SARS-CoV-2 virological and genomic studies in a favipiravir clinical trial cohort

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ABSTRACT

Favipiravir has been shown to reduce viral load and decrease the duration of symptoms in several clinical investigations. The viability of SARS-CoV-2 in the setting of favipiravir treatment, as well as the risk of resistance, are unknown. Between March and May 2020, we sequenced SARS-CoV-2 in nasopharyngeal tissues taken from patients who took part in a randomized clinical trial of favipiravir at hospitals across Japan. Those who remained RT-PCR-positive 5–8 days after starting favipiravir medication had their genomes sequenced in pairs. The cytopathic impact was investigated in daily nasopharyngeal tissues from 69 individuals who were RT-PCR positive at the time of randomization (CPE). Early in the experiment, some strains belonged to clade 19 B, while the majority belonged to clade 20 B. The median period from the beginning of the condition to the discovery of a negative CPE was 9 days. CPE was highly linked to the length of time from the beginning of the illness, viral load, age, and male sex. All except one of the 23 patients for whom paired genomes were available had identical genomes. One patient who got favipiravir had two mutations, none of which was in the RdRp gene. In this clinical study in Japan, the SARS-CoV-2 genome distribution represented an initial inflow of strains from China, followed by strains from Europe. Age, male sex, and viral loads were all linked with CPE, but not with favipiravir treatment. During favipiravir medication, there was no sign of resistance developing.

Key Words: *SARS-CoV-2; Cytopathic effect; Genome epidemiology; Pharmacotherapy*

INTRODUCTION

SARS-CoV-2-caused Coronavirus Disease 2019 (COVID-19) has killed over three million deaths globally. Japan has been hit since the epidemic began, with an initial surge of strains from China over the Lunar New Year, followed by strains from Europe in the spring of 2020. While numerous immunomodulating drugs, such as dexamethasone, have demonstrated to be effective in treating mild to severe COVID-19, antiviral therapeutic choices are limited. Favipiravir is a purine analogue that inhibits viral RNA-dependent RNA polymerase (RdRp) by stopping elongation of the complementary viral RNA strand. It has broad-spectrum efficacy against RNA viruses. In Japan, it was licensed in 2014 for the treatment of new or re-emerging influenza infections. For influenza virus, the barrier to favipiravir resistance is believed to be strong. In the laboratory, a combination of two mutations in the RdRp gene has been linked to favipiravir resistance; however, influenza viruses from 57 patients who took part in favipiravir for influenza clinical trials showed no differences in favipiravir susceptibility before and 1 or 2 days after starting therapy, implying a high resistance threshold.

Several controlled clinical trials have looked at favipiravir as a possible therapy option for COVID-19. A randomized, open-label investigation of 89 individuals with asymptomatic to moderate COVID-19 was previously undertaken. The patients were divided into two groups: early favipiravir therapy (which began on the first day of randomization) and late favipiravir therapy (which began on the second day of randomization) (starting on day 6 of randomization). Viral clearance occurred by day 6 in 66.7 percent and 56.1 percent of cases, respectively, according to RT-PCR, and the mean duration to defervescence was 2.1 and 3.2 days, respectively. The goals of this study were to describe the genome epidemiology in Japan early in the pandemic, determine the viability of the virus in relation to demographics, time since onset, viral load, and favipiravir therapy, and identify mutations that occurred during treatment and might affect viral susceptibility to favipiravir using nasopharyngeal swab specimens obtained in this clinical trial. The median time to negative CPE was 9 days from the commencement of the disease, 7 days shorter than the time to negative RT-PCR, according to the CPE assay of over 400 nasopharyngeal specimens taken from 69 individuals whose day 1 specimens were positive for

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SARS-CoV-2 by RT-PCR. In immunocompetent people with COVID-19, viable virus is typically thought to be present for up to 8 days after illness start. Our findings demonstrate that while live virus may be shed for longer periods of time, the generally accepted practice of 10-day isolation from the beginning of symptoms is still sufficient to prevent transmission in the vast majority of patients, even when RT-PCR stays positive for longer periods of time.

In this clinical trial group, male sex, age, viral loads, and the combination of the latter two were all substantially linked with CPE positive. Favipiravir, on the other hand, was not linked to CPE positive, suggesting that its treatment did not result in viral growth inhibition in this situation. Female sex and young age have been linked to more robust T cell activation during COVID-19, which might explain why these groups had a better clinical result. e a virological corollary of this immunological finding.

CPE positive being associated with male sex and age in our study might b When antiviral medication is used, the development of resistance is a possible problem. SARS-CoV-2 genomes from pre-treatment and on-treatment specimens of 11 patients who received favipiravir revealed no signs of selection for favipiravir-dependent mutations, despite the small number of patients.

CONCLUSION

SARS-CoV-2 initially belonged to clades 19A and 19B in this virological study, which complemented a randomized clinical trial of favipiravir for COVID-19 conducted in Japan between March and May 2020, but was then mostly replaced by clade 20B, reflecting the influx of virus first from China, then from Europe and the United States, which occurred before the travel ban was implemented at the end of March 2020. Viable virus recovery was linked to age, male sex, and viral load, but not to favipiravir treatment.