Review Article

A Narrative Review of Existing Options for COVID-19-Specific Treatments

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The new coronavirus disease 2019 (COVID-19) was declared a global pandemic in early 2020. The ongoing COVID-19 pandemic has affected morbidity and mortality tremendously. Even though multiple drugs are being used throughout the world since the advent of COVID-19, only limited treatment options are available for COVID-19. Therefore, drugs targeting various pathologic aspects of the disease are being explored. Multiple studies have been published to demonstrate their clinical efficacy until now. Based on the current evidence to date, we summarized the mechanism, roles, and side effects of all existing treatment options to target this potentially fatal virus.

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a global pandemic in early 2020. As of July 19, 2020, COVID-19 has claimed around four million lives worldwide, with total cases of more than 189 million. The United States alone corresponds to more than 33 million cases around the globe [1].

COVID-19 continues to impact many countries globally. Primary treatment continues to be centered on alleviating symptoms and managing the complications of COVID-19. Since the advent of COVID-19, several drugs and drug combinations have been studied [2]. Many of these treatments are based on the in vitro activity against SARS-CoV and MERS-CoV. However, diligent work in finding an effective treatment is still in the process, including observational studies, randomized controlled trials, and case series. There are limited evidence and data to support any effective

and gold standard therapy against COVID-19. It is a general understanding that most of the patients who have minimal to mild symptoms of COVID-19 do not require any COVID-19-specific treatment, and therefore, supportive measures are usually sufficient. For example, we rely on quarantine, isolation, and infection control measures to prevent disease spread and supportive care for those who become ill. However, patients with moderate to severe symptoms, including subjective dyspnea, hypoxia, recurrent fever, or signs of organ failure, may be candidates for COVID-19-specific therapy.

2. Methods

We searched the PubMed, EMBASE, and Google Scholar for all articles related to COVID-19-specific therapies using the search words, COVID-19, SARS-CoV-2, Coronavirus, and search keyword for some of the most common medicines, including chloroquine, hydroxychloroquine, remdesivir,

tocilizumab, leronlimab, convalescent plasma, azithromycin, lopinavir-ritonavir, ribavirin, favipiravir, oseltamivir, and umifenovir.

3. Results and Discussion

The treatments reviewed in this summary can be divided into five categories: immunomodulatory drugs, antiviral, COVID-19, specific immunoglobulins, convalescent plasma, and various drugs (Table 1).

3.1. Immunomodulatory Drugs. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may cause severe illness in up to 20% of patients, which can be attributed to a systemic hyperinflammatory response.

Therefore, de-escalation of this response is a potential therapeutic target. Some of the immunomodulators studied and recommended for the treatment of COVID-19 will be discussed in this section.

3.1.1. Chloroquine and Hydroxychloroquine. Chloroquine (CQ) and hydroxychloroquine (HCQ) emerged earlier in the pandemic and have gained tremendous public attention. On March 30th, 2020, the U.S. Food and Drug Administration (US FDA) issued an emergency use authorization (EUA) for CQ/HCQ to treat hospitalized patients with COVID-19 [3]. Guidelines were formulated for this drug to be administered to hospitalized patients who had evidence of pneumonia, and it continues to be widely used in acute COVID-19 worldwide [4].

CQ and HCQ have been long used to treat and prevent malaria in many malaria-endemic countries. Apart from malaria, HCQ is also the cornerstone of the treatment of several autoimmune and inflammatory disorders. There is convincing evidence from in vitro studies that HCQ has antiviral activity against SARS-CoV-2 [5]. It has antiviral potential through multiple mechanisms, mainly through interference with the terminal glycosylation of the cellular receptor ACE2, thereby preventing virus-receptor binding and entry into cell [6]. Secondly, HCQ increases the pH of acidic cellular organelles, hampering various viral proteins [7]. HCQ has an immunomodulatory effect, which could be explained by its propensity to alter intracellular pH leading to the inhibition of lysosomal activity in antigen-presenting cells and B cells, thereby preventing T-cell activation and cytokine production, respectively [7]. The other possible immunomodulatory action is partly mediated by inhibiting tumor necrosis factor (TNF) release from the monocytes and macrophages that play a significant role in activating other immune cells apart from starting the endothelial cells [8–10].

In one of the earliest reports from China containing 100 patients from 10 hospitals, HCQ was associated with improved radiologic findings, enhanced viral clearance, and decreased disease progression [11]. In an open-label, nonrandomized French study by Gautret et al. consisting of 36 COVID-19-positive patients, the group treated with 200 mg of HCQ ($n = 20$) had improved virologic clearance than the control group ($n = 16$) with standard treatment. The

virological clearance measured by nasopharyngeal swab was 70% in the HCQ group versus 12.5% in the control group ($P = 0.001$). Moreover, the addition of azithromycin (AZT) to HCQ in 6 patients was associated with improved viral clearance (6/6, 100%) compared with HCQ monotherapy (8/14, 57%). However, this study had several significant limitations, including a small sample size and not reporting clinical or safety outcomes [12]. In another study by Gautret et al., 80 mildly symptomatic COVID-19 patients received HCQ 200 mg for ten days along with AZT 500 mg for one day, followed by 250 mg for four days [13]. They observed significant clinical improvement and viral clearance. However, this study's major drawback is that it was an observational single-arm study. Therefore, its clinical efficacy and safety cannot be extrapolated to patients with severe disease because this was done in mild diseases. An observational study in China consisting of 30 patients randomized to HCQ 400 mg daily for five days along with the standard of care versus just standard care alone reported no significant difference in viral clearance between the two groups (86.7% vs. 93.3%; $P > 0.05$) or median duration of viral clearance (4 days vs. two days; $P > 0.05$) [14]. Geleris et al., in a study consisting of 1376 patients, reported a primary endpoint of intubation or death in 25.1% of patients with no added risk or benefit of HCQ administration [15]. In contrast, Arshad et al. showed that in patients with COVID-19 treated with HCQ alone and combined with AZT, it was correlated with a decline in COVID-19-associated mortality [16].

A study among 368 COVID-19 patients in which 97 received HCQ alone, 113 received HCQ and AZT, and 158 were unexposed to HCQ resulted in a higher risk of death in patients treated with HCQ alone, without any difference between these groups for the risk of ventilation [17]. In a study of 1438 patients, HCQ use was not associated with decreased in-hospital mortality, whether associated with AZT or used alone [18]. In a survey from Brazil among mild-to-moderate COVID-19 cases, the use of HCQ alone (odds ratio, 1.21; 95% confidence interval [CI], 0.69 to 2.11; $P = 1.00$) or with AZT (odds ratio, 0.99; 95% CI, 0.57 to 1.73; $P = 1.00$), did not improve clinical status at 15 days as compared with standard care [19]. Prolongation of the corrected QT interval and elevated liver-enzyme levels were more frequent in patients receiving HCQ, alone or with AZT [19]. In a randomized clinical trial of 75 patients treated with HCQ with a higher dose loading dose of 1200 mg/day for three days followed by 800 mg/day for 2 or 3 weeks, compared with 75 patients receiving standard of care alone, there was no difference in viral clearance at day 28 and no clinical difference between the two groups [20]. A recent study in ambulatory patients with mild symptoms also indicated that HCQ did not reduce symptom severity at 14 days [21]. Similarly, Mitjà et al. reported no benefit of HCQ in patients with mild COVID-19 beyond routine care [22].

Boulware et al. studied the postexposure prophylactic role of HCQ. They found no significant benefit of HCQ in the incidence of new illness (49 of 414 [11.8%]) for those receiving placebo (58 of 407 [14.3%]) [23]. HCQ could not prevent the occurrence of COVID-19 after moderate or high

TABLE 1: Narrative summary of the commonly used therapeutic agents for COVID-19.

Drug	MOA	Dosage	Duration	COVID-specific indication	Adverse effects	Results	Caution	Evidence
Hydroxychloroquine	Unclear; increases intracellular pH to inhibit lysosomal activity in APC and B cells to prevent T-cell and cytokine activation	600 mg PO BID × 2 days, then 400 mg qd × 4 days	6 days	(i) US FDA emergency use authorized for hospitalized patients (ii) Possible postexposure prophylaxis	(i) Oculotoxicity (ii) Worsening of skin disease (iii) Cardiotoxicity (iv) Arrhythmia		(i) Renal and hepatic impairment is not defined (ii) Psoriasis (iii) G6PD deficiency (iv) QT prolongation (v) Arrythmia/CHF (i) Renal: CrCl <10 decrease 50% dose (ii) Hepatic: not defined	(i) No benefit
Chloroquine	Inhibit early stages of final virus replication	(i) High dose: 600 mg BID × 10 days (ii) Low dose: 450 mg BID × 1 day, then 450 mg qd × 4 days	5–10 days	US FDA emergency use authorized for hospitalized patients			(iii) Seizure history (iv) Psoriasis (v) G6PD deficiency (vi) QT prolongation (vii) Arrythmia/CHF (i) Renal: CrCL < 30 not defined (ii) Hepatic: avoid use in active hepatic disease or baseline AST/ALT >1.5 ULN	(i) No benefit
Tocilizumab	IgG1 IL-6 receptor antibody	400 mg	Single dose	US FDA approved for phase III clinical trial in hospitalized patients with severe infection				(i) Benefit in specified group
Dexamethasone	Unclear; anti-inflammatory			WHO recommends for hospitalized COVID-19	(i) Increased blood glucose (ii) Psychosis (iii) Avascular osteonecrosis		(i) Hepatic: not defined (ii) Osteoporosis (iii) Psychiatric disorder (iv) Diabetes mellitus (v) Hypertension (vi) 1st trimester pregnancy (vii) Immunosuppressed	(i) Benefit in moderate to severe cases
Leronlimab	CCR5 receptor antibody to prevent viral entry into cells	700 mg SC weekly		US FDA approved for phase II trials in patients with mild to moderate respiratory complications				

TABLE 1: Continued.

Drug	MOA	Dosage	Duration	COVID-specific indication	Adverse effects	Results	Caution	Evidence
Lopinavir/ritonavir	Lopinavir: HIV-1 protease inhibitor Ritonavir: P450 CPY3A inhibitor to increase lopinavir levels	400/100 mg PO BID	14 days		(i) Pancreatitis (ii) Diarrhea (iii) Abdominal pain (iv) Hgb drop >2g/dL (v) Liver dysfunction (vi) 2.3% mortality noted in cases with delayed administration		(i) Hepatic: not defined (ii) QT prolongation (iii) History of pancreatitis (iv) Diabetes mellitus (v) Ischemic heart disease (vi) Myasthenia gravis	Mixed data regarding efficacy in viral loads
Remdesivir	RNA-dependent RNA polymerase adenosine nucleotide analog	Day 1 200 mg IV, followed by 100 mg IV QD	10 days	Several trials			(i) Renal: not defined in eGFR<30 (ii) Hepatic: not defined, avoid in ALT>5x ULN	(i) SARS MERS, Ebola use indicated antiviral activity in vitro (ii) Mixed findings
Azithromycin	Unclear for indirect immunomodulation activity	500 mg × 1 day, then 250 mg qd × 4 days	5 days	In COVID-19, used for immunomodulating on role rather than antibiotic benefit.	(i) QT prolongation		(i) Renal: CrCl<10 not defined (ii) Hepatic: not defined (iii) QT prolongation (iv) Ventricular arrythmia (v) CHF (vi) Myasthenia gravis	(i) No benefit
Convalescent plasma IgG	Virus-specific neutralizing antibody promotes virus clearance by host; passive immunity	200–400 mL	Single transfusion		(i) Fever (ii) Chills (iii) Allergic reactions (iv) Bronchoconstriction (v) Volume overload			(i) Used during Ebola and MERS outbreaks (ii) Mixed findings

exposure to COVID-19 [23]. In contrast, in a similar study in healthcare workers, consumption of four or more maintenance doses of HCQ was associated with a significant decline in the odds of getting infected (AOR: 0.44; 95% CI: 0.22–0.88), leaving the question of utility of HCQ postexposure prophylaxis open in that high-risk population [24].

CQ and HCQ, due to their inhibitory effect on potassium channels (IKr current), increase the risk of several arrhythmias and EKG changes [25]. This side effect is dose-dependent; however, serious arrhythmias have been reported even at therapeutic doses. These severe cardiac side effects, including QT prolongation, Torsade de Pointes, and arrhythmia, were reported in many studies [18, 26–29]. In a randomized trial, adverse events were observed in about 30% of patients who received HCQ compared with only 9% of patients in a control group [20]. A QTc >500 ms was observed in 11% to 20% of patients receiving HCQ and AZT [30, 31]. This was frequently seen with a high dose of HCQ (1200 mg/day for ten days) combined with AZT [32]. Among 40 patients with severe infection (admitted to intensive care units) who received either HCQ or HCQ + AZT, there was an increase in QTc in 37 of 40 patients (93%) after drug administration [33]. Besides cardiotoxicity, HCQ also increases the risk of retinopathy, acute pancreatitis, neutropenia, hepatotoxicity, and anaphylaxis [28, 34].

Both CQ and HCQ have clinically significant drug interactions. AZT is a macrolide that may prolong the QT/QTc interval leading to a higher risk of cardiac death [35, 36]. The FDA has warned that AZT can lead to potentially fatal arrhythmias and discourages the use of this antibiotic among patients with underlying heart disease and those with known electrolyte imbalance [37]. Therefore, CQ or HCQ and AZT's concomitant use potentially places patients at a higher risk of cardiotoxicity. Other treatments used in managing COVID-19 patients may show drug interaction with CQ/HCQ. Lopinavir/ritonavir strongly inhibits CYP3A4 and has a large number of significant drug interaction concerns [38]. In in vitro studies, remdesivir appears to be a substrate for the drug-metabolizing enzymes CYP2C8, CYP2D6, and CYP3A4 [39]. Therefore, significant potential drug interactions need to be acknowledged when selecting a treatment.

Taken in totality, the available evidence is limited, and most studies are hampered by limited sample size and study design. Furthermore, meta-analysis does not suggest any efficacy of HCQ in patients with COVID-19 [40]. Early results from in vitro studies and uncontrolled case studies created a massive hype for HCQ, aggravated by media and social excitement, which caused a massive demand despite limited data.

3.1.2. Corticosteroids. Although steroids are usually considered an essential treatment modality in inflammatory conditions, their role in COVID-19 remains debatable. One of the frequently observed causes of mortality is hemophagocytic lymphohistiocytosis (sHLH), another hypercytokinemia syndrome associated with multiorgan failure, thought to be precipitated COVID-19 [41]. Evidence from the limited literature suggests an increased production of cytokines leading to the activation of other inflammatory cells and endothelium activation, resulting in multiorgan damage and failure. The most crucial role of corticosteroids is reducing the exudative fluid in lung tissue, thereby improving hypoxia and minimizing the risk of respiratory failure [42]. Corticosteroids were increasingly used worldwide in as much as 50% of patients affected by COVID-19 particularly in China [39, 43]. The few retrospective studies earlier in the pandemic reported inconclusive results, including patients with severe COVID-19 patients with pulmonary involvement [44–48]. Among the five studies (4 retrospective and one quasiprospective study), three studies have shown a benefit, and the other two studies reported no use. Complicating the decision making, one study observed significant harm, especially in critical and severe cases (propensity-matched adjusted hazard ratio [HR] 2.90; 95% CI, 1.17–7.16; $P = 0.021$) [44–48]. Taken as a whole, the studies suggest that corticosteroids improve the condition of severe and critically ill COVID-19 patients in many ways, including decreased duration of hospital stay, improvement in the status of oxygenation, the reduced requirement to intubate and subsequent ventilation, prevention of ventilator parameters worsening, progression to ARDS, and death [46–48].

A large prospective study conducted in the UK (The RECOVERY Trial) randomized 2104 patients to dexamethasone 6 mg per day (oral or intravenous) for ten days, with 4321 patients receiving usual care [43]. Patients included in this study had various comorbidities, including diabetes (24%), heart disease (27%), and chronic lung disease (21%), and 56% had at least one major comorbidity. In this study, 54% of patients were below 70 years, and 22% were between 70 and 80 years. The primary endpoint was mortality within 28 days, which was significantly less in the dexamethasone group compared with the routine care group (21.6% vs. 24.6%; age-adjusted rate ratio [RR], 0.83; 95% CI, 0.74–0.92; $P < 0.001$). No benefit was observed in mild or moderate cases without oxygen requirement in mortality reduction at the end of 28 days (17.0% vs.13.2%; RR, 1.22; 95% CI, 0.93–1.61; $P = 0.14$). However, there was 35% reduction in mortality in intubated patients (29.0% vs. 40.7%; RR, 0.65; 95% CI, 0.48–0.88; $P = 0.003$) and 20% reduction among the patients on supplemental oxygen therapy (21.5% vs. 25.0%; RR, 0.80; 95% CI, 0.67–0.96; $P = 0.0021$). This study also reported a shorter duration of hospital stay with dexamethasone compared with standard routine care (median 12 days vs. 13 days) and a higher probability of discharge within 28 days with dexamethasone (11%; RR, 1.11; 95% CI, 1.04–1.19; $P = 0.002$) [49].

The most frequently used corticosteroids are methylprednisolone and dexamethasone, secondary to their high bioavailability in the lungs. Some studies have reported that corticosteroid usage is associated with delayed viral clearance in patients with a previous viral illness; the same results were reported in COVID-19 patients [50–52]. Zhou et al. reported delayed clearance of the virus and increased mortality risk with the early administration of corticosteroid in COVID-19 patients [53]. However, a short

course of corticosteroids in some studies was beneficial in this regard [54]. Furthermore, corticosteroid use could predispose patients to secondary bacterial infection and various electrolytes derangements, including hypokalemia hyperglycemia [54]. However, there is inconsistent data to show any superiority among dexamethasone or methyl-prednisone use in COVID-19 [55, 56].

Although the data from retrospective studies do not strongly support corticosteroid use in COVID-19, the RE-COVERY trial, in particular, indicates a beneficent role in reducing mortality and duration of hospital stay among moderate to moderately severe cases.

3.1.3. Tocilizumab.
Tocilizumab is a recombinant humanized monoclonal antibody targeted against the IL-6 receptor. It is approved for the treatment of various autoimmune and inflammatory disorders, including rheumatoid arthritis [57]. A retrospective study by Ruan et al. reported higher IL-6 levels associated with disease progression and fatal outcome [58]. The role of IL-6 in mediating the inflammatory response in COVID-19 is a vital target in halting the marked inflammatory response. In critically ill COVID-19 patients who have elevated levels of IL 6, the efficacy of tocilizumab has been reported by retrospective studies [59]. 20 critically ill patients who received tocilizumab, there was a marked improvement in fever and other clinical symptoms [60]. Moreover, 15 of 20 required less oxygen, and there was an overall improvement in the CT scans in 19 patients. There were no significant adverse reactions observed. Of the 21 patients, 20 fully recovered after tocilizumab treatment and were discharged within two weeks [60]. A retrospective study in fifteen critically ill patients evaluated the efficacy and safety of tocilizumab as a monotherapy or in combination with methylprednisolone. There was a clinical improvement and a decrease in IL-6 and C-reactive protein (CRP) levels [59].

Another phase III clinical trial approved by the FDA evaluates tocilizumab in hospitalized patients with severe COVID-19 pneumonia [NCT04320615]. . Notably, in the latest trial of tocilizumab (COVACTA trial) among 452 patients, tocilizumab ($n = 294$) did not meet the primary endpoint of improved clinical status after seven days of administration ($P = 0.36$) compared with the placebo group ($n = 144$). Moreover, there was no difference in mortality at day 28 between tocilizumab (19.7%) and placebo (19.4%) (0.3% [95% CI, −7.6 to 8.2]; $P = 0.94$) [61]. In a randomized, controlled, open-label trial including 4116 patients (RECOVERY), there was a decrease in 28 days mortality in the tocilizumab arm (rate ratio 0·86; 95% confidence interval [CI] 0·77–0·96; $P = 0.007$). Furthermore, tocilizumab also decreased the chances of mechanical ventilation and death in those patients who were not ventilated. The mortality benefits of tocilizumab were seen in patients taking steroids [62]. However, there is a need for more robust studies to identify the role of tocilizumab in reducing mortality benefits for COVID-19 patients.

3.1.4. Interferons.
Interferons are a broad spectrum of immunomodulators with antiviral properties. IFN-α has been used to treat coronavirus diseases previously, such as SARS and MERS [63, 64]. In addition, interferon -α (IFNα) and −β (IFNβ) have been recommended for the treatment of COVID-19 [65–67].

Interferons bind to its receptor on the cell membrane and then phosphorylate STAT1 and other transcription factors. STAT1 translocates to the nucleus, leading to interferon-stimulated genes (ISGs), which mediates the immunomodulatory effects and interferes with viral replication [67]. IFNα and IFNβ are frequently studied as a combination therapy with ribavirin and or lopinavir-ritonavir [29, 68–70]. IFNβ has superior efficacy against coronaviruses compared to IFNα [70–72]. Furthermore, some in vitro studies indicate that IFNβ induces anti-inflammatory adenosine secretion and maintains endothelial barriers when used in early stages of infection [67]. IFNα, in combination with ribavirin, has been recommended for COVID-19 patients in China [72]. SARS-CoV-2 is more sensitive to prophylactic IFN-1 administration [67, 70–72]. In vitro pretreatment studies with INF-1 have confirmed this [73]. Due to limited evidence, routine usage cannot be recommended until further data can support its efficacy and safety profile.

3.1.5. Leronlimab.
Leronlimab is a monoclonal antibody against CCR5, inhibiting the entry of SARS-CoV-2 into cells. CCR5 receptors are located on several antigen-presenting cells (e.g., T cells, dendritic cells, macrophages, and Langerhans cells) [74]. On March 31st, 2020, the FDA gave clearance for the initiation of a phase II trial evaluating leronlimab in patients with mild to moderate respiratory complications. However, multiple further studies to assess the efficacy, and benefits are still needed.

3.2. Antivirals

3.2.1. Remdesivir.
Developed during the Ebola virus outbreak in 2016, remdesivir is a promising therapy in treating COVID-19 [29, 70, 75]. It is a broad-spectrum antiviral agent. It prevents viral replication by inhibiting RNA-dependent RNA polymerase [2]. Remdesivir has also been used to treat SARS, MERS-CoV, and other viral illnesses. Remdesivir has a superior anti-MERS activity compared with lopinavir and ritonavir both in vitro and in vivo and displayed anti-SARS-CoV-2 ability in vitro [7, 69]. A randomized, placebo-controlled, clinical trial of 1059 COVID-19 patients revealed a median recovery time of 11 days (95% confidence interval [CI], 9–12) versus 15 days (95% CI, 13–19) in those who received placebo (rate ratio for recovery, 1.32; 95% CI, 1.12 to 1.55; $P < 0.001$). However, there was no significant difference in mortality (7.1% vs. 11.9% hazard ratio for death, 0.70; 95% CI, 0.47–1.04) [76]. A randomized, double-blind, placebo-controlled, multicenter, phase-III trial was conducted in China to evaluate the efficacy of remdesivir [75]. The study included 237 severely ill COVID-19 patients among whom 158 received remdesivir

and 79 received placebo. The primary endpoint was time to clinical improvement [7, 77]. Patients receiving remdesivir had a faster time to clinical improvement than those receiving placebo, but this was not statistically significant (hazard ratio, 1·52 [0·95–2·43]). In the USA, compassionate use of remdesivir displayed clinical improvement in 36 of 53 hospitalized severe COVID-19 patients and 14 of 17 patients in an infectious disease ward [78, 79]. In meta-analysis with four studies, remdesivir was found to reduce 14 days mortality (OR, 0.61, CI 0.41–0.91) and need for mechanical ventilation (OR, 0.73; CI, 0.54–0.97) [80]. Remdesivir was given an "emergency use authorization" approval by FDA for patients with severe COVID-19 on May 1st, 2020 [81].

3.2.2. Lopinavir/Ritonavir.

Lopinavir/ritonavir is a combination antiretroviral drug that has been used to treat HIV and has also been part of clinical trials in the treatment of MERS-CoV and SARS-CoV-2. Lopinavir, an HIV-1 protease inhibitor, prevents viral gag-pol polyprotein cleavage, which results in immature, noninfectious viral particles; it was found to have activity against SARS-CoV-2 when used with ritonavir, a P450 CPY3A inhibitor, which increases plasma levels of lopinavir [82–85]. It has been widely used for the COVID-19 treatment in South Korea and Thailand. However, there is limited data on the efficacy and safety among COVID-19 patients [86–88]. Cao et al. found no benefit with lopinavir-ritonavir treatment in 199 hospitalized patients with severe COVID-19, demonstrating similar mortality rates (19.2%) than the standard of care group (25%) [38]. A single-center, controlled trial reached a similar conclusion for hospitalized patients with mild to moderate COVID-19 as compared with standard treatment [89]. In another study by Cheng et al., lopinavir/ritonavir did not shorten the duration of SARS-CoV-2 shedding [89, 90]. Gastrointestinal disturbance was the most common adverse effect associated with lopinavir-ritonavir, seen in 28% of patients. Moreover, the use of lopinavir/ritonavir was also associated with liver damage in COVID-19 [70, 91]. However, when used in combination with interferon-β-1b and ribavirin, lopinavir/ritonavir was found to be effective and superior to lopinavir/ritonavir alone and was associated with clinical improvement and shorter duration of hospital stay [92].

3.2.3. Ribavirin.

Ribavirin acts by inhibiting viral RNA-dependent RNA polymerase. Evidence regarding ribavirin use in COVID-19 patients has revealed no definitive role in some studies [27]. However, based on the data available, combination therapy with interferon-α or lopinavir-ritonavir may provide some clinical efficacy [29, 54, 70, 92, 93]. However, dose-dependent adverse events like liver and hematologic toxicities were the limiting factors [29]. Therefore, its role in treating COVID-19 patients remains inconclusive due to limited data and research.

3.2.4. Favipiravir.

Favipiravir is an inhibitor of RNA-dependent RNA polymerase approved for treating influenza, Ebola, and norovirus [58, 70, 94, 95]. Data from preliminary studies revealed significant clinical benefits (i.e., more rapid viral clearance of 4 days vs. 11 days) and improved chest imaging in COVID-19 patients than lopinavir-ritonavir alone (91.4% vs. 62.2%). In addition, there were fewer adverse events in patients administered favipiravir compared with those taking lopinavir-ritonavir alone (11.4% versus 55.6%) [96]. Another prospective, randomized, clinical trial reported better control of fever, cough, and respiratory symptoms among COVID-19 patients, with an improved recovery rate in patients receiving favipiravir compared with umifenovir (71.4% versus 55.9%) [70, 97]. However, these studies were limited by only evaluating noncritically ill patients.

3.2.5. Oseltamivir.

Oseltamivir is a neuraminidase inhibitor long used for the treatment of influenza A and B [29, 54]. However, current evidence has failed to find any efficacy and benefit for the treatment of COVID-19 patients, and hence, its use in any form should be discouraged [92].

3.2.6. Umifenovir.

Umifenovir is a membrane fusion inhibitor, preventing the interaction between viral S-proteins and ACE2 receptors [70]. It has been used as prophylaxis and for the treatment of influenza A and B [54, 97]. Apart from its benefit for influenza, umifenovir has shown antiviral effects for other viruses like hepatitis C virus, hepatitis B virus, Ebola virus, human herpesvirus 8, Lassa virus, and poliovirus [95]. A retrospective cohort study of 16 COVID-19 patients after 14 days of umifenovir and lopinavir-ritonavir administration versus lopinavir-ritonavir treatment alone showed 4% clearance of SARS-CoV-2 in the umifenovir experimental group compared with 53% patients in the control group [98]. Furthermore, there was an improvement in the chest CT scans in the experimental group (69% compared to 29% in lopinavir-ritonavir monotherapy) [98]. In another similar study of 16 patients taking umifenovir (200 mg TID), there was complete clearance of the virus versus 44.1% viral load detection in patients taking lopinavir-ritonavir monotherapy (400 mg/100 mg BID) [99]. However, other studies have found benefits limited to only nonseverely ill patients [100]. Due to the limited data available, its utilization is not routinely recommended at this time.

3.3. IV Immunoglobulins.

The data regarding intravenous immunoglobulin (IVIG) efficacy and outcomes in COVID-19 patients is scarce. However, IVIG may help severe SARS-CoV-2 infection through immune modulation by saturating the FcγR [101]. In a case series of three critically ill SARS-CoV-2 patients in China who received IVIG at 0.3–0.4 g/kg/day for five days, all respiratory symptoms showed significant improvements in clinical status, and there were alleviated side effects [102]. However, a clear demonstration of therapeutic benefit will require further studies.

3.4. Convalescent Plasma.

Treatment strategies for critically ill COVID-19 patients continue to be hampered by limited evidence. Administration of convalescent plasma

(CP) has been long practiced to improve the survival rate during viral outbreaks, including SARS-CoV, MERS-CoV, and Ebola virus [70, 103–105]. A meta-analysis reported a significant reduction in mortality and viral load with CP immunotherapy, leading to the August 23rd, 2020, FDA decision to authorize emergency use in the treatment of COVID-19 [106]. The role of convalescent plasma transfusion in COVID-19 patients is related to both an increase in viral clearance and inhibition of the cytokine storm that plays a major role in precipitating organ damage [107]. Earlier in the current pandemic, small observational studies revealed promising outcomes and clinical improvements from the CP utilization [108–111]. The first study from Wuhan reported outcomes of 5 critically ill patients who were administered CP [109]. In four of the five patients, there was remarkable improvement in the clinical status measured by the Alveolar-arterial (A/a) gradient and chest CT scan, and there was a decrease in inflammatory biomarkers, as well [109]. Duan et al. reported that after a single transfusion of convalescent plasma in 10 patients, there were no adverse events [108]. Additionally, similar clinical improvements were reported in other small case studies [109, 111].

The timing of infusion appears to play a role in the success of the treatment. Early data appears to support the fact that transfusions done earlier in the disease proved to have better outcomes, including mortality [106, 112, 113]. Zeng et al. reported poor mortality outcomes when convalescent plasma was administered late [114]. A multicenter cohort study consisting of 35,322 patients reported a seven-day mortality rate of 8.7% [95% CI, 8.3%–9.2%] when plasma was transfused within three days of COVID-19 diagnosis compared with 11.9% [11.4%–12.2%] ($P < 0.001$) when the transfusion was done after three days of diagnosis. In addition, there was a significant reduction in 30-day mortality in early transfused patients (21.6% vs. 26.7%; $P < 0.0001$) (NCT04338360). Moreover, in an RCT of 86 patients, the patients were symptomatic for ten days, 79% of tested patients had COVID-19 neutralizing antibodies comparable to median titers with those of donors. As patients developed neutralizing antibodies as early as the first week, convalescent plasma is likely to help only patients with recent clinical symptoms [115]. In another randomized control trial of 103 patients with severe or life-threatening COVID-19 disease, convalescent plasma did not provide any benefit in terms of 28 days mortality (OR, 0.59; 95% CI, 0.22–1.59; $P = 0.30$) or in terms of time from randomization to discharge(HR, 1.61; 95% CI, 0.88–2.95; $P = 0.12$) [116]. A randomized controlled trial that enrolled 334 patients to compare convalescent plasma with placebo could not find any difference in terms of clinical outcomes and mortality. The median days of patient randomized after appearance of symptoms was 8 days [117].

The use of plasma transfusion therapy may be an option for critically ill patients if administered early in the disease course. However, many factors, including the number of transfusions, adjustments based on body mass index, donor antibody titers, and other parameters, need to be evaluated to optimize this therapy.

3.5. Miscellaneous

3.5.1. Angiotensin-Converting Enzyme (ACE) Inhibitors.
The SARS-CoV-2 interacts with the ACE2 receptor to enter the host cell. Inhibiting this step can be a potential target for COVID-19 treatment [118]. German guidelines recommended the compassionate use of ACE-II inhibitors [119]. However, many clinical experts have discouraged their usage. They have postulated that blocking ACE-II receptors with ACE inhibitors may lead to poorer outcomes due to the upregulation of the receptors and thus increasing viral entry into the host cells [120]. However, others have challenged this position because receptor upregulation appears to seldom occur at therapeutic doses [121]. Therefore, it is currently recommended that patients with cardiovascular comorbidities continue to take ACE inhibitors and ARBs as prescribed [122].

3.5.2. Azithromycin.
Azithromycin (AZT), a frequently used antibiotic, has been used in combination therapy with HCQ for COVID-19 patients. A multicenter retrospective study of 1438 hospitalized patients evaluated the efficacy and side effects of HCQ plus AZT combination therapy, compared with HCQ alone, AZT alone, and a placebo control group, and found no significant differences in the experimental groups to the control group [18]. Furthermore, combination therapy was associated with cardiac arrest (OR = 2.13) [18]. Magagnoli et al. reported similar results that combination therapy with HCQ plus AZT did not decrease the risk of death in COVID-19 patients [17].

Additionally, in patients who were only taking HCQ, the risk of death was even higher [17]. Due to the adverse cardiovascular side effects with HCQ and AZT combination therapy, this combination's clinical use requires frequent ECG monitoring [26, 27]. Based on the above data, routine usage cannot be recommended at this time.

3.5.3. Anticoagulation (AC).
One of the major complications associated with hospitalized COVID-19 patients is life-threatening thromboembolic events. Abnormal coagulation in COVID-19 patients is independently associated with an increased risk of mortality [123]. Therefore, identifying high-risk patients and early institutions of antithrombotic is essential to limit thrombus formation and treat systemic thromboembolic complications in COVID-19 patients. The International Society on Thrombosis and Hemostasis has recommended antithrombotic prophylaxis with low-molecular-weight heparin (LMWH) for all hospitalized patients, except contraindicated [123]. However, routine thromboprophylaxis is not preferred in ambulatory patients with active medical illness [124]. Apart from its anticoagulation effects, unfractionated heparin has demonstrated antiviral properties in some studies [125].

Unfractionated heparin is frequently preferred in patients with underlying renal disease [125]. However, the choice of AC should be individualized based on patient clinical status, as many patients might progress from a thrombotic state to a bleeding pattern due to platelet

destruction and coagulation factor consumption [122,123]. In obese patients with BMI $\geq 40\,kg/m^2$, a higher dose of thromboprophylaxis has been shown to decrease VTE risk by 50% [126].

Aggressive thromboprophylaxis with high doses of anticoagulation can be considered in patients who meet the high sepsis-induced coagulopathy (SIC) score criteria or in patients with markedly elevated D-dimer levels [123]. Tang et al. found that aggressive thromboprophylaxis was associated with better outcomes in a study of 449 COVID-19-positive patients [127]. Moreover, in patients on low-molecular-weight heparin (LMWH) with SIC score $\geq$ four or D-dimer ≥ 6 times, the upper limit had a significantly lower 28-day mortality rate than untreated patients (40.0% vs 64.2%; $P = 0.029$) [127].

Few studies have reported improved survival benefits with fibrinolytic therapy in patients with acute lung injury and ARDS [128, 129]. However, in a case series of 3 COVID-19 patients administered tPA (alteplase) suffering from ARDS and respiratory failure, there was an initial, but only transient, improvement in the PaO_2/FiO_2 ratio [129]. Therefore, more studies are required to evaluate outcomes associated with plasminogen activator in COVID-19 patients [129].

4. Conclusion

The treatment of COVID-19 remains an immense challenge worldwide due to limited evidence and rapidly evolving and changing treatment options. The treatment repurposed and showing promising results should be tailored based on clinical conditions and clinical expertise. The ongoing research/trials investigate the safety and efficacy of various drug options.

Data Availability

This is a review article based on secondary data from other articles so we do not have our own data!

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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