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**Title: Vemurafenib-induced toxic epidermal necrolysis: Possible cross-reactivity with other sulphonamide compounds**

**Running head: Vemurafenib cross-reactivity to sulphonamides**

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Conflicts of interest: None

#### **What's already known about this topic?**

- Vemurafenib and dabrafenib are BRAF inhibitors licensed for metastatic melanomas presenting BRAF<sup>V600E</sup> mutation.
- Serious hypersensitivity reactions have been reported for vemurafenib.

#### **What does this study add?**

- Vemurafenib and dabrafenib share a sulphonamide group in their chemical structure.
- Lymphocytes from a patient with vemurafenib-induced toxic epidermal necrolysis reacted *in vitro* to vemurafenib, dabrafenib or sulfamethoxazole.
- Clinical cross-reactivity between these drugs is possible in some patients.

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## ABSTRACT

Vemurafenib is a newly licensed target-directed medication. It has been proven to improve the survival of patients with metastatic melanoma and the BRAF<sup>V600E</sup> mutation; however, adverse cutaneous reactions are frequent. Few cases of life-threatening severe cutaneous adverse reactions (SCARs) induced by vemurafenib have been reported. Dabrafenib, another selective BRAF inhibitor, has been recently licensed as an alternative drug with the same indications. From a molecular point of view, both vemurafenib and dabrafenib contain a sulphonamide group; cross-reactivity to sulphonamide compounds has been reported in allergic patients. We report on a patient with vemurafenib-induced toxic epidermal necrolysis (TEN). *In vitro* analysis of lymphocyte reactivity to vemurafenib showed positive results, confirming drug causality. In addition, lymphocytes from the patient reacted to dabrafenib and to the antibiotic sulphonamide drug sulfamethoxazole. Moreover, lymphocytes from two patients with cutaneous adverse reactions to sulfamethoxazole also reacted to vemurafenib and dabrafenib *in vitro*. These data strongly suggest that there might be clinical cross-reactivity between BRAF inhibitors and sulfonamides in some patients. Thus, precautions should be taken to avoid sulphonamide drugs as much as possible in patients showing serious hypersensitivity reactions to vemurafenib and *vice versa*.

## INTRODUCTION

The selective v-raf murine sarcoma viral oncogene homologue B1 (BRAF) inhibitor vemurafenib was licensed in 2012 for monotherapy of BRAF<sup>V600E</sup> mutation-positive unresectable or metastatic melanomas.<sup>1</sup> Dabrafenib, another specific BRAF inhibitor, has shown similar results as vemurafenib in a phase III trial. Targeting a BRAF mutation with dabrafenib, in combination with a MEK inhibitor such as trametinib, has become an alternate strategy for overcoming tumour resistance to BRAF inhibitors.<sup>2</sup>

Adverse skin reactions to vemurafenib are common, although most are mild and manageable with dose reductions.<sup>3</sup> However, severe cutaneous hypersensitivity reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported.<sup>4-7</sup> Vemurafenib and dabrafenib share a sulphonamide group in their chemical structure. Therefore, cross-reactivity between these drugs and with other sulfonamides is possible in some patients.

## CASE

In August 2013, a 68-year old male patient had a surgical resection of nodular melanoma (grade IV, mediastinal adenopathies and possible lung metastasis) in the right submammary region. A BRAF<sup>V600E</sup> mutation was identified, and vemurafenib was introduced on October 3. Four weeks later (October 31), facial erythema and intense pruritus appeared. Vemurafenib was then stopped. Nevertheless, the cutaneous lesions spread to the trunk and extremities, with palmo-plantar involvement. Bilateral conjunctivitis was also present, and the patient was admitted to a local hospital. No improvement was observed after the initial treatment with antibiotics (piperacillin/tazobactam and doxycycline), and corticoids were prescribed. However, the cutaneous lesions progressed with the additional development of dysphagia, hypotension, and diminished diuresis. Thus, the patient was

transferred to the intensive care unit on November 2. The following day, the patient was transferred to a reference hospital with a major burn unit. At admission, the patient presented with mucosal erosions (ocular, oral, and genital), positive Nikolsky's sign, and greater than 30% body surface detachment (Fig. 1a, b). A skin biopsy revealed epidermal detachment, full epidermal necrosis, and lymphocytic infiltrate (Fig. 1c). The diagnosis of TEN was made and SCORTEN (SCORE of Toxic Epidermal Necrolysis) was calculated as 3. The ALDEN score for vemurafenib was calculated as 5 (probable) and Naranjo score as 5 (probable). The patient reported he did not take any other drugs. Treatment with intravenous cyclosporin (75 mg every 12 h) was started. The patient's back and shoulders were covered with biobrane. The severe bilateral conjunctivitis was treated with an amniotic membrane transplant. We proposed that the patient participate in *PIELenRed*, a Spanish registry of serious skin reactions, and the patient accepted and signed the informed consent. The skin detachment progressed for 4 additional days (Fig. S1, see Supporting Information), then re-epithelialization signs became obvious on day 11. The skin disease ended on November 21, and cyclosporin was tapered to 100 mg (oral dose) for 5 additional days. Nonetheless, a multilayer amniotic membrane graft was performed on November 27 for the left eye due to perforation of the cornea. On November 28, the patient was transferred from the major burn unit to a local hospital, and he was advised not to take vemurafenib in the future (more details on this case can be found in Lapresta et al.).<sup>8</sup>

Upon discharge, the patient returned to visit his oncologist, who prescribed dabrafenib plus trametinib combined therapy. The patient sought advice from the *PIELenRed* consortium regarding the drugs' safety. Upon inspection of the molecular structure of vemurafenib, dabrafenib, and trametinib, a sulphonamide group was identified in both dabrafenib and vemurafenib (Fig. 2).

To avoid possible sulphonamide cross-reactivity, we contacted the patient's oncologist and recommended he prescribe a different treatment. In addition, an LTT assay<sup>9</sup> was performed with vemurafenib to confirm causality, and with dabrafenib and sulfamethoxazole to investigate cross-reactivity. Trametinib was also included, although no molecular homologies were found with vemurafenib or dabrafenib. Briefly, mononuclear cells were incubated for 6 days at  $10^6$  cells mL<sup>-1</sup> in triplicate in round-bottom 96 well plates in a final volume of 200  $\mu$ L. The culture medium was RPMI plus 5% autologous serum and various drug concentrations (5, 1 and 0.1  $\mu$ g mL<sup>-1</sup> for vemurafenib; 1, 0.1 and 0.05  $\mu$ g mL<sup>-1</sup> for dabrafenib, 10 and 1 ng mL<sup>-1</sup> for trametinib, and 50, 25 and 10  $\mu$ g mL<sup>-1</sup> for sulfamethoxazole). Phytohemagglutinin was used as a positive control. <sup>3</sup>H thymidine (0.5  $\mu$ Ci/well) was added 18 h prior to cell harvesting. <sup>3</sup>H incorporation was estimated by scintillation counting. The stimulation index (S.I.) was calculated as the ratio between the mean values of counts per minute in cultures with antigen and those obtained without antigen. A S.I. >2 was regarded as a positive response.<sup>9</sup> In this case, the assay was positive for vemurafenib at 5 and 1  $\mu$ g mL<sup>-1</sup> and for dabrafenib at all concentrations tested, and negative for trametinib. The in vitro response to sulfamethoxazole showed a highly positive result at 25  $\mu$ g mL<sup>-1</sup>. Lymphocytes from two other patients with cutaneous reactions to sulfamethoxazole, a control patient with a cutaneous reaction to an unrelated compound, and a healthy non-allergic donor were also studied. Both sulfamethoxazole-allergic patients showed positive results to vemurafenib and dabrafenib. Table 1 shows the higher S.I. obtained for each donor.

## DISCUSSION

Sulphonamide structures are included in a variety of drugs. Sulphonamide antimicrobials are known causes of drug hypersensitivity reactions and are strongly associated with the most severe clinical entities.<sup>10</sup> Epidemiological, *in vitro*, and skin test studies suggest that cross-reactivity of sulphonamide antibiotics and nonantibiotics is unlikely to occur, and cross-reactivity occurred only within the group of aromatic sulphonamides.<sup>11</sup> Clinicians thus tend to differentiate between allergy to antibiotic sulphonamides and allergy to nonantibiotic sulphonamides. However, this distinction could be misleading in some cases. We relied on *in vitro* tests and refrained from *in vivo* testing on our patient because he had a clear and typical history, life-threatening symptoms, and a positive *in vitro* test that confirmed he had memory T cells able to react to vemurafenib and to other sulphonamides. Therefore, the patient was advised not to use these drugs in the future. Moreover, other studies on the cross-reactivity of various structurally related compounds in drug hypersensitivity showed a good correlation between *in vivo* and *in vitro* LTT.<sup>12,13</sup> It is important to note that a positive LTT can be helpful for identifying cross-reactive agents in certain drug groups, but due to its limited sensitivity<sup>9</sup> it cannot be used to rule out reactivity or cross-reactivity. Because the structural similarity between the antibiotic sulfamethoxazole and vemurafenib or dabrafenib is not obvious to most clinicians, we consider it prudent to avoid sulphonamide compounds as much as possible in patients showing serious hypersensitivity reactions to vemurafenib. This advice does not necessarily mean that all patients with a sulphonamide allergy are also allergic to many different compounds. As has been reported on patients allergic to beta-lactams, some individuals are “selective” for a single chemical structure, whereas others bear memory T cells cross-reactive to various structurally related antibiotics.<sup>14</sup> Along these lines, a successful switch to dabrafenib after vemurafenib-induced TEN has recently been reported.<sup>7</sup> Although dabrafenib has been approved more recently than vemurafenib, no cases of dabrafenib-induced SJS/TEN or DRESS have been reported to date. In conclusion, we describe a patient with vemurafenib-induced TEN whose lymphocytes are cross-reactive *in vitro* to dabrafenib and sulfamethoxazole. This finding strongly suggests against the use of sulphonamide drugs in patients with SCARs to BRAF inhibitors and *vice versa*.

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## FIGURE LEGENDS.

Figure 1. Clinical presentation.(a) Widespread erythematous macules and blistering on day 4 (b) Detailed view of blistering on the trunk. (c) Skin biopsy showing full thickness epidermal necrosis, epidermal detachment at the dermoepidermal junction, and a lymphocytic infiltrate (Hematoxylin and eosin, original magnification 200x).

Figure 2. Molecular structures of vemurafenib, dabrafenib, sulfamethoxazole and trametinib. The sulphonamide groups are circled in red.

Table 1. LTT results from the patient with vemurafenib-induced TEN, 3 additional patients with cutaneous reactions to SMX or structurally unrelated drugs, and a healthy control donor.

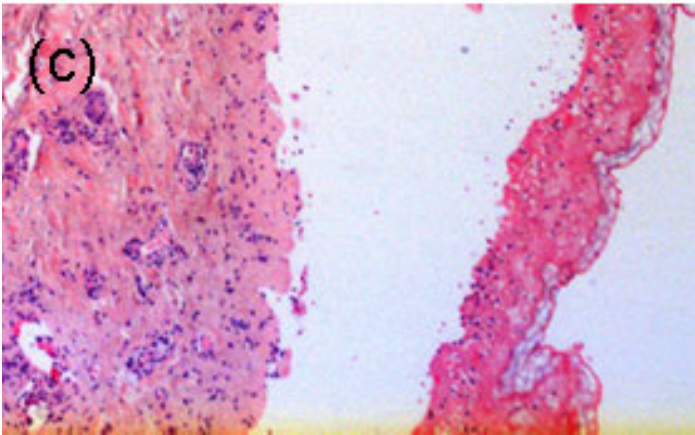
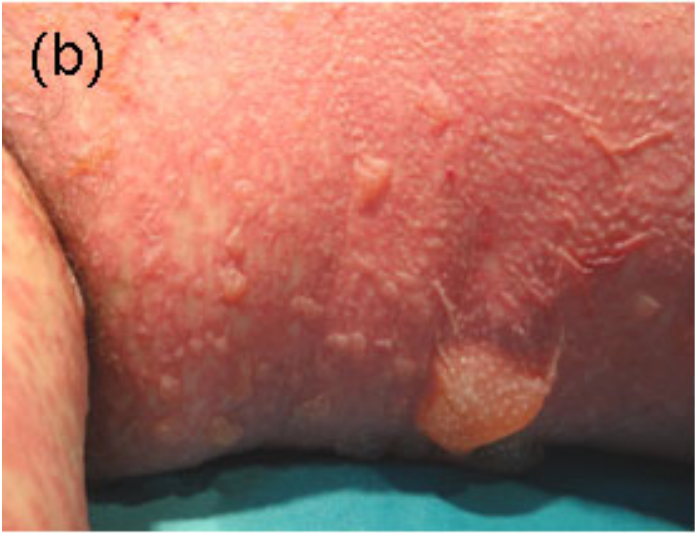
| Patient | Clinical entity | Culprit drug | LTT results (S.I.) |      |       |
|---------|-----------------|--------------|--------------------|------|-------|
|         |                 |              | VMF                | DBF  | SMX   |
| 1       | TEN             | VMF          | 2.48               | 2.56 | 6.34  |
| 2       | DRESS           | SMX          | 2.44               | 2.30 | 43.02 |
| 3       | MPE             | SMX          | 2.12               | 2.20 | 2.72  |
| 4       | MPE             | Diltiazem    | 1.50               | 1.12 | nd    |
| 5       | HD              |              | 1.43               | 1.26 | 1.25  |

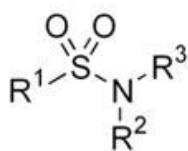
MPE: maculo-papular exanthema; HD: healthy donor; SMX: sulfamethoxazole; VMF: vemurafenib; DBF: dabrafenib; nd: not done

## Supporting Information

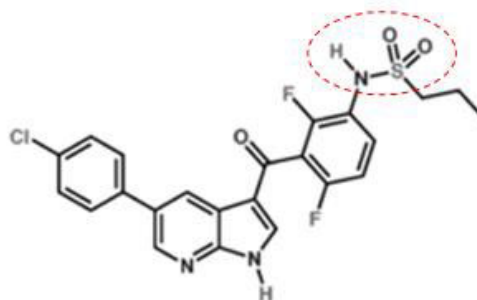
Additional Supporting Information may be found in the online version of this article at the publisher's website:

**Figure S1.** (a) Picture showing widespread skin detachment covered with biobrane. (b) Close up view of the lower back and buttocks.

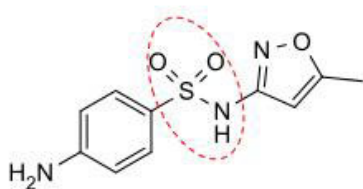




Sulfonamide functional group



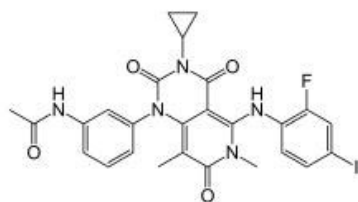
Vemurafenib



Sulfamethoxazole



Dabrafenib



Trametinib

