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Sir,

Response to 'Bevacizumab and type 1 idiopathic macular telangiectasia'

We thank Koay *et al*[1] for their interest in our paper[2] and for presenting an interesting case. We feel that the effectiveness of intravitreal bevacizumab varies among patients with idiopathic macular telangiectasia (MacTel) type 1. In our patients, visual acuity improved only in one of the five eyes at 12 months after the initial treatment. However, Gamulescu *et al*[3] reported that a single intravitreal bevacizumab markedly increased the visual acuity in a MacTel type 1 patient, and Koay *et al*[1] showed a case of MacTel type 1 successfully treated with intravitreal bevacizumab.

One possible reason for this discrepancy may be the different treatment protocol. In our study, the protocol was as follows: all patients were examined for changes in the visual acuity or retinal thickness 2 weeks after treatment; if macular oedema did not reduce, additional treatments were performed one to two times at the discretion of the physician at 4-week intervals. In contrast, Koay *et al*[1] administered a monthly injection of intravitreal bevacizumab three times from the baseline. Thus, a prospective study using a fixed protocol in a larger number of patients is necessary to confirm the efficacy of bevacizumab for the treatment of MacTel type 1.

Recently, He *et al*[4] reported that Coats' disease is associated with an increased intraocular vascular endothelial growth factor (VEGF) level. In their study, intraocular fluid was obtained from three children and one adult diagnosed with Coats' disease. Currently, this disorder is considered as Coats' disease in childhood and is usually referred to as MacTel type 1 when it is diagnosed in an adult, and involves the macula. Further studies on intraocular VEGF level in MacTel type 1 or adult-onset Coats' disease will show whether VEGF has a function in the pathogenesis of MacTel type1.

Conflict of interest

The authors declare no conflict of interest.

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Sir,

Presumed entecavir-induced ocular toxicity

Entecavir (Baraclude, Bristol-Myers Squibb, Princeton, NJ, USA) is a nucleoside analogue used to treat chronic hepatitis B virus infection.[1] We report a case of presumed ocular toxicity and significant visual loss in a patient with chronic hepatitis B infection treated with entecavir.

Case report

A 54-year-old Vietnamese male developed reduced vision sequentially in both eyes over a 2-year period. Past medical history included type 2 diabetes mellitus and chronic hepatitis B. In June 2007, the visual acuity (VA) was 6/9 in both eyes, with mild non-proliferative diabetic retinopathy, and no signs of macular abnormalities. During 2008, the VA worsened to hand movements in the right eye, secondary to subretinal fibrotic bands, tractional macular oedema, and diffuse retinal pigment epithelium (RPE) atrophy (Figure 1a). Fundus fluorescein angiography (FFA) showed abnormal RPE and foveal ischaemia (Figure 1b). At the time, the macular oedema was attributed to tractional elevation from the subretinal bands. Although the visual prognosis was guarded, the patient elected to proceed with right-sided pars plana vitrectomy and removal of subretinal bands to alleviate the macular oedema. The surgery was uncomplicated, although the vision did not improve significantly. Following surgery, Fourier-domain optical coherence tomography (FD-OCT) demonstrated reduction in macular oedema, with diffuse outer retinal atrophy, RPE thickening, and subretinal fluid at the fovea (Figure 1c). All infectious, inflammatory, and autoimmune serological tests were negative.

The patient re-attended in September 2010, with severe left-sided maculopathy and VA 6/48 (Figure 2a). There were no ocular signs of intraocular uveitis or diabetic complications. Indocyanine green angiography was normal. Widefield Optos (Optos, Dunfermline, Scotland) FFA showed loss of the foveal capillary ring and RPE atrophy, confirmed by fundus autofluorescence (Figures 2b and c). FD-OCT demonstrated progressive

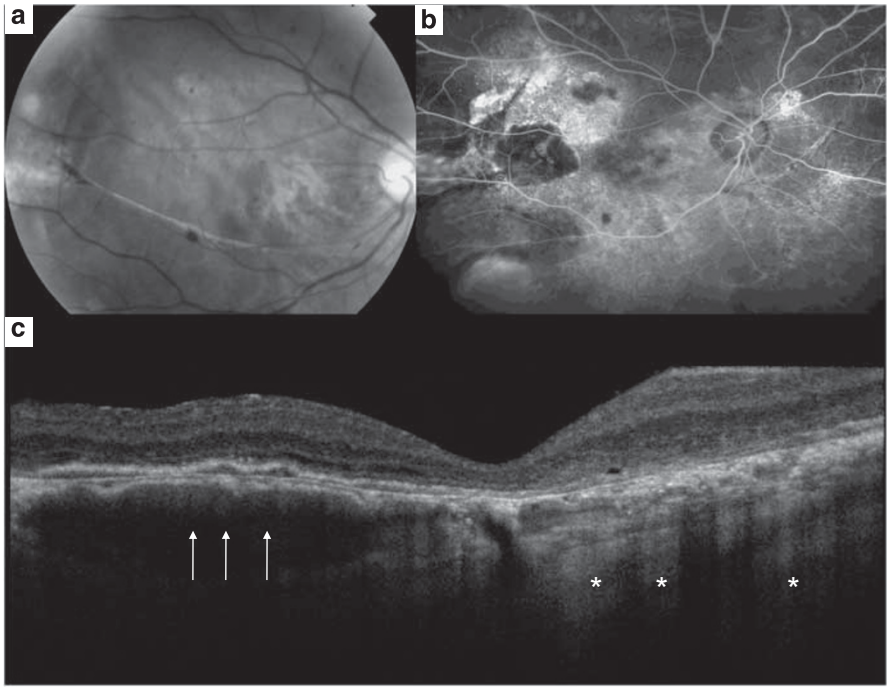

Figure 1 (a) Black and white fundus photograph taken in April 2009, 3 months following induction of entecavir therapy. There is diffuse RPE atrophy in the parafoveal zone, with a subretinal fibrotic band emanating from the peripapillary area, and extending to a foci of pigmented subretinal fibrosis in the temporal retina. There is diffuse subretinal fluid within this region under the tractional band. (b) The Widefield Optos fluorescein angiogram demonstrates loss of the foveal capillary ring and widespread hyperfluorescence in the temporal retina, macular, and peripapillary zones. Areas of RPE atrophy correspond with the hyperfluorescence, and there are no signs of peripheral retinal ischaemia, late leakage or sub retinal/retinal neovascularisation. (c) High-resolution, overlapping optical coherence tomography line scan taken after vitrectomy surgery and removal of subretinal bands. There is RPE thickening across the macula, outer retinal thinning, and disruption of the inner segment/outer segment junction of photoreceptors. The choroidal hyper-reflectivity is attenuated below the RPE thickening (arrowheads), and these reflectivity window defects are markedly increased below areas of RPE atrophy (asterisk).

outer retinal degeneration and exudation (Figure 2d), with features similar to chloroquine-associated retinal toxicity.[2] Visual evoked potentials (Figure 2e) were attenuated with pattern electroretinograms extinguished in both eyes (Figure 2f and g). Ganzfield electro-retinograms were delayed and electro-oculograms subnormal in both eyes.

Under the care of the Infectious Diseases Team, in the last 2 years, there were no positive serological tests for vasculitis, sarcoid, human immunodefiency virus, or syhilis, and inflammatory markers were not elevated. On entecavir therapy, the hepatitis B viral load reduced significantly and remained in remission over the previous 18 months. The Manchester uveitis specialist reviewed the case, and no signs of intraocular inflammation presented over the course, and no underlying inflammatory cause was detected from investigations. There was no family history of eye disease, and there were no symptoms of colour vision problems, nyctalopia, photophobia, or distortion, to suggest an inherited retinopathy.

Drug-induced toxicity was not suspected until 2010. The entecavir was first started in 2008 for 4 weeks, and was temporally associated with the right macular oedema and subretinal bands. Entecavir was restarted between August 2009 and 2010, and coincided temporally with the left-sided maculopathy and visual deterioration. The anti-hepatitis treatment was switched to a different class of drug to prevent any further toxicity; however, after 4 months, VA was perception of light OD and 6/48 OS. The FD-OCT features were unchanged, and the patient registered partial-sighted.

Comment

There was a single report of macular oedema in the literature associated with ETV-027/901 clinical trials ($n = 1/99$); however, this serious adverse event was not deemed related to entecavir treatment.[3] To our knowledge, this is the first report of ocular toxicity presumed secondary to systemic entecavir drug therapy. There were no signs of extraocular drug toxicity in this case. During the course, the non-proliferative diabetic retinopathy consisted of only several scattered intraretinal haemorrhages in the retinal periphery of both eyes. Before the drug toxicity sequentially affecting either eye, the FFA tests did not show any signs of diabetic maculopathy, or any features of foveal vascular zone disruption. These tests excluded the possibility that sub-clinical diabetic disease could have opened up the blood–retinal barrier, for the drug to reach retinal tissue.

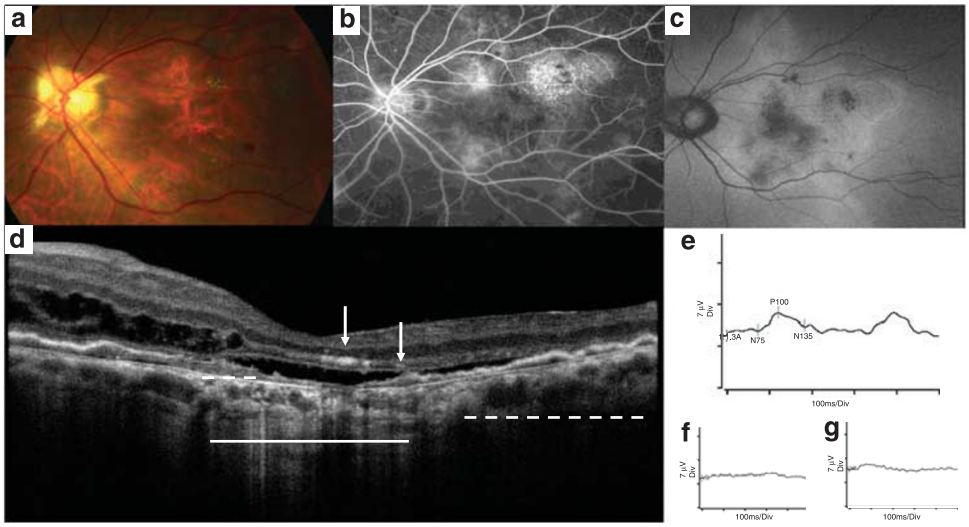

Figure 2 (a) In September 2010, there is generalised loss of retinal transparency and RPE atrophy at the macula. (b) The Widefield Optos fluorescein angiogram demonstrates loss of the foveal capillary ring and areas of hyperfluorescence that correspond to RPE alterations. There are no signs of peripheral retinal ischaemia, late leakage, sub retinal/retinal neovascularisation, or peripheral vasculitis. (c) Widefield Optos scanning laser ophthalmoscopy autofluorescence image of the left posterior pole in October 2010. There is lack of autofluorescence at the macula corresponding to RPE atrophy (white bar). In the superior, temporal, and nasal zones, there is increased autofluorescence that corresponds with RPE thickening and intraretinal/subretinal fluid accumulations (dashed bar). (d) High-resolution, overlapping optical coherence tomography line scan of left macula taken in October 2010. There is diffuse cystic oedema within the outer nuclear and plexiform layers, and subretinal fluid at the fovea. The RPE is atrophic at the fovea (white bar) that corresponds to the lack of autofluorescence in (d), with RPE migration (arrows) in the subfoveal area above the inner segment/outer segment photoreceptor junction. The RPE is irregularly thickened and elevated in the parafoveal zones (dashed bar) that correspond with areas of increased autofluorescence. The outer Bruch's membrane layer is intact and visualised below the elevated RPE as a continuous highly reflective layer. (e) The binocular visual evoked potential shows delayed P100 timing, and reduced amplitude of all waveforms. The right (f) and left (g) pattern electroretinograms undertaken in November 2010 are both severely extinguished.

Possible mechanisms include drug entry via tight junctions between RPE cells, and/or the tight junctions of retinal capillary endothelium; yet, the mechanism of ocular toxicity is unclear in our case.[4] There are no *in vitro* or animal studies that have examined the effects of entecavir in the eye. It is interesting that long-term antiviral therapy with entecavir reverses fibrosis and cirrhosis in patients with chronic hepatitis B virus, whereas in our case, the patient developed subretinal fibrosis and retinal degeneration over time.[5] On the basis of our imaging results, the RPE thickening and photoreceptor degeneration suggest that the drug may bind melanin in the RPE.[6] The autofluorescence imaging suggest that the function of the lysosomal RPE at the macula is disrupted with increased levels of lipofuscin observed within the RPE and outer retina. Photoreceptor degeneration would follow the RPE dysfunction and lipofuscin accumulation in the outer retina, leading to reductions in autofluorescence signals.

The visual and functional prognosis was poor in this case, based on the initial presentation findings of the outer retinal atrophy and degeneration, and subnormal electrophysiology responses. We reported this suspected adverse drug reaction through the yellow card scheme to the Medicines and Healthcare Products Regulatory Agency (Department of Health, London, UK). On the basis of our case, physicians should be aware of the potential rare risk of ocular toxicity in patients on entecavir therapy.

Conflict of interest

The authors declare no conflict of interest.

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