TUTORIAL REVIEW ARTICLE

A Systematic Review of the Efficacy and Safety of Favipiravir (Avigan) for the Treatment of Novel COVID-19 Infections

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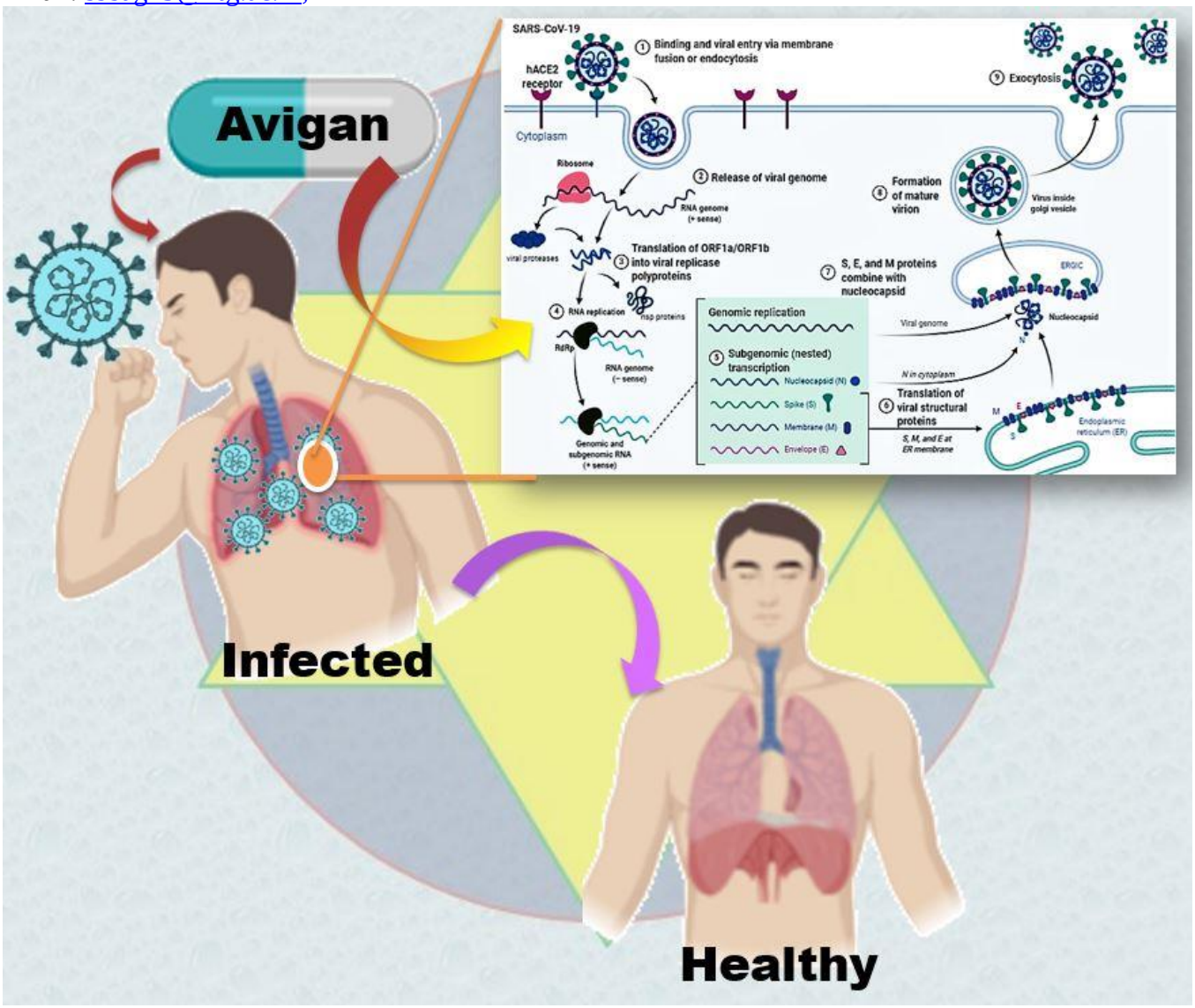

Abstract

The first SARS-CoV-19 infection was detected in the Wuhan city, Hubei province, in China around December 2019. Since then, the world has seen death dance due to the pandemic caused by the spreading of SARS-CoV-19 infections. Unlike SARS-CoV and MERS-CoV, SARS-CoV-2 infects humans and causes the severe acute respiratory syndrome. The spread of infection has caused disease in over 8.1 million people across the globe. However, more than 439 thousand deaths are reported as on 16th June 2020. As a result, the pandemic has put the health care system across the world under grave challenges. The added disadvantage is the stress and unavailability of drugs/vaccines or therapeutics to treat the infection. Presently countries across the globe are trying to stop the spread of the virus by initiating lockdowns and also providing supportive care to patients through supplemental oxygen and mechanical ventilation. Scientists worldwide are engaged in research to understand SARS-CoV-2 pathogenicity and to obtain a rapid solution of the pandemic, with utmost sincerity. Recently with the revelation of SARS-CoV-2 genetic makeup, it has been possible to compare the genome structure of SERS-CoV and MERS-CoV with its mutated neighbor. This study helped scientists to locate potential drug targets in SARS-CoV-2, which are SARS-CoV-2 main protease 3CL^{pro}, papin like protease PL^{pro} and CoV-2 RNA dependent RNA polymerase (RdRp). These drug targets have opened up the window for screening and selecting the existing potential antiviral drugs as a process of drug repurposing.

One such drug is Favipiravir marketed under the brand name Avigan by Fujifilm, Japan. Avigan is an RdRp inhibitor and reported to target the SARS-CoV-2 RdRp and therefore inhibit the viral replication. Recently in the month of April, Fujifilm has initiated the phase-II clinical trial of Avigan against CoV-2 infections in collaboration with Japanese hospitals,Brigham and Women's Hospital, Massachusetts General Hospital, and the University of Massachusetts Medical School. Therefore, at this crucial time, the scientific community must come up with adequate and detailed understanding regarding the interaction of Avigan with CoV-2 as well as the patients infected with the virus. Hence we decided to write this review to focus on a thorough and in-depth knowledge of the mechanistic role of Avigan in interacting with RdRp of CoV-2. We also focus on the pharmacokinetic characteristics of Avigan and potential drug-drug interaction. We believe this review would attract the attention of the scientific community for further development of new drug therapeutics for COVID-19.

1. Introduction

The pandemic caused by infections of bacteria and viruses is not new to the world. Some of the first reported pandemics were Black Death, Cholera, and Flu. All these pandemics were due to bacterial infections. However, the first viral pandemic was reported in 1901 due to the spread of Yellow Fever. [1] In those days, the condition was more threatening and severe due to a lack of sufficient knowledge of the pathogenicity and unavailability of drugs. However, the lack of understanding spurred the initiation of extensive research in disease biology and chemistry. With time the wheel of fortune shined upon the world population and the mid 20th century witnessed the advent and discovery of antibiotics, vaccines, and other anti-infection drugs to treat infections.[2]Similarly, antiviral drugs that were discovered became the front liners to fight viral diseases. However, slowly with the advent of time and excessive use of antibiotics and antiviral drugs, the pathogens started to mutate and become resistant. As a result, since the starting of the 21st century, the world population began to acquire infection from unknown and novel viruses and bacteria, against which effective drugs and vaccines are yet to discover.

The first pandemic in the 21st century was due to the infection by an unknown virus SARS-CoV belonging to the family of corovaviridae. In November 2002, the first case of human disease leading to Severe Acute Respiratory Syndrome (SARS) was detected in Foshan, China.[3]Immediately the infection started to spread in the community. New cases began to emerge by February 2003 in mainland China, and around one-third of the health care workers acquired infections. Slowly the spread of disease was reported across the continent. Till any impairment on travel was declared, many infected individuals traveled cross country, and therefore the outbreak was reported in Canada, Vietnam, and several other countries.[4-5] One month later, in March 2003, a laboratory cluster was set up by WHO to collaborate to identify and study the SARS causative virus. By April 2003, the world came to know about the existence of novel SARS-CoV. However, fortunately, the pandemic lasted until July 2003. But even in this duration of 8 months, the virus infected 8096 individuals, and 447 deaths were reported across 27 countries.[6] Further, there are no reports related to human infections by SARS-CoV. However, zoonotic transmission was reported around December 2003-January2004.[7]

A decade passed since the outbreak of SARS-CoV. There were no new cases until April 2012. An individual in Saudi Arabia was admitted to hospital with acute pneumonia, and later on, the person died within a few days due to excessive respiratory illness and renal failure. A novel coronavirus with the capacity to cause severe respiratory disease was detected and isolated from clinical pathology tests with the sputum collected from the patient. The virus was named Middle East Respiratory Syndrome (MERS)-CoV. Immediately after this, an outbreak in a city hospital of Jordan, Saudi Arabia, was reported. Several cases with patients suffering from severe respiratory illness were diagnosed with MERS-CoV infection. Since then, the disease again started spreading across the borders of the Arabian Peninsula, mainly due to traveling. In September 2012, three cases were reported in the U.K.[8]

Interestingly MERS outbreak has often reported being transmitted nosocomially. In 2015 such an outbreak was reported. An individual traveled from the Middle East to South Korea and got admitted to the hospital with severe illness. From this individual, a nosocomial outbreak was initiated, and it was

reported that 16 hospitals got affected and infections counted to 186 patients.[9] Like SARS-CoV, MERS-CoV has not got eradicated, and also, they have not changed host specificity. However, cases from MERS-CoV are following a restrictive and low profile. Till today 2494 evidence has been reported with 858 death cases across 27 countries [https://www.who.int/emergencies/mers-cov/en/].

The end of 2019 again initiated a third pandemic related to SARS. Towards the end of November 2019, a 55-year-old individual from the Hubei province in China is believed to be the first person to get infected by the novel CoV-2 virus. The case was recorded on 17th November 2019. Following this case, every day henceforth, 1 to 5 individuals were reported to get infected. By 15th December a total of 27 cases were reported, and within 5 days, i.e., by 20th December, over 50 were reported. On December 27thDr.Zhang Jixian, head of the department Respiratory disease, at the Hubei Provincial Hospital officially reported 180 cases of infections to the Chinese government [https://www.livescience.com/first-case-coronavirus-found.html]. On 31st December 2019 Chinese government reported to the WHO country office about the infections from pneumonia of unknown origin. Samples from infected patients were collected and subjected to analysis. The Chinese researchers identified a novel coronavirus (nCoV-19) and reported the same on 7th January 2020. Detailed laboratory testing and analysis ruled out the risk of infection from other respiratory pathogens like influenza, avian influenza, adenovirus, SARS-CoV, and MERS-CoV [https://www.who.int/csr/don/12-january-2020-novel-coronavirus-china/en/]. The National Health Commission of China on 12th January 2020 gave more details regarding the pandemic situation. They provided the world scientific community with the genetic sequence of the isolated novel CoV-2 virus. They also cleared their stand regarding the origin of the pandemic. It was expected that the individuals initially infected by the virus had visited the seafood market hosted in Wuhan. This particular market is known to sell live animals, and the individuals might have come in close contact with infected animals or birds, which they have bought as food. Later on, further investigations suggested that there were few such cases where no connection with the seafood market was established. This observation opened up a new avenue of possible human to the human transmission without the aid of any animal vector.

Interestingly henceforth, the further spread of infections across the world is a result of human to human interaction. The transmission is known to occur via aerosols formed from the cough and sneeze of infected persons. These aerosols are known to infect persons in close proximity of the infected persons through inhalation.[10-13] On 11th February 2020, the SARS-CoV-2 infection was announced as a pandemic and the disease termed as COVID-19 by WHO. COVID-19 has grasped almost the entire world population. The cases of infections are following an exponential growth pattern. Even today, as we are writing this review, the virus has caused disease over 8.1 million people, with more than 439 thousand deaths. As a result, the pandemic has put the health care system across the world under grave challenges and stress. Unavailability of drugs/vaccines or therapeutics to treat the infection is an added disadvantage. Presently countries across the globe are trying to stop the spread of the virus by initiating lockdowns and also providing supportive care to patients through supplemental oxygen and mechanical ventilation. To obtain a rapid solution, scientists worldwide are conducting research to understand SARS-CoV-2

pathogenicity with utmost importance. Recently with the revelation of SARS-CoV-2 genetic makeup, it has been possible to compare the genome structure of SERS-CoV and MERS-CoV with its mutated neighbor. This study helped scientists to locate potential drug targets in SARS-CoV-2. The potential drug targets that have been detected, which are SARS-CoV-2 main protease $3CL^{pro}$, papin like protease PL^{pro} and CoV-2 RNA dependent RNA polymerase (RdRp). Hence, the detection of these drug targets opened up the window for screening and selecting potential antiviral drugs that can be repurposed.

In the present situation, when research related to drug discovery against nCoV-2 is getting accelerated, the most suitable alternative is to start repurposing of available antiviral drugs. The endocytic entry of SARS-CoV-2 into host cells is facilitated by the Angiotensin-converting enzyme 2 receptor (ACE2) and the transmembrane protease serine 2 (TMPRSS2). Recently recombinant human ACE2 has been synthesized and found to reduce the viral entry into the host cells by acting as decoys for virus bindings.[14] Therefore clinical trials involving the application of APN01 for COVID-19 patients are approved or financially supported. Similarly, in other studies, TMPRSS2 inhibitors like camostat[15]have shown promising results and have been approved in Japan for clinical treatment of acute pancreatitis. The use of camostat as a potent inhibitor for nCoV-2 entry is under clinical study and supported by the government bodies of many countries like the Netherlands and Germany. After attaching onto the cell receptor, the virus uses the endolysosomal pathway to gain access into the host cell before initiation of the envelop uncoating. At this stage, two commonly used anti-malarial drugs such as Chloroquine (CQ) and Hydroxycholoroquinine (HCQ) are known to interrupt autophagosome-lysosome fusion. These drugs were successfully applied for treating SARS-CovV-2 infections.[16-17] Recently another commonly used antibiotic, known to block autophagosomal clearance in human cells, is Azithromycin (AZ).[18] Previously this drug was found to be active in treating infections from Zika and influenza virus.[19]

Presently, the clinical trials show that a combination of both HCQ and AZ portrays excellent results. However, these studies faced immense criticism due to the post hoc removal of patient subjects from the study analyses. Moreover, it was found that the use of both HCQ and AZ can lead to fatal arrhythmia as an outcome of cardiac toxicity.[20] In the following events of post uncoating, the viral RNA finds its role in cap-dependent translation. As a result, two polypeptides are formed, which are processed autoproteolytically to produce vital proteins like helicase, RdRp, and proteases. At a glance, the proteases are definitely thought to be the prominent drug targets, because several anti proteases have shown to be effective in treating HIV and other viral infections. However, in the case of COVID-19, the effect of these drugs did not prove beneficial. A combination of HIV protease inhibitors lopinavir and ritonavir was found ineffective against SARS-CoV-2.[21] Previously during SARS-CoV-1 infections, protease inhibitors failed to show any promising results; hence repurposing with these drugs did not attract the interests of many governmental and scientific bodies.

Helicase and RdRp protein complexes are involved in viral genomic replication and production of sub-genomic RNAs, which get translated eventually to form viral coat and structural proteins. Therefore, they serve as a primary drug target for ages. Helicase of nCoV-19 is found to be different from other viruses. Also, available herpes virus helicase

inhibitors like amenamevir or pretelivir did not show any reported efficacy.[20] The only option that is left is to inhibit the function of RdRp. Recently the crystal structure of SARS-CoV-2 RdRp has been reported. Hence it makes an increased possibility for targeting the RDRp. RdRp is involved in viral replication and translation activities and thereby maintains the viral life cycle. For this reason, many anti RdRp drug candidates have been developed and approved overtime. Two such promising drug candidates are favipiravir and remdesivir. Remdesivir was developed to treat infections related to the Ebola virus. During the clinical trials, these drugs have been reported to be safe. Again research on remdesivir was conducted during the spread of SARS-CoV-1 and MERS-CoV infections, and it was reported to be active against this virus in animal model systems.[20] Recently, in-vitro human cell studies reported that both remdesivir and favipiravir effectively stop the replication of SARS-CoV-2.[22] Favipiravir marketed under the brand name Avigan by Fujifilm and was developed in Japan. Avigan got the approval in 2014 to treat critical influenza virus infections and influenza-related viral pandemic outbreaks. Recently in April 2020, Fujifilm has initiated the phase-II clinical trial of Avigan against nCoV-2 infections. The trial is collaborated with Brigham and Women's Hospital, Massachusetts General Hospital, and the University of Massachusetts Medical School. Apart from this, favipiravir is also involved in many other clinical trials. The informal data that is coming out from these studies suggest that favipiravir holds a prominent possibility to cope up as a cure for COVID-19 disease.

Hence through this review, we decided to focus on the pathogenicity of SARS-CoV-2 and how Avigan can interfere to stop the viral replication. A detailed and in-depth discussion of the mechanistic role of Avigan in interacting with RdRp of CoV-2 is provided in this review. We also focus on the pharmacokinetic role of Avigan and its interaction with other drugs. We believe this review would attract the attention of the scientific community, and the information that is presented would definitely be of help in the undergoing trial and clinical studies.

2. SARS-CoV-2 Pathogenicity

Coronaviruses (CoVs) are the only identified virus having the longest RNA. They belong to the coronavridae family of Nidoviriles order. These viruses have +ve sense RNA and protected by an outer envelope.[23-25] The uniqueness of these viruses is the presence of Spiked glycoproteins (S) on their outer surface, thus verifying the origin of their name 'corona'. Coronavirus varies between a cellular dimension of 65-125 nm in diameter with its genomic material ranging between 26 to 32kbs in length.[23] A generalized diagram is shown in Figure 1. Coronavirus are divided into 4 different genera types identified as α, β, δ, and γ virus. The β coronavirus is further divided into 4 groups A, B, C and D. There are seven coronaviruses that can target human cells as their hosts. Amongst these viruses, HCoV-229E and HCoV-NL63 causes, mild influenza type infection belongs to the α genera. Viruses belonging to β coronavirus lineage A are HCoV-OC43 and HCoV-HKU1. While the virus, which caused a pandemic in 2002, the SARS-CoV, and the present SARS-CoV-2 belong to the β coronavirus lineage B, the 2012 pandemic causing virus MERS-CoV belongs to the β-coronaviruses lineage C.[26]

We decided to perform a homology study and generate a phylogenetic tree based on the genomic similarity of the known CoVs. This study would help us identify the closest relative of SARS-CoV-2 and could theoretically predict its lineage of mutation

and also predict the possible origin source. The study was performed based on the genetic sequences present in the NCBI (25 species of CoVs were tested) database. The genomic homology study was performed through the BLAST technique.[23] The phylogenetic analysis was performed using Clustal Omega [23], and the study is represented in **Figure 1**.

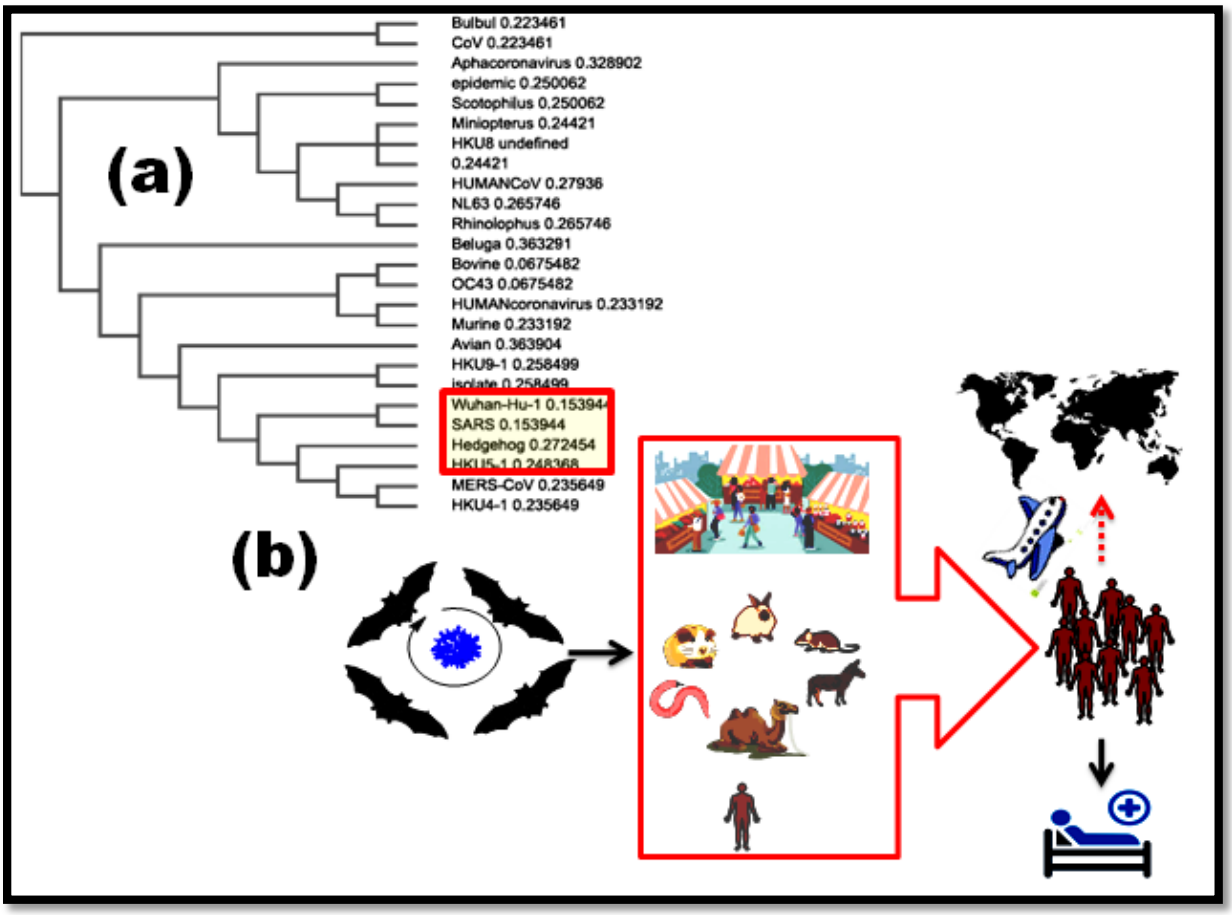

Figure 1. (a) The study was performed with the help of the genetic sequences present in NCBI (25 species of CoVs were tested) database, and the genomic homology study was performed through BLAST technique.[23] The phylogenetic analysis was performed using Clustal Omega.[23] It has been observed that the closest species to SARS-CoV-2 is the SARS-COV-1 followed by Hedgehog coronavirus 1 and Pi-bat coronavirus HKU5. This study supports the assumption that hedgehog and bats are the primary zoonotic carriers of nCoV-19. Interestingly, both of these animals were sold in the animal and seafood markets of Wuhan during the spread of the virus. (b) The pictorial diagram shows the possible route of viral transmission resulting in a pandemic situation worldwide.

It was found out that the closest species to SARS-CoV-2 is the SARS-COV-1 followed by Hedgehog coronavirus 1 and Pi-bat coronavirus HKU5. This study supports the assumption that hedgehog and bats are the primary zoonotic carriers of nCoV-19. Interestingly, both of these animals were sold in the animal and seafood markets of Wuhan

during the spread of the virus.[27] Studying the relativity of SARS-CoV-2 enabled us to understand the steps followed during the infection cycle of the nCoV-19. SARS-CoV-2 gains entry into the host cell through endocytosis. The interaction of Spiked glycoprotein presents on the outer surface of the virus with hACE2 receptors and TMPRSS2 receptors initiates the entry process. The S protein is composed of two subunits S1 and S2. The receptor-binding protein (RBD) of the S1 subunit binds to the hACE2 and is found to show 10-20 times higher binding affinity than SARS-CoV. After that, the RBD of the S1 subunit establishes hooking with hACE2, and the S2 subunit initiates contact between the heptad repeat 1 (HR1) and heptad repeat 2 (HR2) domains. As a result, a six-helix binding (6-HB) fusion core is formed that enables bridging the gap between the virion and host cell surface, thus implementing infection and transfusion. After getting entry into the host cell, the virionuncoats the envelop and releases the genomic RNA (gRNA). Initially, the gRNA undergoes immediate cap-dependent translation to form two polypeptides, which again is acted by an autoproteolytic mechanism to form vital viral proteins like the RdRp, $3CL^{pro}$ main protease and papin like protease PL^{pro}.[28]

The gRNA of SARS-CoV-2 is +ve ssRNA with a 5′-cap structure and a 3′-poly A tail. The gRNA is 30 kb in length and is the longest viral RNA known till now. The gRNA undergoes replication and translation by the interference of replication-transcription complex (RTCs) anchored in double-membrane vesicles. In the process, the open reading frames (ORFs) act as templates to form the sub-genomic mRNAs, and hence translation is carried out. The transcription regulatory sequences present within the ORFs initiates the termination. In general, the coronavirus genome comprises at least six ORFs. Similarly, in SARS-CoV-2, the frameshift between ORF1a and ORF1b produces two polypeptides pp1a and pp1ab. Both these polypeptides undergo proteolytic activity by the action of chymotrypsin, like main protease $3CL^{pro}$ and one or two papin like protease.[29] As a result, 16 non-structural proteins (nsp) are produced. These nsps play a crucial role in locking the host innate immune response.[30] Apart from the ORF1a and ORF1b, other ORFs also plays a vital role in the encoding of structural proteins, spiked proteins, envelop, membrane, and nucleocapsid proteins. Once the translation is successful, and all the said viral proteins are produced, the viral proteins and gRNA get assembled in the endoplasmic reticulum and Golgi apparatus of the host cells. Following these, the virion is transported out of the host cell in vesicles via exocytosis.[23]

The pathogenesis that produces respiratory illness and acute pneumonia is yet to be discovered and studied in detail. However, from the already established and accomplished studies, it is indicated that the viral proteins and nsps are capable of calling excessive immune response in the host. Often these types of responses are termed as 'cytokine storm'. The primary antibody causing the storm is interleukin 6 (IL-6). The IL-6 is known to generate a pro-inflammatory mechanism acting on a large number of tissues and cells, often resulting in tissue damage. IL-6 is often detected during the cytokine release syndrome (CRS), which is associated with acute inflammatory syndrome resulting in acute fever and multi-organ dysfunction.[23] A detailed understanding of the SARS-CoV-2 genome, host cell infection, and pathogenic lifecycle is presented in **Figure 2**.

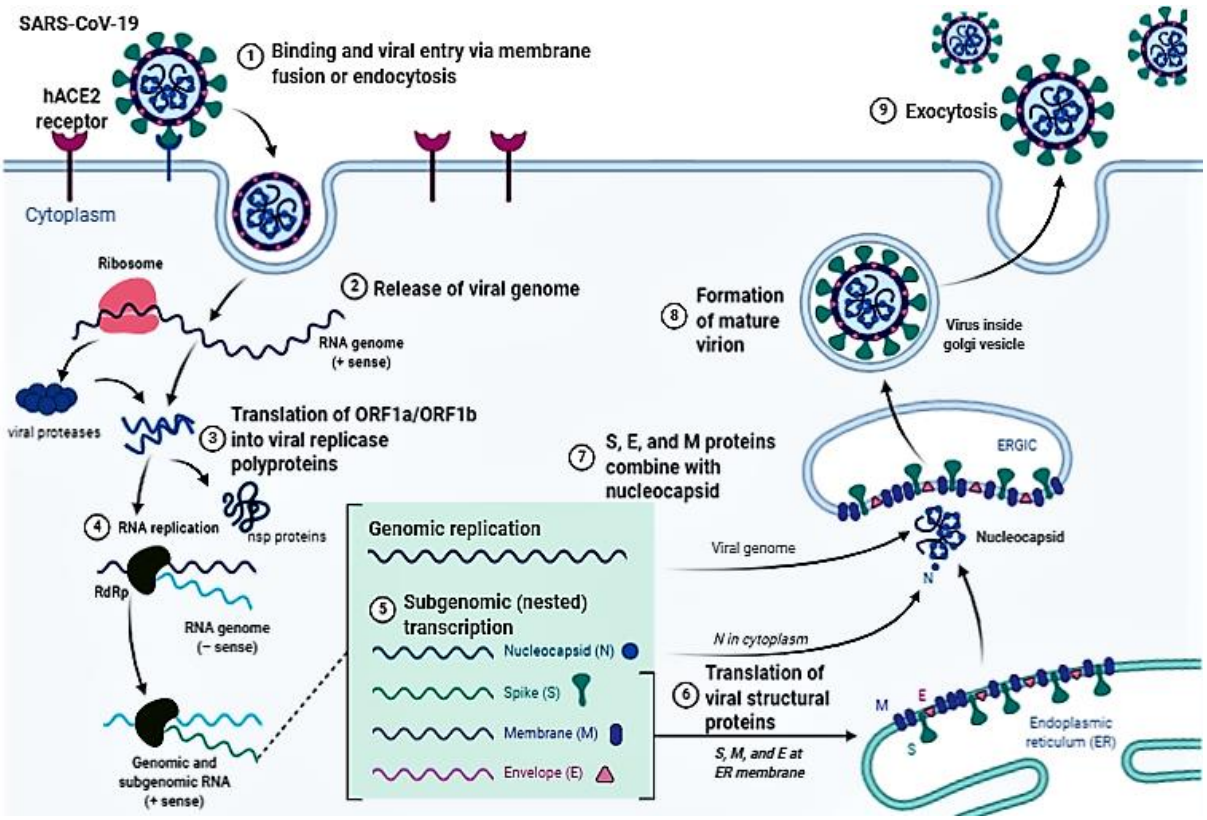

Figure 2. The S glycoprotein of nCoV-19 interacts with the *hACE2* receptors and gains cellular entry. Following the entry, the release of viral gRNA takes place. The ribosome acts on the gRNA. The 43S and eIF4F interact to form a pre-initiation complex and binds to the 5′ end of the capped genome. Following this, the 43S starts scanning the 5′ UTR. The protein synthesis begins with 80S ribosomal subunit binding to the translation initiation codon. The synthesis proceeds until the ribosome encounters the first termination codon and gets dissociated from the template leading to the formation of polyprotein (pp) 1a encoded by ORF1a. Similarly, the synthesis of pp1a/b encoded by ORF1a and ORF1b occurs by a frameshifting before the stop codon is reached. The point of frameshift is located at the overlap region between ORF1a and ORF1b. These two replicase polyproteins encoded by ORF1a and ORF1b undergo proteolytic activity by the ORF1a-encoded viral proteases. As a result, the mature 16 nsps are formed. These nsps (except nsp1 and nsp2) play a crucial role in transcription and replication of nCoV-19 gRNA. Apart from the ORF1a and ORF1b, other ORFs also play a vital role in the encoding of structural proteins, spiked proteins, envelop, membrane, and nucleocapsid proteins. Once the translation is successful, and all the said viral proteins are produced, assembled with the gRNA in the endoplasmic reticulum and Golgi apparatus of the host cells. Following these, the viron is transported out of the host cell in vesicles via exocytosis.

3. Favipiravir in Treatment of SARS-CoV-2

The first discovery of Favipiravir was from the necessity of a drug that can cure influenza infections and can also be used to tackle the outbreak of influenza pandemics. Research Laboratories of Toyama Chemicals Co., Ltd at Japan initiated the research by screening various influenza viruses. Favipiravir was expected to target and inhibit the activity of viral RdRp, thereby preventing replication and translation of the viral genomic RNA. As a result, viral replication and proliferation would be stopped. Just as expectation Favipiravir turned out to be a

promising RdRp inhibitor and is found to inhibit RdRp activity of a broad spectrum virus like arena-, bunya-, flavi- and filoviruses causing hemorrhagic fever.[31]Favipiravir played a miraculous role during the 2012 outbreak of the Ebola pandemic in West Africa. From the data of clinical trial set up at Guinea, we could see that the Ebola-infected patients treated with Favipiravir showed chances of higher survival.[32] A detailed study of the Ebola pandemic showed another fascinating finding. The patients who were under the recommended supportive technology by WHO, took more time to recover, and also the rate of survivability was less in comparison to patients who were receiving the additional supplements of Favipiravir.[33] We now came to know that the RdRp of SARS-CoV-2 has shown a genomic similarity to the RdRp of SARS-CoV-1 and MERS-CoV. It is also well known that Favipiravir showed excellent results in the treatment of SARS-CoV and MERS-CoV. Therefore, this drug is given a green signal to be repurposed in case of the nCoV-19 infection.

The generalized mechanism underlying the action of Favipiravir (T-705) is through inhibition of viral genome replication by blocking the activity of RdRp. Favipiravir is a purine nucleic acid analog. An experiment was conducted to investigate the behaviour of Favipiravir in the presence of purine and pyrimidine nucleosides. It was shown that the Favipiravir exhibited a competitive behavior with purine bases rather than pyrimidine nucleosides.[34] Another study was conducted to realize the fate of Favipiravir once consumed. The Madin Darby Canine Kindney cells (MDCK) were infected with the influenza virus and then treated with Favipiravir. The cellular metabolites were isolated using HPLC. The obtained products were characterized as the phosphorylated and ribosylated derivatives of Favipiravir (T-705). Thus, Favipiravir ribofuranosyl-5B-triphosphate (Favipiravir-RTP), Favipiravir ribofuranose (Favipiravir-R) and Favipiravir ribofuranosyl-5B-monophosphate (Favipiravir-RMP) were analysed (**Figure 3**).[34] Hence, from this observation, it was understood that upon cellular uptake, the Favipiravir is converted into its active form. All the reported derivatives were synthesized chemically and were also tested to find their efficacy against viral RdRp. Thus, it was observed that Favirapir-RTP is the most active form and showed a complete arrest of RdRp activity at a concentration of 10 µmol/L. In contrast, Favipiravir and Favipiravir-RMP did not show activity even at 100 µmol/L.[2]

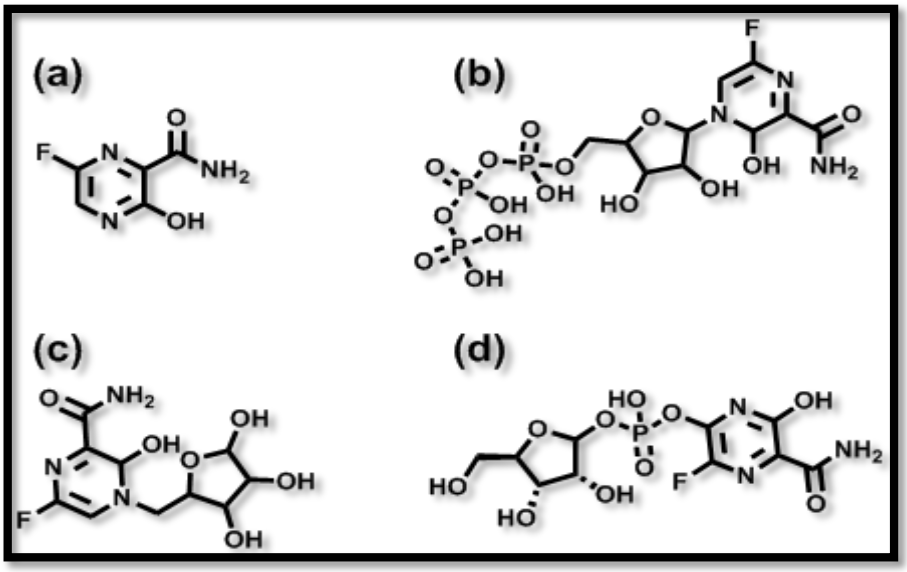

Figure 3. (a) Favipiravir (6-fluoro-3-hydroxy-2-pyrazinecarboxamide); some of its activated substituent are presented (b) Favipiravir-RTP ((5-(3-carbamoyl-5-fluoro-2-hydroxypyrazin-1(2H)-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyltetrahydrogen triphosphate) (c) Favipiravir-R (6-fluoro-3-hydroxy-4-((3,4,5-trihydroxytetrahydrofuran-2-yl)methyl)-3,4-dihydropyrazine-2-carboxamide) (d) Favipiravir-RMP (6-fluoro-3-hydroxy-2-pyrazinecarboxamide ribofuranosyl-5B-monophosphate).

Avigan being one of the most important drugs discovered by Japan, we thought to review the recent developments and updates in Japan. The press conference bulletin published in the website of Ministry of Health, Labour and Welfare, Japan [https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/newpage_00032.html] on 6th June 2020 regarding Japan's COVID-19 Response stated the timeline of COVID cases and preparedness of Japan government. The press meet was addressed by Dr. Shigeru Omi, Chairman of Covid-19 advisory committee on basic action policies and regional director of WHO. The first case of Covid-19 in Japan dated back to January 16th 2020. The first wave was borne from China. Subsequently the first case of infection where no international/travel connection was found was reported on 28th January 2020. In the month of February, the expert panel alerts the Japanese citizens regarding the potentiality of the unknown pandemic. The health department immediately initiated "Development of Clinical Remediation" (Health and Labour Sciences Research Grant) under the leadership of Dr. N. Ohmagari, Director, Disease Control and Prevention Center, National Center for Global Health and Medicine. Under this initiative three projects were started. On February 22nd 2020, Observational Studies: Avigan ® (favipiravir), Kaletra® (lopinavir /ritonavir), Veklury® (remdesivir) was commissioned. Following this, Global Joint Investigator Initiated Clinical Trial: Veklury® (remdesivir) was initiated on 23rd march 2020 and as a result, the use of Remdesivir was approved on March 7th 2020. The third clinical trial on Alvesco ® (ciclesonid) was undertaken on March 27th 2020. In the month of March another project was announced and initiated, "Clinical Development of Favipiravir" Research Group (AMED commission research expenses). Under this project one specified clinical trial with Avigan was set up on 2nd March 2020. Another observational study with Alvesco ® (ciclesonid) was initiated on 16th March 2020 followed by Futhan ®

nafamostat) in 1st of April 2020. Amidst these initiatives and future policies, the Japan Government declared state emergency followed by National emergency on 16th April 2020. In the bulletin, a very interesting observation was shared. It was mentioned that the cases of COVID-19 infection in Japan is found to be comparatively less. The reason that the government has stated was that (i) easy access to medical facilities under the national health insurance system, (ii) Excellent and high quality medical care even in rural areas supported by the local public health care centers (hokenjo), (iii) Excessive cleanliness and hygiene maintained by Japanese citizens, (iv) Early detection of community transmission and prevention through clustering of infected individuals.

Since April we have been following closely any relative updates from the clinical trials in Japan especially the promising drug candidate Avigan. Suddenly news of uncertain efficacy of Favipiravir based on interim results was reported by some government officials as mentioned on 20th May 2020 by The Japan Times [https://www.japantimes.co.jp/news/2020/05/20/national/science-health/avigan-coronavirus-results/#.Xt3xpjozbIU]. However, on 21st May 2020 Dr.YoheiDoi who is the Principle Scientist leading the Japan government sponsored clinical trial of Avigan on COVID-19 patients at Fujita Health University said in an interview with The Japan Times that the interim results are mainly useful to understand whether the efficiency of the drug is better than expected. He has mentioned that it is too early to comment about the efficacy of Favipiravir and is also against the negative results about the interim experiments. He also mentioned that recruitment of patients for trial is undergoing and there is no pause in the trial as of now. The final results of the trial are expected to be around June 2020. An official from the Fujifilm also said to The Japan Times that they are continuing with two clinical trials one in Japan which is likely to be concluded by June 2020 and another is conducted in USA which will extent to December 2020 [https://www.japantimes.co.jp/news/2020/05/21/business/coronavirus-trial-avigan/#.Xt3wwzozbIU]. Soon after this from a news published in The Japan Times on 22nd May 2020 we come to know that Fujifilm has started increasing the production of Avigan from April as per government's request. They are also planning to send the drug to 2 million COVID-19 infected patients worldwide by 2021 [https://www.japantimes.co.jp/news/2020/05/22/business/fujifilm-plans-make-flu-drug-avigan-available-2-million-people-march-2021/#.Xt3qdTozbIU]. Recent news from Nikkei Asian Review on 6th June 2020 stated that the clinical trial with Avigan will most likely to be extended to July. The recent development is based on the fact that with decrease in cases of COVID-19 in Japan, not enough patient volunteers for clinical trial is found at present. Only 70% of the total proposed trial strength is reached. Japan's health ministry is ready to approve Avigan as soon as the trial gets completed and sufficient evidence is obtained [https://asia.nikkei.com/Business/Pharmaceuticals/Avigan-trial-to-stretch-beyond-June-as-Japan-s-coronavirus-cases-plunge]. Also after the trial is completed post medication conditions of patients has to be monitored closely for 28 days. On 6th June 2020 news from Arab emirates published in Arab News stated the comments of Health minister of Kuwait. The report mentioned that the first batch of Japanese medicine Avigan has proved to be effective in treating COVID-19 infected patients in their clinical trial. Dr Abdullah Al Badr of Kuwait's health ministry has stated that Japan Government is sending them shipments of Avigan on humanitarian grounds

[https://www.arabnews.com/node/1685651/middle-east].

The mechanism of interaction of Favipiravir-RTP (T-705-RTP) with viral RdRp is still a subject of study. However, from the experimental data that is present until now, an established hypothesis can be constructed. Favipiravir is believed to work as a result of either misincorporation in a nascent viral RNA or as a strong binder of conserved polymerase domains, thus, preventing the inclusion of nucleotides for carrying out viral replication and transcription. Another school of thought advocates that the interaction of Favipiravir might induce lethal mutagenesis. A study reported that the administration of Favipiravir led to a reduction in viral titer for both the low multiplicity of 0.0001 PFU/cell and the higher multiplicity of 10 PFU/cell. The genomic isolation was carried out, and the sequence analysis of various nucleoprotein (NP) clones suggested an increase in the number of transition mutations between G-A, C-T, and C-U. Also, it was found that the rate of mutations increased abruptly, along with an associated shift in the nucleotide profiles.[35-36]However, in these studies, no reports of Favipiravir resistance were ever found.[35-37] Therefore these studies suggest that Favipiravir implements virucidal effect through lethal mutagenesis and have the capability to block RdRp activity of a broad spectrum of viruses. Favipiravir (T-705), along with some of its activated substituents, are presented in **Figure 3**.

4. Pharmacokinetics Study of Favipiravir

A pharmacokinetic study was conducted on the healthy Japanese volunteers administered with Favipiravir. It was found out that the concentration of favipiravir in the plasma increased in the first two hours of oral administration. Following this, the concentration started decreasing and reached a half-life within 2.5-5 hour.[36] Thus, it was suggested that the parent drug molecule undergoes metabolism in the liver mainly by aldehyde oxidase (AO) and partially by xanthine oxidae (XO). After metabolism, an inactivated oxidative metabolite T-705M1 is excreted by the kidney function.[37] Another experiment was conducted in mice that were administered with favipiravir through venous injection. The study reported the presence of a significant concentration of favipiravir in the liver, followed by the gall bladder and other segments of the intestines. This study suggests rapid excretion of favipiravir by mice livers.[38] The pharmacokinetic behavior of Favipiravir was further evaluated through continuous intravenous administration in cynomolgus macaques. The result initially showed a nonlinear dynamics of drug distribution, while a decrease in concentration was observed in the plasma after 7 days of constant administration.[39] A similar result was observed from the clinical reports of 66 Ebola-infected patients during a clinical trial named JIKI trial. In that study, Favipiravir's concentration was tested on 2nd day and 4^{rth} day of the trail, and almost a decrease of 50% concentration in plasma was observed. These results, therefore, suggest that Favipiravir is excreted effectively by our excretion system both during a single and continuous dosage regime.

Further studies were conducted to understand the biodistribution and mechanism of excretion of Favipiravir after the individual was administered a single and repetitive dosage. An ^{18}F labeled Favipiravir derivative was synthesized. A set of naive mice was given a tail venous injection, and another set of mice were pre-dosed with the ^{18}F-Favipiravir. It was seen that the drug load clearance in naive mice took place through the liver and was more efficient compared to

the sets of pre-dosed mice. In pre-dosed mice, the concentration of drug molecules in plasma decreased by 25-50 %, but at the same time, accumulation in the liver, train, and muscle tissue increased significantly. With these results, the assumption of tissue adsorption was supported. An in-vitro experiment showed that chronic and continuous administration of Favipiravir could result in the inactivation of AO, leading to the possibility of self-inhibiting the metabolism function. As a result, the Favipiravir would not be completely metabolized. Hence, there is a chance of an increased concentration of the inactive Favipiravir metabolites in the plasma.[36]

Recently Avifavir, a Favipiravir based drug analog is developed in Russia under collaboration from Russian Direct Investment Fund, Russia's sovereign wealth fund, and ChemRar Group. This drug is in the final stage of the clinical trial. The trial was initiated on 21st May on approval from Russian Health Ministry. The experiment consisted of 300 COVID-19 patients. From recently obtained data, it is known that 60% of the patients showed cure within four days, while 90% cure was reported within the first ten days. It is expected that by early June 2020, the first batch of Avifavir will get its necessary approval for use from Russia's Federal Service for Surveillance in Healthcare, and by June 11th, 2020, the first batch will be sent to the hospitals [https://www.timesnownews.com/health/article/russia-tests-anti-coronavirus-drug-avifavir-producer-says-drug-s-efficacy-against-covid-19-above/600306]. This particular development was also reported in The Japan Times on 1st of June 2020. In a news, Kirill Dimitriev, Head RDIF, Russia has gratefully acknowledged the contribution of Japan for the discovery of Avigan and report of the clinical trials [https://www.japantimes.co.jp/news/2020/06/01/world/science-health-world/russia-japan-avigan-drug/#.Xt3ZTTozbIU].

5. Favipiravir Dosage and Drug Interaction

One of the most essential part in any clinical trial and drug administration is the dosage regime. Various viral titre experiments showed that the IC_{50} of favipiravir varies from nanomolar to micromolar concentrations.[40] However, in Japan, the approved dose of Favipiravir for treatment of influenza is 3.2 gm (1.6 gm every 12 hr) oral dose in day 1, followed by 600 mg dose administered twice daily for the rest 2-5 days.[41] Another higher dose regime of 3.6 gm in day 1 and 800 mg dose after that is also under monitoring in phase 3.[41] Till now, it is found that both of these doses are responding fine with patients and are safe in case of influenza infections.[42] Post dosage effect was also studied, and it was found out that some patients report adverse reactions. These side effects are mild to moderate diarrhea, a sudden increase in blood uric acid level, and a decrease in neutrophil counts.[42]During the treatment of Ebola patients in the clinical trial JIKI, the dosage of Favipiravir was maintained at 6 gm (divided into three sections with 2.4 gm given at an interval of 8 hrs and then after the next 8 hr 1.2 gm was administered) for the first day. Then the treatment followed with the administration of 2.4 gm (twice with 1.2 gm every 12 hr duration) for the rest 2 to 9 days. In this study, an exciting data came out. On the 2nd day of the clinical trial, Favipiravir metabolites were detected at a concentration of 46.2µg/L in plasma (48 hrs from the initial dose). In comparison, the record on the 4th day showed a drastic decrease to 25.9µg/L (96 hrs after initial dose). A correlation of the results showed that they are much lower in comparison to the expected/predicted drug

concentrations of 54.3µg/L and 64.4µg/L, respectively. These previous trial reports helped medical practitioners during this particular time of Covid-19 emergency.

COVID-19 disease is infecting a large number of individuals. Many patients are already on medication for various diseases like hypertension, diabetes, liver injury, cardiovascular disease, and even critical diseases like cancer, arrhythmia, acute kidney injury/disorder, etc. Hence, from a clinical point of view, it is necessary to study Favipiravir's interaction with other drugs and medicines. We now have the information that AO metabolizes Favipiravir in the cytosol. However, the effect of Favipiravir or T-705-RTP on the other drug-metabolizing enzymes are yet to be studied.[43] Some of the previous reports showed that the Favipiravir increases the retention time of acetaminophen in plasma by 20% and acetaminophen glucuronide by almost 23%-34%. In turn, the effect of Favipiravir resulted in a decrease of acetaminophen sulfate concentration by 29%-35%. Some commonly used drugs, such as gynecological drugs, calcium channel blockers, H2 receptor competitors, antidepressants, and antiarrhythmic drugs, are known to inhibit the activity of AO.[44-49]Therefore, it is crucial to understand the reaction of Favipiravir with or in the presence of these drugs before being allowed for administration.

It is a great concern for the treatment of Covid-19 positive patients who are already suffering from the diseases, such as, asthma and COPD. In some studies, it is seen that the patients who have a clinical record of COPD show more tendency to get infected with SARS-CoV-2 and other viral infections due to compromised innate immune responses to viral infections. However, these findings are also contradicted by some other studies.[50] Even then, it is found out that the patients suffering from lung disorders and detected with COVID-19 are showing deteriorated health conditions, eventually resulting in death. The fatality rate accounted to 6.3%.[51]The common clinical practice is to treat COPD and acute asthma patients with inhaled corticosteroids (ICS).[52-53]However, this practice has started to generate queries and concerns among medical practitioners regarding the effect of ICS in virus-infected patients, especially in COVID-19 patients. It is known that ICS are immunosuppressants. Studies have shown that patients having COPD when treated with ICS develop pneumonia and other upper respiratory illness.[54-56] Some other in-vitro studies showed a weakening of the innate immune response system against rhinovirus when treated with ICS. The study also suggested a longer time for virus clearance.[57-59] However, recently some studies are showing that ICS may become promising antiviral agents, especially against coronavirus. A combination of budesonide, glycopyrronium, and formoterol was used for pretreatment of human epithelial cells in an in-vitro study. Then the cells were subjected to human coronavirus HCoV-299E. Interestingly, the drug combo showed inhibition of HCoV-299E replication and reduced cytokine generation.[41]

Finally, we want to mention, herein, the side effect of clinical administration of Favipiravir in pregnant women. It was reported that the use of Favipiravir on pregnant or lactating women might result in tetragenocity and embryonic deaths.[60] Therefore it is suggested that more detailed study is required before approving the use of Favipiravir on pregnant women. Ministry of Health and Labour, Japan, initially expressed their concern regarding the possibility of adverse side effect of Favipiravir on pregnant patients similar to the effect of Thalidomide (salidomide). However according to some recent reports (not peer reviewed) from Japan, it was found out that no such side

effects were observed in undergoing clinical trials. Still the ministry has imposed stern regulations on the use of Favipiravir to treat COVID-19 infected pregnant patients.

Some interesting data (not yet peer-reviewed) from an in-vitro study has suggested that the the drug, ciclesonide, can arrest the replication of SARS-CoV-2 by preventing the cytopathic action.[61]A similar finding is reported from few case studies in Japan, recently. Three patients suffering from COVID-19 were administered with inhaled ciclesonide. These patients were receiving oxygen but did not required ventilation care. Interestingly all three patients showed miraculous improvement.[62] Presently WHO has advised refraining the practice of using corticosteroids apart from clinical trials.[63] From the studies mentioned here, we believe that this particular drug ciclesonide, marketed under the brand name Alvesco and invented by the US-based pharmaceutical company Covis, can be a promising candidate with which clinical study can be performed on COVID-19 patients. We also advocate that the interaction between Favipiravir and ciclesonide should be studied. This drug combination may result in developing a cure for COVID-19 disease. At the same time, we have already initiated the research on the development of Avigan and ciclesonide analog and study their potential as a promising drug candidate against COVID-19.

6. Conclusion

This review discusses the pathogenicity of the SARS-CoV-2 virus and the possibilities and promising results of Favipiravir or its activated analog Favipiravir-RTP to treat COVID-19 disease based on its reported mechanism of RdRp inhibition. We have also discussed in detail the possible pharmacokinetic outcomes after being treated with Favipiravir. We have discussed reports and results from various clinical trials of those conducted in the past with influenza and Ebola-infected patients and the recent trials with COVID-19 patients. We believe that the information we represent shall be of importance to the scientific community and help conduct experiments and clinical trials. Through this review, we would like to draw attention that Favipiravir is an excellent drug candidate, which can bring a cure to COVID-19 infection. However, medical practitioners have to be careful before administering Favipiravir in combination with other drugs. Finally, we would like to emphasize that worldwide scientists, particularly drug design oriented chemists should contribute more to the development of effective and safe drug for COVID-19 beyond Avigan and Remdesivir.

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