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Note

Skin rash induced by ritonavir-boosted darunavir is common, but generally tolerable in an observational setting

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ABSTRACT

Ritonavir-boosted darunavir (DRV/r) is a protease inhibitor widely used in the treatment of HIV-1 infection. However, skin rash is a well-known adverse event of DRV, and limited data are available from observational settings. This observational study examined the characteristics of DRV-induced skin rash in treatment-naïve patients who commenced once-daily DRV/r-containing antiretroviral therapy (ART). Of the 292 study patients, DRV rashes developed in 31 (11%) patients with a median latency of 10 days (developing from 7 to 14 days in 93%) from initiation of ART. DRV skin rash was generally mild, as only one patient (3%) had grade 3 rash whereas 24 (77%) patients had grade 2 and 6 (19%) patients had grade 1. Only two patients (7%) discontinued DRV/r due to skin rash, and the other continued DRV/r and their rashes disappeared completely without any complications. Interestingly, DRV rash occurred more frequently to patients with less advanced HIV-1 infection than those with advanced infection. The incidence of DRV rash was not significantly different between patients with and without history of sulfonamide allergy ($p = 0.201$). Furthermore, when we exclude patients without history of sulfonamide use and only examine patients with sulfonamide use ($n = 145$), the result was similar ($p = 0.548$). In conclusion, DRV rashes were frequently observed but the prognosis was benign. Most patients tolerated DRV rashes with use of oral steroid or antihistamine without discontinuation of DRV. To date, there is no clear clinical evidence to suggest that DRV should be avoided in patients with history of sulfonamide allergy.

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Once-daily ritonavir (100 mg)-boosted darunavir (800 mg) (DRV/r) is a protease inhibitor placed as one of the preferred treatment choices for HIV-1 infection listed in the American Department of Health and Human Services Guidelines based on its proven efficacy and safety, and high barrier to drug resistance [1–4]. However, skin rash is a well-known adverse event of DRV, and limited data are available regarding the incidence, characteristics, and prognosis of this complication from observational settings apart from the data of the industry-sponsored clinical trials [5]. Here we conducted a single-center observational study to examine

the incidence, characteristics, and prognosis of DRV-induced skin rash in treatment-naïve patients with HIV-1 infection.

All treatment-naïve subjects who commenced once-daily DRV/r-containing antiretroviral therapy (ART) from September 2009 (when once-daily DRV became available in Japan) to June 2012 at the AIDS Clinical Center, Tokyo, were included. Baseline characteristics (age, sex, race, CD4 count, HIV-1 viral load, co-administered antiretroviral agents, history of sulfonamide usage, history of sulfonamide allergy, co-infection with hepatitis B or C infection, history of AIDS, and co-administered medications) were collected from the medical records. The selection of DRV/r with either tenofovir/emtricitabine (TDF/FTC) or abacavir/lamivudine (ABC/3TC) was based on the decision of the attending physician and according to The Japanese guidelines, which consider both TDF/FTC and ABC/3TC as the preferred nucleotide reverse transcriptase inhibitors [6]. DRV-related skin rash was defined as rashes diagnosed of DRV-induced by a treating physician without other apparent

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Table 1
Characteristics of patients with darunavir-induced rash and without rash.

	Darunavir-induced rash (n = 31)	No rash (n = 261)	p Value ^a
Age, years ^b	33 (27–39)	38 (32–44)	0.004
Male sex, n (%)	27 (87)	248 (95)	0.092
East Asian origin, n (%)	30 (97)	237 (91)	0.493
CD4 cell count, cells/ μ L ^b	282 (122–387)	164 (43–273)	0.001
HIV load, log ₁₀ copies/mL ^b	4.64 (4.26–4.94)	5.04 (4.48–5.57)	0.011
HIV load >100,000 copies/mL	6 (19)	134 (51.3)	0.001
Co-administration of tenofovir/emtricitabine, n (%)	27 (87)	215 (82)	0.621
Hepatitis B or C infection, n (%)	6 (19)	26 (10)	0.127
History of AIDS, n (%)	5 (16)	82 (31)	0.097

^a The χ^2 test or Fisher's exact test was used for categorical data, and the Student's *t* test was used for continuous variables.

^b Median (interquartile range).

causes. The latency (time from initiation of DRV/r-containing ART to the appearance of rashes, in days), severity based on the grade table [7], treatment, and prognosis were extracted from the medical records. All study patients were followed for at least 48 weeks. Statistical significance was defined as two-sided *p* values <0.05. All statistical analyses were performed with The Statistical Package for Social Sciences ver. 20.0 (SPSS, Chicago, IL).

The study included 292 patients [median age: 38 years, males: 275 (94%), East Asian origin: 267 (91%)]. Of them, 242 (83%) started DRV/r with TDF/FTC, and 50 (17%) received DRV/r with ABC/3TC. All patients were screened for HLA-B*5701 before initiating ART and all were negative. DRV-induced skin rashes developed in 31 (11%) patients with a median latency of 10 days (IQR 8–10.5 days, developing from 7 to 14 days in 93%) from initiation of ART (this analysis excluded two cases in whom the exact date of development was not specified). Most patients presented with scattered maculopapular eruption in the body trunk and extremities. Patients with DRV skin rash were younger (33 years versus 38 years, *p* = 0.004), had higher baseline CD4 count (282/ μ L versus 164/ μ L, *p* = 0.001), lower HIV-1 viral load (VL) (4.64 log₁₀/ml versus 5.04 log₁₀/ml, *p* = 0.011), and also smaller proportion of patients with baseline VL >100,000 copies/ml (19% versus 51%, *p* = 0.001) than patients without rash (Table 1). DRV rash cases were less likely to be male (87% versus 95%, *p* = 0.092) and had history of AIDS (16% versus 31%, *p* = 0.097).

77 patients had a history of sulfonamide allergy (All sulfonamide allergy cases were sulfamethoxazole/trimethoprim allergy in this study population). Of them, 5 (7%) had DRV-induced rash, whereas among 215 patients with no history of sulfonamide allergy or no sulfonamide use, 26 (12%) had DRV rash. The incidence of DRV rash was not significantly different between patients with and without history of sulfonamide allergy (*p* = 0.201) [Table 2, 1]. Furthermore, when we exclude patients without history of sulfonamide use and only examine patients with sulfonamide use (*n* = 145), the result was similar; DRV-induced rash occurred to 5 (7%) out of 77 patients with sulfonamide allergy, whereas rash occurred to 7 (10%) out of 68 patients without sulfonamide allergy. Again, the difference was not significant (*p* = 0.548) [Table 2, 2].

Table 2
The incidence of darunavir-induced rash 1) between patients with history of sulfonamide allergy and without such allergy or no sulfonamide use (*n* = 292), and 2) between patients with and without history of sulfonamide allergy among patients who used sulfonamide in the past (*n* = 145).

	1) Study patients (n = 292)			2) Patients with history of sulfonamide use (n = 145)		
	Sulfonamide allergy (n = 77)	No allergy or no sulfonamide use (n = 215)	p Value	Sulfonamide allergy (n = 77)	No sulfonamide allergy (n = 68)	p Value
Darunavir-induced rash	5 (7%)	26 (12%)	0.201	5 (7%)	7 (10%)	0.548

DRV skin rash was generally mild, as only one patient (3%) had grade 3 rash, whereas 24 (77%) patients had grade 2 and 6 (19%) patients had grade 1. Oral steroid (for most cases, 20–30 mg per day of prednisolone for 3–4 days were prescribed), with or without oral antihistamine, was used in 14 (47%) patients, while 9 (30%) were treated with oral antihistamine only. Rash disappeared without treatment for 7 (23%) out of 31 patients. Only two patients (7%) discontinued DRV/r due to skin rash (though one patient discontinued DRV/r based on poor adherence); one patient had grade 3 rash with dot hemorrhage from the oral mucosa, and the other with grade 2 rash which did not promptly resolve with oral steroid and the patient desired discontinuation of DRV/r. The other 28 (93%) patients continued DRV/r and their rashes disappeared completely without any complications.

This is the first observational study that reported incidence, characteristics and prognosis of DRV-induced skin rash. Although there is a limitation that all DRV rash cases were of clinical diagnosis, the results emphasized that DRV skin rash is common; occurring in 11% of 292 treatment-naïve patients who initiated DRV/r-containing ART, with a latency of 1–2 weeks after initiation of DRV/r. The prognosis of DRV rash was favorable, with most rashes rated grade 1 or 2 and only 2 (7%) patients had to discontinue DRV/r due to skin rash. It is well-known that DRV shares a sulfonarylamine structure with sulfamethoxazole [8] and the product labeling describes that “DRV should be used with caution in patients with a known sulfonamide allergy” [5]. However, there was no difference in the proportion of DRV-induced rash between patients with history of sulfamethoxazole allergy and without such allergy in this study, which is in agreement with the results of clinical trials [5].

Interestingly, DRV skin rash occurred more frequently to patients with less advanced HIV-1 infection (those with higher CD4 count and lower VL) than those with advanced infection. Patients with HIV-1 infection were prone to present with drug rashes not only to sulfonamide but to a wide variety of medications [9,10]. Although its mechanism is considered multifactorial and is not fully understood, oxidative stress brought about by the Tat HIV-1 viral protein likely contribute [9,11,12]. However, it was unknown whether a degree of disease progression affects susceptibility to drug rashes, and this is the first such study to report that patients with less advanced HIV-1 infection are more susceptible to DRV rashes.

In conclusion, DRV rashes were frequently observed in treatment-naïve patients with HIV-1 infection who initiated DRV/r-containing ART, but the prognosis was benign. Most patients tolerated DRV rashes with the use of oral steroid or antihistamine without discontinuation of DRV. To date, there is no clear clinical evidence to suggest that DRV should be avoided in patients with a history of sulfonamide allergy.

Conflicts of interest

S.O. has received honoraria and research grants from MSD K.K., Abbott Japan, Co., Janssen Pharmaceutical K.K., Pfizer, Co., and Roche Diagnostics K.K.; received honoraria from Astellas Pharmaceutical

K.K., Bristol-Myers K.K., Daiichisankyo, Co., Dainippon Sumitomo Pharma, Co., GlaxoSmithKline, K.K., Taisho Toyama Pharmaceutical, Co., Torii Pharmaceutical, Co., and ViiV Healthcare. H.G. has received honoraria from MSD K.K., Abbott Japan, Co., Janssen Pharmaceutical K.K., Torii Pharmaceutical, Co., and ViiV Healthcare, Co. All other authors declare no conflict of interest.

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