

profound immune system paralysis, eventually being associated with lower probability of rejection post LTx. Ascites is often associated with bacterial translocation leading to constant interaction of translocated bacteria with antigen presenting cells and toll-like receptors. Our study brings evidence, that the absence of ascites prior to LTx is a single most important clinical predictor for TCMR. However, the number of candidates for LTx without ascites in real-life is probably low. Low serum levels of immunosuppressive medication in the early post-transplant period have been described as a risk factor for TCMR (27–29). To date, the impact of TCMR on patient and graft survival after LTx has been evaluated in a single report by (23), revealing that TCMR had no impact on patients' survival.

It has been previously shown, that agreement among clinicians from multiple liver transplant centers on the clinical criteria for selecting patients for liver biopsy is very poor (26). These data probably reflect differences among protocols which are being followed in liver transplant centers. In the management of liver transplant recipients, there is apparently a clinical challenge. On one side, the diagnosis of TCMR requires liver biopsy with its' non-negligible drawbacks. On the other, currently we are unable to diagnose TCMR without liver histology. Although undiagnosed TCMR in our study did not lead to any significant adverse outcome, there is evidence that some patients with undiagnosed TCMR without biochemical graft dysfunction develop clinically overt TCMR over time. In a meta-analysis of 15 studies including 1 566 patients undergoing per-protocol biopsies, 331 of patients had histological evidence of TCMR with no biochemical graft dysfunction, and 36 of them eventually developed clinically significant TCMR. In the study, 7 patients had steroid-refractory TCMR and 9 patients subsequently developed chronic rejection (30, 31). However, the risk of progressive graft dysfunction in undiagnosed TCMR was very low, and authors did not recommend protocol liver biopsies in all patients. Recently, Rodriguez-Peralvarez et al in their multicenter study have proposed a risk score for non-invasive prediction of histologically

diagnosed TCMR (26). This model has not been used in our transplant center while we are currently awaiting results of validation studies. Meanwhile, even the issue of per-protocol liver biopsies in high-risk patients (lower age, autoimmune etiology of the primary disease and potentially patients with less severe liver disease) remains open. Our study brings some more evidence in favor of performing LB in selected patients only, with the selection strategy open to results of additional studies. Alternative strategy would be a pre-emptive use of induction immunosuppressive regimen in patients at risk. For example, basiliximab given in combination with a tacrolimus-based immunosuppressive regimen, has been associated with lower incidence of TCMR, excellent short-term rejection-free graft and higher overall survival after LTx (32–34). In addition, anti-IL-2 induced regimen could prevent subsequent treatment with higher doses of calcineurin inhibitors with potential nephrotoxicity (35). Further studies validating the efficacy and safety of both strategies are warranted.

Our study has several strengths. We report TCMR prevalence in consecutive cases from a single small-volume liver transplantation center for the period of 10 years. The prevalence of TCMR from the Middle or Eastern European transplant centers has not been reported yet. Limitation of our study is a single center experience with relatively low number of cases. However, single center experience provides results for a homogenous group of patients with unified selection criteria for liver transplantation candidates, single immunosuppressive protocol and one protocol for diagnosing TCMR and selecting patients for liver biopsy. Obvious limitation of our study is the lack of pre-scheduled per-protocol liver biopsies in all transplanted patients, but this strategy is not widely recommended.

Conclusions

T-cell mediated rejection diagnosed clinically and confirmed histologically occurred in 21 patients (11.4 %). Etiology of AIH, absence of ascites and lower TAC were independent risk factors for TCMR. TCMR had no impact on overall survival.

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