Commentary

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COVID-19 infection: The prospects of pharmacotherapy

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Abstract:

The disastrous outbreak of coronavirus disease 2019 (COVID-19) has triggered the investigation of several therapeutic options following the redundancy of specific drugs against it. The virus possesses advanced molecular mechanisms to effectively invade the host cell compared to its counterparts. It results in a seamless and coherent infection and transmission, attributing to its enhanced pathogenicity. The drugs that are currently being employed against COVID-19 inhibit the viral load in different stages of infection, including host cell–virus interaction, viral entry into the host cell, and viral replication inside the host including genome replication and polypeptide chain production. This commentary emphasizes the pharmacotherapeutic options available from the perspective of viral life cycle and pathogenicity.

Keywords:

Coronavirus disease 2019, diagnosis, SARS-CoV-2, therapeutics, transmission

The ongoing detrimental effects of the coronavirus disease 2019 (COVID-19) have stipulated the investigation of numerous therapeutics in the absence of specific treatment.[1,2] Unlike MERS-CoV and SARS-CoV-1, the other two viruses of the family, COVID-19 or SARS-CoV-2 has been a global pandemic and it is reported by the WHO as such.[3,4] The pandemic has spread over 208 counties, with China reporting more than 90% of the cases and deaths, being the central hub.[5] Although the disease shows symptoms associated with pneumonia, its genetic constitution and structural features have been attributed to its extensive pathogenicity and infection across the globe.[5,6] Herein, we report the various pharmacotherapeutics used against COVID-19 in brief, so that it can facilitate health-care providers with foundational knowledge on pharmacotherapeutics that are both currently being used and under clinical investigation at the molecular level. The mechanisms of the drugs targeting the virus have been discussed alongside with original indication, possible COVID-19 indication, dosage information, and side effects.

Most of the drugs that are currently being used to treat COVID-19 were once used against both MERS-CoV and SARS-CoV-1, as the SARS-CoV-2 possesses >80% similar genome to that of SARS-CoV-1.[6,7] Along with these, antiviral, antimalarial, antiparasitic, and anti-protozoans are also being used.[8] Although a majority of drugs are designed to interfere with the viral genome replication,[9] they also display an array of mechanisms such as inhibiting host cell–virus interaction. For example, hemagglutinin, a viral glycoprotein that mediates the adsorption of viral particles to host cell membrane, can be targeted by nitazoxanide, an antiprotozoal drug which was used against diarrhea.[10] A metabolite of the drug known as tizoxanide binds to hemagglutinin to deactivate it. Doses recommended are based on age groups; 1–3-year-olds were recommended with

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100 mg, 4–11 years with 200 mg, and above 12 years with 300 mg for 5 days, orally. Adverse effects of nitazoxanide include nausea, headache, and abdominal cramps. Patients may also come across discoloration of urine and eyes, dizziness, and skin rash.[10] Another drug known as arbidol hydrochloride or umifenovir also works in the same mechanism. It was originally designed to treat influenza and arbovirus.[8,9] Since it is under clinical investigations, the doses and side effects are yet to be revealed.

In case of successful adsorption, SARS-CoV-2 tends to enter the host cell using ACE2 protein as a gateway.[10] In this stage, few drugs try to inhibit the virus from entering the host cell. Chloroquine and hydroxychloroquine impair the glycosylation of ACE2, by disrupting viral S protein, thereby preventing the entry of SARS-CoV-2 into the host cell. Both were used to treat malaria, HIV-1, and autoimmune diseases due to their anti-inflammatory and immunomodulatory effects.[8,11] Apart from impairing ACE2, they also increase intracellular pH in host cells, thus inhibiting RNA synthesis. Being weak bases, they impair acid vesicles and inhibit the activity of viral enzymes, ultimately inhibiting the viral entry to the cell in case of pH-dependent endocytosis.[12] Chloroquine is consumed as 500 mg twice for 5 days and hydroxychloroquine as 400 mg on the 1st day, followed by 200 mg twice a day for 4 days, orally.[10] Adverse effects of these drugs include nausea, vomiting, abdominal cramps, and a metallic taste, whereas acute toxicity may pose in the development of neuropathy, retinopathy, and cardiopathy.[10] In addition to these drugs, two more drugs known as emodin and promazine also inhibit ACE2 by the same mechanism. However, their dosage and adverse effects are not reported because they are yet to clear the clinical trials.[8]

Owing to the modified genome structure and advanced structural features, SARS-CoV-2 is more lethal than its counterparts.[6] It can invade the host cell despite maximal efforts from the innate immune system. In such cases, the impairment of its replication proves to be an efficient objective. Drugs designed to interfere with the viral replication exert a mechanism known as molecular mimicry. This phenomenon occurs when a non-functional molecule mimics the action of the actual biomolecule thereby inhibiting the actual process from occurring. For example, an antiviral drug known as remdesivir, which was used against Ebola and MERS-CoV viruses, mimics guanosine nucleoside, and its incorporation into the RNA replication impairs the process finally halting the viral replication and growth.[11,12] The same mechanism is being used by ribavirin, which was formulated to treat hepatitis viruses and SARS-CoV-1.[13] Both the drugs are now been used to treat COVID-19.[9,13] Remdesivir is taken as 200 mg on the 1st day, followed by 100 mg for up to 10 days intravenously, and ribavirin as 400 mg for 14 days, twice a day. Remdesivir has been associated with adverse effects such as nausea, vomiting, and rectal bleeding, whereas ribavirin results in hemolytic anemia, hypocalcemia, hypomagnesemia, and embryonic toxicity in pregnant women.[10] The other two drugs, favipiravir and sofosbuvir, with the same molecular mechanism are under clinical investigation with their dosage and side effects yet to be revealed.[8]

In addition to the binding to RNA as a nucleoside analog, few drugs act as inhibitors of aspartic acid protease inhibitors. These proteases are needed for the production and maturation of viral genomes.[10] The combination of lopinavir and ritonavir is one of the most practiced therapies against COVID-19. Known for their antiviral effects against HIV-1, they are used to treat SARS-CoV-2 by inhibiting the protease enzyme.[8,9] It is recommended that 100–200 mg of the drug should be given for 14 days for patients with symptoms of COVID-19. However, these drugs can cause intolerable gastrointestinal toxic effects such as diarrhea, fatal pancreatitis, and hepatic maladies.[10] Alongside lopinavir/ritonavir, several other drugs are present that are potent enzyme inhibitors. For example, nelfinavir is another protease inhibitor, which is reported to have similar properties like that of lopinavir/ritonavir. It prevents proteolytic cleavage of the viral polyprotein precursors into individual functional proteins. Ivermectin is an antiviral drug once used to treat HIV-1 and dengue, which is now employed against SARS-CoV-2.[11] It can dissociate the preformed IMPα/β1 heterodimer, which aids in the viral protein displacement. As the protein displacement is essential for maintenance of viral replication, targeting this displacement across the host cell would be a feasible option to inhibit the viral life cycle.[11] Yet another serine protease inhibitor, nafamostat, is said to inhibit transmembrane protease serine 2 associated with the fusion process that facilitates the entry of SARS-CoV-2. In addition to this, two more antiviral drugs used to treat influenza known as oseltamivir and zanamivir are reported to inhibit neuraminidase enzyme that may prevent the entry of the virus into host cells.[8] These drugs also reported to aid in the reduction of viral load by reducing the shedding. These drugs, i.e., nelfinavir, ivermectin, nafamostat, oseltamivir, and zanamivir, have not cleared the clinical tests; hence, their dosage level for treating COVID-19 remains unknown.[8]

Among the different types of drugs used against SARS-CoV-2, we comment on only one drug with

original antibacterial indication. Azithromycin possesses the ability to prevent secondary bacterial infection.[14] Originally designed for treating bacterial infections, it is also reported to have antiviral activity. Although precise mechanisms remain unknown, potential mechanisms have been proposed for the putative antiviral properties. One of the first mechanisms is similar to chloroquine and hydroxychloroquine, by increasing the intracellular pH level to dismantle the viral replication process, thereby leading to inhibition of viral growth.[11] The second mechanism proposed is mediated by the amplification of interferon (IFN) pathway of the host cell. Clinical data suggest that the viral load reduction is attributed to the ability of azithromycin to induce pattern recognition receptors (IFNs and IFN-stimulated genes). In addition to this, it acts directly on bronchial epithelial cells to regulate their normal function by reducing mucus secretion.[11] The recommended dosage of azithromycin is 500 mg on the 1st day, followed by 250 mg for 4 days.[8]

In conclusion, owing to the pharmacotherapeutic options currently available, we highlight the fact that the pandemic can be controlled with effective treatment, along with the maintenance of social distancing and quarantine. This is supported by many studies that have been conducted and reported on the significance of stringent lockdown regulations in reducing the viral escalation. Apart from this nonpharmacological management, some of the drugs are now being used, which have already cleared the clinical trials. We also emphasize that, with the absence of specifically designed drug as well as a potential vaccine, a combination of drugs with different and effective doses is the only solution to bring out the optimal management of the disease.

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Conflicts of interest
There are no conflicts of interest.

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