

## **4. Treatment of Cytomegalovirus disease in renal transplant recipients**

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### **Guidelines**

No recommendations possible based on Level I or II evidence

### **Suggestions for clinical care**

**(Suggestions are based on Level III and IV evidence)**

- Ganciclovir is the treatment of choice for CMV disease. Features include:
  - IV administration
  - Dose modification for renal impairment
  - Duration of treatment is 2-3 weeks or until CMV-DNA is not detectable in leukocytes. (Level III evidence)
- Treatment failure may be due to inadequate treatment, superinfection or ganciclovir resistance. (Level III evidence)
- Foscarnet and cidofovir remain second-line agents. (Level III evidence)

### **Background**

Cytomegalovirus (CMV) disease is characterised by clinical symptoms and signs of disease coupled with microbiological evidence of CMV infection. Disease occurs in 8% of renal transplant recipients compared with liver or pancreas (29%) and heart-lung (39%) recipients. Patients at greatest risk of developing disease include D+/R– recipients and those who have been given methyl-prednisolone or anti-lymphocyte antibody. The diagnosis may be complicated by the fact that CMV infection is frequently associated with superinfection with other bacteria, fungi, protozoa and viruses.

Ganciclovir is the treatment of choice for CMV disease and should be administered intravenously with the dose modified according to creatinine clearance. Treatment should be continued for at least 2 weeks or until CMV-DNA is not detectable. While immunosuppressive therapy is frequently reduced in patients with CMV disease, this measure has not been subjected to a clinical trial.

Oral ganciclovir has been used successfully to treat mild to moderate CMV disease. The recent introduction of valganciclovir, with 10 times the bioavailability of oral ganciclovir and kinetics comparable to IV ganciclovir, may provide an alternative to IV

therapy. Valganciclovir has the potential to reduce hospital stay and the complications associated with prolonged IV access.

Ganciclovir resistance has been reported in up to 7% of solid organ transplants and may be treated with second-line agents such as foscarnet and cidofovir. Both of these agents are associated with significant nephrotoxicity and side effects. There is no evidence to support the use of acyclovir, valaciclovir and CMV-Ig in renal transplant recipients. Failure to respond to therapy may be due to inadequate treatment, ganciclovir resistance or superinfection.

## **Search strategy**

Databases searched: MeSH terms and text words for CMV were combined with MeSH terms and text words for solid organ transplantation, including kidney transplantation, then combined with MeSH terms and text words for interventions for CMV, and then combined with the Cochrane highly sensitive search strategy for randomised controlled trials. The search was carried out in Medline (1966 – June Week 1 2002). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.

Date of search/es: 28 June 2002.

## **What is the evidence?**

There are no randomised controlled trials (RCTs) on this topic.

### *Which patients are at greatest risk of CMV disease?*

While many patients will have evidence of CMV infection following transplantation, Sagedal et al (2000) identified donor positive- and recipient-negative CMV status and acute rejection episodes as significant risk factors associated with the development of CMV disease.

A total of 477 consecutive renal transplant recipients (397 first transplants and 80 retransplants) operated on between October 1994 and July 1997 were included in the study. The patients were followed prospectively for 3 months with serial measurements of CMV pp65 antigen being made to detect CMV infection. The incidence of CMV infections in first transplants was 68% in D+R– and D+/R+ serostatus groups, whereas the incidence of CMV disease was higher in D+R– (56%) than in D+/R+ patients (20%,  $p < 0.001$ ).

No difference in severity of CMV disease in D+R– and D+/R+ was seen except for an increased incidence of hepatitis in primary infections. Cox regression analysis

showed that rejection (RR 2.5,  $p < 0.01$ ) and serostatus group D+R– (RR 3.9,  $p < 0.001$ ) were significant risk factors for the development of CMV disease.

#### *Intravenous ganciclovir*

There are over 30 uncontrolled, non-randomised studies using ganciclovir to treat CMV disease. The study by Rondeau et al (1991) was one of the first reported and recommended ganciclovir dose reductions in patients with renal impairment. In this study, 32 renal transplant recipients with proven CMV disease were treated with ganciclovir for 14 days. The mean time to CMV disease was 49 days following transplantation. CMV disease was diagnosed based on the combination of clinical signs and histological/virological studies.

Twenty-nine patients, 10 of whom had moderate to severe disease were improved by treatment. Three deaths occurred, with 2 dying from combined severe pulmonary and hepatic CMV disease. Adverse effects of ganciclovir therapy included leukopenia ( $n = 7$ ), thrombocytopenia ( $n = 2$ ) and abdominal pain ( $n = 1$ ). CMV was no longer found in virological samples from 80% of patients. The clearance of ganciclovir was linearly correlated with creatinine clearance.

#### *Oral ganciclovir*

The inconvenience associated with the administration of IV ganciclovir, requiring hospitalisation and frequent intravenous cannulation, has led to a search for effective oral therapy. Jordan et al (2002) describe a small study using oral ganciclovir for the treatment of moderate CMV disease using quantitative PCR to monitor treatment.

Fifteen patients with donor/recipient CMV status of D+/R– (53%), D+/R+ (40%) and D–/R+ (7%) were studied. All patients were commenced on oral ganciclovir 1g tid with dose reduction in patients with impaired renal function. Treatment continued until the CMV-PCR copy number was negative and symptoms resolved. The mean number of CMV copies at the time of diagnosis was 580 (normal  $< 5$ ) and fell to 65 copies after 5-7 days of treatment. A total of 14/15 patients responded to treatment and 1 non-responder was attributed to non-compliance. While the time to disease onset following transplantation is not indicated in the report, it can be inferred from the prophylactic protocol for D+/R– patients (comprising 1 week IV ganciclovir followed by 4 months of oral ganciclovir therapy) that CMV disease occurred more than 4 months after transplantation.

#### *Oral valganciclovir*

The development of valganciclovir resulted in a 10-fold increase in oral bioavailability. Pescovitz et al (1999) compared valganciclovir at a dose of 900 mg, once daily, with IV ganciclovir in 28 healthy liver transplant recipients, using a 4-way randomised cross-over design. The AUC for IV ganciclovir was 47.61 mg/h/mL compared with 42.69 for valganciclovir. Thus, valganciclovir achieved 90% (90% CI: 83-97) of IV ganciclovir AUC in transplant recipients but it remains to be proven that valganciclovir absorption is maintained in sick patients with CMV disease.

#### *Disease recurrence*

One measure of treatment efficacy is the prevalence of recurrent CMV disease following standard IV ganciclovir therapy. Sawyer et al (1993) address this issue in both kidney and combined kidney/pancreas recipients.

A total of 619 transplant recipients (535 kidney [253 living related and 282 cadaveric donors] and 84 combined cadaveric kidney-pancreas transplants) were studied over a 3.5-year period. Of these, 114 (18.4%) developed tissue-invasive CMV disease and were treated with IV ganciclovir for 14 to 21 days. Twenty-eight (24.6%) developed recurrent disease after more than 30 days from first infection. Proportionally, more kidney-pancreas transplants than kidney transplant alone relapsed. All patients with recurrent disease were retreated with IV ganciclovir, achieving a cure rate at 30 days of 100%.

With the introduction of molecular markers of disease activity, Sia et al (2000) followed CMV-DNA load prospectively in patients with CMV infection and disease and demonstrated that DNA load is predictive of CMV relapse following transplantation. Twenty-four solid-organ transplant recipients (heart, liver, kidney) with CMV infection (42%) or disease (58%) were tested for CMV-DNA load before and after 14 days of IV ganciclovir therapy. Recurrent infection or disease occurred in 8/24 (33%) patients, with no significant difference between CMV infected and CMV disease groups. The median pre-treatment viral loads were higher in the relapsing group than in the cured group. Most importantly, the relapsing group had detectable CMV-DNA after treatment, whereas the CMV-DNA was undetectable in the non-relapsing patients.

#### *Superinfection*

Patients with CMV disease are at risk of superinfection with a variety of microorganisms. *Pneumocystis carinii* pneumonia (PCP) in the early post-transplant period contributes significantly to early transplant morbidity and mortality. The link between CMV disease, allograft rejection episodes and PCP is not clearly defined. Arend et al (1996) attempt to link these in a small study of 15 renal transplant recipients with proven PCP compared with 95 control patients. The number of rejection episodes correlated with increased risk of developing PCP. After 1, 2 or 3 rejection episodes, the relative risk of developing PCP increased to 1.7 (95% CI: 0.2-12.5), 4.8 (95% CI: 0.9-25.5), and 9.5 (95% CI: 1.6-56.4), respectively. Furthermore, CMV infection increased the relative risk of PCP five-fold (95% CI: 1.6-15.8) with the highest relative risk of 5.7 in the D+R- combination (95% CI: 1.4-22.3).

#### *Ganciclovir resistance*

Failure to respond to standard therapy, especially after prolonged exposure to ganciclovir, should raise the possibility of ganciclovir resistance, which can occur in up to 7% of patients (Limaye et al 2000).

#### *Second-line agents*

Only one study was found that had evaluated foscarnet in kidney transplant recipients. Ringden et al (1986) described the pharmacokinetics, safety and their preliminary clinical experiences using foscarnet in the treatment of cytomegalovirus infections in bone marrow and renal transplant recipients.

Fifty-seven episodes of severe CMV infection were treated with IV foscarnet in 13 bone marrow and 33 renal graft recipients. Multiple adverse effects were recorded including decreased haemoglobin, decreased renal function and increased serum calcium. Abnormal liver function tests, hallucinations and tremor were seen in one

uraemic patient with foscarnet levels > 400 mg/L. Improvements, such as eradication of CMV (8/14 assessable patients), resolution of fever (11/22), and improved laboratory values (13/23) were noted in 17/24 (70%) patients.

## **What do the other guidelines say?**

### **International Herpes Management Forum, 2000:**

In any transplant recipient, CMV disease should be treated for 2-4 weeks with intravenous ganciclovir. Acyclovir is ineffective in treating established CMV disease in transplant recipients (IHMF 2000).

### **British Transplantation Society Guidelines, 2002:**

Patients with CMV disease should receive intravenous ganciclovir for at least 14 days. Consideration should be given to reduction in immunosuppression (Newstead et al 2002).

### **Clinical Practice Guidelines of the American Society of Transplantation, 2000:**

No treatment recommendations. Aim to prevent disease with prophylaxis (Kasiske et al 2000).

### **European Best Practice Guidelines for Renal Transplantation (Part 1), 2000:**

All recipients with documented CMV disease (symptomatic CMV infection) must receive a curative treatment. Currently, the only validated treatment is IV ganciclovir at a daily dose of 5mg/kg twice daily, adjusted for renal function, for at least 14 days. Alternatively, they may receive IV ganciclovir for at least 5 days followed by oral ganciclovir at a daily dose of 1000 mg three times daily for a longer period (2-12 weeks) (Berthoux et al 2000).

## **Implementation and audit**

No recommendations.

## **Suggestions for future research**

1. Perform a study to assess the efficacy of IV ganciclovir/introduction of new agents. All new anti-CMV therapy should be tested in RCTs with one arm receiving IV ganciclovir.
2. Run studies of molecular markers of disease activity to determine the optimal duration of therapy.
3. Investigate post-treatment prevention to reduce recurrence. Give oral therapy to high-risk patients?
4. Establish the relationship between ganciclovir exposure and prophylaxis and the emergence of ganciclovir resistance.

## References

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## **Appendices**