Sir,

Cytomegalovirus retinitis successfully treated with ganciclovir implant in a patient with blood ganciclovir resistance and ocular ganciclovir sensitivity

Cytomegalovirus (CMV) retinitis is the most frequent cause of vision loss in patients with AIDS, occurring in ~30%.[1] It may also occur in patients with other causes of immunosuppression.[2] Although antiviral therapy is beneficial, point mutations in viral DNA polymerase genes may result in drug resistance.[3] A case of CMV retinitis successfully treated with ganciclovir (GCV) implant in a patient with UL97 GCV resistance mutation present in the peripheral blood (PB) but absent from ocular specimens is described.

Case report

A 52-year-old African female with AIDS and Hodgkin's lymphoma, after successful chemotherapy, presented with recurrent CMV retinitis OS while on valganciclovir 900 mg twice daily and highly active anti-retroviral therapy with efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg (Atripla, Gilead Sciences Inc., Foster City, CA, USA and Bristol-Myers Squibb, New York City, NY, USA). CD4 count was 135, plasma HIV-RNA < 50 copies/ml, and serologic CMV PCR was 10 600 genome equivalents/ml.

Vision was 20/125 OD and 20/80 OS. A large area of active granular retinitis and inferonasal branch retinal artery occlusion was present in close proximity to the optic nerve head OS, and multiple areas of retinitis and a macular hole OD were noted (Figures 1a and b). PCR of aqueous fluid OS revealed 123 150 CMV copies/ml.

The patient was treated with sequential intravitreal injections of GCV 2 mg/0.1 ml and Foscarnet 1.2 mg/0.1 ml, and aqueous specimens were obtained. The CMV *UL97* and *UL54* genes were sequenced for amino-acid mutations conferring drug resistance from viral DNA from the aqueous and PB. An established resistance mutation, methionine to valine at codon 460 (M460V), in the *UL97* phosphotransferase gene was detected in PB. However, no resistance mutations were detected in the ocular specimens (Figure 2).

Following sustained-release GCV implant (Vitrasert, Bausch and Lomb, Rochester, NY, USA) OS and intravitreal GCV and Foscarnet OD, the patient had an excellent clinical outcome, without recurrence for over 1 year (Figures 1c–e).

Comment

GCV inhibits viral polymerase through intracellular phosphorylation, catalyzed by the CMV *UL97* gene-encoded phosphotranspherase[4] and point mutations in codons 460, 594, and 595 of the *UL97* gene are frequently associated with clinical resistance.[5,6] Drug-resistant CMV isolates can be found in the blood or urine in 15–27.5% of CMV retinitis cases.[7]

However, beacause of varying evolutionary pressures, patients with AIDS may be infected with multiple CMV strains that vary in genotypic resistance patterns at differing body sites.[8] As a result, aqueous analysis is important when treating patients with CMV retinitis, as

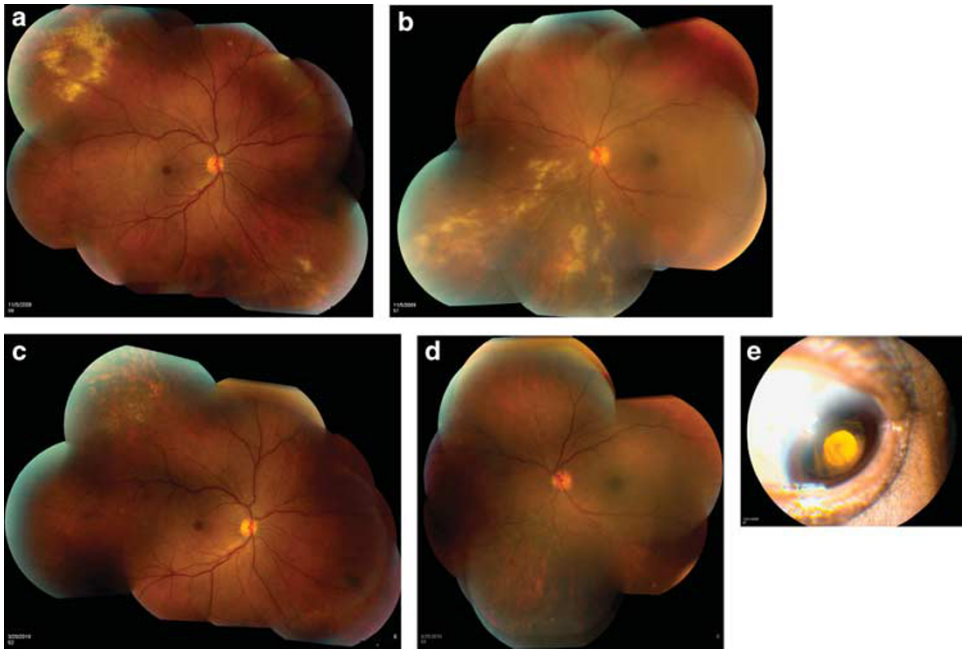

Figure 1 CMV retinitis treated with GCV implant. Fundus photograph of the right (a) and left (b) eye at presentation, with large areas of CMV retinitis and necrosis in the peripheral and mid-peripheral retina. In the left eye, the CMV retinitis is in close proximity to the optic nerve and an inferonasal branch retinal artery occlusion was observed. The right eye also has a long-standing full thickness macular hole. At 1 year following injection of intravitreal Foscarnet and GCV in both eyes and insertion of the GCV implant in the left eye, both eyes remain free of CMV retinitis (c, d). Pigmentary changes are noted at the site of prior retinitis. The GCV implant remains sutured in place at pars plana (e).

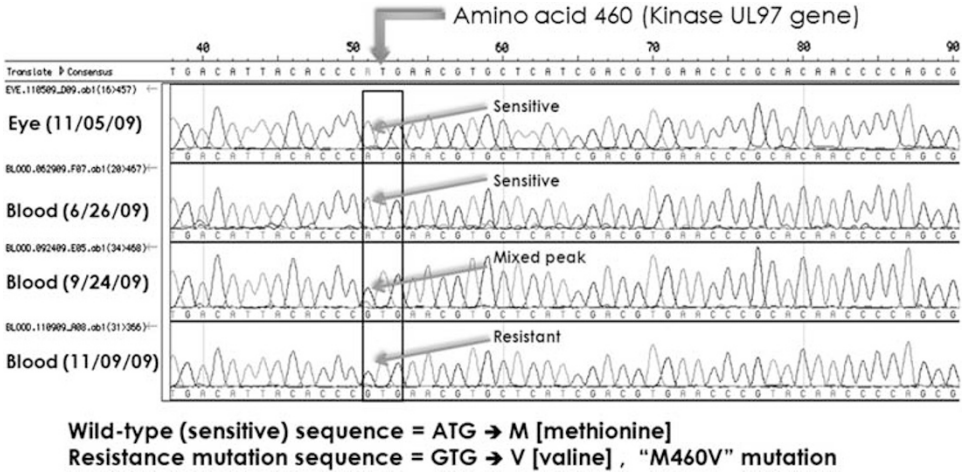

Figure 2 GCV resistance sequencing. Detection of methionine to valine mutation at codon 460 (M460V), in the *UL97* phosphotransferase gene in the PB (fourth panel) but not the ocular specimen (first panel) is shown. Note the change in peak from sensitive to resistant with time (second through fourth panels).

blood resistance does not imply ocular resistance to GCV. As seen in this case, successful local treatment of CMV retinitis was achieved with GCV despite blood GCV resistance. The greater sustained intraocular drug levels that are achieved with the GCV implant likely contributed to its clinical effectiveness.

Conflict of interest

The authors declare no conflict of interest.

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