Poster 1654

Correlation between Cytomegalovirus Breakthrough Disease in High Risk Solid Organ Transplant Recipients and Valganciclovir Dose Modification

Juan Lemos-Ramirez, MD, Odaliz Abreu Lanfranco, MD, Mayur Ramesh, MD, Jonathan Williams, MD, Ramon Del Busto, MD, Pallavi Bhargava, MD, Eloy Ordaya, MD, George Alangaden, MD

Contact: Juan Lemos, MD
Address: 2799 West Grand Blvd.
Detroit, MI – USA
Phone: 313-916-2556
Fax: 313-916-2993
Email: Juan.lemos1222@gmail.com

Abstract

Background: CMV disease in solid organ transplant (SOT) recipients remains an independent risk factor that adversely affects morbidity, mortality, graft function and graft survival. For SOT recipients with CMV seropositive donor status (D+)/recipient negative (R-) or (D±/R+) universal prophylaxis with valganciclvoir (VGCV) is commonly used to prevent CMV disease. However breakthrough and late-onset CMV disease remains a challenge.
Methods: We performed a retrospective study of all SOT recipients at our center from January 2013 to December 2015. VGCV 900 mg daily was used as prophylaxis for a period of 12 months for lung transplants and 6 months for all other SOTs. Primary endpoint was to identify a correlation between CMV breakthrough and VGCV dose modification due to leukopenia and renal function. Secondary endpoints was identification of independent risk factors for CMV breakthrough. Patients with late-onset CMV disease after discontinuation of VGCV were excluded.
Results: Of the 723 SOT recipients during the study period we identified 364 patients: 143 high risk patients (D+/R-) and 221 patients moderate risk (D±/R+). Breakthrough CMV disease occurred in 20 cases. Dose adjustment of VGCV prior to breakthrough was done in 17/20 (85%) of cases. Independent risk factors in patients with breakthrough CMV disease vs. no CMV disease were: (D+/R-) status 15 vs 5 (p <0.001) and steroid use (p=0.02). Mean time to CMV breakthrough disease was 139 days ± 80d Rates of rejection was comparable in both groups.
Conclusions: CMV breakthrough while on VGCV prophylaxis is uncommon in SOT recipients. Dose modification of VGCV preceded breakthrough disease in 85% of cases. CMV (D+/R-) mismatch and steroids use was associated with CMV disease. Careful and frequent monitoring of patients for CMV disease should be conducted whenever dose modification of VGCV is done.

Introduction

- CMV disease in SOT recipients remains an independent risk factor that adversely affects morbidity and graft function.
- Universal prophylaxis with valganciclvoir (VGCV) is commonly used prevent CMV disease in CMV D+/R- and D±/R+ patients.
- However breakthrough and late-onset CMV disease remains a challenge.

Methods

We performed a retrospective study of all SOT recipients at our center from January 2013 to December 2015. VGCV 900 mg daily was used as prophylaxis for a period of 12 months for lung transplants and 6 months for all other SOT. Primary endpoint was to identify a correlation between CMV breakthrough and VGCV dose modification due to leukopenia and renal function. Secondary endpoints was identification of independent risk factors for CMV breakthrough. Patients with late-onset CMV disease after discontinuation of VGCV were excluded.

Results

- 723 SOTs were performed during the study period.
- Breakthrough viremia occurred in:
  - D+/R-: 10.4% (15/144)
  - D+/R+: 2.3% (5/210)
  - D-/R+: 0% (0/161)
- Dose adjustment of VGCV was done in 12/15 (80%) prior to breakthrough.
- Independent risk factors for breakthrough:
  -D+/R- status P<0.001 and corticosteroid use p=0.02.
- Mean time to CMV breakthrough disease was 139 days ± 80 days.
- Rates of rejection were comparable in both groups.

Figure 1: Distribution of patients by SOT type, CMV serostatus and breakthrough CMV disease

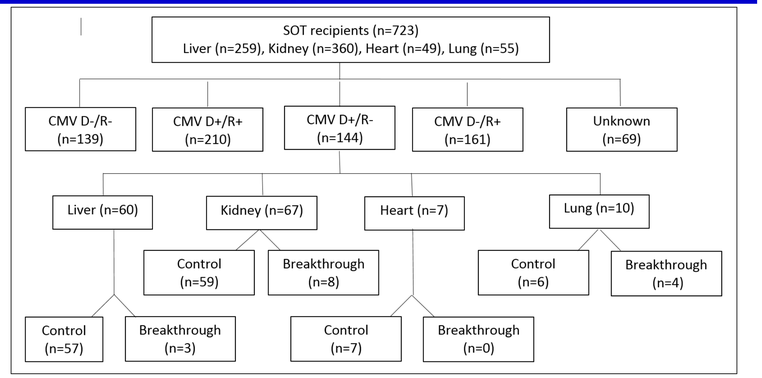

Table 1. Institutional VGCV renal dosing for CMV D+/R- SOT recipients

Estimated CrCl (Cockcroft-Gault) mL/min	VGCV dose (prophylaxis)
CrCl > 60 mL/min	900 mg daily
CrCl 59 – 40 mL/min	450 mg daily
CrCl 39 – 25 mL/min	450 mg every other day
CrCl <25 mL/min	450 mg twice weekly

Table 2: Characteristics of SOT recipients with high risk CMV status (D+/R-)

	Liver	Kidney	Heart	Lung
No. of Transplant	60	67	7	10
Female gender	20 (33%)	25 (37%)	2 (28.5%)	2 (20%)
Age (median)	60	54	59	62.5
Immunosuppression				
Tacrolimus	51(85%)	62 (92.5%)	7 (100%)	10 (100%)
Cyclosporine	8 (13%)	2 (2.9%)	0	0
Mycophenolate mofetil	37 (61.7%)	53 (79%)	5 (71.4%)	8 (80%)
Everolimus (mTOR)	10 (16.7%)	3 (4.5%)	0	0
Prednisone	17 (28.3%)	58 (86.5%)	2 (28.5%)	9 (90%)
Comorbidities				
Diabetes Mellitus	30 (50%)	38 (63.3%)	6 (85%)	4 (40%)
Malignancy	24 (40%)	6 (89%)	1 (14%)	1 (10%)
Heart Disease	12 (20%)	15 (22%)	7 (100%)	2 (20%)
Kidney Disease	36 (60%)	67 (100%)	5 (71.4%)	7 (70%)
Liver Disease	60 (100%)	7 (10.4%	2 (28.5%)	0
Lung Disease	9 (15%)	9 (13%)	1 (16.7%)	10 (100%)
Charlson Comorbidity Index score (median)	9	6	8	7

Table 3: Breakthrough CMV viremia by organ type in CMV D+/R- SOT recipients

Organ Transplanted	No. of patients	Breakthrough
Liver	60	3 (5%)
Kidney	67	8 (11.9%)
Heart	7	0
Lung	10	4 (40%)

Table 4: Characteristics of D+/R- patients with breakthrough CMV disease

	Control Group	Breakthrough Group
No. SOT	129	15
Liver	57	3
Kidney	59	8
Heart	7	0
Lung	6	4
Immunosuppression		
Tacrolimus	116 (90%)	14 (93%)
Cyclosporine	9 (6.9%)	1 (6.7%)
Mycophenolate mofetil	93 (72%)	10 (66.7%)
mTORs	13 (10%)	0
Prednisone	73 (56.5%)	13 (86.7%)
CMV Invasive Disease	0	1 (6.7%) (Colitis)
VGCV prophylaxis change in dose or early discontinuation	5 (3.8%)	12 (80%)

Table 5: Reasons for VGCV dose modification or early discontinuation CMV D+/R- SOT recipients

	Control Group (n=129)	Breakthrough Group (n=15)
Universal VGCV Prophylaxis		
Change in dose	2 (1.6%)	6 (40%)
Early discontinuation *	5 (3.9%)	6 (40%)
Reason for change in dosing		
Leukopenia	4 (3.1%)	8 (53.3%)
Acute Kidney Injury	2 (1.6%)	3 (20%)
GI intolerance	0	3 (20%)
Graft Rejection	0	1 (6.7%)
Organ Transplanted		
Liver	5 (3.9%)	3 (20%)
Kidney	0	8 (53%)
Heart	0	0
Lung	0	4 (26.7%)

* VGCV discontinued before the recommended time for universal prophylaxis in high risk recipients (D+/R-)

Table 6: Characteristics of patients with breakthrough CMV disease

Organ type	Days to breakthrough post-SOT	VGCV dosing modification*	Reason for dose modification
Kidney	189	Discontinued	Leukopenia
Kidney	114	450 mg QOD	Leukopenia
Kidney	76	450 mg QOD	Increase in serum creatinine
Kidney	58	450 mg QOD	Leukopenia
Kidney	58	450 mg QOD	Leukopenia
Kidney	200	Discontinued	Leukopenia
Kidney	137	Discontinued	Leukopenia
Kidney	146	No change*	Diarrhea
Liver	58	No change*	Diarrhea and vomiting
Liver	200	Discontinued	Leukopenia
Liver	59	Discontinued	Leukopenia
Lung	298	No change*	A1 rejection**
Lung	149	450 mg QD	Increase in serum creatinine
Lung	62	Discontinued	Vomiting
Lung	302	450 mg three times weekly	Increase in serum creatinine

*QOD = every other day; QD = every day; No change = dose remained at 900 mg every day. **received high dose steroids for rejection

Conclusion

- CMV breakthrough while on VGCV prophylaxis is uncommon in SOT recipients.
- Dose modification of VGCV preceded breakthrough disease in 85% of cases.
- CMV (D+/R-) mismatch and steroids use was associated with CMV disease.
- Careful and frequent monitoring of patients for CMV disease should be conducted whenever dose modification of VGCV is done.