Uveitis in Patients With Late-Stage Cutaneous Melanoma Treated With Vemurafenib

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IMPORTANCE This case series highlights the risk of uveitis in patients treated with vemurafenib for unresectable or metastatic cutaneous melanoma.

OBJECTIVE To assess the occurrence and severity of uveitis as an adverse effect of vemurafenib therapy.

DESIGN, SETTING, AND PATIENTS In this observational small case series, data were collected successively from May 1, 2012, through February 31, 2013, from patients with clinical signs of ocular inflammation treated with vemurafenib at the Department of Ophthalmology, Cochin-Hôtel-Dieu Hospital.

MAIN OUTCOMES AND MEASURES Patients' demographics, vemurafenib dosages, and the intervals between the onset of treatment and the first ocular symptoms were recorded. The characteristics of ocular inflammatory manifestations were analyzed. The effect of the discontinuation of vemurafenib therapy on ocular manifestations was assessed, as well as the effect of rechallenging when vemurafenib was reintroduced.

RESULTS Seven patients (mean [SD] age, 74.7 [4.0] years) had uveitis. The vemurafenib dose was 960 mg twice per day in 6 patients and a half dose in 1 patient. The mean (SD) time until the appearance of ocular signs was 5.6 (2.3) months (range, 19 days to 7 months), and inflammation ranged from mild or low-grade anterior uveitis to severe explosive panuveitis complicated by retinal detachment. Signs of ocular inflammation were always bilateral. Optical coherence tomography revealed a macular edema in only 1 of the 7 patients. Clinical improvement occurred when vemurafenib therapy was stopped in 5 of 7 patients. The rechallenge at treatment reintroduction was positive in 2 of 7 patients.

CONCLUSIONS AND RELEVANCE This small case series highlights that uveitis can be a noteworthy adverse effect of vemurafenib therapy in patients with metastatic cutaneous melanoma. However, these cases of uveitis were usually restricted to the anterior segment and manageable with local corticosteroid therapy, which justified the continuation of vemurafenib therapy because the benefits regarding the patients' survival were greater than the risk to their vision.

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Vemurafenib is a BRAF (OMIM 164757) enzyme inhibitor developed for the treatment of late-stage melanoma with the V600E BRAF mutation, which is thought to be present in half of all melanomas and responsible for the proliferation of tumoral cells. The name vemurafenib derives from V600E mutated BRAF inhibition.

Vemurafenib received approval from the Food and Drug Administration for the treatment of late-stage melanoma in August 2011 and from the European Medicines Agency in February 2012 as monotherapy for the treatment of adults with the V600 BRAF mutation and nonresectable or metastatic melanoma. In clinical trials, vemurafenib treatment was reported to improve survival in previously untreated and treated patients with advanced melanoma with BRAF V600 mutations.

The most common grade 3 or higher adverse events in patients receiving vemurafenib (at the maximum tolerated dose of 960 mg twice a day) compared with those receiving conventional chemotherapy were cutaneous squamous cell carcinoma (3%) (which could generally be surgically removed), rashes (52%), liver function abnormalities, arthralgia (58%), and photosensitivity (52%).

To our knowledge, no adverse effects, such as uveitis or intraocular inflammation, have been reported so far in the medical literature. However, in phase 1 and 2 clinical trials, 5 cases of uveitis have been reported. The purpose of this study was to describe the detailed ocular features of patients with uveitis related to vemurafenib therapy.

Methods

This was an observational study conducted within the field of approved indications for vemurafenib in France. Informed consent and institutional review board approval were not required in that context. We collected data from patients who were all followed up for metastatic cutaneous melanoma and treated with vemurafenib and who were sent to the Department of Ophthalmology, Cochin Hospital, from May 1, 2012, through February 31, 2013. Vemurafenib-treated patients from 2 departments of dermatology were referred to us in a systematic manner because of ocular symptoms (pain, redness, vision loss, blurred vision, and floaters) but without systematic-specific screening. Patient demographics, vemurafenib dosages, and the interval between treatment onset and first ocular symptoms were recorded. The results of tests used to diagnose other causes of uveitis were reviewed. Optical coherence tomography (OCT) of the macula was performed in a systematic manner. The effect of the discontinuation of vemurafenib therapy on ocular manifestations was assessed, as well as the effect of rechallenging in cases of vemurafenib reintroduction.

Results

Among 78 vemurafenib-treated patients, 8 were referred for ocular symptoms, which led to the diagnosis of uveitis in 7 patients (1 man and 6 women) and of episcleritis in 1 patient. The mean (SD) age at the onset of uveitis was 74.7 (4.0) years (range, 69-81 years). The vemurafenib dosage at onset was 960 mg twice per day for all patients. For 1 patient, it was initially 480 mg twice per day, then 960 mg twice per day. The mean (SD) time between the treatment onset and the first ocular symptoms was 5.6 (2.3) months (range, 19 days to 7 months).

Uveal findings are summarized in the Table. The intraocular inflammation was characterized by low-grade or mild anterior uveitis, except in 1 patient with severe acute onset panuveitis, which was further complicated by retinal detachment and complete visual loss.

Five patients discontinued treatment; in 2 patients, anterior uveitis subsided despite continued vemurafenib treatment. Clinical improvement occurred when vemurafenib treatment was discontinued in 5 of the 7 patients. On rechallenging with vemurafenib (4 patients), an effect of treatment reintroduction was noted in 2 patients, who relapsed after the rechallenge (Table 2).

Patient 1, a 74-year-old woman who had been treated with vemurafenib, 960 mg twice a day, since June 2012 for a meta-

### Table. Vemurafenib Dose and Ocular Findings

<table>
<thead>
<tr>
<th>Patient No./Age, y</th>
<th>Vemurafenib Dose</th>
<th>Time Before Occurrence</th>
<th>Uveitis Presentation</th>
<th>Macular Edema on OCT at Presentation</th>
<th>Initial Visual Acuity at Presentation</th>
<th>Improvement After Treatment Cessation</th>
<th>Positive Rechallenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/74</td>
<td>960 mg twice per day</td>
<td>7 mo</td>
<td>Anterior bilateral</td>
<td>No</td>
<td>20/20 OD 20/20 OS</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>2/78</td>
<td>480 then 960 mg twice per day</td>
<td>5 mo</td>
<td>Anterior and intermediate bilateral</td>
<td>No</td>
<td>20/20 OD 20/40 OS</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>3/81</td>
<td>960 mg twice per day then half dose</td>
<td>7 mo</td>
<td>Anterior bilateral</td>
<td>No</td>
<td>20/40 OD 20/28 OS</td>
<td>...</td>
<td>No</td>
</tr>
<tr>
<td>4/75</td>
<td>960 mg twice per day</td>
<td>7 mo</td>
<td>Anterior bilateral</td>
<td>Yes</td>
<td>20/33 OD 20/200 DS (cataract)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>5/69</td>
<td>960 mg twice per day</td>
<td>3 wk</td>
<td>Explosive bilateral panuveitis</td>
<td>No</td>
<td>Restricted to hand movements</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>6/71</td>
<td>960 mg twice per day</td>
<td>7 mo</td>
<td>Anterior bilateral</td>
<td>No</td>
<td>20/28 OD 20/40 OS</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>7/75</td>
<td>960 mg twice per day</td>
<td>4 mo</td>
<td>Anterior bilateral</td>
<td>No</td>
<td>20/20 OD 20/20 OS</td>
<td>...</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviation: OCT, optical coherence tomography.

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static cutaneous melanoma of the leg, was seen by us in January 2013 (after a 7-month treatment period) and reported having had floaters for a few weeks. Her visual acuity was 20/20 in both eyes. The slitlamp examination revealed a bilateral non-granulomatous anterior uveitis, with thin retrocorneal precipitates, posterior synechiae, anterior chamber (AC) cells (1+). The fundus examination revealed no vitreous haze or vasculitis, and no macular edema was found on OCT. The results of diagnostic tests adjusted to the clinical presentation (HLA-B27 typing, angiotensin-converting enzyme, Treponema pallidum hemagglutination VDRL test, C-reactive protein, blood cell count, Quantiferon tuberculosis) were negative. Inflammatory signs (AC cells) disappeared completely after discontinuation of vemurafenib treatment and with local corticosteroid therapy, which was tapered in 4 weeks.

Patient 2, a 78-year-old woman who had been treated with vemurafenib at half and then full dose (960 mg twice a day) since June 2012 for a metastatic cutaneous melanoma of the leg, was referred to the Department of Ophthalmology, Cochin Hospital, in November 2012 (after a 5-month treatment period). Her visual acuity was 20/20 OD and 20/40 OS. A bilateral anterior non-granulomatous uveitis was diagnosed, and vemurafenib therapy was discontinued for 2 weeks. As the symptoms improved, vemurafenib was reintroduced 15 days later at a 75% dose. In January 2013, a relapse of the anterior bilateral uveitis occurred, with more than half of the AC cells, no synechiae, and vitreous haze (AC cells [2+]). The blood test results were negative. A favorable response to topical corticosteroid therapy was observed.

Patient 3, a 81-year-old man who had been treated with vemurafenib at full dose (960 mg twice a day) then half dose since May 2012 for a metastatic cutaneous melanoma of the elbow, was referred to the Department of Ophthalmology, Cochin Hospital, in December 2012 (after a 7-month treatment period) for a mild bilateral blurred vision. Her visual acuity was 20/40 OD and 20/28 OS. The slitlamp examination revealed a bilateral anterior non-granulomatous uveitis, with posterior synechiae, slightly elevated flare meter measures at 30 photons per millisecond (N=8) without visible AC cells, and a mild cataract. The fundus examination findings were normal, and no macular edema was revealed on OCT. Blood test results were negative. A favorable response to topical corticosteroid therapy was observed.

Patient 4, a 75-year-old woman who had been treated with vemurafenib, 960 mg twice a day, since January 2012 for a metastatic cutaneous melanoma of the back, reported acute pain and vision loss in her left eye at her first visit in the Department of Ophthalmology, Cochin Hospital, in August 2012 (after a 7-month treatment period). Her visual acuity was 20/33 OD and 20/200 OS. The slitlamp examination revealed thin retrocorneal precipitates in both eyes, AC cells (1-2+), and synechiae on 360° with pupillary seclusion in the left eye. Flare meter values were increased to 30 photons per millisecond in the right eye and to 200 photons per millisecond in the left eye. The fundus examination findings were normal in the right eye and could not be seen in the left eye, but the ocular echography revealed no retinal damage. Blood test results were negative. Vemurafenib treatment was immediately discontinued, and topical corticosteroid therapy was initiated. As the clinical examination findings improved, vemurafenib was reintroduced in October 2012, at 75% and then full dose after 6 weeks. Two months later, the reappearance of inflammatory ocular signs (pain, redness, and vision loss in the right eye) led to the diagnosis of a relapse of an anterior and intermediate uveitis of the right eye complicated by macular edema. Visual acuity was 20/50 OD, and thin retrocorneal precipitates, posterior synechiae, and vitreous haze (AC cells [2+]) were observed, as well as cystoid macular edema on OCT with a central macular thickness of 500 μm. These symptoms led for the second time to the discontinuation of vemurafenib treatment.

Patient 5, a 69-year-old woman who had been treated with vemurafenib, 960 mg twice a day, since April 2012 for a metastatic cutaneous melanoma of the ear, was referred to the Department of Ophthalmology, Cochin Hospital, in May 2012 (after a 3-week treatment period) for severe bilateral vision loss with pain and redness. Sltlamp examination revealed a bilateral nongranulomatous acute anterior uveitis, with posterior synechiae and AC cells (3+) (Figure 1A). A topical corticosteroid therapy (1 drop per hour) was initiated, and vemurafenib treatment was stopped immediately. However, despite the
Ocular symptoms varied from low anterior uveitis in 5 of the 7 patients. Vemurafenib has been described in association with uveitis in phase 1 and 2 clinical trials. Flare meter measurements confirmed the presence of an intraocular inflammation in all cases, in particular when the AC cells were not observed during visits. The additional tests excluded other non-drug-related causes in 6 of the 7 patients, especially in patient 5, whose anterior chamber tap test result was negative, excluding an endogenous endophthalmitis. However, patient 6 had a previous history of psoriatic arthritis, compatible with non-vemurafenib-related uveitis. Ocular symptoms varied from low to mild anterior uveitis in 5 of the 7 patients.

Only 1 of these 7 patients (patient 5) had very severe ocular damage (severe explosive panuveitis complicated with retinal detachment), worsening even after the discontinuation of treatment. However, most of these cases of uveitis were restricted to the anterior segment (4 of 7) and responded to topical corticosteroid therapy. Thus, the permanent discontinuation of vemurafenib therapy may not be justified because the benefits of the treatment on patient survival are overall greater than the risk on their vision. However, the benefit-risk balance could be more difficult to assess in patients treated with vemurafenib as an adjuvant therapy, as in an ongoing phase 3 study. The withdrawal of vemurafenib should thereby be discussed jointly on a case-by-case basis by ophthalmologists, dermatologists, and the patients.

Conclusions
This small case series highlights that uveitis can be a noteworthy adverse effect of vemurafenib therapy in patients with unresectable or metastatic cutaneous melanoma. Heteroge-
neous presentations of the inflammation may be observed in this context. The mechanisms that lead to vemurafenib-induced uveitis remain unknown. The continuation of treatment or its discontinuation require careful balancing between the expected benefits of treatment vs its ocular adverse effects.

ARTICLE INFORMATION
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Author Contributions: Dr Guedj had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Guedj, Quéant, Lellouch, Gantzer, Brézin.
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Drafting of the manuscript: Guedj, Quéant, Lellouch, Gantzer, Brézin.
Critical revision of the manuscript for important intellectual content: Quéant, Funck-Brentano, Kramkimel, Monnet, Longvert, Brézin.
Statistical analysis: Guedj.

REFERENCES

OPHTHALMIC IMAGES

Ointment in the Anterior Chamber
Sandro Sbordone, MD; Alfonso Savastano, MD; Vito Romano, MD

Postoperative hypotony presumably allowed ointment to gain entrance into the anterior and posterior chambers (arrowheads) as photographed 4 weeks after phacoemulsification.