Quantiferon®-CMV prior to prophylaxis discontinuation offers no additional predictive utility beyond serostatus-based risk stratification in lung transplant recipients

Bradley J. Gardiner[1], Sue J. Lee[1], Allisa N. Robertson[1], Yvonne Cristiano[2], C. Orla Morrissey[1], Anton Y. Peleg[1,3], Glen P. Westall[2]

[1]Department of Infectious Disease & [2]Respiratory Medicine & Lung Transplantation, Alfred Health & Monash University, Melbourne, Australia. [3]Biomedicine Discovery Institute, Department of Microbiology, Monash University

Introduction

- Cytomegalovirus (CMV) is a significant contributor to morbidity and mortality in lung transplant recipients (LTR)[1,2]
- Predicting who will develop CMV infection remains challenging
- The Quantiferon®-CMV (QF-CMV) assay measures interferon-ɣ release from T-lymphocytes following stimulation with CMV antigens[3,4]
- QF-CMV testing to inform prophylaxis duration was trialed then introduced in our center from 2012[5,6]

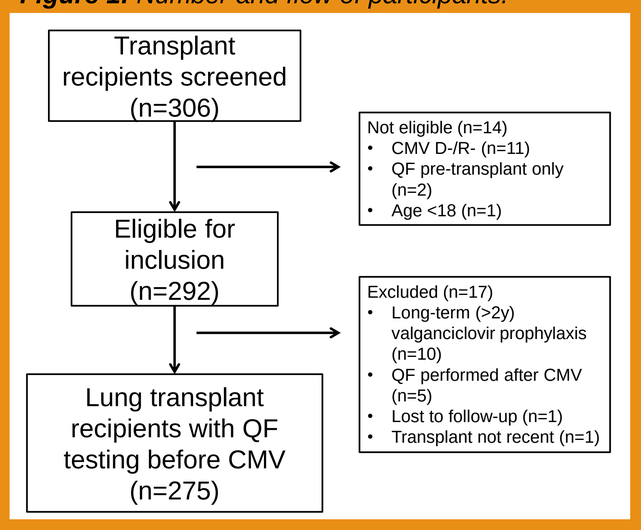
Aims

- Review our experience with QF-CMV testing
- Understand factors associated with the development of a CMV-specific immune response
- Further explore the role of this assay in the prediction of CMV infection

Methods

- Retrospective cohort study, Alfred Health, 2012-2019
- **Inclusion:** LTR at risk of CMV who had QF-CMV testing either as part of an interventional study (n=120), an observational study (n=70) or routine care (n=85)
- **Exclusions:** age <18, valganciclovir prophylaxis >2 years, loss to follow-up before prophylaxis cessation
- **QF-CMV testing:** typically performed at 5 months, with many patients receiving extended prophylaxis based on QF-CMV results
- **Outcomes:** CMV infection in blood and/or bronchoalveolar lavage (BAL) fluid (viral load >150 IU/mL)

Figure 1: *Number and flow of participants.*



Results

- 275 LTR were included; median age 59, 57% male, 43% basiliximab induction *(Figure 1)*
- 62 (23%) D+/R-, 124 (45%) D+/R+, 89 (32%) D-/R+
- 939 tests performed: 72 pre-transplant, 550 during primary prophylaxis, 151 after prophylaxis but before CMV infection, & 161 after CMV
- QF-CMV results available around 5 months in 262 patients; serostatus strongly associated with positivity (*Table 1*)
- D+/R-: highly unlikely to develop a positive QF-CMV until after experiencing CMV infection (*Figure 2*)
- R+: lower rates of CMV with lower peak viral loads (*Table 2*)
- Extended prophylaxis reduced overall CMV infection burden in all serogroups but no major differences by QF-CMV result (*Figure 3, Table 2)*

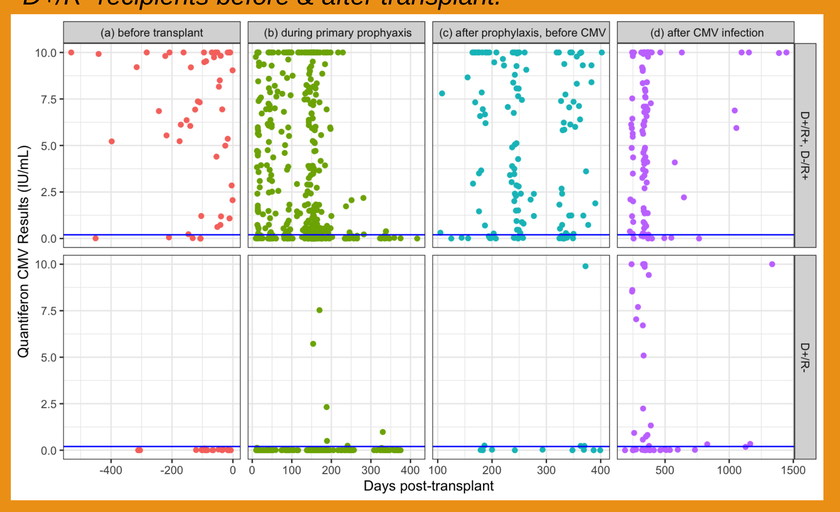
Table 1: *Comparison of patients testing QF-CMV positive vs. negative/indeterminate at 5 months post-transplant.*

Characteristic	Negative or indeterminate (n=102)	Positive (n=160)	p-value
Primary lung disease, no. (%)			
COPD	47 (46%)	69 (43%)	
Pulmonary fibrosis	26 (25%)	37 (23%)	0.93
Cystic fibrosis	12 (12%)	20 (12%)	0.76
Pulmonary hypertension	4 (4%)	6 (4%)	0.98
Other	13 (13%)	28 (18%)	0.32
Male gender, no. (%)	61 (60%)	87 (54%)	0.34
Year of transplant, mean ± SD	2015 ± 1.9	2015 ± 1.8	0.08
Age at transplant, median, IQR	59, 51-64	60, 54-66	0.59
CMV serostatus, no. (%)			
D+/R+	23 (23%)	59 (37%)	
D-/R+	26 (25%)	96 (60%)	0.27
D+/R-	53 (52%)	5 (3%)	<0.0001
Bilateral (vs. single) lung, no. (%)	96 (94%)	145 (91%)	0.31
Days intubated post-transplant, median, IQR	1, 1-2	1, 1-2	0.49
Post-transplant ECMO, no. (%)	9 (9%)	11 (7%)	0.56
Average ischemic time (minutes), median, IQR	290, 219-344	286, 219-358	0.81
ICU length of stay, days median, IQR	5, 3-8	4, 3-7	0.24
ICU readmission, no. (%)	14 (14%)	20 (12%)	0.65
Hospital length of stay, days, median, IQR	19, 16-30	20, 16-27	0.45
Immunosuppression, no. (%)			
Basiliximab induction	45 (45%)	65 (41%)	0.56
Azathioprine (vs. mycophenolate/other)	71 (70%)	120 (75%)	0.34
Acute rejection, no. (%)	13 (13%)	17 (11%)	0.60
Steroids for acute rejection, no. (%)	8 (8%)	12 (8%)	0.92
Absolute lymphocyte count x10^3/µL (n=238), median, IQR	1.01, 0.57-1.69	1.30, 0.70-1.78	0.04

Table 2: *CMV infection by serogroup, Quantiferon®-CMV result at 5 months and prophylaxis duration.*

Serostatus	Quantiferon result at 5 months	Prophylaxis duration (months) No. (%) Median, IQR	CMV viremia		CMV in BAL	
			No. (%) Median onset, months, IQR Peak VL	Peak viral load (IU/mL), median, IQR	No. (%) Median onset, months, IQR	Peak viral load (IU/mL), median, IQR
R+ n=204	Negative/ indeterminate (n=49, 24%)	Standard n=13, 6% 5.4, 5.2-5.6	5 (38%) 7.8, 6.9-7.8	667, 575-950	9 (69%) 8.5, 7.6-9.0	7276, 2061-30593
		Extended n=36, 18% 11.1, 10.8-11.4	5 (14%) 12.3, 12.3-12.4	391, 248-1288	9 (25%) 12.7, 8.8-10.6	1714, 501-3826
	Positive (n=155, 76%)	Standard n=137, 67% 5.3, 5.1-5.6	32 (23%) 8.2, 7.3-9.0	690, 337-2673	81 (59%) 9.1, 8.8-10.6	4531, 1429-21967
		Extended n=18, 9% 8.0, 7.5-8.4	0	-	5 (28%) 12.0, 10.0-12.2	499, 213-9008
	Subtotal	204	42 (21%)	634, 318-2041	104 (51%)	3850, 1108-19473
D+/R- n=58	Negative/ indeterminate (n=53, 91%)	Standard (n=14, 24%) 5.3, 5.1-5.7	12 (86%) 7.2, 6.6-8.1	61670, 15738-214129	11 (79%)	2056, 873-46308
		Extended (n=39, 67%) 11.2, 10.9-11.9	25 (64%) 13, 12.2-13.4	6332, 2805-33187	11 (28%)	1209, 378-10704
	Positive (n=5, 9%)	Standard (n=3, 5%) 5.5, 5.4-5.7	2 (67%) 6.4, 6.4-6.5	38028, 27247-48809	3 (100%)	14030, 9458-18494
		Extended (n=2, 3%) 11.5, 11.4-11.5	1 (50%) 13.8	3825	1 (50%)	483
	Subtotal	58	40 (69%)	13287, 3813-66978	26 (45%)	2315, 476-13523

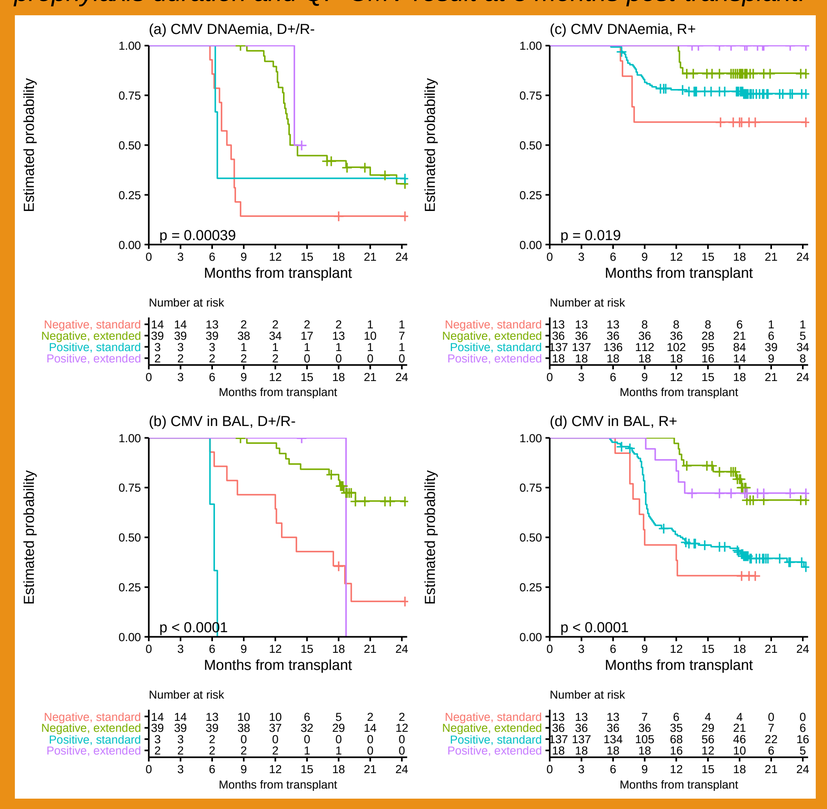
Figure 2: *Comparison of Quantiferon®-CMV results in R+ versus D+/R- recipients before & after transplant.*



Conclusions

- There are key differences in acquisition of CMV-specific immunity and subsequent CMV infection between R+ and D+/R-
- Extended prophylaxis associated with delayed onset and reduced frequency and severity of CMV infection across serogroups
- Post-prophylaxis CMV infection still occurs, typically within 2-3 months of valganciclovir discontinuation
- Many patients with a positive QF developed CMV infection; underpowered to determine whether able to identify a subgroup of R+ at lower risk for severe CMV
- Limitations: less monitoring performed beyond 1 year post-transplant, viral load endpoints only, different cohorts over time, heterogeneity between patients
- Consider extended prophylaxis in all
- Further studies required to determine impact on CLAD-free survival

Figure 3: *Time to CMV infection in blood or BAL by serostatus, prophylaxis duration and QF-CMV result at 5 months post-transplant.*



21st ICHS Symposium on Infections in the Immunocompromised Host

References

1. Paraskeva M, Bailey M, Levvey BJ, et al. Cytomegalovirus replication within the lung allograft is associated with bronchiolitis obliterans syndrome. Am J Transplant **2011**; 11(10): 2190-6.
2. Chmiel C, Speich R, Hofer M, et al. Ganciclovir/valganciclovir prophylaxis decreases cytomegalovirus-related events and bronchiolitis obliterans syndrome after lung transplantation. Clin Infect Dis **2008**; 46(6): 831-9.
3. Manuel O, Husain S, Kumar D, et al. Assessment of cytomegalovirus-specific cell-mediated immunity for the prediction of cytomegalovirus disease in high-risk solid-organ transplant recipients: a multicenter cohort study. Clin Infect Dis **2013**; 56(6): 817-24.
4. Giulieri S, Manuel O. QuantiFERON(R)-CMV assay for the assessment of cytomegalovirus cell-mediated immunity. Expert Review of Molecular Diagnostics **2011**; 11(1): 17-25.
5. Westall GP, Cristiano Y, Levvey BJ, et al. A Randomized Study of Quantiferon-CMV-Directed Versus Fixed Duration Valganciclovir Prophylaxis to Reduce Late CMV Following Lung Transplantation. Transplantation **2018**; 103(5): 1005-13.
6. Gardiner BJ, Lee SJ, Cristiano Y, et al. Evaluation of Quantiferon(R)-Monitor as a biomarker of immunosuppression and predictor of infection in lung transplant recipients. Transpl Infect Dis **2020**: e13550.