



Does Valganciclovir Hydrochloride (Valcyte) Provide Effective Prophylaxis Against Cytomegalovirus Infection in Liver Transplant Recipients?

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ABSTRACT

Introduction. Cytomegalovirus (CMV) infection after solid organ transplantation is one of the most common viral infections, causing significant morbidity and mortality if not treated promptly. Ganciclovir has proven to be effective for the prophylaxis and treatment of CMV. However, oral absorption of ganciclovir is poor. Recently, oral administration of valganciclovir hydrochloride (Valcyte) has been observed to display 10-fold better absorption than oral ganciclovir. Valganciclovir has increasingly been used as prophylaxis against CMV after solid organ transplantation. The purpose of this study was to examine the efficacy of valganciclovir prophylaxis therapy after primary liver transplantation.

Patients and Methods. Between July 2001 and May 2003, 203 consecutive liver transplant recipients, including 129 men and 74 women of overall mean age 53 ± 11 years, received valganciclovir (900 mg/d or 450 mg every other day depending on renal function) for 3 to 6 months after primary liver transplantation. All patients were followed up for a minimum of 6 months. Mean follow-up was 19 ± 5.8 months. CMV DNA in peripheral blood was tested using polymerase chain reaction (PCR) amplification. Symptomatic CMV was stratified according to the CMV immunoglobulin (Ig)G status of the donor and recipient at the time of liver transplantation. Donors and recipients were classified preoperatively into groups according to the presence or absence of CMV as follows: group 1 (n = 73; donor CMV+, recipient CMV+); group 2 (n = 41; donor CMV-, recipient CMV+); group 3 (n = 54; donor CMV+, recipient CMV-; high-risk group); and group 4 (n = 35; donor CMV-, recipient CMV-).

Results. Twenty-nine patients (14.3%) developed symptomatic CMV disease at 169 ± 117 days after liver transplantation: group 1, 16.4% versus group 2, 7.3% versus group 3, 25.9% versus group 4, 0%. Of these patients, 5 also had invasive CMV on liver biopsy, which was performed owing to abnormal liver functions. All 29 patients were treated with intravenous ganciclovir. One patient died owing to disseminated CMV, whereas the remaining 28 patients responded to treatment. Interestingly, 8 patients, including 1 who had invasive CMV hepatitis, developed symptomatic CMV within 90 days of liver transplantation even while on prophylactic valganciclovir.

Conclusion. Valganciclovir failed to provide adequate prophylaxis following liver transplantation in our patients. The overall rate of CMV in seropositive donors and/or recipients was 17%, and in the high-risk group was 26%. Further prospective studies with measurement of ganciclovir concentrations are needed to elucidate the reasons for this unexpected failure.

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THIS STUDY sought to examine the efficacy of a 3- to 6-month course of prophylactic valganciclovir therapy in adult patients following primary liver transplantation. Cytomegalovirus (CMV) infection is one of the most common viral infections after solid organ transplantation. If CMV infection is not treated effectively in these patients, it leads to significant postoperative morbidity and mortality.¹⁻⁴ Ganciclovir has proven to be effective in the treatment and prophylaxis of CMV infection.⁵ Various protocols to prevent CMV infection following liver transplantation have been reported.⁶⁻¹⁰ 2-week short-term course of intravenous ganciclovir followed by 12-week long-term treatment orally has been observed by some investigators to be an effective treatment protocol.¹¹⁻¹⁵ However, <8% of ganciclovir is absorbed after oral administration; therefore, it is not suitable for prophylaxis or treatment of CMV infection.

Recently, valganciclovir hydrochloride (Valcyte) has been observed to display 10-fold greater absorption after oral administration compared with oral ganciclovir. Pharmacokinetic studies have shown that a single oral dose of 450 mg valganciclovir has the equivalent bioavailability of ganciclovir 1 g t.i.d. In addition, a single oral dose of valganciclovir (900 mg) is equivalent in area under the curve (AUC) to that of 5 mg/kg/d intravenous ganciclovir. Prophylactic use of valganciclovir for 3 months following solid organ transplantation prevents reactivation or superinfection from CMV disease.^{4,5,7,12}

PATIENTS AND METHODS

Between July 2001 and May 2003, 203 consecutive liver transplant recipients (129 men, 74 women; mean age, 53 ± 11 years) received valganciclovir prophylaxis for 3 to 6 months (900 mg/d or 450 mg every other day, depending on renal function). All patients were followed up for a minimum of 6 months. Mean follow-up was 19 ± 5.8 months. Routine surveillance to detect CMV DNA in peripheral blood was not performed unless patients were symptomatic, in which case CMV DNA in peripheral blood was tested using polymerase chain reaction (PCR) amplification.¹⁶ The rate of symptomatic CMV was stratified according to pre transplantation donor and recipient CMV immunoglobulin (Ig)G antibody status. CMV IgG titers >1:20 were considered positive. The population was divided into 4 groups as follows: group 1 (n = 73; donor CMV+, recipient CMV+); group 2 (n = 41; donor CMV-, recipient CMV+); group 3 (n = 54; donor CMV+, recipient CMV-); and group 4 (n = 35; donor CMV-, recipient CMV-).

Immunosuppression

All patients received tacrolimus, mycophenolate mofetil (MMF), and steroids. Tacrolimus was given orally every 12 hours at a dosage of 0.1 mg/kg/d. Target 12-hour trough whole blood tacrolimus concentrations were 12 ng/mL in the first month, 10 ng/mL in the second month, 8 ng/mL in the third month, and 6 ng/mL beyond 3 months. MMF (1 g) was administered orally twice a day. One gram of methylprednisolone was given intraoperatively prior to reperfusion of the liver allograft, followed postoperatively by a steroid taper totaling 600 mg during the next 5 days. Subsequent immunosuppressive adjustments were made based on the individ-

ual's clinical course considering the presence of signs of rejection, drug toxicity, or infection.

RESULTS

During follow-up, 29 patients (14.3%) developed systemic CMV, of which 5 patients had invasive CMV on liver biopsy. Mean time to develop CMV infection was 169 ± 117 days (median, 174 days) following liver transplantation. Eight patients developed CMV while on valganciclovir prophylaxis within the first 3 months after liver transplantation. As expected, the highest incidence of symptomatic CMV was observed in group 3, in which 14 of 54 patients (25.9%) developed febrile illness from CMV infection. Rates of CMV infection were 16.4% (n = 16) in group 1, 7.3% (n = 3) in group 2, and 0% (n = 0) in group 4 (Table 1).

Of 29 patients who developed CMV, 2 (6.9%) experienced acute episodes of rejection requiring an additional bolus of steroid before CMV illness. All acute rejections responded to steroid therapy and none required antibody therapy.

Five patients were diagnosed with invasive CMV on liver biopsy, which was performed due to elevated biochemical parameters indicative of hepatic dysfunction. Immunohistochemical studies were positive for CMV in all 5 patients. Most patients with CMV infection responded to intravenous ganciclovir with the exception of 1 patient with invasive CMV hepatitis, who died of widespread, systemic CMV. Liver function at the time of invasive CMV hepatitis and at last follow-up is shown in Table 2. Figure 1 shows hematoxylin and eosin as well as immunohistochemical stains showing inclusion bodies confirming CMV hepatitis among patients who developed CMV hepatitis on day 30 while on valganciclovir.

DISCUSSION

Approximately 70% of the population is exposed to CMV before adulthood. These individuals exhibit mild viral-like symptoms. Most of these individuals develop the IgG antibody for CMV; the virus remains dormant in the body.³ When a host immune system is compromised by immunosuppressive agents, as is the case in solid organ transplantation, CMV can reactivate. The resulting viremia, if not controlled, can invade any organ system and may be life-threatening. In patients without previous virus exposure (CMV IgG- ve) who receive an organ from a donor that has been exposed (CMV IgG+ ve), there is a higher risk of

Table 1. Patient Distribution by CMV IgG Status

Group	Donor IgG	Recipient IgG	No. of Patients	CMV Infection No. (%)	Mean Days to CMV
1	+	+	73 (35.9)	12 (16.4)	99 ± 101
2	-	+	41 (20.1)	3 (7.3)	313 ± 161
3	+	-	54 (26.6)	14 (25.9)	192 ± 83
4	-	-	35 (17.2)	0 (0)	NA

Abbreviation: NA, not applicable.

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