



# Successful use of dabrafenib after the occurrence of drug rash with eosinophilia and systemic symptoms (DRESS) induced by vemurafenib

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## INTRODUCTION

Vemurafenib and dabrafenib are 2 *BRAF* inhibitors that are approved by the US Food and Drug Administration for the treatment of metastatic malignant melanoma with *BRAF* mutation. These drugs improve overall- and progression-free survival. Some severe vemurafenib-induced reactions have been reported, which commonly require treatment withdrawal. We report the case of a patient with metastatic malignant melanoma in whom DRESS developed likely from vemurafenib. Because the patient did not respond to many previous treatments, dabrafenib, another *BRAF* inhibitor, was started without reoccurrence of DRESS.

## CASE REPORT

A 46-year-old man with lentigo maligna melanoma of the ear (Breslow index, 1.71 mm) with V600E *BRAF* mutation was referred for lung, brain, liver, and subcutaneous metastases. He was treated previously with surgical excision of the external auditory meatus, complete parotidectomy, and carotid-jugular dissection. He was then treated with dacarbazine, temozolomide, and stereotactic radiotherapy when metastases occurred. Five years later, vemurafenib was started owing to progression of lung metastases. Twenty-one days later, the patient presented with a generalized maculopapular exanthema with facial edema. He had no fever or lymphadenopathy. Biological tests found blood

### Abbreviation used:

DRESS: drug rash with eosinophilia and systemic symptoms

eosinophilia ( $1.51 \times 10^9/L$ ), liver cytolysis (alanine aminotransferase, 717 U/L; aspartate aminotransferase, 323 U/L [normal range, 10-50 U/L]), and renal insufficiency (creatinine, 1.36 mg/dL [normal range, 0.7-1.2 mg/dL]). DRESS was diagnosed with a REGISCAR score of 6 of 8 points.<sup>1</sup> Because vemurafenib was the only drug taken by the patient, it was considered the culprit drug. Vemurafenib was stopped, and the patient was treated with topical corticosteroids and prednisone, 0.5 mg/kg/d initially, with a 20% tapering of the prednisone dose every 3 weeks, ending prednisone after 9 weeks. The patient's clinical condition and laboratory values improved within 2 weeks of vemurafenib withdrawal and start of corticosteroids. The patient was then treated with nivolumab (3 mg/kg twice a month) for 6 months and thereafter with ipilimumab (4 infusions of 3 mg/kg every 3 weeks) for 3 months. Because the diameter of the liver metastasis increased from 14 to 21 mm and a bone metastasis occurred on the sacral vertebra S1, dabrafenib was started after the patient gave informed consent. Dabrafenib was started at an initial dose of 75 mg/d, which was then gradually increased to 150 mg twice a day within 2 months (day 1, 75 mg; day 3,

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150 mg; day 15, 225 mg; day 56, 300 mg). Dabrafenib was used alone without oral corticosteroids or antihistamines. DRESS symptoms did not reoccur, and the patient achieved partial remission after 3 months of follow-up.

## DISCUSSION

This case suggests the possibility of using dabrafenib in some patients who previously had a severe drug reaction induced by vemurafenib. This observation may have important implications because of the extremely severe course of metastatic malignant melanoma after vemurafenib withdrawal. Additionally, it suggests that DRESS reaction to these medications may be drug specific as opposed to class specific.

The frequency of nonsevere eruptions induced by vemurafenib is estimated between 32% and 64%.<sup>2</sup> Several studies found the possibility of gradually rechallenging vemurafenib after the occurrence of a nonsevere eruption with no visceral involvement.<sup>3</sup> Four cases of DRESS and 3 cases of Stevens-Johnson syndrome induced by vemurafenib, but none by dabrafenib, have been reported.<sup>4,5</sup> The successful use of dabrafenib in a case of vemurafenib-induced Stevens-Johnson syndrome has been reported.<sup>6</sup> The regimen of dabrafenib used in this report consisted of 10 mg on day 1, 20 mg on day 2, 30 mg on day 3, 75 mg on day 4, 150 mg on day 5, 150 mg on day 6, and 300 mg/d thereafter.<sup>6</sup> The absence of severe drug-induced reaction with dabrafenib and the absence of reoccurrence of symptoms after switching from vemurafenib to dabrafenib in our case of DRESS along with the previously reported case of Stevens-Johnson syndrome, suggest that these medications may be drug specific as opposed to class specific.

The P-glycoprotein might be involved in the difference observed between vemurafenib and dabrafenib. Indeed, several in vitro studies found that vemurafenib was both substrate (poor) and inhibitor of the P-glycoprotein,<sup>7</sup> whereas dabrafenib was only

substrate of the P-glycoprotein.<sup>8</sup> One can hypothesize that this difference between the 2 *BRAF* inhibitors might explain the higher incidence of severe adverse effects reported with vemurafenib than with dabrafenib. This finding might be related to the inhibition of the drug excretion, resulting in an increase in the plasma concentration of vemurafenib.

Overall, our observation suggests the possibility of using dabrafenib in some patients who previously had DRESS from vemurafenib and did not respond to other melanoma treatments. Patients must be informed about the risk of such a switch among the same drug class.

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