SUMMARY

Cytomegalovirus (CMV) disease is a common infectious complication in patients after solid organ transplantation. The last decade witnessed major advances in CMV disease prevention. Use of universal prophylaxis or preemptive therapy resulted in a decrease in the incidence of CMV disease from 20-60% to 5-20%. However, the efficacy of preventive approaches in terms of indirect effects of CMV occurrence is problematic. Association with allograft rejection belongs to well documented and clinically extremely important indirect effects of CMV with a prolonged adverse impact on graft survival. Potential mechanisms include overexpression of major histocompatibility complex molecules, growth factors and cytokines, and upregulation of adhesion molecules. A number of questions remain to be answered in evaluating CMV as a risk factor for acute rejection. While CMV disease is associated with an increased incidence of acute rejection, data regarding the role of asymptomatic CMV viremia are controversial. In our research we evaluated the role of CMV in pathogenesis of allograft rejection in the era of modern immunosuppression and CMV prophylaxis as well as optimal preventive strategy to minimize impact of CMV. In the first trial, renal transplant (RTx) recipients were followed prospectively for 12 months to determine the impact of CMV disease and asymptomatic viremia on biopsy-proven acute rejection. By multivariate Cox proportional hazard model CMV disease was an independent risk factor for acute rejection, while asymptomatic CMV infection was not. Moreover, valacyclovir prophylaxis decreased the risk of rejection. In the next study RTx recipients at risk for CMV were randomized to 3-month prophylaxis with high-dose valacyclovir or preemptive therapy with valganciclovir for significant CMV virémie. The 12-month incidence of CMV viremia was higher in the preemptive group while the incidence of CMV disease was not different. The onset of CMV viremia was delayed in the valacyclovir group. Significantly higher rate of biopsy-proven acute rejection was observed in the preemptive group. The average CMV-associated costs per patient were $5525 and $2629 in preemptive therapy and valacyclovir, respectively. The aim of the last prospective study was to determine the impact of CMV viremia on subclinical rejection and interstitial fibrosis and tubular atrophy (IFTA) in protocol biopsy at 3 months after transplantation in patients managed by three-month prophylaxis (valacyclovir or ganciclovir) or by preemptive therapy. Multivariate logistic stepwise regression was used to estimate the effect of CMV viremia and other covariates on subclinical rejection and/or IFTA. CMV viremia was not a risk factor for subclinical rejection; however, viremia of ≥2000 copies/mL increased the risk of IFTA. In conclusion, our studies showed that (1) CMV disease, but not asymptomatic infection, is an independent risk factor for biopsy proven acute rejection during the first 12 months post-RTx. in patients managed by prophylaxis; (2) preemptive valganciclovir therapy and valacyclovir prophylaxis are equally effective in the prevention of CMV disease after RTx, however, higher risk of acute rejection in preemptive therapy is of a concern; (3) CMV viremia is not an independent risk factor for subclinical rejection while CMV viremia with viral load of ≥2000 copies/mL is associated with increased risk of IFTA in protocol biopsy at 3 months after RTx.