AGRA as novel biomarker for the prediction of severe infections in liver transplanted patients

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Project summary

Bacterial infections are a major cause of decompensation and death in liver cirrhosis and remain problematic even after liver transplantation. The liver is an essential immunological organ and with the decline of liver function immune responses become severely impaired. Patients with liver cirrhosis develop an immune dysfunction referred to as cirrhosis-associated immune deficiency syndrome (CAIDS) that affects all immune cells and the cell-free (or humoral) compartment of the immune system. CAIDS is strongly associated with the risk of infection and mortality in these patients. To date, there are no reliable markers in clinical practice that can assess the susceptibility to infections and predict their development in liver disease patients or patients after liver transplantation. The Transplantation Research Unit at the Medical University of Graz has developed a functional biomarker that can be used to predict severe infections in cirrhosis. Acellular growth retardation ability (AGRA) assesses the function of the humoral immune system by challenging live bacteria with patients' sera and quantifying their growth with regression models. However, it is still unclear how AGRA develops after liver transplantation in terms of improved liver function on the one hand and immunosuppressive therapy on the other hand.

The objective of this study is to investigate the predictive value of AGRA for post-transplant infections and to observe and describe the development of AGRA before and after liver transplantation.

Therefore, a clinical study was conducted in which 55 patients undergoing liver transplantation were included. Shortly before transplantation, one day, one week, and three months after the prophylactic antibiotic regime ended, serum samples were collected, and AGRA was assessed. Time to infections, complications, or death were recorded one year after liver transplantation. Infections were also recorded in the year before liver transplantation for comparison.

Patients included in the study were on average 59.7 (±9.6) years old, 31% of them were female. During the first year after transplantation, 60 clinically relevant infections (i.e. hospitalization and medication) were recorded in a total of 28 individual patients. In comparison, 26 pre-transplant infections were recorded in 21 individual patients. While the most common infections before transplantation were urinary tract infections, spontaneous bacterial peritonitis, and pneumonia, urinary tract infections, wound infections, and cholangitis prevailed after transplantations. The composition of infectious events pre- and post-transplant are summarized in Figure 1.

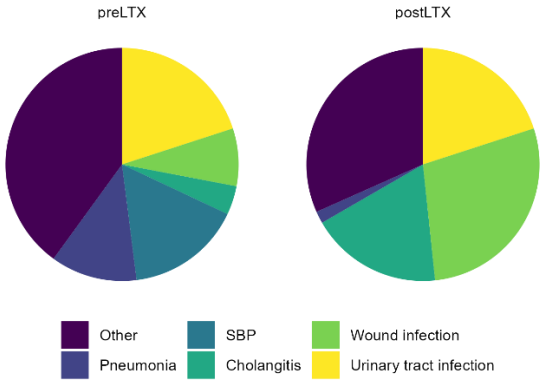

Figure 1: Types of infections observed pre- and post-liver transplantation (LTX).

AGRA as a biomarker for the state of the humoral immune system gradually improved after liver transplantation and became significantly lower compared to pre-transplant measurements one week and three months after transplantation, as shown in Figure 2A. However, AGRA measurements pre-transplant were not able to predict the occurrence of clinically relevant infection after transplantation, as shown in Figure 2B.

A **B**

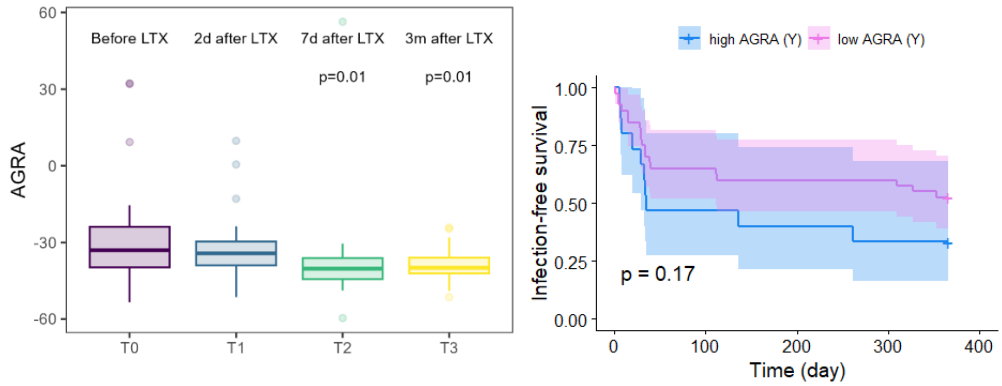

Figure 2: A. AGRA before and after liver transplantation in arbitrary units. B. Kaplan-Meier curve for patients with high and low AGRA (according to optimal cut point calculated with Youden index).

The improvement of AGRA after liver transplantation was comparable to previously observed modulations of AGRA during anti-HCV therapy. Contrary to the HCV setting in which the AGRA improvement coincided with a marked reduction of infections after a sustained viral response, patients after liver transplantation had a significantly higher risk for infections than before transplantations despite the significant improvement in AGRA. A possible explanation for this discrepancy might be that the improvement in AGRA indicates an improvement of liver-derived host-defense molecules such as complement factors, antimicrobial peptides, acute-phase proteins, etc. after transplantation, but does not reflect the net state of immunosuppression which becomes a major influence on infection risk after transplantation. Another possible explanation might be that AGRA is a liver-disease-specific biomarker and might be less applicable in patients without current liver disease. In conclusion, in its current form, AGRA is not a suitable biomarker for the prediction of post-transplant infections.