

**A case of skin rash during oral administration of the anti-androgen receptor inhibitor,
darolutamide**

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Key words: darolutamide, second-generation novel selective inhibitor, drug eruption, skin rash,
maculopapular type

This manuscript contains 616 words, 1 figure.

Funding sources: This work was supported by Takeda Science Foundation, R3-nanchi-
ippan-081 (Health and Labour Sciences Research Grants from the Ministry of Health, Labour
and Welfare of Japan, 20FC1035), and Grants-in-Aid (KAKENHI JSPS 20K08649).

Conflicts of interest: Dr. Kobayashi and Dr. Nomura have served as speakers at an Apalutamide Advisory Board meeting for Janssen Pharmaceutical K.K. Japan. This study was supported by grants from the Takeda Science Foundation and R3-nanchi-ippan-081 (a Health and Labour Sciences Research Grant from the Ministry of Health, Labour and Welfare of Japan, 20FC1035).

Letter to the Editor

Several second-generation novel selective inhibitors of androgen-receptor (AR), including apalutamide and darolutamide, are used to treat prostate cancers (PC).¹ Some cases of apalutamide-caused drug eruption have been reported.² However, cases of darolutamide-induced drug eruption have never been reported. Herein, we report the first case of skin eruption during the administration of darolutamide, which was ameliorated with oral steroid therapy.

A 78-year-old man with a 26-year history of PC was administered anti-androgen medications, including flutamide and bicalutamide, to treat recurrent PC. He developed a rash on his trunk and extremities 44 days after initiation of oral darolutamide (1,200 mg/day). He had been taking atenolol, edoxaban, minodronic acid, bisoprolol fumarate, atorvastatin, telmisartan/amlodipine besilate, magnesium oxide, sitagliptin phosphate hydrate, brotizolam, and rebamipide for years without adverse symptoms. Physical examination revealed a maculopapular rash on his trunk and extremities (Fig. 1a–c). Laboratory test results were within the normal limits, including eosinophil count. Histopathologic examination of an abdominal skin biopsy specimen showed vacuolar-type interface dermatitis with eosinophils (Fig. 1d). We discontinued darolutamide and started oral prednisolone 30 mg/day (0.43 mg/kg/day), oral olopatadine, and topical clobetasol propionate ointment. The erythema improved within a week. The lymphocyte transformation test (LTT) for darolutamide was negative (161 counts per minute [cpm]; control, 119 cpm; phytohemagglutinin, 38914 cpm). One month later, darolutamide was restarted, but the eruption did not recur at least three months after the recommencement of darolutamide.

Darolutamide, apalutamide, and enzalutamide are the second-generation AR inhibitors used to treat PC.¹ In the SPARATAN study, the overall incidence of skin rash among patients who received apalutamide was 24%.³ To date, eight cases of apalutamide-induced skin rash, including two cases of toxic epidermal necrolysis, have been reported.² Apalutamide binds to

serum proteins and increases lymphocyte cellularity in draining lymph nodes, as reported in an *in vivo* mouse drug allergy model.⁴ Enzalutamide resembles apalutamide in its structure and pharmacological action,^{5, 6} but enzalutamide-induced eruption is uncommon.⁷ Darolutamide is the latest anti-AR inhibitor,¹ and its structural formula differs from apalutamide and enzalutamide.^{5, 6, 8} The efficacy of darolutamide, apalutamide, and enzalutamide for nonmetastatic castration-resistant PC was comparable in metastasis-free survival hazard ratios.¹ However, cases of fall, fracture, and skin rash rates were lower with darolutamide than with apalutamide. The incidence of rash caused by darolutamide in the ARAMIS trial was very low (2.9%).⁹ The rash types included combined dermatitis, erythema, rash, macular rash, maculopapular rash, papular rash, and pustular rash, although the details of these cases have not been published. We evaluated the average interval between the introduction of apalutamide and the onset of the eruption at 9.0 weeks (n = 8; median, 8.9; range, 2–20).² The interval of darolutamide in our case was 6.3 weeks (44 days). Hence, darolutamide-induced eruptions may have a longer onset than other common drug eruptions, but similar to that with apalutamide. In our case, the recommencement of darolutamide was tolerated without rash. In cases of apalutamide-induced eruption, apalutamide can be tolerated without skin rash at a reduced dose with or without antihistamines.^{2, 10}

The limitation of this report is that the possibility of a viral rash cannot be ruled out, and further accumulation of similar cases is necessary. The longer interval of darolutamide- and apalutamide-induced rash, as well as the negative LTT and absence of skin rash on the recommencement of darolutamide, suggest the presence of an unknown mechanism of drug eruption that is different from the canonical T-cell-mediated allergic reaction.

Acknowledgements: The patients described in this manuscript provided written informed consent for publication of their case details.

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Figure legends

Figure 1. Clinical and histological findings.

(a), (b), (c) Maculopapular rash on the trunk and extremities. (d) Histopathology of the abdominal papule (hematoxylin-eosin staining; scale bar = 100 μ m). The area demarcated by the black box shows a magnified view. Arrowheads indicate eosinophils (hematoxylin-eosin; scale bar = 50 μ m).

