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(REVIEW ARTICLE)

Treatment of Covid-19: A review

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Abstract

In twenty first century corona virus is considered as a big disaster. According to World Health Organization (WHO) the COVID 19 is becoming a pandemic in this month of March and now affected 203 countries. Scientists are endeavoring to discover drugs for its efficacious treatment. Multiple drug trails are going world-wild since there are no vaccines for this disease. Since there are no vaccines for this disease the best way to combat this virus is by social distancing of the host. In this regards we conduct a systematic review with a drug that can prevent a corona infection for the time being like Chloroquine, Glucocorticoids, Tocilizumab, Lopinavir/ritonavir, Corticosteroids, Ribavirin +/- interferon, Oseltamivir and baloxavir, Melatonin, Teicoplanin and other glycopeptides, Monoclonal or polyclonal antibodies and other therapies.

Keywords: WHO; Corona; Vaccines; Chloroquine; Interferon

1. Introduction

The epidemic of Coronavirus Disease 2019 (COVID-19) first broke out in Wuhan in December 2019, and reached its peak in Wuhan in February 2020. It became a major public health challenge for China, and evolved into a global pandemic in March 2020 [1]. In December 2019, a novel coronavirus (temporarily named severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) caused a cluster of pneumonia cases in Wuhan, China. The virus was officially named 2019-nCoV by the Chinese Center for Disease Control and Prevention [2] and the disease was later termed Coronavirus Disease 2019 (COVID-19) by the World Health Organization (WHO) [3]. During the first month of the outbreak, there were 16,500 confirmed cases, 360 fatalities, and over 20,000 suspected cases in China [4]. By March 11, 2020, the rapid spread of the virus had caused more than 118,000 cases and 4,291 deaths in 114 countries from Asia to the Middle East, Europe and the United States. The WHO, thus declared that the epidemic of COVID-19 had become a "global pandemic".

As of this time there is no known specific, effective, proven, pharmacological treatment. The studies have suggested that chloroquine, an immunomodulant drug traditionally used to treat malaria, is effective in reducing viral replication in other infections, including the SARS-associated coronavirus (CoV) and MERS-CoV [5]. On March 11, 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic. Till March 22, globally, approximately 303,000 confirmed cases, including more than 12,900 deaths in approximately 150 countries. Data from China have indicated that about 20% of patients developed severe disease, older adults, particularly those with serious underlying health conditions, are at higher risk of death than younger ones. A minority of patients presented with respiratory

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failure, septic shock and multiorgan dysfunction resulting in a fatality of 4% [6]. Here, from the perspective treatment of severe COVID-19.

2. COVID treatment with different Drugs

In December 2019 and rapidly propagated in numerous countries, having contaminated more than one million people and killing more than 55,000 up to April 3, 2020. Antiviral treatments are warranted to contain the epidemics. Several candidates are already being investigated, including type 1 interferon (IFN-I) [7,8]. Indeed, in the context of emerging viral infections, IFN-I are often evaluated (usually in combination with other drugs) before specific treatments are developed, due to their unspecific antiviral effects [9,10]. We aimed to review the evidence supporting the evaluation of IFN-1 in the treatment of corona viruses and to discuss its potential in SARS-CoV 2.

Type 1 interferons (IFN-I) designate a group of cytokines comprising the ubiquitous α and β subtypes (themselves subdivided in several isoforms), as well as the ε, ω and κ subtypes [11]. They are secreted by various cell types, notably plasmacytoid dendritic cells, upon recognition of viral components by Pattern Recognition Receptors (PRR) [12]. IFN-I are thus among the first cytokines produced during a viral infection. They are recognized by the IFNAR receptor present at the plasma membrane in most cell types. Interferon fixation on IFNAR induces the phosphorylation of transcriptional factors such as STAT1 and their relocalization to the nucleus, where they activate interferon-stimulated genes (ISG). Most ISGs are involved in inflammation, signaling and immunomodulation. They interfere with viral replication and spread by several mechanisms such as a slowdown of cell metabolism or secretion of cytokines which promote the activation of the adaptive immunity. ISGs (Immune Serum Giobulin) include PRRs (Pathogen Recognition Receptor), which further sensitize the cell to pathogens, proteins which decrease membrane fluidity, preventing viral egress or membrane fusion, and antivirals that specifically inhibit one step of the viral cycle [13,14].

IFN-I (Interferon-I) thus play a major role in antiviral immunity. Because of their immunomodulatory properties, IFN-I are used in the treatment of numerous diseases: for example, subcutaneous injections of IFNβ have been used for more than 20 years for the treatment of patients with multiple sclerosis. The role of IFNβ in the treatment of multiple sclerosis is still debated and likely results partly from the down-regulation of the major histo compatibility complex (MHC) class II expression on antigen-presenting cells, the induction of IL-10 secretion and the inhibition of T cell migration [15]. MERS-CoV and SARS-CoV is coronaviruses closely linked with SARS-CoV-2 and presenting similar properties, despite differences in their epidemiology, pathology and in several of their proteins [16]. IFN-I treatment has been studied against MERSCoV (Middle East Respiratory Syndrome Coronavirus) and SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus) [17] in numerous experiments, both *in vitro* and *in vivo*, and in combination or not with lopinavir/ritonavir [18,19], ribavirin [20,21], remdesivir, corticosteroids or IFNγ [22,23]. IFNα and β were systematically relatively efficient *in vitro* and succeeded in certain animal models [24], but generally failed to significantly improve the disease in humans. For example, a combination of IFNβ with lopinavir/ritonavir against MERS-CoV (Middle East Respiratory Syndrome Coronavirus) improved pulmonary function but did not significantly reduce virus. The combination of IFNα2a with ribavirin delayed mortality in the replication or lung pathology severity without decreasing it in long run. Similarly, the combination of IFNα2b with ribavirin gave excellent results in the rhesus macaque [25], but was inconclusive in human [26]. The lack of significant disease improvement with IFN-I treatment in numerous studies can be explained by the mechanisms of inhibition of the IFN signaling pathway used by MERS-CoV and SARS-CoV (Severe Acute Respiratory Syndrome- Coronavirus), by the limited number of patients or animals used in the studies, or by the difficulty to decipher whether disease improvements were caused by IFN-I or the drugs used in combination with it. In addition, results often differ substantially between studies because of inconsistencies in the experimental settings or the clinical conditions: for example, a study on SARS-CoV revealed a positive effect of IFN-I treatment, while another study with a larger cohort did not detect any significant effect. It has also been proposed that interferon was efficient in patients only if they lacked comorbidities [27,28]. Subtype diversity could be another explanation of inconsistencies between studies. It was repeatedly shown that IFNβ is a more potent inhibitor of Coronaviruses than IFNα: depending on the studies, IFNβ1b or IFNβ1a were the most potent IFN-I subtype in the inhibition of SARS-CoV and MERS-CoV [29-30].

Consequently, IFNβ1 appears to be most relevant interferon to treat Coronavirus infections. This fact can be related to the protective activity of IFNβ1 in the lung: it up-regulates cluster of differentiation 73 (CD73) in pulmonary endothelial cells, resulting in the secretion of anti-inflammatory adenosine and the maintenance of endothelial barrier function. This process explains why clinical data indicate a reduction of vascular leakage in acute respiratory distress syndrome (ARDS) with IFNβ1a treatment [31]. However, this effect is insufficient to decrease ARDS mortality [32]. It has been suggested from *in vivo* studies in mice that the timing of IFN-I administration plays a crucial role: positive effects were observed if IFN-I was administered shortly after infection, but IFN-I failed to inhibit viral replication and had side-effects when administered later [33]. Following a study showing that IFNβ1b was as efficient as lopinavir/ritonavir against

MERS-CoV in marmosets, the combination of IFNβ1b (injected intravenously) and lopinavir/ritonavir is currently investigated in a clinical trial in Saudi Arabia [34].

This is to our knowledge the only clinical trial against MERS-CoV. MERS-CoV is valuable in the selection of potential treatments against SARS-CoV-2. SARSCoV and MERS-CoV are able to disrupt the interferon signaling pathway. For example, the Orf6 protein of SARS-CoV disrupts karyopherin transport [35] and consequently inhibits the import in the nucleus of transcriptional factors such as STAT1, resulting in the interferon response. Similarly, the Orf3b protein of SARS-CoV inhibits the phosphorylation of IRF3 [36], a protein involved in the activation of IFN expression. However, the Orf6 and Orf3b proteins of SARSCoV- 2 are truncated and may have lost their anti-interferon functions. It could explain why SARS-CoV-2 displays *in vitro* a substantial sensitivity to IFNα [37].

3. Hydroxychloroquine

The Dutch Center of Disease control (CDC), in a public document on its website, suggested to treat severe infections requiring admission to the hospital and oxygen therapy or admitted to the ICU (Intensive Care Unit) with chloroquine. However, the document also stated that treating patients only with optimal supportive care is still a reasonable option, due to lack of supportive evidence. The suggested regimen in adults consists of 600 mg of chloroquine base (6 tablets A-CQ 100 mg) followed by 300 mg after 12 h on day 1, then 300 mg × 2/die per OS on days 2–5 days. This document also underlined 1) the needs for stopping the treatment at day 5 to reduce the risk of side effects, considering the long half-life of the drug (30 h); Regimens based on chloroquine phosphate and chloroquine base since 500 mg on the first correspond to 300 mg of the second (ICi-2020).

The panel recommended using several precautions, including blood testing to rule out the development of anemia, thrombocytopenia or leukopenia as well as serum electrolyte disturbances and/or hepatic and renal function dysfunction. Also recommended were routine electrocardiography to rule out the development of QT interval prolongation or bradycardia and patient interviews to seek the appearance of visual and/or mental disturbance/deterioration. The panel recommended avoiding concurrent administration of other drugs known to prolong the QT interval (i.e.Chinolones, macrolides, ondansetron) as well as various anti arrhythmic, antidepressant and antipsychotic drugs. 15 clinical trials have been conducted in China to test the efficacy and safety of CQ (Chloroquine) or HCQ (Hydroxychloroquine) in the treatment of COVID-19, 8 of which were CQ, 6 were HCQ, and another included both CQ and HCQ [38].

So far, in a clinical trial involving more than 100 patients, the chloroquine phosphate group showed efficacy in reducing the exacerbation of pneumonia, improving lung imaging findings and increasing negative rate of the virus nucleic acid test. Given these findings, the Guidelines (version 6) for treatment of COVID-19 recommended a chloroquine phosphate is orally administered at a dose of 500 mg (300 mg of chloroquine) for adults, 2 times/ day (no more than 10 days).

“Hydroxychloroquine's therapeutic effect on new coronavirus (COVID-19)” was registered (NO: ChiCTR2000029559). As of February 17-2020, 20 patients have been enrolled in HCQ & basic treatment group. After 1–2 days of HCQ treatment, clinical symptoms in all patients improved. After 5 days of HCQ treatment, 19 patients improved on lung imaging findings. In addition, none of the mild patients had an exacerbation of disease in HCQ group. Regarding to safety, two of them had adverse reactions of mild rash and slight headache, and the adverse reactions disappeared after adjusting the regimen. The results of this clinical trial confirmed the short-term efficacy of HCQ in the treatment of COVID- 19, which can effectively improve lung imaging findings, promote a virus-negative conversion, and shorten the disease course. Although the number of cases in HCQ group was relatively small, the current data can provide insights for clinicians. The efficacy and safety of HCQ in the treatment of COVID-19 need to be confirmed in further preclinical and clinical trials.

COVID-19 is a viral infectious disease mainly manifested as fever and pneumonia, anti-viral and respiratory supportive therapies are the mainstream of treatments for severe cases. As CS (Caesarean section) occurs in critical patients, which leads to ARDS and multiple organ damage, and even death, anti-inflammatory treatment may be applied. However, given the viral nature of the COVID-19 CS (Caesarean section), and considering a substantial impureness of the host immune system in severe cases, it is critical to balance the risk and benefit ratio before starting anti inflammation therapy. In addition, a timely anti-inflammation treatment initiated at the right window time is of pivotal importance and should be tailored in individual patient to achieve the most favorable effects.

4. Glucocorticoids

In the treatment of coronavirus pneumonia (such as SARS and MERS) or influenza pneumonia, but no consensus has been reached. During the SARS epidemic in 2003, glucocorticoid was the main medication of immunomodulatory therapy. Timely usage of glucocorticoid could improve the early fever, promote the absorption of pneumonia and obtain better oxygenation. However, some studies didn't show beneficial effects with glucocorticoid, or even adverse reactions or delayed virus clearance, leading to deterioration of the disease [39]. According to international guidelines for management of sepsis and septic shock, if glucocorticoid is to be used, small dosage and short-term application should be applied only for patients in whom adequate fluids and vasopressor therapy do not restore hemodynamic stability [40]. At present, systemic glucocorticoids administration was empirically used for severe complications in order to suppress CS manifestations in patients with COVID-19, such as ARDS (Acute respiratory distress syndrome), acute heart injuries, acute kidney complication, and patients with higher D-dimer levels. However, there is no evidence from randomized clinical trials to support glucocorticoids treatment for COVID-19. Chen *et al.,* reported that 19 (19%) patients were treated with glucocorticoids for 3–15 days (median 5) [41], and methylprednisolone (1–2 mg/kg per day) are recommended for patients with ARDS (Acute respiratory distress syndrome), for as short a duration of treatment as possible [42].

However, some evidences indicate that the benefit of the use of glucocorticoids is likely outweighed by adverse effect. Wang *et al.* reportedly 44.9% patients of COVID-19 were given glucocorticoid therapy, with no effective outcomes observed. The clinical evidence did not support corticosteroid treatment for COVID-19 lung injury [43]. Due to the lack of evidences, the interim guideline of WHO (World Health Organization) does not support the use of systemic corticosteroids for the treatment of viral pneumonia and ARDS for suspected COVID-19 cases in 22 February 2020. Therefore, efficacy and associated adverse effects of glucocorticoids in COVID-19 need further elucidated.

5. Tocilizumab treatment

Tocilizumab (TCZ) is a recombinant human IL-6 monoclonal antibody, which specifically binds to soluble and membrane-bound IL-6 receptors (IL-6R), thus blocking IL-6 signaling and its mediated inflammatory response. TCZ has been widely used in rheumatic diseases, such as rheumatoid arthritis. On August 30, 2017, TCZ was approved in the United States for severe life-threatening cytokine release syndrome caused by chimeric antigen receptor T-cell (CART) immunotherapy. Wei Haiming, *et al.* conducted a retrospective study observing the efficacy of tocilizumab in treating severe or critical COVID-19 patients. Along with the basic anti-virus treatment, TCZ was applied to 20 patients 400 mg once intravenously. Within a few days, the fever returned to normal and other symptoms improved remarkably. 75.0% had improved oxygenation. The opacity lung lesion on CT scans absorbed in 90.5% patients. In addition, the percentage of peripheral lymphocytes returned to normal in 52.6% patients. Their data suggests TCZ might be an effective treatment in severe patients of COVID-19. Till now, several clinical trials have been registered on safety and efficacy of tocilizumab in the treatment of severe COVID-19 pneumonia in adult inpatients, including a multicenter, randomized controlled trial for the efficacy and safety of tocilizumab in the treatment of novel coronary pneumonia (NCP) (ChiCTR2000029765), a single arm open multicenter study on tocilizumab (ChiCTR2000030796), and combination of tocilizumab and other drugs (ChiCTR2000030442 and ChiCTR2000030894).

6. JAK inhibitors

The receptors of novel coronavirus pneumonia (2019-nCoV), might be ACE2, which is a cell-surface protein widely existed on cells in the heart, kidney, blood vessels, especially alveolar epithelial cells. 2019-nCoV could invade and enter cells through endocytosis. One of the known regulators of endocytosis is the AP2-associated protein kinase 1 (AAK1). AAK1 inhibitors can interrupt the passage of the virus into cells and can be helpful in preventing virus infections. Baricitinib, a JAK inhibitor as well as an AAK1 inhibitor, was suggested a possible candidate for treatment of COVID-19, considering its relative safety and high affinity. Therapeutic dosage with either 2 mg or 4 mg once daily was sufficient to reach the plasma concentration of inhibition [44].

However, as we mentioned above, the biggest concern about JAK inhibitors is that it can inhibit a variety of inflammatory cytokines including INF-a, which plays an important role in curbing virus activity. Further clinical trials and detailed analysis are warranted to confirm their efficacy. To date, there are some registered clinical trials of JAK inhibitor: “Study for safety and efficacy of Jakotinib hydrochloride tablets in the treatment severe and acute exacerbation patients of novel coronavirus pneumonia (COVID-19)” (ChiCTR2000030170); “Severe novel coronavirus pneumonia (COVID-19) patients treated with ruxolitinib in combination with mesenchymal stem cells: a prospective, single blind, randomized controlled clinical trial” (ChiCTR2000029580). The structure of SARS-CoV-2 S protein has been revealed, and this

should enable the rapid development and evaluation of medical countermeasures to address the ongoing public health crisis [45]. These findings provide the basis for further studies to optimize vaccination strategies for this emerging infection. The majority of the vaccines being developed for coronaviruses target the spike glycoprotein or S protein Vaccine development is a long process, and no vaccines are available at the time of a pandemic outbreak. For example, the Ebola epidemic outbreak occurred in 2013, and three years later, the rVSV Ebola Vaccine was selected for phase I clinical trials for its safety and immunogenicity in Africa and Europe [46].

In November 2019, the European Commission granted marketing authorization to Merck Sharp and Dohme B.V. in Europe for their Ebola vaccine, Ervebo. Fortunately, Moderna company announced on February 24, 2020 that the company's experimental mRNA COVID-19 vaccine, known as mRNA-1273, is ready for human testing. It is a remarkably fast development cycle to develop an initial vaccine is just weeks after identifying the SARS-CoV-2 genetic sequence. The clinical trial of safety and immunogenicity of mRNA-1273 in the treatment of COVID-19 is under investigation (Clinical trials. Gov Identifier: NCT04283461). Moreover, a new oral SARS-CoV-2 vaccine has been successfully developed at Tianjin University, which uses food-grade safe *Saccharomyces cerevisiae* as a carrier and targets the S protein. There are 18 biotechnology companies and universities in China working on SARS-CoV-2 vaccines. Vaccines for SARS-CoV-2 have been developed much faster than those for Ebola because of the collaborative effort of scientist s around the world and the fast-track approval of SARS-CoV-2 vaccine development effort s by the Chinese health organizations.

7. Lopinavir/ritonavir

Lopinavir is a human immunodeficiency virus 1 (HIV-1) protease inhibitor administered in fixed-dose combination with ritonavir (LPV/r), a potent CYP3A4 inhibitor that "boosts" lopinavir concentrations. Lopinavir appears to block the main protease of SARS-CoV-1, inhibiting viral replication [47]. In 2003, Chu and colleagues evaluated a series of antivirals for *in vitro* activity against SARS-CoV-1. They reported lopinavir at 4 mg/mL and ribavirin at 50 mg/mL inhibited SARS-CoV-1 after 48 hours of incubation and the agents were synergistic when used together [48]. de Wilde and colleagues later described the antiviral activity of lopinavir against SARS-CoV-1 and demonstrated an EC50 17.1 ± 1 in Vero E6 cells which is near the upper range of LPV plasma concentrations previously measured in patients with HIV-infected patients. Sheahan and colleagues evaluated the *in vitro* efficacy of LPV/r in combination with interferon beta (INFb) against MERS-CoV and found the addition of LPV/r did not significantly enhance antiviral activity of INFb alone (EC50 =160 IU/mL vs 175 IU/mL, respectively). They also described the EC50 of LPV/r (8.5 μM) and LPV alone (11.6 μM), suggesting similar activity to that described for SARS CoV-1. Despite *in vitro* activity against MERS-CoV, therapeutic doses of LPV/r + INFb in mice models failed to reduce virus titer and exacerbated lung disease.

This is notable as this was the same study where remdesivir demonstrated both more potent *in vitro* activity as well as *in vivo* efficacy. However, the *in vivo* animal data for MERS-CoV appears equivocal given a nonhuman primate model demonstrated improved clinical and pathological features following LPV/r treatment. A randomized controlled trial of LPV/r and recombinant interferon-β1b versus placebo is currently enrolling for patients with MERS-CoV, which might help clarify the apparent discrepancy between *in vitro* and animal models. Based on *in vitro* findings, Chu and colleagues utilized combination therapy with LPV/r, ribavirin, and corticosteroids for any newly diagnosed patient with SARS-CoV-1 without ARDS starting in April 2003. Patients receiving LPV/r combination therapy (N=41) were matched to historical patients receiving ribavirin plus corticosteroids (N=111) and a significant reduction in the development of ARDS or death at 21 days was observed (2.4% vs 28.8%, $P < 0.001$). This was corroborated by an expanded case-control matched study of 75 LPV/r treated patients from the same center that demonstrated a significant reduction in pulse steroid use (27.3% vs 55.4%), intubation (0% vs 11%), and mortality (2.3% v 15.6%) among patients who received LPV/r combination versus no LPV/r, respectively, as initial therapy [49]. Importantly, the benefits of LPV/r were only demonstrated in patients who received initial treatment with LPV/r (defined as initiation of drug at time of SARS-CoV-1 diagnosis).There was no observed benefit when LPV/r was added as rescue or salvage therapy (death rate 12.9% vs 14%).

8. Corticosteroids

As demonstrated, the data for corticosteroids are inconsistent, confusing, and inconclusive. While target patients where corticosteroids will improve outcomes may exist (e.g., those with cytokine-related lung injury who may develop rapidly progressive pneumonia), that population remains ill-defined [50]. Clinicians need to carefully weigh the risks and benefits of corticosteroids on the individual patient level. This need for a risk benefit assessment in individual patients and careful consideration of dose is exemplified in the COVID-19 Diagnosis and Treatment Guide from the National Health Commission of the People's Republic of China where the authors state "Based on respiratory distress and chest

imaging, may consider glucocorticoid that is equivalent to methylprednisolone 1-2 mg/kg/day for 3-5 days or less. Note that large-dose glucocorticoid suppresses immune system and could delay clearance of SARS-CoV-2. A recent consensus statement from the Chinese Thoracic Society recommends a lower dose, ≤0.5-1 mg/kg/day methylprednisolone for ≤ 7 days in select patients, after careful consideration of risks and benefits. Randomized controlled trial data are urgently needed to clearly define the role of corticosteroids in COVID-19.

9. Ribavirin +/- interferon

Interferons (α, β) may stimulate innate antiviral responses and are expected to have *in vitro* activity against SARS-CoV-2, given the previously described activity demonstrated against MERS-CoV (EC50 175 IU/mL). However, toxicities are substantial including severe cytopenias, hepatoxicity (including fatality), neuropsychiatric events, and risk of developing fatal or life-threatening ischemia or infection, particularly when combined with ribavirin. This combination was not associated with improved mortality or enhanced viral clearance in a retrospective analysis of patients infected with MERS-CoV who were initiated on combination therapy within 1-3 days of ICU admission. In spite of the limited to poor data, Chinese guidelines recommend ribavirin 500 mg IV 2-3 times daily in combination with lopinavir/ritonavir or inhaled INF-α (5 million units nebulized twice daily) as one of the "standard treatment" options for COVID-19. Various combinations of ribavirin, interferon, and other antiviral agents are currently being studied in several clinical trials. Based on the poor *in vitro* activity, an absence of animal or human data supporting its use, and a significant toxicity profile, we recommend avoiding use of ribavirin in patients with COVID-19 at this time. Although interferons may be useful as adjunctive care, they pose a significant risk to critically ill patients, and in the absence of supportive data they also cannot be currently recommended [51].

10. Oseltamivir and baloxavir

Given their antiviral activity against influenza, considerable attention has been paid to oseltamivir, and to a lesser degree baloxavir, as potential treatment options for COVID-19. This was exacerbated by the initial report from Huang and colleagues in Wuhan where patients managed with COVID-19 received oseltamivir in addition to broad spectrum antimicrobials.1 It is important to note that use of oseltamivir was not as targeted therapy of SARS CoV-2, but rather driven by the lack of a knowledge of the causative pathogen at the time of treatment and the desire to empirically treat influenza. The authors do not suggest the use of oseltamivir for COVID-19 in that publication, and there are no data that suggest *in vitro* activity of oseltamivir against SARS CoV-2. In fact, the only data assessing oseltamivir activity against coronaviruses demonstrated it to be ineffective at inhibiting SARS CoV-1, even at a concentration of 10,000 μM/L. Coronaviruses do not utilize neuraminidase and thus there is no enzyme to be inhibited by oseltamivir. This would hold true for zanamivir, peramivir, or any other neuraminidase inhibitor agents. Similarly, defined mechanism or *in vitro* data have suggested that baloxavir would demonstrate activity against SARS CoV-2 or other coronaviruses. Therefore, given the critical need for these agents in the management of influenza and concern for drug shortages with oseltamivir, these agents should be avoided in patients with COVID-19 once influenza has been ruled out.

11. Melatonin

Although there is obviously no report related to the use of melatonin in COVID-19 patients, in subjects with other diseases and an increased level of inflammation, the application of melatonin showed promising results regarding the attenuation of circulating cytokines levels. In a randomized controlled trial, 8-week oral intake of 6 mg/d melatonin caused a significant decrease in serum levels of IL-6, TNF-α and hs-Creactive protein (hs-CRP) in patients with diabetes mellitus and periodontitis [52]. In another trial of patients suffering with severe multiple sclerosis, orally 25 mg/d of melatonin for 6 months also promoted a significant reduction in serum concentrations of TNF-α, IL-6, IL-1β and lipoperoxides [53]. In the acute phase of inflammation, including during surgical stress (Kucukakin), brain reperfusion, and coronary artery reperfusion [54], melatonin intake of 10 mg/d, 6 mg/d and 5 mg/d of melatonin for less than 5 days induced a reduced level of pro-inflammatory cytokines. A recent meta-analysis of a total of 22 randomized controlled trials suggested that a supplementary use of melatonin is associated with a significant reduction of TNF-α and IL-6 level. This clinical evidence suggests that the use of melatonin as a supplement may effectively reduce the levels of circulating cytokines, and may potentially also lower pro-inflammatory cytokine levels in COVID- 19 patients.

12. Teicoplanin and other glycopeptides

The other antibiotics worth mentioning in this review are glycopeptides. Teicoplanin (Sanofi Pharmaceuticals, Paris, France) was demonstrated to potently prevent the entry of Ebola envelope pseudotyped viruses into the cytoplasm, and also has an inhibitory effect on transcription- as well as replication-competent virus-like particles in the low

micromolar range (IC50, 330 nM). Moreover, teicoplanin is able to block the MERS and SARS envelope pseudo typed viruses as well [55]. Mechanistic investigations revealed that teicoplanin specifically inhibits the activities of host cell's cathepsin L and cathepsin B, which are responsible for cleaving the viral glycoprotein allowing exposure of the receptor-binding domain of its core genome 260 and subsequent release into the cytoplasm of host cells (Thus, teicoplanin blocks Ebola virus entry in the late endosomal pathway. These studies indicate the potential role of teicoplanin and its derivatives (dalbavancin, oritavancin, and telavancin) as novel inhibitors of cathepsin L-dependent viruses.

13. Monoclonal or polyclonal antibodies and other therapies

Monoclonal or polyclonal antibodies have been suggested as prophylactic and therapeutic tools (targeting hemag glutinin binding) against some viral infections, such as influenza [56]. Current efforts in developing monoclonal and polyclonal antibodies against coronaviruses mainly target MERS-CoV. For example, a human polyclonal antibody SAB-301 (50 mg/kg) that was generated in trans chromosomic cattle was observed to be well tolerated and safe in healthy participants of a phase 1 clinical trial. However, the observed that immune-based therapy with human monoclonal antibodies only provided protection against early stage disease caused by MERS-CoV in mouse models [57]. Numerous *in vitro* studies have shown that the spike protein 279 of SARS-CoV is important in mediating viral entry into target cells. Furthermore, the cleavage and subsequent activation of the SARS-CoV spike protein by a protease of the host cell is absolutely essential for infectious viral entry [58]. Type II trans membrane serine protease TMPRSS2 was suggested to be an important host protease that cleaves and activates the SARS-CoV spike protein in cell cultures, and was thus explored as a potential antiviral agent. In the past decade, the serine protease inhibitor camostat mesylate was shown to inhibit the enzymatic activity of TMPRSS2 [59]. Additionally, the cysteine PI K11777 showed promising potency in inhibiting MERS-CoV and SARS-CoV replication within the sub micromolar range [60]. Use of stem cells against COVID-19 has been under evaluation in China recently. Additionally, to cilizumab (Roche Pharmaceuticals, Basel, Switzerland) is a monoclonal antibody that is used in the treatment of RA exacerbation. It was designed to inhibit the binding of interleukin-6 to its receptors, thus alleviating cytokine release syndrome. Currently, it is also being investigated for treatment of COVID-19 [61].

Table 1 Agents under investigation for sars-cov-2

Agent	**Comments**
Anakinra	Interleukin-1 (IL-1) receptor antagonist hypothesized to quell cytokine storming. No data for use as adjunctive therapy for COVID-19 currently. No clinical trials are enrolling in China or the United States exploring this agent.
Arbidol (Umifenovir)	Antiviral used in Russia and China for influenza, being studied in Chinese clinical trials (200mg by mouth three times daily for no more than 10 days) for COVID-19 claiming potent *in vitro* activity. No clinical data exist currently; not available in the United States.
Baricitinib	A Janus kinase family (JAK) enzyme inhibitor, suggested as a COVID-19 treatment from artificial intelligence.58 No clinical data exist.
Bevacizumab	Recombinant humanized monoclonal antibody which prevents vascular endothelial growth factor (VEGF) association with endothelial receptors Flt-1 and KDR approved for multiple cancers in the United States. Is on critical, national shortage. Being evaluated in a clinical trial in China for COVID-19 (NCT04275414), no data exist at this time to support the use.
Brilacidin	A host defense peptide mimetic in clinical development by Innovation Pharmaceuticals. The company recently announced they will begin testing the molecule against SARS-CoV-2 beginning the week of March 16, 2020.
Convalescent plasma	Convalescent plasma from patients who have recovered from viral infections has been used previously for SARS-CoV-1, Middle East respiratory syndrome, Ebola, and H1N1 influenza with reported success. The safety and efficacy of convalescent plasma transfusion in SARS-CoV-2-infected patients have not been established and no protocols exist currently in the United States. Protocols are reportedly being developed at The Johns Hopkins University Hospital.

Darunavir/cobicistat	HIV-1 protease inhibitor currently being evaluated in a clinical trial (NCT04252274), but no *in vitro* or human data exist to support us at this time.
Disulfiram	Thiuram derivative which blocks alcohol oxidation. Demonstrated ability to competitively inhibit the papain-like proteases of SARS; however, no clinical data exist.60 No *in vitro* or clinical data exist for COVID-19.
Eculizumab	Humanized, a monoclonal IgG antibody that binds to complement protein C5 and prevents formation of membrane attack complex (MAC). Being evaluated in a clinical trial (NCT04288713) for COVID-19 to quell immune response, no data exist at this time to support the use.
Favipiravir	RNA-dependent RNA polymerase inhibitor with broad-spectrum antiviral activity, however, demonstrated high EC50 (decreased potency) against SARS-CoV-2 but was effective in protecting mice against Ebola virus despite similarly high EC50 values.3 Currently being evaluated in Clinical Trial NCT04273763 for patients with COVID-19. This agent is not FDA approved or available in the United States.
Galidesivir (BCX4430)	Nucleoside RNA polymerase inhibitor with reported wide spectrum of antiviral activity, currently in pipeline of Biocryst Pharma and previously evaluated for Ebola and other hemorrhagic fever virus infections.
Griffithsin	Algae-derived lectin and potent HIV entry inhibitor agent which demonstrated in vitro activity against SARS-COV-1.61
IVIG	IVIG remains on critical national shortage in the United States. The benefit of patients with COVID-19 is unclear.
Nelfinavir	Nelfinavir, an HIV-1 protease inhibitor, might be active against SARS-CoV-2 based on a pre-print publication that utilized homology modeling. (Xu *et al.,* 2020) No clinical data exist.
Niclosamide	Anthelminthic drug with in vitro efficacy against SARS-COV-1, however, low absorption and oral bioavailability resulting in a wide range of serum concentrations in healthy volunteers following a single dose may limit utility as antiviral treatment (Xu *et al.,* 2020).
REGN3048	Human monoclonal antibody discovered by Regeneron that reportedly binds to the S protein of MERS-CoV. Currently in phase 1 trial in healthy volunteers (NCT03301090). The company reportedly announced recruitment for phase 2 and 3 trials for SARS-CoV-2, however, these are not registered on ClinicalTrials.gov.
Sarilumab	IL-6 receptor antagonist FDA-approved for rheumatoid arthritis. Recently announced a US-based trial will begin enrolling at medical centers in New York for patients with severe COVID-19 disease.
Sofosbuvir	Antiviral used to treat hepatitis C, in vitro activity against SARS-COV-1, no clinical data exist (Elfiky *et al.,* 2020).
TZLS-501	A novel, fully human anti-interleukin-6 receptor (anti-IL6R) by Tiziana Life Sciences. The company recently announced they are moving forward with clinical development for patient use in patients with COVID-19 and excessive IL-6 production.
Vitamin C	There is an ongoing clinical trial of 12g IV BID Vitamin C in China for treatment of COVID-19 (NCT04264533). Use of this agent is not recommended at this time.
Xue Bi Jing	Chinese herbal medicine extract infusion formulation given at 100mL IV twice daily, suggested as a "may consider" treatment for severe and critical cases in the National Health Commission of the People's Republic of China: the COVID-19 Diagnosis and Treatment Guide, 7th Edition. This previously demonstrated improved mortality in patients with severe community acquired pneumonia in China (Song *et al.,* 2019)

Table 2 Potential drugs for COVID-19

Study	Method	Medicine	Mechanism of Action
Wang *et al.,* (2020)	In vitro study	Chloroquine Remdesivir	Reducing viral copy numbers in the cell supernatant and viral in-fection
Zhang *et al.,* (2020)	In vitro study	Teicoplanin	Preventing the entrance of SARS-CoV-2-Spike-pseudoviruses into the cytoplasm
Xu *et al.,* (2020)	Virtual screening	Nelfinavir	Binding to SARS-CoV 2 M^{pro}
Liu *et al.,* (2020)	Virtual screening	ColistinValrubicin Icati-bant Bepotastine Epirubicin Epoprostenol Vapreotide Aprepi-tant Caspofungin perphenazine	Binding to SARS-CoV-2 M^{pro}
Shang *et al.,* (2020)	Virtual screening	Rupintrivir Lopinavir Remdesivir	Binding to SARS-CoV-2 M^{pro}
Jin *et al.,* (2020)	Virtual screening	Ebselen	Binding to SARS-CoV-2 M^{pro}
Sekhar *et al.,* (2020)	Virtual screening	Beclabuvir Saquinavir	Binding to SARS-CoV-2 M^{pro}
Contini *et al.,* (2020)	Virtual screening	(Angiotensin II human acetate) GHRP-2 Indinavir Cobicistat Caspofungin acetate Lopinavir Atazanavir	Binding to SARS-CoV-2 M^{pro} : Angiotensin II human acetate, GHRP-2, Indinavir, and Cobicistat Binding to SARS-CoV-2 3C-like proteinase ($3CL^{pro}$): Angiotensin II human acetate, GHRP-2, In- dinavir, Caspofungin acetate, Lopinavir, and Atazanavir
Wang *et al.,* (2020)	Virtual screening	Carfilzomib Eravacycline Valru- bicin Lopinavir Elbasvir Strepto-Mycin	Binding to SARS-CoV-2 protease
Wang *et al.,* (2020)	Virtual screening	Thymopentin Carfilzomib Saquinavir	Binding to SARS-CoV-2 3C-like proteinase ($3CL^{pro}$)
Chen *et al.,* (2020)	virtual screening	Ledipasvir velpatasvir	Binding to SARS-CoV-2 3C-like proteinase ($3CL^{pro}$)
Beck *et al.,* (2020)	Molecule Transformer-Drug Tar-get Interaction (MT-DTI)	Atazanavir Efavirenz Ritonavir Dolutegravir	Binding to SARS-CoV-2 3C-like proteinase ($3CL^{pro}$)

Elfiky *et al.,* (2020)	Virtual screening	Mycophenolic acid Grazoprevir Telaprevir Boceprevir	Binding to SARS-CoV-2 papain- like protease (PL^{pro})
Arya *et al.,* (2020)	Virtual screening	Formoterol Chloroquine	Binding to SARS-CoV-2 papain-like protease (PL^{pro})
Smith *et al.,* (2020)	Virtual screening	Eriodictyol Isoniazid pyruvate Ni- trofurantoin Cepharanthine Er-goloid Hypericin	Binding potency to Viral S-protein at its host receptor region or to the S protein-human ACE2 interface
Li *et al.,* (2020)	Connectivity map (Cmap)	Ikarugamycin molsidomine	Effective on the genes co- expressed with ACE2
Richardson *et al.,* (2020)	Using Benevolent AI	Baricitinib	Binding to AP2-associated protein kinase 1 (AAK1)
Nowak *et al.,* (2020)	Brief review	Lithium	Probably by reducing apoptosis and inhibition of glycogen syn- thase kinase 3 beta (GSK-3β)
Sun *et al.,* (2020)	Brief review	Angiotensin converting enzyme inhibitors and Angiotensin1 receptor inhibitors	Rebalancing Renin-Angiotensin-Aldosterone System (RAAS) (might reduce the pulmonary inflammatory response and mortality)

14. Conclusion

All over the world four million people have tested positive for the novel Corona virus and the number is quickly increasing, researchers are also involved in drug discovery for it. In this reviewed article, the above said drugs were presently in use for treating infected peoples temporarily. Among this the antimalarial drug Hydroxychloroquine were using for the possible treatments for COVID - 19. Indian medical team are testing the empirical use of convalescent plasma therapy and it can be a potential treatment against COVID-19 Although social distancing and personal hygiene are somewhat beneficial, but the best solution for cure this corona infection is to find out the effective drugs is mandatory.

Compliance with ethical standards

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Disclosure of conflict of interest

All authors declare that they do not have any conflict of interests.

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