One Year of Preemptive Valganciclovir Administration in Children After Liver Transplantation

Abstract

Objectives

Valganciclovir (VGCV) is used as prophylaxis against CMV infection after pediatric living donor liver transplantation (LDLT). The purpose of this study was to examine the efficacy of 1 year of preemptive VGCV administration compared with a shorter administration after pediatric LDLT.

Methods

VGCV was administered to 56 children who underwent LDLT. CMV and EBV antibody status, pp65 antigenemia, and other laboratory data were assessed at 1 year after LDLT. Patients were divided into the 1-year group (n=32), who had 1 year of VGCV administration, and the < 1 year group (n=24), who had less than 1 year of VGCV administration.

Results

Study participants consisted of 34 females and 22 males, with a mean age of 4.2 years at transplant. Regarding pre-transplant donor (D)/recipient (R) CMV antibody status, 13 were D positive (+)/R negative (-), 27 were D+/R+, 8 were D-/R+, and 8 were D-/R-. For EBV, 22 were D+/R+, 32 were D+/R-, and 2 were D-/R-. In the 1-year group, only 2 patients (6.5%) developed CMV infection whereas 8 patients (33.3%) developed CMV infection in the < 1-year group. The CMV pp65 antigenemia assay was positive in 2 patients. CMV IgM was positive in 7 patients. One

year of preemptive VGCV administration was associated with a lower incidence of CMV infection (*P*=.008), but not EBV infection. No adverse effects were observed.

Conclusions

One year of preemptive VGCV administration after LDLT is safe and suppresses CMV infection. It was useful after pediatric LDLT.

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Introduction

Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) infection are the most common viral infections in pediatric transplant patients [1, 2]. Recently, there has been interest in valganciclovir (VGCV), a highly bioavailable oral form of ganciclovir (GCV), as an alternative to intravenous or oral GCV. VGCV, an antiviral medication used to treat CMV infection, is the prodrug of GCV. After oral administration, it is rapidly converted to GCV by intestinal and liver with good bioavailability [3]. VGCV has been used as prophylaxis against CMV after pediatric living donor liver transplantation (LDLT). The optimal strategy for preventing CMV infection in pediatric LDLT patients remains controversial. A prospective randomized study of CMV prophylaxis in solid organ transplant recipients recently demonstrated that oral VGCV and oral GCV had similar effect [4]. Within the Studies of Pediatric Liver Transplantation (SPLIT) group, the duration of antiviral prophylaxis varies significantly [5]. The purpose of this study was to examine the safety and efficacy of long-term VGCV prophylaxis after pediatric LDLT.

Methods

Patients under 18 years of age at the time of LDLT at our institution were eligible. Patients were tapered from tacrolimus-based immunosuppression and steroids according to our protocol. The standard protocol for tacrolimus tapering was as follows: the target tacrolimus trough level was

10–15 ng/mL for the first month after transplantation and tapered to 3–5 ng/mL thereafter. All patients initially received steroids. Steroids were usually tapered off by 4 months after transplantation. However, prednisolone was continued for patients who had an episode of biopsy-proven acute cellular rejection or post-transplant hepatitis over 4 months.

After intravenous GCV (5 mg/kg/day) for 10 days, daily VGCV (18 mg/kg) was administered to children who underwent LDLT. VGCV was stopped at the time that steroids were discontinued, regardless of CMV status. If a patient was on steroids beyond 4 months after LDLT, VGCV was continued until steroids were discontinued, up to 1 year after LDLT.

Patients were divided in two groups: the 1-year group who had 1 year of VGCV and the < 1-year group, who had less than 1 year of VGCV. CMV and EBV antibody status, pp65 antigenemia assay results, and other laboratory data of the 2 groups were compared. Adverse effects of VGCV were assessed based on white blood cell count (WBC) and platelet count.

Data were analyzed using the JMP version 11.0 software package (SAS, Cary, NC, USA). Continuous variables are presented as means. Continuous variables were compared using paired t-tests. A *P* value less than .05 was considered statistically significant.

Results

Of the 56 patients included in this study, 34 were female and 22 were male, with a mean age at transplant of 4.2 years (range, 0.2–16.6 years). Underlying diseases included biliary atresia

(n=37), metabolic disease (n=5), fulminant hepatic failure (n=5), hepatoblastoma (n=3), and other (n=6). With regards to pre-transplant donor (D)/recipient (R) CMV antibody status, 13 were D positive (+)/R negative (-), 27 were D+/ R+, 8 were D-/R+, and 8 were D-/R-. For EBV, 22 were D+/R+, 32 were D+/R-, and 2 were D-/R- pairs.

There were 32 patients in the 1-year group and 24 patients in the < 1-year group. The profile of each group is shown in **Table 1.**

In the 1-year group, only two patients developed CMV infection (6.5%) whereas CMV infection was observed in 8 patients (33.3%) in the < 1-year group. The CMV pp65 antigenemia assay was positive in 2 patients and CMV IgM was positive in 7 patients in < 1-year group. One year of preemptive VGCV administration was statistically significantly associated with a lower incidence of CMV infection (*P*=.008). Results are also shown in **Table 1**.

Eleven EBV R- patients (55%) of 20 EBV R- patients in the 1-year group remained seronegative, whereas 5 EBV R- (36%) patients of EBV R- (n=14) remained seronegative in the < 1-year group. One of year VGCV prophylaxis tended to prevent EBV seroconversion. (*P*=.17) No cases of posttransplant lymphoproliferative disorder (PTLD) were observed during the study period. No adverse effects were observed.

Mean WBC counts before transplant and at 3 and 12 months after LDLT are shown in **Fig 1a**. Although WBC counts decreased slightly at 3 months after LDLT during the observation period

(*P*=0.02), WBC counts were within normal range. Mean platelet counts are shown in **Fig 1b**. Platelet counts increased slightly over time, but this increase was not statistically significant (*P*>.07).

None of the patients had discontinuation of long-term prophylaxis due to treatment-related adverse events. There were no serious adverse events attributable to prophylactic VGCV treatment.

Discussion

CMV is the most commonly documented viral infection after solid organ transplantation [6]. CMV infection in immunosuppressed transplant patients is associated with opportunistic infections, increased risk of graft loss, and significant morbidity and mortality. There are 2 major approaches to controlling CMV infection after liver transplantation: universal prophylaxis and preemptive therapy. Universal preemptive therapy for CMV infection after LDLT was successful in reducing the use of antiviral agents and controlling CMV infection and disease in children [7]. We demonstrated effectiveness of universal prophylaxis for pediatric LDLT.

VGCV use in adult solid organ transplant patients has been shown to be safe and efficacious in some studies [6, 8, 9]. Preemptive VGCV therapy and VGCV prophylaxis are equally effective in terms of preventing CMV disease after renal transplantation [10].But evidence in pediatric liver transplant recipients specifically is limited. Few trials have included pediatric

transplant patients, and fewer still have included pediatric liver transplant patients [11, 12].

Universal prophylaxis includes antiviral therapy for a certain period of time in subjects at high risk of developing CMV disease, such as seronegative recipients receiving seropositive grafts. However, GCV is not a convenient prophylactic agent because it requires intravenous administration. Therefore oral VGCV is beneficial for pediatric patient.

Primary EBV infection occurs in 80% of seronegative patients within 3 months of liver transplantation. Clinical symptoms are rare and are strongly associated with PTLD [2]. The major role of the host immune response in preventing PTLD is known. Therefore, a decrease in the dose of immunosupression is considered the mainstay of EBV infection management after LDLT. However, this needs to be balanced with the risk of acute cellular rejection; only severe EBV infection should rapidly decrease in immunosuppression. When Hierro et al studied children with liver transplants and a persistently elevated EBV viral load treated with VGCV and no changes in immunosuppression, they found that a decrease in viral load could be achieved with prolonged VGCV treatment; EBV DNA became undetectable in about half of patients [13].

Some adverse effects have been reported with VGCV. In pediatric patients, the most common adverse events were diarrhea, fever, hypertension, upper respiratory tract infection, vomiting, anemia, neutropenia, constipation, nausea, and cough [14]. However, no adverse effects were observed in our series. 18mg/kg once a day dose might be adequate for pediatric

patients. Our study demonstrates the safety, feasibility, and effectiveness of a 1-year regimen of oral VGCV.

Conclusion

Long-term VGCV prophylaxis for CMV and EBV infection after LDLT is safe in pediatric patients. VGCV suppressed CMV pp65 antigenemia and disease related to CMV and EBV infections despite failing to prevent seroconversion.

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