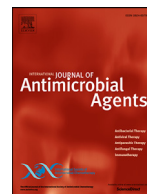




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Hot Topic

Combating devastating COVID-19 by drug repurposing

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ABSTRACT

Despite advances in drug discovery, viral infections remain a major challenge for scientists across the globe. The recent pandemic of COVID-19 (coronavirus disease 2019), caused by a viral infection with SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), has created a disastrous situation all over the world. As no drugs are available to treat this life-threatening disease and the mortality rate due to COVID-19 is high, there is an utmost need to attempt to treat the infection using drug repurposing. Some countries are against the use of these drugs because of adverse effects associated with drug repurposing and lack of statistically significant clinical data, but they have been found to be effective in some countries to treat COVID-19 patients (off-label/investigational). This article emphasises possible drug candidates in the treatment of COVID-19. Most of these drugs were found to be effective in *in vitro* studies. There is a need to re-assess *in vitro* data and to carry out randomised clinical trials. Further investigations of these drugs are recommended on a priority basis.

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1. Introduction

COVID-19 (coronavirus disease 2019) is a respiratory tract infection caused by a novel coronavirus that was first identified in the city of Wuhan, Hubei Province, China, at the end of 2019. Genetically, the virus closely resembles the severe acute respiratory syndrome coronavirus (SARS-CoV) [1] and has been named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It has spread across the globe to more than 190 countries within a short period, i.e. within 45–90 days of its initial recognition. The COVID-19 pandemic has created a devastating situation not only in developing countries but also in developed nations. To date, there is no specific treatment available to treat infection with SARS-CoV-2 and the disease COVID-19.

By the end of March 2020, approximately 750 000 people have been infected with SARS-CoV-2 globally and the situation is overwhelming in countries such as China, Italy, Spain and the USA. As no specific treatments or vaccine for COVID-19 are available, there is a need of drug repurposing, where approved drugs can be effectively used to treat novel diseases with minimal or no side effects. The benefits of drug repurposing are that the safety, optimal dosage and pharmacokinetics of drugs are well known.

In India, most of the drugs and antibiotics used to treat COVID-19 have been repurposed (off-label/investigational use) and have

been found to be very effective in affected individuals. This might be one of the reasons for the low mortality rate in India (0.02 deaths per million persons) compared with Italy (178 deaths per million persons) [2].

Chloroquine and its hydroxyl analogue hydroxychloroquine have been reported for their use as an antiviral agent in various studies. Apart from their antimalarial use, they have also shown *in vitro* activity against SARS-CoV-2 [3,4]. The pH increase induced by chloroquine and hydroxychloroquine within acidic organelles such as lysosomes, endosomes and Golgi vesicles is responsible for their antiviral activity [3,4]. In one mechanism of action, these drugs mainly inhibit virus entry into their host cell by a pH-dependent step. In another mechanism of action, chloroquine and hydroxychloroquine inhibit post-translational modification of the virus envelope glycoproteins inside the endoplasmic vesicles and trans-Golgi network [3,4]. The major stages of the coronavirus replication cycle and the probable sites of action of different drugs are shown in Fig. 1.

Few researchers are against the use of antibacterial agents and antibiotics to treat viral infections, but drugs such as teicoplanin can inhibit the growth of viruses in human cells [5]. Staphylococci infections can be treated with teicoplanin and it was also shown to be efficacious in the first stage of the Middle East respiratory syndrome coronavirus (MERS-CoV) viral cycle. Teicoplanin mainly inhibits the low-pH cleavage of the spike (S) protein by cathepsin L in the late endosomes, hence preventing viral RNA release and replication of virus [5,6].

Other glycopeptide antibiotics such as oritavancin, dalbavancin and telavancin also have the potential to inhibit the entry of

Abbreviations: CoV, coronavirus; MERS-CoV, Middle East respiratory syndrome coronavirus; SARS-CoV, severe acute respiratory syndrome coronavirus.

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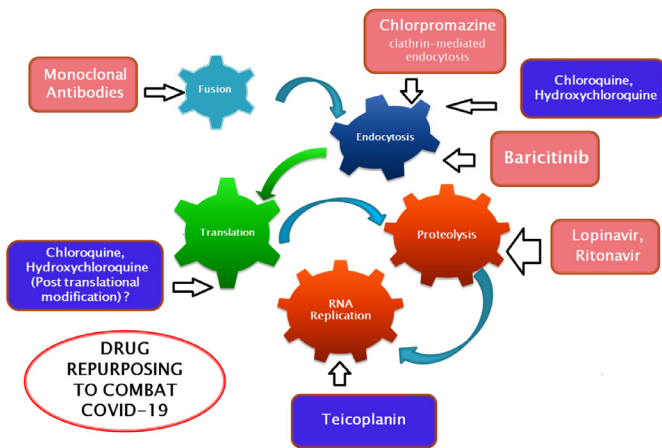


Fig. 1. Major stages of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) life cycle in host cells and probable site of action of different drugs.

SARS-CoV, Ebola virus and MERS-CoV transcription and replication-competent virus-like particles (trVLPs) [5,6].

The major mechanism by which MERS-CoV [7,8] and SARS-CoV [9] enter host cells is clathrin-mediated endocytosis. A drug that acts by inhibiting clathrin-mediated endocytosis is chlorpromazine, which can inhibit the entry of these coronaviruses into host cells [10]. Chlorpromazine is a widely used antipsychotic agent that is safely used to treat schizophrenia. It may be efficacious to treat COVID-19 patients provided that adequate clinical trials are conducted.

The macrolide antibiotic bafilomycin A1 may be a promising candidate to treat COVID-19. It is an endo/lysosomal V-ATPase inhibitor that mainly interrupts the function of angiotensin-converting enzyme 2 (ACE2), the receptor for SARS-CoV and SARS-CoV-2, by which it may stop the viral cycle at the early entry stage [9].

Remdesivir, an antiviral agent initially developed for Ebola virus infection, revealed more effective results against SARS-CoV-2 in vitro [11]. It is an adenosine analogue that incorporates into nascent viral RNA chains and results in premature termination. Further investigations of remdesivir are anticipated in human COVID-19 patients on an urgent basis.

Nitazoxanide is used to treat parasitic infections and has also been found to be effective in treating a wide range of viruses, including human coronaviruses, in vitro at very low concentrations. It selectively blocks haemagglutinin intracellular trafficking and insertion of this protein into the host plasma membrane, a key step for correct assembly and exit of the virus from the host cell [12].

Padmanabhan reported a combination therapy approach using hydroxychloroquine and nitazoxanide [12]. A synergistic effect can be produced by using both drugs, as hydroxychloroquine inhibits viral entry and fusion whilst nitazoxanide upregulates the innate immune response to prevent ongoing viral replication.

Tocilizumab, an immunosuppressive agent originally used to treat rheumatoid arthritis, was also found to be effective in vivo in COVID-19 patients in China [13]. Tocilizumab effectively reduces the clinical symptoms of viral infection, however the number of patients tested in the study was very small [13].

Another antibiotic found to be effective in viral infections is the macrolide azithromycin. The drug effectively inhibits the growth of Zika virus and Ebola virus in vitro [14,15]. The synergistic effects of the combination of azithromycin and hydroxychloroquine were also reported in the treatment of COVID-19 patients [16]. The report highlights the efficacy of this combination in clearing viral nasopharyngeal carriage within a short time in COVID-19 pa-

Table 1
Recommended drugs (off-label) for treatment of COVID-19 (coronavirus disease 2019) [18]

Drug	Dosage
Hydroxychloroquine	400 mg b.i.d. × two doses, then 200 mg b.i.d. for 5 days
Remdesivir	200 mg i.v. loading dose, then 100 mg i.v. for up to 10 days
Oseltamivir	150 mg b.i.d. for 5 days
Lopinavir	400 mg b.i.d. for 10 days
Ritonavir	100 mg b.i.d. for 10 days
Ribavirin	2 g loading dose, then 600 mg t.i.d.

b.i.d., twice daily; i.v. intravenous; t.i.d., three times daily.

tients compared with patients receiving only hydroxychloroquine. Hydroxychloroquine increases the pH within acidic organelles and also inhibits entry of the virus [3,4], producing an antiviral effect (as explained earlier), whilst the exact antiviral action of azithromycin is not known. It may have immunomodulatory properties that could be beneficial in the treatment of pulmonary viral infections. The molecule may decrease the inflammatory responses and the production of excessive cytokines ('cytokine storm') accompanying viral infections. The immunomodulatory mechanism may be due to decreased chemotaxis of neutrophils to the lungs by inhibiting cytokines as well as the formation of reactive oxygen species [16,17].

In India, hydroxychloroquine plus the antiviral combination lopinavir/ritonavir have been used to treat COVID-19 patients. Lopinavir/ritonavir affects the viral protease 3CLpro responsible for proteolysis in the coronavirus replication cycle [18].

The Japanese antiviral drug favipiravir used to treat influenza, developed by FUJIFILM Toyama Chemical Co., Ltd., showed considerable success in clinical trials of more than 340 patients [19] where it was found to be safe and effective in the treatment of COVID-19 patients. Further investigations are recommended in this context.

Ascorbic acid (vitamin C) possesses antioxidant properties. It does not have a direct lethal effect on viruses, but it has been reported that viral respiratory infections in humans are affected by vitamin C levels [20]. When viral infection occurs, the subsequent cytokine surge is activated and neutrophils accumulate in the lungs, destroying alveolar capillaries. Early clinical studies have shown that vitamin C has the potential to inhibit these processes [21]. Combining ascorbic acid with other drugs will definitely be helpful for affected COVID-19 individuals.

Baricitinib is another drug used in the treatment of rheumatoid arthritis. It can be also used to treat novel coronavirus [22], possibly by targeting the process of endocytosis. The receptor used by SARS-CoV-2 to infect lung cells is ACE2, which are prone to viral infection. The AP2-associated protein kinase 1 (AAK1) is one of the known regulators of endocytosis, and disruption of AAK1 might interrupt the passage of virus into cells and also the intracellular assembly of virus particles [23].

2. Recommended drugs (off-label) for treatment of COVID-19

Recommended drugs for the treatment (off-label/investigational use) of COVID-19 are shown in Table 1.

3. Current status of investigational drugs to treat COVID-19

Table 2 summarises the current status of investigational drugs/vaccines to treat COVID-19 across the globe.

Table 2
List of investigational drugs/vaccines to treat COVID-19 (coronavirus disease 2019)

Name	Organisation	Study phase	Current status	Reference
Remdesivir	Gilead Sciences	III	Initiated two phase III clinical studies. Randomised studies will enrol ~1000 patients: (i) 400 patients with severe clinical manifestations of COVID-19; and (ii) 600 patients with moderate clinical manifestations of COVID-19	[24]
Kevzara® (sarilumab)	Regeneron Pharmaceuticals and Sanofi	II/III	Assessing safety and efficacy in 400 hospitalised adult COVID-19 patients using the IL-6 receptor antagonist Kevzara® (sarilumab)	[25]
Lopinavir/ritonavir combination	AbbVie	I/II (?)	Clinical trial for use of the anti-HIV combination medication lopinavir/ritonavir to treat COVID-19 has been initiated	[26]
Antibody	Regeneron Pharmaceuticals Inc.	Preclinical/clinical (?)	Initiated development of a novel multi-antibody cocktail for COVID-19	[27]
Antibody (TJM2)	I-Mab Biopharma	Phase I completed	Completed phase I study; safety, tolerability and immunogenicity studies showed favourable results	[28]
Antibody OYA1 (investigational)	Medicago OyaGen, Inc.	Preclinical	Successfully formulated virus-like particle (VLP)	[29]
		Preclinical	Safety and efficacy studies are ongoing	[30]

IL-6, interleukin-6; HIV, human immunodeficiency virus.

4. Concluding remarks

In conclusion, based on previous studies, use of these drugs in the treatment of viral diseases should be thoroughly investigated to save the lives of affected individuals, despite some adverse effects. All of the above-listed drugs may be potential candidates to treat COVID-19 patients, and sufficient *in vivo* data regarding their interactions and efficacy are urgently required. Preliminary *in vitro* data are required to be reassessed and clinical studies are recommended at the earliest opportunity.

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Competing Interests

None declared.

Ethical Approval

Not required.

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