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Current Treatment of Coronavirus Disease 2019 (COVID-19)

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Abstract

Coronavirus disease 2019 (COVID-19) is an ongoing pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2). The disease was first identified in December 2019 in Wuhan, China and since then, hundreds of scientific teams and biotech companies have been developing and testing an array of drugs approved for other indications, as well as multiple investigational agents to treat the disease. So far, no specific antiviral medicine is available either to treat or prevent the aggravation of COVID-19. Herein, we provide an overview of the current research findings and guidelines concerning the main treatments of COVID-19, with a brief reference to the management of the infection in children.

Key words: *COVID-19; SARS-CoV-2; treatment guidelines*

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), the causative agent of COVID-19 (coronavirus disease-2019), originated from Wuhan, China during late December of 2019 and led to the greatest global health crisis since the 1918 Spanish flu pandemic. It rapidly spread outside of China to the rest of the world, consequently, the World Health Organization (WHO) declared COVID-19 as a global pandemic on March 11, 2020 [1] that is currently shows no significant plateauing.

Coronaviruses are enveloped positive-stranded RNA viruses. SARS-CoV-2 is a beta coronavirus of the same subgenus as the severe acute respiratory syndrome (SARS) virus (as well as several bat coronaviruses), but of a different clade. The SARS-CoV-2 enters the host cells through the S spike protein by binding to ACE2, aided by the type 2 transmembrane serine protease (TMPRSS2). Viral entry into the lung cells, myocytes and endothelial cells of the vascular system results in inflammatory changes mainly mediated by pro-inflammatory cytokines including IL-6, IL-10, tumor necrosis factor α and granulocyte colony stimulating factor (GCSF) [2]. These changes contribute to lung injury pathogenesis, hypoxia-related myocyte injury, body immune response, intestinal and cardiopulmonary changes. The spectrum of coronavirus disease-2019 can range from asymptomatic infection to severe pneumonia with ARDS and death. Although COVID-19 is primarily a pulmonary disease, emerging data suggest that it also leads to cardiac, dermatologic, hematological, hepatic, neurological, renal and other complications.

So far, no specific antiviral medicine has been available either to treat or prevent the aggravation of COVID-19. Current management consists of supportive care (invasive and noninvasive oxygen support) and treatment with off-label or compassionate-use therapies including antiretrovirals, anti-inflammatory and

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antiparasitic agents and convalescent plasma. [2, 3] The scientific community is actively exploring treatments that would potentially be effective against COVID-19.

The scope of the present review is to look for and update all the information currently available concerning the main treatments of COVID-19, including a brief report on the management of pediatric COVID19. We will review potential antiviral drugs and immune-based therapies (human blood-derived products and immunomodulatory therapies) under evaluation for the treatment of COVID-19 in addition with adjunctive therapies frequently used in patients with COVID-19 to treat the infection (Table 1).

SEARCH STRATEGY

A search of international publications was undertaken using PubMed and Google Scholar databases and the following search terms: coronavirus; 2019-nCoV; SARS-CoV-2; treatment; guidelines and COVID-19. Further relevant articles were identified from the citations referenced in the reviewed articles. The main selection of treatments in this review is based on the COVID-19 treatment guidelines of National Institutes of Health (NIH). Active clinical trials were identified using the disease search term 'coronavirus infection' on ClinicalTrials.gov

A. ANTIVIRAL TREATMENT

Remdesivir

It is an experimental anti-viral medicine which as an adenosine analogue prodrug putatively disrupts viral RNA transcription and is considered a broad-spectrum antiviral agent [4, 5]. Initially developed to treat Ebola (where it was not effective), it showed potential effectiveness in treating SARS and Middle East respiratory syndrome (MERS) also caused by coronaviruses in animal studies in a rhesus macaque model of SARS-CoV-2 infection; remdesivir-treated animals had lower viral levels in the lungs and less lung damage compared to the control animals [6].

The recommendations for remdesivir are largely based on data from the Adaptive COVID-19 Treatment Trial [7]. This is a multinational, randomized, placebo-controlled trial which included 1,063 hospitalized patients with COVID-19 and evidence of lower respiratory tract infection who received IV remdesivir or placebo for 10 days. Patients who received remdesivir had a shorter time to clinical recovery than those who received placebo (median recovery time was 11 days vs. 15 days respectively, $p<0.0001$) but a non-significant reduction in overall mortality was detected (7.1% versus 11.9%). Greater benefit was reported for those requiring oxygen and no benefit for patients with mild or moderate COVID-19. This trial contributed to the FDA's decision to authorize the emergency use of remdesivir as a COVID-19 treatment on May 1, 2020 [7,8].

In June and July 2020, remdesivir was conditionally approved in several other countries/regions worldwide, including the European Union [9]. The drug is indicated for the treatment of COVID-19 in adults and adolescents (aged ≥ 12 years and with a body weight ≥ 40 kg) with pneumonia requiring supplemental oxygen. For patients who require oxygen delivery through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO), there is uncertainty regarding whether starting remdesivir confers clinical benefit, according to the current guidelines of National Institute of Health [10].

Remdesivir is administered intravenously and is available as a solution and/or lyophilized powder for infusion over 30–120 min. Data from a multinational,

Table 1. *Agents under evaluation for the treatment of COVID-19*

Antiviral Drugs	Immune Based Treatment	Adjuctive Therapy
• Remdesevir • Chloroquine and Hydroxychloroquine +_ Azithromycin • HIV Protease Inhibitors -Lopinavir/Ritonavir -Darunavir/Ritonavir • Ivermectin • Favipavir	• Corticosteroids • Interferons • Anti-GM-CSF • IL-6 inhibitors • IL-1 inhibitors • Convalescent plasma and neutralizing antibodies • SARS-CoV-2-Specific Monoclonal Antibodies	• Thrombolytic treatment • Vitamins -VIt D -Vit C • Zinc

open-label trial of hospitalized patients with severe COVID-19 showed that remdesivir treatment for 5 or 10 days had similar clinical benefit [11]. The optimal duration of therapy for patients who do not improve after 5 days of receiving remdesivir is unclear [10].

Remdesivir should not be used in patients with an estimated glomerular filtration rate (eGFR) of < 30 mL/min and can cause side effects like gastrointestinal symptoms (e.g., nausea, vomiting), elevated transaminase levels, and an increase in prothrombin time (without a change in the international normalized ratio)

Chloroquine or hydroxychloroquine may decrease the antiviral activity of remdesivir; co administration of these drugs is not recommended [12].

A double-blinded RCT in China (n = 237) revealed no superiority of remdesivir over placebo in time to clinical recovery, 28-day mortality or viral clearance [13]. Even though remdesivir was proposed as a promising option for treating COVID-19 based on data from compassionate use, its safety and effect in humans requires high-quality evidence from well-designed strong clinical trials for further clarification.

Chloroquine and Hydroxychloroquine with or without Azithromycin

Chloroquine (CQ) and hydroxychloroquine (HCQ) are antimalarial agents with immunomodulatory properties that exhibit antiviral activity in vitro against SARS-CoV-2 [14,15]. The in-vitro activities of CQ and HCQ have been shown to have an inhibitory effect on SARS-CoV-2 mRNA production, with HCQ showing greater efficacy than CQ [16]. However, in vitro activity cannot necessarily be interpreted as clinical activity against COVID-19; in vitro activity of CQ/HCQ against many other viruses, such as Ebola virus has been reported previously, but their clinical efficacy did not reach that seen in vitro. Literature on azithromycin alone as a treatment option for COVID-19 is scarce, and it is not clear whether macrolides can be used alone or should be used in combination with HCQ. Masashi et al. support that macrolides alone, or in combination with other drugs, are effective against SARS-CoV-2 [17].

In a non-randomized trial in France on 36 patients with COVID-19, HCQ was administered alone or in combination with azithromycin and reduced SARS-CoV-2 viral burden, although the clinical significance was unclear [18]. Based on these limited data combined with early series from China which revealed shortened disease course among patients diagnosed with COVID-19 when treated with CQ [19] and under the intense pressure to prescribe a medication to COVID-19 patients, on March 28, 2020 the FDA issued an emergency use authorization of hydroxychloroquine for the treatment of COVID-19 [20].

In contrast, several recent subsequent studies have not shown a benefit with HCQ but rather a trend towards potential harm, as CQ and HCQ have a narrow therapeutic index and can cause QT interval prolongation, arrhythmia, bone marrow suppression, seizure, retinopathy, and myopathy [21]. High-dose CQ (600 mg twice daily for 10 days) has been associated with more severe toxicities than lower-dose CQ (450 mg twice daily for 1 day, followed by 450 mg once daily for 4 days) [22].

On 5 June 2020, the large randomized RECOVERY study announced that HCQ will no longer be used to treat COVID-19 given that more than 1100 deaths were reported questioning the safety of the drug. On 4 July 2020, WHO accepted the recommendation from the Solidarity Trial's International Steering Committee to discontinue the trial's HCQ arm and the United States National Institutes of Health terminated its trial of HCQ in hospitalized patients, as preliminary data from the trials did not show any benefit [23, 24, 25]. In another open-label trial of hospitalized patients who required no or only low-flow oxygen supplementation (≤4 L/min), HCQ (with or without azithromycin) did not improve clinical status at 15-day follow-up compared with standard of care [26]. Given the lack of evidence and the potential of toxicity, the use of HCQ or CQ to treat COVID-19 in hospitalized patient is no longer recommended in current guidelines but only in the context of a clinical trial [10].

HIV Protease Inhibitors (lopinavir/ritonavir-darunavir/ritonavir)

Lopinavir and ritonavir (LPV/RTV) are both antiviral protease inhibitors typically used in HIV (lopinavir is the actual antiviral agent, with ritonavir boosting lopinavir levels). Lopinavir was found to inhibit the in vitro replication of MERS-CoV and SARS-CoV [27] but the plasma drug concentrations achieved using typical doses of lopinavir/ritonavir seem to be far below the levels that may be needed to inhibit SARS-CoV-2 replication [28]. The Chinese Clinical Trial (Registered Number, ChiCTR2000029308) failed to report benefits with LPV/RTV treatment alone (400/100 mg administered orally twice daily for 14 days) compared to standard care and reported gastrointestinal adverse effects (nausea, vomit-

ing, and diarrhea) induced by LPV/RTV [29].

On March 2020, at the RECOVERY trial, a total of 1596 patients were randomized to lopinavir-ritonavir and compared with 3376 patients randomized to usual care alone. There was no significant difference in the primary endpoint of 28-day mortality and there was also no evidence of beneficial effects on the risk of progression to mechanical ventilation. As a result, on July 2020 WHO discontinued the Solidarity trial's lopinavir/ritonavir arm [25].

Lopinavir/ritonavir acts synergistically with ribavirin. It is suggested that adding ribavirin increases lopinavir's potency by about 400%. Ribavirin in combination with interferon-α 2b was shown to be active against MERS-CoV in a rhesus macaque model [10]. Additionally, the regimen of LPV/RTV plus ribavirin was shown to be effective against SARS-CoV in patients and tissue culture. In a clinical trial, triple combination of interferon beta-1b, LPV/RTV, and ribavirin for the treatment of patients admitted to hospital with COVID-19 was safe and superior to LPV/RTV alone in alleviating symptoms and shortening the duration of viral shedding and hospital stay in patients with mild to moderate COVID-19 but as participants in both arms received LPV/RTV, it is impossible to determine whether LPV/RTV contributed to the observed treatment effects [30].

Darunavir /ritonavir (DRV/c), another promising protease inhibitor against SARS-CoV-2 in vitro, typically used in HIV infection, is under investigation. Five days of DRV/c did not increase the proportion of negative conversion vs standard of care alone, although it was well tolerated according to a recent study [31].

At this point there are no data from clinical trials that support the use of HIV protease inhibitors to treat COVID-19 in clinical practice

Ivermectin

In the late 1970s, ivermectin was developed as a new class of drug to treat parasitic infections and has been previously studied as a therapeutic option for viral infections with in vitro data showing some activity against viruses like Dengue, Influenza and Zika virus [32]. In a recent study, Wagstaff et al. demonstrated that ivermectin was a potent in-vitro inhibitor of SARS-CoV-2, showing a 99.8% reduction in viral RNA after 48 hours [33].

Ivermectin was associated with lower mortality during treatment of COVID-19, especially in patients who required higher inspired oxygen or ventilatory support according to the ICON (Ivermectin in COvid Nineteen) [34] study but overall, the available clinical data on the use of ivermectin to treat COVID-19 are limited.

Favipiravir

Favipiravir is an antiviral agent which inhibits RNA polymerase, halting viral replication. Most of favipiravir's preclinical data are derived from its anti-influenza and anti-Ebola activity; however, the agent also demonstrated broad activity against other RNA viruses [35, 36].

Favipiravir was first used against SARS-CoV-2 in Wuhan at the very epicenter of the pandemic. Then, as the pandemic spread to Europe, this drug received approval for emergency use in Italy [37], and currently has been in use in Japan, Russia, Ukraine, Uzbekistan, Moldova, and Kazakhstan. Approval has also recently been granted in Saudi Arabia, Turkey, Bangladesh, and most recently Egypt

On May 30, 2020, the Russian Health Ministry approved a generic version of favipiravir, named avifavir, as it was found to be highly effective in a randomized, open-label trial that included hospitalized patients who were on room air or receiving supplemental oxygen through mask or nasal cannula; favipiravir enabled SARS-CoV-2 viral clearance in 62.5% of patients within 4 days, and was safe and well-tolerated [38]. In a non-randomized Chinese study in patients with non-severe disease, the use of favipiravir was associated with faster rates of viral clearance (median time to clearance 4 versus 11 days, p=0.003) and more frequent radiographic improvement (in 91 versus 62 percent by day 14, p= 0,004) compared with lopinavir-ritonavir [39] The results should be interpreted with caution as the co-administration of other drugs in both trials could affect the results. In June 2020, favipiravir received The Controller General of India (DCGI) approval in India for mild and moderate COVID-19 infections [40].

Favipiravir, has a similar mechanism of action to remdesivir but is orally administered, has less strong supportive data to back its use, but is nevertheless emerging as an agent that is worth considering in mild to moderate cases. An expanded phase 2 clinical trial in the US, evaluating the safety and efficacy of the antiviral tablets for the control of coronavirus 2019 (COVID-19) outbreaks in long-term care facilities is ongoing [41].

B. IMMUNE-BASED THERAPY

Corticosteroids

Infection with COVID-19 causes exuberant lung

inflammation leading to respiratory failure, ARDS, and death. It has been proposed that the potent anti-inflammatory effects of corticosteroids might prevent or mitigate these deleterious effects. Different studies have found corticosteroid effects ranging from harmful to beneficial [10].

Observational studies of other respiratory infections (e.g., SARS, MERS, influenza) [42] and randomized controlled studies of ARDS suggested an increased risk of multiorgan dysfunction, no mortality benefit, and possibly an increased risk of death with the use of corticosteroids [43]. The World Health Organization (WHO) on 13th March 2020 recommended against the routine use of systemic corticosteroids in the clinical management of severe viral pneumonia, if COVID-19 is suspected [42].

In contrast, a preliminary report of the RECOVERY trial in June 2020 suggested that dexamethasone reduced mortality in COVID-19 patients, but the benefit was restricted to patients with severe and critical COVID-19 [44]. The use of corticosteroids has been evaluated in patients with ARDS by several randomized, controlled trials (RCTs). A meta-analysis of 7 RCTs concerning the use of corticosteroids in 851 patients demonstrated that, compared with placebo, corticosteroid therapy reduced the risk of all-cause mortality (risk ratio 0.75; 95% CI, 0.59–0.95) and the duration of mechanical ventilation (mean difference, -4.93 days; 95% CI, -7.81 to -2.06 days) [45].

On the basis of this report, the COVID-19 Treatment Guidelines NIH panel recommends using dexamethasone 6 mg per day for up to 10 days or until hospital discharge, whichever comes first, for the treatment of COVID-19 in hospitalized patients who are mechanically ventilated and in hospitalized patients who require supplemental oxygen but who are not mechanically ventilated [10]. The Surviving Sepsis Campaign COVID-19 subcommittee (a joint initiative of the Society of Critical Care Medicine and the European Society of Intensive Care Medicine) recommends against the routine use of systemic corticosteroids in mechanically ventilated adults with COVID-19 and respiratory failure (without ARDS) [46]. However, these experts generally support a weak recommendation to use low-dose, short-duration systemic corticosteroids in the sickest patients with COVID-19 and ARDS. On 2 September, the WHO recommended treatment with systemic steroids for patients with severe and critical symptoms, but continued to advise against their use for other patients [47]. Whether the use of other corticosteroids (e.g., prednisone, methylprednisolone, hydrocortisone) for the treatment of COVID-19 provides the same benefit as dexamethasone is unclear [10].

Interferon (IFN)

Interferon induces several antiviral processes by triggering viral RNA degradation, RNA transcription changes, protein synthesis inhibition and apoptosis [48]. Literature reviews point out that interferons have been in use for many years against emerging viruses when no other treatment options have been available. Interferons have been used for both SARS-CoV and MERS-CoV in the past and have shown positive results both in vitro and in vivo [49].

SARS-CoV and MERS-CoV are able to influence interferon signaling pathways by interfering with proteins involved in interferon expression. The excessive in vitro sensitivity of SARS-CoV2 to interferons is probably explained by the fact that SARS-CoV-2 might have lost these anti-interferon actions [50]. An open-label, uncontrolled retrospective study on SARS showed that treatments including Alfacon-1(IFN-α) and corticosteroids were associated with accelerated lung recovery and shorter duration of intubation time compared with corticosteroids as monotherapy. Moreover, a randomized, four-arm open-label, retrospective study on SARS in Guangzhou, China, demonstrated that IFN plus high-dose steroid therapy achieved respiratory improvement, faster resolution of pulmonary infiltrates and less need for mechanical ventilation [48].

Moreover, as interferon treatment is more effective at earlier stages, IFN can be used prophylactically against SARS-CoV2 and this is further supported by the in vitro efficacy of interferon pre-treatment against the virus. Shen et al. reported that interferon-2α can effectively reduce the infection rate of SARS-CoV-2, which further supports the above statement [50].

The recommended guidelines for the treatment of SARS-CoV-2 in China include administering 5M units of interferonα via an inhaler in combination with oral ribavirin twice a day. The advantage of inhalation therapy is that it acts directly on the respiratory tract [49].

Anti-granulocyte-macrophage colony stimulating factor antibodies (anti- GM-CSF)

Granulocyte-macrophage colony stimulating factor (GM-CSF) is believed to be a key cytokine mediator of the pro-inflammatory state in patients with SARS-

CoV-2 infection. In later stages of COVID-19, illness severity appears to be driven by the inappropriate release of several cytokines, such as IL-6 and GM-CSF. These mediators are involved in inflammatory lung injury, predisposing patients to respiratory failure and eventually ARDS. Therefore, inhibition of GM-CSF signaling may be a reasonable treatment in this stage of the disease [51].

Although there has been no clinical data on its use in patients with COVID-19, mechanistically, blocking the GM-CSF pathway is expected to reduce the severity of cytokine-induced inflammation. Based on this, a randomized control trial was planned to assess the efficacy and safety of lenzilumab, a humanized recombinant monoclonal antibody against GM-CSF. Lenzilumab has undergone phase I and II studies where it was assessed as a treatment of the cytokine release syndrome which is believed to be associated with COVID-19 infection [52]. Lenzilumab has received FDA approval for compassionate use in COVID-19 patients (FDA), while a phase 3 study is ongoing [51].

Gimsilumab has been tested in a phase I study of healthy volunteers. It has also been proved that by binding to GM-CSF receptor it will block the signaling pathway that leads to cytokine release syndrome (CRS), which is also believed to characterize the pro-inflammatory stage of COVID-19 [54]. A clinical trial has also been approved for gimsilumab for the treatment of COVID-19 and is now enrolling patients in the US [53].

Another prospective interventional single-center cohort study tested the efficacy and safety of mavrilimumab in patients with severe COVID-19 pneumonia and evidence of hyper-inflammation in Italy. Thirteen non-mechanically ventilated patients with severe COVID-19 pneumonia and hyper-inflammation were treated with a single intravenous dose of mavrilimumab 6 mg/kg upon admission to the hospital. Twenty-six non-mechanically ventilated patients with severe COVID-19 pneumonia and hyper-inflammation and with similar baseline characteristics were evaluated as a control-group. Over the course of the 28-day follow-up period, mavrilimumab treated patients experienced earlier and improved clinical outcomes than control patients. Death occurred in 0% (n = 0/13) of mavrilimumab-treated patients by day 28 compared to 27% (n = 7/26) of control patients [53].

IL-1 inhibitors

Another option in tackling the cytokine storm which characterizes COVID-19 infection is targeting interleukin -1 (IL-1), by inhibiting IL-1 binding to the IL-1 type I receptor.

Canakinumab, is a monoclonal antibody against IL-1-beta, which has been approved by the Italian Drug Agency (AIFA) for COVID-19 pneumonia. It is used for the treatment of Familial Mediterranean fever and atherosclerotic diseases for its anti-inflammatory properties. A clinical phase 2 trial of Canakinumab is ongoing in patients with COVID-19 pneumonia [53].

Anakinra is another option in targeting IL-1 receptor, which is used for rheumatoid arthritis. Anakinra is a biopharmaceutical drug with a wide therapeutic range and high safety. Anakinra is tested with tocilizumab in a phase 2 clinical trial (COVID-19 Clinical Trials, 2020). It is also being tested in COVID-19 patients combined with emapalumab (Phase 2/3 multicenter randomized clinical trial [52]. The SARS CoV-2 virus uses the angiotensin-converting enzyme 2 (ACE2) as a receptor to enter cells. After entering to type II alveolar epithelial cells of the lungs, SARS CoV-2 triggers life-threatening cytokine release syndrome in its host, which can result in excessive levels of pro-inflammatory cytokines production including IL-6, TNF-a and IL-1b. A group of American researchers suggested that continuous intravenous anakinra infusions might have significant survival benefits possibly by reversing the cytokine storm in patients with COVID-19 [54].

IL-6 inhibitors

IL-6 has been considered the main culprit of the "cytokine storm" found in COVID-19 infection [55]. In critically ill patients with COVID-19, IL-6 levels were almost 10-fold higher. For that reason, blocking IL-6 by using monoclonal antibodies has gained space as a significant potential therapeutic option.

Tocilizumab is a recombinant humanized IL-6 receptor antagonist [56]. A recent single-group, multicentre study showed that within a few days of administration of tocilizumab, temperature curve was normalized and oxygen intake was lowered in 75% of patients with severe or critical SARS-CoV-2 infection [49]. This suggests that tocilizumab may be a new therapeutic strategy. In China, tocilizumab has been used to treat severely or critically ill COVID-19 patients with extensive lung lesions and high IL-6 levels. An initial dose of 4–8 mg/kg is infused over more than 60 minutes. If initial dose is not effective, a second dose can be administered after 12 hours but no more than 2 doses should be given [56].

Sarilumab is another human monoclonal antibody that inhibits the IL-6 pathway by binding and blocking the IL-6 receptor. Common toxicities include neutropenia, thrombocytopenia, infusion reaction and infection. Global clinical trials of sarilumab in COVID-19 treatment have been initiated to evaluate clinical outcomes such as fever, the need for supplemental oxygen, mortality, mechanical ventilation, ICU stay and hospitalization [49]. A clinical trial involving sarilumab for the treatment of severe COVID-19 is ongoing, where the efficacy and safety of sarilumab 200 mg and 400 mg doses administered intravenously over 1 hour are being compared with standard of care. Because measurement of IL-6 levels is not readily available in most institutions, C-reactive protein (CRP) levels may be used as surrogate markers of the increased pro-inflammatory state. IL-6 inhibitors rapidly decrease CRP levels after administration; therefore, CRP levels may be used to monitor the response to therapy [57].

Siltuximab, which is approved in the USA to treat patients with multi-centric Castleman disease, is the third potential IL-6- targeted therapy for COVID-19 trials. Recently, an Italian clinical team reported that among 21 COVID-19 patients with ARDS who received siltuximab (70 0–120 0 mg, median 90 0 mg), the serum CRP level was reduced in 16 patients. Moreover, 33% of patients exhibited clinical improvement, 43% remained stable and 24% deteriorated [58] The efficacy and safety of siltuximab in the treatment of COVID-19 patients need to be further studied [49].

NIH COVID-19 Treatment Guidelines Panel recommends against the use of IL-6 inhibitors in the treatment of COVID-19, except in a clinical trial [10].

Convalescent plasma and neutralizing antibodies

The US FDA has approved the emergency investigational use of convalescent plasma (CP) for the treatment of critically ill patients with COVID-19. CP is collected from COVID-19 recovered individuals who are eligible for blood donation and their symptoms have resolved at least 14 days before donation. They should also have negative PCR for SARS-CoV-2 and high SARS-CoV-2 neutralizing antibody titers [52]. It seems that CP acts through viral neutralization, cellular cytotoxicity induced by antibody, activation of complement system, and phagocytosis but the exact mechanism of action has remained elusive. Although, almost all studies on CP (in severe patients) reported its effectiveness, only one study supported that there was no significant difference in time to clinical improvement compared to control group [55].

A preliminary report of a series of five patients with severe COVID-19 pneumonia complicated by ARDS showed that the administration of CP containing neutralizing antibody (SARS-CoV-2 IgG titers greater than 1:1000 by enzyme linked immunosorbent assay and neutralizing antibody titer >40) led to clinical improvement. There was a normalization of body temperature in four patients within 3 days, the sequential organ failure assessment score decreased, and viral load declined to negativity by day 12. ARDS resolved within 12 days in four patients. These preliminary findings seem promising for the future [56].

Available data suggest that serious adverse reactions following the administration of COVID-19 CP are infrequent and consistent with the risks associated with plasma infusions for other indications.

SARS-CoV-2-Specific Monoclonal Antibodies

Monoclonal antibodies (mAbs) used in the treatment or prevention of infectious diseases are engineered versions of antibodies naturally produced by the immune system in response to invading viruses or other pathogens. SARS-CoV-2-specific mAbs are designed to directly target the virus and may act as neutralizing antibodies (nAbs). Most SARS-CoV -2-specific mAbs being investigated target epitopes on the spike protein (S protein) of the virus and block the receptor-binding domain (RBD) of the S protein from interacting with human angiotensin-converting enzyme 2 (ACE2), thereby preventing the virus from entering cells thus inhibiting viral replication [59].

REGN-COV2 is a combination of two monoclonal antibodies (REGN10933 and REGN10987) and was designed specifically to block infectivity of SARS-CoV-2 COVID-19. Antibodies produced by mice, which have been genetically modified to have a human immune system, as well as antibodies identified from humans who have recovered from COVID-19 were used in a clinical trial of 275 patients with laboratory-confirmed COVID-19 treated in the outpatient setting. Enrolled patients were randomized 1:1:1 to receive a single IV infusion of 8 g of REGN-COV2 (high dose), 2.4 g of REGN-COV2 (low dose), or placebo. Regeneron Pharmaceuticals (the manufacturer of REGN-COV2) stated that data analysis showed that the drug reduced viral load and time to alleviation of symptoms and there was a positive trend in reduction of medical visits; the greatest treatment benefit appeared to be in patients who had

not mounted their own effective immune response (no measurable antiviral antibodies) [60]. On 2 October 2020, it was announced that US President Donald Trump had received "a single 8 gram dose of REGN-COV2" after testing positive for SARS-CoV-2.The drug was provided by the company in response to a "compassionate use" (temporary authorization for use) request from the president's physicians [61].

In addition to this trial in non-hospitalized patients, REGN-COV2 is currently being studied in a Phase 2/3 clinical trial for the treatment of COVID-19 in hospitalized patients, the Phase 3 open-label RECOVERY trial of hospitalized patients in the UK and a Phase 3 trial for the prevention of COVID-19 in household contacts of infected individuals. Recruitment in all 4 trials is ongoing.

LY-CoV555 is another Neutralizing IgG1 mAb whose preclinical studies demonstrated protective effects against SARS-CoV-2 infection and viral replication in an animal model [62]. A randomized, double-blind, placebo-controlled phase 2 study is evaluating efficacy and safety of LY-CoV555 used alone or in conjunction with a second mAb (LYCoV016 [LY3832479]) for early treatment of COVID-19 in adults who are outpatients with mild to moderate disease is ongoing and an interim analysis of the study suggested [63].

SARS-CoV-2-specific mAbs are not commercially available. Although results of many controlled clinical trials are needed to provide information on the safety and efficacy of mAbs that specifically target SARS-CoV-2, it has been suggested that such mAbs may offer some advantages over other immunotherapies used for the treatment of COVID-19 (e.g., COVID-19 convalescent plasma, IGIV) in terms of specificity and safety.

C. ADJUNCTIVE THERAPY

Antithrombotic therapy

COVID-19 may predispose patients to thrombotic disease, both in the venous and arterial circulations, due to excessive inflammation, platelet activation, endothelial dysfunction, and stasis. Hematologic and coagulation parameters have been associated with worse clinical outcomes in hospitalized patients with COVID-19 [64].

The incidence of Venus Thromboembolism (VTE) in COVID-19 patients is not well established. Reports have ranged between 8% in all COVID-19 patients to 69% in ICU patients screened with lower extremity ultrasound [65].

Several studies have examined the prophylactic use of anticoagulants, mainly in the form of low molecular-weight heparin (LMWH) and unfractionated heparin (UFH), to reduce the risk of VTE in COVID-19 patients [66].

No difference in overall mortality has been observed when thromboprophylaxis with either enoxaparin or UFH (29.7% in treatment group vs 30.3% in no-treatment group, p=0.91). However, significant mortality reduction has been observed when treatment was given to patients with D-dimer levels increased by more than six-fold compared to the upper normal limit (32.8% vs 52.4%, p=0.017) and patients with a sepsis-induced coagulopathy (SIC) score of 4 or greater (40.0% vs 64.2%, p=0.029). Significant reduction in hospital mortality has also been observed in mechanically ventilated patients given anticoagulants (29.1% vs 62.7%, p<0.001) [59]. In a French prospective multicenter cohort of 150 ICU patients, 16.7% had pulmonary embolism despite prophylactic anticoagulation [66].

According to the NIH guidelines, hospitalized adults with COVID-19, should receive VTE prophylaxis, and the standard of care like any other hospitalized adults. Routine post-discharge VTE prophylaxis is not recommended for patients with COVID-19. However, the benefits of post-discharge prophylaxis for certain high-risk patients without COVID-19 led to the Food and Drug Administration approval of two regimens: rivaroxaban 10 mg daily for 31 to 39 days, and betrixaban 160 mg on Day 1, followed by betrixaban 80 mg once daily for 35 to 42 days [10].

Vitamins

Vitamin D has important functions beyond those of calcium and bone homeostasis, which include modulation of the innate and adaptive immune responses. Vitamin D has immunomodulatory effects that could potentially decrease the severity of COVID-19 infection; vitamin D supplements may also increase T regulatory cell activity [10].

Two randomized, double-blind, placebo-controlled clinical trials (VIOLET, VITdAL-ICU) in critically ill patients with vitamin D deficiency (but not with COVID-19) showed that high-dose vitamin D did not reduce hospital stay or mortality rate compared with placebo. Patients in both studies received a single enteral dose of 540,000 international units (IU; units) of vitamin D3 [67, 68].

There are many ongoing trials administering vitamin D alone or in combination with other agents to participants with and without vitamin D deficiency to evaluate the use of vitamin D for the prevention or treatment of COVID-19 [69].

There is some evidence suggesting that similarly to vitamin D, vitamin C might help manage the immunopathologic responses contributing to the pathogenesis of severe respiratory viral infections [70]. A recent meta-analysis compared the effect of vitamin C versus non-vitamin C infusion in patients with sepsis. Data from 10 studies (4 randomized controlled trials [RCTs] and 6 retrospective studies) involving 1671 patients indicated that the use of vitamin C did not reduce the risk of 28-day, intensive care unit or in-hospital mortality and only two RCTs suggested that vitamin C treatment showed reduced 28-day mortality. Several trials of oral and IV vitamin C supplementation in people with COVID-19 are also ongoing [71].

Zinc

The importance of the trace element zinc for the development and function of the immune system has been proven in numerous studies as well as the impressive intersection of known zinc deficiency and the predisposition for a severe COVID-19 infection. Zinc supplementation might already prevent viral entry and also suppresses its replication, while it supports the anti-viral response of the host cells [72].

A retrospective, observational study compared zinc supplementation to no zinc supplementation in 932 hospitalized patients with COVID-19 who received hydroxychloroquine and azithromycin from March 2 to April 5, 2020. Zinc was given as a zinc sulfate 220-mg capsule (50 mg of elemental zinc) twice daily for 5 days. The addition of zinc did not affect the length of hospitalization, duration of ventilation, or ICU duration but in univariate analyses, zinc sulfate increased the frequency of patients being discharged, and decreased the need for ventilation, admission to the ICU, and mortality or transfer to hospice for patients who were never admitted to the ICU [73]. The optimal dose of zinc for the treatment of COVID-19 is not established. Reversible hematologic defects (i.e., anemia, leukopenia) and neurologic manifestations (i.e., myelopathy, paresthesia,) have been reported with long-term zinc supplementation. The data so far are insufficient to guide clinical practice.

Treatment options for children with COVID-19

Due to the lack of evidence from trials in children, all cases should be discussed at an individual basis and decisions to treat with antivirals usually occur within the context of a relevant clinical trial.

As expected, antiviral therapy for COVID-19 should be reserved for children with severe SARS-CoV-2 infection. Remdesivir has not been evaluated in clinical trials that include children with COVID-19. A phase 2/3 open-label trial (CARAVAN) of remdesivir started in June 2020 to assess safety, tolerability, pharmacokinetics, and efficacy in children from birth to age 18 years [74]. The use of HCQ or CQ for the treatment of COVID-19 in children is currently not recommended due to concerns about its efficacy and could only be considered as part of a clinical trial. HCQ should be avoided in children with underlying QTc abnormalities and those who require other medications that could interact. The pediatric glucocorticoid arm of the RECOVERY trial is ongoing.

Low-dose glucocorticoids may be beneficial in children with COVID-19 when given up to 10 days and include: dexamethasone 0.15 mg/kg orally, intravenously (IV), or nasogastrically (NG) once daily (maximum dose 6 mg); prednisolone 1 mg/kg orally or NG once daily (maximum dose 40 mg); or methylprednisolone 0.8 mg/kg IV once daily (maximum dose 32 mg).

At present, immune modulators such as IL-6 inhibitors, interferon-beta 1b, CP from recovered COVID-19 patients are not recommended due to lack of efficacy data in children

CONCLUSION

Although the fact that an array of drugs approved for other indications, as well as multiple investigational agents, are being studied for the treatment of COVID-19 in clinical trials and can be accessed through Emergency Use Authorization, or compassionate use mechanisms, the optimal approach to treatment of COVID-19 is uncertain. Literature data suggest a clinical benefit with remdesivir and a mortality benefit with dexamethasone, but no other therapies have clearly proven effective. SARS-CoV-2-Specific Monoclonal Antibodies offer some advantages over other immunotherapies and seem to help prevent and treat early infections of COVID-19 but more data are needed. As far as the other medication agents discussed in the review are concerned, outcomes from case reports and case series cannot be generalized for a larger population and their use is recommended only in clinical trials.

This review does not include, nitazoxanide, angiotensin II receptor blockers, famotidine, colchicine and other medications that have been suggested for SARS-CoV-2 that are awaiting evidence, or any oral-route traditional Chinese medications with insufficient evidence of qual-

ity, safety and efficacy.

In conclusion, management of COVID-19 disease remains largely supportive with particular emphasis on prevention and management of complications. It is important to caution readers that new data emerges daily regarding treatment options for COVID-19. Further well-designed RCTs in COVID-19 therapies are warranted before final conclusions on efficacy could be made..

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