BRONCHIOLITIS OBLITERANS SYNDROME AFTER LUNG TRANSPLANTATION: BIOMARKERS FOR INFLAMMATION AND FIBROGENESIS

Lisanne Tacken-Kastelijn, MD

January 17th, 2012

Promotors: prof dr JC Grutters, MD PhD; prof dr J-WJ Lammers, MD PhD

Co-promotors: dr ir HJT Ruven, PhD; dr CHM van Moorsel, PhD

Lung transplantation is the last option in the treatment of patients with end-stage lung disease. However, long-term survival may be limited due to the development of chronic rejection in the donor lung of the transplant recipient, called bronchiolitis obliterans syndrome (BOS).

BOS is diagnosed after lung transplantation by a decline in lung function occurs, which is not due to rejection, infection or problems of the bronchial anastomosis. The development of BOS is characterized by persistent injury of the airway epithelium that is caused by several factors. This process leads to inflammation and remodeling, subsequently followed by an aberrant repair response, and finally fibrosis and occlusion of the small airways of the allograft.

When BOS is diagnosed, the process is already at an advanced and often irreversible stage. Treatment options are limited at that time moment. The current status of diagnosis of BOS clearly indicates the need for biomarkers in serum and DNA that may detect processes leading to BOS before the decline in lung function occurs. These unmet needs are the basis of this thesis.

Toll-like receptors (TLRs) are critical molecules for activation of the innate immune system by recognition of pathogens, and they can prevent the induction of allograft tolerance. Genetic polymorphisms in TLR-2, TLR-4 and TLR-9 might contribute to susceptibility for BOS. These genetic polymorphisms could predispose to increased secretion of pro-inflammatory cytokines, causing injury and inflammation of the airway epithelium.

The exact role of different types of cytokines in rejection or tolerance of the allograft is under debate. We showed that the T helper (Th)1 cytokines were similar between patients who developed BOS (BOSpos) and those who did not (BOSneg) patients. However, the Th2 cytokines revealed a different pattern between these two groups. This suggests that Th2 cytokines are involved in the process of chronic rejection, possibly due to the inhibition of transplant tolerance, the absence of inhibition of the Th1 response and the influence on proliferation of regulatory T-cells.

In relation to excessive injury and chronic inflammation, the process of fibrogenesis is considered to be of central importance to the development of BOS. Normally, after injury of the airway epithelium an adequate repair mechanism is required to prevent fibrogenesis. BOSpos patients, however, seem to have an impaired repair mechanism and a profibrotic airway milieu. First of all they showed a different genotype distribution of matrix metalloproteinase (MMP)-7 and lower levels of MMP-7 than BOSneg patients. These differences might contribute to an impaired repair mechanism of the airway epithelium. Moreover, there is more degradation and turnover of the extracellular matrix in BOSpos patients than in BOSneg patients as shown by increased levels of MMP-9. Lastly, the genetic polymorphisms in the caveolin-1 (CAV1) gene might contribute to fibrogenesis. Even though the functionality of CAV1 is not yet fully understood, the latter may be an important factor in the transforming growth factor beta signaling pathway.

In conclusion, genetic polymorphisms in TLRs, MMP-7 and CAV1 and biomarkers in serum, such as Th2 cytokines, MMP-7 and MMP-9, are related to the development of BOS after lung transplantation, and may be potential biomarkers for clinical decision making.