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

K. Shima, T. Nomura, Y. Yamada, T. Kobayashi and K. Kabashima

1Department of Dermatology, Kyoto University Graduate School of Medicine, Kyoto, Japan
2Department of Urology, Kyoto University Graduate School of Medicine, Kyoto, Japan
3Singapore Immunology Network (SIgN) and Skin Research Institute of Singapore (SRIS), Agency for Science, Technology and Research (A*STAR), Singapore, Singapore

Correspondence to: Takashi Nomura MD, PhD
54 Shogoin-Kawahara, Sakyo-ku, Kyoto 606-8507, Japan
Phone: +81-075-751-3111
Fax: +81-075-751-4949
Email: tnomura@kuhp.kyoto-u.ac.jp

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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).\textsuperscript{1} Some cases of apalutamide-caused drug eruption have been reported.\textsuperscript{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.\textsuperscript{1} In the SPARATAN study, the overall incidence of skin rash among patients who received apalutamide was 24%.\textsuperscript{3} To date, eight cases of apalutamide-induced skin rash, including two cases of toxic epidermal necrolysis, have been reported.\textsuperscript{2} Apalutamide binds to
serum proteins and increases lymphocyte cellularity in draining lymph nodes, as reported in an
in vivo mouse drug allergy model. Enzalutamide resembles apalutamide in its structure and
pharmacological action, but enzalutamide-induced eruption is uncommon. Darolutamide is
the latest anti-AR inhibitor, and its structural formula differs from apalutamide and
enzalutamide. The efficacy of darolutamide, apalutamide, and enzalutamide for
nonmetastatic castration-resistant PC was comparable in metastasis-free survival hazard
ratios. 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%). 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). 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.

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.

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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 μm). The area demarcated by the black box shows a magnified view. Arrowheads indicate eosinophils (hematoxylin-eosin; scale bar = 50 μm).