equally effective in preventing CMV disease after renal transplantation (Reischig *et al*., 2008). Preemptive therapy involves initiation of therapy based on laboratory evidence of CMV replication (increases in CMV DNA or antigens in blood cells or plasma) before development of symptoms. Finally, in an analysis of 23 renal transplant patients who developed CMV antigens or DNA in blood during or at the end of oral valaciclovir prophylaxis, ganciclovir resistance (by UL97 genotyping) was detected in only 1 out of 23 (Alain *et al*., 2004), suggesting that valaciclovir prophylaxis did not foster development of ganciclovir-resistant CMV strains.

The most recent guidelines for prevention, preemptive treatment, and treatment of CMV infection in solid organ transplant by the American Society of Transplantation and the American Society of Transplant Surgeons recommend oral ganciclovir and valganciclovir as preferred agents for prophylaxis, but valaciclovir is listed as an alternative for prophylaxis (but not treatment) of CMV in kidney transplant recipients only (Razonable *et al*., 2013). Oral aciclovir has also been used in a number of studies of patients undergoing solid organ transplantation to prevent CMV infection and disease (Pay *et al*., 1993; Prentice *et al*., 1994). The data from these studies suggest that, although in some cases aciclovir can prevent infection or delay the development of disease, it is inferior in efficacy to ganciclovir (see Chapter 215, Ganciclovir and valganciclovir). However, there are two drugs currently under investigation for prevention of CMV infections, both unlikely to cause the neutropenia that is so common with ganciclovir or valganciclovir, and it is likely that at least one will become available for clinical practice (see Chapter 220, Letermovir and Chapter 223, Maribavir).

The current guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients recommend as tertiary-line agents aciclovir or valaciclovir as prophylactic therapy in allogeneic hematopoietic stem cell transplant recipients (engraftment to day 100 post-transplant, i.e., phase II) (Tomblyn *et al*., 2009). Aciclovir 500 mg/m^2 i.v. three times per day or 800 mg orally four times daily and valaciclovir 2 g three to four times daily both in combination with screening for CMV are listed as a recommended agents, although not one of the first- or second-line agents. Published data showed that high-dose aciclovir (10 mg/kg i.v. every 8 hours or 500 mg/m^2) prevented CMV disease (Meyers *et al*., 1988; Prentice *et al*., 1994). Aciclovir or valaciclovir should not be used for preemptive therapy of CMV infections developing after autologous hematopoietic stem cell transplantation because of its lack of efficacy (Boeckh *et al*., 1995; Boeckh *et al*., 1998).

To further support such recommendations several other studies have investigated the role of aciclovir and valaciclovir in hematopoietic stem cell transplant recipients. In one study, hematopoietic stem cell transplant recipients were treated with intravenous aciclovir (500 mg/m^2 for 28 days) and then were given either valaciclovir 2 g four times daily or aciclovir 800 mg four times daily until week 18 post-transplantation. CMV infection or disease developed in 28% (102) of the valaciclovir-treated patients versus 40% (143) of the oral aciclovir-treated patients ($p < 0.001$) (Ljungman *et al*., 2002). In another trial, CMV-seropositive patients who received an allogenic bone marrow transplant were treated with intravenous aciclovir (500 mg/m^2 for 28 days) followed by either valaciclovir (2 g four times daily; $n = 83$) or intravenous ganciclovir (5 mg/kg every 12 hours for 7 days followed by ganciclovir 6 mg/kg daily for 5 days a week; $n = 85$) to day 100 (Winston *et al*., 2003). CMV infection occurred in 12% of the oral valaciclovir-treated patients versus 19% of those on intravenous ganciclovir ($p = 0.9$), and CMV disease occurred in 2 patients on valaciclovir and 1 patient receiving intravenous ganciclovir ($p = 0.6$).

In a study of 93 patients with symptomatic HIV infection, high-dose aciclovir failed to suppress the excretion of CMV in urine; of potential importance in this patient population, aciclovir therapy was not associated with the development of ganciclovir-resistant strains of CMV (Drew *et al*., 1995). In a small, open-label study of patients with HIV-related CMV retinitis who were treated with intravenous aciclovir (10 mg/kg of body weight every 8 hours) following a course of ganciclovir induction therapy, the median time to disease progression was only 32 days, suggesting that aciclovir is inactive and inferior to ganciclovir or foscarnet (Sha *et al*., 1991). The ACTG phase III clinical trial 204 evaluated the efficacy of valaciclovir (2.0 g four times daily) versus oral aciclovir (800 mg four times daily or 400 mg twice daily) for prevention of CMV end-organ disease in HIV- and CMV-co-infected individuals with < 100 CD4 cells/μl. This study was conducted before the availability of highly active combination antiretroviral therapy. A total of 1227 patients were enrolled, with a median CD4 count of 32 cells/μl. The study was prematurely stopped after the interim data analysis by an independent monitoring board revealed a trend toward earlier mortality in those randomized to receive valaciclovir compared to the aciclovir group ($p = 0.06$). However, compared with patients given aciclovir, the risk of confirmed CMV disease was reduced by 33% with valaciclovir, and the time to confirmed CMV disease was significantly longer in the valaciclovir group ($p = 0.03$). Patients receiving valaciclovir were more likely to discontinue study medication than aciclovir recipients, and there was a higher incidence of gastrointestinal side effects in those receiving valaciclovir (Feinberg *et al*., 1998). The explanation for the apparent increase in mortality is unknown.

7d. Epstein–Barr virus infection

In vitro activity of aciclovir against Epstein-Barr virus has been demonstrated; however, its clinical application is limited due to its lack of activity in latent cellular infection (Van der Horst *et al*., 1987; Bacon and Boyd, 1995; Table 213.1). Hanto *et al*. (1982) reported a patient with EBV-associated polyclonal B-cell lymphoproliferative disease after renal transplantation, whose disease underwent regression on two occasions after treatment with intravenous aciclovir, before finally succumbing to the illness. However, intravenous aciclovir was of no apparent benefit in other reported cases of life-threatening EBV infection (Sullivan *et al*., 1982; Sakamoto *et al*., 1992).