Use of COVID-19 Drugs: A Brief Review on Indian Perspective

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Abstract- ***The first evidence of severe acute respiratory syndrome corona virus-2 (SARS CoV-2) was traced in Wuhan city, China, in December 2019. The global outbreak of the novel coronavirus surpassed in early 2020. Because of the mutation of coronavirus, a large number of mutated strains have been observed in various countries. WHO designated the most important and rapid spreading variants as alpha, beta, gamma, delta, and omicron. The rapid clinical trial of several drugs has been started since early 2019 for the treatment of patients infected by the novel coronavirus. At the beginning of the pandemic, some drugs such as chloroquine and hydroxychloroquine were recommended for treatment of the covid-19 patients without any adequate clinical trials. The drugs used for the treatment of coronavirus infection can be divided into protocol drugs and non-protocol drugs. Here, the efficacy of several protocol and non-protocol drugs towards the prevention and treatment of coronavirus infection, their interaction with coronavirus, and side effects of such recommended drugs are described in this chapter.***

Indexed Terms- COVID-19: Corona Virus Disease 2019
SARS CoV-2: Severe Acute Respiratory Syndrome Corona Virus-2
WHO: World Health Organization
FDA: Food and Drug Administration
CQ: Chloroquine
HCQ: Hydrochloroquine
RNA: Ribonucleic Acid
DCGI: Drugs Controller General of India

I. INTRODUCTION

Though the first case of coronavirus was detected in China in December 2019 [1], the global outbreak of novel coronavirus surpassed in early 2020. Although there are differences of opinion as to the origin of the novel coronavirus, scientists all agree that it is not a new kind of virus. Scientists have long observed the existence of SARS-CoV-2 in the body of bats [2]. But scientists were not aware of the transmission of this type of virus in the human body or its mutation in the human body. For this reason, scientists were not aware of its treatment in the first wave of covid-19. In the beginning, symptomatic treatment was the only way to cure this disease. However, some patients started using some anti-viral drugs due to their more complex symptoms. However, most of these drugs were used without adequate clinical trials.

The first case of COVID-19 infection was reported in India on 27th January 2020. A 20-year-old woman who returned from Wuhan city to Thrissur, Kerala on 23rd January, was the first COVID-19 infected person in India [3]. From the beginning of March 2020, the number of Covid-19 infected patients in India has been increasing. Initially, all infected people had a history of emigration, but later the virus spread rapidly to the common people. In India, in the first wave of Covid-19, the daily maximum number of infected people reached about 97,000 (97399 new cases on 09.07.2020, Source: Aaragya Setu, the official Covid-19 monitoring app of Govt. of India). The Covid situation in our country reached its worst in the second wave. At that time, the maximum number of daily infections reached over four lakhs (401993 new cases on 30.04.2021, Source: Aaragya Setu, the official Covid-19 monitoring app of Govt. of India). Due to lack of adequate infrastructure for this huge number of patients, lack of liquid medical oxygen, insufficient number of ventilators, etc., the second wave of covid-19 reached the highest death rate in India.

Most of the patients infected by novel coronavirus are asymptomatic or have mild symptoms. The common symptoms of Covid-19 are fever, headache, muscle aches, diarrhea, cough and cold, runny nose, alteration

of the sense of smells and taste, fatigue, shortness of breath, and rhinorrhea [4].

Drugs used in the treatment of COVID-19 in India and all over the world are mainly existing antiviral drugs used in the treatment of various diseases. These previously developed drugs are mainly used to treat severe acute respiratory syndrome (SARS), the Middle East respiratory syndrome (MERS), human immunodeficiency virus (HIV), malaria, and many other diseases [5]. Most drugs were used at a substantial rate before adequate clinical trials were completed. All of these drugs are used only in patients with complex symptoms. These drugs mainly reduce the patient's tendency to be hospitalized, help reduce the number of days the patient is on ventilation, or increase the patient's SpO2. Several types of anti-viral drugs, inflammation inhibitors/ antirheumatic drugs, low molecular weight heparins, or plasma therapy are recommended to patients with moderate to severe COVID-19 patient [6]. Chloroquine, hydroxyl chloroquine, lopinavir/ritonavir, and remdesivir are mainly recommended for critically ill older patients [5].

II. VARIANTS OF SARS-COV-2

Coronavirus is a typical RNA virus. When a human is infected by coronaviruses, the human cells are attached to the viruses, and finally, viruses enter into the human cell. In human cells, coronavirus spreads very fast by making copies of their RNA. The mutation of the virus occurs if there is a copying mistake. Those changes occur randomly and by accident. The different variants of coronavirus are obtained due to such type mutation of coronavirus. Mutation is a change in the genetic sequence. If the mutation occurs in such a way that the genomes differ from each other in genetic sequence, the mutated virus is called variants. One or more mutations are observed in the case of variants. A variant may contain several strains if they have a phenotypic difference.

Variants of concern (VOC): This category includes variants that exhibit higher morbidity, further disease severity, including hospitalization and death, a significant reduction in antibody neutralization, decreased treatment effectiveness, and failure of diagnostic detection. Extensive efforts are needed to control the spread by creating testing kits for this class, and research needs to be increased to ensure the effectiveness of treatment against vaccines and variants. Currently, WHO designated Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529) as variants of concern of SARS-CoV-2.

Variant of interest (VOI):
A variant with specific genetic markers associated with changes in receptor binding, predisposition to a decrease in neutralization by antibodies made against a previous infection or vaccination, a decrease in treatment effectiveness, a potential diagnostic effect, or an increase in infectivity or disease severity. Currently, WHO designated Lambda (C.37) and Mu (B.1.621) as VOI of SARS-CoV-2.

Variant of High Consequence (VOHC)
A VOHC has clear evidence that preventive or anti-medical measures (MCMs) have significantly reduced efficacy compared to previously promoted forms. This type of variant is responsible for failure of a conventional diagnostic test, reduced effectiveness of vaccines, more disease transmission between vaccinated people, more severity of disease, and increased hospitalization.

Currently, no variants of SARS-CoV-2 are designated as VOHC.

Variants under monitoring (VUM)
This type of variant of SARS-CoV-2 requires advanced monitoring and repeated evaluation as the evidence of phenotypic and epidemic effects is currently unclear. This type of variant shows certain genetic mutations that may affect the characteristics of the virus and may pose a future risk. Currently, WHO designated B.1.1.318, C.1.2, and B.1.640 as VUM of SARS-CoV-2.

The existence of two different types of coronavirus strain was noticed by the researchers at the earlier stage of COVID-19 pandemic. Researchers designated those strains as “S” and “L”. These two variants were very similar in structure except for two places where some structural differences were noticed. Researchers are investigating 103 samples of the new coronavirus collected from humans and animals.

Alpha (B.1.1.7) variant: World health organization gives the name of different important and widely spreading variants of coronavirus by Greek alphabets. The first variant of concern recognized by WHO was Alpha (B.1.1.7). This variant of coronavirus was first noticed in September 2020 in the south eastern part of the United Kingdom and the date of the designation of that variant was 18th December 2020 [7]. Alpha variant spread rapidly throughout the world and the existence of this variant is still observed in the USA. This variant contained three important mutations namely, N501Y, 69/70 deletion, and P681H. Davies et al. reported that the mortality due to this variant was approximately 55% higher compared to other strains. Researchers reported that the variant was 40-80% more contagious compared to the original strain. The mutation of the Alpha variant occurs on spike protein and it helps the virus to infect its host. Such type of spike protein is the main target of COVID-19 vaccine, but sometimes a single new mutation of the Alpha variant makes the vaccine less effective.

Beta variant (B.1.351): The second reported variant of coronavirus was the beta variant (B.1.351) which was first reported in South Africa in May 2020. Who designated the variant as a Beta variant on 18th December 2020 [7]. Beta variant spread very fast compare to the original virus but it was unable to make serious illnesses.

Gamma (P.1) variant: Gamma (P.1) variant of coronavirus was first noticed in Brazil in November 2020. It was more contagious than its predecessors and also it was able to infect persons who were already affected by previous variants of coronavirus. It contained 35 mutations with 17 amino acid changes. The important mutations of this variant reported by the researchers are K417T, E484K, and N501Y. It was found that the variant had an almost equal rate of infection in the older and younger patient. This variant has similar receptor-binding mutations compared to B.1.351 and has the capability of reducing the efficacy of vaccines. A laboratory study revealed that the Pfizer-BioNTech vaccines could neutralize the fast-spreading Gamma strain. More study on this conclusion is still to be performed.

Delta (B.1.617.2) variant: The earliest documented sample of the Delta (B.1.617.2) variant was collected from India in October 2020. WHO designated this variant on 11th January 2020 [7]. Mutation on spike protein may make the Delta variant up to 50% more contagious than other variants, according to researchers. Due to its high spreading efficiency, this variant spreads in 178 countries including the US, Brazil, Australia, and all of Europe. The second wave of COVID-19 in India came with that variant and the country faced a major strain on the healthcare system, including a shortage of liquid medical oxygen.

Omicron (B.1.1.529) variant: On 26th November 2021, WHO designated variant B.1.1.529 as Omicron [7]. This variant might spread more easily compare to other variants. But it is not yet established that the variant cause more severe illness compared to other variants. The earliest sample of this variant was collected from South Africa on 09th October 2021 [8]. This variant spread from South Africa to the world in a very short time because of its high contagious character. It is observed that the monoclonal antibodies are less effective against the omicron variant.

Lambda (C.37) and Mu (B.1.621) variants: Both Lambda and Mu variants of SARS-CoV-2 were founded first in South America. The first case of the Mu variant was identified in Colombia in January 2021 whereas the Lambda variant first emerged in Peru in December 2020. Lambda and Mu variants were designated as a variant of interest on 14th June 2021 and 30th August respectively [7]. These two variants were highly transmissible and resistant to the immune defenses generated by vaccines. But none can spread faster than Delta.

Brazilian variant (B.1.1.28): This variant was detected first in Rio de Janeiro, Brazil. It contains only one notable mutation namely E484K in the S protein. The efficacy of the vaccine and therapeutic performance against this strain is not performed yet.

Double mutant variant: The existence of this variant was first detected in India. The name ‘double mutant ‘ is used as the same virus contains two mutations. The notable mutations of this variant are E484Q and L452R. According to the ICMR virology lab, COVAXIN is 78% effective against this variant.

Triple mutant variant (B.1.618): Triple mutant variant was also found in India. The first case was reported on 20th April 2021. Infections were found mainly in Maharastra, Delhi, West Bengal, and Chhattisgarh. Higher transmissibility of this variant was also characterized. Two of the three mutations show resistance against antibodies.

N440K variant: This variant was first reported in Andhra Pradesh. Mutation in S protein has been found in this variant. This variant contains an enhanced binding to ACE2 receptors. It is resistant to class 3 monoclonal antibodies and 10 to 1000 times more transmissible.

Europe variants: Several variants of SARS-Cov-2 have been found in Europe. Some common examples are discussed here. The 20A.EU2 Variant was reported first in France in June 2020. It is the second dominant variant in Europe. The notable mutations of this variant are S477N, E484K, and N501Y. The 20A/S:439K variant was first found in Ireland. This variant has S:N439K mutation with the deletions of amino acids at positions 69 and 70 of S proteins. For this reason, an increase in ACE2 binding was observed and it was responsible for the resistance to antibodies. The 20A/S:98F variant was predominantly detected in Belgium and Netherlands. This variant contains S:98F mutation. The 20C/S:80Y variant and the 20B/S:626S variant were found in 10 and 15 countries of Europe respectively. The 20C/S:80Y variant has 18 nucleotide mutations and the variant 20B/S:626S has S:626S mutation. The 20B/S:1122L variant was found in Sweden, Norway, and Denmark. This variant contains S:V1122L mutation.

III. COVID-19 DRUGS

At the beginning of COVID-19 pandemic, researchers were not aware of the treatment of novel coronavirus infection. Some existing drugs were recommended based on a few clinical trials. Several types of anti-viral, anti-parasitic, anti-inflammatory, and anti-arthritic drugs are examined for the treatment of COVID-19. Here, the use of few protocol and non-protocol drugs towards COVID-19 treatment in India is discussed.

3.1 Chloroquine and hydroxycloroquine:

Chloroquine (CQ) and hydroxycloroquine (HCQ) are 4-aminoquinoline drugs that were developed in India for the treatment of malaria. These drugs are also useful for the treatment of rheumatoid arthritis, lupus, and porphyria cutanea tarda. In the early stage of COVID-19 pandemic, CQ and HCQ had been put forward for the treatment of the person infected by coronavirus. But, the recent clinical study reveals that the drugs are inefficient for the patients who need care in hospitals. WHO and FDA strongly recommend against the use of CQ and HCQ for the treatment of COVID-19 due to their inefficiency towards coronavirus and several side effects such as diarrhea, loss of appetite, muscle problems, vomiting, seizures, and low vision. The chemical structure of CQ and HCQ is given in Fig.1.

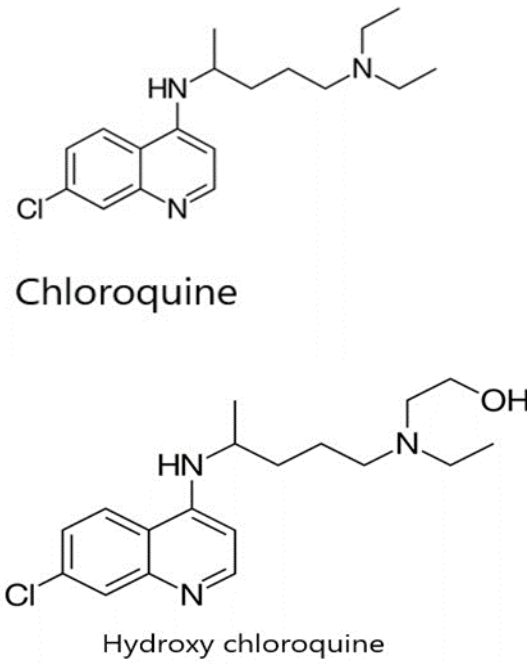

Fig.1: Structure of Choloquine and Hydroxy chloroquine

3.2 Remdesivir:

Remdesivir was originally tested as an antiviral against Ebola and Hepatitis C. It is a carbocyclic ester that has potent antiviral activity against several types of RNA viruses. It is very useful for the treatment of patients infected by SARS CoV-2. Remdesivir is the

first drug that gets approval from the FDA for the treatment of COVID-19. Generally, the drug is injected into a vein and the molecule inserts itself into the gene of coronaviruses. For this reason, the mutation occurs in virus-cell such a way that the viruses lose their ability to replicate. In India, DCGI approved the use of remdesivir as a potential drug for the treatment of suspected or laboratory-confirmed severe COVID-19 patients. In India, remdesivir is available in different brand names such as Remdac (manufactured by Zydus Cadila), Covifor (manufactured by Hetero labs), Cipermi (manufactured by Cipla), and Redyx (manufactured by Reddy's Lab). The chemical structure of remdesivir is given in Fig.2.

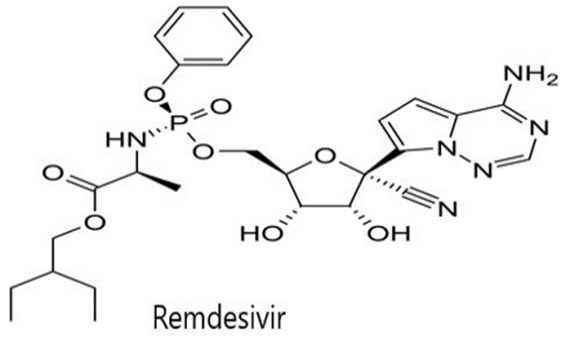

Fig.2: Structure of Remdesivir

3.3 Ivermectin:

Ivermectin is an antiparasitic drug that is generally used to treat intestinal strongyloidiasis and onchocerciasis, two conditions caused by parasitic worms. It can also be used to treat head lice and skin rosacea (Source: U.S. Food and drug administration). Ivermectin is used for the treatment of COVID-19 in different countries including India because it inhibits the replication of SARS-CoV-2 in cell cultures. World Health Organization approves the drug for the treatment of COVID-19 only for clinical studies. Current studies on the use of ivermectin as a potential drug for the treatment of Covid-19 are inconclusive [9]. Ivermectin has common side effects such as headache, dizziness, muscle pain, nausea, or diarrhea. Prolonged use of this drug can cause chest pain, fast heartbeat, confusion, seizures, loss of consciousness, and many other critical side effects.

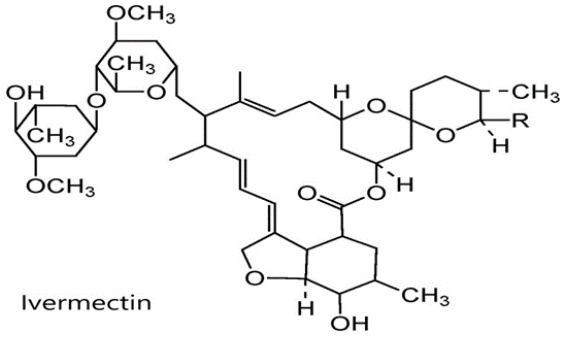

Fig.3: Structure of Ivermectin

3.4 Favipiravir

Favipiravir (6-fluoro-3-hydroxy-2 pyrazinecarboxamide) is an anti-viral agent that can inhibit selectively the RNA-dependent RNA polymerase of RNA viruses [10]. This drug is prescribed for the treatment of mild to moderate covid patients in different countries. Previously, the drug showed its efficacy against Ebola viruses. It was also used in the pandemic influenza in Japan in 2014 [11].

In June 2020, DCGI approved the Favipiravir, the drug developed in Japan for the treatment of influenza, for the treatment of mild to moderate COVID-19 infected patients. In India, Favipiravir is available in different brand names such as Fabiflu (manufactured by Glenmark), FluGuard (manufactured by Sun Pharma), Favivir (manufactured by Hetero Lab), etc.

Fig4: Structure of Favipiravir

3.5 Methylprednisolone:

Methylprednisolone is on the list of WHO's essential medicine for its efficacy against lymphoid leukemia. It was first synthesized by 'The Upjohn Company' (now Pfizer) and FDA approved the drug in the U.S. in 1957 [12]. Clinical trials report that the medicine can reduce overall mortality and severity of

symptoms of COVID-19 patients. Indian doctors frequently use this medicine for mild to moderate COVID-19 infected patients. It is supported by a large trial and is a cost-effective drug.

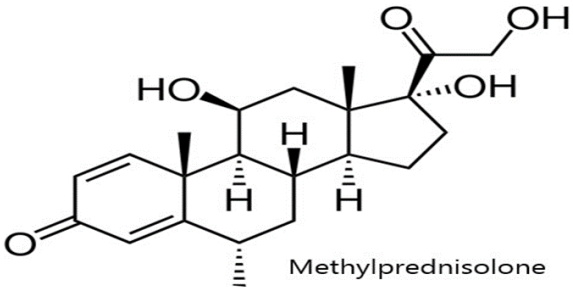

Fig.5: Structure of Methylprednisolone

3.6 Dexamethsone:

Dexamethasone is an anti-inflammatory and immunosuppressant corticosteroid drug. This drug was clinically tested for critically ill COVID-19 patients in the U.K. and was found to have benefits for critically ill patients [13]. This drug is also recommended in India for patients with severe or critical COVID-19. This corticosteroid drugs treatment reduces mortality by one-third for patients on ventilators, and for patients requiring only oxygen, mortality was reduced by about one-fifth. Some common side effects of this drug are headache, vomiting, dizziness, insomnia, depression, stomach irritation, anxiety, etc.

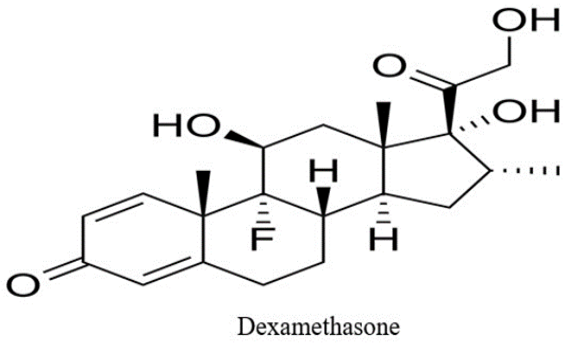

Fig.6: Structure of Dexamethasone

3.7 Tocilizumab

Tocilizumab is a monoclonal antibody. The molecular formula of the drug is [$C_{6428}H_{9976}N_{1720}O_{2018}S_{42}$]. A clinical study revealed that the use of tocilizumab for patient with severe COVID-19 pneumonia was quite beneficial. COVID-19 is associated with immune dysregulation and hyperinflammation, including elevated interleukin-6 levels [14]. This monoclonal antibody acts against the interleukin-6 receptor and has resulted in better outcomes in patients with severe Covid-19 pneumonia.

3.8 Apixaban

The results of the study led researchers to conclude that apixaban was safe and effective in ICU patients with severe COVID-19 disease, and these data encourage future trials that explore the possibility of enhancing anticoagulation strategies in severe COVID-19 patients [15].

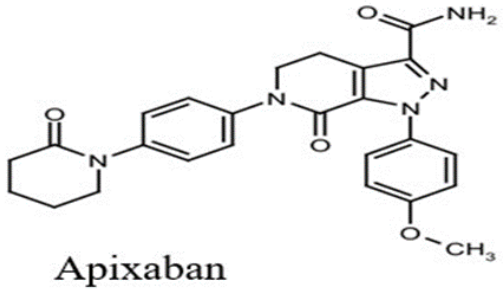

Fig.7: Structure of Apixaban

3.9 Enoxaparin

Enoxaparin is an anticoagulant medication and it is useful for the prevention of blood clots. It is used to treat and prevent deep vein thrombosis and pulmonary embolism. This medication is also used for the treatment of COVID-19 patients. It prevents COVID-19 infection by decreasing virus cell entry and hence viral load [16]. Prevention of activation of the coagulation cascade, venous thromboembolism, and thrombosis of small and middle-size vessels leading to lung failure are the beneficial aspects of enoxaparin.

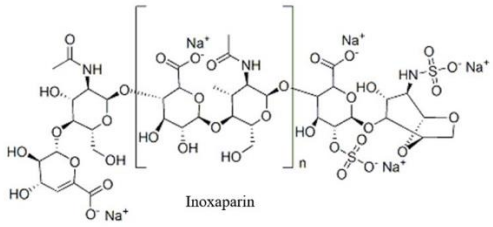

Fig.8: Structure of Enoxaparin

3.10 Amphotericin B

Amphotericin B is a polyene group compound that has in *vitro* and *in vivo* antimicrobial activity against fungi

and parasites. It is an effective anti-fungi drug for the treatment of novel therapeutic options to treat COVID-19. Amphotericin B is recommended for the treatment of COVID-19 as it can alter the structure of the viral envelope, membrane integrity of cells, and internal cellular organelles [17].

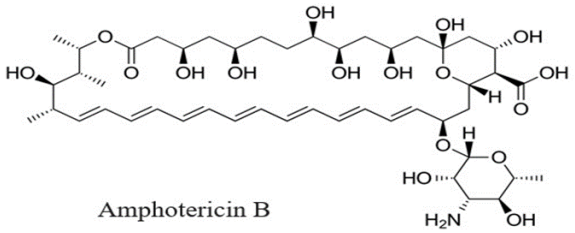

Fig.9: Structure of Amphotericin B

CONCLUSION

Most countries of the world including India, the United Kingdom, the USA, Russia, and Brazil are still affected by COVID-19 infection. Vaccination, social distancing, and the use of face masks can't stop the spreading of coronavirus infection. Mutation of viruses results in a more contagious strain which is making the pandemic far longer. For this reason, the prevention and treatment of COVID-19 patients using several existing and newly synthesized drugs are duly examined. A large number of clinical trials are going on using various anti-viral, anti-parasitic, anti-inflammatory, and anti-arthritic drugs. In this paper, the usefulness of various protocol and non-protocol drugs, those are used in the treatment of COVID-19 infected patients, has been discussed. At the beginning of the pandemic, CQ and HCQ were recommended for the treatment of COVID-19, but they became ineffective after a long clinical trial. WHO and FDA strongly recommended against the use of CQ and HCQ for any kind of COVID-19 infections. Remdesivir was the first approved drug for the treatment of COVID-19. It is a very efficient drug for COVID-19 infection. This drug is authorized to treat even non-hospitalized patients. Apixaban, enoxaparin, dexamethasone, and tocilizumab drugs are recommended only for severe COVID-19 patients. Favipiravir is also a useful drug for the treatment of mild to moderate COVID-19 patients.

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