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Cytomegalovirus in renal transplant recipients: what role does valganciclovir play?

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ABSTRACT

Background: Cytomegalovirus infection is still a significant cause of morbidity and mortality in renal transplant recipients. While valganciclovir has been used with good results in prophylactic therapy, the efficacy of this drug in clinical disease has not yet been firmly established. The aim of this study was to evaluate the safety and efficacy of valganciclovir in cytomegalovirus disease treatment.

Methods: We prospectively monitored 20 renal transplant recipients with cytomegalovirus disease. Cytomegalovirus disease was diagnosed using clinical criteria and detection of pp65 antigenaemia (≥5 positive cells/10^5) in peripheral blood leucocytes. Valganciclovir was administered in a dose of 900 mg twice daily until a negative antigenaemia value was reached and then maintained at a dose of 900 mg once daily for 4 months. Evaluation of white blood cell count (WBC), serum creatinine and cytomegalovirus antigenaemia was performed at the time of diagnosis, weekly in the first month, every two weeks in the second and third months and monthly thereafter.

Results: Clinical presentation was a viral syndrome in 14 patients and gastroenteritis in 6. The mean initial level of antigenemia was 83.6 positive cells per 10^5 peripheral blood leucocytes and a negative value was achieved after a mean time of 16.6±7.3 days (range 5-32 days). During a mean follow up of 16 months there was only one case of disease recurrence. The most important adverse event registered was leucopaenia (WBC ‹4000x10^9/L) occurring in 10 patients, but serious neutropaenia (neutrophils ‹1000 x10^9/L) was only noted in 5 of them. There were no acute rejection episodes and the serum creatinine was stable during follow up.

Conclusion: Valganciclovir is an effective treatment for cytomegalovirus infection, but the optimal duration of therapy and the best options for control of adverse events are still not completely understood.

Key-Words:
Cytomegalovirus disease; renal transplantation; valganciclovir.

INTRODUCTION

Cytomegalovirus (CMV) is an important pathogen affecting renal transplant recipients.

The morbidity and mortality still associated with this viral infection result from the direct effects of the clinical disease itself, from tissue injury and from the less well characterised indirect effects, including allograft rejection, cardiac complications and atherosclerosis, that can affect long-term patient and graft survival[1,2].

Ganciclovir (GCV) is a highly effective drug for the treatment of CMV infection and disease, but its low oral bioavailability means it requires intravenous administration and prolonged hospital admission.

Valganciclovir (VGC) is a valyl ester prodrug of ganciclovir that has better oral bioavailability enabling a drug plasma concentration equivalent to IV GCV to be achieved[3].

The efficacy of oral VGC has been established in a randomised controlled study that demonstrated comparable results with this drug and IV GCV in the treatment of CMV retinitis in patients with AIDS[4]. In solid organ transplant recipients, oral VGC showed similar results to that obtained with oral GCV in CMV prophylaxis without greater adverse effects[5].

The aim of this study was the prospective evaluation of the safety and efficacy of oral VGC in the treatment of CMV disease in renal transplant recipients.

PATIENTS AND METHODS

All adult renal transplant recipients who developed CMV disease from January 2004 to April 2007 in our hospital were enrolled in the study.

Viral disease was defined by either CMV syndrome (fever, flu-like or mononucleosis-like illness, leucopaenia or thrombocytopaenia) or tissue invasive disease[6] and the presence of CMV antigenaemia in peripheral blood samples.

Laboratory diagnosis was performed by detecting CMV protein pp65 directly in circulating leucocytes by immunoperoxidase staining. The results were expressed as the number of positive cells per 10^5 leucocytes examined. A positive antigenaemia count was established by a value superior or equal to 5 positive cells per 10^5 peripheral blood leucocytes (PBL).

The patients received oral VGC 900 mg twice daily until the CMV antigenaemia dropped to negative values (induction therapy) and were then maintained on 900mg once daily for 4 months (maintenance therapy). The VGC dose was adjusted according to the glomerular filtration rate (GFR) estimated by the MDRD study equation. Dose adjustment according to GFR was superior to 60ml/min/1.73m^2 no modification was made, from 40 to 59 ml/min/1.73m^2 induction dose was 450mg twice daily and maintenance dose was 450mg once daily, from 25 to 39 ml/min/1.73m^2 induction dose was 450mg once daily and maintenance dose was 450mg every 2 days, from 10 to 24 ml/min/1.73m^2 induction dose was 450mg every 2 days and maintenance dose was 450mg twice weekly.

Laboratory evaluation was performed at baseline, weekly in the first month, every two weeks in the second and third months and once monthly thereafter, and included white blood cell count, serum creatinine and CMV antigenaemia.

Clinical data collected at the time of transplantation included donor/recipient CMV serology and the use of immunosuppressive induction therapy. In the post-transplant period, the use of CMV prophylaxis was recorded. CMV-negative patients who received a kidney from a CMV-positive donor and patients submitted to immunosuppressive induction therapy with antithymocyte immunoglobulin received prophylaxis with valganciclovir 450 mg daily for 3 to 4 months.

All patients followed an immunosuppressive schedule that included a calcineurin inhibitor, an anti-metabolite drug (mycophenolate mofetil) and prednisolone. In accordance with previous studies[5,10,11] we decided to reduce the dose of the anti-metabolite drug by half at the beginning of therapy with VGC to reduce the risk of leucopaenia.

A leucocyte count of ‹4000 x10^9/L was defined as leucopaenia, and a neutrophil count ‹1000x10^9/L was considered severe neutropaenia. In severely neutropaenic patients, MMF was stopped and granulocyte colony-stimulating factor was added to the therapy until normalisation of the white blood cell count was achieved.

Clinical response to VGC therapy was defined by the resolution of symptoms with a negative value for CMV antigenaemia.

The primary outcome was attaining a clinical response. Secondary outcome measures were rates of relapse of antigenaemia, disease recurrence after stopping VGC therapy and adverse effects.

Statistical analyses performed were the mean, median and standard deviation of continuous variables. The Student paired t-test was used to compare variables over time.

RESULTS

A total of 137 patients underwent a renal transplant at our institution between January 2004 – April 2007.

Twenty renal transplant recipients developed CMV disease in the study period. Their baseline characteristics are shown in Table I.

CMV disease occurred in a mean time of 94.4±66 days after transplantation. Three high-risk CMV negative patients who received a kidney from positive donors and one patient treated with the polyclonal anti-thymocyte antibody for induction immunosuppressive therapy had received VGC prophylaxis. In these cases CMV disease occurred an average 4 months after stopping VGC prophylactic therapy.

CMV syndrome with fever, flu-like or mononucleosis-like illness, leucopaenia and thrombocytopaenia were the most common clinical presentations. More severe disease with gastroenteritis was seen in the remaining patients.

Table I

Baseline characteristics of the study patients

Characteristics	Patients with CMV disease (n= 20)
Age, mean±SD – years	44.8±12.1
Sex (M/F) – no.	13/7
Time from transplant – mean±SD – days	94.4±66
Pretransplant CMV serologic tests (donor/receptor) – no.	
D+/R-	3
D+/R+	17
D-/R+	0
D-/R-	0
Previous CMV prophylaxis – no.	4
Immunosuppression – no.	
Ciclosporin/mycophenolate mofetil/prednisolone	19
Tacrolimus/mycophenolate mofetil/prednisolone	1
Monoclonal and polyclonal antibodies	
ATG	1
Anti-CD25 antibodies	12
Clinical presentation of CMV disease- no.	
CMV syndrome	14
Gastroenteritis	6
Serum creatinine at time of disease – mean± D – mg/dl	1.9±1.5
Initial CMV antigenaemia- mean±SD positive cells per 10^5 PBL	83.6±58

The initial mean level of antigenaemia was 83.6±58 positive cells per 10^5 PBL and a negative value was achieved after a mean time of 16.6±7.3 days (range 5-32 days). Resolution of symptoms always preceded the disappearance of antigenaemia.

There was only one case of disease recurrence 2 months after stopping maintenance therapy.

Valganciclovir was clinically well tolerated even in patients with viral gastro-intestinal involvement and dose adjustment to renal function was made in 4 cases. Mean leucocyte count did not differ throughout the study although leucopaenia occurred in 10 patients (Fig. 1). Serious neutropaenia was present in 5 of these 10 patients and in 70% of the cases the onset was between the fourth week and third month of therapy. In the 5 cases of severe neutropaenia, MMF had to be suspended for an average of 16 days (range 5-30 days) and granulocyte colony-stimulating factor was added to the therapy.

There was no acute rejection episode and mean serum creatinine values did not change significantly throughout the study (serum creatinine 1.9mg/dl at the beginning *vs.* 1.67mg/dl at the end of the study, p=ns). Renal function was stable even in the group of patients that stopped MMF (serum creatinine 1.31mg/dl at the beginning *vs.* 1.26mg/dl at the end of the study, p=ns).

The patients were followed up for a mean time of 16±10 months (range 5-30 months).

DISCUSSION

Valganciclovir is a well accepted drug for CMV prophylaxis in renal transplant recipients. Its safety and efficacy has been established in this particular situation by a prospective, randomised, double-blind trial that showed similar results compared to oral GCV[5]. Additionally, the incidence of viraemia was significantly lower in the VGC group (2.5% *vs.* 10.4%; p=0.001)[5]. Furthermore, Wiltshire *et al.*[7] demonstrated that the systemic exposure to ganciclovir was 65% higher with VGC than with oral ganciclovir. In another study comparing the two drugs for the emergence of viral resistance, the mutation occurred in 1.9% of patients using oral GCV but none was

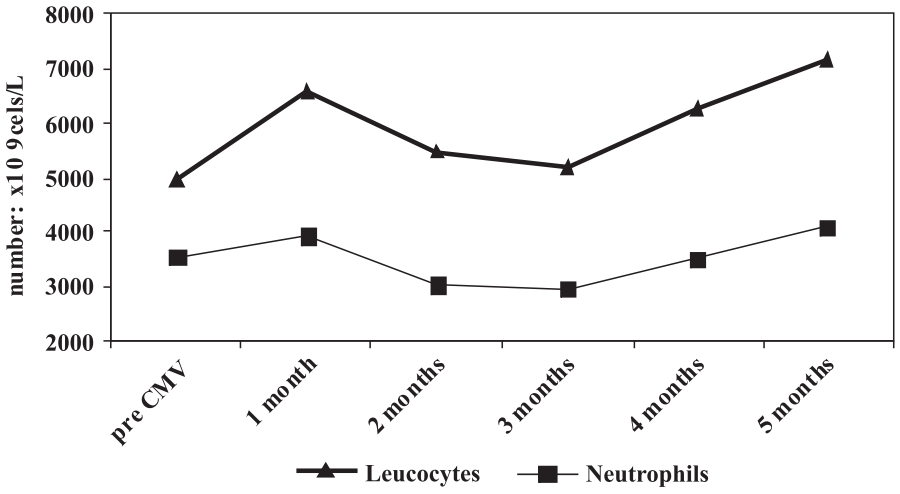

Figure 1

Time variation of the mean value of peripheral blood leucocytes and neutrophils in the study patients after starting valganciclovir therapy

recorded with VGC[8]. Another argument for the use of VGC is better patient adherence, since it is administered once daily compared with three times daily for oral GCV.

VGC has been also used in pre-emptive therapy with good results. Diaz-Pedroche *et al*[9] used VGC for treatment of 24 patients with asymptomatic CMV infection and in 9 cases of prior use of an anti-lymphocytic drug. During a mean follow-up of 14 months there was no disease development and only two patients had a relapse of CMV antigenemia.

Although VGV has shown good results in CMV prophylaxis and pre-emptive therapy, there are only limited reports of the use of this drug in the treatment of clinical disease.

In our study, VGC was an effective drug in the treatment of CMV disease.

The use of induction (900 mg twice daily, adjusted according to renal function, until the CMV antigenaemia dropped to negative values) and maintenance therapy (900mg once daily for 4 months) appears to be a good option as there was only one case of disease recurrence. In the few small studies published using VGC as therapy for CMV disease, different protocols were employed for the use of maintenance treatment. Humar *et al*[10] followed 23 patients with symptomatic disease and nine patients with only high viraemia, with whom they used VGC (900mg twice daily) for an average of 20.5±10.2 days. Disease relapse was noted in 4 patients and in 11 cases there was a viraemia recurrence. Fellay *et al*[11] evaluated 5 patients with asymptomatic CMV infection and 9 with disease. VGC was given in therapeutic dose for 2 to 3 weeks followed by a period of 2 to 4 weeks of maintenance therapy. In this study viraemia recurrence occurred in 6 patients in a 6 months follow-up.

In our opinion, a more extended treatment is advisable not only to reduce the risk of relapse but also to prevent long periods of low level viral replication that may be responsible for a number of the indirect effects of this viral infection[1,2].

In our study, leucopaenia was the most serious reported adverse event, as in other studies that employed this drug for anti-CMV prophylaxis[5] or therapy[10,11]. The mechanism of this undesirable effect is an inhibition of DNA polymerase in haematopoietic progenitor cells that is dose-dependent[12]. Although the role of VGC in this process is not clear, leucopaenia is often a result of multiple mechanisms including CMV infection itself and the effect of immunosuppressive drugs such as azathioprine or MMF.

To try to minimise the likelihood of this adverse event, we decided to reduce the dose of the anti-metabolite immunosuppressive drug in order to maintain an efficient viral infection treatment. Although an increased risk of acute rejection with reduction in MMF dose has been described[13], in our study this did not occur. A possible explanation for this may be an immunosuppressive effect of GCV itself[14] or of the combination of GCV with MMF[15]. Nevertheless, to reduce the risk of graft loss by the decrease of the immunosuppression, another option (one we are already starting to use) could be a progressive reduction of the dose of VGC to 450 mg once daily in the maintenance therapy period, but continuing with 4 months treatment. The use of granulocyte colony-stimulating factors is also a good choice in the most serious cases as already shown by other published studies[16,17].

Our study shows that VGC can be a therapeutic option for CMV disease, without hospitalisation, thus decreasing costs and being more acceptable to patients. In contrast to IV ganciclovir, the oral formulation of VGC makes the use of an intravenous line unnecessary, thus diminishing the risk of infection, which is significant in these patients because of the systemic immunosuppression related to CMV infection[1].

Further studies are needed to find the proper treatment schedule and the best options to minimise adverse events.

Conflict of interest statement. None declared.

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