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Retrospective Review of the Incidence of Cytomegalovirus Infection and Disease Post Liver Transplantation in Pediatric Patients: Comparison of Prophylactic Oral Ganciclovir versus Oral Valganciclovir

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Abstract

Cytomegalovirus (CMV) is the commonest viral infection after solid organ transplantation (SOT). Safe and effective prophylactic regimens that decrease incidence post-SOT are essential for long term graft survival. Although valganciclovir is not FDA approved for CMV prophylaxis in liver transplant recipients, post-marketing studies have shown valganciclovir to be as effective as ganciclovir in high risk adult SOT. Currently such data is lacking in pediatric liver transplantation. The purpose of this study was to compare the efficacy and safety of valganciclovir and ganciclovir for CMV infection prophylaxis in pediatric liver transplant recipients.

This was a retrospective study of 56 pediatric liver transplant recipients prescribed either oral ganciclovir (n=37) or valganciclovir (n=19). Patients were followed until 200 days post-transplant or death. Primary outcome measure compared incidence of early onset CMV infection and CMV disease between the two medication groups. Secondary outcome measure identified patient specific factors that contributed to CMV acquisition as well as the incidence of late onset CMV infection or disease. Rate of adverse drug effects and discontinuation were also evaluated.

Early onset CMV disease was documented in 0% vs. 5.4% of valganciclovir and ganciclovir patients respectively (p=0.54). There were no statistically significant differences in secondary outcomes. A trend for increased incidence of late onset CMV disease was seen in the valganciclovir group (22.2 vs. 8.1%; p=0.23). No differences in adverse events were reported. Conclusion: No statistically significant difference was found when comparing the incidence of CMV infection and disease between oral valganciclovir and ganciclovir.

Keywords

Antiviral prophylaxis; Opportunistic Infection; Solid Organ Transplantation

Introduction

Cytomegalovirus (CMV) is the most common viral infection documented post solid organ transplantation (SOT) (1). Infection with CMV in immune-compromised transplant patients is associated with enhanced immune suppression leading to opportunistic infection, increased risk of graft loss, and significant morbidity and mortality. Utilized strategies to decrease the rate of infection include pre-emptive and prophylactic antiviral regimens. Cincinnati Children's Hospital Medical Center (CCHMC) follows an evidence based care

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guideline for CMV prophylaxis following SOT(2), utilizing a primary regimen of induction IV ganciclovir for fourteen days followed by maintenance oral ganciclovir, or valganciclovir as an alternative regimen. In liver transplant patients this is continued until 120 days post-transplant. Valganciclovir is FDA approved for prophylactic use post heart, kidney and pancreas transplantation(3), but is currently not FDA approved for use post liver transplantation secondary to data from the Valganciclovir SOT Study Group(1). This study found a higher incidence of CMV infection and CMV tissue invasive disease in a subgroup analysis of adult liver transplant patients using valganciclovir. Subsequent studies have found valganciclovir to be a safe and efficacious alternative to ganciclovir(4, 5). The International Consensus Guidelines on the Management of CMV in SOT (6) recommend oral ganciclovir or valganciclovir in liver transplant recipients. Given the contradictory data on valganciclovir our institution had been using ganciclovir in liver transplant recipients up until a national shortage of the oral formulation of ganciclovir resulted in valganciclovir becoming the regimen of choice at CCHMC as of July, 2009.

Ganciclovir is an antiviral agent classified as a nucleoside analogue. It acts to inhibit viral DNA replication by interfering with DNA elongation(7). When administered orally, ganciclovir has a low bioavailability ranging from 5–9%, requiring every eight hour dosing (7–9). Valganciclovir is the L-valyl ester pro-drug of ganciclovir. Valganciclovir has an oral bioavailability of ~60% (8, 10) and has been shown to provide comparable systemic exposure to that of ganciclovir with equivalent dosing(8, 10, 11). Due to the once daily dosing regimen, the current unavailability of oral ganciclovir capsules and proven comparable effectiveness, valganciclovir is now used in the majority of all SOT recipients. Despite the fact that it is not an FDA approved regimen for liver transplant recipients, valganciclovir is utilized by 73% of responding liver transplant centers throughout the United States and Canada(12).

There are multiple studies demonstrating the effectiveness of prophylactic antiviral medications in reducing the incidence and severity of CMV disease in adult transplant recipients (1, 4, 5, 13). There are however no studies that we could find that specifically look at incidence in pediatric liver transplant patients, and therefore the impact and effectiveness of CMV prophylaxis on this population, remains relatively unknown. Although previous studies give preliminary information on the safety and efficacy of valganciclovir, the results cannot adequately be extrapolated to the pediatric liver transplant population.

Compared to the adult transplant population, it is very well understood that pediatric transplant recipients are at increased risk of acquiring CMV infection given that they are more often CMV naïve at the time of transplant(5, 14). Children usually receive organs from adults who are more likely serology status positive due to age and increased time of exposure to CMV. Therefore, pediatric transplant recipients are most often categorized as high risk for acquiring CMV infection, which is attributed to age and decreased exposure to CMV prior to transplant. There is a paucity of data on the incidence of CMV infection and subsequent disease in the pediatric liver transplant population. Symptomatic infection occurs within the first 30–90 days post-transplant (4) in 22–60% of liver transplant recipients who are not treated with a CMV prophylaxis regimen (13, 15). When CMV prophylaxis is used to treat intermediate and high risk patients, infection and disease can be delayed until prophylaxis is discontinued. Despite effective prophylaxis, it has been documented that 10–20% of transplant recipients will present with evidence of CMV replication with or without end organ disease within two years of transplant (6).

We felt that it was therefore important to determine if the pediatric population has varying outcomes from that observed in the adult population. The purpose of this retrospective study

was to determine the incidence of CMV disease in pediatric post-liver transplant patients treated with one of two oral antiviral regimens for CMV prophylaxis: ganciclovir (Cytovene®) or valganciclovir (Valcyte®). Our hypothesis was that prophylactic oral valganciclovir is associated with fewer occurrences of early onset CMV infection and disease when compared to oral ganciclovir in a pediatric liver transplant population.

Patients and Methods

Our population was pediatric liver transplant recipients at CCHMC who received oral ganciclovir or valganciclovir post-transplantation from January 2006 until March 2011. IRB approval was obtained prior to the start of data collection. Patients were identified through use of electronic databases and electronic medical records (ChartMaxx®, Epic©, ICIS© and the Liver Group Portal©). A retrospective chart review was performed.

Patients were eligible for inclusion based on the following criteria: liver transplant recipient followed at CCHMC until 200 days post-transplant or death, documented donor/recipient (D/R) CMV serology status pre-transplant, prescribed oral ganciclovir or valganciclovir post-transplant and ≤ 21 years old on the date of liver transplant.

Patients were excluded based on the following criteria: multi-visceral organ transplant recipient, HIV positive (increased risk of adverse effects and infection in this population), D (−)/R (−) CMV serology status not treated per CCHMC protocol, transplanted prior to 2006 (due to hospital protocol change from acyclovir to ganciclovir), recipient of acyclovir or if switched treatment groups during study period (ganciclovir to valganciclovir).

Due to a national shortage of the raw materials necessary to manufacture oral ganciclovir, valganciclovir became the prophylactic agent of choice in 2009 per the transplant protocol. At CCHMC prophylactic antiviral regimens utilizing either ganciclovir or valganciclovir for 120 days post-transplant are the standard of care. Ganciclovir was initiated at a dose of 30–40mg/kg/day divided Q8h up to the maximum adult dose of 1000mg Q8h(9). Doses were adjusted as recommended in renal impairment (CrCl<70ml/min/1.73m^2) on patient specific bases. Valganciclovir was dosed using the validated dosing equation of 7 * body surface area * creatinine clearance (CrCl)(16). The CrCl was calculated using a measured Cystatin C value if available or the modified Schwartz equation, with a maximum CrCl value of 150ml/min/1.73m^2. However dose adjustments were not collected as a part of this chart review. CMV quantitative PCRs, per protocol are obtained in all patients every two weeks for the first three months post-transplant, and monthly thereafter until 1 year post transplant.

Outcomes

The purpose of this study was to determine the incidence of CMV infection and disease in pediatric liver transplant recipients in order to validate the use of valganciclovir. The primary outcome was the incidence of CMV infection and disease within 120 days of liver transplant (early onset) between patients given antiviral prophylaxis with oral ganciclovir or valganciclovir. CMV infection was defined as evidence of CMV replication in a clinical specimen without associated symptoms. CMV disease was defined as the presence of CMV infection in addition to tissue biopsy confirmed tissue invasive disease or a clinical diagnosis of CMV syndrome made by the liver transplant team due to the presence of symptoms including but not limited to fever, muscle pain, leukopenia and/or thrombocytopenia. These definitions were obtained from the CCHMC evidence based care guideline(2) for CMV prophylaxis following SOT.

Secondary outcomes were the incidence of infection and disease between ganciclovir and valganciclovir when compared by age, risk stratification based on pre-transplant serology

status, incidence of acute graft rejection, incidence of sepsis (defined as documentation in the electronic medical record or equivalent record of diagnosis of sepsis with subsequent antibiotic treatment for longer than forty eight hours) and duration of antibiotic therapy, length of IV ganciclovir therapy, the incidence of CMV infection and disease from day +120 to +200 (defined as late onset CMV infection/disease) and the incidence of opportunistic infection (OI). EBV, HSV and Adenovirus were counted as an OI if there was a documented viremia via PCR. Quantitative EBV PCR monitoring was performed in all patients every two weeks for the first 3 months post-transplant and monthly thereafter for the first year. Risk stratification based on CMV serology was defined as: high risk: donor positive/ recipient negative (D+/R−), intermediate risk: donor positive/ recipient negative or donor negative/recipient positive (D+/R+; D−/R+).

Tertiary outcomes included the incidence of adverse events of neutropenia, leukopenia, thrombocytopenia, and anemia between comparison groups, and comparison of the discontinuation rate due to adverse effects. Neutropenia was defined as an absolute neutrophil count of <1000. Leukopenia was defined as a white blood count less than the Age Specific Laboratory Value ranges from CCHMC central Laboratory Reference Ranges (listed in supplementary appendix). Thrombocytopenia was defined as a platelet count of <100,000/μL. Anemia was defined as values less than the Age Specific Laboratory Values from the CCHMC central Laboratory Reference Ranges (listed in supplementary appendix).

Data Collection

The data collection process was performed utilizing a standard form for all patients. The following data variables were collected: date of birth, sex, race, ethnicity, primary liver disease, age at transplant, CMV serology, HIV status, date of transplant, prophylactic antiviral therapy initiation date, results of quantitative and qualitative CMV PCRs, results of all tissue biopsies, length of IV ganciclovir induction therapy, concurrent medications, incidence of sepsis and subsequent length of antibiotic therapy, incidence of acute cellular rejection and opportunistic infection, as well as the date the antiviral was discontinued, any adverse effects reported and lab values pertaining to the adverse effects of neutropenia, thrombocytopenia, leukopenia, and anemia.

Statistics

Statistical comparison of patient demographics was performed utilizing Fischer's Exact Test and the Chi Square Test for categorical variables and the t-test for continuous variables. Primary and secondary outcome variables were analyzed using the Fischer's Exact Test and the Chi Square Test. A logistic regression analysis was performed to analyze risk stratification associated with the variables of age, incidence of sepsis, antibiotic treatment duration, incidence of acute graft rejection and the duration of IV ganciclovir therapy. Analyses were performed using the Statistics Online Computational Resource (www.SOCR.ucla.edu)(17). A p-value of <0.05 was considered statistically significant.

Results

Patient Characteristics

From January 2006 until March 2011, 73 patients received a liver transplant at Cincinnati Children's Hospital Medical Center with 22 of them receiving valganciclovir prophylaxis and 51 receiving ganciclovir as prophylaxis against CMV. Three valganciclovir patients were excluded due to prior use of ganciclovir during the study period (n=2) and for prior use of acyclovir (n=1). Fourteen ganciclovir patients were excluded due to: D (−)/R (−) CMV serology status not treated with ganciclovir or valganciclovir (n = 4), being a recipient of a multivisceral transplant (n = 4), and switching therapy during the study period (n = 6).

Therefore 56 patients were included in the study; 19 in the valganciclovir group and 37 in the ganciclovir group.

Patient demographics: The only statistical difference found in the demographic variables between treatment groups was that the valganciclovir arm had more patients with cirrhosis as the underlying primary liver disease as compared to the ganciclovir arm (p=0.02). The majority of patients in both groups were classified in the high risk CMV serology category (58% in the valganciclovir and 54% in the ganciclovir group) (Table 1). Of note, the ganciclovir group did have a larger number of patients in the 0–2 year range (n = 17), than the valganciclovir group (n = 7); however there was no statistical difference in the age distribution between the two groups.

Primary Outcome

The incidence of CMV infection within 120 days post-transplant was 0% in both groups. The incidence of CMV disease was 0% in the valganciclovir group and 5.4% in the ganciclovir group (n = 2); p = 0.54. This data was also analyzed in the high risk patient population alone. Eleven valganciclovir patients and 20 ganciclovir patients were of the D(+)/R(−) serology status. Zero of eleven and 2/20 (10%) ganciclovir patients had early onset CMV disease; p = 0.53. There were no statistically significant differences identified. Of the two patients who had documented CMV disease one had CMV colitis and the other had CMV cystitis. Both patients had the high risk CMV serology status of D (+)/R (−). These 2 ganciclovir patients did not have the same age range, sex, race or primary liver disease (Table 2).

Secondary Outcomes

There were no statistically significant differences identified between the secondary outcome variables of acute graft rejection, opportunistic infection, documented sepsis, duration of antibiotic therapy, or length of IV ganciclovir induction therapy. The most common opportunistic infection (OI) was Epstein Barr Virus (11 documented cases). Six ganciclovir and 5 valganciclovir patients had document EBV. Two ganciclovir patients had documented Adenovirus viremia. Eighteen patients in the valganciclovir group could be followed until day +200. One patient died within the study period and all 37 ganciclovir patients were followed through day + 200. The incidence of late onset CMV infection (day 120 to day +200) was 0% in both treatment groups. The incidence of CMV disease was 22.2% in the valganciclovir group (n = 4) and 8.1% in the ganciclovir group (n = 3); p = 0.23 (Table 3). Of the seven patients who acquired late onset CMV disease, six were diagnosed within 60 days of antiviral prophylaxis discontinuation (range 42–55 days). The three ganciclovir patients had CMV syndrome and of the four valganciclovir patients, one had CMV colitis and three had CMV syndrome. Three patients were in the high risk serostatus category of D (+)/R (−), and four patients were D (+)/ R (+).

A risk stratification analysis was performed using logistic regression to determine if any patient specific variables were associated with a higher risk of acquisition of CMV. None of the variables of age, sepsis, antibiotic duration, incidence of acute graft rejection or IV ganciclovir therapy duration had a statistically significant confidence interval or increased odds ratio. The small number of occurrences of CMV infection and disease, as well as the study population size limited the utility of this analysis.

Tertiary Outcomes- Safety

Documented adverse effects thought to be due to the study medication were validated via laboratory result review. There were three patients in the valganciclovir group (15.8%) who had one or more adverse effects (1 thrombocytopenia, 2 leukopenia, 2 neutropenia)

compared to three (8.1%) ganciclovir patients (3 neutropenia) (p=0.49). This was not a statistically significant difference. The three valganciclovir patients with an adverse drug effect discontinued the medication prior to day +120, in addition to one other patient who discontinued therapy 9 days early. Ten ganciclovir patients discontinued therapy prior to day +120. The reasons for early discontinuation included acquisition of CMV disease (n = 2), adverse drug effect (n=3), and unknown (n=5) (Table 4). Due to the retrospective nature of this study, documented explanations for early discontinuation of both valganciclovir and ganciclovir were not found. The duration of prophylactic therapy was not available for all patients due to having IRB approval to only collect data until day +200, and the retrospective nature of the data acquisition. The median duration of antiviral prophylaxis was 117 days in the valganciclovir group (n= 17) compared to 118 days in the ganciclovir group (n=34) (Table 4).

Discussion

Valganciclovir usage in adult SOT patients has been shown to be safe and efficacious in some studies and controversial in others (18, 19). It is widely utilized in pediatric SOT although evidence in pediatric liver transplant recipients specifically is limited. Few trials are available that include pediatric patients, and fewer still that only include liver transplants. This current study included patient's ≤ 21 years of age who received a liver transplant at CCHMC. There was not a trend in primary liver disease and incidence of CMV infection or disease, or with any other demographic variable. There was a higher percentage of patients in the ganciclovir group in the 0–2 years age range as compared to the valganciclovir group. Due to the increased risk of acquisition of CMV in younger patients this difference could skew the results in the ganciclovir group, and could be a source of bias. No statistically significant difference was found between the numbers of patients in each age range. Of the total 56 patients evaluated 0/19 valganciclovir patients and 2/37 ganciclovir patients had documented early onset CMV disease. Late onset incidence of infection and disease was also evaluated due to information alluding to the idea that antiviral prophylaxis may only delay the onset of CMV (20–22). Four of 18 valganciclovir and 3/37 ganciclovir patients had documented late onset CMV disease. This difference was not statistically significant. Due to the small sample size and discrepancy between the numbers of patients in each group it is difficult to discern clinical significance from this result. Six of the seven cases of late onset disease occurred within 60 days of discontinuation of antiviral therapy. Of the nine cases of CMV disease, three were considered to be tissue invasive and six were defined as CMV syndrome. Overall the incidence of CMV disease in the studied population was 16%, which is similar to that reported in previous studies (1, 6, 15). There were no documented recurrences of CMV infection or disease in any patient within 200 days of transplant.

This study found no statistically significant difference when comparing the incidence of early and late onset CMV infection and disease between patients treated with oral ganciclovir or valganciclovir, although it was not adequately powered to do so. The original hypothesis that the incidence of early onset CMV infection was less in the valganciclovir group as compared to the ganciclovir group could not be accepted or rejected due to the small population size; no difference was found between the groups. The rates of discontinuation of antiviral therapy as well as the incidence of bone marrow toxicity, defined as anemia, thrombocytopenia, neutropenia and leukopenia, were similar between the two groups.

This study's limitations include its design being one of a retrospective chart review wherein rare instances the definitions dictated by the CCHMC evidence based care guidelines were not followed in chart documentation and diagnosis codes by physicians. Further some

patients were on sulfamethoxazole/trimethoprim therapy which can also cause bone marrow suppression. A limitation of this study method was the interpretation of chart documentation to determine the true cause of bone marrow suppression. Many more patients exhibited signs of anemia, thrombocytopenia, leukopenia and/or neutropenia, however only the sulfamethoxazole/trimethoprim was discontinued as the probable offending agent. The practice of discontinuing sulfamethoxazole/trimethoprim alone versus sulfamethoxazole/trimethoprim and the antiviral agent appeared physician specific. Some patients (n=valganciclovir, ganciclovir) also received other immune suppressing agents including azathioprine (n=1,0), mycophenolate mofeteil (n=7,7), sirolimus (n=2,2), pentamidine (n=7,11), and mercaptopurine (n=1,0). All patients in both treatment groups were receiving tacrolimus during all or part of the study period. Differences in cytopenia outcomes when taking into account these medications were not compared due to the small sample size. The true rate of adverse effects from valganciclovir and ganciclovir may therefore be higher than reported. The indication of the antiviral agent as the primary cause of the abnormal lab value of anemia, thrombocytopenia, leukopenia or neutropenia was dependent on documentation by the physician. Another limitation was the ability to determine reasoning for early discontinuation of therapy. Besides documentation of adverse drug events the reason for early discontinuation is unknown. Two patients were difficult to classify because they were treated as high risk patients despite the fact that their CMV serology status was unknown at the time of transplant.

There were only 56 patients that were able to be included in this study, thus with the small number that met inclusion criteria, this study was not powered to find a difference between the treatment groups. Therefore we are unable to make any concluding statements that one antiviral agent is superior or inferior to the other based on this study's results. Although the total patient population included is small, when considering the fact that this is a pediatric study evaluating a very specific population, the (n) is actually relatively large for a single center pediatric liver transplant cohort.

Our study raises the need for future research to investigate the true incidence of late onset disease and whether there is an association between valganciclovir and an increased risk of late onset disease. This current study found an increased percentage of CMV disease in the valganciclovir group of 22.2% compared to 8.1% in the ganciclovir group. Although this difference was not statistically significant and the low number of occurrences limits the ability to determine a true clinical significance, this finding is concerning and does warrant future research. This result is particularly alarming considering the results of the Valganciclovir SOT Study Group led by Paya and colleagues (1). The Valganciclovir SOT Study Group published an article which compared the Efficacy and Safety of Valganciclovir versus Oral Ganciclovir for Prevention of CMV Disease in Solid Organ Transplantation. It included patients greater than the age of thirteen who received their first heart, liver, kidney, kidney-pancreas, kidney-heart, or kidney-liver transplant with a CMV serology status of (D +)/ (R−). A population of 185 out of 372 total patients was liver transplant recipients. Incidence of CMV disease in the liver subgroup was 19% with valganciclovir and 12% with ganciclovir. Significant tissue invasive CMV disease was also found to be 4.5 times higher in the valganciclovir group (14% vs. 3%) at the time point of 6 months post-transplant. Due to the outcome of increased CMV disease in the valganciclovir arm compared to oral ganciclovir in liver transplant patients, valganciclovir did not receive FDA approval for CMV prophylaxis. Subsequent studies have shown no difference in the incidence of late onset CMV disease (4, 5); however this current study's results do mimic those reported by Paya et al. Reasons for this reported difference in the liver transplant population are not known.

Thus to conclude, our results are inconclusive as to whether a difference exists in the safety and efficacy outcomes between ganciclovir and valganciclovir for prophylaxis of both early and late onset CMV infection and disease in pediatric liver transplant patients. Valganciclovir's association with late onset CMV disease warrants further investigation. A larger multi-center prospective clinical trial in the pediatric liver transplant population may be warranted to address the important concerns raised by our single center retrospective review.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations

CMV	Cytomegalovirus
SOT	Solid Organ Transplantation
CCHMC	Cincinnati Children's Hospital Medical Center
IV	Intravenous
FDA	Food and Drug Administration
IRB	Institutional Review Board
D/R	Donor/Recipient
+	Positive
−	Negative

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Table 1

Patient Demographics

	Valganciclovir (n=19)	Ganciclovir (n=37)	p-value
Age in years (median) Age (Range)	5.3 0.4–21.8	2.3 0.3−19.5	0.30
Sex; n (%) • Male • Female	7 (36.8) 12 (63.2)	17 (45.9) 20 (54.1)	0.97
Race; n (%) • White • Black • Other	12 (63.2) 3 (15.7) 4 (21.1)	20 (54.1) 5 (16.7) 12 (33.3)	0.05
Primary Liver Disease*; n • Cholestatic • Metabolic • Acute Liver Failure • Cirrhosis • Other	9 1 1 6 2	18 7 5 2 5	0.07 0.02
D/R CMV Serology Status; n • D (+)/ R (−) • D (+)/ R (+) • D (−)/ R (+) • Unknown	11 5 1 2	20 10 7 0	0.13

*Cholestatic = Allagille's syndrome, biliary atresia, idiopathic cholestasis, primary schlerosing cholangitis, idiopathic cholestasis; Metabolic = antitrypsin 1 deficiency, citrillunemia, glycogen storage deficiency, hemochromatosis, OTC, urea cycle disorders, Wilson's disease; Acute Liver Failure = viral, autoimmune, drug toxicity, indeterminate; Cirrhosis = autoimmune hepatitis, cryptogenic cirrhosis, neonatal hepatitis; Other = tumor s (blastoma, carcinoma, hemangioenothelioma), cystic fibrosis.

Table 2

Primary Outcome

Outcome Variable	Valganciclovir N = 19 (%)	Ganciclovir N = 37 (%)	p-value
CMV Infection	0	0	1.0
CMV Disease	0	2 (5.4)	0.54
High Risk Patients D(+)/R(−) • Infection • Disease	N = 11 0 0	N = 20 0 2 (10)	 0.53

Table 3

Secondary Outcomes

Outcome Variable	Valganciclovir N = 19 (%)	Ganciclovir N = 37 (%)	p-value
Acute Graft Rejection	9 (47.4)	16 (43.2)	1.0
Opportunistic Infection	5 (26.3)	8 (21.6)	1.0
Documented Sepsis	9 (47.4)	9 (24.3)	0.39
Duration of Antibiotic Therapy (days; mean)	13.8	16.8	0.77
Length of IV Canciclovir (days; mean)	16.8	16.1	0.82
Late Onset • Infection • Disease	N = 18 0 4 (22.2)	N = 37 0 3 (8.1)	 0.23

Table 4

Tertiary Outcomes

Outcome Variable	Valganciclovir N = 19 (%)	Ganciclovir N = 37 (%)	p-value
Number of Patients with a Medication Related Adverse Drug Event (n)	3 (15.8)	3 (8.1)	0.49
Medication Related Adverse Drug Event (n) • Anemia • Thrombocytopenia • Leukopenia • Neutropenia	0 1 2 2	0 0 0 3	
Discontinuation prior to day +120	4 (21.1)	10 (27.0)	1.0
Duration of Prophylaxis • Median (days) • Range (days)	N = 17* 117 92–138	N = 34* 118 32–194	1.0

* Data unable to be collected on all patients