Associations between Invasive Aspergillosis and Cytomegalovirus Infections in Lung Transplant Recipients

SM Wulff[1], M Perch[2,3], J Helweg-Larsen[4], P Bredahl[5], MC Arendrup[6,7], J Lundgren[1], M Helleberg[1,4], CG Crone[1]

[1]CHIP, Copenhagen University Hospital, Rigshospitalet - [2]Department of Cardiology,Section for Lung Transplantation, Copenhagen University Hospital, Rigshospitalet. - [3]Department of clinical medicine, University of Copenhagen, Copenhagen, Denmark - [4]Department of Infectious Diseases, Copenhagen University Hospital, Rigshospitalet - [5]Department of Thoracic Anaesthesiology, Copenhagen University Hospital, Rigshospitalet - [6]Unit of Mycology, Statens Serum Institut - [7]Department of Clinical Microbiology, Copenhagen University Hospital, Rigshospitalet

BACKGROUND

Cytomegalovirus **(CMV)** and invasive aspergillosis **(IA)** are important causes of morbidity and mortality among lung transplant recipients **(LTXr)**. These opportunistic infections share risk factors, but their interrelationship need further evaluation. Early diagnosis and treatment may improve outcomes.

AIM

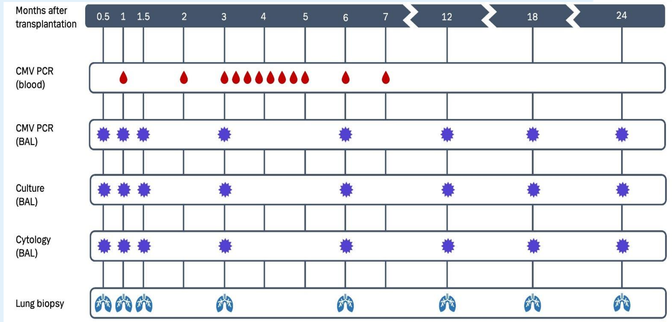
To examine incidence rates of CMV after IA and vice versa to assess whether screening for one of these infections may be indicated when the other is diagnosed.

METHODS

All adults receiving a lung transplant in Denmark, 2010-2019 were included and followed for 2 years after LTX.

- IA was defined using ISHLT criteria.
- CMV was based on positive CMV PCR in blood and/or bronchoalveolar lavage **(BAL)**
- Standardized screening for CMV and IA was performed during the study period.
- Incidence rates (IR), incidence rate ratios **(IRR)** and adjusted incidence rate ratios **(aIRR)** of CMV and IA was estimated by multivariate Poisson regression.

Figure 1: Screening protocol for cytomegalovirus (CMV) and invasive aspergillosis following lung transplantation



Valganciclovir prophylaxis was administered to patients with CMV serostatus D+/R–, D+/R+, and D–/R+ for three months after transplantation. In 2010-2016 voriconazole was administered as antifungal prophylaxis for all LTXr three months after transplantation. In 2016-2019 posaconazole and inhaled amphotericin B was administered for three months after transplantation for patients at high risk of IA.D, Donor; R, Recipient; PCR, Polymerase Chain Reaction; CMV, cytomegalovirus; BAL, bronchoalveolar lavage; Lung biopsy, transbronchial biopsy

RESULTS

We included 295 LTXr, among who CMV and IA were diagnosed in 122 (41.4%) and 57 (19.3%).

CMV after IA

Among LTXr diagnosed with IA, 15.8% developed CMV within 3 months.

The first 3 months following IA the risk of CMV was increased, although not statistically significant aIRR 1.60 (95% CI 0.80-3.20).

IA after CMV

Among LTXr diagnosed with CMV, 10.7% developed IA within 3 months.

In the first 3 months following CMV, the risk of IA was significantly increased, aIRR 2.58 (95% CI 1.19-5.61).

Numbers needed to screen to diagnose one case of CMV following IA, and one case of IA following CMV were approximately 6 and 18, respectively.

Table 1: Characteristics of lung transplant recipient and infectious outcomes, n (%)

	All patients, n= 295
Sex, female	146 (48.5)
Age at TX, median (IQR)	53 (43, 58)
Double lung transplantation	265 (89.8)
Underlying disease	
Cystic Fibrosis*	54 (18.3)
Sarcoidosis*	15 (5.1)
Retransplantation*	7 (2.4)
Pulmonary fibrosis	83 (28.1)
COPD/emphysema	136 (46.1)
High risk CMV serostatus (D+/R-)	73 (24.8)
CMV	122 (41.4)
Positive in blood and BAL	28/122 (23.0)
Positive in blood only	71/122 (58.2)
Positive in BAL only**	22/122 (18.0)
Positive in biopsi only	1/122 (0.8)
Invasive aspergillosis	48 (16.3)
Proven	20/48 (41.7)
Probable	28/48 (58.3)

*IA high-risk conditions; **Number of patients negative in blood samples but positive in BAL samples (minimum >3000 CMV copies/mL). Invasive aspergillosis defined by the ISHLT criteria including anastomosis infection, tracheobronchitis and pneumonia. TX, Transplantation; COPD, Chronic obstructive pulmonary disease; CMV, cytomegalovirus; D, Donor; R, Recipient; BAL, Bronchoalveolar lavage.

ACKNOWLEDGEMENTS

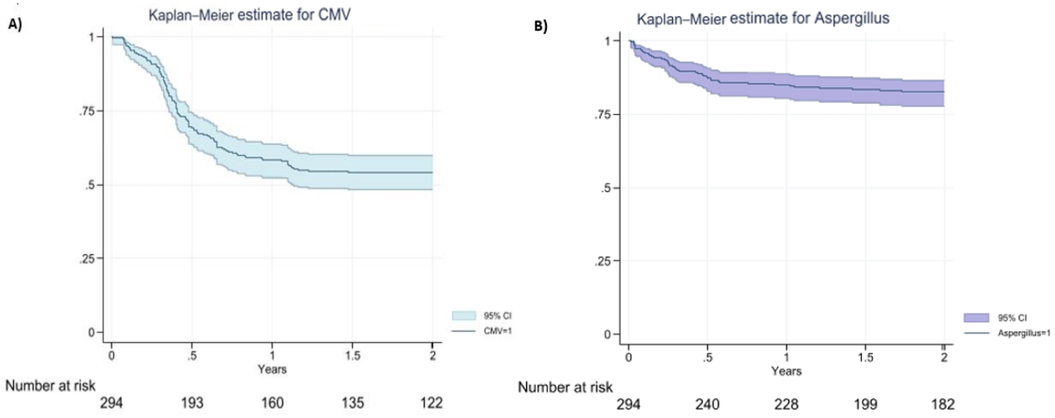
This PERSIMUNE study was funded by the Danish National Research Foundation grant number DNRF126

Table 2: Incidence rates and incidence rate ratios of cytomegalovirus (CMV) and invasive aspergillosis (IA)

CMV	IR per 100 PYFU (95% CI)	IRR (95% CI)	aIRR (95% CI)
Full period	35 (29-41)		
0-3 months after TX	38 (26-56)	Ref.	Ref.
3-6 months after TX	**97 (74-126)**	2.62 (1.64-4.17)	2.67 (1.68-4.26)[1]
6-12 months after TX	35 (24-49)	0.90 (0.53-1.52)	1.02 (0.60-1.73)[1]
12-24 months after TX	6 (7-12)	0.19 (0.09-0.40)	0.22 (0.104-0.48)[1]
Before/without IA	36 (30-43)	Ref.	Ref.
0-3 months after IA	**98 (47-206)**	2.74 (1.27-5.88)	**1.28 (0.59-2.79)[2]**
>3 months after IA	32 (16-68)	0.36 (0.43-1.96)	**1.36 (0.61-2.99)[2]**
IA			
Full period	11 (9-14)		
0-6 months after TX	**27 (20-38)**	Ref.	Ref.
6-24 months after TX	4 (2-7)	0.14 (0.07-0.27)	0.14 (0.07-0.27)[3]
Before/without CMV	10 (7-14)	Ref.	Ref.
0-3 months after CMV	**30 (15-60)**	3.00 (1.38-6.51)	**2.58 (1.19-5.61)[4]**
>3 months after CMV	8 (4-16)	0.77 (0.36-1.67)	**2.98 (1.14-7.77)[4]**

[1]Adjusted for age >50 years, sex, and high-risk CMV serostatus. [2]Adjusted for time after transplantation, age >50 years, sex, and high-risk CMV serostatus. [3]Adjusted for age >50 years, sex, and IA high-risk underlying condition. [4]Adjusted for time after transplantation, age >50 years, sex, and IA high-risk underlying condition. CMV, cytomegalovirus; IR, incidence rate; PYFU, Person-years of follow-up; IRR, incidence rate ratios; aIRR, adjusted incidence rate ratio; CI, confidence interval; TX, transplantation; IA, invasive aspergillosis.

Figure 2: Kaplan-Meier estimates for CMV (A) and invasive aspergillosis (B) after lung transplantation



CONCLUSION

Systematic screening for cytomegalovirus following diagnosis of invasive aspergillosis, and vice versa, may improve the management and outcomes for LTXr.