Neutropenia and associated infectious complications among kidney transplant recipients receiving valganciclovir prophylaxis in United States: An administrative claims database study

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Introduction

- In the United States, over half of the population has been infected with cytomegalovirus (CMV)
- CMV remains in the body after infection and can be reactivated during an immunosuppressed state
- Valganciclovir (VGCV) prophylaxis is commonly utilized to prevent CMV infection among high-risk (transplant donor CMV-positive and recipient CMV-negative) and intermediate-risk (transplant recipient CMV-positive) kidney transplant recipients (KTR)
- VGCV is associated with myelosuppressive events but the characterization and clinical outcomes have not been adequately captured

Objective

- To quantify the clinical burden of neutropenia and leukopenia among adult KTRs receiving VGCV prophylaxis

Methods

- Study design: Retrospective cohort of adults undergoing kidney transplants (KT) between 2012 and 2018 (**Figure 1**)
- Data source: IBM MarketScan Research – HIPAA-compliant de-identified data of Commercial and Medicare Advantage plan enrollees – a medical and drug insurance claims database of approximately 220 million (since 1995)
- The database includes inpatient, outpatient, facility, and pharmacy claims from private-sector health data from approximately 350 payers across the United States
- Inclusion/exclusion criteria:
  - Age ≥18 years on the index date
  - At least one procedure claim of KT during the patient identification period. The earliest date of KT will be assigned as an index date
  - At least 1 year of continuous pharmacy and medical coverage before (baseline period) and after (follow-up period) index date
  - No history of other solid organ transplantation prior to index
  - Filled ≥1 prescription of VGCV 450 mg or 900 mg per day within 30 days of the index date
- Exposure:
  - Presence of neutropenia: ≥1 inpatient or ≥2 outpatient claims within 14 days of each other with ICD-9 [288.0x] or ICD-10 [D70.x] diagnosis codes
  - Presence of leukopenia: ≥1 inpatient or ≥2 outpatient claims within 14 days of each other with ICD-9 [288.5x] or ICD-10 [D72.81x] diagnosis codes
- Outcomes
  - All outcomes were assessed within the 1-year follow-up period after the kidney transplant index event
  - Opportunistic infection: Identified as either CMV, bacterial, fungal, or other non-CMV viral infections
    - CMV infection – ICD-9: 078.5x codes. ICD-10: B25.x, B27.1x, H32.00, K87.00, K93.820
    - Bacterial infection: ICD-9 and ICD-10 codes for septicemia, pneumocystis pneumonia, tuberculosis, or other bacterial infections
    - Invasive fungal disease: Including candidiasis, coccidioidomycosis, blastomycosis, aspergillosis, cryptococcosis, histoplasmosis, zygomycosis, and other mycoses
    - Other non-CMV viral infections: Including adenovirus, BK virus, herpes simplex virus, human herpes-6 virus, Epstein-Barr virus, *Varicella zoster* virus, and other unspecified viral infections
  - Graft failure was assessed for patients with ICD-10 coding and was identified from any of the following three conditions: 1) T86.12 kidney transplant failure ICD-10 code, 2) dialysis treatment more than 35 days after the transplant, 3) a kidney transplant procedure code occurring more than 35 days after the transplant. Return to dialysis and re-transplant were also assessed independently for the full study period
  - New-onset diabetes: Patients with diabetes codes in the follow-up period who had no pre-existing diabetes in the baseline period
  - Dialysis: Identified with CPT procedure codes, ICD-10-PCS procedure codes, and claims service category codes
  - All-cause Mortality was identified with a death discharge status from the database. This death indicator became unavailable after Dec 31st 2015 in the Marketscan database, therefore only patients with a 1-year follow-up ending in Dec 31st 2015 were considered to have available mortality data. Death discharge statuses for patients who had additional billing claims more than a week afterwards were disregarded
- Statistical analysis
  - Chi-squared *P* values are reported for categorical variables, t-test and ANOVA were used for testing means among variables with Gaussian distribution (eg, age), Wilcoxon rank-sum test was used for comparing non-Gaussian variables, and log-rank test was used for time-to-event variables

References
1. Hurst FP, et al. *Transplantation.* 2011;92(1):36-40.
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Figure 1. Observation period

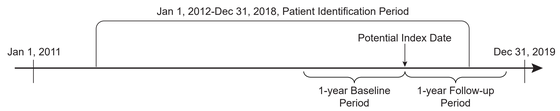

Table 1. Patient selection

Criteria	Subjects Remaining	
	N	%
First KT procedure during the patient identification period	11,900	100
Age at index ≥18 years	11,546	97
1 year of continuous enrollment in medical and pharmacy benefits prior to index date	7656	66.3
1 year of continuous enrollment in medical and pharmacy benefits post-index date (or up to death)	5218	68.2
No prior medical claims with KT or other solid organ transplant[a]	4965	95.2
Received valganciclovir prophylaxis post-transplant	3582	72.1
Valganciclovir prescription dose of 450 mg per day or 900 mg per day within 30 days of index date	3258	91

KT, kidney transplant
[a]Other solid organ transplants include lung, liver, pancreas, bowel.
554 patients have either neutropenia or leukopenia; 97 patients have both neutropenia and leukopenia.

Figure 2. Comparison of cumulative incidence of opportunistic infections between those who do not develop neutropenia and those who develop neutropenia

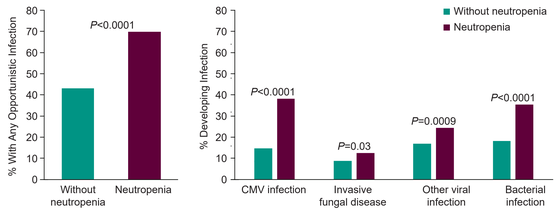

Table 2. Baseline demographic characteristics

Characteristics	Overall N=3258	Neutropenia			Leukopenia		
		With neutropenia N=311	Without neutropenia N=2947	*P* value	With leukopenia N=340	Without leukopenia N=2918	*P* value
Male	1950 (59.9%)	190 (61.1%)	1760 (59.7%)	0.6389	191 (56.2%)	1759 (60.3%)	0.144
Mean age (SD)	52.2 (12.25)	50.9 (12.87)	52.3 (12.18)	0.178	51.9 (12.48)	52.2 (12.23)	0.6065
Age categories				**0.7366**			**0.8746**
18-44	844 (25.9%)	86 (27.7%)	758 (25.7%)		89 (26.2%)	755 (25.9%)	
45-64	1966 (60.3%)	188 (60.5%)	1778 (60.3%)		200 (58.8%)	1766 (60.5%)	
65-74	389 (11.9%)	32 (10.3%)	357 (12.1%)		45 (13.2%)	344 (11.8%)	
75+	59 (1.8%)	5 (1.6%)	54 (1.8%)		6 (1.8%)	53 (1.8%)	
Geographic region				**0.7025**			**0.0459**
Northeast	657 (20.2%)	63 (20.3%)	594 (20.2%)		54 (15.9%)	603 (20.7%)	
North Central	695 (21.3%)	70 (22.5%)	625 (21.2%)		64 (18.8%)	631 (21.6%)	
South	1402 (43.0%)	138 (44.4%)	1264 (42.9%)		169 (49.7%)	1233 (42.3%)	
West	492 (15.1%)	40 (12.9%)	452 (15.3%)		51 (15.0%)	441 (15.1%)	
Unknown	12 (0.4%)	0	12 (0.4%)		2 (0.6%)	10 (0.3%)	
Primary payer type				**0.3006**			**0.8472**
Commercial	2719 (83.5%)	266 (85.5%)	2453 (83.2%)		285 (83.8%)	2434 (83.4%)	
Medicare	539 (16.5%)	45 (14.5%)	494 (16.8%)		55 (16.2%)	484 (16.6%)	

Table 3. Baseline clinical and transplant characteristics

Characteristics	Overall N=3258	Neutropenia			Leukopenia		
		With neutropenia N=311	Without neutropenia N=2947	*P* value	With leukopenia N=340	Without leukopenia N=2918	*P* value
Charlson Comorbidity Index[a]				**0.5501**			**0.2952**
1-2	1000 (30.7%)	99 (31.8%)	901 (30.6%)		101 (29.7%)	899 (30.8%)	
3-4	834 (25.6%)	83 (26.7%)	751 (25.5%)		101 (29.7%)	733 (25.1%)	
≥5	408 (12.5%)	31 (10.0%)	377 (12.8%)		37 (10.9%)	371 (12.7%)	
Comorbidities							
Diabetes with complications	1276 (39.2%)	114 (36.7%)	1162 (39.4%)	0.3405	127 (37.4%)	1149 (39.4%)	0.4695
Diabetes	740 (22.7%)	63 (20.3%)	677 (23.0%)	0.2771	64 (18.8%)	676 (23.2%)	0.0705
Congestive heart disease	550 (16.9%)	51 (16.4%)	499 (16.9%)	0.8736	62 (18.2%)	488 (16.7%)	0.4912
Chronic pulmonary disease	408 (12.5%)	38 (12.2%)	370 (12.6%)	0.9283	52 (15.3%)	356 (12.2%)	0.1186
Mild liver disease	382 (11.7%)	43 (13.8%)	339 (11.5%)	0.2285	46 (13.5%)	336 (11.5%)	0.2849
Cancer	248 (7.6%)	21 (6.8%)	227 (7.7%)	0.6526	21 (6.2%)	227 (7.8%)	0.3313
Rheumatological disease	168 (5.2%)	17 (5.5%)	151 (5.1%)	0.7872	28 (8.2%)	140 (4.8%)	0.0095
Year of transplant				**<0.0001**			**<0.0001**
2012	541 (16.6%)	38 (12.2%)	503 (17.1%)		37 (10.9%)	504 (17.3%)	
2013	456 (14.0%)	25 (8.0%)	431 (14.6%)		33 (9.7%)	423 (14.5%)	
2014	466 (14.3%)	44 (14.1%)	422 (14.3%)		54 (15.9%)	412 (14.1%)	
2015	485 (14.9%)	41 (13.2%)	444 (15.1%)		38 (11.2%)	447 (15.3%)	
2016	440 (13.5%)	64 (20.6%)	376 (12.8%)		57 (16.8%)	383 (13.1%)	
2017	434 (13.3%)	53 (17.0%)	381 (12.9%)		61 (17.9%)	373 (12.8%)	
2018	436 (13.4%)	46 (14.8%)	390 (13.2%)		60 (17.6%)	376 (12.9%)	
Immunosuppressants[b]							
Anti-thymocyte globulin-ATG	101 (3.1%)	15 (4.8%)	86 (2.9%)	0.0653	18 (5.3%)	83 (2.8%)	0.0136
Alemtuzumab	3 (0.1%)	0	3 (0.1%)	1	1 (0.3%)	2 (0.1%)	0.2816
Basiliximab	47 (1.4%)	5 (1.6%)	42 (1.4%)	0.8006	1 (0.3%)	46 (1.6%)	0.0859
Rituximab	23 (0.7%)	6 (1.9%)	17 (0.6%)	0.0179	4 (1.2%)	19 (0.7%)	0.292
Cyclophosphamide	9 (0.3%)	0	9 (0.3%)	1	1 (0.3%)	8 (0.3%)	1
Cyclosporine	104 (3.2%)	10 (3.2%)	94 (3.2%)	0.9804	15 (4.4%)	89 (3.1%)	0.1765
Tacrolimus	2103 (64.5%)	203 (65.3%)	1900 (64.5%)	0.7788	211 (62.1%)	1892 (64.8%)	0.3105
Sirolimus	47 (1.4%)	5 (1.6%)	42 (1.4%)	0.8006	7 (2.1%)	40 (1.4%)	0.331
Everolimus	9 (0.3%)	0	9 (0.3%)	1	5 (1.5%)	4 (0.1%)	0.0011
Azathioprine	54 (1.7%)	5 (1.6%)	49 (1.7%)	0.9424	7 (2.1%)	47 (1.6%)	0.5402
Mycophenolate mofetil	1782 (54.7%)	164 (52.7%)	1618 (54.9%)	0.4646	188 (55.3%)	1594 (54.6%)	0.8149
Methotrexate	4 (0.1%)	0	4 (0.1%)	1	0	4 (0.1%)	1
Leflunomide	5 (0.2%)	0	5 (0.2%)	1	1 (0.3%)	4 (0.1%)	0.4239
Prednisone	2226 (68.3%)	198 (63.7%)	2028 (68.8%)	0.0633	228 (67.1%)	1998 (68.5%)	0.5962
Methylprednisolone	387 (11.9%)	50 (16.1%)	337 (11.4%)	0.0161	52 (15.3%)	335 (11.5%)	0.0397
HMG-CoA reductase inhibitors							
Statins	1652 (50.7%)	157 (50.5%)	1495 (50.7%)	0.9339	166 (48.8%)	1486 (50.9%)	0.4632

[a]Excludes renal disease.
[b]Includes baseline period (1 year prior to transplant), index hospitalization, and up to 14 days post-transplant.

Table 4. Valganciclovir treatment characteristics

Characteristics	Overall N=3258	Neutropenia			Leukopenia		
		With neutropenia N=311	Without neutropenia N=2947	*P* value	With leukopenia N=340	Without leukopenia N=2918	*P* value
Days of continuous VGCV use: mean (SD)	108.6 (70.40)	112.2 (72.91)	108.2 (70.14)	0.342	104.2 (66.97)	109.1 (70.79)	0.186
Duration of VGCV use (categorical)				0.15			0.848
<100 days	1890 (58.0%)	165 (53.1%)	1725 (58.5%)		198 (58.2%)	1692 (58.0%)	
100-199 days	1053 (32.3%)	115 (37.0%)	938 (31.8%)		112 (32.9%)	941 (32.2%)	
200+ days	315 (9.7%)	31 (10.0%)	284 (9.6%)		30 (8.8%)	285 (9.8%)	
Days from index to first VGCV fill: mean (SD)							
450 mg/day	4.9 (6.61)	5.4 (7.43)	4.9 (6.53)	0.704	6.0 (7.57)	4.8 (6.49)	0.01
900 mg/day	4.6 (5.84)	4.4 (5.89)	4.6 (5.83)	0.228	4.5 (4.97)	4.6 (5.95)	0.288
VGCV discontinued (gap ≥15 days)	1176 (36.1%)	161 (51.8%)	1015 (34.4%)	<0.0001	174 (51.2%)	1002 (34.3%)	<0.0001

Table 5. Clinical outcomes at follow-up

Characteristics	Overall N=3258	Neutropenia			Leukopenia		
		With neutropenia N=311	Without neutropenia N=2947	*P* value	With leukopenia N=340	Without leukopenia N=2918	*P* value
Any OI (CMV, viral, fungal, or bacterial)	1491 (45.8%)	217 (69.8%)	1274 (43.2%)	<0.0001	239 (70.3%)	1252 (42.9%)	<0.0001
CMV infection	552 (16.9%)	119 (38.3%)	433 (14.7%)	<0.0001	134 (39.4%)	418 (14.3%)	<0.0001
Other viral infection	574 (17.6%)	76 (24.4%)	498 (16.9%)	0.0009	87 (25.6%)	487 (16.7%)	<0.0001
Invasive fungal disease	299 (9.2%)	39 (12.5%)	260 (8.8%)	0.0308	49 (14.4%)	250 (8.6%)	0.0004
Bacterial infection	647 (19.9%)	110 (35.4%)	537 (18.2%)	<0.0001	113 (33.2%)	534 (18.3%)	<0.0001
Patients with graft failure data[a]	1438 (44.1%)	174 (55.9%)	1264 (42.9%)		190 (55.9%)	1248 (42.8%)	
Graft failure	214 (14.9%)	29 (16.7%)	185 (14.6%)	0.4804	42 (22.1%)	172 (13.8%)	0.0027
Return to dialysis after 35 days	114 (3.5%)	17 (5.5%)	97 (3.3%)	0.0471	18 (5.3%)	96 (3.3%)	0.057
Re-transplant procedure after 35 days	10 (0.3%)	1 (0.3%)	9 (0.3%)	1	0	10 (0.3%)	0.6124
Other autoimmune conditions, including lymphoproliferative syndrome	112 (3.4%)	18 (5.8%)	94 (3.2%)	0.0168	27 (7.9%)	85 (2.9%)	<0.0001
No baseline diabetes	2518 (77.3%)	248 (79.7%)	2270 (77.0%)	0.2771	276 (81.2%)	2242 (76.8%)	0.0705
New onset of diabetes[b]	230 (9.1%)	14 (5.6%)	216 (9.5%)	0.0446	16 (5.8%)	214 (9.5%)	0.0414
Nephrotoxicity	1693 (52.0%)	193 (62.1%)	1500 (50.9%)	0.0002	224 (65.9%)	1469 (50.3%)	<0.0001
Patients with mortality data[c]	1463 (44.9%)	107 (34.4%)	1356 (46.0%)		124 (36.5%)	1339 (45.9%)	
All-cause mortality[c]	2 (0.1%)	1 (0.9%)	1 (0.1%)	0.141	0 (0%)	2 (0.1%)	1

[a]Specific kidney transplant failure codes are available after the transition to the ICD-10 coding system on October 1, 2015.
[b]Percentage among patients with no baseline diabetes.
[c]Patients with mortality data are those with 1 year follow-up ending prior to December 31, 2015.

Results

- Of the 4965 adult KTRs with baseline and follow-up enrollment, 3258 (66%) used VGCV prophylaxis at the 450 mg/day or 900 mg/day dose (**Table 1**)
- 311/3256 (9.5%) developed neutropenia and 340 (10.4%) developed leukopenia within 1 year post-KT
- Baseline demographic characteristics and clinical characteristics were similar between those with and without neutropenia and similarly for leukopenia (**Table 2** and **Table 3**)
- A significant difference in the year of transplant was found between patients with and without neutropenia (*P*<0.0001) as well as with and without leukopenia (*P*<0.0001) (**Table 3**), with later years of transplant showing higher complication rates (**Figure 2**)
- The majority received the following pre-transplant immunosuppression: tacrolimus, mycophenolate mofetil and steroids, prednisone, or methylprednisolone (**Table 3**)
- Interruptions in VGCV prophylaxis (gap between fills >15 days) were more common in KTRs with neutropenia (*P*<0.0001) and leukopenia (*P*<0.0001). The development of leukopenia was also associated with a slightly later initiation of VGCV therapy for those receiving 450mg/day (**Table 4**)
- Patients who developed neutropenia or leukopenia had significantly higher rates of opportunistic infections as compared to those without neutropenia (neutropenia: 69.8% vs 43.2%, *P*<0.0001, leukopenia 70.3% vs 42.9%, *P*<0.0001, **Table 5**)
- The biggest differences in opportunistic infections were observed for CMV infection (38.3% vs 14.7%, *P*<0.0001 for neutropenia, 39.4% vs 14.3%, *P*<0.0001 for leukopenia) and bacterial infection (35.4% vs 18.2%, *P*<0.0001 for neutropenia, 33.2% vs 18.3%). Significantly higher rates of other non-CMV viral infections and invasive fungal infections were also observed in patients with neutropenia (*P*=0.0009 and *P*=0.0308, respectively)
- A return to dialysis after 35 days post transplant was more frequent in those with neutropenia. The same trend was seen in Leukopenia, though it did not reach statistical significance (**Table 5**)

Strengths and Limitations

- As an observational study, it is subject to threats to validity, particularly selection bias. Defining the enrollment criteria prospectively mitigates this bias.
- Our neutropenia/leukopenia definition may only capture the more severe and persistent cases, as reflected through a lower percentage of patients developing neutropenia (9.5%) in our study compared to other studies (11%-37%).[1-4] One reason for this is that we required two outpatient episodes/claims to classify a patient as having neutropenia or leukopenia. Another reason is that many patients with less severe presentations may not have been billed for the condition. Using data with lab values could provide a more accurate incidence.
- Retrospective database studies are dictated by what is billed. Misclassification is of particular concern when using administrative claims data, as coding and management is a moving target. Managing a patient and billing a patient over time, especially in an advancing field differs over time
- However, as a large multicenter geographically representative database, it is only minimally prone to lack of generalizability. This is a large database study, including over 3000 high- and intermediate-risk kidney transplant patients who used VGCV prophylaxis
- All geographic regions of the USA were covered, though there was stronger representation from the South

Conclusions

- Findings from this large-scale commercial and Medicare advantage enrollees database study suggests a strong association of viral, bacterial, and fungal opportunistic infections among valganciclovir-treated kidney transplant recipients with medical billing claims for neutropenia and leukopenia.
- The findings highlight the need for treatment options that reduce the risk of neutropenia and its associated clinical outcomes

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