vention of HCMV infections in HCMV-seropositive HSCT recipients (clinical trial NCT02137772). However, based on its novel mechanism, safety profile, and lack of cross-resistance with other anti-HCMV agents, letermovir may be an effective agent for HCMV prevention or therapy in a number of clinical settings. Specifically, letermovir avoids the treatment-limiting adverse reactions of ganciclovir and valganciclovir (neutropenia) (see Chapter 215, Ganciclovir and valganciclovir) or those of cidofovir or foscarnet (renal dysfunction) (see Chapter 216, Cidofovir and brincidofovir and Chapter 219, foscarnet). The myelosuppressive effects of ganciclovir principally prevent its use during the preengraftment period, a time of particular vulnerability for HSCT patients and when a safer HCMV chemoprophylactic drug would be very useful (Griffiths and Emery, 2014).

7a. Prevention of HCMV infection after stem cell transplantation

The safety and potential efficacy of letermovir in 131 adult CMV-seropositive allogeneic HSCT recipients was studied in a phase II, multicenter, multinational, randomized, placebo-controlled dose-ranging study (Chemaly *et al.*, 2014). Patients were randomized to receive letermovir (60, 120, or 240 mg orally daily) or a matching placebo for up to 12 weeks. Viral reactivation was common among placebo recipients and occurred in 29% of this group. After excluding patients with evidence of viral reactivation after randomization but before receipt of the study drug, reactivation was significantly reduced in the 120- and 240-mg dosage arms (8% and 0%, respectively) versus placebo (29%). The insignificant protective effect of the 60-mg dose (17% reactivation rate) and progressive reduction with increased daily dosing support a strong dose-dependent effect of letermovir on HCMV reactivation in this population. It is interesting that no patients in this study developed HCMV end-organ disease. These findings, in combination with the apparently wide safety margin of letermovir, have led to a higher dose (480 mg daily) being studied in the ongoing phase III trials.

7b. Preemptive treatment of HCMV infection after kidney transplant

A smaller phase II trial was initially planned as an evaluation of the potential effect of letermovir in HCT recipients with HCMV viremia; however, logistical issues led to a change of the target population to renal transplant recipients after the enrollment of only one HSCT recipient (Stoelben *et al.*, 2014). A total of 26 renal transplant recipients and 1 HSCT recipient were enrolled at 10 European centers after identification of HCMV viremia; they were randomized to receive letermovir at either 40 mg orally twice daily, 80 mg once daily, or therapy as per local standard of care. Overall, 50% of patients in the letermovir groups had viral clearance at day 15 of therapy in comparison to 28.6% of patients who received standard of care and, notably, no patients in either arm developed HCMV end-organ disease. Although these results are promising, no phase III studies are currently registered to further explore this use.

7c. Other HCMV infections

A single case report describes the effect of letermovir in a lung transplant recipient with multidrug resistant HCMV infection involving multiple organs (lung, colon, and retina) (Kaul *et al.*, 2011). The patient had clinically failed ganciclovir, foscarnet, cidofovir, leflunomide, and artesunate, and the virus had multiple resistance mutations identified in *UL54* and *UL97*. After 16 days of oral letermovir at 120 mg/day by mouth, plasma concentrations of letermovir were at the lower end of what was observed in the phase I trials; consequently, the dose was increased to 240 mg orally daily. A reduction in the viral load was demonstrated after 28 days of treatment with letermovir, with subsequent improvement of HCMV-associated end-organ damage.

Additional data on the use of letermovir in patients with HCMV disease or reactivation are unavailable. Given the safety profile of the drug, relatively low genetic barrier to resistance, and steep dose–response curves, 240 mg or 480 mg daily may be available, after successful phase III clinical trials, for the treatment of active HCMV infection.

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