

BIOMARKERS FOR THE PREDICTION OF THE BRONCHIOLITIS OBLITERANS SYNDROME AFTER LUNG TRANSPLANTATION

Annelieke Paantjens

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Promotors: prof dr JC Grutters, MD PhD; prof dr L Meyaard, PhD

Co-promotors: dr HG Otten, PhD; dr EA van de Graaf, MD PhD

The main limitation for overall survival after lung transplantation (LTx) is the development of chronic rejection, which is represented by the bronchiolitis obliterans syndrome (BOS). The diagnosis BOS is based on lung function testing, however, it is a surrogate marker. Because BOS is an irreversible and unmanageable disease, a better prediction of patients at risk could be beneficial for treatment after LTx. In this thesis we focus on finding a biomarker in the blood of LTx recipients. After LTx, patients receive a stringent immune suppressive regimen. Therefore, many factors in the blood of LTx patients are altered when compared to healthy controls.

We found that there was a distorted distribution of PBMC. Moreover, NKT cells were elevated but central memory CD8 T cells were decreased in the blood of patients with BOS compared to non-BOS patients, but these were not predictive. Furthermore, NK cells were more activated after LTx compared to prior to LTx.

Cells of donor origin could also be detected in the peripheral blood of patients: this microchimerism could be observed for several cell types. However, plasmacytoid dendritic cells were never detected.

HLA antibodies are a major risk factor for the development of BOS. However, in our patient group IgM or IgG HLA antibodies were only weakly present and did not correlate with the development of BOS. The HLA antibodies are probably influenced by the immune suppressive regimen applied after LTx. Studying HLA antibodies of

both the IgM and IgG isotypes no isotype switch could be detected. BOS patients had higher titers IgM HLA antibodies but lower titers IgG HLA antibodies, but these titers were not predictive of BOS. Non-HLA antibodies can also be detected after LTx. These antibodies might fix and activate the complement system.

MBL, one pathway of the complement system, was studied prior to and after LTx and it was observed that low MBL leads to more CMV infections but also better overall survival. However, there was no relation with BOS.

Clara cell secretory protein (CCSP) is produced by cells in the lungs. These cells are damaged during the development of BOS, and a decrease in serum CCSP in all patients developing BOS is observed. But serum CCSP levels are very fluctuating and as the decrease is observed when the process is ongoing serum CCSP is not predictive of BOS.

The chemokine TARC is able to migrate T cells expressing CCR4 to the site of inflammation. It was observed that patients developing BOS had lower serum TARC levels 1 month after LTx and this was predictive of development of BOS when compared to non-BOS patients. This relation was not seen for its receptor CCR4.

In conclusion, we found that risk factors for the development of BOS are influenced by the type of immune suppressive regimen applied after LTx. And that CCSP although decreasing in all BOS patients cannot be used as a biomarker for the development of BOS. However, serum TARC levels at 1 month after LTx might be a promising easy to detect biomarker for the development of BOS.