In contrast, a subsequent randomized controlled trial of ganciclovir alone versus ganciclovir plus foscarnet (each at half dose) for preemptive therapy of CMV infection (based on CMV viremia) in 48 transplant recipients showed clearly that combination therapy (at least at this dose) was unsuitable (Mattes *et al.*, 2004). It was reported that 71% of patients in the ganciclovir arm cleared their CMV viremia compared with only 50% in the combination arm ($p = 0.12$), and toxicity was greater in the combination therapy arm. This study supports Drew's (2006) contention that the evidence for better outcomes after combined therapy compared with monotherapy for CMV infections is weak.

7c. Treatment of CMV infections in patients with immunosuppression unrelated to HIV infection

CMV RETINITIS

Although not approved by regulatory agencies for the indication, some clinical evidence supports the efficacy of foscarnet for treatment of CMV retinitis in patients with immunosuppression of other causes.

Ohta and colleagues (2001) studied three children who had received hematopoietic stem cell transplants from HLA-mismatched donors and who developed CMV retinitis. Because these patients had developed progressive retinitis while on ganciclovir therapy, they were presumed to be ganciclovir-resistant and were given foscarnet, 60 mg/kg every 8 hours. Retinitis resolved quickly in all three cases. Intravitreal foscarnet combined with systemic ganciclovir was used to treat CMV retinitis in a premature infant (Tawse and Baumal, 2014).Wong and co-workers (2010) studied 74 patients who had 81 eyes with acute retinal necrosis (ARN). The mean age patients with HSV ARN was 34 years but it was 51 for those with VZV ARN. In patients with VZV ARN intravitreal foscarnet reduced the rate of retinal detachment by 40% ($p = 0.08$) compared with those given nothing (Wong *et al.,* 2010). A middle-aged man with acute retinal necrosis caused by VZV was also treated with intravitreal foscarnet. He had failed initial intravenous aciclovir therapy and subsequent intravenous foscarnet had to be discontinued after 1 day due to renal failure. Intravitreal foscarnet was given weekly with marked improvement in his condition (Lee *et al.,* 2011). Another patient with acute retinal necrosis in the setting of HSV encephalitis failed initial intravenous aciclovir therapy but the intravitreal foscarnet resulted in "immediate clinical improvement" (Patel *et al.,* 2010).

OTHER CMV INFECTIONS

Foscarnet has been used to treat nonocular CMV infections in HIV-negative patients with mixed success. A recent review pointed out that although virtually all stem-cell transplant patients with CMV infections received initial ganciclovir for treatment, about a third of them had to be switched to foscarnet because of neutropenia or development of CMV resistance (Bacigalupo *et al.,* 2012). Comparative studies have shown that foscarnet is equally as effective as ganciclovir, albeit often more toxic.

Hubacek *et al.* (2009) reported a young patient immunosuppressed because of an unrelated hematopoietic stem cell transplantation. Initial preemptive monotherapy (begun on the basis of levels of CMV DNA in plasma of 1,000 to 10,000 copies/ml) with ganciclovir, valganciclovir, cidofovir, and foscarnet (90 mg/kg/day) was unable to control the CMV viral load, and after 6 months the CMV viral load increased, and the patient began complaining of headache and poor vision. A lumbar puncture was performed and analysis of the CSF showed CMV DNA to be 2,600,000 copies/ml, and ocular exam showed CMV retinitis. Initial treatment with cidofovir and ganciclovir was unsuccessful, and the clinicians found that the patient's CMV strain had become resistant to ganciclovir on the basis of phosphotransferase (*UL97*) mutations. Consequently, treatment was changed to a combination of cidofovir (5 mg/kg/week) and foscarnet (120 mg/kg/day) with CMV hyperimmunoglobulin, which successfully cured the patient (Hubacek *et al.,* 2009).

A dose-ranging study of foscarnet for the treatment of CMV infections in bone marrow and renal graft recipients found there was clinical improvement in 70% of patients (Ringden *et al.*, 1986). A study designed to evaluate the efficacy of foscarnet for the treatment of CMV infection in bone marrow transplant recipients demonstrated a clinical improvement in approximately half of the patients. However, all patients with interstitial pneumonia died despite foscarnet therapy (Aschan *et al.*, 1992). Bone marrow transplant recipients with ganciclovir-resistant CMV infections were reported to respond well to foscarnet therapy (Razis *et al.*, 1994). On the other hand, a more recent study showed long-term ganciclovir may select both *UL97* and *UL54* mutations, thereby generating foscarnet-resistant CMV strains causing pneumonitis that responds poorly to foscarnet (Gilbert *et al.,* 2011; Minces *et al.,* 2014). Likewise, a study by Isada *et al.* (2002) painted a fairly gloomy picture of the efficacy of foscarnet for treatment of ganciclovir-resistant CMV infections in patients who had received solid organ transplants (chiefly lung and kidney). Only 1 of 10 patients treated with foscarnet survived.

Reddy and colleagues (2007) reported experience in treating CMV infections in lung transplant recipients. Of 210 lung transplant recipients studied over a 4-year period, 113 (54%) developed CMV infections, with 6 of those (5%) being caused by ganciclovir-resistant CMV strains. All patients had *UL97* (phosphotransferase gene) mutations, and 3 also had *UL54* (polymerase gene) mutations (the latter may have been foscarnet resistant; the former would not have been). All patients were treated with a combination of ganciclovir and foscarnet, or foscarnet alone for ganciclovir-resistant infections, and the CMV viral load was reduced in all patients. In 15 of 25 transplant patients with ganciclovir-resistant CMV infection, replacing ganciclovir with foscarnet therapy resolved the infection in 87% (Reusser *et al.*, 1996).

Yaari and co-workers (2010) described two cases of severe CMV-related thrombocytopenia in otherwise-healthy women who had acute CMV mononucleosis. Foscarnet therapy