WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 10, Issue 10, 138-145. Review Article ISSN 2277– 7105

A REVIEW ON THE USE OF FAVIPIRAVIR IN TREATMENT OF COVID 19

Amitha Mary Samson[1]*, Pranith P. L.[1], E. Samjeeva Kumar[2] and Prasobh G. R.[3]

[1]Doctor of Pharmacy Student Sree Krishna College of Pharmacy and Research Centre Parassala, Thiruvananthapuram Kerala.

[2]Associate Professor Department of Pharmacy Practice, Sree Krishna College of Pharmacy and Research Centre Parassala -Thiruvananthapuram Kerala.

[3]Principal and Head of the Department of Pharmacy Practice, Sree Krishna College of Pharmacy and Research Centre Parassala -Thiruvananthapuram Kerala.

Article Received on
06 June 2021,

Revised on 26 June 2021,
Accepted on 16 July 2021

DOI: 10.20959/wjpr202110-21127

***Corresponding Author**
Amitha Mary Samson
Doctor of Pharmacy Student
Sree Krishna College of Pharmacy and Research Centre Parassala, Thiruvananthapuram Kerala.

ABSTRACT

COVID 19 was originated from the province of Hubei in China in 2019 and now it has already spread all around the globe and has cause great socioeconomic impact. It's is an infectious disease associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). In early phase of infection there might be only mild symptoms and then the symptoms progresses in elderly population and persons with comorbidity are at high risk of infection. Commonly the symptoms appears within 2 to 14 days of exposure. The main symptoms include fever, cough, tiredness, sore throat, diarrhea and in serious condition it can lead to breathing difficult, chest pain, loss of speech and movement. Repurposed drugs are being evaluated to hasten the treatment process. Use of several drugs are being evaluated for the treatment of COVID 19. Favipirarvir is one such drug, the oral form of the drug have been approved for the new and re-emerging pandemic influenza in Japan in 2014. It has shown potent in vitro activity against SARS CoV -2. Favipiravir showed better therapeutic response on COVID-19 in both disease progression and viral clearance. The main intention of this study is to produce a comprehensive review of the role, safety, efficacy of favipiravir in treatment of COVID 19.

KEYWORDS: Favipiravir, SARS - CoV-2, anti viral, Pneumonia.

INTRODUCTION

The spread of COVID 19 outbreak all over the world has led the researchers to strive for developing drug or vaccine to prevent or reduce the progression of this aliment. The symptoms of COVID 19 include fever, cough, pneumonia and respiratory symptoms.[1,2,3,4] SARS-CoV-2 has genome sequence that is 75%–80% identical to that of SARS-CoV, and has more similarities to several bat coronaviruses.[5] The clinical and epidemiological features of COVID 19 patients showed that SARS-CoV-2 infection can lead to intensive care unit (ICU) admission and high mortality.[1,4] Favipiravir triphosphate acts as a competitive inhibitor of RNA-dependent RNA polymerase and it is a purine nucleoside analogue, Repurposed drugs are being evaluated to hasten the treatment process. Favipirarvir is one such drug, the oral form of the drug have been approved for the new and re-emerging pandemic influenza in Japan in 2014. It has shown potent in vitro activity against SARS CoV -2. For high dose it has wide therapeutic safety as Indicated by wide CC50/EC50 ratio. It has shown rapid viral clearance as compared to lopinavir/ritonavir and superior recovery rate than umifenovir from the clinical studies in COVID 19. In the clinical studies conducted in China, Russia and Japan have showed promising results and more trials are underway in multiple countries including USA, UK, India. Recently, treatment guidelines from some states in india mad many countries have included favipiravir in treatment protocol.[6] In the study conducted by Qingxian Cai the multivariable Cox regression showed that FPV was independently associated with faster viral clearance. It also has fewer adverse events in FPV arm than in control arm. Favipiravir showed better therapeutic response on COVID-19 in both disease progression and viral clearance.[7]

Background

In December 2019 in Hubei province of china the first case if corona virus disease 2019 (COVID 19) was reported and now has walloped every continent except Antarctica. It's is an infectious disease associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[8,9] Although the world has survived several pandemic before, but COVID 19 is an unprecedented global health challenge that has redefined our lives and continue to have devastating impact around the world. Approximately 80-90% of infectious are mild, moderate and sometimes to severe condition and many may be asymptomatic.[10] In the early phase viral titers may be at its peak. There might be no symptoms in approximately 30-60% of patients infected with virus. In elderly population and persons with comorbidity are at high risk of infection. In most cases the symptoms appears with in 2 and 14 days after exposure.

Most common symptoms are fever, cough, tiredness and less common symptoms include aches, sore throat, loss of smell, diarrhea and in serious condition Chest pain or pressure, difficulty breathing or shortness of breath, Loss of speech or movement. Dyspnoea occurs in approximately 40% patients after a week of onset of symptoms and lead to including the hyper inflammatory phase causing multiorgan system failure.[11]

Structural, Active Site and Amino acid sequence of the rdrp

In all positive-stranded RNA viruses the RdRp are the key catalytic subunits of the viral replication complex. The central role in RNA synthesis is Nsp12 is one of the RdRps in the RNA-synthesizing machinery.[12] The most conserved protein in corona virus is Nsp12. N-terminal of Nsp12 has RdRp activity butvthe exact function is unknown.[13,14] Viral RdRps use an arginine (Arg) residue in the motif F to form electrostatic interactions in order to place the nucleotide three phosphates (NTP) during the RNA synthesis.[15] The Arg is stabilized by using a salt bridge to a glutamic acid (Glu) residue in the same motif in many RdRps of the positive-strand RNA viruses. Relaxation in the positioning of NTPs and decreases the fidelity of the RdRp for Watson-Crick base pairing in the active site occurs during RNA synthesis.[16,17]

Table 1: Features and properties of favipiravir.

Chemical name	6-fluoro-3-oxo-3,4-dihydropyrazine-2-carboxamide
Class	Antiviral agent
Alternative name	T-705, fapilavir, and favilavir
Spectrum of activity	Rna virus include yellow fever virus, foot-and-mouth disease virus, west nile virus, enterovirus, and rift valley fever
Posology	Prophylaxis 1600 mg orally bd day 1 followed by 800 mg orally bd on days 2–25. Treatment 1800 mg bd on day 1, followed by 800 mg bd up to 14 days of covid-19.
Route of administration	Oral
Adverse effects	Diarrhea, decreased neutrophil, increased transaminases, uric acid, vomiting.

Mechanism of action

Favipiravir a purine analogue by intracellular phosphoribosylation is converted to active favipiravir ribofuranosyl-5B-triphosphate (favipiravir-RTP). It selectively inhibit RNA-dependent RNA polymerase (RdRp) of RNA viruses. Favipiravir incorporates into viral RNA error prone viral RdRp which causes chain termination and viral mutagenesis.[18] Favipiravir exhibit broad spectrum of antiviral activities as RdRp existing in various types of RNA

viruses.[19,20] Once favipiravir cause incorporation to viral RNA favipiravir-RTP works as a mutagen which can lead to inhibition of repair machinery in coronavirus. The cytosine in the SARS-CoV-2 genome is low and favipiravir-RTP adds to the pressure on CoV nucleotide content. Favipiravir – RTP has a positive effect on SARS-CoV-2 by a cytopathic effect, which is induced by the virus, reduction in the number of viral RNA, and infectious particles.

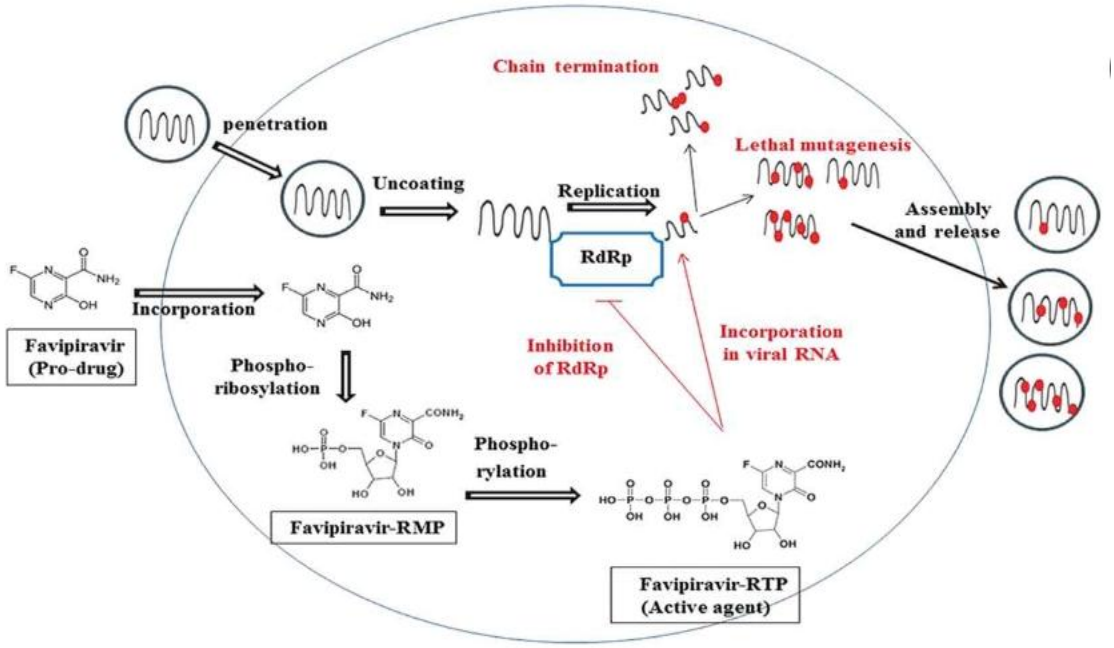

Figure 1: Favipiravir MOA in SARS-CoV-2.

Favipiravir - repurposed drug for covid 19

The favipiravir was discovered by Toyama chemical Co, Ltd by chemical modification of a pyrazine analog in a pyrazine carboxamide derivative (6-fluoro-3-hydroxy-2-pyrazinecarboxamide) through the screening of a chemical library for antiviral activity against the influenza virus.[21] Favipiravir has low molecular weight of 156.1 g/mol and is a prodrug and was approved for medical use in Japan in 2014 for treatment of new or reemerging pandemic influenza virus infection.[22,23] Favipiravir has proven efficacy against a broad spectrum of influenza viruses including A (H7N9) avian virus, A (H1N1), A(H5N1). Additionally it may halt the replication of several other RNA viruses noroviruses, and ebola virus, phleboviruses, hantaviruses, arena viruses, flaviviruses, Western equine encepha.[24]

In -vitro studies reports demonstrate that favipiravir can be effective against the SARS-CoV-2 infection within a safe therapeutic dose. As favipiravir is an oral formulation and effective

in mild to moderate COVID 19, and it is likely to address the unmet clinical needs of a sizeable majority of the population of COVID-19. The COVID 19 task force committee of India based on readiness score considering the strength of scientific evidence, availability of human safety data, bioavailability, clarity, importance of mechanism of action and target, strength of results at the preclinical stage and certainty of formulation method, progress of clinical trials in COVID-19, and certainty of manufacturing has ranked favipiravir as one of the most promising drugs. In terms of reduction in viral load as well as improvement in clinical and radiological outcomes early clinical studies from China have shown promising results.

Indication and Dosage regimen

For successful antiviral therapy dosage regimen is important part. The dosage regimen of favipiravir for influenza is a loading dose of 3200 mg on day 1 followed by a maintenance dose of 600 mg twice daily on days 2–5 and this dosage regimen is approved in Japan.[25] During Ebola virus disease outbreak the JIKI trial conducted demonstrated an improved survival rate in patients with moderate to high viral load with the higher dose of favipiravir (day 0:6000 to 9:2400 mg /day from day 1 to 9).[26] Significant reduction in viral load with favipiravir in patients with moderate viral load at baseline were found in similar Studies. A higher dose of favipiravir needs to be considered to have an impact on the viral load, since EC50 of favipiravir is higher than that of influenza in the perspective of COVID-19 treatment. The recommendation of regimen of favipiravir is 1800 mg of loading dose BID on day 1 followed by 800 mg BID from day 2 to maximum of day 14.

Safety profile

Pilkington et al study showed that favipiravir has an established and well-characterized safety profile from 4000+ patients.[27] The adverse effects of favipiravir include gastrointestinal adverse events, increase of aspartate aminotransferase (SGOT), increase of alanine transaminase (SGPT), psychiatric symptom reactions,uric acid elevations, decrease of neutrophil count, increase in blood triglycerides. Discontinuation were caused due to adverse events in 0.4% to 1.1% of cases. Even between low and high dose of favipiravir similar proportion of adverse events were reported which demonstrates favorable safety profile with respect to serious adverse events.

Contraindication

Because of the observation of its teratogenic potential in animal studies favipiravir is contraindicated in pregnant and lactating mothers. Since it is found to be distributed in sperms it is advised to use effective contraceptive method by both male and female of reproductive age during the 7 days post therapy and course.[28,29] It is also contraindicated insevere renal impairment, hypersensitivity, severe hepatic impairment. It should as be administered with care in patients with gout and hypercalcemia.[30]

Pharmacokinetics and Pharmacodynamics

Pharmacodynamics study revealed that Plasma protein-bound of favipiravir is 54% and it undergoes ribosylation and phosphorylation intracellularly. The bioavailability of favipiravir was found to be 97.6%, mean Cmax 51.5 µg/mL, elimination half life was found to be 2-5.5 hours, parent volume of distribution is 15–20 L and metabolites are really cleared.

In the AVIGAN package insert the pharmacokinetics study (day 1: 1,600 mg b.i.d., day 2–5: 600 mg b.i.d.) showed that concentration of favipiravir in healthy subjects was 20–60 µg/mL. The patients receiving the same regimen in the study conducted by the trough concentrations (within 8–12 hours) were mostly lower than the LLOQ. In severely ill patients with COVID-19 underexposure to FPV of great concern as the half-maximal effective concentration (9.7µg/mL) against SARS-CoV-2 tested in vitro is is much higher than that against influenza virus. Two patients under oral favipiravir and is under intubation had higher FPV concentrations than the other patients who were intubated with FPV. These reports suggest that that exposure to FPV is different depending on the severity of illness.

CONCLUSION

Favipiravir is an antiviral agents and a purine analogue by intracellular phosphoribosylation is converted to active favipiravir ribofuranosyl-5B-triphosphate (favipiravir-RTP). In -vitro studies reports demonstrate that favipiravir can be effective against the SARS-CoV-2 infection within a safe therapeutic dose. . However further studies need to be conducted to increase the information regarding the use of favipiravir in treatment of COVID-19.

REFERENCES

1. D. Wang, B. Hu, C. Hu, F. Zhu, X. Liu, J. Zhang, et al., Clinical characteristics of 138 hospitalized patients with novel coronavirus-infected pneumonia in Wuhan, China, JAMA, 2019; 323(11): 1061-1069.

2. C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet, 2020; 395(10223): 497-506.
3. Q. Li, X. Guan, P. Wu, X. Wang, L. Zhou, Y. Tong, et al., Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia N Engl J Med, 2020; 382: 1199-1207.
4. D. Wang, B. Hu, C. Hu, F. Zhu, X. Liu, J. Zhang, et al., Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China, JAMA, 2020; 323(11): 1061-1069.
5. R. Lu, X. Zhao, J. Li, P. Niu, B. Yang, H. Wu, et al., Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding, Lancet, 2020; 395(10224): 565-574.
6. Shashank Joshi, Jalil Parkar e. tal, Role of favipiravir in the treatment of COVID-19, International Journal of Infectious Diseases, 2021; 102: 501-508.
7. Qingxian Cai, Minghui Yang e.tal, Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study, Research Coronavirus Disease, 2019.
8. S. Perlman, Another decade, another coronavirus, N Engl J Med, 2020; 382: 760-762.
9. T. Zhang, Q. Wu, Z. Zhang, Probable pangolin origin of SARS-CoV-2 associated with the COVID-19 outbreak, Curr Biol, 2020; 30: 1578.
10. Auwaerter PG. Coronavirus COVID-19 (SARS-CoV-2), 2020; 3.
11. D.A. Berlin, R.M. Gulick, F.J. Martinez, Severe Covid-19, N Engl J Med (May) Epub ahead of print, 2020; PMID: 32412710.
12. Ubissi L, Imbert I, Ferron F, et al. SARS-CoV ORF1b-encoded nonstructural proteins 12–16: replicative enzymes as antiviral targets. Antiviral Res, 2014; 101: 122–130.
13. Te Velthuis AJW, Arnold JJ, Cameron CE, et al. The RNA polymerase activity of SARS-coronavirus nsp12 is primer dependent. Nucleic Acids Res, 2010; 38(1): 203–214.
14. Cheng A, Zhang W, Xie Y, et al. Expression, purification, and characterization of SARS coronavirus RNA polymerase. Virology, 2005; 335(2): 165–176.
15. Gong P, Peersen OB. Structural basis for active site closure by the poliovirus RNA-dependent RNA polymerase. Proc Natl Acad Sci, 2010; 107(52): 22505–22510.
16. Peersen O, A comprehensive superposition of viral polymerase structures. Viruses, 2019; 11(8): 745.
17. Shannon A, Selisko B, Huchting J, et al. Favipiravir strikes the SARS-CoV-2 at its achilles heel, the RNA polymerase. bioRxiv, 2020.

18. Baranovich, S.S. Wong, J. Armstrong, H. Marjuki, R.J. Webby, R.G. Webster, et al., T-705 (favipiravir) induces lethal mutagenesis in influenza A H1N1 viruses in vitro, J Virol, 2013; 87: 3741-3751.
19. A. Shannon, B. Selisko, N. Le, J. Huchting, F. Touret, G. Piorkowski, et al., Favipiravir strikes the SARS-CoV-2 at its Achilles heel, the RNA polymerase, bioRxiv, 2020.
20. Z. Jin, L.K. Smith, V.K. Rajwanshi, B. Kim, J. Deval, The ambiguous base-pairing and high substrate efficiency of T-705 (Favipiravir) Ribofuranosyl 5′-triphosphate towards influenza A virus polymerase, PLoS One, 2013; 8: e68347.
21. Y. Furuta, T. Komeno, T. Nakamura, Favipiravir (T-705), a broad spectrumbroad-spectrum inhibitor of viral RNA polymerase, Proc Jpn Acad Ser B Phys Biol Sci, 2017; 93: 44.
22. K. Shiraki, T. Daikoku, Favipiravir an anti-influenza drug against life-threatening RNA virus infections, Pharmacol Ther, 2020; 209: 107512.
23. F.G. Hayden, N. Shindo, Influenza virus polymerase inhibitors in clinical development, Curr Opin Infect Dis, 2019; 32: 176-186.
24. G. Li, E. De Clercq, Therapeutic options for the 2019 novel coronavirus (2019-nCoV), Nat Rev Drug Discov, 2020; 19: 149-150.
25. M. Wang, R. Cao, L. Zhang, X. Yang, J. Liu, M. Xu, et al. ,Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro, Cell Res, 2020; 30: 269-271.
26. F D. Sissoko, C. Laouenan, E. Folkesson, A.B. M'Lebing, A.H. Beavogui, S. Baize, et al., ExperimentalExperimental treatment with favipiravir for Ebola virus disease (the JIKI Trial): a historically controlled, single-arm proof-of-concept trial in Guinea, PLoS Med, 2016; 13: 1001967.
27. V. Pilkington, T. Pepperrell, A. Hill, A review of the safety of favipiravir — a potential treatment in the COVID-19 pandemic, J Virus Erad, 2020; 6: 45-51.
28. T. Nagata, A.K. Lefor, M. Hasegawa, M. Ishii, Favipiravir: a new medication for the Ebola virus disease pandemic, Disaster Med Public Health Prep, 2015; 9: 79-81.
29. L. Delang, R. Abdelnabi, J. Neyts, Favipiravir as a potential countermeasure against neglected and emerging RNA viruses, Antivir Res, 2018; 153: 85-94.
30. Fabiflu prescribing information, 2020.