

Isotretinoin for the treatment of severe acneiform eruptions associated with the MEK inhibitor trametinib



Marco Caruana, MD,^{a,c} Afshin Hatami, MD,^{a,c} Danielle Marcoux, MD, FRCPC,^{a,c}
Sébastien Perreault, MD, FRCPC,^{b,c} and Catherine C. McCuaig, MD, FRCPC^{a,c}
Montreal, Canada

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Trametinib is a selective inhibitor of mitogen-activated protein kinase (also known as *MEK*) blocking the phosphorylation of mitogen-activated protein kinase. Trametinib has been approved as a treatment for metastatic non–small cell lung cancer and unresectable or metastatic melanoma with specific *BRAF* mutations. Other off-label uses in the pediatric population include treatment of glioma with mitogen-activated protein kinase activation, low-grade glioma with *BRAF* fusion and neurofibromatosis type 1 (NF1) with plexiform neurofibroma, or low-grade glioma. Trametinib is administered at a dose of 0.025 mg/kg/d (maximum, 2 mg). The dose can be reduced if there is a severe adverse effect; however, this may diminish efficacy; currently serologic levels are not measured routinely. Acneiform eruptions have been reported to be the most common adverse effect associated with trametinib occurring in up to 77% of users.¹ Effective treatment of this eruption is important to allow for continued use of MEK inhibitors. However, some patients do not respond to traditional therapy.² We report our experience with isotretinoin as a treatment of severe acneiform eruptions to MEK inhibitor trametinib.

CASE 1

A 16-year-old girl with NF1 and a voluminous plexiform neurofibroma of the right thigh, began trametinib and, 2 weeks later, presented with a dramatic monomorphic papulopustular eruption

Abbreviations used:

EGFR: epidermal growth factor receptor
NF1: neurofibromatosis type 1

on her forehead, nose, and chin. The patient was started on doxycycline, 100 mg twice daily. At 6-week follow-up, there was marked improvement of the eruption, but a subsequent visit 4 weeks later found recurrence and worsening of skin lesions in spite of persistent therapy (Fig 1, A). She was started on isotretinoin, 10 mg/d (0.2 mg/kg/d) for 1 month, followed by 20 mg/d (0.35 mg/kg/d). Three months later, there was significant clearing with only erythematous macules remaining (Fig 1, B). Isotretinoin was well tolerated and she continues with the same treatment for 1 year.

CASE 2

A 16-year-old boy with NF1 and an unresectable painful right paravertebral plexiform neurofibroma was treated with trametinib and subsequently had a monomorphic papulopustular eruption on his nose and back 4 weeks later. The patient was started on isotretinoin, 10 mg/d (0.15 mg/kg/d), and topical dapsone gel twice daily. At 1-month follow-up, the patient had dramatic clearing of inflammatory lesions, and he continues with the same treatment for 6 months.

From the Divisions of Pediatric Dermatology^a and Pediatric Neurology^b and the Department of Pediatrics,^c CHU Sainte-Justine, University of Montreal.

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Correspondence to: Catherine C. McCuaig, MD, FRCPC, CHU Sainte-Justine Division of Dermatology in Pediatrics, University of Montreal, 3175 chemin Côte Sainte-Catherine, Montreal, Quebec, Canada, H3T 1C5. E-mail: catherine.mccuaig.hs@sssss.gouv.qc.ca.

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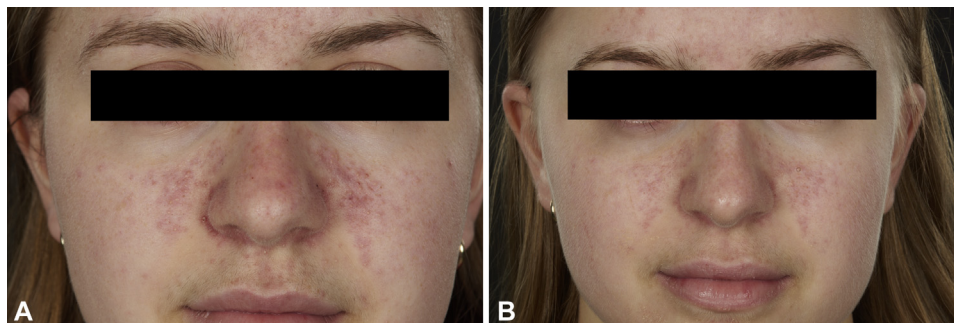


Fig 1. **A**, Monomorphic papulopustular eruption on the forehead, nose, and chin 2 weeks after starting trametinib for a plexiform neurofibroma of the right thigh. **B**, Significant clearing of acneiform eruption with only erythematous macules remaining 3 months after starting isotretinoin treatment.

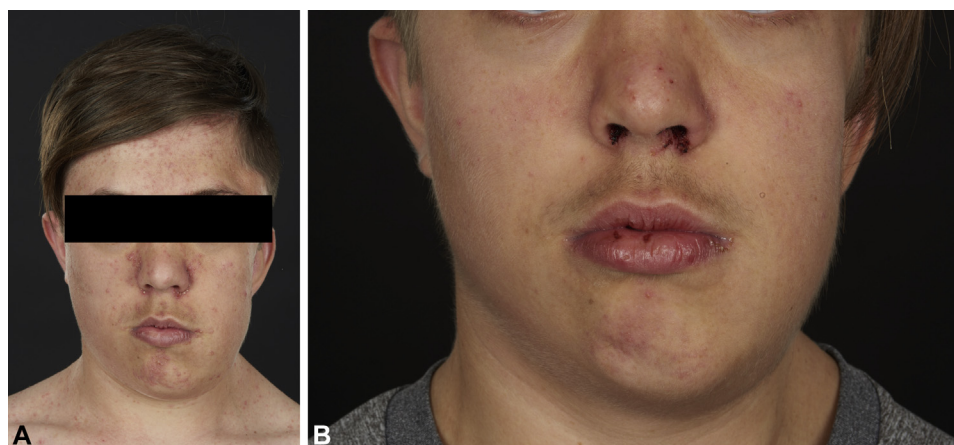


Fig 2. **A**, Monomorphic papulopustular eruption of the face 4 weeks after starting trametinib for facial neurofibromas. **B**, Dramatic improvement of facial acneiform eruption after 3 months on isotretinoin.

CASE 3

A 13-year-old boy with NF1 presented with worsening of baseline comedonal and mild inflammatory acne 4 weeks after starting trametinib for multiple facial neurofibromas despite application of topical 0.025% tretinoin cream. He had multiple comedones and an extensive monomorphic papulopustular eruption on his face, chest, and back (Figs 2, A and 3, A). The patient was started on isotretinoin, 10 mg/d (0.2 mg/kg/d). At 3 months follow-up (Fig 2, B), the patient showed significant improvement of the face with clearing of the back and he continues with the same treatment for 1 year (Fig 3, B).

DISCUSSION

Time to onset of acneiform eruptions after initiation of trametinib was fast, varying from 2 to 4 weeks, which is consistent with previously reported data.¹⁻³ One review of 14 trials of cancer patients on 3 MEK inhibitors reported the relative risk of acneiform

dermatitis at 8.44 (95% confidence interval, 2.39-29.81; $P = .0009$).⁴ This eruption does not always respond to traditional acne therapy with topical treatment and oral antibiotics.² Skin toxicities are considered an important cause for treatment interruption of MEK inhibitors.⁴ The cutaneous side-effect profile of MEK inhibitors closely resembles those of epidermal growth factor receptor (EGFR) inhibitors.^{1,3,5} Although use of isotretinoin has been reported for treatment of EGFR inhibitor-induced acneiform eruptions, it has not been reported for those induced by MEK inhibitors.⁵ We expect to be able to eventually wean off isotretinoin, as is the experience with EGFR inhibitors. A report of EGFR inhibitor-related acneiform eruption notes that 8 of 11 patients showed at least moderate response to isotretinoin. Of these, 4 showed complete response and were able to stop isotretinoin. For the patients who stopped treatment because of significant xerosis, although prescribed dosing was not reported, we hypothesize these complications may have been in



Fig 3. **A**, Monomorphic papulopustular eruption of the back 4 weeks after starting trametinib for facial neurofibromas. **B**, Dramatic improvement of back acneiform eruption after 12 months on isotretinoin.

relation to higher dosing of isotretinoin (ie, ≥ 0.5 mg/kg/d).⁵

Our 3 cases support the use of low-dose isotretinoin (0.15 to 0.35 mg/kg/d) for satisfactorily improving MEK inhibitor–induced acneiform eruptions. Use of isotretinoin in this population is easily manageable, as it does not have a known clinically significant interaction with trametinib. Routine laboratory testing, including fasting lipid panel and liver function tests, should be performed periodically during treatment with isotretinoin.⁵ For our patients, in the context of the trametinib study, laboratory testing was done at baseline for most patients and repeated every 2 to 3 months. Isotretinoin was well tolerated in all 3 patients without significant increases in triglycerides or hepatotoxicity, and rapid improvement was noted within 1 to 3 months. All patients continued low-dose isotretinoin with consistent suppression of the acneiform eruption.

We report 3 cases of severe acneiform eruptions occurring shortly after initiation of therapy with trametinib, which responded with very good

efficacy and tolerance to low-dose oral isotretinoin. Successful treatment of these eruptions with oral isotretinoin is of important clinical significance, as it permits continuation of treatment with trametinib.

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