Author’s response to reviews

Title: Case report: Ocular toxicity due to Trametinib and Dabrafenib

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Author’s response to reviews:

Dear Ms Carreno,

According to the comments we changed the manuscript as follows:

1) In the case presentation: "The therapy with Trametinib and Dabrafenib was stopped immediately after diagnosis", later in the discussion "The therapy with Trametinib was stopped immediately after eye examination showing chorioretinopathy". It is not clear if both agents were stopped at the same time or the Trametinib was stopped first.

Answer: Thank you for the comment. We changed the sentence in the discussion as Trametinib and Dabrafenib were stopped immediately: “The therapy with Trametinib and Dabrafenib was stopped immediately after eye examination showing chorioretinopathy…”. (Discussion, page 4, line 11)

2) In the discussion: "Treatment has to be stopped when severe ocular side effects, most frequently uveitis and retinal detachment, occur." I will strongly encourage to rephrase this sentence.
Answer: Thank you for the comment. We changed the conclusion after a second review of the literature to “Treatment doses should be reevaluated based on the severity of ocular side effects.” (conclusion, page 5, line 11).

3) Figure 2 legend: "Fluoreszensangiography" should be corrected to "Fluorescein angiography"

Answer: Done (Figure Legend, Figure 2)

4) Discussion needs to include some mention about uveitis cases already reported with Vemurafenib (also a BRAF-inhibitor).

Answer: Thank you for the comment. We mentioned Vemurafenib in the discussion on page 4, line 6).

Piergiorgio Neri, BMedSc, MD, PhD, FEBOphth (Reviewer 1): This is a nice and well written case report. the content presents a topic that can be of interest for the readers and I believe can be suitable for BMC Ophthalmol.

Simon R J Taylor, MA PhD FRSB FRCOphth (Reviewer 2):

This is an interesting case report with good illustrations (especially the ICGA). These drugs are becoming more common, so knowledge of their ocular side-effects is important. Minor English language editing is required throughout. My major criticism is that the authors need to think about what they are recommending - this patient's uveitis was symptomatic and was reversible with cessation of therapy/topical steroids, so why is screening required? They present no evidence of asymptomatic ocular pathology that would be better treated with early therapy, so there is no evidence here to support the institution of a screening programme for these patients. Surely one could simply tell patients that they may get a reduction in vision and provide a pathway for them to access if they do?

Answer: Thank you for the comment. We think that a screening of patients is required as the combined therapy with Trametinib and Dabrafenib was launched for the treatment of malignant
melanoma. Second, most patients have no or only mild symptoms although a retinopathy appears (de la Cruz-Merino L, et al. Clinical features of serous retinopathy observed with cobimetinib in patients with BRAF-mutated melanoma treated in the randomized coBRIM study. J Transl Med. 2017). In accordance to the study the authors reduced the doses of therapy. We made some changes in the manuscript (Discussion, page 5, line 10).

Also, does treatment have to be stopped if there are side-effects (P5L13)? What if it's just anterior uveitis which can be well-controlled with topical steroids. Wouldn't these patients be better treated with a potentially life-saving drug for their melanoma and just continuing to take the topical steroids, rather than stopping the drug? I do think the authors need to be careful about making sweeping statements based on their one case here.

Answer: Thank you for the comment. We changed the conclusion after a second review of the literature to “Treatment doses should be revaluated based on the severity of ocular side effects.” (discussion, page 5, line 11).

A couple of small things where the text does not make sense, e.g.

P4L7 - 'prevents the T-cells from inactivity'? - meaning what exactly?

Answer: We changed it into “It binds at the receptor PD-1 of active T-cells and leads to an increased activity of T-cells.” (Case presentation, page 4, line 5)

P4L16 - 'visual loss of 10%'? - measured how?

Answer: We changed the spelling into “20/200 (0.1)”. (Case presentation, page 4, line 9).