disease, a trial on 199 hospitalized COVID-19 patients found no decrease in mortality or time to clinical improvement [3].

- **Remdesivir**

The nucleoside analogue GS-5734 (Remdesivir) has been reported to potently inhibit coronaviruses in vitro and in a SARS-CoV mouse model [4]. Clinical trials on this antiviral agent in treatment of Ebola are currently underway. It seems that remdesivir has acceptable clinical safety, based on comparisons between healthy volunteers and patients treated for Ebola [5]. It has been shown that combination of remdesivir and chloroquine can be highly effective against COVID-19 in vitro [6]. In a cohort study on 53 hospitalized patients with severe COVID-19, who were treated with at least one dose of remdesivir, clinical improvement has been observed in 68% patients [7]. In a clinical trial, it was shown that time to recovery of patients in remdesivir treatment arm decreased from 15 to 11 days. It has also been stated that mortality rate was also lower in remdesivir treatment arm, though the difference was not significant [8].

- **Favipiravir**

Favipiravir (discovered by Toyama Chemical Co., Ltd for influenza treatment) is an antiviral medicine that selectively inhibits RNA polymerase of some RNA viruses [9]. This antiviral agent has been approved for use against influenza infections in 2020. Since COVID-19 is caused by an RNA virus, favipiravir may have potential therapeutic effects on this disease [10]. In a study, the clinical response of 7 days of favipiravir treatment was compared to arbidol. According to the results of the study, no significant difference was observed; however, favipiravir could decrease the duration of fever and cough [5].

- **Arbidol**

Arbidol is a non-nucleoside antiviral agent that has been approved for influenza treatment in Russia and China in 1990 [11]. Arbidol has been recommended in the Guidelines for the Prevention, Diagnosis, and Treatment of Novel Coronavirus-induced Pneumonia issued by the National Health Commission (NHC) of the People's Republic of China. The treatment regimen has proposed a 200 mg dose in adults, 3 times/day for a maximum of 10 days [10]. Arbidol is mostly excreted in the bile. Allergic reactions, nausea, diarrhea, dizziness and elevated serum transaminase are the main adverse effects of arbidol [12].

- **Sofosbuvir**

This nucleotide analog has been approved for Hepatitis C virus infection, and has many advantages including high potency, few side effects, and oral preparation [13]. In the third month of the novel Coronavirus epidemic in Wuhan, the use of sofosbuvir alongside other antiviral agents such as remdesivir was suggested for COVID-19 treatment [14]. A clinical trial is currently performed in Iran, comparing the clinical response to sofosbuvir plus daclatasvir regimen with routine care in treatment of 70 moderate to severe patients with COVID-19 [15].

- **Chloroquine and Hydroxychloroquine**

Chloroquine and Hydroxychloroquine are well-known and old medications that are used for treatment and prophylaxis of malaria and for chronic inflammatory diseases, such as systemic lupus erythematous and rheumatoid arthritis [16, 17]. An important therapeutic effect of these two is the immunomodulatory effect, which is due to different mechanisms, such as decreasing cytokine production, interference with lysosomal acidification, and reducing antigen presentation [17, 18]. According to in vitro studies, these medications can have antiviral effects through prevention of viral fusion and cell entrance [19]. In this regard, many have endorsed the application of these medications even before robust studies. They have recommended consuming 500 mg of chloroquine orally once or twice daily and 400 to 800 mg of hydroxychloroquine per day [17, 20, 21]. Until now, the results of only two studies have been released. In a study, treatment with hydroxychloroquine (600 mg/day) was able to speed up the clearance of virus [21]. But the results were questioned because of several methodological flaws. Another trial was performed in china, but it did not show any effectiveness in treatment arm. While the medications have acceptable safety profile, including during pregnancy, they should be used cautiously due to resource allocation and risk of ventricular tachycardia due to QT-prolongation [16, 22]. Although there are some studies with promising results in the pipeline, their prescription is not justifiable at the moment based on evidence-based medicine [23].

Immunomodulators

Inflammatory cytokines and chemokines (e.g. interleukin-6, interleukin-1β) are significantly elevated in COVID-19 patients [24]. It has been proposed that coronavirus dysregulates the immune response, mainly by acting on T-cell lymphocytes [25]. In this way, reducing

inflammation would improve patient outcomes. So, the effects of some drugs are currently being investigated for this purpose [26-28]. However, reducing the systemic inflammatory response in patients with critical condition could have detrimental effects due to severe secondary infections [29-31]. Therefore, it is not considered as first approach in this population and should be approached with caution.

- **TNF antagonist**

Tumor necrosis factor (TNF) antagonists (i.e. infliximab or adalimumab) are widely used for the treatment of rheumatologic diseases and inflammatory bowel disease (IBD) [32-35]. Although cytokine inhibition might be considered equal to 'immune suppression' and concluded to be harmful in the COVID-19, these agents neutralize mediators in the inflammation cascade rather than leading to broad immune suppression [36]. Previous studies have shown that clinical exposure to thiopurines in patients with active IBD might increase the risk of viral infections [37, 38]. However, this is not the case regarding coronaviruses in IBD patients [39-42]. In IBD, use of steroids results in a higher risk of infection in comparison to anti-TNFα administration [41, 42]. The most appropriate time to start an immunomodulatory treatment is also on discussion.

- **Anti-IL6 antibody**

IL-6 is one of the cytokines that play a pivotal role in activation of macrophages and the generation of T helper 17 cells [43]. In this view, elevated IL-6 serves as a predictor of disease severity [44]. In rheumatoid arthritis, TNF blockage would results in a rapid decline of IL-6 and IL-1 concentrations in patients [45]. In addition, reduction in adhesion molecules and vascular endothelial growth factor (i.e. vascular permeability factor) signifies its importance in alveolar-capillary blood-gas exchange dysfunction [46-48]. Tocilizumab, an anti-IL-6R recombinant humanized monoclonal antibody, binds IL-6R and inhibits signaling [49]. After treatment with tocilizumab, 69% of patients responded with fever and hypotension resolution within hours and vasopressors could be weaned in days [50]. The most common serious adverse effect is infection among patients with chronic maintenance therapy [51]. In addition, there is a possible medication-related risk of osteonecrosis in the jaws [52]. COVID-19 patients in critical conditions are susceptible to secondary infection especially those who have comorbid chronic infections (e.g. hepatitis B and tuberculosis) [44]. A study showed that IL-6 levels were significantly elevated in COVID-19 patients with considerably varying degrees among both ICU and non-ICU patients [53]. Although IL-6 level, alone, may not be sufficient to reflect its function, this finding raises the question whether IL-6 blockade is only effective in patients with elevated serum IL-6 levels. In this view, C-reactive protein (CRP), is proposed as a reliable marker of IL-6 bioactivity and is used to monitor IL-6 blockade efficacy [51, 52, 54, 55]. Although several trials on tocilizumab are currently underway, initial reports on 21 severe and critical COVID-19 patients in China and a case study from France showed the clinical benefit of tocilizumab in COVID-19 [56, 57].

- **Intravenous immunoglobulin**

Intravenous immunoglobulin (IVIG) contains more than 95% unmodified immunoglobulin G (IgG) and only trace amounts of IgA or IgM the IgG [58]. This product performs multiple immunomodulating activities including complement activation, antibody suppression, macrophage Fc receptor saturation, and inflammatory mediator suppression [59]. IVIG is used to treat various infectious, autoimmune, and idiopathic diseases.

There is a report on 3 patients with COVID-19, who received high-dose IVIG (25 g/d for 5 days) at the time of initiation of respiratory distress, which resulted in clinical and radiographic recovery [60]. However, due to lack of sufficient data, guidelines on the management of adults with COVID-19 suggest against the routine use of this medication [61].

- **Corticosteroids**

Corticosteroids are well-known anti-inflammatory agents, which are sometimes prescribed for treating COVID-19 patients in the ICU [62]. Several studies had reported outcomes of SARS, MERS, and influenza patients treated with corticosteroids. In an RCT performed on 17 patients in 2004, early intravenous hydrocortisone was used. The results showed that initiation of corticosteroid during viral replication, in the first week of illness, resulted in delayed viral clearance and a higher subsequent plasma viral load. As a result, the patients are more likely to require mechanical ventilation, vasopressors, and renal replacement therapy [63]. A retrospective observational study on 309 adults, who were critically ill with MERS, revealed similar results [49]. A 2019 systematic review and meta-analysis found increased mortality in influenza patients who were given corticosteroids [64]. In a study on 41 COVID-19 patients, 21% received corticosteroids and showed decreased lung inflammation [65]. Another concern regarding corticosteroids is their short- and long-term adverse effects. In a retrospective study on those

with SARS, 36.3% of the patients were diagnosed with corticosteroid-induced diabetes and more than 50% suffered from joint pain and bone marrow abnormalities after treatment [66, 67]. Methylprednisolone dose varies depending on disease severity. Current interim guidance from the WHO and Chinese guidelines on COVID-19 treatment, advise against the use of corticosteroids [53, 68]. However, according to our clinical experience, corticosteroids could/should only be prescribed at the right time and for the right patients.

- **Cyclosporine, Tacrolimus**

Cyclosporine (CSA) and Tacrolimus (TAC) are calcineurin inhibitors. They inhibit production and release of interleukin II and induce activation of T-lymphocytes. They are used in many rheumatologic diseases such as Crohn's disease, rheumatoid arthritis, psoriasis and also in nephrotic syndrome and in organ transplants [69, 70]. CSA also inhibits replication of some viruses but it has not been specifically tested in COVID-19 patients. Based on a meta-analysis, there are reports of sustained virological response rates with both medications; however, firm conclusion cannot be drawn [71]. While there is an ongoing clinical trial on TAC, the data on these medications is insufficient [72].

Others

- **Plasma treatment**

In the treatment of COVID-19 patients with severe symptoms such as shortness of breath, decreased level of consciousness, decreased O2 saturation, tachypnea, underlying diseases such as diabetes or heart disease, age over 65 years, and severe respiratory distress in ICU-admitted patients, one of the recommended treatments is to use plasma transfusion [73, 74]. Accordingly, plasma donation is encouraged by FDA and is being performed in Iran and in many other medical centers around the world, including Turkey, China, and many European countries. In a study by Cortegiani et al., a recovered patient's plasma was transfused to 5 intubated patients with high viral load. All patients were receiving routine antiviral drugs and they had a very poor general condition; severe respiratory distress with decrease in saturation. After 12 days of plasma transfusion, the oxygenation condition improved and the virus load decreased along with the severity of the disease [75]. In another study by Duan et al. in China, 10 patients with severe COVID-19 (6 men and 4 women) with the average age of 52 years were treated with plasma. All had severe illness and three were under mechanical ventilation. In addition to respiratory support and maintenance therapy, all patients were receiving antiviral therapy include arbidol, ribavirin, or remdesivir. Some of these patients also received intravenous methylprednisolone 20 mg daily. Plasma was extracted from patients who had previously improved and had high antibody titer (at least1:160). Two hundred cc of plasma was transfused to the cases. As a primary outcome, patients' clinical symptoms improved significantly within 3 days of receiving plasma and showed an increase in arterial oxygen saturation, as well as improvement in laboratory test results such as increase in lymphocyte count and decrease in CRP. There were no serious and significant complications observed with plasma transfusion. In terms of imaging, pulmonary involvement was improved within 7 days of receiving plasma. Of Note, the viral load became undetectable in 7 out of 10 patients following plasma administration. It has been proposed that plasma transfusion can be effective in patients with severe COVID-19 if it is performed in the first 14 days [76]. However, there is no consensus on the volume of transfusion or frequency, and duration of treatment. This has to be explored in future studies. Currently, plasma separation is performed using cell separator. The plasma ABO group of the donor must be compatible with recipient and about 200 to 400 cc of plasma is extracted, which should be stored at a temperature below -40°C. This product should be tested for corona virus contamination using techniques such as methylene blue, to ensure that the virus is not stored in the plasma. Currently, this treatment has been used on more than 200 patients in Iran and the results will be published soon.

- **Vitamins**

Researchers proposed that vitamin deficiency might be harmful in COVID-19 patients as vitamins have immuno-modulatory effects and downregulate pro-inflammatory cytokines; however, treatment can be effective in these patients [20, 77]. There are no trials on COVID-19 and vitamins but there are some recommendations based on molecular and physiologic mechanisms. A review article in china suggests that vitamin A can be considered an option for treatment of the novel coronavirus, as it enhances the innate immune response. They have stated that vitamin B is also important, considering that riboflavin would reduce infection with MERS-CoV in human [77]. Similarly, Kandeel et al. suggest that use of vitamin B12 and nicotinamide could help based on molecular modeling performed in their study [78]. Another water-soluble vitamin, is vitamin C. Its

antioxidant effects can protect the cells and tissues from damage by oxidative agents [79]; therefore, it can be a good choice for treating the novel coronavirus disease [80]. A trial on high-dose vitamin C in patients with COVID-19 has begun in china [81]. Some experts suggest use of vitamin D in COVID-19 that may be an opportunity treatment. Vitamin D3 has a preventive effect on interstitial pneumonitis caused by the pathogens in parenchyma of lung, and can also reduce inflammatory cytokines [77, 80, 82].

- **Selenium, Zinc, Iron**

There are not any documented trials about minerals (e.g. Selenium, Zinc, and Iron) and their efficacy in treating COVID-19, but some experts suggest the effectiveness of these supplements, specially zinc, as it has shown effectiveness against the SARS [83, 84].

- **Statins**

Statins are well-known agents with anti-inflammatory effects used in cardiovascular diseases [85]. There are hypotheses regarding the efficacy of statins in patients with novel corona virus. Dashti-Khavidaki et al. suggest using statins in patients with COVID-19 and acute cardiac injury. Yet, hey do not recommend statins as a routine for treatment of these patients [86].

- **Non-steroidal anti-inflammatory drugs**

So far, we do not have any significant evidence pro or against use of NSAIDs and its routine use is not recommended in management of COVID-19 [87]. Many guidelines have not approved NSAIDs for treating the novel corona virus [88].

- **ACE-Inhibitors**

There was a hypothesis stating Angiotensin-converting enzyme (ACE) inhibitors (ACEis) and Angiotensin II receptor blockers would upregulate the receptor ACE2, which is important to SARS-CoV-2 entry into cells. According to recently published studies, treatment with ACEis does not result in increased risk to the patients [88-90]. One guideline has not recommended stopping use of ACEis, unless there is contraindication for patients to receive ACEis. They suggest that, if the patients have primary indication for using ACEis, it can be started [91].

- **Tetracyclines**

There are theories that believe tetracyclines may be effective in treatment of the novel corona virus but there are no trials or strong evidence [92].

- **Tissue Plasminogen Activator (tPA)**

There is not enough evidence for tPA and its efficacy in COVID-19 treatment. In a case series, Wang and et al. expressed that tPA may be helpful in patients with COVID-19 and acute respiratory distress syndrome (ARDS) but more studies are needed [93].

Conclusions

WHO clinical management interim guidance (March 13, 2020) emphasizes that there is no definitive treatment for COVID-19. The guidelines emphasize the role of supportive care based on disease severity and we have to wait for approved treatment options from robust clinical trials for further recommendations.

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Authors' contribution

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Conflict of interest

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