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# Potential antiviral therapies for coronavirus disease 2019 (COVID-19)

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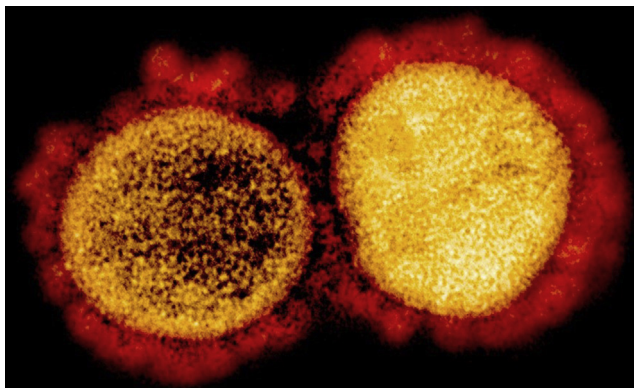
## 1. Introduction

Viral diseases tend to evolve rapidly and pose a significant threat to public health globally. The current coronavirus disease 2019 (COVID-19) pandemic has affected more than 3 million people worldwide, resulting in over 208,112 reported deaths. COVID-19 shares many similarities in terms of its transmission and pathogenicity with severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). Therefore for understanding the nature of infection or pathogenicity of this novel coronavirus, it becomes important to evaluate the chronologic background of these outbreaks. In the past 20 years, three major viral epidemics have occurred and caused widespread infection and mortality worldwide, viz., severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002–03, H1N1 influenza in 2009, and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012–14. Out of these epidemics, two belonged to betacoronaviruses, i.e., SARS-CoV and MERS-CoV, and triggered widespread infections with more than 10,000 confirmed cumulative cases and with high death rates of 10% and 37% for SARS-CoV and for MERS-CoV, respectively. The mortality data is available as per the WHO reports [1,2].

The first epidemic of SARS-CoV originated in the Guangdong region of South China in 2002 and spread quickly across 30 countries in South-East Asia, including Singapore, Hong Kong, and Taiwan, and Canada, resulting in 800 deaths, out of approximately 8000 reported cases and ended in July 2003 [3,4]. Although the mortality rate for SARS-CoV outbreak was 9.6%, in patients over 65 years, it was alarmingly high (up to 50%) [5]. SARS-CoV incubation time was 2–7 days, with viral pneumonia symptoms including high fever accompanied by dry cough and shortness of breath. At that time, no medications were approved, and the outbreak was regulated by robust public health interventions that included patient isolation [6].

The second coronavirus outbreak was reported in September 2012 as MERS-CoV outbreak [7]. The MERS-CoV outbreak has spread to countries primarily in the Middle East (Saudi Arabia, Jordan, Qatar, Oman, Kuwait, and the United Arab Emirates), several European countries (Great Britain, France, Italy, Germany, and Greece), North Africa (Tunisia and Egypt), Asia (Malaysia), and the United States of America; 614 cases and 181 deaths were confirmed by the WHO by May 2014 [8,9].

In December 2019, a third outbreak of coronavirus, which was associated with pneumonia, was reported in Wuhan, Hubei province, that originated in a wet “seafood market” in China. Previously named as the coronavirus disease (COVID-19), it was identified as an infectious zoonotic disease triggered by a newly discovered SARS-CoV-2 (Fig. 37.1). The virus propagates quickly by transmission from human to human. Although SARS-CoV-2 is less pathogenic than SARS-CoV and MERS-CoV, its high virus spread and mortality has become a big concern. The COVID-19 outbreak was proclaimed a public health emergency of international importance on January 30, 2020, and subsequently, on February 28, 2020, the WHO increased the disease danger to an “extremely high” level as COVID-19 crossed global boundaries. On March 11, the WHO confirmed COVID-19 as a pandemic, and as on March 30, 2020, 203 countries worldwide have been affected with an alarming high 638,146 confirmed cases besides 30,105 deaths [10]. At present, by April end, there have been 3,024,059 confirmed cases of COVID-19, including 208,112 deaths, as per the WHO report, and the United States is the worst hit with 983,457 confirmed cases and 50,492 deaths. The governments and organizations across the world are coordinating to implement strong countermeasures, including strict social distancing and lockdown, to control the possible devastating effects of this pandemic situation. Although SARS-CoV-2/COVID-19 virus has been successfully isolated and sequenced, there is still scope for the understanding of the viral antigenic structure, mode of action, and pathogenicity, as the lack of selective COVID-19 treatment remains an issue of concern.



**FIGURE 37.1** Transmission electron micrograph of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).  
*Image Source: NIAID, [New Images of Novel Coronavirus SARS-CoV-2 Now Available](#) | NIH: National Institute of Allergy and Infectious Diseases.*

Considering the fact that the development of new, efficient, and targeted antiviral drugs is a very complex process, the knowledge of biological characteristics of this virus should be updated in time. Most antiviral drugs target specific viruses, while some are broad-spectrum and are effective against a wide range of viruses. Furthermore, antiviral drugs do not directly destroy their target virus but instead they inhibit their development, for example, inhibit viral entry, viral replication, viral proteases, etc. Therefore clinical studies reporting antiviral therapies to manage COVID-19 need to be summarized to help optimize control measures and make therapeutic decisions.

Our main aim is to present up-to-date knowledge of the current antiviral therapies and ongoing clinical trials in the treatment of COVID-19. We have also reviewed studies evaluating the efficacy of existing antiviral drugs in the management of SARS-CoV and MERS-CoV. We believe that such repurposed antiviral therapies are easily available, with safety parameters known, and thus can be highly effective against this novel virus of COVID-19, until the development of vaccines or specific therapeutics are found.

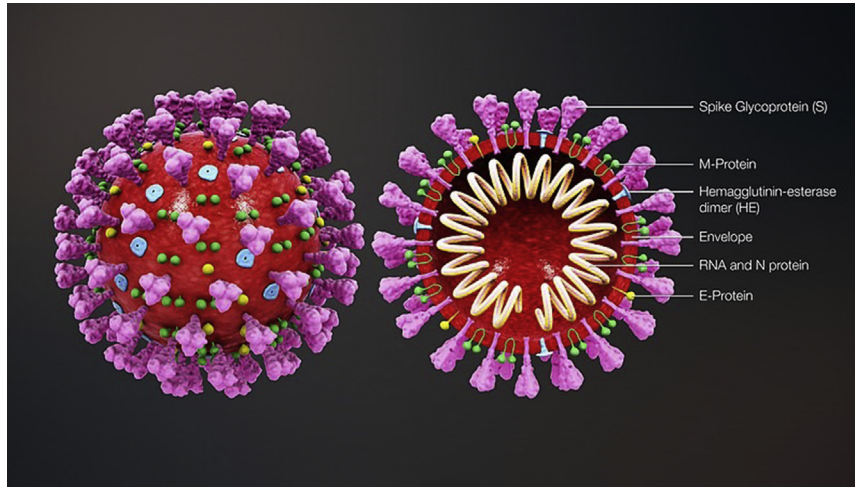
In this chapter, we summarize the genomic and biological features of the novel coronavirus, including its origin, epidemiology, clinical, and pathologic features. Lastly we provide a comprehensive description of potential antiviral therapies, along with their modes of actions, which are at present under consideration for treatment of COVID-19.

## 2. Genome organization

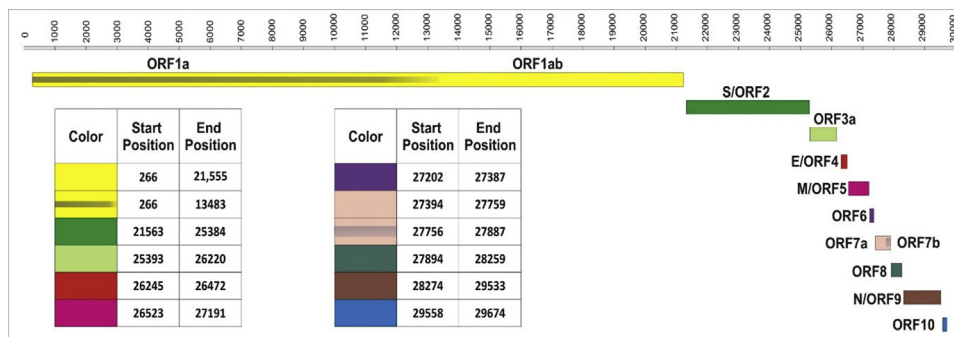
The genetic sequence and phylogenetic study showed that SARS-CoV-2 or COVID-19 virus matched 96% to a bat coronavirus (BatCoV RaTG13, China) and is associated to SARS-CoV and MERS-CoV with 79% and 51.8%, respectively, nucleotide similarity [11]. SARS-CoV, MERS-CoV, and SARS-CoV-2/COVID-19 virus all belong to the Coronaviridae family. The virus family is named as “corona,” which is the Latin word for “crown,” because of the spike structures present on the surface of coronaviruses (Fig. 37.2).

All these are positive-stranded enveloped RNA viruses and represent the biggest RNA viruses with an approximate length of 30,000 nucleotide base pairs that can be isolated in different animal species. The coronavirus genome consists of three regions: the first two regions code for 16 nonstructural proteins (nsps) from open reading frames (ORFs), i.e., 1ab, whereas the third region consists of nine ORFs and codes for structural proteins named spike or surface globular (S), envelope (E), membrane (M), and nucleocapsid (N). Along with these 10 ORFs, the COVID-19 virus has terminal sequences of 265 and 229 bp at both 5' and 3' ends, respectively, which make up its genome size of 21,903 bp (Fig. 37.3). The 5' terminal sequence is followed by 10 genes in sequential manner as follows:

1. Gene ORF1ab is 21,290 bp long and starts from 266 to 21,555 bp and codes for two polyproteins ORF1a/pp1a (266–13,483 bp) and ORF 1ab/PP1ab (266–21,555 bp). ORF1a is 13,218 bp in length and codes for 4405 amino acids (aa) polyprotein, whereas ORF1ab is 21,290 bp long and codes for 7096 aa polyprotein.



**FIGURE 37.2** Structure of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Image Source: Wikimedia user ScientificAnimations.*



**FIGURE 37.3** Genomic organization of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *ORF*, open reading frame.

- Gene S location is 21,563–25,384, and it is 3822 bp long. It codes for the surface glycoprotein/spike structural protein, which is 1273 aa in length and is highly N-glycosylated. The S protein in its trimeric form facilitates virus attachment to the host cell surface via its receptor. Host furinlike protease cleaves the S protein into two functional domains, S1 (binds to receptor) and S2 (provides structural support in the form of the stalk) [12].
- Gene ORF3a lies from 25,393 to 26,220, and it is 828 bp long. It codes for ORF3a protein of 275 aa length.
- Gene E lies from 26,245 to 26,472 bp, and its length is 228 bp. It codes for ORF4/envelope structural protein/E protein, which is 75 aa long. It is a transmembrane protein and has an ion channel activity that is crucial for the pathogenesis of SARS-CoV and probably SARS-CoV-2. The E protein is mainly involved in the process of virus assembly and release [13].

5. Gene M lies from 26,523 to 27,191 bp, and it is 669 bp in length and codes for the membrane glycoprotein/ORF5, which is 222 aa in length. It is quite abundant, is found as a dimer in the virion, and has three transmembrane domains including N-terminal and C-terminal domains. Its main role is to maintain the virion shape [14].
6. Gene ORF6 lies from 27,202 to 27,387, and it is 186 bp long and codes for ORF6 protein, which is 61 aa in length.
7. Gene 7 consists of two genes 7a and 7b that lie from 27,394 to 27,759 bp and 366 bp in length and from 27,756 to 27,887 bp and 132 nucleotides in length, respectively. Both these ORFs code for 121- and 43-aa-long polyproteins, respectively.
8. Gene 8/ORF8 lies from 27,894 to 28,259 bp, and it is made of 366 bp and codes for the 121-aa-long ORF8 polyprotein.
9. Gene N starts from 28,724 to 29,533 bp, and it is 1260 nucleotide long and codes for nucleocapsid phosphoproteins/ORF9 that is 419 aa in length. It is highly phosphorylated and has N-terminal and C-terminal domains, which can bind to RNA. Thus N protein performs a significant role in the packaging of viral genome into the viral particles by interacting with the M protein and nsp3, which is a component of the replicase complex facilitating binding to the replicase-transcriptase complex [15,16].
10. The last gene that follows gene N is ORF10 from 29,558 to 29,674 bp, and it is made up of 117 nucleotides and codes for 38-aa-long polyproteins. ORF10 is further terminated by 3' untranslated regions of 229 bp sequence (NCBI reference sequence: NC\_045512.2).

### 3. Epidemiology and clinical features

Available evidence, along with WHO reports, directs that the COVID-19 virus is extremely contagious and is transmitted mainly through close contact (within 1 m), through respiratory droplets (for example, sneezing, coughing) and by fumes [17]. It can live in the air for 2 h and, moreover, asymptomatic transmission has been documented, which allows the disease to spread globally via carriers [18]. The estimated incubation time is 14 days (average, 5.2 days). Transmission through fecal-oral route may also be possible [19]. Yet another likely way is vertical transmission of virus from infected mothers to the newborns. However, Chen et al. [20] reported that newborns of nine infected mothers did not have SARS-CoV-2 infection, thus ruling out this possibility.

Clinical symptoms of COVID-19-related pneumonia include high fever, tiredness, dry cough, and dyspnea; the less severe symptoms include sore throat and diarrhea [21]. The Centers for Disease Control and Prevention revised its list of symptoms for coronavirus infection to include headache and muscle pain, repeated shivering, new loss of taste or smell, new confusional arousal, and bluish lips/ears/face. The COVID-19-related

respiratory indications vary from minor symptoms to severe hypoxia of acute respiratory distress syndrome (ARDS), which can also be fatal. Mortality occurs in approximately 2.5% of diseased individuals [22]. High C-reactive protein levels are observed in blood profiles, and lymphopenia (82.1%), thrombocytopenia (36.2%), and leukopenia (33.7%), confirmed at early stages. In addition, severely infected patients also exhibited elevated levels of alanine aminotransferase, aspartate aminotransferase, creatine, and creatine kinase. In confirmed COVID-19 patients, the pneumonia was distinguished by ground-glass opacity (50%) and bilateral patchy shadowing (46%) in the chest computed tomography and even subsegmental consolidation in serious patients [23]. The majority of COVID-19 patients who were admitted to the intensive-care unit were elderly adults and with other comorbid disorders including asthma, coronary disease, and lung disease, thus correlated with higher mortality rates. Furthermore, these disorders are observed to be more common in men and often linked to smoking and alcohol intake.

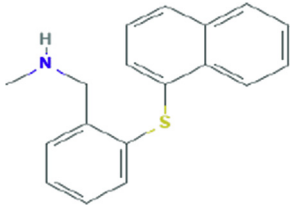
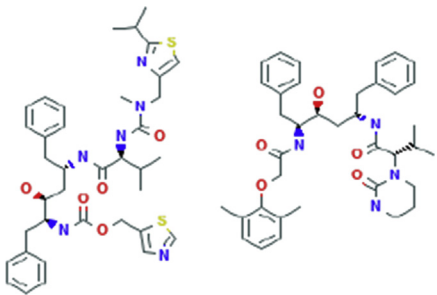

Currently no targeted therapy against COVID-19 is available and medical management is largely supportive. Countries around the world have suggested stringent social isolation and lockdown to reduce the transmission of the virus further. Several drugs and antiviral treatments are being studied in clinical trials, including lopinavir-ritonavir, remdesivir, hydroxychloroquine, and azithromycin, and convalescent plasma therapy; however, none of these have yet proved to be a successful treatment.

#### 4. Potential antiviral therapies under consideration

At present no specific vaccine or drug is available that can target COVID-19, but many clinical studies are being conducted. In attempts to find drugs for the treatment of this disease, scientists are exploring various existing antiviral therapies with proven efficacy against SARS, MERS, or influenza. These strategies, elaborated in [Table 37.1](#), include the use of anti-inflammatory drugs (interferon [IFN]- $\alpha$ , corticosteroids, ribavirin), virus-binding molecules such as peptides targeting spike protein and inhibitors of host cell endocytosis, inhibitors of viral RNA polymerase and nucleoside analogues (favipiravir, remdesivir, galidesivir), inhibitors of helicase (bananins, RNA aptamers), inhibitors of proteases (lopinavir-ritonavir, serine protease inhibitor), and chloroquine phosphate. Other possible treatment options include the use of small interfering RNAs targeting viral structural proteins and the use of Chinese traditional medicine (Shufeng Jiedu capsule).

In the category of molecules that bind viruses as the therapy of COVID-19 pneumonia, one of the options is to find inhibitors of renin-angiotensin system (RAS) as the SARS-CoV spike (S) proteins bind to the angiotensin-converting enzyme 2 (ACE2) receptor for entry into the host [24]. Therefore activation of the ACE2/Ang (1–7)/Mas signaling pathway or inhibition of the ACE/Ang II/AT1R pathway can reduce the pulmonary inflammatory response and may be an important treatment for pneumonia and preventing mortality [25].

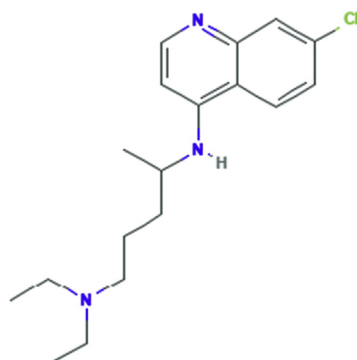
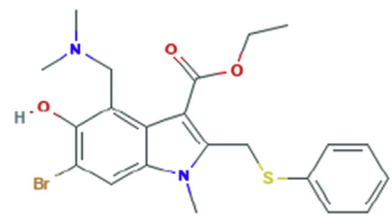
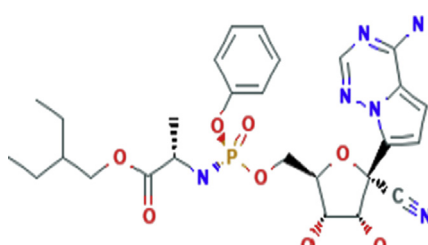
**Table 37.1** Antiviral drugs options for the treatment of COVID-19.

Drug	Originally approved for treating disease	Mode of action	Method of administration; dosage	2D structure
IFN- $\alpha$	Hepatitis B virus	Anti-inflammatory	Vapor inhalation; 5 million U or equivalent dose each time, 2 times/day continued for 10 days	
Lopinavir/ ritonavir	HIV/AIDS	Protease inhibitors	Oral; 200 mg/50 mg/capsule, two capsules each time, 2 times/day continued for 10 days	
Ribavirin	Hepatitis C virus	Guanosine nucleoside, interferes with the viral messenger RNA synthesis	Intravenous infusion; 500 mg each time, 2–3 times/day in combination with IFN- $\alpha$ or lopinavir/ritonavir continued for 10 days	

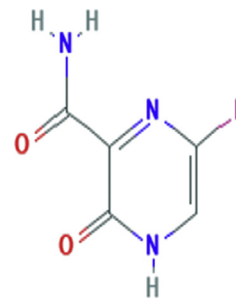
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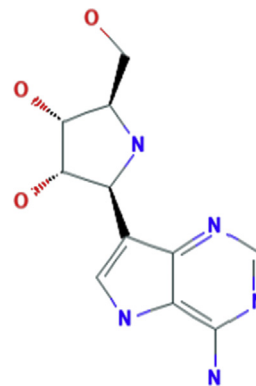
**Table 37.1** Antiviral drugs options for the treatment of COVID-19.—cont'd

Drug	Originally approved for treating disease	Mode of action	Method of administration; dosage	2D structure
Chloroquine phosphate	Malaria, autoimmune disease	pH dependent, host immune modulation, inhibitor of endocytosis	Oral; 500 mg (300 mg for chloroquine) each time, 2 times/day and continued for 10 days (approved for emergency use)	
Arbidol	Influenza	Blocks viral fusion	Oral; 200 mg each time, 3 times/day continued for 10 days	
Remdesivir (GS-5734)	Ebola virus disease	Nucleotide analogue prodrug, inhibitor of RdRp and viral replication	Oral, 200 mg on first day and 100 mg daily continued till 10th day (entered phase 3 clinical trial against SARS-CoV-2)	

Favipiravir (T-705) or Avigan	Influenza, Ebola	Guanine analogue prodrug, RdRp inhibitor	Oral, two doses of 1600 mg on first day followed by two doses of 600 mg per day and continued for 10 days (complemented with IFN- $\alpha$ treatment as mentioned earlier)
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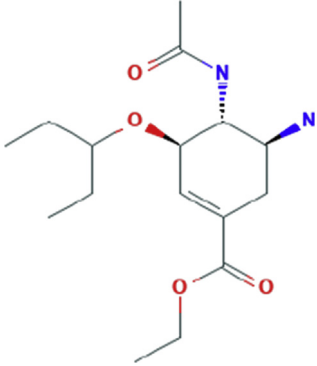
Galidesivir	Hepatitis C virus	Adenosine analogue and inhibitor of RdRp	—
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**Table 37.1** Antiviral drugs options for the treatment of COVID-19.—cont'd

Drug	Originally approved for treating disease	Mode of action	Method of administration; dosage	2D structure
Oseltamivir	Influenza virus A	Neuraminidase inhibitor, prevents budding from the host cell, viral replication	—	

*IFN- $\alpha$* , interferon alfa; *RdRp*, RNA-dependent RNA polymerase; *SARS-CoV-2*, severe acute respiratory syndrome coronavirus 2.

## 4.1 Interferon $\alpha$ and interferon beta

IFN- $\alpha$  is an antiviral drug of wide scope that can be used to treat hepatitis B virus. Coronaviruses including SARS-CoV-2 and MERS-CoV have acquired mechanisms that inhibit endogenous IFN- $\beta$  development, thus allowing the virus to circumvent the inborn immune system and improve respiratory susceptibility. Therefore exogenous addition of IFN- $\beta$  to the lung cells may prevent or reduce cell damage and control viral infection. Gao et al. [26] have provided evidence of viral clearance in lungs by IFN- $\alpha$  treatment of SARS-CoV-infected mice and cynomolgus macaques. However, other studies have reported recombinant IFN- $\beta$  as more potentially antiviral than IFN- $\alpha$  against both SARS-CoV and MERS-CoV in in vitro and in vivo studies in mice [27,28]. Also subcutaneous injections of IFN- $\beta$ -1b have also shown improvement in common marmosets infected with MERS-CoV [26]. IFN- $\beta$ -1b mediates therapeutic effects partly by modulating functions of the B cells.

IFN- $\beta$  basically acts as an immunostimulant by binding to type I interferon receptors, i.e., IFNAR1 and IFNAR2c, in a more stable manner than IFN- $\alpha$  to activate Jak1 and Tyk2 tyrosine kinases, which phosphorylate the receptors leading to the activation of more than 100 immunomodulatory and antiviral proteins via binding to signal transducers and transcription activators, for example, Stat1 and Stat2.

Benefits of using recombinant interferons for 2019-nCoV patients are uncertain, but many clinical trials are utilizing IFN- $\alpha$  and IFN- $\beta$  alone (given by nebulization, 6 million IU) or in combination with other antiviral drugs such as lopinavir/ritonavir, ribavirin (with 0.25 mg IFN- $\beta$ -1b administered subcutaneously on alternate days for 3 days), or lopinavir/ritonavir plus IFN- $\beta$ -1a as 44  $\mu$ g in three doses over a period of 6 days (day 1, day 3, and day 6).

## 4.2 Corticosteroids

Corticosteroids are anti-inflammatory drugs that may be helpful in controlling immune response at the lung level because SARS-CoV, MERS-CoV, and COVID-19 infections are associated with cytokine induction. But at the same time, overall immune depression state may result in lung superinfections. Furthermore, some studies evaluating treatment effects against SARS and MERS have suggested that patients receiving methylprednisolone as treatment rather showed delayed viral clearance instead of recovery [29,30]. Hence the WHO has advised against the regular use of corticosteroids either alone or in combination with interferons for COVID-19 therapy.

## 4.3 Chloroquine (9-aminoquinoline) and its analogue hydroxychloroquine

Chloroquine and its analogue hydroxychloroquine are approved drugs for treating autoimmune disorders and malaria and have been used since 1934 with proven prophylactic efficacy and safety with known side effects [31]. Chloroquine can induce

antiviral effects by inhibiting viral fusion/replication in a pH-dependent manner and by preventing glycosylation of proteins present on either the virus envelope or the host receptor [32]. It can also attenuate the expression of proinflammatory factors and host cell receptors, without any intervention for the virus, thus relieving the ARDS, which is the chief cause for coronavirus-related deaths [22]. Previous *in vitro* studies have demonstrated potential antiviral activities of chloroquine for human coronavirus (HCoV-OC43) *in vivo* [33] as well as for SARS-CoV in cell culture of Vero E6 cells [31]. Moreover, as per the clinical trials conducted in China, chloroquine phosphate treatment has shown to be effective in treating pneumonia caused by COVID-19 [34]. One purported mechanism of chloroquine against SARS-CoV-2 is to inhibit the Phosphatidylinositol Binding Clathrin Assembly Protein (PICALM) that is required for the proper assembly of clathrins, thus inhibiting the cell's ability to perform endocytosis [35,36]. Moreover, following the announcement of the US president and the subsequent emergency use authorization by the FDA, this drug is being widely used for the treatment of COVID-19. The Indian Council of Medical Research (ICMR) has also suggested the use of hydroxychloroquine for health staff and the asymptomatic contacts of reported cases to shield them from COVID-19. Although immunomodulatory roles of both these drugs have shown positive outcomes, some negative results have also been reported indicating the need for further evaluation of their efficacy to treat COVID-19.

#### 4.4 Ribavirin

Ribavirin is a guanine analogue that can interfere with the replication of both RNA and DNA of viruses. Its antiviral effects, however, are not limited to polymerase, as ribavirin often interferes with RNA capping, which is essential to preserve the integrity of RNA. In addition, ribavirin inhibits normal guanosine biosynthesis by direct inhibition of inosine monophosphate dehydrogenase, which is essential to generate the guanine precursor, thus facilitating the destabilization of viral RNA. Ribavirin is approved for treatment of hepatitis C virus and respiratory syncytial virus infections. It has also been assessed for the treatment of SARS and MERS but has shown anemia as the side effect at high doses [37]. Previous clinical studies using ribavirin treatment, alone or in combination with IFN- $\alpha$ 2a/IFN- $\alpha$ -2b/IFN- $\beta$ -1a, for MERS and SARS patients had shown no significant improvement [38–40]. Subsequent *in vitro* and *in vivo* analyses in Hong Kong, China, however, found that patients receiving a combination treatment of lopinavir/ritonavir and ribavirin had a lower incidence of ARDS and mortality and recovered faster than those undergoing treatment with ribavirin and corticosteroid alone [41,42]. Whether ribavirin has the potential to treat 2019-nCoV is still uncertain, but three studies based on molecular docking have revealed efficient binding of ribavirin to SARS-CoV-2 RNA-dependent RNA polymerases (RdRps) (binding energy from  $-6.5$  to  $-9.0$  kcal/mol). Moreover, a few clinical studies are underway, involving ribavirin in combination with other antiviral drugs against SARS-CoV-2 infection.

## 4.5 Lopinavir and ritonavir

Lopinavir is an approved human immunodeficiency virus protease inhibitor, which is commonly used with ritonavir for inhibiting enzymes responsible for lopinavir biotransformation and also acts as a booster for antiviral treatment. The rationale of using lopinavir as a repurposed drug for COVID-19 relies on the evidence of improved results in patients diagnosed with SARS-CoV and MERS-CoV. The first recursive, sequential, and double-blind randomized clinical trial (NCT02845843) for MERS, using lopinavir/ritonavir in combination with IFN- $\beta$ -1b, started in November 2016, known as the MIRACLE trial. The MIRACLE trials are currently in progress and the authors have recently identified the statistical analysis strategy for the MERS treatment trial [43]. Dayer et al. [44], based on molecular docking experiments, showed lopinavir as the most effective inhibitor of coronavirus proteinase in aqueous solution under physiologic conditions of specific pH, temperature, and pressure. Currently as many as 12 COVID-19 trials are ongoing across China, the United States, and Korea where lopinavir/ritonavir is being administered along with various other antiviral drugs such as hydroxychloroquine, oseltamivir, favipiravir, arbidol, IFN- $\beta$ , and other protease inhibitors.

A retrospective cohort study in Zhejiang, China, spanning 7 weeks, i.e., from January 17, 2020, to 1 March 1, 2020, recorded 661 cases of COVID-19, 36 of which were children. All the children were treated and recovered from COVID-19 within 14 ( $\pm$ 3) days using antiviral drug combinations, i.e., IFN- $\alpha$  and lopinavir/ritonavir (twice a day), and some children required inhalation of oxygen [45]. Two other clinical studies in China demonstrated the positive clinical efficacy of lopinavir/ritonavir therapy against SARS-CoV-2 [46,47]. However, a retrospective study in 134 COVID-19 patients [48] and randomized, controlled, open-label trial with 199 COVID-19 patients [49] revealed no significant outcomes for lopinavir/ritonavir treatment, indicating the need for further verification efficacy of lopinavir/ritonavir in treatment of SARS-CoV-2 infection.

## 4.6 Favipiravir (T-705) or Avigan

Favipiravir is a prodrug guanine analogue with inhibitory action against RdRp and previously approved for the treatment of influenza pandemic in Japan in 2014. Favipiravir has proven effective against various strains of influenza virus, including the ones that are drug-resistant. This prodrug following phosphoribosylation inside the cell is converted into an active drug that acts as a substrate of RNA polymerase and is thus capable of inhibiting viral replication of many RNA viruses, such as influenza virus, Ebola virus, chikungunya virus, yellow fever virus, norovirus, arenavirus, and enterovirus [50]. These unique antiviral broad-range profiles make favipiravir a highly promising drug for COVID-19, and it is currently being studied in 18 clinical trials. A study reported effective antiviral activity of favipiravir, along with other drugs, in the SARS-CoV-2 viral culture of African green monkey kidney epithelial cells (Vero E6 cells).

Also in China, two clinical trials were approved to evaluate the efficacy of favipiravir therapy for 2019-nCoV-infected patients with (1) favipiravir plus IFN- $\alpha$  (ChiCTR2000029600) and (2) favipiravir plus baloxavir marboxil (ChiCTR2000029544). In an open-label nonrandomized control study conducted at Shenzhen, China, Cai et al. clinically examined and compared the effect of favipiravir treatment (i.e., 1600 mg twice on day 1, followed by 600 mg twice daily for 14 days in 35 patients) with lopinavir and ritonavir treatment (i.e., 400 mg lopinavir + 100 mg ritonavir twice daily for 14 days in 45 patients) on COVID-19 patients. Both the treatment types were complemented with IFN- $\alpha$  given by aerosol inhalation (5 million U twice daily). The findings showed that treatment with favipiravir was more effective in treating infection with SARS-CoV-2 in terms of viral clearance and quicker recovery compared to treatment with lopinavir/ritonavir [47].

## 4.7 Remdesivir

Remdesivir (nucleotide prodrug) is a broad-spectrum RNA polymerase inhibitor originally licensed to treat Ebola virus disease. Prior studies on *in vitro* and animal models had demonstrated inhibitory actions against other RNA viruses, such as MERS and SARS. Therefore with safety data available, this therapeutic drug is currently being clinically tested against SARS-CoV-2. Two clinical trials (NCT04252664 and NCT04257656) that were started in February have entered phase 3 to evaluate intravenous administration of remdesivir, with a dosage of 200 mg on day 1 followed by 100 mg twice for 9 days, in patients with 2019-nCoV, and are estimated to be completed by April 2020. A study that assessed five FDA-approved drugs against COVID-19 *in vitro* in culture of Vero E6 cells reported that remdesivir effectively inhibited the virus with  $EC_{50} = 0.77 \mu\text{M}$  and  $EC_{90} = 1.76 \mu\text{M}$  [46]. The researchers further demonstrated the antiviral activity of remdesivir in Huh-7 cells, which is a human liver cancer cell line sensitive to 2019-nCoV infection. The first recorded case of the novel coronavirus in the United States in January 2020 has completely recovered after intravenous remdesivir treatment [51]. Remdesivir therapy, begun early during infection, has demonstrated clinical benefit in SARS-CoV-2-infected rhesus macaques, indicated by a substantial reduction in virus titers in bronchoalveolar lavage and significantly reduced lung viral loads indicated by decreased pulmonary accumulation on radiographs.

## 4.8 Galidesivir

Galidesivir (also known as BCX4430 or immucillin-A) is another broad-spectrum synthetic adenosine analogue and therefore is an inhibitor of RdRp that was originally developed for hepatitis C virus and provided protection from many filovirus diseases such as Ebola virus disease and Marburg virus disease. As of now, only phase 1 clinical and safety trials have been conducted and the results are yet to be published. But a few preclinical studies have shown that it can be possibly used against many other viruses including SARS-CoV and MERS-CoV [52]. Galidesivir therefore is one of the many

candidate antiviral drugs being tested for COVID-19, and clinical trials (NCT03891420) have been started by BioCryst, funded by the National Institute of Allergy and Infectious Diseases (NIAID), in April 2020. This trial is presently in the recruitment stage and is engaged in enrolling COVID-19 patients to assess the antiviral effects of galidesivir. Moreover, acyclic fleximer nucleoside analogues, designed by incorporating fleximers into known nucleoside analogues, such as acyclovir to increase binding affinity, have been used to inhibit replication of MERS-CoV and HCoV-NL63 in different (Huh7, Vero cells, and Vero-118 cells) cell culture models [53].

#### 4.9 Convalescent plasma therapy

With the recent US FDA approval, several countries around the world have initiated clinical trials of plasma therapy to treat COVID-19, in which plasma derived from the blood of recovering COVID-19 patients (hypothesized to be abundant in neutralizing IgG and IgM antibodies against the coronavirus) is transfused against extremely ill patients. Initial pilot project results showed that a single dose of convalescent plasma (approx. 200 mL) in 19 severely affected patients was well tolerated with significant rise in the level of neutralizing antibodies and subsequently led to clearance of the virus in 7 days [54]. Although this is a promising option for the treatment of COVID-19, more trials with large sample sizes should be conducted to establish an optimum dose and time relation for the effectiveness of this therapy.

#### 4.10 Suppression of excessive inflammatory response

Studies on SARS and MERS diseases provided evidence of highly upregulated levels of proinflammatory cytokines referred to as cytokine storm in severely ill patients. Likewise, patients infected with SARS-CoV-2 exhibited dysregulated cytokine response in which interleukin (IL)-6 and GM-CSF are significantly upregulated leading to a hyper-inflammatory condition in the lungs [55]. In view of this, inhibiting IL-6 receptor or GM-CSF could reduce excessive inflammatory response and thus may be a potential strategy for treating COVID-19 [56]. One such candidate that targets the IL-6 receptor is tocilizumab, a monoclonal antibody that binds specifically to both soluble and membrane-bound IL-6 receptors and acts as an immunosuppressant. At least three clinical trials for tocilizumab are underway to treat pneumonia in patients with COVID-19. First, a randomized, double-blind, placebo-controlled study (NCT04320615) in 330 patients receiving intravenous 8 mg/kg (up to a maximum dose of 800 mg) dose of tocilizumab is ongoing in phase 3. Second is a phase 2, single-arm, open-label study with the same dosage strategy as the first trial is ongoing in 400 COVID-19 patients (NCT04317092). A third multicenter, randomized, controlled trial is underway in China to examine the efficacy and safety of tocilizumab in 94 patients with COVID-19 (ChiCTR2000029765). All these studies are yet to be completed, but preliminary results of phase 1 or 2 are quite promising. However, being an immunosuppressant, tocilizumab lowers the ability of the immune system to fight bacterial (including tuberculosis), fungal, or viral infections.



Meanwhile, the Council for Scientific and Industrial Research (CSIR) has started a multicenter clinical trial in collaboration with Cadila Pharmaceuticals Ltd to evaluate Mycobacterium W (Mw) for adjunctive treatment of patients severely infected with COVID-19. Mycobacterium W, heat-killed *Mycobacterium indicus pranii*, is an antileptospory vaccine with immunomodulatory functions that help in boosting  $T_H1$  and  $T_H2$  cell responses. Initial results and safety assessment in four patients suggest that Mw can potentially decrease the cytokine storm observed in COVID-19 patients with severe sepsis and may thus be of potential benefit in managing these patients and reducing mortality.

## 5. Conclusion and future work

The emergence of COVID-19 pandemic caused by a novel coronavirus, i.e., SARS-CoV-2, has put public health at high risk and has caused severe global economic loss. There is an urgent need to better understand this new virus and to develop ways to control this health emergency. Although scientists around the world have shown promising results toward finding potential COVID-19 vaccines, these are under animal trial stage and testing in human trial may take several months. Moreover, time deterrent and constrained cost of drug development has shifted the emphasis on the use of repurposed drugs that are already approved for treating similar viral infections such as SARS and MERS. We presented a review focused on the currently undergoing clinical trials of antiviral drugs against COVID-19 that are previously approved to treat SARS-CoV and MERS-CoV with known efficacy and safety.

Drugs that target the SARS-CoV-2 entry include chloroquine phosphate, which is an inhibitor of endocytosis, and arbidol, which blocks viral fusion. Other potential drugs targeting SARS-CoV-2 transcription and replication include ribavirin, remdesivir, favipiravir, and galidesivir. Lopinavir/ritonavir treatment's activity is against the protease, while oseltamivir is a potent neuraminidase inhibitor and interferes with the release of viral particles from the host cells. On the other hand, the potential drugs that modulate host immune cell response against SARS-CoV-2 include interferons; tocilizumab, i.e., IL-6 receptor inhibitor; and Mycobacterium W.

For the near future, a combination of host and viral inhibitors will provide a variety of drug regimens appropriate for the treatment of SARS-CoV-2 infection. So far antiviral drugs, viz., lopinavir/ritonavir, remdesivir, and favipiravir, have shown potential efficacy to treat COVID-19.

The increasing knowledge about SARS-CoV-2 and its mechanisms of infection, combined with the rapid discovery of vaccine and novel antiviral strategies, will embark a new era of COVID-19 treatment. The future of drug discovery for COVID-19 relies highly on the development of new computational methods and data mining strategies.

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