Drug Corner

Position of Favipiravir in COVID-19 Therapeutics – What is The Interim Status!

Shambo Samrat Samajdar[1], Santanu K Tripathi[2]

Development of anti-COVID 19 therapeutics is generally centered on principles of drug repurposing. Drug repurposing (also called drug repositioning, re-profiling or re-tasking) is a way to identify new indications or uses for already approved drugs[1]. To compress the timeline for drug development it is the only way to search drugs for managing COVID 19. It is difficult to afford time for a new drug development now in this pandemic situation as it may cost minimum 10-12 years. Starting from hydroxy-chloroquine, remdesvir, lopinavir-ritonavir and favipiravir; all these agents were actually approved for some other indications but now used for COVID 19 management. Glenmark pharmaceuticalafter receiving manufacturing and marketing approval from India's drug regulator, had launched on June 20, 2020, first oral Favipiravir for the treatment of mild to moderate COVID-19 infected patients.

Favipiravir – Mechanism of Action :

Favipiravir was approved in Japan in March 2014, for treatment of new or re-emerging influenza virus infections. Favipiravir is a prodrug which is converted into T-705-ribosyl triphosphate (T-705RTP) in vivo and inhibits viral RNA polymerase selectively[2]. It is postulated that favipiravir is a broad spectrum anti RNA viral agent. The EC50 of favipiravir for COVID-19 in vitro is 61.88 μM[2]; whereas EC50 of remedsvir is 1.76 μM[3] and hydroxychloroquine is 0.72[4]. Larger the value of EC50 generally suggests lesser potency of the drug. This is why we need a very high dose of favipiravir for its anti-viral effects.

Evidences with Favipiravir :

One prospective, multicenter, open-label, randomized controlled trial[5] was conducted in Wuhan, China in February, 2020; to compare the efficacy and safety of favipiravir and umifenovir in COVID 19 pneumonia patients. In this trial clinical recovery rate at 7 days or the end of treatment was considered as primary outcome. favipiravirgroup and umifenovir group were assigned with 120 patients each. 7 day's clinical recovery rate was 55.86% in the umifenovir group and 71.43% in thefavipiravir group (P = 0.0199). Without comorbidities COVID-19 patients and COVID-19 patients with hypertension and/or diabetes, the time of fever reduction and cough relief in favipiravir group was significantly shorter than that in umifenovir group (both P < 0.001). Regarding secondary outcome like need of auxiliary oxygen therapy or noninvasive mechanical ventilation rate, there were no statistical significant differences. Hyperuricemia, abnormal LFT reports and psychosomatic adverse effects were concerns in favipiravir arm. In this trial effect on viral load was not assessed.

Dosage :

1800 mg twice daily on Day 1 and followed by 800 mg twice daily for Day 2 to day 14.

Need to Vigilant[6] :

1. There is a chance to have potential adverse drug – drug interactions with pyrazinamide, repaglinide, theophylline, famciclovir. Need to be cautious while using this drug in back ground of hyperuricemia and altered hepatic function.
2. When oral administration is extremely difficult there is a possibility to prepare the drug suspension by adding water heated to 55 ° C and deliver it to the subject via insertion of a nasogastric tube.
3. Contraindicated in pregnancy or woman who may have pregnancy as this drug is highly toxic to embryo. Screening of pregnancy is an absolute necessity before prescribing favipiravir.
4. The risk of teratogenic effect of favipiravirshould be fully explained to patients. Both the partners should be informedto use contraceptive measures duringthe administration period and for 7 days after the administration.
5. Favipiravir is secreted into semen; the risk

[1]MD, DM Resident in Clinical Pharmacology, School of Tropical Medicine, Kolkata 700073 and corresponding author
[2]MD, DM (Clinical Pharmacology), Professor & Head, Department of Clinical & Experimental Pharmacology, School of Tropical Medicine, Kolkata 700073
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should be elaborately explained when administering to male patients. They should use contraceptive preferably condom during sexual intercourses while taking the medicine and 7 days after stopping favipiravir.

6. Sexual intercourse with pregnant women during taking favipiravir should be prohibited.

7. Increase of plasma level of favipiravir had been seen in patients with impaired hepatic function.

8. Psychoneurotic symptoms such as abnormal behavior after administration of favipiravirwere seen and been reported but the causal relationship is not yet established. Need to be vigilant in this regard. Influenza encephalopathy may be a differential diagnosis. But this vulnerable period requires close attention from family members, which may hamper the classic rule of isolation.

Adverse Effects of Favipiravir :

Major adverse reactions included hyperuricemia, diarrhoea, neutropenia and increase in SGOT and SGPT level. Patients on favipiravir need cautious monitoring and may require urgent de-challenge of the drug and further care if patients develop shock, anaphylaxis, pneumonia, fulminant hepatitis, hepatic dysfunction, jaundice, toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, acute kidney injury, leucopenia, neutropenia, thrombocytopenia, neurological and psychiatric symptoms (like altered consciousness, behavioral abnormality, delirium, hallucination, delusion, convulsion, etc) and hemorrhagic colitis. Adverse drug reporting form should be filled up and reported to the nearest ADR monitoring center.

Favipiravir and Umifenovir Combination :

Favipiravir and umifenovir Combination is also being tried to see the efficacy on SARS COV 2. Favipiravir prevent viral replication by inhibiting RNA dependent RNA polymerase; whereas umifenovir interacts with viral attachment. Umifenovir[7] inhibits fusion between the viral envelope and the cell membrane of the target cell. Viral entry to the target cell would be prevented. So we have to wait to get the clinical trial reports to finally comment on synergistic effect of this combination against SARS COV 2.

Interim Indian Guidelines and Favipiravir :

Till date 'Clinical Management Protocol: COVID-19' by GOI version 4 (dated 27/06/2020) not includes favipiravir as a treatment option[8]. 'Standard Treatment Protocol for COVID 19'by Maharashtra government revision 2 Dated-22.06.2020 includes favipiravir. Symptomatic upper respiratory tract infection mild category COVID 19 patients with comorbidity and moderate category COVID 19 patients were advised to be administered with favipiravir 1800 mg twice daily on day 1 followed by 800 mg BD for 7 days ad if needed can be continued up to maximum 14 days[9].

Conclusion :

A phase 3 clinical trial is ongoing in Japan with favipiravir, a phase 2 trial is planned to be conducted in the United States and that would enroll approximately 50 patients with COVID-19[10]. In India, Glenmark pharmaceutical has started a phase 3 trial combining 2 antiviral agents, favipiravir and umifenovir, recently[11]. We have to wait for the results to have a clear knowledge on the efficacy and safety of this novel drug.

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