Cytomegalovirus Prophylaxis in Renal Transplant Patients

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Introduction

Renal transplantation is a well established mode of renal replacement therapy. It offers the best quality of life, much better rehabilitation and also much better survival figures among all the modes of renal replacement therapy. As at 31/3/2005, there are about 2500 renal transplant patients being followed up by the Hospital Authority and about 1200 patients in the cadaveric renal transplantation waiting list in Hong Kong1. However, despite continuous refinement in immunosuppressive protocol, graft preservation and surgical techniques, infection remains a significant cause of morbidity and mortality in post renal transplant patients. The evaluation of infection risk and attempt to minimise post transplant infection should begin at the pre-transplant level, with evaluation of both the donor and the recipient. The current article will mainly focus on the prophylactic issue on cytomegalovirus (CMV) infection in the post transplant period.

Cytomegalovirus in post transplant patients

In developed countries, about 70% of adults have asymptomatic latent CMV infection. It can be reactivated if individual becomes immunosuppressed. CMV is the most common viral infection after kidney transplantation. Clinical presentations can range from asymptomatic infection to CMV syndrome with fever, leucopenia and/or thrombocytopenia, to invasive CMV disease with hepatitis, pneumonitis, retinitis, colitis or enteritis, central nervous system involvement and direct involvement of the renal allograft. It can cause significant morbidity or even death. It has been shown that CMV disease is associated with increase in overall mortality and even asymptomatic CMV infection was associated with a relative risk of overall mortality of 2.92. CMV infection is also associated with immune modulation and dysregulation. It has been postulated that CMV infection can potentiate the development of other opportunistic infection, cause allograft dysfunction or rejection3 and can lead to the development of post transplant lymphoproliferative disease. CMV infection can be acquired from the donor by the allograft, by blood products transfused from a seropositive donor or by sexual contact, or CMV disease can develop from the reactivation of the latent recipient virus. Most CMV disease develops between one to four months post renal transplant when prophylaxis is not used. Patients at highest risk for CMV disease are seronegative CMV recipient receiving an allograft from a seropositive donor (D+/R-) and those patients with CMV infection receiving antilymphocyte preparation for induction or treatment of rejection. The uses of OKT3 and mycophenolate mofetil are associated with increased reactivation while calcineurin inhibitors (cyclosporine A, tacrolimus) are associated with increased replication.

Is prophylaxis effective and necessary?

The efficacy of CMV prophylaxis in preventing CMV disease in these high risk patients is well documented. In a systematic review of 19 randomised controlled trials of CMV prophylaxis in 1981 solid organ transplant recipients demonstrated that compared with placebo, prophylaxis with acyclovir, ganciclovir or valaciclovir significantly reduced the risks of CMV disease (relative risk 0.42, 95% CI 0.43-0.52), CMV infection (relative risk 0.61, CI 0.48-0.77) and all cause mortality (relative risk 0.63, CI 0.43-0.92). The reduction in mortality was primarily due to lower mortality from CMV disease4. Whether prophylaxis is necessary and the choice of the agent depends on the risk of development of CMV disease, which is in turn determined by the CMV serostatus of the donor and the recipients. The lowest risk being seronegative for both the donor and the recipients and prophylaxis is probably not necessary, while the highest risk being, as mentioned, CMV negative recipients receiving an allograft from a seropositive donor.

Approaches for CMV prophylaxis

There are two approaches for the prevention of CMV disease: universal prophylaxis and preemptive therapy. Universal prophylaxis involves giving anti-viral prophylaxis to all at risk patients for a defined period of time while preemptive therapy employ a strategy of regular monitoring of evidence of CMV disease by CMV-PCR or pp65 antigenaemia and start treatment once there is evidence of CMV replication to prevent symptomatic CMV disease. Universal prophylaxis may be used for all recipients but is particularly advisable to those at very high risk of development of disease, such as seronegative recipients receiving seropositive graft, or seropositive patients exposed to intense immunosuppression. It can also protect against other human herpes virus and result in fewer opportunistic infection. However, prolonged antiviral exposure may result in resistance, the cost will be high and it may just delay the occurrence of CMV disease. For preemptive therapy, fewer patients will be exposed to antiviral, this decrease resistance and also decrease the individual development of side effects of drugs. However, there will be a need of efficient testing facilities and the patient is required to adhere diligently to the screening protocol.

Prophylactic Agents for CMV infection

The current prophylactic agents of choice for CMV
infection are ganciclovir or valganciclovir.

**Ganciclovir**

Ganciclovir can be given by intravenous route or by per oral route. However, since oral ganciclovir has poor bioavailability, relatively high doses are needed (1000mg tds). In a study done by the Hibberd group, 113 seropositive renal transplant recipients were randomly assigned to no anti-CMV therapy or to ganciclovir 2.5mg/kg as a single daily dose during the period they received antilymphocyte treatment. Dosage adjustment was made for patient with more severe renal impairment. They found that the administration of ganciclovir was associated at 6 months with a significantly lower incidence of CMV infection (14 versus 33% in the control group) and of CMV isolation from buffy-coat specimens (17 versus 35 %) 5. In various trials directly comparing intravenous or oral ganciclovir with acyclovir for 3 months as CMV prophylaxis demonstrated that ganciclovir markedly reduced the incidence of CMV infection in both CMV antibody-positive and antibody negative recipients and the ganciclovir group also had a significantly lower incidence of CMV viraemia at 6 months, after discontinuation of prophylaxis for 3 months6,7,8. Some also employ a strategy of intravenous ganciclovir for 2-3 weeks, during the course of antilymphocyte treatment, then followed by oral ganciclovir for a total of 3-4 months9,10. The dosing for CMV prophylaxis will be intravenously 5mg/kg daily for 90-100 days, or per orally 1000mg tds for 90-100 days.

**Valganciclovir**

Valganciclovir is a valyl-ester prodrugs of oral ganciclovir. It has a bioavailability of nearly 70% (compared with 7% for oral ganciclovir). At dose 450 to 900mg, it produces serum ganciclovir levels that are similar to that measured with intravenous administration of ganciclovir at 2.5 to 5mg/kg. In the phase III PV 16000 international, double-dummy, double-blinded trial of oral valganciclovir versus oral ganciclovir for the prevention of CMV infection in 364 donor seropositive,recipient seronegative solid organ transplant recipients (including 120 renal transplant recipients), the patients were randomly assigned at a 2:1 ratio to receive oral valganciclovir 900mg per day or oral ganciclovir 1000mg tds with dose adjustment for renal impairment11. Treatment was initiated within 10 days of transplant and continues for 100 days. During prophylaxis, only 0.8 and 1.6% of patients in the valganciclovir and ganciclovir groups developed CMV disease respectively. At 6 months and at 12 months, both agents were similarly effective with similar incidence of CMV disease. Valganciclovir is contraindicated in dialysis patient or patient with creatinine clearance of less than 10ml/min. The dosing for CMV prophylaxis will be 900mg daily for 90-100 days with dosing adjustment in renal impaired patient.

**Other agents**

**CMV hyperimmune globulin**

CMV hyperimmune globulin is prepared from human serum that contains a high titre of anti-CMV antibodies. It was initially developed in the 1980s for the prophylaxis of CMV disease. The efficacy was proven by multicentre study that, when compared with placebo, it decreased the incidence of CMV disease, from 60 to 20% 12. The usual regimen is 150mg/kg within 72 hours of transplant operation, then 100mg/kg at 2, 4, 6, and 8 weeks, then 50mg/kg at 12 and 16 weeks.

**Ayclovir**

Ayclovir has been investigated as a prophylactic agent for CMV disease in post transplant patient. Dosage range from 600mg to 4000mg per day has been employed with adjustment according to renal function. In some study, it is noted to be effective even in high risk donor seropositive,recipient seronegative patients13, yet this is not confirmed in other study14,15. Nowadays, acyclovir is considered effective only in lower risk patient (donor negative,recipient negative or positive). For high risk cases, ganciclovir or valganciclovir are the drugs of choice.

**Valacyclovir**

Valacyclovir has also been investigated as a prophylactic agent for CMV disease. In some studies, it has been shown to be effective in significantly reducing the incidence of disease among both seronegative and seropositive recipients16.

**Conclusion**

CMV infection causes significant morbidity and even mortality in renal transplant recipients. Risk of CMV disease depends on the serostatus of the donor and recipient and also the immunosuppressive treatment received. Effective prophylactic agents are available and the choice, the duration and also the prophylactic strategy employed will depend on the risk of the development of CMV disease in individual patients and also the preference of individual centres.

**References**