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Favipiravir induce cutaneous adverse reactions in COVID-19-infected patients

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Learning points

- Favipiravir induced cutaneous adverse reactions in COVID-19-infected patients were observed
- The incidence of Favipiravir induce cutaneous adverse reactions in COVID-19-infected patients was 0.7%
- Maculopapular rash, urticarial rash, and Steven-Johnson syndrome were observed in Favipiravir induced cutaneous adverse reactions.
- Median duration between Favipiravir treatment and rash occurrence was 7 days
- Cutaneous adverse reactions from Favipiravir had mean duration of 3.5 days for urticarial rash and 5 days for MP rash, which were shorter than duration of rash in cutaneous manifestation of COVID-19.
- Drug allergy should be aware and excluded as a cause of the rash during the treatment of COVID-19.

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Abstract

Favipiravir has been used for treatment of COVID-19 in many countries. To determine Favipiravir induced cutaneous adverse reactions in COVID-19-infected patients, we observed COVID-19-infected patients who were hospitalized at Bamrasnaradura Infectious Diseases Institute, a principal centre of emerging infectious disease in Thailand, and presented with cutaneous eruption following Favipiravir prescription. There were 5 cases of Favipiravir induced cutaneous adverse reactions; 2 patients with maculopapular rash, 2 with urticarial rash, and one with Steven-Johnson Syndrome. Median duration between Favipiravir treatment and rash occurrence was 7 days. Mean duration of the rash was 5 days. This findings highlighted that Favipiravir induced cutaneous adverse eruptions in COVID-19-infected patients. Drug allergy should be aware and excluded as a cause of the rash during the treatment of COVID-19.

Introduction

The emerging coronavirus disease 2019 (COVID-19) is still an ongoing global pandemic. A wide range of signs and symptoms of the disease has been observed, including cutaneous manifestation.[1] To date, due to the best specific treatment being non-existent and the treatment was vary in each country. Reports of cutaneous reactions of pharmacologic interventions for COVID-19 have been published and reviewed.[2] Differential diagnosis of cutaneous manifestation in COVID-19-infected patients should be considered whether it was related to the virus or drug reaction.

Favipiravir (FVP) is an antiviral drug. Currently, the drug 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 among COVID-19-infected patients.[4]

Report

An observational case series study reported 5 cases of cutaneous reaction, occurred following FVP prescription in COVID-19-infected patients, who were treated at Bamrasnaradura Infectious Disease Institute (BIDI) during April 2021 and June 2021. Over 714 COVID-19-infected patients in BIDI had been treated with FVP since January 2020. The demographic data of patients was shown in Table 1. Timeline of each patient's medications concurring the cutaneous reactions were demonstrated in Figure 1.

Case 1

A 28-year-old woman was diagnosed with COVID-19 pneumonia. FVP and systemic corticosteroid was prescribed for COVID-19 treatment. After 7 days of FVP treatment, she developed itchy rashes on her face then progressed to her trunk and extremities without fever. Physical examination showed generalized maculopapular (MP) rash without mucosal involvement, no lymphadenopathy, and no hepatosplenomegaly

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(Figure 2a). Drug allergy was suspected. FVP was stopped after 10 days of treatment and topical corticosteroid and oral antihistamine drugs were prescribed. The rash subsequently resolved 2 days after stopping FVP.

Case 2

A 62-year-old woman was diagnosed with COVID-19 pneumonia. She complained of itchy rash on her face 7 days after FVP was prescribed. Urticarial rash on her face (Figure 2b) and extremities were observed without angioedema, dyspnea, nor fever. Oral antihistamine was prescribed. The cutaneous symptoms were resolved after discontinuation of FVP for 1 day.

Case 3

A 32-year-old woman was diagnosed with COVID-19 pneumonia. After 3 days of treating with FVP, she developed itchy rashes on her arms and legs, but her fever and cough were resolved. The dermatological examination showed MP rash on her trunk (Figure 2c) and extremities without mucosal involvement. No lymphadenopathy nor hepatosplenomegaly was observed. Complete blood count showed no leukocytosis, no eosinophilia, and the liver function test showed no transaminitis. Topical corticosteroid and oral antihistamine drug were prescribed. Her rashes resolved 3 days after FVP cessation.

Case 4

A 19-year-old woman was diagnosed with COVID-19. On the second day after starting FVP, she developed itchy rashes on her face, trunks, and extremities. Generalized urticarial rash with puffy eyelids (Figure 2d), but no fever, dyspnea, nor swelling of the lips. Favipiravir allergy was suspected and the drug was discontinued. Her skin lesions were resolved dramatically after stopping FVP for 1 day.

Case 5

A 64-year-old woman was diagnosed with COVID-19 pneumonia. After thirteen days of treatment with FVP, she complained of soreness in both eyes and a burning sensation on her mouth, then itchy rash on her face, neck, chest and both arms. Physical examination showed afebrile, no lymphadenopathy or hepatosplenomegaly. Her skin examination showed ill-defined erythematous papules confluent to plaques on her face, trunk and extremities, mild injected conjunctiva of both eyes, and erosion with necrosis of both lips. (Figure 2e) The laboratory showed no eosinophilia in complete blood count, but liver function test showed transaminitis. Steven-Johnson syndrome (SJS) was diagnosed and FVP was stopped immediately. The systemic corticosteroid was continuously prescribed, and she was also prescribed topical corticosteroid and oral antihistamine. All symptoms improved after 7 days of FVP cessation.

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Among 5 cases, 2 patients characterized with MP rash, 2 with urticarial rash, and one with SJS. Median duration between Favipiravir treatment and rash occurrence was 7 days. Mean duration of the rash was 5 days. Rashes resolved without post-inflammatory hyperpigmentation, except the last case.

Discussion

The incidence of cutaneous drug eruption is low but crucial because it can lead to morbidity and mortality. COVID-19 has been disrupting the world. Emergency drugs and vaccines have been approved concurrent with ongoing studies. Although from literature review FVP induced cutaneous adverse reactions had never been reported. We observed 5 cases in this study, 2 patients presented with MP rash, 2 with urticarial rash, and one with SJS. All cases were diagnosed by clinical presentation and relationship of the rash and timeline of using medication. In case 1-4, skin eruptions had mean duration as 3.5 days for urticarial rash and 5 days for MP rash. The differential diagnosis of the rashes were COVID-19 induced cutaneous eruption. 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.[5] Moreover, mean duration of all rashes were resolved after discontinue FVP was 1.75 days. Therefore, FVP induced cutaneous adverse reaction was the diagnosis in these 4 cases. In case 5, SJS case was diagnosed based on clinical presentation. From the literature review, none of COVID-19 cutaneous manifestation presented with SJS-like.[6]

The limitations of the study was lack of laboratory or test to help with confirmation of the diagnosis. To confirm drug allergy, gold standard was re-challenged the offending medication.[7] This re-challenging test issue was unable to conduct due to limited resources in an emergency pandemic situation and risks overweighting benefits on patient, due to one of our case presented with SJS that is one of Severe Cutaneous Adverse Reactions (SCARs).

This report aimed to increase awareness for physicians and dermatologists on cutaneous side effects of FVP especially in countries which have approved using the medication in their COVID-19 treatment guideline. Nonetheless, further study are needed in order to analyse and confirm the issue of FVP allergy.

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Figure legend:

Figure 1: Demonstration of timeline of each patient's medications concurring the cutaneous reactions

Figure 2: Cutaneous manifestation in each cases (a) Maculopapular rash on hand of case 1 (b) Urticarial rash on the face of case 2 (c) Maculopapular rash on chest wall of case 3 (d) Urticarial rash on leg of case 4 (e) Erosion with necrosis of both lips and erythematous plaque on face of case 5

Table 1: The demographic data of patients

Patients' characteristics	Case 1	Case 2	Case 3	Case 4	Case 5

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General information	**Age (year)/sex**	28/ Female	62/ Female	32/ Female	19/ Female	64/ Female
	Underlying diseases	No	Hypertension	No	Obesity	Allergic rhinitis
	Current medication	No	-Losartan 100mg/day -Atenolol 50mg/day	No	No	No
Past history	**History of allergy**	No	NSAIDs	No	No	Quinine sulfate
	History of vaccination	No	No	No	No	No
	History cutaneous diseases	No	No	No	No	No
	Family history of allergy	No	No	No	No	No
COVID-19	**Confirmation technique**	RT-PCR	RT-PCR	RT-PCR	RT-PCR	RT-PCR
	Diagnosis	COVID-19 pneumonia	COVID-19 pneumonia	COVID-19 pneumonia	COVID-19 infection	COVID-19 pneumonia
	Treatment	-FVP -Systemic corticosteroi -Amoxy/ Clavulonic acid -Supportive treatment	-FVP -Supportive treatment	-FVP -supportive treatment	-FVP -supportive treatment	-FVP -systemic corticosteroid -supportive treatment
Skin lesion	**Onset (Days after starting**	7 days	7 days	3 days	1 day	13 days

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	FVP)					
	Characteristics	MP rash	Urticarial rash	MP rash	Urticarial rash	SJS
	Duration of rash	5 days	4 days	5 days	3 days	8 days
	Duration between FVP cessation to resolving rash	2 days	1 day	3days	1 day	7 days
	Treatment	-Oral antihistamine -Topical corticosteroid	-Oral antihistamine	-Oral antihistamine -Topical corticosteroid	-Intravenous corticosteroid -Intravenous antihistamine -Oral antihistamine	-Oral antihistamine -Topical steroid -Systemic corticosteroid

MP, maculopapular rash; SJS, Steven-Johnson Syndrome; FVP, Favipiravir; COVID-19, coronavirus disease 2019; RT-PCR, real-time reverse transcription polymerase chain reaction assay for SARS-CoV-2 RNA; NSAIDs, non-steroidal antiinflammatory drugs; mg, milligram

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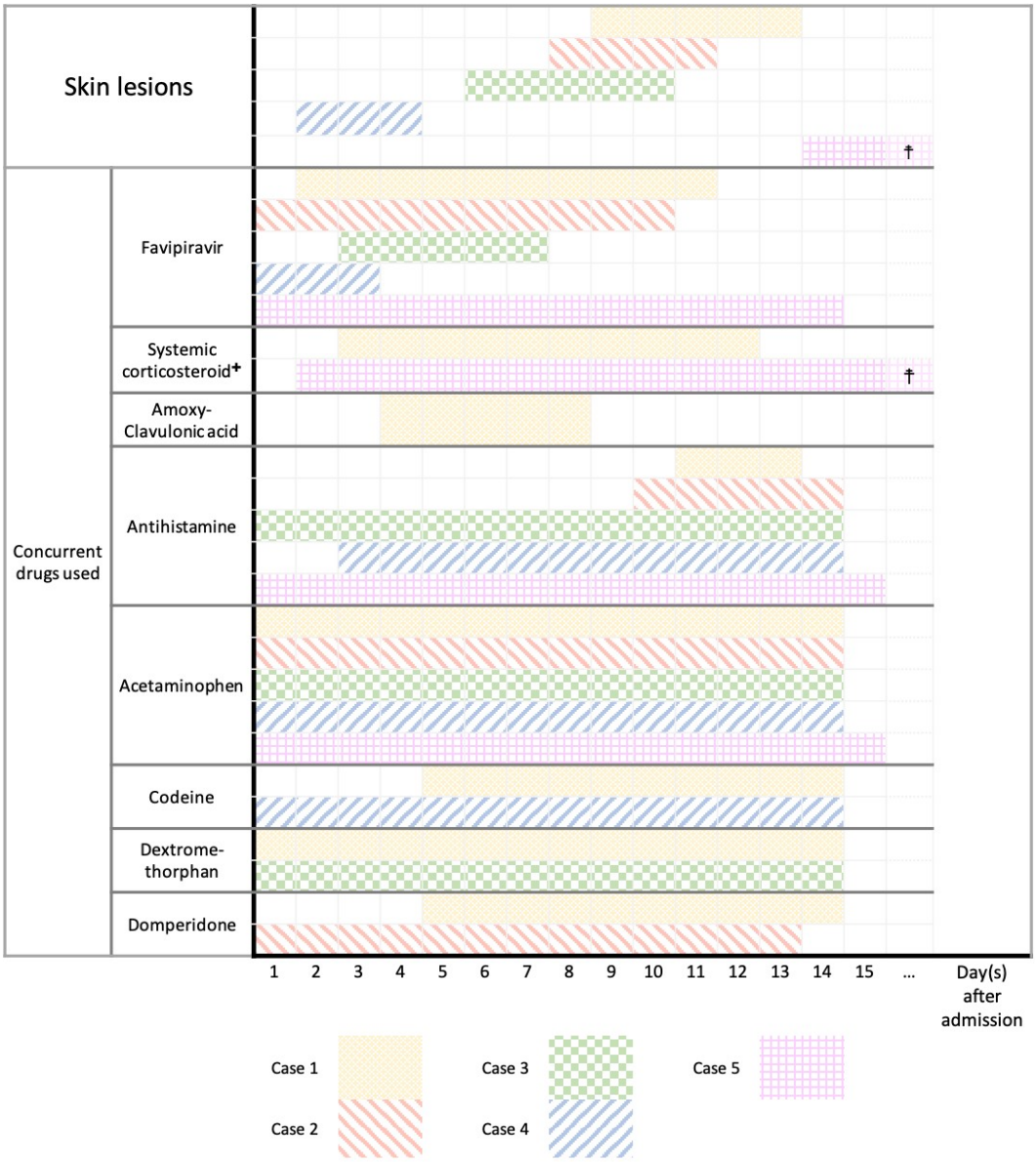

Figure 1 : Demonstration of timelines with skin lesions onsets and concurrent drugs used on each cases (Labeled by colors and pattern)

† Case 5's skin lesion lasted for a total of 8 days, and she was prescribed systemic corticosteroid for a total of 29 days

✚ Case 1 was prescribed dexamethasone 6 mg IV OD for 10 days, while Case 4 was prescribed dexamethasone 6 mg IV OD for 21 days and tapered with oral prednisolone for 8 days

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