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Low-dose valaciclovir prophylaxis against cytomegalovirus disease in renal transplant recipients

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Abstract High-dose valaciclovir at up to 8 g/day has been shown to be effective in prophylaxis against cytomegalovirus (CMV) disease in renal transplant recipients. We report our experience with low-dose valaciclovir prophylaxis of up to 3 g/day, adjusted to creatinine clearance. A group of patients at high risk of developing CMV disease who received prophylaxis were selected as the study group. This included all CMV-positive patients who received antilymphocyte therapy (R+, $n=20$) and all CMV-negative recipients of CMV-positive organs (D+R−, $n=15$). D+R− patients receiving antilymphocyte therapy were excluded, as most of the patients in the control group had received ganciclovir prophylaxis. A historical control group was used, which consisted of patients who did not receive prophylaxis. Low-dose valaciclovir prophylaxis resulted in a statistically significant decrease (8.5 vs 37%, $P=0.004$) in CMV disease in the study group at 6 months. On subgroup analysis the decrease was statistically significant only in the R+ group (5 vs 45%, $P=0.003$), not in the D+R− group (13.3 vs 26.6%, $P=0.651$). Low-dose valaciclovir prophylaxis seems to be adequate for R+ patients receiving antilymphocyte therapy. The role of low-dose valaciclovir prophylaxis needs to be assessed further in a prospective trial.

Keywords Valaciclovir · Cytomegalovirus · Prophylaxis · Renal · Transplantation

Introduction

Cytomegalovirus (CMV) is an important pathogen that can cause infection in patients undergoing organ transplantation [1]. The risk of disease is highest in sero-negative recipients from sero-positive donors (D+R−) and patients receiving antilymphocyte therapy [2]. Strategies for decreasing the risk of development of CMV disease are either prophylaxis or pre-emptive therapy [3]. The prophylactic medications used are high-dose aciclovir, immunoglobulin, ganciclovir and, recently, valaciclovir. Intravenous ganciclovir has been shown to be the most effective, but it requires long-term central venous access [4]. Intravenous immunoglobulin is more expensive, and the efficacy is inferior to that of ganciclovir [4]. The efficacy of oral aciclovir has been demonstrated in some studies, but, in others, it has not been shown to be effective in preventing CMV disease in sero-negative recipients of sero-positive organs [5, 6]. A recent randomised controlled trial demonstrated the benefit of high-dose valaciclovir prophylaxis using up to 8 g/day, adjusted to creatinine clearance [7]. The same study also demonstrated that prophylaxis results in large cost savings in the high-risk groups (D+R−) and also provides a clinically effective therapeutic option for moderate-risk (recipient-positive) patients at a modest

incremental cost [8]. Following a report of this study by Lowance et al. [7], valaciclovir prophylaxis was used in our unit in high-risk patients, defined as D+R− and sero-positive recipients receiving antilymphocyte therapy. However, neurological side effects were noted in 38% (5/13) patients, especially in those patients with delayed graft function, despite the adjustment of the dose of valaciclovir to creatinine clearance. This led to the discontinuation of prophylaxis. We therefore adopted a policy of low-dose prophylaxis (maximum of 3 g/day), adjusting the dose of valaciclovir to creatinine clearance.

Patients and methods

Study design

This is a retrospective study of renal transplant recipients who received low-dose valaciclovir prophylaxis against CMV disease at the Oxford Transplant Centre. The study group, comprising 35 patients, consisted of sero-positive donors to sero-negative recipients (D+R−) and sero-positive recipients (R+) who were receiving antilymphocyte therapy (OKT3 and ATG, antithymocyte globulin). Thirty-five consecutive patients who had similar CMV mismatch status and who had received transplants immediately prior to the introduction of valaciclovir prophylaxis were chosen as the control group. Most of the patients received triple immunosuppression comprising cyclosporine, azathioprine and prednisolone, details of which are given in Table 1. In both study and control groups, 15 patients were D+R− and 20 patients were R+ receiving antilymphocyte therapy. These two groups of patients were given prophylaxis, as they were deemed to be at a high risk of developing CMV disease. D+R− patients receiving antilymphocyte therapy were not included in the study, as most of these patients received oral ganciclovir prophylaxis before oral valaciclovir prophylaxis was introduced.

Diagnosis of CMV disease

Patients were considered to have CMV disease if they had positive antigenaemia with any of the following features: unexplained fever, leukopenia, thrombocytopenia, deranged liver function tests, symptoms/signs of gastrointestinal or pulmonary disease, ophthalmologically proven retinitis, or demonstration of inclusion bodies in renal or gastrointestinal biopsy material.

CMV antigenaemia testing

Leukocyte buffy coats were prepared from peripheral blood samples. The cell suspension was adjusted to 5×10^5 cells/ml. Aliquots of 100 µl were cyto-centrifuged, the slides air-dried overnight, and alkaline phosphatase anti-alkaline phosphatase immuno-labelling was performed, which incorporated a monoclonal primary antibody that targeted the human CMV pp65 antigen. The number of anti-alkaline phosphatase-positive cells per 5×10^4 leukocytes was counted for each sample.

Statistical analysis

Statistical analysis was undertaken with SPSS software, version 10.1. Comparison of categorical data was by the χ^2-test and Fisher's exact test (for small sample size) and comparison of continuous data by the unpaired *t*-test.

Results

Valaciclovir dosing

Valaciclovir was started within 72 h of transplantation in D+R− patients or the start of antilymphocyte therapy in R+ patients. The dosage used was adjusted to the creatinine clearance (CrCl) calculated by the Cockcroft and Gault equation. The drug was stopped in two patients due to neurological side effects (days 2 and 35; hallucinations and vivid dreams, respectively).

The dose of valaciclovir was based on drug company prescription information for the treatment of the herpes zoster virus (HZV) using aciclovir. The oral aciclovir dose used for CMV prophylaxis is the same as the HZV treatment dose. Since valaciclovir is a pro-drug of aciclovir, the same strategy was applied:

- CrCl < 15 ml or dialysis: 1 g once daily.
- CrCl = 15-30 ml/h: 1 g twice daily.
- CrCl > 30 ml/h: 1 g thrice daily.

Patients' demographic characteristics

The patients' demographic characteristics are given in Table 1. Both groups were similar in terms of age,

Table 1 Patients' demographic characteristics (*Cya* cyclosporine, *FK* tacrolimus, *MMF* mycophenolate mofetil, *Aza* azathioprine, *Pred* prednisolone)

Characteristic	Prophylaxis ($n=35$)	Control ($n=35$)	*P*
Age in years, mean ± SD	42.4 ± 12.2	43.8 ± 12.2	0.546
Gender, male:female	19:16	20:15	0.81
Transplant type, living/cadaver donor	13/22	7/28	0.112
No. of transplants			
1	22	31	0.029
2	11	4	
3	2		
HLA mismatches, mean	2.69	2.71	0.94
Immunosuppression			
CyA, Aza, Pred	28	33	0.151
CyA, MMF, Pred	6	2	
FK, Aza, Pred	1	0	

Table 2 Outcome in prophylaxis and control groups

Outcome	Prophylaxis ($n=35$)	Control ($n=35$)	P
CMV disease at 6 months	3 (8.5%)	13 (37%)	0.004
Graft loss at 6 months	0	2 (5.7%)	0.493
Mortality at 6 months	0	1 (2.8%)	1.0

Table 3 Outcome in D+R− and R+ groups

Group	Prophylaxis ($n=35$)	Control ($n=35$)	P
R+ (CMV disease at 6 months)	1/20 (5%)	9/20 (45%)	0.003
D+R− (CMV disease at 6 months)	2/15 (13%)	4/15 (27%)	0.651

gender ratio and the mean number of HLA mismatches. There were more living donor transplants in the prophylaxis group, due to the recent increase in living-related transplant activity in the unit. More patients in the prophylaxis group had received a second or third transplant.

Outcome

The outcome of the prophylaxis and control groups is given in Table 2. The incidence of CMV disease at 6 months was 8.5% in the prophylaxis group compared with 37% in the control group ($P=0.004$). Results of subgroup analysis of the incidence of CMV disease are given in Table 3. There was a significant decrease in incidence of CMV disease in the R+ group (5 vs 45%, $P=0.003$), but no significant difference in graft loss or mortality ($P=$NS). In the D+R− group, the incidence of CMV disease was halved from 27 to 13%, but this was not statistically significant ($P=0.651$). There was no graft loss or mortality at the end of 6 months in the prophylaxis group. The single death and two graft losses in the control group were not related to CMV disease.

Discussion

CMV disease is a major cause of morbidity in renal transplant recipients and can add to the cost of transplantation by increasing hospitalisation costs. At greatest risk of developing the disease are D+R− patients and those receiving antilymphocyte therapy [2]. Prophylaxis is known to be effective in decreasing the risk of CMV disease [9].

In our study there was a statistically significant decrease in CMV disease in the prophylaxis group compared with the control group (8.5 vs 37%, $P=0.004$). The study by Lowance et al. [7] showed that the use of high-dose valaciclovir is effective in reducing the incidence of the disease (16 vs 45% in D+R− patients and 1 vs 16% in R+ patients, respectively). However, this protocol was associated with a substantial incidence of neurological side effects (31 vs 21% in controls) and, in our experience, the use of a similar protocol was not tolerated by nearly 40% of patients, leading to the discontinuation of treatment. With low-dose prophylaxis, the medication had to be stopped in two (6%) patients, with both demonstrating symptomatic improvement after they stopped taking the drug. However, Ostermann et al. [10], when reviewing their retrospective experience with high-dose valaciclovir prophylaxis, reported no neurological side effects. Sund et al. [11] reported no neurological adverse effects in 25 patients treated with low-dose valaciclovir prophylaxis.

In our study, the incidence of CMV disease in the prophylaxis group vs the control group was 13 vs 27% in D+R− patients and 5 vs 45% in R+ patients, respectively. The high incidence of CMV disease in our R+ control group was due to these patients having received antilymphocyte therapy either for rejection or for delayed graft function with withdrawal of calcineurin inhibitors, and these are known to be risk factors for CMV disease. It should be pointed out that this study is not directly comparable with that of Lowance et al. because of differences in patient selection. We excluded some high-risk patients (D+R− receiving antilymphocyte therapy) and some low-risk patients (R+ patients not receiving antilymphocyte therapy). The decreased incidence of CMV disease in this study was statistically significant only in the R+ group receiving antilymphocyte therapy. The substantial reduction in the incidence of CMV in the D+R− group was not statistically significant in our study. However, Sund et al. [11] reported an incidence of 24% CMV disease in D+R− patients who received low-dose valaciclovir compared with 54% in the historical control group, and this decrease was statistically significant.

In our study there was no statistically significant difference in graft loss in the prophylaxis group compared with the control group. However, Hirata et al. [12] reported increased graft loss in transplants from CMV-positive donors compared with CMV-negative donors, although the negative impact of CMV infection and disease on acute rejection and chronic graft loss has not

been proven in a prospective study by Dickenmann et al. [13] and a meta-analysis by Couchoud et al. [9].

In conclusion we have shown that low-dose valaciclovir prophylaxis in renal transplantation decreases the incidence of CMV disease in R+ patients receiving antilymphocyte therapy. This protocol is associated with a much lower incidence of neurological side effects than is high-dose therapy. The role of low-dose valaciclovir prophylaxis should now be evaluated in a large randomised prospective trial.

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