Favipiravir-induced cutaneous adverse reactions in patients infected with COVID-19

P. Punyaratabandhu and S. Vanitchpongphan
Bamrasnaradura Infectious Diseases Institute, Department of Diseases Control, Ministry of Public Health, Nonthaburi, Thailand
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Summary

Favipiravir (FVP) has been used for treatment of COVID-19 in many countries. We analysed the incidence of FVP-induced cutaneous adverse reactions (CARs) in patients infected with COVID-19 who were hospitalized at Bamrasnaradura Infectious Diseases Institute, a principal centre of emerging infectious disease in Thailand, and who presented with cutaneous eruption following FVP prescription. We identified five cases of FVP-induced CARs: two patients with maculopapular rash, two with urticarial rash, and one with Stevens–Johnson syndrome. The median interval between FVP treatment and rash occurrence was 7 days and the mean duration of the rash was 5 days. This report highlights that FVP can induce CARs, particularly eruptions, in COVID-19-infected patients. Clinicians should be aware of this possible drug-related allergy, and it should be excluded as a cause of rash during FVP treatment of COVID-19.

COVID-19 is still an ongoing global pandemic. A wide range of signs and symptoms of the disease has been observed, including cutaneous manifestations.1 As there is as yet no global consensus on the best specific treatment, therapies may vary in each country. Reports of cutaneous reactions of pharmacological interventions for COVID-19 have been published and reviewed.2 When reviewing the possible differential diagnoses of cutaneous manifestations in patients with COVID-19, consideration should be given to whether this could be a reaction related to the virus or any drug treatment.

Favipiravir (FVP) is an antiviral drug, which has been used for treatment of COVID-19 in Japan, Russia, Saudi Arabia, India and Thailand.3 To our knowledge, there is no report of FVP-induced cutaneous adverse reactions (CARs) among patients with COVID-19.4 We report the findings of an observational case series of patients with COVID-19 infection treated with FVP.

Report

The study was approved by the institutional review board of the Bamrasnaradura Infectious Diseases Institute. This was an observational case series study of patients with COVID-19 infection treated with FVP who developed CARs.

In total, 714 COVID-19-infected patients were treated with FVP since January 2020; however, no cases of CARs occurred until April 2021, following a change in the protocol (more indications for a wider range of disease severity), and there were more severe cases needing longer treatment duration with FVP in our institute. We identified five cases of CARs occurring after FVP treatment in COVID-19-infected patients during the period April–June 2021, giving an incidence of 0.7%. The demographic data of these patients are shown in Table 1, and the timeline of each patient’s medications concurring with the CARs is shown in Fig. 1.

Patient 1 was a 28-year-old woman diagnosed with COVID-19-related pneumonia, and treated with FVP...
and systemic corticosteroid. At Day 8 of FVP treatment, the patient developed an itchy rash on her face, which then progressed to her trunk and limbs; there was no fever. Physical examination showed a generalized maculopapular (MP) rash without mucosal involvement, no lymphadenopathy and no hepatosplenomegaly (Fig. 2a). Drug allergy was suspected. FVP was stopped after 10 days of treatment and topical corticosteroid and oral antihistamine drugs were prescribed, which resulted in resolution of the rash 2 days later.

Patient 2, a 62-year-old woman, was diagnosed with COVID-19-related pneumonia, and treated with FVP. She developed an itchy rash on her face 7 days later. On physical examination, an urticarial rash was observed on her face (Fig. 2b) and limbs, without angio-oedema, dyspnoea or fever. FVP was discontinued on Day 3 of the rash and oral antihistamine was prescribed, and the cutaneous symptoms resolved within 1 day after FVP was stopped.

Patient 3 was a 32-year-old woman, who was diagnosed with COVID-19-related pneumonia. After 3 days of treatment with FVP, her fever and cough resolved but she developed itchy rashes on her arms and legs. She was found to have an MP rash on her trunk (Fig. 2c) and limbs, without mucosal involvement, and with no lymphadenopathy or hepatosplenomegaly. Full blood count showed no leucocytosis or eosinophilia, and liver function test showed no transaminitis. FVP was discontinued on Day 2 of the rash, and treatment with topical corticosteroid and oral antihistamine was started, leading to resolution of the rash within 3 days.

Patient 4, a 19-year-old woman, was diagnosed with COVID-19 infection. On Day 2 of FVP treatment, skin lesions

Table 1 Demographic data of the patients.

| Patient characteristics | 1  | 2  | 3  | 4  | 5  |
|-------------------------|---|----|----|----|----|
| General                 |   |    |    |    |    |
| Age, years              | 28| 62 | 32 | 19 | 64 |
| Sex                     | F | F  | F  | F  | F  |
| Underlying conditions   | No| Hypertension | No| Obesity | Allergic rhinitis |
| Current medication      | No| Losartan 100 mg/day; atenolol 50 mg/day | No| No| No |
| Medical history         |   |    |    |    |    |
| Personal history of drug and food allergy | No | NSAIDs | No | No | Quinine sulfate |
| Personal history of cutaneous diseases | No | No | No | No | No |
| COVID-19 Diagnosis      | Real-time RT-PCR COVID-19-related pneumonia | Real-time RT-PCR COVID-19-related pneumonia | Real-time RT-PCR COVID-19-related pneumonia | Real-time RT-PCR COVID-19 infection | Real-time RT-PCR COVID-19-related pneumonia |
| Treatment               | FVP, systemic corticosteroid, ACA, supportive treatment | FVP, supportive treatment | FVP, supportive treatment | FVP, supportive treatment | FVP, systemic corticosteroid, supportive treatment |
| Skin lesions            |   |    |    |    |    |
| Interval between starting FVP and onset of lesions, days | 7 | 7 | 3 | 1 | 13 |
| Characteristics of lesions | MP rash | Urticarial rash | MP rash | Urticarial rash | SJS |
| Duration of rash, days  | 5 | 4 | 5 | 3 | 8 |
| Interval between FVP cessation and rash resolution, days | 2 | 1 | 3 | 1 | 7 |
| Treatment               | Oral antihistamine, topical corticosteroid | Oral antihistamine, topical corticosteroid | Oral antihistamine, topical corticosteroid | Intravenous corticosteroid, intravenous antihistamine, oral antihistamine | Oral antihistamine, topical steroid, systemic corticosteroid |

ACA, amoxicillin/clavulanic acid; FVP, favipiravir; MP, maculopapular; NSAIDs, nonsteroidal anti-inflammatory drugs; RT-PCR, reverse transcription PCR; SJS, Stevens–Johnson syndrome.
she developed an itchy rash on her face, trunks and limbs. Physical examination revealed a generalized urticarial rash with puffy eyelids (Fig. 2d), but no fever, dyspnoea or swelling of the lips. FVP allergy was suspected and the drug was discontinued; the rash resolved dramatically after 1 day.

Patient 5 was a 64-year-old woman, who was diagnosed with COVID-19-related pneumonia. After

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**Figure 1** Demonstration of timeline of each patient’s medications concurring the cutaneous reactions.
13 days of treatment with FVP, she reported soreness in both eyes and a burning sensation in her mouth, then an itchy rash developed on her face, neck, chest and both arms. Physical examination showed no fever, lymphadenopathy or hepatosplenomegaly. On her face, trunk and limbs, she had ill-defined erythematous papules, coalescing to plaques in some areas, as well as mild injected conjunctiva of both eyes and erosion with necrosis of both lips (Fig. 2e). Full blood count showed no eosinophilia but liver function test showed transaminitis. Stevens–Johnson syndrome (SJS) was diagnosed and FVP was stopped immediately. The patient was treated with systemic corticosteroid, topical corticosteroid and oral antihistamine. All symptoms improved after 7 days of FVP cessation.

The incidence of drug-related CARs is low but crucial because they can lead to morbidity and mortality. COVID-19 has been disrupting the world since the pandemic began, and it has led to emergency drugs and vaccines to be approved concurrent with ongoing studies. Based on a literature review, FVP-induced CARs have not been reported previously, to our knowledge.

In this study, we identified five cases: two with MP rash, two with urticarial rash and one with SJS. All cases were diagnosed by clinical presentation and the temporal relationship of the rash and medication. The median interval between FVP treatment and rash occurrence was 7 days, while the mean duration of the rash was 5 days. In Patients 1–4, the skin eruptions had a mean duration of 5 days for the MP rash (Patients 1 and 3) and 3.5 days for the urticarial rash (Patients 2 and 4). The rashes resolved without postinflammatory hyperpigmentation except in Patient 5.

The differential diagnosis of the rashes included cutaneous manifestations of COVID-19. In a previous
study, the mean duration of COVID-19 skin manifestation was reported as 6.8 days for urticarial rash and 8.6 days for MP rash, respectively. In our study, the mean time to rash resolution after discontinuing FVP (in Patients 1–4) was 1.75 days, therefore these four cases were all diagnosed as FVP-induced CAR, while the fifth was diagnosed as SJS based on the clinical presentation. Based on our literature review, none of the previously reported cutaneous manifestations of COVID-19 were SJS-like reactions.

The limitations of the study include the lack of specific laboratory tests at the time to help with confirmation of the diagnosis. To confirm drug allergy, the gold standard test is rechallenge with the offending medication, which we were unable to conduct due to limited resources in the emergency pandemic situation and the likelihood of the risks outweighing the benefits to the patients, particularly in the case of Patient 5, as SJS is considered a severe CAR.

We hope that this report increases awareness of physicians and dermatologists about possible CARs of FVP especially in countries that have approved the medication for use in their COVID-19 treatment guidelines. Nonetheless, further studies are needed to analyse and confirm the issue of FVP allergy.

Acknowledgement

We thank the patients for providing written informed consent to publication of their case details and photographs.

| Learning points |
|------------------|
| • FVP-induced CARs were observed in COVID-19-infected patients, with an incidence of 0.7%. |
| • MP rash, urticarial rash and SJS were the FVP-induced CARs observed. |
| • Median duration between FVP treatment and rash occurrence was 7 days. |
| • FVP-induced CARs had a mean duration of 5 days for MP rash and 3.5 days for urticarial rash, which is shorter than the usual duration of MP and urticarial rash when they appear as cutaneous manifestations of COVID-19. |
| • Physicians should be aware of the possibility of drug allergy with FVP, and it should be excluded as a cause of the rash during the treatment of patients with COVID-19. |

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