Drug Corner

Consensus Statement on : Favipiravir as an Empirical Therapy for Influenza-like Illness during COVID-19 Pandemic

Vijayalakshmi Thanasekaran[1], J K Samaria[2], Surya Kant[3], Parvaiz Koul[4], Narayan Mishra[5], PS Tampi[6], Agam Vora[7], Mangesh Tiwaskar[8], Rajesh Swarnakar[9], Nitin Abhyankar[10], Prashant Chhajed[11], V Rajesh[12], KS Satish[13], Arjun Khanna[14], SK Munjal[15], Akash Deep Singh[16], Mahavir Modi[17], Arpan Shah[18]

The COVID-19 pandemic continues to have a serious impact on the lives of millions of people worldwide. Empirical therapy is being used to reduce morbidity and mortality of COVID-19 patients. Favipiravir, which is an oral broad-spectrum anti-viral agent with proven efficacy against various RNA viruses, acceptable tolerability profile and favorable benefit-risk ratio in short term use, has got an emergency use authorization in many countries including India for the treatment of mild to moderate cases of COVID-19. It has demonstrated promising results in terms of rapid viral clearance, quick symptom control, and pulmonary radiographic improvement. Due to reasons such as lockdown, isolation, diagnostic delays, fear of quarantine or getting tested, cost, etc., the golden time period (first 24-48 hrs) is lost in COVID-19 patients which is crucial for initiating antiviral therapy. Therefore, the panel members of *'Academy of Advanced Medical Education'* propose that favipiravir can be recommended in confirmed, early probable and possible cases of mild and moderate severity as an empirical therapy during current pandemic. It is important to counsel the patients and explain to them about the limited clinical evidences with favipiravir, therefore, a signed consent form from patient must be kept before initiating treatment. Well-designed double-blind controlled trials are urgently required to understand this further.

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Key words **: COVID-19, Favipiravir, SARS Cov-2, Pandemic, Anti-viral.**

Introduction & Epidemiology :

COVID-19 pandemic has affected more than 29.50 million people worldwide, more than 4.94 million people in India and the number is going up daily. Mortality in COVID-19 is also climbing rapidly, in India alone nearly 81,000 have died.[2] Older adults and people of any age who have comorbidities namely hypertension and

[1]MBBS, DTCD, MD (Medicine), Chennai
[2]MD (Chest & TB), FNCCP, FIACM, FIAMS, FICP, Varanasi
[3]MD (Chest & TB), Lucknow
[4]MD, Fellowship of Pulmonary & Critical Care Medicine, Long Island Jewish Health System, NY USA, Fellow of American College of Chest Physicians, FRCP, Royal College of Physicians (London), SKIMS, Srinagar
[5]MD, FIAB, FNCCP, FICS, FIRD, FICAAI, FRCP (Glasgow), FCCP (USA), Bhubaneshwar
[6]MD (Med) DM - Pulmonary & Critical Care, FCCP (USA), Mumbai
[7]MBBS, DETRD, MD (Chest & TB), Mumbai and Corresponding Author
[8]MBBS, MD (Med), FICP, Mumbai
[9]MBBS DNB Chest, DTDC, MNAMS FCCUSA, Nagpur
[10]MD (Medicine), ERS Diploma in Respiratory Diseases, Pune
[11]DNB (Respiratory Diseases), MD (TB & Chest), DETRD
[12]DNB (Pulmonary Medicine), Cochin
[13]MD, DNB, FRCP, Bengaluru
[14]MD, DNB (Internal Medicine), DM - Pulmonary& Critical Care, FCCP (USA), European Diplomate in Respiratory Medicine, MNAMS, New Delhi
[15]MD (Chest & TB), Delhi
[16]MD (Medicine), DM (Pulmonary & Critical Care) FCCP, Ludhiana
[17]MD, DNB (Chest Medicine), Pune
[18]MBBS, DTCD, DNB (Respiratory Medicine), FCCP, FAPSR, Baroda
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Editor's Comment :

- **There is no definitive therapy against COVID-19, therefore, empirical therapy with repurposed antiviral agents are being used in an attempt to reduce morbidity and mortality in COVID-19 patients.**
- **On 20 June 2020, favipiravir, was approved with 'restricted emergency use authorization' by the DCGI in India for mild to moderate cases of COVID-19.**
- **Due to variety of patient related, diagnostic and operational challenges, the golden time i.e. the first 24 to 48 hours are lost which are crucial for initiating antiviral therapy. Favipiravir, being a broad-spectrum anti-viral agent with promising results and mild/ manageable side effect profile in mild to moderate cases of COVID-19 patients, can be used empirically in confirmed, early probable and possible cases during pandemic period for rapid viral clearance, quick symptom control, and pulmonary radiographic improvement.**

diabetes, have shown severe disease and worse prognosis. As of today, there is no vaccine available for COVID-19 nor there is any definite drug therapy. Therefore, many older molecules are being studied vigorously. A various group of drugs including broad spectrum antivirals, antimalarials, antibiotics, anti-helminth, vaccines like BCG, MMR as immuno-modulators, minerals, vitamins, anti-inflammatory, etc. are being employed as experimental adjuncts to supportive care against COVID-19.[3]

Phases of COVID-19 Infection :

It has been proposed that COVID-19 infection in the lungs includes three important phases:

1. An initial phase encompassing viral replication and relatively mild symptoms; also called the "early infection phase".

2. A second phase, which is characterized by adaptive immunity stimulation and predominance of respiratory symptoms; also called the "pulmonary phase".

3. And, in few cases, a third and the last phase with progress to a hyperinflammatory condition; also known as the "hyper inflammation phase".

Per the infection phase, clinical features range from mild symptoms (fever, cough, myalgia or fatigue, sore throat, headache) to acute respiratory distress syndrome (hypoxemia, shortness of breath) to ARDS, shock, multi-organ failure respectively.4Many Indian pulmonologists, especially from our expert group, reported that there is a 4th phase, the "Recovery phase with/without Fibrosis" or post-discharge phase of prolonged symptoms of residual hypoxia and shortness of breath which they are seeing in many of their Indian patients who need to be on prolonged oxygen therapy, steroids and even antifibrotics.

Case Definitions of COVID-19[5]— *(Based on clinical, epidemiological and laboratory parameters)*

• Possible Case

■ A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath), AND a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset; OR,

■ A patient with any acute respiratory illness AND having been in contact with a confirmed or probable COVID-19 case in the last 14 days prior to symptom onset; OR,

■ A patient with severe acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath; AND requiring hospitalization) AND in the absence of an alternative diagnosis that fully explains the clinical presentation.

• Probable Case

■ A possible case for whom testing for the COVID-19 virus is inconclusive. OR,

■ A possible case for whom testing could not be performed for any reason

• Confirmed Case

A person with laboratory (RT PCR or Rapid Antigen Tests) confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.

Clinical Severity & Assessment Parameters of COVID-19[6] :

(Clinical Management Protocol: Covid-19 Version 5 03.07.20 Government of India Ministry of Health and Family Welfare Directorate General of Health Services)

• Mild

Patients with uncomplicated upper respiratory tract infection may have mild symptoms such as fever, cough, sore throat, nasal congestion, malaise, and headache with no evidence of breathlessness or Hypoxia (normal saturation).

• Moderate

Patients with pneumonia with no signs of severe disease but with the presence of clinical features of dyspnoea and or hypoxia, fever, cough, including SpO2 <94% (range 90-94%) on room air, Respiratory Rate more or equal to 24 per minute.

• Severe

Patients with Severe Pneumonia, Acute Respiratory Distress Syndrome, Sepsis, and Septic shock. Clinical parameters include clinical signs of Pneumonia plus one of the following: respiratory rate >30 breaths/min, severe respiratory distress, SpO2 <90% on room air.

Unmet Need: An Outpatient Treatment that Helps Prevent Hospitalization :

Early Outpatient Management of Symptomatic, High-Risk Covid-19 Patients that Should be Ramped-Up Immediately as Key to the Pandemic Crisis:

Based on various studies that addressed the treatment of mildly symptomatic high risk COVID -19 patients, investigators have suggested that there is a compelling argument for early outpatient treatment of symptomatic, high-Risk Covid-19 patients that should be ramped-up immediately as a key to the pandemic crisis.[7]

Early Intervention Initiation in High-Risk COVID-19 Patients :

Owing to the understanding that disease progression can occur quickly in stable patients and that viral loads are the highest early in the infection course, and hence rapid initiation of therapy in high-risk populations (patients who are hospitalized or outpatients who are at high risk of complications) is rational and should be considered.[8]

Early intervention is vital to halt the fatal pulmonary immunopathology. Thus, it is strongly recommended that the current treatment guideline be modified to initiate treatment very early in COVID-19 patients. This may be particularly crucial for high-risk patients.[9]

While there are weak or no pieces of evidence for benefits of drugs like hydroxychloroquine and lopinavir-ritonavir, few drugs like favipiravir, dexamethasone, and remdesivir were found to be effective in the management of COVID-19.[10]

Early Intervention Initiation to Diminish Virus Replication and Improve Outcomes:

Over 80% of COVID-19 patients have mild disease. The clinical improvement rates at 7 days with Favipiravir were 73.8%, 66.6% and 40.1% for mild, moderate and severe disease, in that order.[11]

The phase 3 SIMPLE II trial in patients with moderate COVID-19 disease showed that 5 days of remdesivir treatment was 65% more likely to yield clinical improvement at day 11 than the standard of care (P = 0.18). These data show that early intervention with a 5-day treatment course can significantly improve outcomes.[12]

Indian Favipiravir Clinical Trial demonstrated 40% faster accomplishment of "clinical cure" in the Favipiravir treatment arm (3 days), compared to the control arm (5 days) (p=0.029). 69.8% of patients in the Favipiravir treatment group achieved clinical cure by Day 4, which was statistically significant in comparison to 44.9% observed in the control group (p=0.019).[13]

Expert Group Opinion and Recommendations:

A panel of senior respiratory physicians and pulmonologists having vast experience in the management of COVID-19 was constituted by 'Academy of Advanced Medical Education' for developing the consensus statement and recommendations regarding the use of favipiravir in mild to moderate cases of Covid-19 as an attempt to guide the medical fraternity.

"Owing to its overall acceptable tolerability profile and favorable benefit-risk ratio in short term use, Favipiravir can be recommended in confirmed, early probable and possible cases of mild and moderate severity as empirical therapy. The Expert Group further opined that some of the tests such as LDH, D-dimer, CRP, CBC (especially Neutrophils/Lymphocytes Ratio), serum Ferritin should be suggestive of COVID-19. CT scan findings could serve as a significant diagnostic tool as it has the advantage of quick turn over time & is widely available.

There could be strong clinical suspicion of Covid-19 infection despite of negative RTPCR. In our country, there are times when testing is not done for operational reasons or it may be false negative - pending confirmation. There could be sampling or processing errors in laboratories. Real Time PCR at many places is done by appointment and it may take up to 3 days for reports to be available.

Per the Expert Group, empirical Favipiravir therapy should be initiated within 24 to 48 hours as the drug is mainly effective in initial phase (it acts on the viral replication). It is recommended that all possible tests like basic biochemistry including liver and renal function test, tests for inflammatory markers &x-ray chest / CT scan/ HRCT chest must be done as per the facility before the initiation of Favipiravir therapy. One may have to investigate further depending on associated co-morbidities.

Additionally, the Expert Group proposed (no published evidence) that any acute febrile illness suggestive of COVID-19 should be treated as COVID-19 in this pandemic situation unless proved otherwise. When used empirically, if the diagnosis is proved otherwise, the treatment may be discontinued."

The expert group strongly feels that robust double-blind control studies involving a larger group of patients are required to understand this further. Nevertheless, with the available clinical evidence and the panel's

expertise, the expert group believes that if Favipiravir is used early in the course of the disease, it may be able to bring about early improvement and may help reduce hospitalizations and prevent complications. Clinical judgment may be taken on a case-to-case basis. When used empirically, if the diagnosis is proved otherwise, treatment could be discontinued. For diagnosis, if the Rapid Antigen Test is positive, the patient is categorized as a confirmed case. Probable cases with a negative Rapid Antigen Test should undergo RT-PCR tests and these cases should be offered Favipiravir treatment option. RT PCR can be false negative is up to 30% cases and treatment may not be stopped in such cases if the clinical suspicion and the ancillary diagnostic tests are suggestive of SARS Cov2 infection (i.e probable case). Approach to continuation of favipiravir treatment in such cases should be defined by the clinical judgement of the treating physician. It is crucial to counsel the patient and explain to them about the limited clinical evidence and get a consent form signed from patient before starting the treatment with favipiravir. Also, this drug Favipiravir should be available as soon as possible in all retail medicine stores to be dispensed with a prescription of authorized medical practitioner for the early institution of treatment.

The expert panel was also in the opinion that moderate to severe cases with rapidly worsening situation should be evaluated further to start another antiviral agent Remdesivir. Remdesivir is an injectable drug and has received 'restricted emergency use authorization' by DCGI in India for the management of patients with severe COVID-19 infection only.[14]

Favipiravir Mechanism of Action :

Favipiravir is a derivate of pyrazine carboxamide. Its chemical name is 6-fluoro-3-hydroxy- 2-pyrazinecarboxamide. It works via inhibition of viral RNA dependent RNA polymerase (RdRp). Favipiravir is approved for novel epidemic influenza strains that do not respond to standard antiviral therapies in Japan. As a purine analogue, it functions as a chain terminator at the site of incorporation of the viral RNA and decreases the viral load. Favipiravir ends elongation after the incorporation of a single favipiravir molecule and after the incorporation of two consecutive favipiravir molecules, and the synthesis of this complementary viral RNA strand cannot be finished. Favipiravir treatment increases the frequency of transition and transversion in viral genomes, and these mutations are hypothesized to be caused by favipiravir, resulting in lethal mutagenesis. Among antiviral drugs, one distinctive feature of favipiravir is its broad-spectrum activity toward RNA viruses, comprising influenza virus, rhinovirus, poliovirus, ebola and respiratory syncytial virus.[15]

Safety/ Adverse Reactions[16]:

The most common adverse drug reaction with favipiravir include mild to moderate diarrhea, an asymptomatic increase of blood uric acid and hepatic transaminases, and a decrease in the neutrophil counts.

Contraindications, Warnings & Precautions[16]:

Favipiravir is contraindicated in patients having severe renal, hepatic impairment, and during pregnancy and lactation. It is also contraindicated in those having hypersensitivity to the active substance or any of its excipients. It is advised to the female patients of childbearing age that they rule out pregnancy before starting therapy with favipiravir. Adults are advised to use the most effective contraceptive methods, for up to 7 days, post the completion of the treatment. Instruct the male undergoing treatment to refrain from sexual intercourse with a pregnant woman. Patients with a history of abnormalities in the metabolism of uric acid or having gout should be cautious as blood uric acid level may increase, and symptoms may get aggravated with favipiravir use. Although the causal relationship has not been established yet, psychoneurotic symptoms such as abnormal behavior after administration of anti-influenza drugs like Favipiravir have been reported.

Use in Special Populations[16]:

- *Pregnancy & Lactation*: Favipiravir is contraindicated in pregnant women due to its teratogenic potential and embryotoxicity in animals. It is also contraindicated in lactating mothers.
- *Pediatric*: Favipiravir has not been approved in children.
- *Elderly*: Should be administered with care by monitoring their general conditions.
- *Liver function*: An increase of plasma level of Favipiravir has been reported with liver impairment and it may transiently increase hepatic transaminases.
- *Renal impairment*: Not studied in trials.
- Use with care in mild to moderate hepatic and renal impairment.

Dosage[16] :

The approved dosage of favipiravir in India for adults is 1800 mg orally twice daily on 1st day followed by 800 mg orally twice daily from 2nd day onwards and

based on clinical evaluation, it can be given up to a maximum of 14 days.

International Status :

Favipiravir was primarily used for the treatment of Influenza and was developed by Toyoma Chemicals in Japan. The drug has shown positive results in terms of reducing treatment duration and improved lung conditions in Covid-19 patients.

COVID-19 therapeutic management guidelines include Favipiravir in Russia, Japan, UAE & Saudi Arabia and it is currently being used for mild to moderate cases of COVID-19 and has a dosage duration of up to 14 days based on the condition of the patient. Approximately 18 global CTs are ongoing with favipiravir in more than 3000 subjects in clinical trials globally including India, USA, Canada, Italy, China, France, UK, and other countries. It has been approved by Italy & China for experimental use/ compassionate use in COVID-19.

Indian Status :

Favipiravir has been approved with restricted emergency use authorization by DCGI in India for mild to moderate COVID-19 management. Treating physician or prescriber needs to get a consent form signed from patient before starting the treatment with favipiravir.[14]

Favipiravir in Co-morbid Patients :

Data from the Japanese registry regarding the clinical use of Favipiravir in COVID-19 which included a total of 2,158 patients across 407 hospitals had about 49% of comorbid patients (including diabetes, hypertension) and 52% aged above 60 years. The study results demonstrated clinical improvement in 84.5% and 87.8% patients with Favipiravir in moderate and mild COVID-19 patients respectively at the 14thday.[17]

Evidence from Clinical Trials Globally :

• **Favipiravir vs Lopinavir/ Ritonavir —** An open-label, double arm, non-randomized study was conducted wherein patients who tested positive for the novel coronavirus RNA either received Favipiravir or Lopinavir/Ritonavir. In the Favipiravir (FPV) Arm (n=35), the patients received 1600 mg twice daily on Day 1 and 600 mg twice daily on Days 2–14 while those in the comparator arm (n=45) received Lopinavir (LPV) 400 mg/ritonavir (RTV) 100 mg twice daily. In addition, all participants received IFN-a1b 60 mg twice daily by aerosol inhalation. The endpoints of the study consisted of comparison of the time of viral clearance, and the improvement rate of chest computed tomography (CT) scans on Day 14, after treatment and safety assessment. The median time of viral clearance for the patients managed with FPV was 4 days which was significantly lower than LPV/RTV patients (11 days). Patients on FPV demonstrated greater improvement in chest CT after treatment (at day 14) compared to another arm (91.4% versus 62.2 %).The total adverse events in the FPV arm was four (11.43%), which was significantly lesser than those in the comparator arm (55.56%).[18]

• **Favipiravir vs Umifenovir —** A prospective, multi-centric, comparative trial, consisting of 240 patients with chest CT imaging and laboratory-confirmed COVID-19 infection, aged 18 years or older was conducted. The patients were randomly assigned to receive either the conventional therapy plus Favipiravir or control (Umifenovir) drug. The primary outcome considered was clinical recovery rate at day[7]. Duration of fever, cough relief latency, and auxiliary oxygen therapy or non-invasive mechanical ventilation rate were considered as the secondary outcomes. A total of 120 patients were allocated to the Favipiravir group (116 assessed) while 120 to the control group (120 assessed). Seven day's clinical recovery rate was found to be 55.86% in the control group while 71.43% in the Favipiravir group (P = 0.0199). The latency to fever reduction and cough relief in the Favipiravir group was found to be significantly shorter than that in the control group (both P<0.0001). Furthermore, no statistical difference was noted of auxiliary oxygen therapy or noninvasive mechanical ventilation rate (both P>0.05).[19]

• **Japanese observational study —** A multicenter observational study was conducted to examine and understand the clinical course of moderate and severe COVID-19 patients receiving Favipiravir. In this study, a total of 2,158 patients received Favipiravir. Largely, in mild to moderate COVID-19 patients, clinical improvement with Favipiravir was observed in up to 74% by day 7 of treatment which further improved to 88% by Day 14 of the treatment.[20]

• **Russian Study basis approved by the Russian Ministry of Health** — A total of 390 patients (Part 1-60 and Final part 360) were considered in a study conducted in Russia. The median elimination time for the SARS CoV-2 observed was 4 days with Favipiravir while 9 days with the standard therapy. In the favipiravir group, on day 4 of treatment, 65% of patients became RT-PCR negative, on day 10 of treatment, 90% of patients were found to be real-time PCR negative for SARS CoV-2. Approximately 68% of patients in the favipiravir group reached fever resolution on day 3 as

opposed to those on standard therapy on day 6.The overall reported efficacy of favipiravir was observed to be >80% with regards to virus elimination proven with negative test report and symptomatic improvement.[21]

• **Indian Favipiravir Clinical Trial —** A randomized, multi-centric study was conducted in India across 11 centers to assess the efficacy and safety of Favipiravir with the standard of care vs. standard of care alone in mild to moderate COVID-19 patients. The sample size considered was 150, further consisting of 90 mild and 60 moderate patients). The study population chosen consisted of hospitalized patients with confirmed RT-PCR positivity. The dosing regimen considered was Favipiravir tablets 3,600 mg (1,800 mg BID) on Day 1 and 1,600 mg (800 mg BID) from day 2 onwards for up to a maximum of 14 days, in conjunction with supportive care.

• The results from the phase 3 study demonstrated numerical improvements in primary endpoint with 28.6% quicker viral clearance in the overall population as quantified by the median time until cessation of oral shedding of virus in the Favipiravir treatment arm compared to those in the control arm. The results also pointed out 40% quicker achievement of "clinical cure" which was in turn defined as the physician's assessment of normalization of clinical signs namely temperature, oxygen saturation, respiratory rate, and cough. Also, it was observed that there was a statistically significant reduction in median time to clinical cure in the Favipiravir treatment arm (3 days [95%CI 3.0, 4.0]), compared to the control arm (5 days [95%CI 4.0,6.0]) (HR 1.749 [95% CI 1.096, 2.792]; p=0.029). About 69.8% of patients in the Favipiravir treatment arm accomplished clinical cure by Day 4, which was statistically significant as compared to 44.9% observed in the control arm (p=0.019). In patients who showed clinical deterioration and required oxygen support, those receiving Favipiravir exhibited a longer median time to first-time use of oxygen of 5 days (95%CI 1.0,6.0) versus 2 days (95% CI 1.0-4.0) in the control group. Favipiravir was found to be well tolerated with no serious AE. AEs were reported in 26 patients in the favipiravir treatment group (35.6%) vs 6 patients in the control group (8%). Most of these AEs were mild to moderate and none resulted in drug discontinuation or dosing adjustments. The most commonly encountered AE was asymptomatic transient increases in uric acid (12 patients in the Favipiravir treatment arm while none in the control arm); most resolved in the first follow up. There was minimal GI disturbance and no clinically significant differences were found between the treatment groups.[22]

Limitations :

Based on the currently available evidences, favipiravir has shown clinical benefits and acceptable tolerability profile in mild to moderate cases of COVID-19. Nonetheless, members of expert panel of 'Academy of Advanced Medical Education' opine that more well-designed, multicentric, double-blind controlled trials with a higher number of sample size are urgently required to understand the extent of benefit with favipiravir in the management of COVID-19 patients. It is not yet clear whether favipiravir has any role in severe cases of COVID-19 and whether it reduces need of ventilatory support and affects mortality. Also, the dose and duration of favipiravir treatment are higher and longer, respectively, in COVID-19 patients than in influenza, therefore, close monitoring of any adverse events should be done in patients using favipiravir as part of phase 4 study or post marketing surveillance exercise.

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