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Risk Factors for Failure of Primary (Val)ganciclovir Prophylaxis Against Cytomegalovirus (CMV) Infection and Disease in Solid Organ Transplant (SOT) Recipients

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BACKGROUND

- Following solid organ transplantation (SOT), the optimal dose of primary (val)ganciclovir prophylaxis against CMV infection is debated[1]
- Viral breakthrough infection and treatment-limiting side effects are frequently seen[1-3]

AIMS

- To investigate to what extent different dosages of (val)ganciclovir prophylaxis affect the risk of experiencing prophylactic viral breakthrough during active administration of prophylaxis
- To identify reasons and risk factors for premature prophylaxis discontinuation

METHODS

- All SOT recipients ≥18 years of age transplanted (tx) between 2012-2016 at Rigshospitalet, and who were initiated on primary prophylaxis ≤14 days post-tx were followed from this time (baseline) until **90 (±7) days post-tx**
- A prophylaxis score for each patient/day was calculated during the follow-up time (score of 100 corresponding to the manufacturers' recommended dose for a given eGFR) **(Figure 1)**
- Score = actual dose (mg) / optimal dose (mg) adjusted for eGFR x 100
- Prophylaxis breakthrough was defined as PCR verified CMV DNA positivity in plasma or BAL (i.e. infection) and premature stop of prophylaxis as >7 days with a score of 0
- Time to event and hazard ratios (HR) were estimated with Cox models after adjustment for relevant risk factors

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Table 1. Baseline Characteristics of 585 SOT Patients, Stratified For Breakthrough Infections and Prophylaxis Discontinuation

	Characteristic	All recipients	No breakthrough infection	Breakthrough infection	p-value	No stop in prophylaxis	Stop in prophylaxis	p-value
	All	585 (100.0)	544 (93.0)	41 (7.0)		552 (94.4)	33 (5.6)	
Tx type — no. (%)	Heart	51 (8.7)	50 (98.0)	1 (2.0)	0.024	51 (100.0)	0 (0.0)	< 0.001
	Kidney	311 (53.2)	284 (91.3)	27 (8.7)		305 (98.1)	6 (1.9)	
	Liver	117 (20.0)	114 (97.4)	3 (2.6)		113 (96.6)	4 (3.4)	
	Lung	106 (18.1)	96 (90.6)	10 (9.4)		83 (78.3)	23 (21.7)	
Gender — no. (%)	Male	351 (60.0)	324 (92.3)	27 (7.7)	0.424	331 (94.3)	20 (5.7)	0.942
Year tx — no. (%)	2012	130 (22.2)	121 (93.1)	9 (6.9)	0.838	118 (90.8)	12 (9.2)	0.021
	2013	98 (16.8)	92 (93.9)	6 (6.1)		91 (92.9)	7 (7.1)	
	2014	132 (22.6)	125 (94.7)	7 (5.3)		129 (97.7)	3 (2.3)	
	2015	142 (24.3)	130 (91.6)	12 (8.4)		132 (93.0)	10 (7.0)	
	2016	83 (14.2)	76 (91.6)	7 (8.4)		82 (98.8)	1 (1.2)	
D/R status — no. (%)	D-/R+	137 (23.4)	133 (97.1)	4 (2.9)	< 0.001	121 (88.3)	16 (11.7)	0.005
	D+/R+	324 (55.4)	307 (94.8)	17 (5.2)		311 (96.0)	13 (4.0)	
	D+/R-	124 (21.2)	104 (83.9)	20 (16.1)		120 (96.8)	4 (3.2)	
Median Age (IQR)		50.5 (40.9 - 58.9)	50.8 (41.1 - 58.9)	47.8 (36.3 - 59.4)	0.636	50.3 (40.6 - 58.8)	54.4 (46.2 - 59.3)	0.22
Prior transplant — no. (%)		23 (3.9)	23 (4.2)	0 (0.0)	0.065	13 (8 - 80)	86 (45 - 90)	< 0.001
Median Weight (Kg) on Day 1* (IQR)		74 (61 - 85)	74 (61 - 85)	70 (60 - 84)	0.45	74.7 (63.5 - 82.5)	68 (59 - 73)	0.01

*368 out of 585 patients had available weights post-transplant

Figure 1

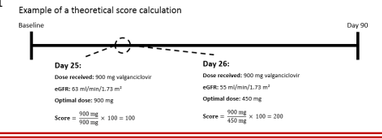
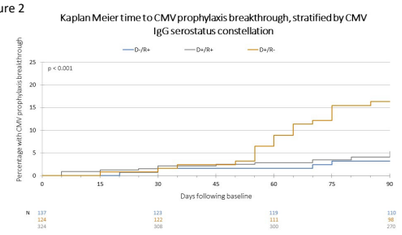


Figure 2



Baseline defined as the first date of starting prophylaxis or day 14 after transplant

Kaplan-Meier curve depicting the time to prophylaxis breakthrough stratified by seroconstellation within the first 90 days post-transplantation. D+/R- SOTs had a significantly higher rate of breakthrough compared to the D-/R+ and D+/R+ SOTs.

Table 2

Reasons for prophylaxis termination by solid-organ transplantation (SOT) type

	SOT				
Reason for termination	Heart	Lung	Kidney	Liver	Total
Liver-related	0	9	1	0	10
Kidney-related	0	3	0	0	3
Liver- and Kidney-related	0	1	0	0	1
Patient- and/or Physician-related[1]	0	5	2	3	10
Subsitute medication received[2]	0	0	0	1	1
Myelosuppression	0	5	1	0	6
Skin irritation	0	0	1	0	1
Faecal issues	0	0	1	0	1
Total	0	23	6	4	33

[1]Misunderstanding or unknown reason for stop
[2]Zelitrex

Figure 3

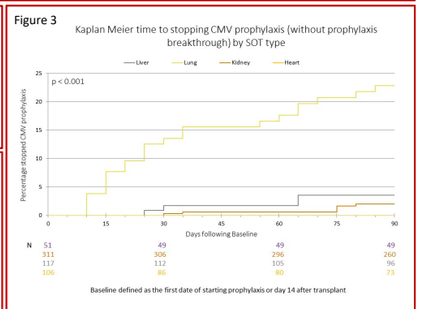


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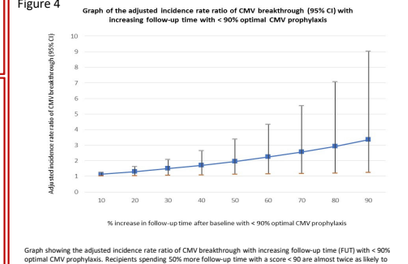
Figure 4



Graph showing the adjusted incidence rate ratio of CMV breakthrough with increasing follow-up time (FUT) with < 90% optimal CMV prophylaxis. Recipients spending 50% more follow-up time with a score < 90 are almost twice as likely to experience prophylaxis breakthrough. A score of 100 is defined as optimal; a score < 90 would thus be sub-optimal.

RESULTS

- Of 585 SOTs (311 kidney, 117 liver, 106 lung, 51 heart) included, 41 (7%, 95% CI 4.9-9.1%) experienced CMV prophylaxis breakthrough **(Figure 2 and Table 1)**, of which 9/41 [22%, 9.2-34.6%] developed viral resistance to (val)ganciclovir
- 33/585 (5.6%, 3.7-7.5%) ceased prophylaxis for other reasons during the first 90 days after tx **(Figure 3)**
- After adjustment for tx type, CMV IgG D+/R- mismatch and increasing % of FUT with a prophylaxis score < 90 were associated with increased risk of breakthrough (HR 4.83 [95% CI 2.39-9.79] p<0.001 and HR 1.14 [1.03 - 1.28] p=0.016/10% longer follow-up time with a score < 90 respectively) **(Figure 4)** whereas tx type was not
- Main risk factor for stopping prophylaxis for reasons other than breakthrough was lung tx (HR 13.11 (versus kidney SOT) [2.47-69.70] p=0.003), mainly due to liver or myelotoxicity **(Table 2)**

CONCLUSIONS

- SOTs receiving (v)gcv primary prophylaxis doses below the manufacturers' recommended doses according to latest eGFR were at an increased risk of CMV prophylaxis breakthrough, particularly in case of CMV IgG D+/R- mismatch
- Lung tx recipients are at a higher risk of premature prophylaxis discontinuation
- Adjusting the administered dosage of prophylaxis according to the current eGFR is important, as well as acknowledging the continued need for newer and less toxic agents against CMV

REFERENCES

1. Kotton CN, Kumar D, Caliendo AM, et al. Updated International Consensus Guidelines on the Management of Cytomegalovirus in Solid-Organ Transplantation. *Transplant J*. 2013;96(4):333-360. doi:10.1097/TP.0b013e31829df29d.
2. Kotton CN. CMV: Prevention, Diagnosis and Therapy. *Am J Transplant*. 2013;13(s3):24-40. doi:10.1111/ajt.12006.
3. Andrews PA, Emery VC, Newstead C. Summary of the British Transplantation Society Guidelines for the Prevention and Management of CMV Disease After Solid Organ Transplantation. *Transplantation*. 2011;92(11):1181-1187. doi:10.1097/TP.0b013e318235c7fc.