therapy of 14 days. Clinical response, as measured by resolution of fever, usually occurs within 2–9 days (mean 5.3 days) (Paya *et al.*, 1988). Relapses can often be successfully retreated with GCV.

Liver transplantation

GCV treatment has a high success rate in liver transplant patients with CMV disease (Stein *et al.*, 1988; Savage *et al.*, 1989; Stratta *et al.*, 1989; Lumbreras *et al.*, 1992). In one retrospective analysis, 74% of patients who developed CMV disease responded to GCV therapy, with ~ 20% developing recurrent disease within 3 months. The 18-month survival after GCV therapy was 76%, similar to that of patients who did not develop disease due to CMV infection (Stratta *et al.*, 1991b).

Heart and/or lung transplantation

GCV treatment is associated with an 80–90% survival in heart and heart–lung transplant recipients with serious CMV disease, including pneumonitis, gastrointestinal disease, retinitis, and disseminated infection (Keay *et al.*, 1988; Watson *et al.*, 1988; Cerrina *et al.*, 1991; Cooper *et al.*, 1991; Smythe *et al.*, 1991; Kirklin *et al.*, 1994). The onset of CMV disease ranges from 3 weeks to 18 months after heart transplantation (Cooper *et al.*, 1991). While treatment often results in prompt resolution of symptoms, in one study the disease recurred in up to 37% of patients and required repeated GCV therapy (Arabia *et al.*, 1993), although others report a much lower incidence of relapse (Cooper *et al.*, 1991). Acute rejection is reportedly more common in patients who develop CMV disease than those who do not, despite GCV therapy (Cooper *et al.*, 1991; Steinhoff *et al.*, 1991).

7d. Cytomegalovirus infections in normal adults

Although exceedingly rare, CMV encephalitis, esophagitis and pneumonitis has been reported in young adults with no apparent immune compromise. Cases of apparently immunocompetent people have been reported to respond favorably to GCV therapy (Pantoni *et al.*, 1991; Manian and Smith, 1993; Altman *et al.*, 1995; Lopez-Contreras *et al.*, 1995). However, given GCV's potential for severe, possibly irreversible, gonadal toxicity (see section 6c, Gonadal toxicity), clinicians should be certain that the condition putatively caused by CMV is not likely to be self-limited before administering the drug.

7e. Congenital cytomegalovirus infection

CMV is now the most common serious, congenital infection that occurs outside of resource-limited settings. In the USA, an estimated 8000 infants are born yearly with congenital CMV disease (Fowler *et al.,* 1992). Cognitive impairment and hearing loss are the most important sequelae. CMV-seronegative mothers are at highest risk for having a child with congenital CMV disease. To date, no vaccine has been approved by a regulatory agency for CMV prevention in seronegative young women.

Intravenous GCV is not licensed for congenital CMV, and early case reports had mixed results. Randomized trials have suggested efficacy when GCV is used to treat symptomatic neonates. Kimberlin *et al.*, (2003) reported infants treated with 6 weeks of GCV 6 mg/kg i.v. every 12 hours had less deterioration in hearing and fewer neurological abnormalities at 6 and 12 month followup when compared to infants receiving no treatment. Similarly, in a study by Oliver *et al.*, (2009), neonates with symptomatic congenital CMV were randomized to receive 6 weeks of GCV ($n = 48$) or no treatment ($n = 52$). When evaluated at 6 and 12 months, the GCV group showed fewer neurologic developmental delays on standardized evaluations compared to the untreated infants.

As with intravenous GCV, oral VGCV, has not gained FDA approval for treatment of congenital CMV; however, the pharmacokinetics of a commercially available VGCV solution is similar to that of intravenous GCV while achieving comparable clinical outcomes (Kimberlin *et al.*, 2008). A retrospective study of 23 infants with congenital CMV infection suggested that a treatment regimen of 6 weeks of intravenous ganciclovir followed by oral VGCV up to age 12 months was safe and reasonably effective, and better than historical controls (Amir *et al.*, 2010). A recent randomized clinical trial evaluated VGCV efficacy in symptomatic neonates. The investigators enrolled 96 neonates with gestational age ≥ 32 weeks and postnatal age ≤ 30 days. The infants were randomized to receive oral VGCV 16 mg/kg twice daily for 6 weeks ($n = 47$) or 6 months ($n = 49$). Those receiving 6 months of treatment were more likely to have improved or have normal hearing at 12 months compared with those treated for 6 weeks (73% vs, 57%, respectively; $p = 0.01$) and 24 months (77% vs. 64%, respectively; $p = 0.04$). They also had modestly improved scores on neurodevelopmental screening tests (Kimberlin *et al.,* 2015).

7f. Other viral infections

Data on GCV therapy of other viral infections have generally been documented only in case reports or small series, with no randomized placebo controlled trials. Herpesvirus simiae infection resulting in subtle features of brainstem encephalitis was reported to respond to GCV therapy in one case (Davenport *et al.*, 1994). GCV administered in combination with recombinant interleukin 2 to a young girl with chronic active EBV infection resulted in clearance of the viral genome from her peripheral blood mononuclear cells and symptomatic improvement (Ishida *et al.*, 1993). GCV was used successfully to treat a bone marrow transplant patient with meningoencephalitis due to EBV (Dellemijn *et al.*, 1995). A total of 12 symptomatic patients with elevated antibody titers to both HHV-6 and EBV were treated with a 6-month course of VGCV; 75% experienced near-resolution of their symptoms (Kogelnik *et al.*, 2006). Combined therapy with GCV and foscarnet has been reported to successfully control