HUMAN HERPESVIRUS TYPE 8

HHV-8, also known as Kaposi's sarcoma-associated virus, has been associated with Kaposi's sarcoma and Castleman disease. To assess the effectiveness of antiviral therapy, a real-time polymerase chain reaction (PCR) assay of HHV-8 plasma viral load (the amount of HHV-8 DNA in plasma) has been developed (Sergerie and Boivin, 2003; Friedrichs *et al.*, 2004). This assay has shown that GCV is only moderately effective against HHV-8. *In vitro* drug susceptibility assays further highlight the modest activity of GCV against HHV-8, with reported ED_{50} values of 2.7–4 μM (Kedes and Ganem, 1997) and 5.1 μM (Medveczky *et al.*, 1997). What remains to be determined is why the HHV-8 DNA load reduction by active antiviral drugs like GCV does not always correlate with clinical outcome (Boivin *et al.*, 1999). In a brief report assessing the use of GCV to treat multicentric Castleman disease in three HIV-infected patients, two patients had a reduction in the frequency of flares and in detectable HHV-8 DNA while the third patient recovered from an acute episode (Casper *et al.*, 2004).

OTHER VIRUSES

Duck hepatitis B virus replication in primary hepatocytes was inhibited by GCV during continuous short-term treatment of the cultures, but GCV was less efficient in inhibiting replication during longer-term exposure (Shaw *et al.*, 1994). GCV treatment of ducks congenitally infected with duck hepatitis B qualitatively decreased serum virus DNA levels, although circulating duck hepatitis B virus surface antigen levels did not decline (Luscombe *et al.*, 1994). Markers of hepatitis B virus infection, including hepatitis B virus DNA and viral DNA polymerase, have been reported to fall to undetectable levels in patients during therapy with GCV (Locarnini *et al.*, 1989).

GCV has no activity against HIV-1 (Causey, 1991; Cox *et al.*, 1993). There has been one report that the human papovavirus Creutzfeldt-Jakob virus, the causative agent of progressive multifocal leukoencephalopathy, responded to GCV *in vitro* when human fibroblasts were co-infected with CMV (Heilbronn *et al.*, 1993). Aujeszky disease virus (pseudorabies virus) is sensitive to GCV *in vitro*, with a mean EC_{50} in mouse embryo fibroblasts of 6 μM (Field, 1985). GCV is superior to aciclovir against pseudorabies virus *in vivo* (Rollinson and White, 1983); a dose of 60 mg/kg/day protected mice from encephalitis caused by this virus (Rollinson, 1987). Herpesvirus simiae (B virus) is relatively resistant to GCV *in vitro*, with an EC_{50} in the range of 14.5–23.5 μM in Vero cells (Focher *et al.*, 2007). Available evidence suggests that GCV has no activity against human papillomavirus, or any RNA virus, including influenza (Crumpacker, 1996).

2b. Emerging resistance and cross-resistance

Repeated cell culture passage of CMV in increasing concentrations of GCV or the chronic administration of GCV to immunocompromised patients may lead to the emergence of GCV-resistant strains of CMV. *In vitro* passage of CMV in GCV for up to 5 weeks did not alter the susceptibility of the isolate (Cole and Balfour, 1987), but longer passage through increasing concentrations of GCV up to 100 μM elicited resistant mutants (Biron *et al.*, 1986). GCV-resistant strains of CMV are generally defined as strains having an EC_{50} of > 6 μM (Crumpacker *et al.*, 1996). GCV-resistant strains of CMV are cross-resistant to aciclovir, even at the highest doses.

Resistance has been related to impaired monophosphorylation of GCV in some reports (Lurain *et al.*, 1992; Baldanti *et al.*, 1995). GCV resistance can arise from mutations in either the UL97 gene, which codes for CMV kinase (functionally homologous to the thymidine kinase [TK] gene of HSV), or the UL54 gene, which codes for DNA polymerase gene (herpes simplex and CMV) (Crumpacker *et al.*, 1984; St Clair *et al.*, 1984; Sullivan *et al.*, 1992a). Mutations in the UL97 gene are more commonly associated with the development of resistance in clinical isolates than mutations in the DNA polymerase gene. The UL97 mutations reduce the intracellular phosphorylation of GCV, resulting in low-level GCV resistance (Limaye, 2002; Chou, 2008). Mutations at codons 460, 594, and 595 have been described in drug-resistant isolates (Lurain *et al.*, 1994; Baldanti *et al.*, 1995; Chou *et al.*, 1995; Wolf *et al.*, 1995); they have not been found in susceptible strains. Several reported mutations in the DNA polymerase gene of CMV (G987A and L501I) also confer GCV resistance. Although cross-resistance to cidofovir (Lurain *et al.*, 1992) and foscarnet (Tatarowicz *et al.*, 1992) has been described for CMV, other investigators have found that GCV-resistant strains remain susceptible to these drugs as well as to vidarabine, cidofovir, fialuridine, and the fluoroarabinose cytidine analog 2′-fluoro-5-iodo-aracytosine (Biron *et al.*, 1986; Biron, 1991; Drew *et al.*, 1991; Stanat *et al.*, 1991). A complete summary of specific mutations involved in CMV resistance to GCV is provided in Table 215.2.

CMV strains that are clinically resistant to GCV and whose resistance has been confirmed by *in vitro* testing or genotyping have been described in transplant and AIDS patients (Stanat *et al.*, 1991; Avery, 2008; Razis *et al.*, 1994). Clinical CMV strains resistant to GCV almost invariably have mutations in the UL97 gene (mutations that render them unable to monophosphorylate GCV) and less frequently in the UL54 DNA polymerase gene (making the enzyme nonsusceptible to inhibition by GCV triphosphate; the latter are often also associated with UL97 mutations (Drew *et al.*, 2001). A study noted that GCV resistance decreased from 28% before 1996 to less than 9% after 1996 in a population of HIV-infected patients (Martin *et al.*, 2007). The authors attributed this decrease to increased usage of VGCV (with its much better oral bioavailability than GCV) and possibly to better CMV control due to patients being on highly active antiretroviral therapy.

Ganciclovir resistance is now clinically more prevalent in transplant patients than in those with advanced HIV disease. Among 301 patients who received a solid organ transplant and had CMV prophylaxis with VGCV, the incidence of UL97 mutations was 1.9% after 100 days of prophylaxis (Boivin *et al.*, 2004). In another observational study, 6.2% of 65 solid organ transplant recipients who developed delayed-onset pri-