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SAFETY AND EFFICACY OF PROLONGED CYTOMEGALOVIRUS PROPHYLAXIS WITH INTRAVENOUS GANCICLOVIR IN PEDIATRIC AND YOUNG ADULT LUNG TRANSPLANT RECIPIENTS

John F. Spivey, MD[1], **Dana Jewell, RN**[1], **Stuart Sweet, MD, PhD**[1], **Gregory A. Storch, MD**[1], **Robert J. Hayashi, MD**[1], **Charles B. Huddleston, MD**[2], and **Lara A. Danziger-Isakov, MD, MPH**[3]

1 *Divisions of Allergy/Pulmonary, Hematology/Oncology, and Infectious Diseases, Department of Pediatrics at Washington University School of Medicine*

2 *Division of Cardiothoracic Surgery, Department of Surgery at Washington University School of Medicine*

3 *Division of Infectious Diseases, Department of Pediatrics at The Cleveland Clinic*

Abstract

Background— Cytomegalovirus (CMV) infection causes morbidity and mortality after transplantation. Despite a wide range of prevention strategies among pediatric lung transplant programs, the optimal duration of prophylactic therapy against CMV infection in pediatric lung transplantation is unknown.

Objective— To assess the feasibility, safety, and short-term efficacy of extending intravenous ganciclovir administration from 6 weeks duration to 12 weeks duration in pediatric lung transplant recipients.

Design/Methods— An open-label pilot study was performed in primary pediatric lung transplant recipients with donor and/or recipient CMV seropositivity. Intravenous ganciclovir was given for 12 weeks post-transplantation. Subjects were tracked for protocol completion. Toxicities monitored included renal dysfunction, myelosuppression, gastrointestinal and neurological complications, as well as infection related to indwelling catheter placement. Serial CMV levels were measured to determine short-term efficacy of the intervention.

Results— Nine of nine subjects enrolled completed the pilot study. Subjects' ages ranged from 6 to 18 years. Indications for lung transplantation included cystic fibrosis (n=7), idiopathic pulmonary hypertension (n=1), and complex congenital heart disease with pulmonary hypertension (n=1). Seven subjects underwent deceased donor bilateral lung transplantation and two subjects underwent heart-lung transplantation. No subjects had protocol defined drug toxicity. No episodes of neutropenia, thrombocytopenia, or renal toxicity occurred. Five subjects had catheter-related infections (three after week 12 of ganciclovir). Seven of nine subjects had CMV detected by polymerase chain reaction (PCR) (four prior to ganciclovir completion) with only one subject having a positive viral culture for CMV viremia (prior to ganciclovir completion). No subjects had UL-97 mutation for ganciclovir resistance detected.

Correspondence: Lara A Danziger-Isakov, MD, MPH, Pediatrics/A-120, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, Email: DANZIGL@ccf.org

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Conclusions— The use of prolonged prophylactic administration of ganciclovir for 12 weeks duration is a feasible, safe, and effective treatment to prevent CMV viremia based on viral culture in at risk pediatric lung transplant recipients. Further clinical studies are underway to determine optimal CMV prevention strategies.

Keywords

Lung transplantation; Cytomegalovirus (CMV); Pediatrics; Viremia; Ganciclovir

INTRODUCTION

Lung transplantation has become an important treatment option for pediatric patients with end-stage lung disease. Based on studies of adult and pediatric patients, infectious etiologies cause substantial morbidity and mortality in lung transplantation. Prior to the introduction of prophylaxis for CMV, viremia developed in 60–98% of lung transplant recipients with over 50% developing CMV disease (1–4). In attempt to diminish infectious complications, many transplant centers have focused upon prophylactic use of antiviral agents at the time of transplantation.

Despite prophylactic regiments, CMV remains a significant infectious risk. In a French pediatric lung transplant cohort, CMV-positive donor organs were associated with a decreased 3-year survival (5). Despite this meaningful association, the investigators did not report the incidence or associated mortality of CMV viremia in these patients. In a review of the course of 194 first-time lung transplant patients at Washington University School of Medicine/St. Louis Children's Hospital (WUSM/SLCH), CMV viremia occurred in 23.1% of patients. Patients receiving donor seropositive organs had the greatest risk of developing subsequent viremia. Moreover, 80% of first positive CMV viral cultures occurred by 120 days after transplant with 69% occurring from the time ganciclovir prophylaxis was discontinued until 120 days. A first episode of CMV viremia was associated with a fourfold increase in the risk of death or retransplantation in the first year after transplantation (6). Based upon these findings, the pediatric transplant team at SLCH/WUSM extended intravenous (IV) ganciclovir prophylaxis from 42 days (6 weeks) to 84 days (12 weeks) in July 2002.

The objectives of this study were to evaluate prolonged IV ganciclovir administration in pediatric lung transplant recipients. We hypothesize that extending the duration of IV ganciclovir prophylaxis from 6 weeks to 12 weeks after pediatric lung transplant is a feasible, safe, and effective intervention for the suppression of CMV viremia in the early post-transplant period.

METHODS

Study Design

Institutional review board approval was obtained at WUSM/SLCH. Informed consent/assent was obtained prior to subject enrollment. The study was an open-label, single-center, single-arm pilot trial. Children and young adults aged 0–21 years old undergoing primary lung transplantation at WUSM/SLCH with either donor or recipient CMV seropositivity as determined Cytomegalovirus IgG ELISA II (Wampole Laboratories, Princeton, NJ) prior to 11/03 or Captia™ CMV IgG assay (Trinity Biotech, Bray Ireland) after 11/03 were eligible. Subjects older than 21 years old, receiving a second transplant, or both donor and recipient seronegative for CMV at time of transplantation were excluded.

Standard Therapy and Procedure

The study followed both the pretransplant and post-transplant protocols for lung transplantation at WUSM/SLCH. Medical histories, medical examinations, and laboratory surveillance studies followed standard care and occurred at additional intervals at the discretion of the attending physician. After transplantation, subjects received daclizumab for one month and triple-drug immunosuppression with cyclosporine, azathiprine, and prednisone. By institutional protocol, indwelling catheters were maintained for a minimum of 3 months to facilitate access for various procedures and laboratory testing unrelated to ganciclovir administration. Initiation of IV ganciclovir started on day of transplantation at a dose of 5 mg/kg/dose every 12 hours for 21 days. Then IV ganciclovir dose was decreased to 5mg/kg/dose every 24 hours to complete 12 full weeks of therapy. Schwartz formula was utilized to calculate glomerular filtration rate and adjust dose accordingly (7–8). Ganciclovir dosing regimen was modified per protocol for laboratory evidence of myelosuppresion or renal dysfunction. Continuation of IV ganciclovir longer than 12 weeks duration was at the discretion of the attending physician. A Data Safety Monitor ensured quality of the clinical trial, safeguarded against protocol violations and adverse events, and approved ongoing amendments to the trial.

Feasibility was assessed by identifying the proportion of subjects enrolled in the study that successfully completed IV ganciclovir prophylaxis during the treatment phase of the study (12 weeks). During IV ganciclovir administration, safety was monitored with weekly patient questionnaires and laboratory surveillance. Toxicities evaluated included episodes of renal toxicity, liver toxicity, myleosupression, and number of catheter-related bacterial infections. Efficacy was assessed by identifying the number of subjects with CMV viremia by viral culture. Further, episodes of quantitative CMV polymerase chain reaction (CMV qPCR) positivity in the study period are reported. CMV qPCR was performed on whole blood using a modification of the assay described by Sanchez et al (9). This assay measures genome copies per milliliter (mL) of whole blood, and has a lower level of detection of 200 copies per mL. Quantitation is accurate for levels above 2000 copies/mL. Specimens with positive results but less than 2000 copies/mL were reported as “positive, unable to quantitate.” Other surrogate markers for efficacy included episodes of CMV pneumonitis, development of ganciclovir resistance, episodes of acute rejection, bronchiolitis obliterans syndrome (BOS), posttransplant lymphoproliferative disease (PTLD), and death or retransplantation. Viral blood cultures and CMV qPCR were obtained once every other week while receiving IV ganciclovir (first 12 weeks after transplant), once a week for 6 weeks after prophylaxis was discontinuation (weeks 13–18), and then once a month for the remaining year (weeks 19–52) or until death or retransplantation. Additional CMV cultures and CMV qPCR were performed at the discretion of the attending physician. If duration of IV ganciclovir was extended beyond 12 weeks duration serial CMV laboratory studies were maintained at every two week intervals as described. Once IV ganciclovir discontinued, weekly laboratory CMV evaluations were obtained for 6 consecutive weeks followed by once a monthly evaluations until completion of study. Transbronchial biopsies were obtained routinely at 1 week, 1 month, 2 month, 3 month, 6 month, 9 month, and 12 month post transplant. Additional biopsies or an open lung biopsy were obtained at the discretion of the attending physician. Specific staining for CMV was performed on transbronchial and open lung biopsies. Ganciclovir resistance by testing for mutation in the CMV UL97 gene was performed on the first positive CMV qPCR, with two consecutive positive CMV qPCR, or at the discretion of the attending physician.

Definitions

CMV viremia was defined as a positive viral culture from blood for CMV. A positive *CMV qPCR* was any number of CMV copies/mL > 200 copies/mL (9). *CMV pneumonitis* was defined as detection of CMV inclusion bodies or immunoperoxidase staining, detected on lung tissue obtained from a transbronchial biopsy or an open lung biopsy. *Neutropenia* was defined as an

absolute neutrophil count (ANC) < 500/mm^3. *Thrombocytopenia* was defined as a platelet count < 50K/mm^3. *Renal toxicity* was defined as tripling of the creatinine level persisting for more than two weeks or significant change in creatinine clearance requiring adjustment in the dosing regimen of ganciclovir. *Bronchiolitis obliterans syndrome* (BOS) was defined as end-stage, chronic rejection of the lung allograft based upon pathology of open lung biopsy, or pulmonary function testing with standardization of forced expiratory volume $(FEV)_1$ as outlined by the International Society for Heart and Lung Transplantation (ISHLT) (10). *Acute rejection* (AR) was evaluated by pathology and was graded according to the ISHLT scale range of A0–A4 (vessels) and B0–B4 (airways) (11). *Post transplant lymphoproliferative disorder (PTLD)* was defined as a morphologically diverse B-cell lymphoidal tumor diagnosed by pathology.

Statistical Analysis

All data were entered into a database. Data were analyzed using SPSS 11.0 (Statistical Package for the Social Sciences, Chicago, IL). Spearman two-tailed correlation was used to determine if CMV viremia was associated with the diagnosis of BOS or episodes of acute rejection.

RESULTS

Patient Demographics

From February 2003 to November 2003 nine subjects with CMV seropositive status (D+/R+, D+/R−, D−/R+) undergoing first time lung transplantation were enrolled in the trial. Two subjects were male. Subjects' ages ranged from 6–18 years old. All subjects were Caucasian, non-Hispanic. All nine received deceased donor organs; seven received bilateral lung transplantation and two received heart-lung transplantation. Indications for lung transplantation include cystic fibrosis (n=7), idiopathic pulmonary hypertension (n=1), and complex congenital heart disease with pulmonary hypertension (n=1). Seven out of nine subjects survived for one year post-transplantation while two subjects received retransplantation for BOS at 10 months and 9 months, respectively. Table I displays demographic data with duration of IV ganciclovir therapy in the cohort.

Feasibility of administration of IV ganciclovir

A total of seventeen pediatric lung transplants were performed at WUSM/SLCH from 2/03 to 11/03. Of those seventeen patients, nine subjects met inclusion criteria and agreed to participate in the current study. Of the remaining eight patients, three declined study participation, three patients were CMV donor and recipient seronegative, and two patients received a second transplant. All nine subjects who agreed to participate completed the study protocol of IV ganciclovir for 12 weeks duration. No subjects required termination of IV therapy or change in dosage for first 12 weeks of IV administration. No protocol violations or home health incident reports were noted during in the administration of IV ganciclovir. Moreover, many subjects in the cohort were treated beyond 12 weeks of IV ganciclovir with a range of 92–303 days (12 weeks to 44 weeks).

Safety of extending administration of IV ganciclovir to 12 weeks

No subject had protocol defined drug toxicity during the 12 week study period. No episodes of protocol defined myleosuppression (neutropenia or thrombocytopenia) or renal toxicity were recorded. ANC ranged from 1,040–20,560/mm^3 while platelet count ranged from 91–775/mm^3 during the 12 week administration of IV ganciclovir, Table II. No subject required discontinuation of drug or dose alteration of IV ganciclovir based on toxicities or intolerable side effects. Only minimal toxicities were reported even with extended duration of IV ganciclovir beyond the 12 week study period. Hematologic and renal toxicity based upon NCI

toxicity criteria (Version 2) throughout the subject's first year of transplant or until retransplantation were minimal, Table III. Upon subject questionnaire, minimal to no side effects were noted during the 12 week study period. Most common side effects noted over a total of 108 patient questionnaires were gastrointestinal: nausea, vomiting, diarrhea, and anorexia. Neurological side effects were rare except for headache, Table IV.

Five subjects had a catheter-related infection with three occurring after the 12 weeks of ganciclovir. Of the two subjects who had a line infection during therapy, one subject had a port infection at 3 weeks post-transplantation (*Bacillus cereus*) and was empirically treated with IV gentamicin and vancomycin and line removal. A second subject had *Pseudomonas aeruginosa* from an indwelling tunneled central catheter exit site without bactremia at 11 weeks post-transplantation. This subject was treated with IV tobramycin and ceftazadime which cleared the superficial infection without central catheter removal. The remaining three subjects with line-related infections occurred after 12 weeks post-transplantation. Two of three subjects were not receiving IV ganciclovir therapy at the time of their line-related infection, and the subject receiving IV ganciclovir developed a line-related infection with methicillin-resistant *Staphylococcus aureus* after surgical manipulation of the indwelling catheter. Decision to maintain IV access with an indwelling tunneled central catheter or a port was at the discretion of the primary attending physician and not solely based upon IV ganciclovir administration.

Effect of extending IV ganciclovir to 12 weeks on CMV viremia

Only one subject (11%) had a positive viral culture for CMV occurring on day 84 while concurrently on IV ganciclovir therapy. A detectable CMV qPCR was common in our cohort with seven of nine subjects having a positive CMV qPCR detected during their first year post-transplant. Mean time to detectable CMV qPCR was 80.6 days with a range of 28 to 127 days. Six of seven detectable CMV qPCR for CMV were noted while subject was on IV ganciclovir therapy. Initial level of detection within the subjects ranged from 200–2000 copies/mL (lowest level of detection in 4 of 7 patients) to 33,580 copies/mL. Only one subject was symptomatic with cough at the time of first positive CMV qPCR. Events preceding positive testing included intensified immunosuppression in two subjects and bacterial pneumonia in another subject. Response to positive CMV qPCR included increased dose of ganciclovir in one case, extension of IV ganciclovir in three cases, and reinstitution of ganciclovir therapy in two cases. Overall CMV qPCR throughout the first post-transplantation year ranged from 200–2000 copies/mL to 55,240 copies/mL (Table V). Further, no subject had a UL-97 mutation for ganciclovir resistance detected.

Low Frequency of CMV pneumonitis or other CMV associated complication

Extending IV ganciclovir resulted in a low incidence of CMV pneumonitis or other CMV associated complications. No subjects had CMV pneumonitis based on protocol defined criteria. Four of nine subjects had a positive CMV culture from BAL fluid; however no CMV inclusion bodies or immunoperoxidase staining for CMV was detected on lung tissue obtained from transbronchial biopsy or open lung biopsy. No episodes of PTLD were diagnosed within the cohort. CMV viremia was not associated with BOS (Spearman correlation coefficient = −0.250; p=0.516). Three subjects had BOS diagnosed within the first year at 10 weeks, 18 weeks, and 28 weeks from time of transplantation. No subject with BOS had an episode of CMV viremia. No association between CMV viremia and episodes of acute rejection were detected (Spearman correlation coefficient =−0.427; p=0.252). Episodes of acute rejection (Grade A2 or higher) were common in the cohort with a range of 0 to 4 episodes per subject in the study period. Total of 16 episodes of acute rejection (Grade A2 or higher) was noted in the entire cohort or 5.12 episodes of rejection per 1,000 patient days. The one subject with CMV viremia had four episodes of A2 rejection in the first year post-transplantation or an incidence of 10.9 episodes of rejection per 1,000 patient years. Of the six subjects without

CMV viremia but a detectable CMV qPCR three of them had at least 2 episodes of A2 rejection acute rejection in the first post-transplantation year or an incidence of 4.77 episodes of rejection per 1,000 patient years. The two subjects without detectable CMV qPCR each had one episode of acute rejection graded A2 and A3 respectively and an incidence of 3 episodes of rejection per 1,000 patient years (Table V).

DISCUSSION

CMV is a preventable infection in pediatric lung transplant recipients. Despite its associated morbidity and mortality, there is no standard care across transplant centers for specific type of therapy, route of administration, or overall duration of treatment for effective CMV prevention (12). Previously, in at risk subjects, we reported a high incidence of CMV viremia (32%) and CMV pneumonitis (20%) in the first post-transplantation year, often shortly after discontinuation of IV ganciclovir prophylaxis (6). Based upon this information, our program changed the institutional protocol for CMV prevention extending IV ganciclovir from 6 weeks to 12 weeks duration for patients with known CMV seropositivity. In this current study, we have found that this strategy is feasible, safe, and effective for the suppression of CMV viremia and CMV pneumonitis.

In our cohort, no subject had protocol defined toxicity, although NCI grades 0–III toxicities occurred. Toxicities based on NCI criteria did not vary during time periods of ganciclovir administration and discontinuation. No episodes of myleosuppression, renal toxicity, or untoward side-effect requiring early discontinuation or dose modification of IV ganciclovir occurred. No subject had a UL-97 mutation for ganciclovir resistance detected. Catheter-related bacterial infections did occur in our cohort with 2 cases noted within 12 weeks of lung transplantation and overall infectious rate of 2.6 episodes per 1000 catheter days similar to previous findings observations at this institution indicating that extending the length of ganciclovir prophylaxis did not influence the infection rate (13). Extending IV ganciclovir beyond 12 weeks post-transplant was performed for continued prophylaxis against CMV based upon a positive CMV qPCR detected prior to 12 weeks of therapy or at the discretion of the treating attending physician. No specific dosing regimen was used for continued prophylaxis. Ganciclovir was extended for repeated episodes of acute rejection and/or augmented immunosuppression. Furthermore, as CMV qPCR was a newer detection method in this population at our center in 2003, the clinical significance of low copy detection was uncertain and prompted some physicians to continue ganciclovir.

Extending IV ganciclovir from 6 weeks to 12 weeks may be effective in the suppression of episodes of CMV viremia and CMV pneumonitis in our pediatric lung transplant recipients. Comparing our pilot study (n=9 subjects, receiving 12 weeks IV ganciclovir) versus our previously reported 10-year review study (n=128 CMV seropositive subjects, receiving 6 weeks IV ganciclovir), incidence of CMV viremia decreased from 32% to 11% and CMV pneumonitis decreased from 20% to 0%. A strength of our findings is the comparisons of at risk patients with documented CMV seropositivity (CMV status either D+/R−, D−/R+, or D+/R+ status) matched according to type of solid-organ transplant (lung) at a single institution (WUSM/SLCH). Extrapolation inference regarding the short term efficacy of IV ganciclovir to at least 12 weeks duration must be interpreted cautiously as efficacy was a secondary endpoint. A larger, multi-center study is required to assess the long-term efficacy, if any is associated with extended CMV prophylaxis.

As with any study, limitations exist within our study design. Several protocol violations occurred with the delay of home collection for laboratory surveillance screening. Each isolated event was noted in the chart and in most cases appropriate delinquent laboratory studies were obtained quickly within the following week. A second limitation involves decreased viability

of CMV viral blood culture with mailing of blood specimens to our clinical microbiology laboratory after the subject has returned home. However, only one patient was identified with CMV viremia. Our historical comparisons group also provided mailed specimens. CMV qPCR is documented to be more sensitive than viral culture and the majority of documented CMV qPCR with 4 of 7 subjects were at the lowest detectable range of 200–2000 copies/mL (14, 15). Another limitation was the use of ganciclovir beyond the 12 week period, which may influence the presence of CMV detected by viral culture or CMV qPCR. However, use of more than 12 weeks of IV ganciclovir highlights the ability of patients and families to complete prophylactic therapy (feasibility). As demonstrated in Table III, use of more than 12 weeks of ganciclovir was not associated with an increase in side effects measured during the trial (safety).

The current study has shown extending IV ganciclovir to at least 12 weeks after pediatric lung transplantation in the population evaluated appears to be a feasible and safe treatment for the prevention of CMV acquisition. Extending IV ganciclovir duration may be effective by reducing the number of episodes of CMV viremia and CMV pneumonitis in patients at risk with known CMV seropositivity status at transplant. The use of newer therapeutics, including the orally available valine ester of ganciclovir, valganciclovir, may provide alternatives to prolonged intravenous therapy in this population (16). Evaluation of pharmacokinetics in pediatric patients and availability of oral valganciclovir suspension are needed. Further clinical studies are underway to fully assess the effectiveness of CMV prevention strategies to optimize treatment in pediatric lung transplant recipients.

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Table I

Demographics and Duration of IV Ganciclovir Therapy in Nine Pediatric Lung Transplant Recipients

Patient	Age (years)	Gender	CMV Status	Medical Indication	Duration of IV Ganciclovir (days)
1	12	F	D+ / R−	CF	303 days
2	6	F	D+ / R−	CF	125 days
3	14	F	D+ / R+	CF	283 days
4	18	F	D+ / R−	CF	136 days
5	11	F	D+ / R+	IPH	94 days
6	11	F	D+ / R−	CF	255 days
7	10	M	D+ / R−	CF	92 days
8	14	F	D− / R+	CHD/PHT	98 days
9	16	M	D+ / R−	CF	94 days

D=Donor

R=Recipient

CF=Cystic Fibrosis

IPH=Idiopathic Pulmonary Hypertension

CHD/PHT=Congenital Heart Disease & Pulmonary Hypertension

Table II

Safety Data during IV Ganciclovir study duration (12 weeks) in Nine Pediatric Lung transplant Recipients

Patient	Range of ANC (in thousands)	Range of Platelets (in thousands)	Number and timing of catheter-related infections (post-transplant)
1	1.70–12.73	91–493	0
2	1.04–11.23	150–413	0
3	2.34–17.76	236–403	1 (6–12 weeks)
4	2.00–3.40	139–302	1 (> 12 weeks)
5	3.74–20.56	238–503	0
6	2.50–12.40	131–550	0
7	1.48–5.48	99–228	1 (< 6 weeks)
8	5.10–16.63	221–473	1 (> 12 weeks)
9	1.30–12.20	193–775	2 (> 12 weeks)

ANC=Absolute Neutrophil Count

Table III

Safety Data. NCI Grading Score for Each Distinct Time Period One Year After Pediatric Lung Transplantation.

	NCI Grading*				
Time period of Ganciclovir given:	**0–I**		**II–III**		**IV**
Transplant to 12 weeks:					
Neutropenia	8/9		1/9		0
Anemia (Hemoglobin)	4/9		5/9		0
Thrombocytopenia	9/9		0		0
Creatinine	3/9		6/9		0
12 weeks to IV Ganciclovir discontinued (patient specific):					
Neutropenia	8/9		1/9		0
Anemia (Hemoglobin)	6/9		3/9		0
Thrombocytopenia	9/9		0		0
Creatinine	4/9		5/9		0
Time from IV Ganciclovir therapy discontinuation to study completion:					
Neutropenia	8/9		1/9		0
Anemia (Hemoglobin)	7/9		2/9		0
Thrombocytopenia	9/9		0		0
Creatinine	2/9		6/9		1/9
***NCI Grading**					
Adverse Event	**0**	**I**	**II**	**III**	**IV**
Neutropenia	WNL	≥1500–<2000/mm^3	≥1000–<1500/mm^3	≥500–<1000/mm^3	<500/mm^3
Anemia (Hb)	WNL	LLN- 10 g/dL	8–10 g/dL	6.5–8 g/dL	<6.5 g/dL
Thrombocytopenia	WNL	<LLN -75,000/mm^3	≥50,000–<75,000/mm^3	≥10,000–<50,000/mm^3	<10,000mm^3
Creatinine	WNL	>ULN-1.5 × ULN	≥ 1.5–3 × ULN	≥ 3–6 × ULN	≥ 6 × ULN

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Table IV

Safety Data. Ganciclovir Side Effect Profile and Complications Noted on Study Questionnaire for Nine Subjects During 12 Week Study Period

	Number of Patients with a Side Effect Noted During the 12 Week Study Period	Total Number of Episodes Noted in 108 Patient Questionnaire during 12 Week Study Period
Nausea	6 (67%)	28 (26%)
Emesis	7 (78%)	15 (14%)
Diarrhea	5 (56%)	13 (12%)
Anorexia	5 (56%)	13 (12%)
Fever > 38°C	4 (44%)	6 (6%)
Headache	6 (67%)	13 (12%)
Confusion	1 (11%)	1 (<1%)
Walking Erratically	1 (11%)	1 (<1%)
Swelling Around Catheter	2 (22%)	3 (3%)
Redness Around Catheter	2 (22%)	3 (3%)
Drainage From Catheter	1 (11%)	1 (<1%)

Nine subjects were asked if any of the following side effects were noted within the past seven days Data collected during study period (12 weeks of IV Ganciclovir)

Table V

Short-term Efficacy Data During the First Post-transplant Year in Nine Pediatric Lung transplant Recipients

Patient	CMV Status	Duration of Ganciclovir (days)	Timing to 1st + CMV qPCR and level in copies/mL	Timing to and Highest level CMV qPCR in copies/mL	Timing to 1st + BAL	Timing to 1st + Viral Culture in blood	+ CMV in lung tissue	# Hosp Admits	# AR Stage ≥ A2	BOS and time from transplant
1	D+ / R−	303	77 days / 1,743	114 days / 3,808	84 days	84 days	0	5	4	N
2	D+ / R−	125	28 days / 200–2,000	28 days / 200–2000	292 days	N/A	0	3	4	N
3	D+ / R+	283	83 days / 200–2,000	182 days / 20,640	N/A	N/A	0	2	2	N
4	D+ / R−	136	86 days / 33,580	86 days / 33,580	181 days	N/A	0	2	0	N
5	D+ / R+	94	108 days / 6,396	115 days / 13,142	N/A	N/A	0	0	0	N
6	D+ / R−	255	55 days / 200–2,000	84 days / 55,240	N/A	N/A	0	6	0	Y (10 weeks)
7	D+ / R−	92	N/A	N/A	N/A	N/A	0	2	1	N
8	D− / R+	98	127 days / 200–2,000	280 days / 11,778	286 days	N/A	0	9	4	Y (28 weeks)
9	D+ / R−	94	N/A	N/A	N/A	N/A	0	6	1	Y (18 weeks)

BAL=Bronchial alveolar lavage

AR=Acute Rejection

BOS=Bronchiolitis Obliterans Syndrome

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