Prevent viral infection: imperative for lung transplantation

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Variable	HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
Respiratory virus infection ("ever")				
Age	1.01 (0.99-1.03)	0.22	1.01 (0.99-1.03)	0.27
Bilateral transplant	0.87 (0.39-1.93)	0.73	1.15 (0.49-2.71)	0.74
Rejection	2.33 (1.30-4.18)	<0.01	2.16 (1.18-3.93)	0.01
RVI	2.14 (1.20-3.82)	0.01	1.92 (1.07-3.45)	0.03
CMV pneumonia	1.44 (0.74-2.80)	0.28	1.16 (0.59-2.29)	0.67
Risk period following RVI*				
Respiratory virus infection				
3 months	5.36 (2.20-13.04	<0.01	4.77 (1.91-11.64)	<0.01
6 months	3.75 (1.69-8.29)	<0.01	3.37 (1.50-7.54)	<0.01
12 months	2.70 (1.34-5.41)	<0.01	2.44 (1.20-4.96)	0.02

RVI: Respiratory virus infection; CMV: Cytomegalovirus
*HR adjusted for age, bilateral vs. single transplant, rejection and CMV pneumonia in multivariate analysis, but HR were similar to no risk period, so data not shown.

Univariate and multivariate analyses of the development of CLAD modeled for differing risk periods for respiratory virus infection.

Image provided by Dr. Cynthia Fisher.

Lung transplantation is the last resort for patients affected by several end-stage lung diseases, such as cystic fibrosis and chronic obstructive pulmonary disease, which have not improved with other available treatments. Risks associated with this procedure include acute and chronic rejection of the transplanted organs, which are recognized as non-self by the immune system. Chronic lung allograft dysfunction (CLAD), a major cause of long-term allograft failure, is considered a form of chronic allograft rejection. Two major phenotypes of CLAD are bronchiolitis obliterans syndrome and restrictive CLAD, both characterized by loss of respiratory function. The etiology of CLAD is still not clarified, and, despite evidence that viral infections are linked to this syndrome, the association has not been confirmed.

For this reason, Dr. Cynthia Fisher and colleagues from the Vaccine and Infectious Disease Division at Fred Hutch and the University of Washington, designed a retrospective study to identify whether respiratory viral infections are associated with CLAD. "Lung transplantation is a life-saving treatment for a broad range of advanced lung diseases, but outcomes are worse than all other organ transplants. The single most common cause of late allograft failure and death in lung transplant recipients (LTRs) is chronic lung allograft dysfunction (CLAD), a progressive, irreversible, and currently untreatable process leading to obliteration of small airways," explained Dr. Fisher.

Their study, published in the December issue of *Clinical Infectious Diseases*, utilized a vast cohort of subjects undergoing lung transplantation at the University of Washington and relied upon state-of-

the-art diagnostic tests for twelve upper and lower respiratory tract infections. CLAD was defined following the most recent guidelines, as a 20% decrease of forced expiratory volume lasting at least three weeks. Fifty out of 250 patients were diagnosed with CLAD, at a median of 95 weeks post-transplantation. CLAD was associated with a higher mortality rate. Almost 32% of transplanted patients were affected by viral respiratory infection, mostly rhinovirus, followed by parainfluenza and influenza infections. Acquisition of a viral infection was independently associated with CLAD, and the association was stronger for shorter modeled periods of risk following the respiratory virus episode but was also present when the whole follow-up time was analyzed. The study also compared the association of viral infection with the two phenotypes of CLAD separately. Although the numbers were too low to perform statistical analyses, a higher percentage of restrictive CLAD had at least one preceding viral episode.

The study, by analyzing a large cohort of patients, and by using molecular techniques to detect several viruses, gives a clear answer as to whether respiratory viral infection can be linked to a form of chronic rejection of lung transplant. "Our study suggests that respiratory virus infection (RVI) may be a major contributor to CLAD development. This association is relevant as RVI could represent a distinct, diagnosable, and potentially treatable major cause of allograft dysfunction and loss in LTRs, particularly as there are several new anti-virals currently in clinical trial." said Dr. Fisher. Indeed, the results of the study she led are clinically substantial, and support the importance of preventing viral infections as a fundamental part of post-transplant care.

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Fisher CE, Preiksaitis CM, Lease ED, Edelman J, Kirby KA, Leisenring WM, Raghu G, Boeckh M, Limaye AP. (2016). Symptomatic Respiratory Virus Infection and Chronic Lung Allograft Dysfunction. *Clin Infect Dis*. 62(3):313-9.