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SPECIAL REPORT

Old and re-purposed drugs for the treatment of COVID-19

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ABSTRACT

Introduction: The coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has developed since December 2019. It has caused a global pandemic with more than three hundred thousand case fatalities. However, apart from supportive care by respirators, no standard medical therapy is validated.

Areas covered: This paper presents old drugs with potential *in vitro* efficacy against SARS-CoV-2. The *in vitro* database, adverse effects, and potential toxicities of these drugs are reviewed regarding their feasibility of clinical prescription for the treatment of patients with COVID-19. To obtain convincing recommendations, we referred to opinions from the US National Institute of Health regarding drugs repurposed for COVID-19 therapy.

Expert opinion: Although strong evidence of well-designed randomized controlled studies regarding COVID-19 therapy is presently lacking, remdesivir, teicoplanin, hydroxychloroquine (not in combination with azithromycin), and ivermectin might be effective antiviral drugs and are deemed promising candidates for controlling SARS-CoV-2. In addition, tocilizumab might be considered as the supplementary treatment for COVID-19 patients with cytokine release syndrome. In future, clinical trials regarding a combination of potentially effective drugs against SARS-CoV-2 need to be conducted to establish the optimal regimen for the treatment of patients with moderate-to-severe COVID-19.

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1. Introduction

Since December 2019, Wuhan city (the capital city of Hubei province, China) experienced a major outbreak caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1,2]. Owing to its high transmission potential, the SARS-CoV-2 infection has become a global public health menace [3]. According to the COVID-19 research information published in the PubMed database, fever (67–89%), cough (43–81%), dyspnea (31–55%) and myalgia (3–44%) were the most prevalent manifestations among patients with COVID-19. Elevation of serum aspartate aminotransferase, creatine kinase, creatinine, and C-reactive protein levels were more frequently seen in the complicated COVID-19 patients than the uncomplicated group, while a normal serum procalcitonin concentration was noticed among most COVID-19 patients [4,5]. Additionally, 20.3% of COVID-19 patients required the hospitalization at intensive care units, 32.8% presented with acute respiratory distress syndrome (ARDS), 6.2% had shock, and 13.9% of hospitalized patients had fatal outcomes. The pandemic caused by COVID-19 has brought a huge burden to healthcare facilities for many countries, especially in patients with comorbidities [4]. Unfortunately, standard treatment against COVID-19 is currently lacking. In addition to developing new treatment options (such as immunotherapies and host-directed therapies), scientists worldwide continue to simultaneously explore the efficacy of existing drugs against SARS-CoV-2. This article summarizes old drugs that could be potentially re-purposed for COVID-19 treatment.

2. Inhibitors of RNA-dependent RNA polymerase

2.1. Remdesivir

Remdesivir, which targets the viral RNA-dependent RNA polymerase (RdRp) and induces premature termination of viral RNA transcription [6], is considered as the most promising drug against SARS-CoV-2 [7,8]. Initially, uncertainties regarding the adverse effects (such as nausea, vomiting, rectal hemorrhage, and hepatic toxicity) and clinical efficacy of remdesivir were reported in the clinical treatment of COVID-19 [8]. An important study reported the outcomes of the 53 hospitalized patients (22 in the US, 22 in Europe or Canada, and 9 in Japan) who were treated with compassionate-use remdesivir for severe COVID-19 recently [9]. Among these patients, 30 patients (56.7%) received mechanical ventilation and 4 (7.5%) underwent extracorporeal membrane oxygenation prior to initiation of remdesivir treatment. All these patients received a 10-day course of remdesivir administered intravenously, consisting of 200 mg on day 1 and followed by 100 mg daily for the remaining 9 days of treatment. The overall mortality was 13.2%. Of note, clinical improvement was observed in 36 (68%) patients, and the abnormality of

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hepatic function was the most frequent adverse effect (23%), followed by diarrhea (9%), skin rash (8%), acute kidney injury (8%), etc. Limitations of this study included the small size of the cohort, no viral load data collections at baseline and follow-up periods, and the lack of a randomized control group [9]. Ongoing randomized controlled trials for evaluating the clinical efficacy of remdesivir is absolutely needed.

2.2. Favipiravir

The other RdRp inhibitor favipiravir is known to be active *in vitro* against oseltamivir-resistant influenza A, B, and C viruses [10]. Although favipiravir has been reported to significantly shorten the duration of clinical recovery for COVID-19 patients by Cai *et al*., who published their investigational results in Engineering, this article has been temporarily withdrawn. In spite of unfavorable pharmacokinetic (PK) profile and no conclusive data regarding its efficacy in the treatment of COVID-19, favipiravir was approved for marketing in the treatment of COVID-19 patients in China in March 2020.

2.3. Ribavirin

Ribavirin, a guanosine analogue, is an antiviral drug that has been used to treat several viral infections, including hepatitis C virus and respiratory syncytial virus (RSV). It was recommended for COVID-19 treatment by the National Health Commission and State Administration of Traditional Chinese Medicine in the 7th edition of their report, 'Novel Coronavirus Pneumonia Diagnosis and Treatment Plan' [11]. The *in vitro* antiviral activity of ribavirin against SARS-CoV, however, was estimated at concentrations up to 50 μg/mL [12]. The regimen of lopinavir/ritonavir (see as follows) plus ribavirin was also shown to be effective against SARS-CoV in patients and in tissue culture [13]; however, its clinical efficacy is currently unproven.

3. Protease inhibitor

3.1. Lopinavir/ritonavir (LPV/RTV), darnunavir

For the Orthocoronavirinae family, protease inhibitors (PI) are used to target papain-like protease and 3 C-like protease [6]. Among the PIs that inhibit the coronavirus, the antiviral activity of LPV against MERS-CoV is controversial in the tissue culture model [12]. Notably, treatment with LPV/RTV alone (400/100 mg administered orally twice daily for 14 days; Chinese Clinical Trial Register number, ChiCTR2000029308) failed to demonstrate clinical improvement and reduction of viral RNA load compared to standard care alone in patients with severe SARS-CoV-2 [14]. The other PI darunavir, which has been extensively used for the treatment of HIV infection in both naïve and experienced subjects, has been shown to have promising potential against SARS-CoV-2 *in vitro*; nevertheless, this drug needs to be further investigated (http://www.sd.chinanews.com/2/2020/0205/70145.html). Because of their unfavorable PK profiles and negative clinical trial data, however, the US National Institute of Health (NIH) Consensus Treatment Guidelines Panel recommended against the use of LPV/RTV and other human immunodeficiency virus (HIV) PIs alone in treatment of COVID-19 in April, 2020 [15].

4. Immunomodulatory drugs

4.1. Chloroquine, hydroxychloroquine, and azithromycin

Chloroquine is an important drug in the treatment of malaria and autoimmune diseases (such as rheumatoid arthritis [RA] and lupus erythematosus). Additionally, chloroquine was shown to increase endosomal pH, which eliminates an important prerequisite for virus/cell fusion and interferes with the glycosylation of the cellular receptors of SARS-CoV [16]. Notably, hydroxychloroquine has been shown to be significantly more potent than chloroquine *in vitro* (EC_{50} values, 0.72 and 5.47 μM, respectively); additionally, there are fewer concerns regarding drug-drug interactions for hydroxychloroquine than for chloroquine. Consequently, despite conflicting opinions [17], hydroxychloroquine has been recently proposed as having the ability to control cytokine storms and shorten the clinical recovery time among critically ill SARS-CoV-2-infected patients [18,19]. Recently, hydroxychloroquine sulfate was approved by the US Centers for Disease Control and Prevention for emergent use in treating adolescent or adult patients (body weight ≥50 kg) with severe COVID-19 on 28 March 2020. According to data from physiologically based pharmacokinetic models, a loading dose of 400 mg twice daily of hydroxychloroquine sulfate, which is followed by a maintenance dose of 200 mg twice daily for 4 days, has demonstrated significant superiority (5 days in advance) to chloroquine phosphate (500 mg twice daily, 4-fold higher than that used in malaria treatment) in inhibiting SARS-CoV-2 *in vitro* [18]. Additionally, the cardiac toxicity might temper the enthusiasm for the widespread use of chloroquine in the treatment of COVID-19. It is noteworthy that one randomized controlled trial in Wuhan, China validates the clinical superiority of hydroxychloroquine (200 mg twice daily for 5 days) over the control group in significantly shortening recovery time [20].

According to one notable study, azithromycin (500 mg on day 1, followed by 250 mg per day on days 2–5) was shown to significantly reinforce the efficacy of hydroxychloroquine (200 mg thrice daily for 10 days) in the treatment of 20 patients with severe COVID-19. The positive clinical outcome in these COVID-19 patients is attributed to the excellent efficiency of virus elimination after administration of this combination regimen [21]. Consequently, hydroxychloroquine in combination with azithromycin might be deemed a promising alternative to remdesivir in the treatment of patients with SARS-CoV-2 infection. Nevertheless, the warning on QTc prolongation caused by this combination regimen should be cautiously considered. Despite excellent efficacy on a small group of patients with COVID-19, the US NIH Consensus Treatment Guidelines Panel recommended against the use of this combination regimen in the treatment of COVID-19 due to its cardiac toxicity [15].

4.2. Monoclonal antibody inhibiting the action of interleukin (IL)-6

Tocilizumab is a monoclonal antibody employed in treatment of RA exacerbation. It was originally designed to inhibit the

binding of IL-6 to its receptors for alleviating cytokine release syndrome. Tocilizumab is currently being investigated in a randomized, double-blind phase 3 trial for its clinical efficacy and safety in patients with COVID-19 compared to placebo plus standard care in the US [22]. Recently, in China, an open label, non-controlled study (ClinicalTrials.gov Identifier: NCT04322773) investigated the efficacy of tocilizumab for reducing oxygen requirement. Although no control group was included in that study, the preliminary report shows a promising potential for tocilizumab on the basis of the outcome in the COVID-19 patients, who had mild-to-moderate ARDS and received a single intravenous dose of 400 mg tocilizumab [23].

4.3. Janus kinase inhibitor

The efficacy of a Janus kinase inhibitor ruxolitinib, which was originally used in the treatment of intermediate- or high-risk myelofibrosis, is currently being evaluated in a phase 3 trial for the treatment of patients with COVID-19-associated cytokine storm [23,24]. Despite a theoretically promising role in alleviating cytokine release storm, the US NIH Consensus Treatment Guidelines Panel recommended against use of the Janus kinase inhibitors in the treatment of COVID-19 presently due to their broad immunosuppressive effects [15].

5. Miscellaneous drugs

5.1. Teicoplanin and lipoglycopeptides

Teicoplanin was demonstrated to potently prevent the entry of Ebola, MERS, and SARS envelope pseudotyped viruses into the cytoplasm, as well as exhibit an inhibitory effect on transcription- and replication-competent virus-like particles in the low micromolar range (IC_{50}, 330 nM) [25]. Mechanistic investigations showed that teicoplanin specifically inhibits the activities of the host cell's cathepsin L and cathepsin B, responsible for cleaving the viral glycoprotein and allowing the exposure of the receptor-binding domain of its core genome and its subsequent release into the cytoplasm of the host cells (i.e., the late endosomal pathway) [26,27]. Although the clinical efficacy of teicoplanin against SARS-CoV-2 is not proven presently, these studies indicate the potential role of teicoplanin as a novel inhibitor against cathepsin L-dependent viruses. Apart from teicoplanin, lipoglycopeptides (dalbavancin, oritavancin, and telavancin) are also considered as potentially repurposable drugs for COVID-19 treatment [26].

5.2. Ivermectin

Ivermectin is an FDA-approved broad-spectrum anti-parasitic (helminths, scabies, etc) agent. It is usually administered with a single dose of 150 μg/kg orally [28]. Of note, it has been shown to boost human immunity (including enhancement of production of IL-1 and other cytokines, activation of superoxide anion production, and augmentation of lymphocyte response to mitogens) [29]. Originally, ivermectin was identified as an inhibitor of the interaction between the HIV-1 integrase protein (IN) and α/β1 heterodimer of the importin, which is responsible for IN nuclear import [30], thus inhibiting HIV replication. Additionally, ivermectin has also been demonstrated to effectively control infections caused by several other RNA viruses (such as dengue, influenza, RSV, and rabies) [31]. Its broad-spectrum antiviral activity was considered to be related to the reliance of multiple RNA viruses on IMPα/β1 during infection [32]. Caly *et al*. recently demonstrated that a single-dose treatment with ivermectin induced an approximately 5000-fold reduction in the viral RNA of SARS-CoV-2 at 48 h in a Vero-hSLAM cell culture model [31]. The therapeutic potential of this drug against human COVID-19 is currently being evaluated. Although severe adverse effects about potentiation of the GABAergic synaptic transmission (depression, ataxia), and psychosis, confusion, seizure were occasionally reported in few patients with diseases other than onchocerciasis [33], the conventional dose (≤200 μg/kg) of ivermectin is considered to be as a safe regimen in human therapy [34].

5.3. Neurokinin-1 receptor antagonist inhibiting the neurally-mediated lung inflammation

The neurokinin-1 (NK-1) receptor, encoded by the TACR1 gene, is the main receptor for substance P. Numerous insults, including multiple viral infections, likely facilitate the interaction between substance P and NK-1 receptor, resulting in serious lung parenchymal injury through neuro-inflammatory processes [23]. Recently, US Food and Drug Administration (FDA) approved the phase 3, double-blind ODYSSEY study (ClinicalTrials.gov Identifier: NCT04326426, initiated on 12 April 2020) to investigate the efficacy and safety of tradipitant at a dosage of 85 mg orally twice daily for the treatment of inflammatory lung injury following critical COVID-19 infection [35].

5.4. Inhaled nitric oxide

Among SARS patients, a group treated with inhaled nitric oxide experienced a reversal of pulmonary hypertension, thereby exhibiting a significant improvement in hypoxia and requiring a shorter duration of ventilatory support, compared to the matched control group [36]. Nevertheless, the Society of Critical Care Medicine recommends against its routine use for patients with COVID-19 pneumonia unless they are refractory to other strategies [37].

5.5. Angiotensin converting enzyme 2 (ACE2) inhibitor, angiotensin receptor blocker (ARB), and statins

The ACE2 within the lower respiratory tract is the primary target of the SARS-CoV-2 infection [2]. SARS-CoV-2 and SARS-CoV can effectively utilize the ACE2 receptors expressed on the epithelial cells of the lung, intestine and kidney for human invasion [8]. Therefore, despite conflicting opinions [15], a cautious administration of ACE inhibitors or ARB might be advised for COVID-19 patients [8]. Interestingly, a high ACE2 activity is observed in association with reduced severity of ARDS among patients with lower respiratory tract infection

caused by RSV [38]. Fedson *et al*. observed that statins target the host response to infection (endothelial dysfunction) rather than the virus itself and suggested that combination therapy with ARB and statins might accelerate a return to homeostasis, allowing patients to recover on their own [39]. Despite above-mentioned benefits, the US NIH Consensus Treatment Guidelines Panel recommended against routine addition of this combination regimen in COVID-19 treatment [15].

6. Expert opinion

We are fighting an indefinite battle against a dangerous and highly contagious virus with significantly higher spread potential than 2003 SARS-CoV. As stated in the aforementioned paragraphs, most drugs that are being considered for COVID-19 therapy are under scrupulous investigations to assess their adverse effects as well as efficacy against SARS-CoV-2. Several medicines have been withdrawn because of adverse reactions after showing clinical promise [17]. Presently, no drug or specific therapy against SARS-CoV-2 is formally recommended by the US FDA. Till date, except for supportive management, COVID-19 is 'essentially untreatable' [34,40].

Nevertheless, among the numerous drugs with potentially good *in vitro* efficacy against SARS-CoV-2, we identified some that have been validated to have acceptable safety as well as favorable pharmacokinetic profiles in human therapy. Apart from remdesivir that was shown to have acceptable clinical efficacy against moderate-to-severe COVID-19 and acceptable side effects, the potential antiviral drugs that are likely useful in the treatment of patients with mild-to-moderate COVID-19 included hydroxychloroquine, teicoplanin, and ivermectin. Moreover, among the anti-IL-6 receptor monoclonal antibodies under evaluation regarding the efficacy of improvement in oxygenation function of lung parenchyma and cytokine storm in COVID-19 patients with moderate ARDS, tocilizumab probably has a better effect than others. However, the immunosuppression induced by tocilizumab is a cause for concern as many patients with COVID-19 likely have leukopenia or lymphopenia. In fact, despite the current unproven clinical efficacy through stringent trials, a combination of the above-mentioned useful drugs ought to be carefully considered to combat SARS-CoV-2. In future, we sincerely hope that effective vaccines and documented drug regimens specifically targeting SARS-CoV-2 can be developed to authentically prevent COVID-19 and cure critically ill COVID-19 patients as soon as possible.

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•• **Issuing many potentially effective drugs against SARS-CoV-2 and other practical therapies in treatment of critical COVID-19 in detail.**