Overview of the status of the development of antiviral drugs for COVID-19

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Running Title: Development of COVID-19 vaccines and drugs

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ABSTRACT

In this study, we surveyed worldwide media reports and research papers on the development of vaccines and antiviral drugs for COVID-19 treatment published over the past few months. We found that more studies were being conducted on the use of already approved drugs (remdesivir, lopinavir/ritonavir, chloroquine, niclosamide, and ivermectin) as new COVID-19 treatments, than on the development of new antiviral drugs. This could be due to the urgent need for drug development. We found that till date, there seem to be no results on current or future COVID-19 vaccine development. However, media reports showed that numerous companies have invested in vaccine development and some clinical trials are already underway (mostly in phase I–II). According to the results of our survey, the drugs that have been previously approved to treat other diseases have not yet been found to be very effective in treating COVID-19 patients; however, remdesivir is the most promising drug. Due to the pandemic situation, the number of patients participating in these clinical trials, compared to that in other previous clinical studies, is small. Therefore, due to the low reliability of the findings, additional experiments must be continued.

Keywords: SARS-CoV-2, COVID-19, Vaccine development, Antiviral drug

Introduction

The novel coronavirus epidemic (COVID-19), which started in Wuhan, China, has spread to more than 190 countries, infecting many people and causing many deaths. This virus appears to be very contagious, making it difficult to contain it effectively (Hur *et al.*, 2020). The COVID-19 outbreak in each country was quite different, and the case fatality rate varied greatly from country to country. Due to this, effective control of 2019-nCoV infection is considered very difficult (Hur, et al., 2020). Rapid development of a vaccine to prevent COVID-19 is a global imperative (Graham, 2020), and most of the therapeutic options available for managing COVID-19 are based on previous experiences of treating severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) (Dhama *et al.*, 2020). Therefore, many scientists and pharmaceutical companies around the world are increasing their efforts in developing antiviral drugs and vaccines against COVID-19, considering that the COVID-19 pandemic has been predicted to be resolved only after vaccine and antiviral drug development. Currently, drug repurposing is being used to identify potential drugs against the coronavirus (Boopathi *et al.*, 2020), and enormous efforts have been made for the reuse of FDA-approved/preclinical trial drugs for COVID-19 treatment (Boopathi, et al., 2020). Therefore, this study aimed to provide helpful information on the status of the development of vaccines and antiviral drugs for COVID-19.

Status of the vaccine development

Coronaviruses, including the newly discovered SARS-CoV-2, are spherical positive single-stranded RNA viruses that are characterized by spike proteins projecting from the

virion surface (Ashour *et al.*, 2020). Coronaviruses are enveloped viruses (envelope is a lipid bilayer derived from the host cell membrane), and the viral structure is primarily formed of structural proteins such as spike, membrane, envelope, and nucleocapsid proteins. Haemagglutinin-esterase protein is found in some β-coronaviruses (Ashour, et al., 2020). Multiple strategies have been adopted for the development of coronavirus vaccines; most of them target the surface-exposed spike glycoprotein or spike protein because it is the major inducer of neutralizing antibodies (Dhama, et al., 2020). Le et al. (2020) reported that as of 8 April 2020, numerous vaccine developers have planned to initiate human testing in 2020 (Le *et al.*, 2020). The global COVID-19 vaccine research and development landscape includes 115 vaccine candidates, of which 78 are confirmed to be active and the remaining 37 are unconfirmed. Of the 78 confirmed active candidates, 73 are currently at the exploratory or preclinical stages (Le, et al., 2020) (it may have increased further). Indeed, the most advanced candidates, including mRNA-1273 from Moderna, Ad5-nCoV from CanSino Biologicals, INO-4800 from INOVIO (DNA-based), LV-SMENP-DC and pathogen-specific aAPC from Shenzhen Geno-Immune Medical Institute, BNT162 from BioNTech/Pfizer, and mRNA-based COVID-19 vaccine from CuraVac, have recently moved into the clinical developmental stage (Corey *et al.*, 2020; Le, et al., 2020). Moderna's mRNA-based SARS-CoV-2 candidate entered the phase I clinical trial on 16 March 2020, less than 10 weeks after the first genetic sequences of the virus were released. The first phase I trial of a non-replicating vector-based vaccine has been given regulatory clearance for the commencement of phase I studies in China (Lurie *et al.*, 2020). DNA- and mRNA-based vaccines can be generated quickly based on the viral sequence, resulting in their rapid progress to clinical trials

(Corey, et al., 2020). mRNA-based vaccines use lipid nanoparticles to protect and deliver the mRNA and effectively adjuvant the immunogen (Corey, et al., 2020).

In January 2020, Vaxart Inc. initiated a program to develop a COVID-19 vaccine based on its VAAST^{TM} oral vaccines platform. Antibody responses in all vaccinated groups, compared to the untreated controls, were statistically significant. Vaxart oral vaccines have been shown to provide mucosal immunity against respiratory infection, and must be administered orally using a room temperature-stable tablet, demonstrating an enormous logistical advantage over injectables in large vaccination campaigns (https://investors.vaxart.com) (Vaxart, 2020).

According to the news and company press releases, Massachusetts Eye and Ear and Massachusetts General Hospital announced their progress in the testing and development of an experimental vaccine called AAVCOVID, which is a novel gene-based vaccine candidate against SARS-CoV-2, the virus that causes COVID-19. The AAVCOVID Vaccine Program is a unique gene-based vaccine strategy where AAVCOVID is used to deliver genetic sequences of the SARS-CoV-2 spike antigen to the body for the development of an immune response to the coronavirus. It has been reported that preclinical vaccine development, with a plan to start clinical trials on humans later this year, is currently underway.

NOVIO recently announced that 40 healthy volunteers enrolled for its phase I U.S. clinical trial of the COVID-19 DNA-based vaccine INO-4800. The volunteers have received their first dose, and interim immune responses and safety results are expected in late June. The phase I study was designed to assess the safety profile and immunogenicity of INO-4800, after which it can advance rapidly to a phase II/III efficacy trial, which has been planned to be initiated this summer.

Researchers at the University Hospital Southampton and the University of Southampton are set to begin trials of a vaccine that has been pioneered in the UK and has been reported to provide protection against COVID-19. Up to 510 healthy volunteers between the ages of 18 and 55 years will be included in the study, and approximately 187 participants are expected to be recruited in Southampton. The trials of the vaccine, developed by clinical teams at the University of Oxford's Jenner Institute and Oxford Vaccine Group, began in January. The vaccine is called ChAdOx1 nCoV-19, and is developed using a weakened version of adenovirus that is found in chimpanzees because it cannot survive in humans due to genetic modifications.

The International Vaccine Institute (IVI) announced that the Coalition for Epidemic Preparedness Innovations has granted a funding of $6.9 million to INOVIO to work with the IVI and the Korea National Institute of Health on the phase I/II clinical trial of INOVIO's COVID-19 vaccine candidate (INO-4800) in South Korea. The IVI will conduct the trial in parallel with INOVIO's INO-4800 phase I study, which is currently underway in the US since 6 April 2020. The INO-4800 phase I study included 40 healthy adults who received the vaccine candidate, and will eventually expand to older adults. The biotechnology company GeoVax Labs Inc. announced that it is developing vaccine candidates for the prevention/control of SARS-CoV-2 using its GV-MVA-VLP™ vaccine platform.

We found that to date, there seem to be no results on current or future COVID-19 vaccine development, but media reports showed that numerous companies have invested in vaccine development and some clinical trials are already underway. Antiviral drugs are relatively easier to find through repurposing, but vaccine development requires more time because the repurposing of vaccines is not very effective. After re-

viewing the current situation, we expect that it will be difficult for vaccine development to be completed by the end of this year, and if the process proceeds at a normal pace (considering the scale and time of conducting clinical trials and approving drugs), we expect that vaccine development will not be possible until next year.

Status of antiviral drug development

Remdesivir

Remdesivir was originally developed by Gilead Sciences in 2009 for the treatment of hepatitis C and was then repurposed for Ebola virus disease. Remdesivir has been recently recognized as a promising antiviral drug against a broad spectrum of RNA viruses in cultured cells, mice, and non-human primate models (Scavone *et al.*, 2020). The antiviral mechanism of remdesivir includes delayed cessation of the nascent viral RNA chain (Al-Tawfiq *et al.*, 2020). Cao et al. (2020a) reported that SARS-CoV-2 entered target cells by allowing the S protein to bind to the angiotensin-converting enzyme-2 receptor on the cell surface and remdesivir, the nucleotide analogue that acts as a RNA-dependant RNA polymerase (RdRp) inhibitor, blocked RNA replication (Cao *et al.*, 2020).

First, Gilead Science reported that in this cohort of hospitalized patients with severe COVID-19 that were treated with compassionate-use remdesivir, clinical improvement was observed in 36 out of 53 patients (68%). Measurement of efficacy will require ongoing randomized, placebo-controlled trials of remdesivir therapy (Grein *et al.*, 2020). Wang et al. (2020a) reported that two compounds, remdesivir and chloroquine, potently blocked viral infection at low-micromolar concentrations and showed high selectivity index (Wang *et al.*, 2020). Choy et al. (2020) reported that remdesivir inhibited SARS-

CoV-2 replication in Vero E6 cells at a half-maximal effective concentration (EC_{50}) of 23.15 μM. Lopinavir, but not ritonavir, inhibited SARS-CoV-2 replication at an EC_{50} of 26.63 μM. Homoharringtonine and emetine inhibited SARS-CoV-2 replication at EC_{50} values of 2.55 μM and 0.46 μM, respectively (Choy *et al.*, 2020). A combination of remdesivir and emetine showed synergistic effects *in vitro*.

Williamson et al. (2020) reported that animals treated with remdesivir showed reduced pulmonary infiltrates on radiographs and no signs of respiratory disease (Williamson *et al.*, 2020). Virus titres in bronchoalveolar lavages were significantly reduced as early as 12 h after administration of the first treatment. On performing necropsy on day 7 after inoculation, lung viral loads of remdesivir-treated animals were significantly lower and a clear reduction in lung tissue damage was observed. Thus, these findings supported early remdesivir treatment initiation in COVID-19 patients to prevent progression to severe pneumonia (Williamson, et al., 2020).

Wang et al. (2020c) reported that remdesivir treatment was not associated with a difference in the time to clinical improvement (Wang *et al.*, 2020). Although not statistically significant, a numerically faster time to clinical improvement was observed in remdesivir-treated patients than in placebo-treated patients who showed symptoms for at most 10 days. Adverse events were reported in 102 out of 155 (66%) remdesivir recipients, compared to 50 out of 78 (64%) placebo recipients. Adverse events occurred in 18 (12%) patients for whom remdesivir was stopped early, compared to 4 (5%) patients for whom placebo was stopped early. Wang et al. (2020) concluded that in this study of adult hospitalized COVID-19 patients, remdesivir was not associated with statistically significant clinical benefits. However, the numerical reduction in the time to clinical

improvement in those treated with this drug earlier requires confirmation using a larger number of samples.

According to the results of our survey, even though the effect of remdesivir was not as high as we expected, it is considered the most valuable antiviral drug till date. For this reason, the FDA approved remdesivir to be used as a COVID-19 treatment, and the South Korean government is urgently approving its use and pushing for its purchase. Although some researchers recently argued that remdesivir was ineffective for Asians, we assume that it will most likely be used as a treatment for COVID-19, especially if no new drug candidates are identified in the near future. Nevertheless, earlier clinical trials at the Centers for disease control and prevention (CDC) reported side effects of remdesivir, such as nausea, vomiting, stomach paralysis, liver damage, and temporary gastrointestinal symptoms including rectal bleeding. Therefore, further verification of the exact effects of remdesivir is required.

Chloroquine/hydroxychloroquine

Chloroquine is used to prevent and treat malaria, and is being studied for COVID-19 treatment (Cortegiani *et al.*, 2020). Chloroquine inhibits the pre-entry step in the viral cycle by interfering with the binding of the viral particles to their cellular surface receptors (Devaux *et al.*, 2020). Chloroquine inhibits activation of cells by MAP kinase and post-translational modification of M proteins, thereby altering viral assembly and budding (Kumar *et al.*, 2020). For this reason, it is being studied as a candidate for COVID-19 treatment, and currently, 23 clinical trials of chloroquine are underway in China (Cortegiani, et al., 2020).

In early *in vitro* studies, chloroquine was found to block COVID-19 infection at low-micromolar concentrations, an EC_{50} value of 1.13 μM, and a half-cytotoxic concentration >100 μM (Gao *et al.*, 2020). Keyaerts et al. (2020) reported that chloroquine inhibited SARS-CoV replication in Vero E6 cells (Keyaerts *et al.*, 2004). Since immunopathological factors may play a significant role in SARS-CoV infection, it will be of interest to study whether chloroquine is also effective in modulating the inflammatory responses to SARS-CoV infection (Keyaerts, et al., 2004). Wang et al. (2020a) also found that chloroquine functioned at both the entry and post-entry stages of the 2019-nCoV infection in Vero E6 cells (Wang, et al., 2020).

Gao et al. (2020) suggested that approximately 100 chloroquine-treated COVID-19 patients, compared to the controls, experienced a more rapid decline in fever and an improvement in the lung computed tomography (CT) images and required a shorter time to recover, showing no obvious serious adverse effects (Gao, et al., 2020). The Chinese medical advisory board has suggested the inclusion of chloroquine in the SARS-CoV-2 treatment guidelines (Devaux, et al., 2020). Chen et al. (2020c) reported that the body temperature recovery and cough remission times were significantly shortened in the hydroxychloroquine treatment group. Besides, more patients with improved pneumonia were observed in the hydroxychloroquine treatment group (80.6%, 25 out of 31) than in the control group (54.8%, 17 out of 31) (Chen *et al.*, 2020). However, two patients in the hydroxychloroquine treatment group developed mild adverse reactions. Therefore, Chen et al. (2020c) suggested that hydroxychloroquine treatment could significantly shorten the time to clinical recovery and promote the absorption of pneumonia (Chen, et al., 2020).

In France, the combination of hydroxychloroquine and azithromycin was used for the treatment of 1061 COVID-19 patients (46.4% male, mean age 43.6 years, age range 14–95 years) (Million *et al.*, 2020). Good clinical outcomes and virological cure were observed in 973 patients within 10 days (91.7%). Prolonged viral carriage was observed in 47 patients (4.4%), and was associated with a higher viral load at diagnosis; however, viral culture was negative on day 10. A poor clinical outcome was observed for 46 patients (4.3%), and 8 patients (0.75%, age range 74–95 years) died. Therefore, Million et al. (2020) suggested that the administration of the hydroxychloroquine and azithromycin combination before the occurrence of COVID-19 complications was safe and was associated with a very low patient fatality rate (Million, et al., 2020).

In contrast, Mehra et al. (2020) reported that compared with the control group, the hydroxychloroquine, hydroxychloroquine plus a macrolide, chloroquine, and chloroquine plus a macrolide treatment groups independently showed an association with an increased risk of *de-novo* ventricular arrhythmia during hospitalization (Mehra *et al.*, 2020). Mehra et al. (2020) confirmed no benefits of hydroxychloroquine or chloroquine, when used alone or with a macrolide, in the in-hospital COVID-19 outcomes (Mehra, et al., 2020). Each of these drug regimens, when used for COVID-19 treatment, was associated with decreased in-hospital survival and an increased frequency of ventricular arrhythmias (Mehra, et al., 2020). Although a number of *in vivo* clinical trials are underway, there is limited evidence of the *in vitro* activity of chloroquine/hydroxychloroquine against SARS-CoV-2 (Gbinigie and Frie, 2020). The empirical data available from two of these trials revealed conflicting results (Gbinigie and Frie, 2020). Both trials were characterized by a small number of participants (n = 30 and n = 36, respectively), and suffered methodological limitations(Gbinigie and Frie, 2020). No

medium- or long-term follow-up data was available (Gbinigie and Frie, 2020). Additionally, there are several reports on the side effects of chloroquine, such as severe diarrhoea, hearing loss, and increased burden on the heart. Hence, further verification of the exact effects of chloroquine/hydroxychloroquine is required.

Niclosamide

Niclosamide is an FDA-approved anthelminthic drug that has been widely used in humans to treat tapeworm infections for several decades, and is currently listed on the World Health Organization's list of essential medicines (Xu *et al.*, 2020). After screening a small-marketed drug library, Wu et al. (2020) suggested that niclosamide inhibited SARS-CoV replication and completely abolished viral antigen synthesis at a concentration of 1.56 μM. Niclosamide suppressed the cytopathic effect (CPE) of SARS-CoV at a concentration as low as 1 μM and inhibited SARS-CoV replication at an EC_{50} value <0.1 μM in Vero E6 cells (Wu *et al.*, 2004). Gassen et al. (2019) reported that niclosamide inhibited the S-Phase kinase-associated protein 2, enhanced autophagy, and reduced MERS-CoV replication (Gassen *et al.*, 2019). This could be the potential antiviral mechanism of niclosamide against SARS-CoV-2. Gassen et al. (2020) also found that niclosamide inhibited SARS34 CoV-2 propagation by 85, 88, and >99%, respectively *in vitro* (Gassen *et al.*, 2020). Jeon et al. (2020) screened a panel of 48 FDA-approved SARS-CoV-2 drugs, which were pre-selected by a SARS-CoV assay, and identified 24 potential antiviral drug candidates against SARS-CoV-2 infection. Niclosamide exhibited highly potent antiviral activity against SARS-CoV-2 at a half-maximal inhibitory concentration [IC_{50}] of 0.2871 μM (Jeon *et al.*, 2020). Since there are insufficient studies on niclosamide, further clinical trials must be conducted to verify its efficacy.

Ivermectin

Ivermectin is an FDA-approved broad-spectrum anti-parasitic agent, and has been shown to have antiviral activity against a broad range of viruses *in vitro* (Caly *et al.*, 2020). Caly et al. (2020) reported that viral RNA was reduced (99.98%) after 49 h of ivermectin (5 μM) treatment in SARS-CoV-2 infected cells (Caly, et al., 2020). Taken together, these results demonstrated that a single dose of ivermectin showed antiviral action against the SARS-CoV-2 clinical isolate *in vitro* within 24–48 h by controlling viral replication. Caly et al. (2020) hypothesized that ivermectin possibly inhibited importin α/β1 heterodimer (IMPα/β1)-mediated nuclear import of viral proteins (Caly, et al., 2020). Paz et al. (2020) suggested that ivermectin was capable of docking with the 3CL protease and the HR2 domain, possibly promoting structural changes in these proteins by inducing unfolding/folding (Paz *et al.*, 2020). Specifically, ivermectin brings the protease to a significantly more deployed conformational state and the HR2 domain to a more compact state, compared to their native states (Paz, et al., 2020). These results suggested a possible inhibitory effect of ivermectin on SARS-CoV-2 survival due to the synergistic role of this drug in spontaneously binding with two important proteins involved in viral proliferation (Paz, et al., 2020). In contrast, Momekova and Momekova (2020) reported that the available pharmacokinetic data on ivermectin indicated that the SARS-CoV-2 inhibitory concentrations were not practically attainable at the doses routinely used for parasitic disease management (Momekov and Momekova, 2020). Therefore, Momekova and Momekova (2020) suggested that because ivermectin failed to demonstrate antiviral effects beyond the *in vitro* level, its application in COVID-19 pa-

tients must be decisively discouraged until the paucity of reliable data from controlled studies has been resolved.

Lopinavir/ritonavir

Lopinavir/ritonavir is a medication used in combination with other medications to treat human immunodeficiency virus (HIV)-1 infection in adults and children over 14 days of age (Dong *et al.*, 2020). There are some reports on the use of lopinavir/ritonavir for COVID-19 treatment (Kim *et al.*, 2020). Lim et al. (2020) reported that within a day of lopinavir/ritonavir administration (2 tablets [lopinavir 200 mg/ritonavir 50 mg]), the β-coronavirus load started to decrease and no detectable or lesser coronavirus titres were observed (lopinavir/ritonavir was started on day 8 of hospitalization [day 10 of illness]) (Lim *et al.*, 2020). Wang et al. (2020b) reported that after lopinavir/ritonavir treatment of four COVID-19 patients, three patients showed significant improvement of pneumonia-associated symptoms, two of whom were then confirmed to be COVID-19 negative and discharged. The remaining patient was negative for the virus according to the first test (Wang *et al.*, 2020). Yao et al. (2020) suggested that this study showed the positive effects of lopinavir/ritonavir therapy (Yao *et al.*, 2020). Ye et al. (2020b) reported that compared with the treatment using pneumonia-associated adjuvant drugs alone, the combination treatment using lopinavir/ritonavir and adjuvant drugs showed a more evident therapeutic effect in lowering the body temperature and restoring normal physiological mechanisms, with no evident toxic and side effects (Ye *et al.*, 2020). Therefore, Ye et al. (2020b) suggested that the use of lopinavir/ritonavir, combined with pneumonia-associated adjuvant drugs, for the clinical treatment of COVID-19 patients should be promoted. Yu et al. (2020) also suggested that the combination of lopinavir/ritonavir,

interferon (IFN), and arbidol could be a good choice for antiviral therapy, especially in adults (Yu *et al.*, 2020). Deng et al. (2020) analysed 16 patients who received oral arbidol and lopinavir/ritonavir in the combination group and 17 patients who received only oral lopinavir/ritonavir in the monotherapy group; after 14 days, SARS-CoV-2 could not be detected in 15 out of 16 (94%) and 9 out of 17 (52.9%) patients, respectively (Deng *et al.*, 2020). The chest CT scans improved for 11 out of 16 (69%) patients in the combination group, compared with 5 out of 17 (29%) patients in the monotherapy group, after 7 days. Based on these results, Deng et al. (2020) suggested that arbidol combined with lopinavir/ritonavir could delay the progression of lung lesions and lower the possibility of respiratory and gastrointestinal transmission by decreasing the COVID-19 viral load and the high faecal COVID-19 viral concentration.

In contrast, Cao et al. (2020b) recently reported the results of a clinical trial that included 199 patients with laboratory-confirmed SARS-CoV-2 infection (Cao *et al.*, 2020). They found that lopinavir/ritonavir treatment, compared to standard care, was not associated with a difference in the time to clinical improvement and mortality at 28 days, and viral the RNA percentage was similar in both the lopinavir/ritonavir treatment and standard care groups. However, in a modified intention-to-treat analysis, lopinavir/ritonavir treatment, compared to standard care, led to a median time to clinical improvement that was shorter by 1 day. Gastrointestinal adverse events were more common in the lopinavir/ritonavir treatment group, but serious adverse events were more common in the standard care group. Therefore, Cao et al. (2020b) concluded that no benefit beyond standard care was observed in patients on lopinavir/ritonavir treatment. As mentioned above, Dalerba et al. (2020) reported different experimental results of the antiviral effects of lopinavir/ritonavir treatment (Dalerba *et al.*, 2020). They re-

ported that after reviewing the findings of Cao et al. (2020b), many clinicians were abandoning the use of lopinavir/ritonavir for COVID-19 treatment. This action was considered premature (Dalerba, et al., 2020). According to Dalerba et al. (2020), it was crucial to realize that the trial was statistically underpowered to show a significantly better time to clinical improvement in lopinavir/ritonavir-treated severe COVID-19 patients, compared to patients administered standard care. Dalerba et al. (2020) also suggested that because the SARS-CoV-2 pandemic diffusion is causing a shortage in alternative drugs, lopinavir/ritonavir must be retained as a treatment option against COVID-19. We strongly agree with this suggestion by Dalerba et al. (2020). Even though several previous studies have shown that lopinavir/ritonavir does not show therapeutic effects against COVID-19, future studies on lopinavir/ritonavir must be continued. Further clinical trials for various patient groups (different gender, age, health status, race, or vaccination status) are required in the near future. It is also necessary to study the efficacy of lopinavir/ritonavir further through different combinations of various drugs, which could be used if another virus emerges in the future.

Favipiravir

Favipiravir is a pyrazine carboxamide derivative and a broad-spectrum antiviral drug approved in Japan for influenza treatment. Cai et al. (2020) examined the effects of favipiravir and lopinavir/ritonavir for COVID-19 treatment (Cai *et al.*, 2020). COVID-19 patients who received oral favipiravir plus IFN-α by aerosol inhalation were included in the favipiravir treatment group in this study, whereas patients who received lopinavir/ritonavir plus IFN-α by aerosol inhalation were included in the control group. The favipiravir treatment group, compared to the control group, showed significant im-

provement in chest images. Multivariable Cox regression showed that favipiravir was independently associated with faster viral clearance. Additionally, fewer adverse events were observed in the favipiravir-treated patients than in the controls. Therefore, Cai et al. (2020) suggested that favipiravir showed better therapeutic responses to COVID-19 in terms of disease progression and viral clearance.

Shinoda et al. (2020) reported that on days 3 and 4 after favipiravir administration, the polymerase chain reaction (PCR) results were negative, and the preliminary results of the clinical studies showed that favipiravir showed promising potency in treating Chinese SARS-CoV-2 patients. Subjects treated with favipiravir tested negative for the virus in the PCR analysis at the early stage; it showed potential in preventing acute respiratory distress syndrome. Based on these results, Shinoda et al. (2020) concluded that favipiravir administration in a patient with rapidly progressing hypoxemia caused the symptoms to be alleviated rapidly and PCR to yield negative results early (Shinoda *et al.*). Thus, favipiravir was effective for COVID-19 treatment, but it is necessary to conduct trials on more cases to ascertain its efficacy (Shinoda, et al.). Chen et al. (2020a) conducted clinical trials of favipiravir (116 patients) and umifenovir (120 patients) for COVID-19 treatment in Wuhan, China. They found that favipiravir (1600 mg twice on day 1 and then 600 mg twice daily for another 7-10 days) showed superior efficacy in terms of increased rate of clinical recovery by day 7 and reduced incidence of fever and cough. The clinical recovery rate at day 7 was 55.8% in the umifenovir group and 71.4% in the favipiravir group. Despite these findings, some media spokespersons and experts raised concerns about the government rushing to approve favipiravir and undermining strict medical procedures in place to authorize its use. Even though favipiravir was approved by the National Medical Products Administration of China as the

first anti-COVID-19 drug in China (Yanai, 2020) in March 2020, the Japanese government decided to postpone the approval of favipiravir (Avigan®) for COVID-19 treatment until at least June on the grounds of insufficient clinical tests and the presence of side effects (including birth defects). Based on this survey, we believe that since the side effects of favipiravir are being reported, it is still early to decide whether favipiravir can be used for COVID-19 treatment.

EIDD-2801/EIDD-1931

β-D-N^4-hydroxycytidine (NHC; EIDD-1931), an available oral prodrug, is a ribonucleoside analogue with broad-spectrum antiviral activity against multiple RNA viruses, including the current SARS-CoV-2, SARS-CoV-1, and MERS-CoV (Neerukonda and Katneni, 2020). Sheahan et al. (2020) reported that NHC showed a broad-spectrum antiviral activity against SARS-CoV-2, MERS-CoV, SARS-CoV, and a related zoonotic group 2b or 2c bat-coronavirus. In SARS-CoV- or MERS-CoV-infected mice, both prophylactic and therapeutic administration of EIDD-2801, a bioavailable oral NHC prodrug (β-D-N^4-hydroxycytidine-5′-isopropyl ester), improved pulmonary function and reduced viral titre and body weight loss (Sheahan et al., 2020). NHC/EIDD-2801 potency against multiple coronaviruses and oral bioavailability highlight its potential utility as an effective antiviral agent against SARS-CoV-2 and other future zoonotic coronaviruses (Sheahan et al., 2020). The FDA has approved an Investigational New Drug application for EIDD-2801, allowing human clinical testing to be initiated in the United States.

Convalescent plasma

Convalescent plasma has been used for the treatment of SARS, pandemic 2009 influenza A (H1N1), avian influenza A (H5N1), several haemorrhagic fevers such as Ebola fever, and other viral infections (Roback and Guarner, 2020). Deploying passive antibody therapies against the rapidly increasing number of COVID-19 cases provides an open window for the clinical testing of antiviral drugs (Roback and Guarner, 2020). Convalescent plasma or immunoglobulins (Igs) have been used as a last resort to improve the survival rate of SARS patients, whose condition continued to deteriorate despite treatment with pulsed methylprednisolone (Chen *et al.*, 2020). One possible explanation for the efficacy of convalescent plasma therapy is that the antibodies from convalescent plasma possibly suppress viraemia (Chen, et al., 2020). The administration of convalescent plasma is not a common treatment, but it is an important treatment in the absence of specific treatment agents for new infectious diseases (Ahn *et al.*, 2020). Ahn et al. (2020) reported that convalescent plasma was obtained from a male donor (in his 20s) who had recovered from COVID-19 for 18 days. In this study, two patients presented with severe pneumonia and acute respiratory distress syndrome and showed a favourable outcome after convalescent plasma and systemic corticosteroid administration.

In a study by Shen et al. (2020), patients received a transfusion of convalescent plasma with a SARS-CoV-2-specific antibody (IgG) that had been obtained from five patients that had recovered from COVID-19 (Sheahan *et al.*, 2020). Following plasma transfusion, the body temperature normalized within 3 days, the sequential organ failure assessment score decreased, and P_{AO_2}/F_{IO_2} ratio increased within 12 days in four out of five patients. Viral loads also decreased and became negative within 12 days after the transfusion. Based on these results, Shen et al. (2020) concluded that administration of

convalescent plasma that contained neutralizing antibodies was followed by an improvement in the patient clinical status. Ye et al. (2020a) reported positive findings of convalescent plasma test, with no adverse effects being observed during the treatment (Ye *et al.*, 2020). Convalescent plasma transfusion led to the resolution of the ground glass opacities and consolidations in the patient chest images. In two patients whose throat swabs tested positive for SARS-CoV-2, convalescent plasma therapy elicited virus elimination. Serologic analysis indicated an immediate increase in the anti-SARS-CoV-2 antibody titres in the two patients. Thus, based on these results, Ye et al. (2020a) suggested that convalescent plasma therapy was effective and specific for COVID-19.

Meanwhile, Zeng et al. (2020) performed a clinical test using convalescent plasma and reported that six patients with COVID-19 and respiratory failure received convalescent plasma 21.5 days (median) after viral shedding was first detected (Zeng *et al.*, 2020). All patients tested negative for SARS-CoV-2 RNA within 3 days of plasma infusion, and five patients eventually died. Thus, based on these results, Zeng et al. (2020) concluded that convalescent plasma treatment could eliminate SARS-CoV-2 shedding, but could not reduce the mortality rate of critically ill patients with end-stage COVID-19. Hence, treatment should be initiated at an earlier stage. According to our survey, there remains a lack of research on the treatment of COVID-19 using convalescent plasma to date. Clinical trials of convalescent plasma require convalescent plasma donation from a sufficient number of patients who have recovered from COVID-19. To date, more than 10,000 people in South Korea have recovered, and approximately 150 recovered patients have donated their convalescent plasma. Therefore, it appears that a global

collaboration is required to obtain convalescent plasma until the development of effective antiviral drugs.

Conclusion

In this overview, we surveyed the worldwide media reports and research papers on the development of vaccines and antiviral drugs published over the past few months. To our knowledge, vaccine development takes a considerable amount of time, but numerous institutions and companies around the world are now fully engaged in conducting clinical trials. However, clearer results on vaccine development are yet to be reported. To date, most clinical trials of vaccine development are in phase I. Furthermore, there are no studies on the discovery of certain antiviral drugs that can effectively treat COVID-19 yet, and clinical studies of potential drugs must still be reported. Fortunately, the possibility of treating COVID-19 using previously developed antiviral drugs or anthelmintics, instead of vaccine development, is being actively studied. According to our survey, the development of new vaccines and antiviral drugs will be achieved only by next year, and hence, previously approved drugs, such as remdesivir, which are currently under experimentation, must be used in the meantime. Indeed, numerous companies and institutes around the world have been studying or developing more than 100 COVID-19-related drugs; however, many of these studies have not reported specific clinical trial results yet. This survey showed that the number of participants in these clinical trials was often lesser than that in the previous clinical trials. Hence, drugs must be urgently developed to resolve the COVID-19 pandemic. This survey led to the conclusion that further research to develop antiviral drugs against COVID-19 must be continued, irrespective of a few negative findings.

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This paper is dedicated to all mankind fighting the novel coronavirus.

Author contributions

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Competing interest declaration

The authors declare no competing interests.

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689 **Table 1. The status of the development of COVID-19 vaccine candidates, focusing on the developer and human trials**

Type of COVID-19 vaccine candidates	Platform	Developer	Current stage of clinical evaluation/regulatory status coronavirus candidate	References
mRNA-1273	RNA	Moderna/NIAID	Phase II NCT04405076 Phase I NCT04283461	((WHO), 2020; Corey, et al., 2020; Le, et al., 2020;
Adenovirus Type 5 Vector (Ad5-nCoV)	Non-replicating viral vector	CanSino Biological Inc./Beijing Institute of Biotechnology	Phase II ChiCTR2000031781 Phase I ChiCTR2000030906	Lurie, et al., 2020)
INO-4800	DNA (DNA plasmid vaccine with electroporation)	INOVIO Pharmaceuticals	Phase I NCT04336410	
LV-SMENP-DC	Modified lentiviral vector	Shenzhen Geno-Immune Medical Institute	Phase I NCT04276896	
COVID-19/aAPC	Pathogen-specific aAPC (artificial antigen-presenting cell)	Shenzhen Geno-Immune Medical Institute	Phase I NCT04299724	

BNT162	RNA	BioNTech/Pfizer	Phase I/II
ChAdOx1	Non-replicating viral vector	University of Oxford/AstraZeneca SARS	Phase IIb/III 2020-001228-32 Phase I/II 2020-001072-15
MVA encoded VLP	Non-replicating viral vector (GV-MVA-VLP™)	GeoVax/BravoVax	Preclinical
COVID-19 vaccine	mRNA	CuraVac Inc.	Private-for-profit
AAVCOVID	Novel gene	Massachusetts Eye and Ear and Massachusetts General Hospital	Testing in humans
Oral Vaccine platform	Non-replicating viral vector	Vaxart Inc.	Preclinical

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691 **Table 2. The status of the development of the antiviral drugs for COVID-19, focusing on the main mechanisms of action and an-**
692 **tiviral effects of the drugs**

Antiviral drugs (Representative name)	Range of use	Main mechanisms of action	Antiviral effects	References
Remdesivir (GS-5734)	Ebola virus SARS infection MERS infection	RNA-dependent RNA polymerase (RdRp) inhibitor, can provide a scheme for blocking RNA replication	· Two compounds (remdesivir and chloroquine): inhibition of virus infection · Inhibition of SARS-CoV-2 replication in Vero E6 cells at a half-maximal effective concentration (EC_{50}) of 23.15 μM · Reduction of pulmonary infiltrates on radiographs	(Cao, et al., 2020; Choy, et al., 2020; Scavone, et al., 2020; Wang, et al., 2020; Williamson, et al., 2020)
Chloroquine/ hydroxychloroquine	Malaria	Chloroquine can inhibit a pre-entry step in the viral cycle by interfering with the binding of the viral particles to their cellular surface receptors	· Reduction in fever · Improvement of lung computed tomography images · Inhibition of activation of cells by MAP kinase and post-translational modification of M proteins · Blockage of COVID-19 infection at an EC_{50} of 1.13 μM · Inhibition of SARS-CoV replication in Vero E6 cells · Reduction in body temperature and cough remission times · Improvement of pneumonia symptoms	(Chen, et al., 2020; Cortegiani, et al., 2020; Devaux, et al., 2020; Gao, et al., 2020; Kumar, et al., 2020; Million, et al., 2020; Wang, et al., 2020; Wang, et al., 2020; White, 1996)

Niclosamide	SARS-CoV Tapeworm infection MERS-CoV Anthelminthic drug	Uncoupling of oxidative phosphorylation or stimulation of ATPase activity	· Suppression of cytopathic effects of SARS-CoV at a concentration of 1 μM · Inhibition of SARS-CoV replication in Vero E6 cells at an EC_{50} of 0.1 μM · Inhibition of viral antigen synthesis at concentration of 1.5 μM · Inhibition of MERS-CoV replication in Vero B4 cells at concentration of 10 μM · Antiviral effect towards SARS-CoV-2 at half-maximal inhibitory concentration (IC_{50}) of 0.28 μM	(Andrews *et al.*, 1982; Gassen, et al., 2019; Jeon, et al., 2020; Wen *et al.*, 2007; Wu, et al., 2004)
Ivermectin	SARS-CoV-2 Anti-parasitic drug COVID-19 candidate	Inhibition of nuclear transport mediated by the importin α/β1 heterodimer (IMPα/β-1), responsible for the translocation of various viral proteins	· Reduction in the SARS-CoV-2 viral RNA at a concentration of 5 μM · Inhibition of IMPα/β1-mediated nuclear import of viral proteins · Promotion of structural changes in proteins by inducing unfolding/folding	(Caly, et al., 2020; Paz, et al., 2020; Wagstaff *et al.*, 2012)

Lopinavir/ritonavir (Kaleta®)	2019-nCoV pneumonia COVID-19 candidate	Inhibition of the protease activity of the coronavirus	· Inhibition of SARS-CoV-2 replication at an EC_{50} of 26.63 μM · Lopinavir 400 mg/ritonavir 100 mg: Improvement of dyspnoea and oxygen requirement and reduction in lung lesions on chest radiographs · Lopinavir 200 mg/ritonavir 50 mg: Reduction in β-coronavirus load, coronavirus titres · Compounds (lopinavir/ , arbidol and Shufeng Jiedu Capsule): Improvement of pneumonia symptoms · Compounds (lopinavir 80 mg/ritonavir 20 mg, interferon [IFN] aerosol 5 million units [MU], arbidol 200 mg): Restoration of body temperature and physiological mechanisms, no evident toxic effects, reduction in the abnormal proportion of white blood cells, lymphocytes, and C-reactive protein · Compounds (lopinavir 200 mg/ritonavir 50 mg, IFN 5 MU, arbidol 200 mg): Antiviral therapy · Compounds (lopinavir 400 mg/ritonavir 100 mg, arbidol 200 mg): Alleviation of lung lesions and decrease in the COVID-19 viral load	(Cao, et al., 2020; Choy, et al., 2020; Deng, et al., 2020; Kim, et al., 2020; Lim, et al., 2020; Yu, et al., 2020)

Favipiravir (T-705, Avigan®)	COVID-19 candidate	RdRp inhibitor, has been shown to be effective for influenza and Ebola virus infection treatment	· Favipiravir (Day 1: 1600 mg twice, Days 2–14: 600 mg twice daily); plus IFN-α by aerosol inhalation (5 MU twice daily): Improvement in chest images · Favipiravir (1,800 mg orally in the morning and evening, 800 mg twice daily from the evening): Alleviation of fever and acute respiratory distress syndrome · Favipiravir (1600 mg twice on day 1 and then 600 mg twice daily for another 7-10 days): Reduction in fever and cough and efficacy in the clinical recovery rate	(Cai, et al., 2020; Chen *et al.*, 2020; Shinoda, et al.)
EIDD-2801/EIDD-1931 (β-D-N4-hydroxycytidine [NHC])	SARS-CoV-2 SARS-CoV-1 MERS COVID-19 candidate	Targets viral RdRp (vRdRp) to induce error catastrophes beyond the error threshold allowed to sustain RNA virus quasi species	· Inhibition of SARS-CoV-2 at an EC_{50} of 0.08–0.3 μM, MERS at an EC_{50} of 0.15 μM, SARS-CoV-1 at an EC_{50} of 0.14 μM in Calu-3 cell lines and primary human airway epithelial cells · Reduction in lung viral load and improvement of pulmonary function in SARS- and MERS-CoV mouse models · Reduction in body weight loss and lung haemorrhage · Non-synonymous substitutions through increased nucleotide transitions · Antiviral activity against related zoonotic group 2b or 2c bat-coronavirus	(Sheahan, et al., 2020)

Convalescent plasma	COVID-19 candidate	The donor anti-SARS-CoV-19 immunoglobulins (IgG and IgM) neutralizes the virus	· Improvement in body temperature, Sequential Organ Failure Assessment scores, and P_{AO2}/F_{IO2} ratio · Increase in neutralizing antibody titres and negative testing for SARS-CoV-2 ·The convalescent plasma obtained from a male donor: Improvement of severe pneumonia and acute respiratory distress syndrome ·The convalescent plasma obtained from recovered COVID-19 donor: Improvement of symptoms, increased resolution of consolidation, and discontinuation of SARS-CoV-2 shedding and respiratory failure	(Ahn, et al., 2020; Chen, et al., 2020; Roback and Guarner, 2020; Ye, et al., 2020; Zeng, et al., 2020)

693