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Favipiravir, an antiviral for COVID-19?

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Sir,

A novel coronavirus, SARS-CoV-2, emerged in December 2019 in Wuhan, China, which is spreading far more rapidly than its predecessors, having already infected millions of patients worldwide as of 19 April 2020.[1] As the scale of the ongoing COVID-19 outbreak has reached pandemic proportions, intensive worldwide public health efforts are underway to control the outbreak. However, as definitive therapies for established COVID-19 remain to be defined, significant interest exists in repurposing existing antiviral agents for use against COVID-19.

Favipiravir triphosphate is a purine nucleoside analogue, which acts as a competitive inhibitor of RNA-dependent RNA polymerase.[2] It has activity against influenza A and B, including activity against oseltamivir- and zanamivir-resistant influenza viruses, several agents of viral haemorrhagic fever and SARS-CoV-2 *in vitro*.[2–4] Favipiravir is approved for novel epidemic influenza strains that are unresponsive to standard antiviral therapies in Japan.

Favipiravir was identified to have activity *in vitro* against SARS-CoV-2, albeit requiring a high concentration compared with chloroquine or remdesivir (EC_{50} = 61.88 μM).[3] Despite a similarly elevated EC_{50} identified for favipiravir and Ebola virus, it was identified in previous animal models to be highly effective as post-exposure prophylaxis for mice exposed to Ebola virus challenges, with rapid virological response preventing mortality.[5,6] Based on the dosing strategies and pharmacokinetic data from human influenza trials, an intensified dosing strategy of 6000 mg loading on day 1 followed by maintenance therapy of 1200 mg orally twice daily for 10 days was employed in a single-arm clinical trial for Ebola virus disease in Guinea.[7]

In a retrospective analysis of 124 patients with Ebola virus disease in Sierra Leone, those treated with favipiravir had a significantly higher survival rate compared with patients receiving supportive management (56.4% versus 35.3%; $P = 0.027$).[8] Patients received favipiravir 800 mg orally twice daily on day 1 and 600 mg orally twice daily on days 3–11. Viral loads were quantified for 35 patients twice during their hospitalization and were significantly reduced amongst patients receiving favipiravir.

Favipiravir has also been used as pharmacological post-exposure prophylaxis for Ebola virus disease.[9] In a case series of four healthcare workers with higher risk Ebola virus exposures, including two hollow-bore needlestick injuries, none of the patients who received 10 days of high-dose favipiravir developed Ebola virus disease.

Early clinical experience with favipiravir for COVID-19 is promising. An open-label non-randomized trial of 80 patients with COVID-19 in China identified a significant reduction in the time to SARS-CoV-2 viral clearance in patients treated with favipiravir compared with historical controls treated with lopinavir/ritonavir.[10] Patients with mild or moderate COVID-19 were enrolled within 7 days from disease onset; those ≥75 years old, with severe or critical disease, chronic liver disease or end-stage renal disease were excluded. Patients in the intervention arm received favipiravir 1600 mg orally twice daily on day 1 followed by 600 mg orally twice daily on days 2–14. Both arms were co-treated with inhaled IFN-α1b 60 μg twice daily and therapy was continued until viral clearance, up to a maximum of 14 days. Thirty-five patients were assigned to favipiravir and 45 patients to lopinavir/ritonavir, with a median age of 47 years (IQR = 35.8–61); 13.7% were ≥65 years old. There was a significant reduction in the median time to viral clearance with favipiravir (4 days; IQR = 2.5–9) compared with lopinavir/ritonavir (11 days; IQR = 8–13; $P < 0.001$). Further, by day 14, 91.4% of patients in the favipiravir arm had radiographic improvement versus 62.2% in the lopinavir/ritonavir arm. There was a significantly lower rate of adverse events in patients receiving favipiravir (11.4% versus 55.6%; $P < 0.01$).

Given the demonstrated *in vitro* of activity of favipiravir against SARS-CoV-2 and signals of benefit in early clinical experience for COVID-19, further studies are urgently needed. The results of several ongoing randomized controlled trials to assess the efficacy of favipiravir for COVID-19 will further elucidate the role of favipiravir in the management of the ongoing coronavirus pandemic.

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