with doses of intravenous CDV, ranging from 0.5 to 10 mg/kg. In these studies, antiviral activity could be shown in urine and semen at doses above 3 mg/kg while none of the patients evaluated cleared HCMV from blood.

Subsequently, two randomized controlled phase II/III clinical studies have been conducted to investigate the effect of the drug on median time to progression to HCMV retinitis in patients with AIDS (Lalezari *et al*., 1997b; Anonymous, 1997). In the trial by the Studies of Ocular Complications of AIDS Research Group in collaboration with the AIDS Clinical Trials Group (SOCA-ACTG), patients with untreated HCMV retinitis were randomized to immediate treatment with one of two different doses of CDV or to deferred treatment given if and when retinitis progressed. The CDV groups received CDV at either a high dose (5 mg/kg once weekly for 2 weeks followed by 5 mg/kg every 2 weeks) or a low dose (5 mg/kg once weekly for 2 weeks followed by 3 mg/kg every 2 weeks). To minimize nephrotoxicity, both doses of CDV were given with the recommended hydration and probenecid. Both CDV regimens delayed the progression of previously untreated HCMV retinitis. The median time to progression in the deferred group was 21 days; it was 64 days in the low-dose group, and the median time to progression was not reached in the high-dose group. After 3 weeks of CDV therapy, the frequency of HCMV viruria fell from about 65% to about 30% in both CDV treatment groups, while it was unchanged in the deferred group at 67%. Blood cultures were positive in roughly a third of patients, and viremia was not affected by CDV therapy (Anonymous, 1997).

In the study by Lalezari *et al*. (1997b), patients with the same characteristics as the SOCA-ACTG study subjects were randomized to receive either CDV (at the high dose used in the SOCA-ACTG study) or deferred treatment. The median time to progression in the deferred treatment group was similar to that in the SOCA-ACTG study, 22 days (95% confidence interval [CI]: 10–27) and for the treated group was 120 days (95% CI: 40–134). In this study, three of the eight centers participating performed HCMV cultures on their patients, and there was a decrease in the proportion of patients who were HCMV culture positive, but details as to whether the cultures were of blood, or urine, or both were not provided. Because the incidence of HCMV extraocular disease in this population was low, as it has been in other clinical trials of drugs to treat HCMV infections, no information about the utility of CDV for treatment of HCMV infections at other sites was obtained.

Intravenous CDV was then evaluated in 150 patients with AIDS and HCMV retinitis that had progressed or was persistently active despite treatment with ganciclovir, foscarnet, or both (Lalezari *et al.,* 1998). This study compared two maintenance doses (3 or 5 mg/kg every two weeks) after an initial induction of 5 mg/kg once weekly for 2 weeks. Concomitant probenecid and intravenous hydration were administered with each CDV dose. CDV delayed progression of HCMV retinitis for these patients. Median time to retinitis progression, as assessed by retinal photography, was not reached in the 5 mg/kg group, and was 49 days in the 3 mg/kg group. Based on the better results obtained with the 5 mg/kg maintenance therapy, this schedule was chosen as standard treatment for HCMV retinitis in AIDS patients. Maintenance therapy at 3 mg/kg every two weeks was recommended for patients with mildly impaired renal function or for those previously treated with nephrotoxic drugs (Safrin *et al*., 1997).

Another SOCA-ACTG study compared CDV given intravenously to ganciclovir intraocular implant plus oral ganciclovir. The two treatments were similarly effective in controlling HCMV retinitis in patients with AIDS also receiving highly active combination antiretroviral chemotherapy (Anonymous, 2001). Retinitis progression occurred at a rate of 0.67 per person-year in the ganciclovir group and 0.71 per person-year in the CDV group. Similarly, no differences in a loss of visual acuity were observed between the ganciclovir and CDV groups.

Combination therapy with intravenous CDV and oral ganciclovir was studied in eight AIDS patients with HCMV retinitis included in a phase I study (Jacobson *et al.*, 1999). Three patients developed limiting adverse ocular effects whereas only one patient had retinitis progression. No further study was designed to explore a more optimal schedule of administration.

Intraocular administration of CDV has been tested as a possible option, but due to the frequent occurrence of severe adverse effects, this approach was abandoned (Plosker and Noble, 1999).

7b. Human cytomegalovirus infections—transplant recipients

Ljungman *et al*. (2001) conducted an extensive retrospective study of 82 patients to collect information on the role of CDV in treatment of HCMV infections in allogeneic stem cell transplant recipients. The indications for therapy were HCMV disease (20 patients), primary preemptive therapy (24 patients), and secondary preemptive therapy (38 patients). Half of the patients treated for HCMV disease (pneumonia, gastrointestinal disease, hepatitis, and encephalitis) including 9 of 16 with HCMV pneumonia responded to CDV therapy. Further, 25 of 38 patients given secondary preemptive therapy (treatment based on early laboratory evidence of HCMV infection or reactivation) and 62% of the patients in whom CDV was used as primary preemptive therapy responded to therapy. About 25% of patients developed renal toxicity; for more than half of these patients, the condition persisted after cessation of the treatment. Ljungman *et al*. (2001) recommended additional studies, to clarify the potential role of CDV in the preemptive therapy of HCMV infections in this group of patients. They considered CDV as second-line treatment for those patients failing to answer classic anti-CMV treatment based on ganciclovir and/or foscarnet.

Other studies targeting similar groups of patients have been conducted, all with a relative small number of patients, but suggesting similar conclusions (Cesaro *et al*., 2005; Chakrabarti *et al*., 2001). In another prospective study of 56 hematopoietic stem cell transplant recipients of whom 14 were