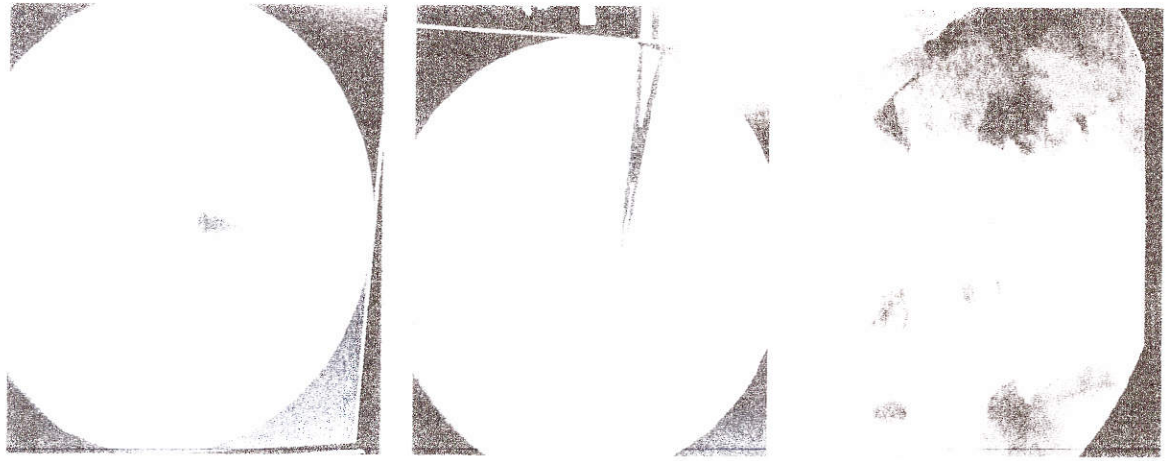

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MINI REVIEW CORONA EXPERIENCE

Antiviral therapy for COVID-2019

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Abstract

The whole world is experiencing a global pandemic caused by Coronavirus disease 2019. As the pandemic progresses, there has been much research on antiviral drugs, such as hydroxychloroquin, chloroquine, remdesivir, lopinavir-ritonavir, favipiravir, oseltamivir, and umifenovir. Specific antiviral drugs proven to be effective against SARS-CoV-2 have not been found and approved for the medication of COVID-19. Currently, case detection, infection control, monitoring, prevention, and supportive care are the means focused on the treatment of COVID-19. A large scale research is currently underway to analyze safety and efficacy of antiviral drugs, while trials of the SAR-CoV-2 vaccine are rapidly expanding. This mini review briefly introduces the current antiviral therapy for COVID-19.

Key word: Antiviral therapy; Drugs; COVID-19

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1. Introduction

The whole world is experiencing a global pandemic caused by Coronavirus disease - 2019.[1] Based on data according to the World Health Organization, Globally, as of 18 May 2021, there have been 163,312,429 confirmed cases of COVID-19, including 3,386,825 deaths, reported to WHO. As of 18 May 2021, a total of 1,407,945,776 vaccine doses have been administered.[1,2] COVID-19 infection rates continue to increase sharply.[3] As of 18 May, 2021 there have been 880,362 confirmed cases and 19,617deaths in Pakistan.[1]

Compared to COVID-19, Severe Acute Respiratory Syndrome (SARS–CoV) had the incidence of 8,422 cases with a case fatality rate (CFR) of 11%, and the Middle East Respiratory Syndrome (MERS) 2574 laboratory-confirmed cases, including 886 associated deaths (case-fatality ratio 34.4%). While the diagnostic ctiteria of COVID-19 is still being periodically reviewed, it might take years for the actual number of cases to be known.[4] As the pandemic progresses, there has been extensive research on antiviral drugs, namely hydroxychloroquin, chloroquine, remdesivir, lopinavir-ritonavir, favipiravir, oseltamivir, and umifenovir.[5] We present here an overview of the current anti-viral drugs being used.

2. Antiviral therapy

Due to the clinical manifestations of COVID-19 caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication, antiviral therapy that can treat COVID-19 is being investigated. Mechanism of action of antiviral drugs is by inhibiting the entry of the virus (by transmembrane serine

protease 2 (TMPRSS2) and the angiotensin-converting enzyme 2 (ACE2) receptor; fusion inhibitors inhibit the fusion process and endocytosis or the action of the RNA-dependent RNA polymerase and the SARS-CoV-2 3-chymotrypsin-like protease (3CLpro).[3,6,7] Antivirals may have the biggest impact because viral replication is probably very active initially in the progression of COVID-19 before the disease moves to the high inflammation syndrome state that can lead towards the next step of disease inclusive of hypercritical stage. Therefore, the role of antiviral drugs needs to be understood in curing minor, moderate, major and critical disease, so that the treating physicians may optimize medication for the COVID-19 patients.[3,6]

In clinical trials antiviral therapy was investigated to find the efficacy of SARS-CoV-2 treatment. It is reported that single therapy or combinations therapy for the COVID-19 patients differs in different countries of the world. These methods of therapy usually depend on the number of deaths and the frequency of mechanical ventilation the patients use. In addition, there is no specific medication for the COVID-19. Currently, various countries around the world have been investigating different antiviral therapies for the COVID-19 (Table 1).[8] Specific antiviral drugs proven to be effective against SARS-CoV-2 have not been found and approved for the medication of COVID-19. Therefore, rapid assessment of the antiviral drugs currently available for use in COVID-19 patients is critical at this time of crisis, as well as for finding newer drugs.[9]

2.1. Antimalarial

2.1.1. Hydroxychloroquine and Chloroquine

Hydroxychloroquine and chloroquine are antimalarial drug. Hydroxychloroquine is a chloroquine analogue. June 15, 2020, the FDA withdrew the emergency use authorization for hydroxychloroquine, throwing out that it is unlikely to be effective in medicating COVID-19. In Addition, given the processing of that viral fusion does not occur, and cytokine release converting enzyme 2 (ACE2) cellular receptor, pyrazinecarboxamide derivative prodrug of a nucleoside analogue that can be triphosphorylated in and RNA polymerase of the virus, protein glycosylation, assembly of the virus, new virus acidification of the cell membrane at the surface, so immunomodulation.[10] Neither drugs are approved by FDA for the medication of COVID-19 patients. Have serious cardiac adverse events and other serious side effects (methemoglobinemia) of hydroxychloroquine do not justify its continued use.[10,11] Chloroquine was introduced in 1934, while hydroxychloroquine was introduced in 1946.[6] Hydroxychloroquine used to medicate systemic lupus erythematosus (SLE), rheumatoid arthritis, and also malaria. Normally, hydroxychloroquine has less and lower toxicity (including a small tendency to interval QTc prolongation) and minor drug-drug interactions than chloroquine (Table 1).[6] Mechanisms may include inhibiting viral enzymes or processes such as DNA.

2.2. HIV Protease inhibitor

2.2.1. Lopinavir/Ritonavir

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication relies on the splitting of a helicase, and polyproteins become an RNA-dependent RNA polymerase. In the splitting, protease, which is responsible, namely: 3-chymotrypsin-like protease (3CLpro) and papain-like protease (PLpro).[6] Ritonavir acts to increase plasma level of lopinovir by inhibiting the CYP3A-mediated metabolism of lopinavir.[11] The combined use of these drugs can increase the bioavailability of lopinavir significantly, and the effect of antiviral is improved in vivo.[12] Lopinavir and ritonavir have mechanism of action may bind to primary enzyme, it called Mpro, supressing the repilicationof the coronavirus so that it does not occur. This can suppress activity of the corona virus.[13] Lopinovir and ritonavir have been researched in patients with COVID-19. The clinical trials on lopinavir/ritonavir have not established their efficacy for the treatment of COVID-19.[6,13] The common adverse events of lopinavir/ritonavir observed are diarrhea, nausea and vomiting, while severe adverse event include interval QTc prolongation and hepatotoxicity (Table 1).[3,6]

2.3. Nucleotide reverse transcriptase inhibitor

2.3.1. Remdesivir and Favipiravir

Remdesivir is a nucleotide prodrug of an adenosine analog, and is infised intravenously. Favipiravir is a cells and acts as the virus RNA-dependent RNA polymerase (RdRp) substrate.[12]

Remdesivir and favipiravir inhibit viral replication through premature termination of RNA transcription.[6,12] Food and Drug Administration (FDA) hs approved remdesivir for the medication of COVID-19 in hospitalized pediatric patients of at least 40 kg and 12 years or older and the adults.[11] Remdesivir should be administered in a hospital or a healthcare setting that can provide the same level of care to an inpatient hospital.[6] Remdesivir is administered as a loading dose 200 mg on day 1, followed by once daily 100 mg IV dose for a total of 10 days, similar to the doses used in the clinical trials to medicate Ebola for adults (Table 1).[3,11] Remdesivir can lead to gastrointestinal symptoms such as nausea, raised levels of transaminase, an elevated time of prothrombin, and hypersensitivity reactions.[6]

Favipiravir was developed in Japan in 2014. Initial clinical trial outcome indicate that favipiravir produces much greater improvement in chest imaging in COVID-19 patients compared to lopinavir. Faster viral clearance and fewer adverse events were also viewed in patients taking favipiravir compared to those taking lopinavir-ritonavir.[3] The most serious adverse events of favipiravir is teratogenicity. Common adverse events were gastrointestinal symptoms, liver enzyme abnormalities, raised serum uric acid, and psychiatric issues.[12]

Several clinical trials analyzing remdesivir and favipiravir for the medication of COVID-19 are currently underway or in development.[6]

2.4. Neuraminidase inhibitor (Virus release inhibitor)

2.4.1. Oseltamivir

Oseltamivir is inhibitor of a neuraminidase and is used to treat influenza A and B. It is also being researched for the medication of COVID-19. It has been reported potentially inhibiting the SARS-CoV-2. Case reports suggest a better prognosis in COVID-19 patients taking oseltamivir. However, oseltamivir efficacy for the medication of COVID-19 needs long term clinical trials.[5]

2.5. Fusion Inhibitor

2.5.1. Uminefovir

Umifenovir, also called as arbidol, is another antiviral agent whish acts by inhibiting spike protein /ACE2 binding and fusion of viral envelopes providing antiviral effects. Initial studies showed that arbidol medication was likely to raise the discharge rate and reduce the mortality rate for patients with COVID-19. Currently, arbidol effectiveness still has no clear evidence and needs further research.[5]

3. Conclusion

COVID-19 infection rates continue to increase sharply, as well as the number of antiviral drugs that work as a treatment for COVID-19. Currently, case detection, infection control, monitoring, prevention, and supportive care are the mean focus in the treatment of COVID-19. No specific antiviral therapy has been confirmed to be effective in curing COVID-19. Studies are currently underway to analyze the safety and efficacy of antiviral drugs, while trials of the SAR-CoV-2 vaccines are rapidly expanding.

4. Conflict of Interest

The authors declare no conflict of interest.

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Table 1. Review of antiviral therapy to treat COVID-19[3,8,11,13]

Drug	Mechanism of action	Trial or Clinical Experiance Dosage	Approved indication(s)	Adverse drug reaction	Drug interaction	country that use drugs
Remdesivir	inhibitor of RNA-dependent RNA polymerase	administration; 200 mg day 1 loading dose one times daily followed by 100 mg one times daily for a total of 10 days (IV)	None	Common: Gastrointestinal:nausea (3-7%) Serious: cardiac arrest, Transaminase level raised, hepatotoxicity, anaphylaxis, hypersensitivity reaction (less than 2%), infusion reaction	• CYP3A4 inducers decrease effectiveness • Major Interaction; Chloroquine , Hydroxychloroquine	Italy, spain, germany
Lopinavir-ritonavir (kaletra)	inhibitor of 3CL protease	400mg/100 mg twice daily for maximum to 14 days (oral)	HIV	Gastrointestinal disturbances (nausea 10.3% vomiting 6.8% adult ,pediatric 12%, diarrhea adult 19.5%, pediatric 12%), raised transaminase,raised bleeding, insulin resistance , hyperlipidemia, hyperglycemia, , prolong of QT interval, possible renal dysfunction risk, steven-Johnson syndrom, central nervous depression, respiratory depression	• inhibitor of CYP3A4 and substrate - substrate of CYP2D6 • Contraindicated Interaction: Amiodaron, fluconazole, simvastatin, phenytoin, rifampin, ketoconazole	Italy, pain, South Korea, USA, China
Favipiravir	inhibitor of RNA-dependent RNA polymerase	1600-1800 mg daily on day1, then 600 mg two times daily for 7-14 days (oral)	Ebola virus, Influenza A and B, Norovirus	Gastrointestinal disturbances (nausea, vomiting diarrhea), hyperuricemia, elevated transaminases, decreased neutrophil count	• Mainly mediated by aldehyde oxidase, not substrat CYPs	Turkey
Chloroquine Aralen)	inhibitor of Viral entry	500 mg orally one or two times daily for 5–10 days (oral)	Autoimmune disease: rheumatoid arthritis (RA), Systemic lupus erythematosus (SLE). malaria	Gastrointestinal disturbances (e,g, vomiting diarrhea, nausea), headache, delirium, QT prolongation, Torsades de Pointes, arrhythmia, agranulocytosis, extrapyramidal disease, seizures, retina disorder rare renal toxicity, anorexia, bitter taste	• CYP3A4/5, 2D6, and 2C8 substrat • increased risk of prolonging QT interval with other QT prolongation agents (antibiotikquinolon, macrolide) • raised digoxin levels	Italy, spain, South Korea, USA, Brazil, China
Hidroxychloroquine Plaquenil)	inhibitor of Viral entry	Day 1 400 mg two times daily, followed by 200 mg two times daily for 5–10 days Alternative: 200 mg Three times daily for 10 days or 400 mg one daily for 5 days (oral)		Gastrointestinal disturbances (nausea), QT prolongation, hypoglycemia, neuropsychiatric effects, agranulocytosis, extrapyramidal disease, disorder muscle, hearing loss, angiodema	• raised risk of hypoglycemia with blood glucose-lowering agents • major interaction: Azitromycin • Metabolized by CYP3A4; monitor closely CYP3A4 strong inducers/inhibitors • Antacids	Italy, Spain, Turkey, Russia, South Korea, Brazil
Oseltamivir	Neuraminidase inhibitor	75 mg every 12 hours (oral)	Influenza A and B	Gastrointestinal disturbances (nausea 8-10%, vomiting 2-8% adult 8-16% pediatric), headache, cardiac dyrhythmia, hepatitis, seizure, , anaphylaxis	Major interaction: warfarin	Italy,USA, China,
Umifenovir	Spike protein/ACE2 membrane fusion inhibitor	200 mg 3 times daily for duration of 7-10 days/longer (oral)	Influenza A and B	Gastrointestinal disturbances (nausea,vomitting), allergic reaction, elevated transaminases	Metabolized by CYP3A4; monitor strong inducers/inhibitors of CYP3A4	Russia