epithelial, vascular, and hemopoietic tumors. In dogs administered up to 6 mg/kg daily for 1 year, toxicities included low leukocyte counts (at a dose of 6 mg/kg daily), and at doses of 0.6–6 mg/kg daily a reduced cellularity of the bone marrow, testicular atrophy, and decreased sperm counts were noted, all of which were completely or partially reversible after cessation of the drug (Roche, data on file). In men, VGCV may cause temporary or permanent inhibition of spermatogenesis, with animal data suggesting fertility suppression in females (Genentech, 2015).

In a randomized study of 160 AIDS patients with newly diagnosed CMV retinitis, patients received 21 days of VGCV or intravenous GCV and then received 7 days of the corresponding maintenance therapy before patients were assessed for CMV progression by retinal photographs. The frequency of adverse reactions was clinically similar in the VGCV and intravenous GCV groups (Genentech, 2015), unsurprising because oral VGCV is converted to systemic GCV. The frequency of neutropenia was 11% in the VGCV-treated group and 13% in those given intravenous GCV. With 79 patients per arm, a statistical difference was not reported. The only difference between the two arms was the frequency of catheter-related infections (3% in the VGCV recipients compared with 11% in those given intravenous GCV). A pooled sample from two clinical studies reported 27% neutropenia, 26% anemia, and 6% thrombocytopenia out of 370 patients (Genentech, 2015).

6h. Adverse reactions and toxicity of ocular administration

Intravitreal GCV was administered to rabbits one to three times weekly at a dose of up to 400 μg per injection without evidence of GCV-induced toxicity (Roche, data on file). Although toxicity associated with intravitreal injections of GCV in humans is relatively uncommon (Henry *et al.*, 1987), a number of complications have been reported, including retinal detachment (Ussery *et al.*, 1988; Cochereau-Massin *et al.*, 1991), retinal artery occlusion (Teoh *et al.*, 2012), and intravitreal hemorrhage (Cochereau-Massin *et al.*, 1991); however, it was unclear whether these adverse reactions were due to the GCV or the intravitreal injection, which is known to be associated with these complications. In a single case report of accidental intravitreal administration of 40 mg/0.1 ml of GCV, immediate surgery was unable to prevent permanent retinal damage and blindness (Saran and Maguire, 1994).

6i. Toxicity in pediatric patients

The need for GCV drug monitoring in children is highlighted by a case report of a 13-year-old boy with acute lymphoblastic leukemia (Peyriere *et al.*, 2006). The patient was being treated for CMV retinitis with 450 mg VGCV every 2 days. When creatinine clearance decreased to 20 ml/minute, the patient developed hallucinations and mental confusion, thought to be related to VGCV. A trough level of GCV obtained 2 days after the last dose was 2.6 μg/ml. After the acute neurotoxicity resolved, VGCV was reinitiated at 225 mg twice weekly with no recurrence of symptoms.

7. CLINICAL USES OF THE DRUG

GCV and VGCV are indicated for prevention or preemptive therapy of CMV disease in high-risk transplant recipients and in the treatment of CMV end-organ disease in patients with late-stage HIV infection. This activity was first demonstrated in the late 1980s (Collaborative DHPG Treatment Study Group, 1986). GCV and VGCV have also been used for treating CMV end-organ disease in other immunocompromised patients.

7a. Cytomegalovirus infection in patients with HIV infection

Before the advent in the late 1990s of effective combination antiretroviral drug regimens for treating HIV, CMV end organ disease was one of the most common opportunistic infections affecting patients with advanced HIV disease. In one trial of oral GCV prophylaxis that enrolled patients with advanced HIV disease in whom CMV disease was excluded at entry, 26% of placebo arm subjects developed CMV disease (92% of whom had retinitis) by 12 months of followup (Spector *et al.*, 1996).

CMV RETINITIS

Randomized trials have shown that both intravenous GCV and oral VGCV are effective for treating CMV retinitis in patients with end-stage HIV infection (Anonymous, 1992; Anonymous, 1994; Martin *et al.*, 2002). Both GCV and VGCV have been used to treat other CMV end-organ diseases in patients with end-stage HIV infection (e.g. gastrointestinal and neurologic); however, there are few efficacy data available.

For treatment of CMV disease in patients with HIV infection, most experts use an initial induction regimen of twice-daily dosing (5 mg/kg intravenous GCV or 900 mg VGCV orally) for 2–3 weeks to treat new CMV retinitis and for 3–6 weeks to treat other CMV end-organ diseases. However, after stabilization, life-long once-daily maintenance therapy must be given unless the patient's immune system can be reconstituted by combination antiretroviral therapy. The current expert consensus is that such maintenance therapy can be discontinued in patients whose CMV disease symptoms have resolved or stabilized and whose absolute CD4+ T-cell count has been sustained at > 100 cell/μl for at least 6 months. While there is less experience with intravitreal administration, this appears to be an effective alternative for maintenance administration of the drug in areas where VGCV is unavailable. For other forms of CMV disease in this patient population, either GCV and VGCV appears to have efficacy. Maintenance therapy may not be required for localized gastrointestinal disease.

Although GCV and foscarnet are equally efficacious in treating CMV retinitis (Moyle *et al.*, 1992; Anonymous, 1992), in one study patients treated with foscarnet were reported to survive longer than GCV recipients (12.6 vs. 8.5 months,