In the largest randomized trial of prophylactic versus preemptive therapy in the pre-VGCV era, 226 HCT recipients were randomized at engraftment to receive placebo or intravenous GCV until day 100 (Boeckh *et al.*, 1996). In patients who developed CMV pp65 antigenemia, open-label GCV was initiated. More patients in the preemptive group developed CMV disease before day 100; however, there was no significant difference in CMV disease by day 180 after transplantation or thereafter. CMV-related death, transplant survival, and neutropenia were not significantly different between the groups, and early invasive fungal infections occurred more frequently in the prophylactic group.

A subsequent randomized double-blind placebo-controlled study was performed to evaluate continuous prophylaxis with oral VGCV 900 mg daily or placebo in 184 allogeneic HCT recipients (Boeckh *et al.*, 2015). Those who became CMV viremic received open-label GCV, VGCV, or foscarnet (i.e. preemptive therapy). The primary end point was a composite outcome of CMV disease, invasive bacterial or fungal infections, or death by 270 days posttransplantation. While CMV viremia rates were lower in in the prophylaxis group compared to those given preemptive treatment (11% vs. 36%; $p < 0.001$), there was no difference in rates of CMV disease, other invasive infections, or death (20% vs. 21%; $p = 0.9$). Both groups had high rates of severe neutropenia (absolute neutrophil count < 500 cells/μl), but the rate was significantly higher in the VGCV than the placebo group (55% vs. 40%; $p = 0.04$). The investigators concluded that either VGCV prophylaxis or preemptive therapy is an effective strategy in preventing late CMV disease.

TREATMENT OF CMV END-ORGAN DISEASE IN HCT PATIENTS

Once CMV pneumonitis is established in HCT recipients, GCV given either alone or with glucocorticoids has resulted in either only minor or no clinical benefit (Shepp *et al.*, 1985; Reed *et al.*, 1986; Aulitzky *et al.*, 1988; Winston *et al.*, 1988; Reed *et al.*, 1990; Enright *et al.*, 1993), despite evidence of virologic efficacy. In one open-label trial, CMV viruria and viremia ceased after 4 days of GCV treatment in all 10 patients with cultures initially positive from these sites, yet only 1 patient survived the pneumonia (Shepp *et al.*, 1985). This is in contrast to CMV pneumonitis in patients after solid tissue transplants or other forms of immunosuppression, where there is clinical benefit from GCV therapy (Winston *et al.*, 1988). Other manifestations of CMV disease after HCT in both children and adults, including gastrointestinal, retinal, and disseminated disease without pneumonitis, are more responsive to GCV monotherapy than those with pulmonary disease (Rosecan *et al.*, 1986; Reed *et al.*, 1988b; Gudnason *et al.*, 1989; Reed *et al.*, 1990; Engelhard *et al.*, 1993).

Retinitis, a rare manifestation of CMV disease in HCT recipients, has been reported to improve with GCV therapy (Kaulfersch *et al.*, 1989). Some authors note an increasing incidence of retinitis in HCT recipients and that the disease tends to be progressive and associated with a high morbidity (Crippa *et al.*, 2001; Larsson *et al.*, 2002; Xhaard *et al.*, 2007; Eid *et al.*, 2008a).

Letermovir (Chapter 220, Letermovir) and maribavir (Chapter 223, Maribavir) are recently developed alternative anti-CMV agents that have each demonstrated efficacy in a randomized prophylaxis trial for HCT recipients without the hematologic toxicity associated with GCV and VGCV administration.

7c. Cytomegalovirus infection in solid organ transplant recipients

As with HCT, CMV infection or reactivation can cause life-threatening disease in recipients of transplanted solid organs. Active CMV infection is also a risk factor for organ rejection. Risk factors for serious disease are similar to those in HCT, and prevention of CMV infection in CMV-seronegative patients who receive solid organ transplants is advocated via use of seronegative donors and leuko-depleted blood products. As with HCT, there are prophylactic and preemptive treatment approaches to preventing CMV disease, and there is substantial variability in the clinical application of these two strategies among different transplant centers as well as for different organs transplanted. Detailed international consensus guidelines for each approach have been developed by a panel of clinical experts (Kotton *et al.*, 2013).

PREVENTION OF CMV INFECTION AND DISEASE IN RENAL TRANSPLANT RECIPIENTS

The incidence of CMV infection in CMV-seronegative recipients of renal transplants from seropositive donors is 70–90%, with 50–60% developing symptoms (Farrugia and Schwab, 1992). This subpopulation of renal transplant recipients constitutes the major group at risk of CMV disease; however, CMV seropositive recipients are also at risk for reactivation. Most therapeutic approaches are designed to prevent CMV disease in the few months after transplantation when immunosuppression is maximal.

Some method for CMV prevention is recommended for all kidney transplant recipients except those in which both the donor and recipient are seronegative. Generally, universal prophylaxis or preemptive therapy are considered effective options, though universal prophylaxis tends to be preferred in high-risk transplant recipients (e.g. CMV-seronegative recipients of a kidney from a CMV-seropositive donor).

VGCV has replaced GCV for prophylaxis based on results of a trial in which 110 patients were randomized to receive VGCV 900 mg daily for 2 weeks ($n = 23$) or 3 months ($n = 46$) or intravenous GCV 5 mg/kg ($n = 41$) for 2 weeks while receiving induction immunosuppression (Said *et al.*, 2007). Patients were followed for a minimum of 6 months post-transplantation. The incidence of the presence of CMV DNA in plasma with fever was higher in the VGCV 2-week arm (30.4%) than in either the 3-month arm (8.7%) or intravenous GCV arm (14.6%). At 3 and 6 months, renal function was worse in the VGCV 2-week arm than the other two arms.

A randomized double-blind trial of 318 CMV seronegative kidney transplant recipients with seropositive donors compared outcomes in patients receiving VGCV 900 mg once daily for 100 days versus 200 days (Humar *et al.*, 2010). The longer duration of therapy was associated with lower