Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Short Communication

Favipiravir-induced fever in coronavirus disease 2019: A report of two cases

Hiroyuki Takoi\textsuperscript{a}, E, Yuki Togashi\textsuperscript{a}, Daiki Fujimori\textsuperscript{b}, Haruki Kaizuka\textsuperscript{c}, Shunsuke Otsuki\textsuperscript{d}, Takuya Wada\textsuperscript{c}, Yoshikazu Takeuchi\textsuperscript{e}, Shinji Abe\textsuperscript{a}

\textsuperscript{a} Department of Respiratory Medicine, Tokyo Medical University, 6-7-1 Nishi-shinjuku, Shinjuku-ku, Tokyo, 160-0023, Tokyo, Japan
\textsuperscript{b} Department of Rheumatology, Tokyo Medical University, 6-7-1 Nishi-shinjuku, Shinjuku-ku, Tokyo, 160-0023, Tokyo, Japan
\textsuperscript{c} Department of Gastroenterology and Hepatology, Tokyo Medical University, 6-7-1 Nishi-shinjuku, Shinjuku-ku, Tokyo, 160-0023, Tokyo, Japan
\textsuperscript{d} Department of Hematology, Tokyo Medical University, 6-7-1 Nishi-shinjuku, Shinjuku-ku, Tokyo, 160-0023, Tokyo, Japan
\textsuperscript{e} Department of Cardiology and Division of Preemptive Medicine for Vascular Damage, Tokyo Medical University, 6-7-1 Nishi-shinjuku, Shinjuku-ku, Tokyo, 160-0023, Tokyo, Japan

\textbf{ARTICLE INFO}

Article history:
Received 26 August 2020
Received in revised form 12 September 2020
Accepted 22 September 2020

Keywords:
Favipiravir
Drug fever
COVID-19

\textbf{ABSTRACT}

Favipiravir, an antiviral agent, is undergoing clinical trials for treating novel coronavirus disease 2019 (COVID-19). Here, we report two cases of COVID-19 with favipiravir-induced fever. In both cases, pyrexia was observed following the administration of favipiravir despite improvements in symptoms of COVID-19. No other cause for fever was evident after careful physical examination and laboratory investigations. The fever subsided in both patients after the discontinuation of favipiravir. To the best of our knowledge, this is the first report of favipiravir-induced fever in COVID-19 patients.

© 2020 The Author(s). Published by Elsevier Ltd on behalf of International Society for Infectious Diseases. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

\section*{Introduction}

The coronavirus disease 2019 (COVID-19) pandemic is one of the most significant public health crises in recent history. A randomized clinical trial showed that treatment with remdesivir accelerated recovery in patients with severe COVID-19 (Wang et al., 2020). Therefore, this antiviral agent has become one of the standard therapies for COVID-19. Favipiravir, a promising antiviral agent, is undergoing clinical trials as an alternative drug for treating COVID-19 (Arab-Zozani et al., 2020) in several countries, including China (Chen et al., 2020), Iran, Germany, and Japan.

Drug fever is difficult to diagnose in patients with febrile illnesses, especially if the drug is a novel drug for an emerging infectious disease such as COVID-19. Reporting such cases might contribute to the accurate diagnosis of future cases. Here, we report two cases of favipiravir-induced fever in patients hospitalised with COVID-19.

\section*{Case presentation}

\textbf{Case 1}

In April 2020, a 42-year-old man was admitted to hospital with COVID-19, 13 days after the onset of symptoms. He was taking febuxostat for hyperuricaemia. On admission, he was asymptomatic and did not require supplemental oxygen. Chest computed tomography (CT) showed ground-glass opacity in both lungs. Favipiravir was started on the day of admission. He received two doses of 1800 mg on Day 1 and 800 mg twice daily thereafter. His uric acid level became elevated, possibly as a side effect of favipiravir administration; therefore, benz bromarone was added to his treatment regimen. On Day 12 of favipiravir treatment, his temperature increased to 38 °C with blood eosinophilia (630 cells/μL), despite an improvement in his chest X-ray findings. His general condition was good, except for fever and relative bradycardia. Favipiravir treatment was discontinued on Day 14, and his temperature returned to normal the following day (Figure 1). His blood eosinophil count also returned to normal. Benz bromarone was initially considered to be the causative agent of the fever; however, clinical improvement occurred before benz bromarone was discontinued. Thus, he was diagnosed with favipiravir-induced fever.

\vspace{0.5cm}

https://doi.org/10.1016/j.ijid.2020.09.1450

1201-9712/© 2020 The Author(s). Published by Elsevier Ltd on behalf of International Society for Infectious Diseases. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
In August 2020, a 28-year-old woman with an unremarkable medical history was admitted 5 days after the onset of COVID-19 symptoms. She had a fever of 39 °C, and her chest CT revealed mild ground-glass opacity at the base of each lung. She did not require supplemental oxygen. Favipiravir treatment was started on the day of admission. She received two doses of 1800 mg on Day 1 and 800 mg twice daily thereafter. Her temperature returned to normal the following day; however, on the following day, her temperature again increased to 39 °C. Physical examination, laboratory investigation, and bacteriological and radiological findings could not reveal the cause of fever. Her respiratory symptoms improved, but she experienced relative bradycardia. Drug fever was suspected, and favipiravir was discontinued on Day 10. She became afebrile the following day and was discharged on Day 15 (Figure 2). In contrast to Case 1, she did not develop blood eosinophilia.

**Discussion and conclusion**

To the best of our knowledge, this is the first report of favipiravir-induced fever. Favipiravir is used to treat influenza A subtype H1N1. It exhibits antiviral activity against other RNA viruses and is thought to have an antiviral effect on severe acute respiratory syndrome coronavirus-2 (Shiraki and Daikoku, 2020). This drug has been approved in Japan for treating novel influenza virus diseases. In a case series of 11 patients, favipiravir in combination with nafamostat mesylate was found to have an antiviral effect in critically ill COVID-19 patients (Doi et al., 2020).

In both our cases, a discrepancy was observed between the patients’ clinical course and their fever, and no possible cause of pyrexia other than favipiravir was identified.

A definition of drug fever is “a disorder characterized by fever coinciding with the administration of a drug and disappearing after the discontinuation of the drug, when no other cause for fever is evident after a careful physical examination and laboratory investigation,” with a period of 1.3 ± 1.1 days from discontinuation of the causative drug to pyretolysis (Mackowiak and LeMaistre, 1987). Drug fever can be ruled out if pyretolysis is not confirmed within 72 h after the discontinuation of the drug (Mourad et al., 2003).

A wide variety of drugs have been implicated in drug fever (Patel and Gallagher, 2010). Favipiravir has not been previously reported to cause drug fever. This preliminary report may help differentiate paradoxical fever in patients receiving favipiravir therapy for COVID-19. Early accurate diagnosis may reduce not only inappropriate, potentially harmful, and expensive diagnostic and therapeutic interventions, but it may also avoid unnecessary patient isolation and bed occupation and save the efforts of healthcare workers.

**Consent for publication**

Both patients have provided written informed consent for the publication of this report.

**Conflict of interest**

None declared.
Funding

None declared.

References

Arab-Zozani M, Hassanipour S, Chhodooesi-Nejad D. Favipiravir for treating patients with novel coronavirus (COVID-19): protocol for a systematic review and meta-analysis of randomised clinical trials. BMJ Open 2020;10:e039730. doi:http://dx.doi.org/10.1136/bmjopen-2020-039730.

Chen C, Zhang Y, Huang J, Yin P, Cheng Z, Wu J, et al. Favipiravir versus arbidol for COVID-19: a randomized clinical trial. medRxiv 2020; doi:http://dx.doi.org/10.1101/2020.03.17.20037432.

Doi K, Ikeda M, Hayase N, Moriya K, Morimura N. Nafamostat mesylate treatment in combination with favipiravir for patients critically ill with Covid-19: a case series. Crit Care 2020;24:392.

Mackowiak PA, LeMaistre CF. Drug fever: a critical appraisal of conventional concepts. An analysis of 51 episodes in two Dallas hospitals and 97 episodes reported in the English literature. Ann Intern Med 1987;106:728–33, doi:http://dx.doi.org/10.7326/0003-4819-106-5-728.

Mourad O, Palda V, Detsky AS. A comprehensive evidence-based approach to fever of unknown origin. Arch Intern Med 2003;163:545–51, doi:http://dx.doi.org/10.1001/archinte.163.5.545.

Patel RA, Gallagher JC. Drug fever. Pharmacotherapy 2010;30:57–69.

Shiraki K, Daikoku T. Favipiravir, an anti-influenza drug against life-threatening RNA virus infections. Pharmacol Ther 2020;209:107512, doi:http://dx.doi.org/10.1016/j.pharmthera.2020.107512.

Wang Y, Zhang D, Du G, Du R, Zhao J, Jia Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020;395:1569–78, doi:http://dx.doi.org/10.1016/S0140-6736(20)31022-9.