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Favipiravir as RNA Polymerase Dependent (Rdrp) in COVID-19

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ABSTRACT

Coronavirus disease 2019 or Coronavirus disease 2019 (COVID-19) is a contagious disease caused by a new virus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). This disease became a pandemic and is being discussed around world because it has significant consequences on public health and global economy. Favipiravir is an anti-viral agent that selectively and potently inhibits RNA-dependent RNA polymerase (RdRp) from RNA viruses. Favipiravir was discovered through a screening list of chemicals with anti-viral activity against influenza virus by Toyama Chemical Coorperation. Use of Favipiravir in clinical trials has shown radiological improvement in lung CT scans and a faster viral clearance time than or antivirals.

Keywords: Favipiravir, COVID, COVID-19, antiviral, RdRp.

1 Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by a new virus, namely Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). This disease became a pandemic and is a topic of discussion around world because of its significant impact on public health and global economy [1]-[3].

Structurally, SARS-CoV-2 virus is similar to SARS-CoV-1 virus which became an outbreak in 2003 and Middle East Respiratory Syndrome coronavirus (MERS-CoV) virus which became an outbreak in 2012. This virus is a type of beta-single-chain RNA virus. coronavirus, enveloped, positive-sense. Corona virus is transmitted between animals and humans, which can n be transmitted from human to human via respiratory tract. This virus can proliferate in mucosal epilial cells of airways to cause damage to airways and lung parenchyma, and can enter bloodstream and will cause pathological changes in tissues / organs outside respiration [3]-[5].

Taking into account threat of COVID-19 epidemic and previous experience with SARS and MERS rapies, efforts to develop rapeutic strategies and vaccines are being undertaken on a large scale worldwide. Currently, re are no specific management recommendations for COVID-19 patients, including antivirals or

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vaccines. Management that can be done is symptomatic rapy and oxygen, until mechanical ventilation is done in respiratory failure. China's National Health Commission (NHC) has been researching several drugs that have potential to overcome this viral infection, one of which is favipiravir, which is known as Avigan® product. This is based on a finding in Japan that states favipiravir has potential in treatment of COVID-19 [7]-[9].

Favipiravir is an anti-viral agent that selectively and potently inhibits RNA-dependent RNA polymerase (RdRp) from RNA viruses. Favipiravir was discovered through a screening list of chemicals with anti-viral activity against influenza virus by Toyama Chemical Coorperation. Use of Favipiravir in clinical trials has shown improved radiologic CT scan of lungs and faster viral clearance time than or antivirals [9]-[12].

2 Coronavirus Disease (COVID-19)

2.1 Definition

Coronavirus Disease 2019 / Coronavirus Disease 2019 (COVID-19) is a new disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) type coronavirus [3,10].

2.2 Classification

Terminology "Corona" comes from Greek which means crown. Shape of this crown is characterized by presence of "S protein" known as "spiked protein", which is scattered around surface of virus. "Protein S" is what plays an important role in process of viral infection against humans. Overall, corona virus also resembles a solar eclipse. Prior to COVID-19 outbreak, there were 6 types of coronavirus that could infect humans, namely alphacoronavirus 229E, alphacoronavirus NL63, betacoronavirus OC43, betacoronavirus HKU1, Severe Acute Respiratory Illness Coronavirus (SARS-CoV), and Middle East Respiratory Syndrome Coronavirus (MERS-CoV). Coronavirus as etiology of COVID-19 belongs to genus betacoronavirus [3-5,10]

Based on Baltimore classification, this virus is included in group IV, namely single-stranded RNA (+). In replication process, this type of virus can use its RNA genome directly into mRNA and can produce dependent RNA polymerase [3-5,10,21].

Structure of virus consists of Spike protein (S) which has an important role in binding to host cell receptors. Nucleocapsid protein (N) has a function to bind to RNA genome to make nucleocapsid. Protein envelope (E) combines with membrane protein (M) to form viral envelope. Protein membrane (M) is a central regulator preparation of coronavirus and determines shape of virus envelope. Coronavirus uses angiotensin converting enzyme 2 (ACE-2) as a receptor for viral binding and entry. ACE 2 is an enzyme that attaches to outer surface of cells of several organs such as lungs, arteries, heart, kidneys and intestines. Viral entry is mediated by fusion of viral envelope with host cell membrane or by receptor-mediated endocytosis [10, 21].

Structure of viral genome has a pattern like that of coronavirus in general (Figure 2). SARS-CoV-2 sequence has similarities with coronavirus isolated in bats, hypothesis arises that SARS-CoV-2 originated from bats which then mutated and infected humans. Mammals and birds are thought to be intermediate reservoirs [16,21-24].

This virus basically infects mainly animals which include bats and camels. Results of phylogenetic analysis show that this virus is included in same subgenus as coronavirus that caused Severe Acute Respiratory Illness (SARS) outbreak in 2002-2004, namely Sarbecovirus. On this basis, International Committee on Taxonomy of Viruses proposed name SARS-CoV-2 [10, 13-15, 23].

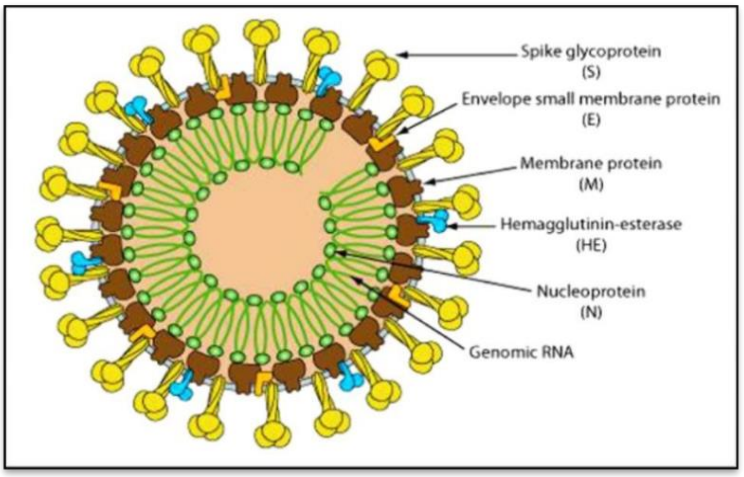

Figure 1. Structure of Corona virus [15].

Structural proteins of corona virus are spike (S), envelope (E), membrane (M) and nucleocapsid (N) genes. In its genome, there is an open reading frame (ORF) 1ab which is largest gene in SARS-CoV-2 which encodes pp1ab protein and 15 non structural protein (NSP). ORF 1a is a gene for pp1a protein which also contains 10 NSP. SARS-CoV-2 phylogenetic tree is located close to SARS coronavirus group. Recent studies have shown important variations in SARS-CoV and SARS-CoV-2, including absence of protein 8a and fluctuation in amount of amino acids in 8b and 3c protein in SARS-CoV-2. In addition, it is also known from homologous modification of recombinant spike glycoprotein of Wuhan coronavirus SARS-CoV-2 is a mixture of unknown SARS-CoV and Beta-CoV bats. In fluorescence studies, it was confirmed that SARS-CoV-2 also used same ACE2 (angiotensin-converting enzyme 2) receptor as SARS Cov to enter host cells. A single N501T mutation in SARS-CoV-2 Spike protein might significantly increase its binding affinity for ACE2[23].

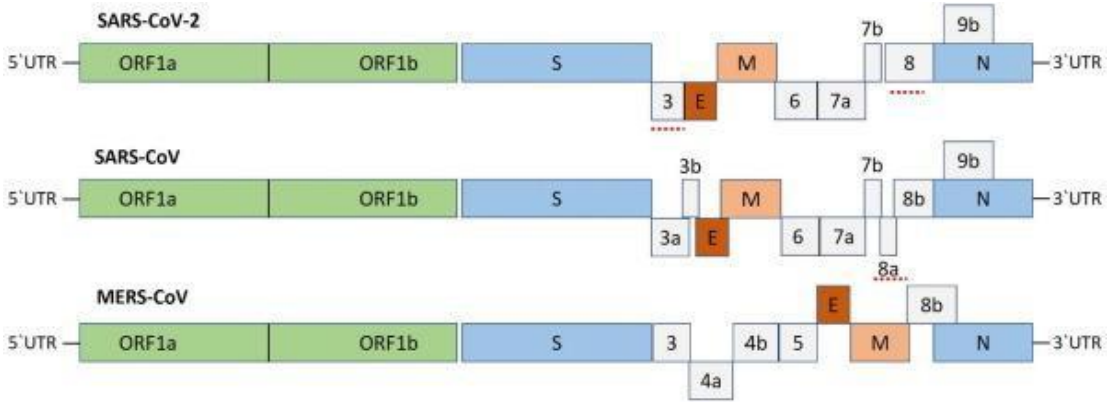

Figure 2. Structure of viral genome. ORF: open reading frame, E: envelope, M: membrane, N: nucleocapsid [23].

SARS-CoV-2 has three-dimensional structure in receptor-binding spike domain protein that is almost identical to SARS-CoV. In SARS-CoV, this protein has a strong affinity for angiotensin-converting-enzyme 2 (ACE2). In vitro results were obtained that supported possibility of virus being able to enter cells using ACE2 receptor. Study also found that SARS-CoV-2 did not use or coronavirus receptors such as Aminopeptidase N (APN) and Dipeptidyl peptidase-4 (DPP-4) [16-18, 23-24].

SARS-CoV-2 transmission from symptomatic patients occurs via droplets that are released when coughing or sneezing. SARS-CoV-2 can be viable to aerosols (generated through a nebulizer) for at least 3 hours. Human-to-human spread of SARS-Cov2 has become main source of transmission [19,20-24].

2.3 Pathogenesis

Pathogenesis of SARS-CoV-2 isn't much different from SARS-CoV. There are many similarities between SARS-CoV-2 and SARS-CoV. From results of biochemical interaction studies and analysis of glycoprotein crystal structure contained in envelope spike, virus will bind strongly to ACE2 cellular receptor. ACE2 will catalyze conversion of angiotensin II (a vasoconstrictor peptide) to angiotensin 1-7 (a vasodilator) [17,24-25].

RNA virus replication basically occurs through stages of attachment, penetration, replication, synthesis, maturation and release. After virus enters cell through interaction of S protein and ACE2 receptor, viral RNA genome leaves viral membrane. Another part of RNA genome function as mRNA and partly as a template for RNA synthesis. Genome that functions as mRNA will be translated into various proteins with help of host cell ribosomes. Among these proteins, there are those that function to form body of virus and some function for replication/multiplication process of RNA. One of protein expressing replicase enzyme complex is RNApolymerase dependent RNA (RdRP) for replication. Meanwhile, some or RNA genomes are used for synthesis of negative RNA. This negative RNA, used as a template again for positive RNA synthesis. And so on, this process takes place repeatedly. With this process, finally positive RNA that becomes genome will increase in number. Positive multiplication of RNA is wrapped by proteins that make up body of virus, so that a new virus is formed (progeny). This new virus finally leaves cell and has a function as a normal virus that can infect next cell [17-26].

Glycoproteins in newly formed viral envelope enter membrane of endoplasmic reticulum or Golgi cells. Formation of nucleocapsid which is composed of RNA genome and nucleocapsid proteins. Viral particles will grow into endoplasmic reticulum and Golgi cells. In final stage, vesicles containing viral particles will combine with plasma membrane to release new viral components [26].

3 Favipiravir

Favipiravir is generally known by code number T-705. In chemical compound naming system of International Union of Pure and Applied Chemistry (IUPAC), favipiravir is a 6-fluoro-3-hydroxy-2-pyrazincarboxamide compound with chemical formula C5H4FNO3O2. This drug was discovered based on chemical modification of pyrazine analogue initially screened for in vitro anti-influenza virus activity in cells [9,12].

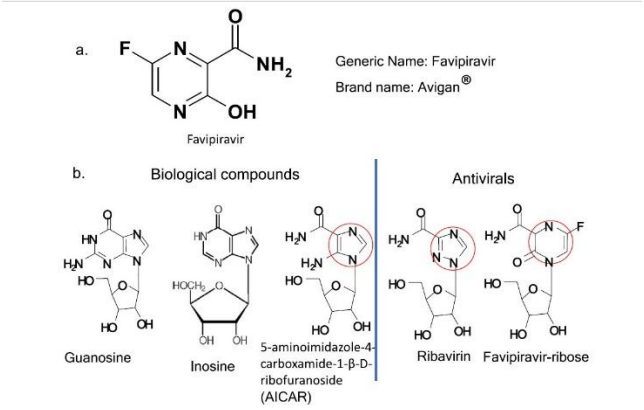

Figure 3. Chemical Structure of Fapiviravir [12].

5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside (AICAR), guanosine and inosine are components of compounds that are biosynsized de novo from amino acids, while ribosyl-favipiravir and ribavirin are antiviral compounds derived from favipiravir that resemble analogues. purine nucleosides (adenine and guanine). There are three compounds, AICAR, ribosyl-favipiravir and ribavirin respectively which have similar chemical structures (Figure 6), this indicates that favipiravir functions homologous to purine and inhibits viral RNA synthesis [9, 12].

In living things, synthesis of purine nucleotides is produced through de novo synthesis process, namely synthesis derived from amino acid precursors, ribose-5 phosphate, CO2, and one-carbon units. In addition, process of nucleotide synthesis is through a salvage pathway derived from pre-formed bases. However, many parasitic organisms cannot synsize purines via de novo pathway and must rely on an enzyme in rescue pathway, namely phosphoribosyltransferase. Enzymes in this escape route are used as potential targets of therapeutic agents for treatment of diseases caused by parasites.

Favipiravir (T-705; 6-fluoro-3-hydroxy-2-pyrazincarboxamide) is an antiviral agent that selectively and potently inhibits RNA-dependent RNA polymerase (RdRp) from viral RNA. Favipiravir was discovered through a screening list of chemicals with anti-viral activity against influenza virus by Toyama Chemical Co., Ltd in Japan. This drug acts as a chain breaker at site of incorporation of viral RNA and reduces viral load. Favipiravir was successful in curing all of mice in deadly model of influenza infection, while oseltamivir failed to cure mice. refore, favipiravir contributes to curing animals with deadly infections. Apart from influenza, favipiravir has a broad spectrum of anti-RNA viral activity in vitro and efficacy in animal models with lethal RNA viruses and has been used for treatment of human infections with Ebola virus, Lassa virus, rabies, and severe fever with life-threatening thrombocytopenia syndrome [9,12].

4 Pharmacokinetics

4.1 Concentration in plasma

Studies conducted on healthy Japanese volunteers showed that maximum plasma favipiravir concentrations occurred at 2 hours after oral administration and decreased rapidly with a half-life of 2 - 5.5 hours. Bioavailability of this drug is 97.6%. Maximum plasma concentration was 51.5 μg / mL. Binding of plasma protein to favipiravir in humans is 54%. Diet delayed peak plasma levels of favipiravir by 1.5 hours, reduced Cmax by about 50%, and decreased AUC by 13%. Percentages of favipiravir binding to human serum albumin and α1-acid glycoprotein were 65.0% and 6.5%, respectively [9,12,48].

Pharmacokinetic analysis of intravenous favipiravir in mammalian cynomolgus macaques after several repeated doses showed clear nonlinear pharmacokinetics over time and over a range of doses, and also observed a continuous decrease in plasma concentrations after 7 days of administration in nonhuman primates. Data obtained from 66 patients enrolled in experimental therapy with favipiravir showed that concentrations had decreased on day 4 (25.9 μg / mL) compared to day 2 (46.1 μg / mL), which supports a decrease in post-drug concentrations. use. Linear Cmax values at doses of 30 mg to 1600 mg. Half-life of faviripavir is ± 6 hours, and is prolonged at high doses (≥800 mg) [9,12,4].

4.2 Drug Metabolism

Drug is metabolized in liver mainly by aldehyde oxidase (AO), and partly by xanthine oxidase, resulting in inactive oxidative metabolite T-705M1 which is excreted by kidneys, while active metabolite (favipiravir-RTP) is formed intracellularly. This drug is not metabolized by cytochrome P-450 (CYP). Rapid emergence of favipiravir in liver, followed by gallbladder and several segments of intestinal tract after venous injection in mice, suggests rapid liver excretion of favipiravir in mice [9,12,48].

4.3 Distribution and Excretion

Favipiravir is widely distributed in body, including trachea and lungs. To understand in vivo biodistribution and kinetics of favipiravir uptake and clearance after single and repeated administration, a radiolabel-treated favipiravir 18F ([18F] favipiravir) was developed. Dynamic distribution of [18F] favipiravir was assessed by dynamic positron emission tomography scanning and gamma counting in naive mice as well as in mice predosed on favipiravir (oral administration, loading dose: 250 mg / kg twice daily, day 1; dose maintenance: 150 mg / kg, twice daily for 3 days). In naive mice, injection of favipiravir into a

vein in tail results in rapid absorption and clearance through liver, kidneys and intestines. In contrast, in predosed mice, plasma concentrations decrease by 25-50% and tissue distribution in liver, stomach, brain, and muscle tissue increases 2–5 times. Assuming that retention of favipiravir is dependent on its own fibosylated and phosphorylated form, increased distribution with predosing or chronic use should increase cellular uptake and efficacy of antiviral. In vitro studies have shown that favipiravir can inhibit AO activity depending on concentration and time, which explains auto-inhibition of metabolic inactivation of parent drug and an increase in plasma host / inactive metabolite ratio (T705 / T705M1) after chronic dosing [48]. In vitro studies have shown that favipiravir can inhibit AO activity depending on concentration and time, which explains auto-inhibition of metabolic inactivation of parent drug and an increase in plasma host / inactive metabolite ratio (T705 / T705M1) after chronic dosing [48].

Increasing circulating T-705 / T-705M1 ratio in mice should facilitate cellular uptake and retain tissue favipiravir by increasing extracellular to intracellular concentration gradient. This helps explain accelerated clearance of circulating favipiravir after repeated administration. However, strong evidence of monitoring T-705-RTP levels in tissues during continuous use of favipiravir is still needed. T-705-RTP is also formed in human peripheral blood mononuclear cells (PBMCs), and terminal half-life (t1 / 2) of T-705-RTP is about 2 hours in PBMC. Although t1/2 of T-705-RTP in PBMC was shorter than in lungs (t1 / 2 about 4.2 hours), detection of T-705-RTP in peripheral blood mononuclear cells may serve as a substitute given availability of peripheral blood tests. Favipiravir metabolites are excreted via kidneys [12,48].

4.4 Indication

Favipiravir demonstrated anti-viral activity against all subtypes of influenza virus strains, including types A, B and C. In studies using laboratory strains of influenza viruses with an effective concentration of 50% (EC50) ranging from 0.014 to 0.55 ug / mL. Favipiravir was evaluated in vitro for its ability to block proliferation of representative influenza viruses, including strains A (H1N1), A (H1N1) pdm09, A (H3N2), and B; avian influenza virus is highly pathogenic A (H5N1) isolated from humans. These strains contain those that are resistant to oseltamivir or zanamivir, and some that are resistant to both NA inhibitors. It was noted that favipiravir exhibited anti-viral activity against all strains tested [48].

Combinations of anti-viral agents with different mechanisms of action are used to enhance therapeutic effect or to reduce appearance of resistant viral clones. A synergistic effect was demonstrated by combination of favipiravir with oseltamivir in a murine influenza virus model. Combination of favipiravir and oseltamivir significantly increased survival rates of mice infected with influenza A / Victoria / 3/75 virus (H3N2), while both single agents alone showed limited effects. Similar combined effects were shown in mice infected with influenza A / NWS / 33 (H1N1) or A / Duck / MN / 1525/81 (H5N1) viruses. These results provide a wider range of therapeutic options for treatment of epidemic influenza viruses that are resistant to existing anti-influenza agents or for patients with severe symptoms [48].

Favipiravir can also treat severe fever with thrombocytopenia syndrome (SFTS), which is caused by SFTS virus (SFTSV). This drug was approved for use in Japan in 2014 for treatment of diseases caused by new influenza viruses (novel or re-emerging in fluenza viruses). In Japan, approval for use of this drug is accompanied by strict regulations because data on effectiveness of this drug in humans are still limited to influenza infection, and there are side effects of teratogenesis and embryotoxicity [48].

4.5 Pharmacodynamics

Favipiravir inhibits replication of RNA viral genome. Favipiravir is a purine nuleoside analogue of both guanine and adenosine. This is evidenced by competition between favipiravir and purine nucleosides rar than pyrimidine nucleosides. When formation of viral RdRP enzyme complex, purine bases adenine guanine will compete with favipiravir, which will cause disrupted termination of RNA to produce premature

RNA. This premature RNA causes disruption of viral RdRP. In addition, it also causes replication of RNA virus to take longer, and causes virus mutation due to genome transitions on nucleotides [48,53].
In Furuta study, 2005, using mammalian cell of Madin Darby Canine Kidney (MDCK) as an in vitro test for influenza viruses. MDCK cells were treated with favipiravir, and cellular metabolites were analyzed by High Performance Liquid Chromatography (HPLC), compound Favipiravir ribofuranosyl-5'-triphosphate (favipiravir-RTP), favipiravir ribofuranose (favipiravir-R) and favipiravir ribofuranosyl-5'-monophosphate-RMP). Results showed that favipiravir activation occurred in cells. Favipiravir-RTP was chemically synsized and tested for inhibition of influenza virus RNA polymerase activity as assessed by including Guanosine Triphosphate (32P-GTP). Favipiravir-RTP inhibits viral RNA polymerase activity in concentrations ranging from nanomolar to micromolar [48,53].

Results of Furuta's study that favipiravir exerts anti-viral activity as a pro-drug (inactive form), intra-cellular phosphorybosylation to become favipiravir ribofuranosyl-5'-monophosphate (favipiravir-RMP) and phosphorylation process into an active form, favipiravir ribofuranosyl-5'-triphosphate (favipiravir-RTP), which works to inhibit viral replication by interacting with viral RNA polymerase [12,48,53].

Mechanism for interaction of favipiravir-RTP with RdRp molecule has not been fully elucidated. It was hyposized that favipiravir could be misused in newborn viral RNA, or that favipiravir could act by binding to polymerase domain, thus preventing incorporation of nucleotides for viral RNA replication and transcription. Favipiravir induces lethal mutagenesis during influenza virus infection, and reduces viral titers at eir low (0.0001 PFU / cell) or high (10 PFU / cell) multiplication of infections in vitro. Sequence analysis of various nucleoprotein (NP) clones revealed an increase in number of detectable G → A and C → T or C → U transition mutations, along with an increase in mutation frequency, and a change in nucleotide profile. It is important that none of mutants were resistant to favipiravir [12,48-53].

Furuta et al. And Jin et al. Performed primary extension tests using influenza H1N1 extract as a source for RdRp and viral RNA templates. Addition of 5'Cap1 RNA to test mixture provides cap-snatching and transcription. Using favipiravir-RTP compound, experiments were conducted to efficiently insert a single molecule of favipiravir-RTP into newborn RNA, inhibiting extension of viral RNA strand. Meanwhile, dual incorporation of favipiravir-RTP molecule into viral RNA completely blocks further extension of RNA strand. these two studies showed that favipiravir-RTP efficiently inhibited expansion of viral RNA strands [12,48-53].

Synthesis of nucleic acids is essential for life in viruses and humans. Unlike RNA viruses, humans do not have RdRp, but have DNA-dependent RNA polymerase (DdRp) and DNA-dependent DNA polymerase. In polymerase inhibitory activity test by Kiso, et al. 2010, favipiravir-RTP inhibited RdRp influenza with IC50 0.341 μmol / L, but did not inhibit human DNA polymerase α, β, μ to 1000 μmol / L. Favipiravir slightly inhibits human RNA polymerase II, which is included in DdRp, with an IC50 of 905 μmol / L.9) these results are consistent with evidence that favipiravir does not inhibit DNA and RNA synthesis at 637 μmol / L in MDCK cells [12,48-53].

Once introduced into host cells, favipiravir undergoes further phosphoryibosylation and phosphorylation to become favipiravir-RTP, which inhibits RdRp virus. Mechanism of action of favipiravir is quite unique, because influenza drugs currently on market work by blocking entry or exit of virus. Selective inhibition of RdRp virus by favipiravir has implications for a broader antiviral spectrum. Further investigations are needed to clarify correlation between anti-viral activity of favipiravir RNA viruses and ir inhibition of ir RdRp activity [12,48-53].

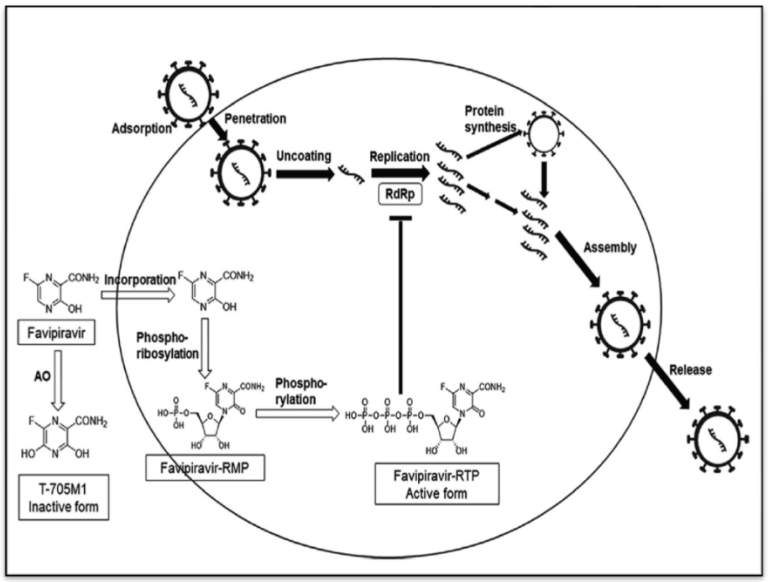

Figure 4. Favipiravir activity mechanism [48].

Effect of favipiravir on viral load was investigated in mice infected with H1N1 influenza virus (A / California / 04/09). Oral therapy with favipiravir at doses of 60 and 300 mg / kg / day decreased viral load in lungs 3 and 6 days after infection. Favipiravir demonstrated similar or more potent antiviral effectiveness than oseltamivir and zanamivir in a mouse model infected with influenza A (H1N1) pdm09 virus. In addition, favipiravir was significantly more efficient than oseltamivir in a mouse model with viral titers 100 times higher with influenza A / PR / 8 (H1N1) virus, or delayed dose (up to 96 hours post infection) [48,53].

Combinations of antiviral agents with different mechanisms of action are used to enhance therapeutic effect or to reduce appearance of resistant viral clones. A synergistic effect was demonstrated by combination of favipiravir with oseltamivir in a murine influenza virus model. Combination of favipiravir and oseltamivir significantly increased survival rates of mice infected with influenza A / Victoria / 3/75 virus (H3N2), whereas administration of their single agent showed limited effects. Similar combined effects were shown in mice infected with influenza A / NWS / 33 (H1N1) or A / Duck / MN / 1525/81 (H5N1) viruses. these results provide a wider range of therapeutic options for treatment of epidemic influenza viruses that are resistant to available anti-influenza agents or for patients with more severe condition [12,48-53].

5 Favipiravir Clinical Trial on COVID-19

Currently, there are> 100 clinical trials designed to test pre-identified drugs that have been approved by US Food and Drug Administration (FDA) and several experimental antiviral agents, which have been shown to be safe and effective against or viral infections [53].

From various previous studies it was said that favipiravir could be used in treatment of infections not only by influenza viruses but also various kinds of RNA viruses, so there are some researchers who have proposed favipiravir as an option in treatment of coronavirus. Favipiravir is a drug that needs attention. Favipiravir was approved for new influenza treatment on February 15, 2020 in China. This drug is currently undergoing clinical trials in treating COVID-19 [54].

On February 14, a clinical trial of favipiravir for treatment of COVID-19 initiated by Clinical Medical Research Center of National Infectious Diseases and Third People's Hospital of Shenzhen achieved promising results. baseline results of a total of 80 patients (including experimental and control groups) indicated that favipiravir had stronger antiviral action than lopinavir / ritonavir. No significant

adverse reactions were recorded in favipiravir treatment arm, and it had significantly fewer side effects than lopinavir / ritonavir arm [54].

A published study on use of favipiravir in COVID-19 therapy is a study by Cai Qing xian et al, in Shenzhen China in January - February 2020. In this study, they examined effects of favipiravir (FPV) versus lopinavir (LPV) / ritonavir (RTV) as therapy for COVID-19. Laboratory-confirmed COVID-19 patients receiving oral FPV (Day 1: 1600 mg twice daily; Day 2–14: 600 mg twice daily) plus interferon (IFN) -α via aerosol inhalation (5 million U twice daily) were included in FPV group in this study, while patients treated with LPV / RTV (Day 1-14: 400 mg / 100 mg twice daily) plus IFN-α via aerosol inhalation (5 million U twice daily) were included in group control. Comparisons of changes that occur on chest CT scan and virus clearance are performed. and drug safety in both groups. For 35 patients enrolled in FPV group and 45 patients in control group, all baseline characteristics were found to be comparable between two groups. Shorter viral clearance times were found in FPV group than in control group (median (interquartile range, IQR), 4 (2.5–9) days versus 11 (8–13) days, P <0.001) [56].

FPV group also showed significant improvements in chest imaging compared to control group, with an improvement rate of 91.43% versus 62.22% (P = 0.004). Shorter viral clearance times were found in FPV group than in control group (median (interquartile range, IQR), 4 (2.5–9) days versus 11 (8–13) days, P <0.001). FPV group also showed significant improvements in chest imaging compared to control group, with an improvement rate of 91.43% versus 62.22% (P = 0.004). 56 Shorter viral clearance times were found in FPV group than in control group (median (interquartile range, IQR), 4 (2.5–9) days versus 11 (8–13) days, P <0.001). FPV group also showed significant improvements in chest imaging compared to control group, with an improvement rate of 91.43% versus 62.22% (P = 0.004) [56].

After adjustment for potential confounders, FPV group also showed a much higher rate of improvement in chest imaging. Multivariable Cox regression showed that FPV was independently correlated with faster viral clearance. In addition, fewer adverse side effects were found in FPV group than in control group. In this open-label non-randomized controlled study, FPV demonstrated a significantly better therapeutic effect in COVID-19 in terms of disease progression and viral clearance; if causal, these results provide important information for establishing standard therapy guidelines for fighting SARS-CoV-2 infection [56].

A clinical study by Chen Cang, et al (ChiCTR200030254) conducted in Wuhan, (N = 240) compared efficacy of favipiravir with arbidol in treatment of COVID-19. there was no difference in clinical recovery at 7 days in all populations (61.21% vs 51.67%; p = 0.14). However, in patients with COVID-19 who were not critical and without hypertension and diabetes, comparison of time to reduce fever and cough reduction in favipiravir therapy group also changed significantly (71.43%) compared to arbidol (55.86%). = 0.02. Research conducted in various countries such as China, Thailand, America, Egypt, France and Italy were evaluation for efficacy of using drug favipiravir in COVID-19. Most of registered clinical trials are still in progress until end of 2020 [56].

6 Conclusions

SARS-CoV-2 infection has now spread rapidly throughout world. Various clinical trials have been carried out in an effort to find effective treatments to deal with COVID-19 disease pandemic. One of antivirals that has been approved for use in Japan is Favipiravir with drug name Avigan ®. Favipiravir is a nucleoside analogue that is phosphorylated in cells into an active form, namely favipiravir-RTP, selectively and potently inhibits viral RNA-dependent RNA polymerase, reby breaking chain at site of incorporation of viral RNA and reducing viral load. Current clinical trial results suggest favipiravir has been shown to have higher antiviral potency and better therapeutic effects than or antivirals. However, use of favipiravir must be strictly regulated because of side effects of teratogenesis and embryotoxicity. There is limited clinical evidence of effectiveness of favipiravir, as well as its dangerous side effects. Until now, clinical trials in various countries are still ongoing to evaluate efficacy of favipiravir in COVID-19.

7 Competing Interests

Author indicate no potential conflict of interest from this literature.

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