Plasma monocyte chemotactic protein-1 levels at 24 hours are a biomarker of primary graft dysfunction after lung transplantation

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Monocyte chemotactic protein-1 (MCP-1), also known as "chemokine ligand 2" (CCL2), is a monocyte-attracting chemokine produced in lung epithelial cells. We previously reported an association of increased levels of plasma MCP-1 with primary graft dysfunction (PGD) after lung transplantation in a nested case-control study of extreme phenotypes using a multiplex platform. In this study, we sought to evaluate the role of plasma MCP-1 level as a biomarker across the full spectrum of PGD. We performed a prospective cohort study of 108 lung transplant recipients within the Lung Transplant Outcomes Group cohort. Plasma MCP-1 levels were measured pre-transplantation and 6 and 24 hours after transplantation. The primary outcome was development of grade 3 PGD within 72 hours of transplant, with secondary analyses at the 72-hour time point. Multivariable logistic regression was used to evaluate confounding. Thirty subjects (28%) developed PGD. Median MCP-1 measured at 24 hours post-transplant was elevated in subjects with PGD (167.95 vs 103.5 pg/mL, $P = .04$). MCP-1 levels at 24 hours were associated with increased odds of grade 3 PGD after lung transplantation (odds ratio for each 100 pg/mL, 1.24; 95% confidence interval, 1.00–1.53) and with grade 3 PGD present at the 72-hour time point (odds ratio for each 100 pg/mL, 1.57; 95% confidence interval, 1.18–2.08), independent of confounding variables in multivariable analyses. MCP-1 levels measured preoperatively

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and 6 hours after transplant were not significantly associated with PGD. Persistent elevations in MCP-1 levels at 24 hours are a biomarker of grade 3 PGD post-transplantation. Monocyte chemotaxis may play a role in the pathogenesis of PGD. (Translational Research 2012;160:435–442)

Abbreviations: ACR = acute cellular rejection; BOS = bronchiolitis obliterans syndrome; CCL2 = chemokine ligand 2; CF = cystic fibrosis; CI = confidence interval; COPD = chronic obstructive pulmonary disease; IPF = idiopathic pulmonary fibrosis; IQR = interquartile range; IRI = ischemia–reperfusion injury; MCP-1 = monocyte chemotactic protein-1; OR = odds ratio; PGD = primary graft dysfunction

AT A GLANCE COMMENTARY

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Background

MCP-1 is important in macrophage activation after injury and thought to be a mediator of acute lung injury. This study examines the role of MCP-1 in PGD, a form of early allograft dysfunction occurring within 72 hours of lung transplantation.

Translational Significance

We demonstrate an association between MCP-1 levels at 24 hours and PGD, which was strongest with the most severe phenotype, grade 3 PGD at 72 hours. Persistent elevation of MCP-1 leading o prolonged macrophage activation may be important in the pathogenesis of PGD.

Lung transplantation is the only life-prolonging therapy for many end-stage lung diseases.[1] It has become an increasingly common procedure, with 3272 lung transplants reported in 2009.[2] However, lung transplantation has consistently lagged behind other organs in survival rates, with a median survival of only 5.3 years.[3-5]

Primary graft dysfunction (PGD) is a form of acute lung injury that develops within 72 hours of transplant. It affects 10% to 30% of all subjects undergoing lung transplantation[4-6] and is associated with an increased risk of bronchiolitis obliterans syndrome (BOS), prolonged hospitalization, and increased short- and long-term mortality.[7,8] The exact pathogenesis of PGD is unclear; however, ischemia–reperfusion injury (IRI) is thought to be a driving force in its development.[9]

Monocyte chemotactic protein-1 (MCP-1), also known as "chemokine ligand 2" (CCL2), is a monocyte-attracting chemokine produced by many cell types, including endothelial, fibroblast, dendritic, and epithelial cells.[10] MCP-1 is important in mediating the early injury response by recruitment of monocytes, memory T cells, and natural killer cells.[11] Elevation in MCP-1 levels after lung IRI has been established in a rat model.[12] In addition, MCP-1 has been identified as a promoter of systemic inflammation in response to alveolar hypoxia.[13] Furthermore, animal research has demonstrated that blockade of MCP-1 attenuates IRI in pulmonary and renal models.[12,14] On the basis of the relationship between MCP-1 and IRI, we hypothesized that MCP-1, may be related to the development of PGD. We previously reported an association of increased levels of plasma MCP-1, among other mediators, with PGD using a multiplex immunoassay platform in a nested case-control study of grade 3 PGD compared with no PGD (grade 0).[15]

In the current study, we tested the hypothesis that plasma MCP-1 is a biomarker of PGD within 72 hours after transplantation, using a prospective cohort study including all grades of PGD, a monoplex assay specific to MCP-1, and multivariable adjustment of important confounding variables.

MATERIALS AND METHODS

Selection of subjects. The Lung Transplant Outcomes Group is a multicenter, prospective cohort study of lung transplant recipients that has been described previously.[16-18] Our prospective cohort study included all subjects enrolled between October 2006 and May 2008 at the University of Pennsylvania and Columbia University. Two centers were selected to reduce variability secondary to center effects, and these centers have the highest volume of lung transplants. Sample size was determined on the basis of results of our prior case-control study of MCP-1.[15] Plasma samples were prospectively collected pretransplant and 6 and 24 hours after allograft reperfusion. These time points were chosen to reflect immediate post-transplant lung injury and lung injury that is contemporaneous with measurement of MCP-1.