**Immunosuppression and Transplant Hepatology**

**by Tomohiro Tanaka, Eleonora De Martin, and David Victor**

The prime focus on immunosuppressive strategies was on CNI reduction for renal protection, immune tolerance and tailored immunosuppression. LT for alcoholic hepatitis, and impact of newer antivirals on wait list mortality and outcomes were keenly discussed.

**O-051** **Incidence and treatment of rejection in patients converted to Everolimus (EVL) after liver transplantation (LT): long-term histological data from the Everoliver multicenter observational French registry**

***Faouzi Saliba, Villejuif, France***

Although not an ITT analysis, this French study included a large number of recipients (>1000) in whom conversion to everolimus from CNI-based immunosuppression was performed at different times after LT (in more than half, this was more than 1 year after LT). The major reasons for the conversions included chronic kidney disease and intra/extrahepatic malignancy. The rates of acute and chronic rejection (3% in those converted beyond 1 year) did not increase with conversion, and majority of them (>60%) experienced mild disease as per Banff criteria. Eight patients underwent re-LT (four were due to chronic rejection). A step-wise, late conversion (>12months after LT) of an everolimus-based regimen seemed safe and feasible.

**O-052** **PIRCHE-II algorithm may predict allograft dysfunction in calcineurin inhibitors (CNI) free maintenance immunosuppression liver transplant patients**

***Magdalena Meszaros, Montpellier, France***

In this retrospective study, the usefulness of PIRCHE (predicted indirectly recognizable HLA epitopes)-II score in predicting alloimmune response was analysed. PIRCHE-II algorithm takes into account the number of epitopes involved in alloimmune response, the molecular weight of epitopes and the strength of the bounding, and is reported to predict immune-mediated graft dysfunction in renal transplant recipients. This is more widely used in bone marrow transplantation in clinical practice. Forty LT recipients on CNI-Free immunosuppressive regimen including everolimus, sirolimus and/or MMF, or none of these (mainly due to chronic kidney disease) were enrolled. Mean PIRCHE-II score was 94.8. Those with biopsy proven immune mediated allograft injury had higher score (mean 117.8), than those without (83.1) [p<0.025]. The area under the curve (AUC) of the score in predicting such abnormal liver biopsy was 0.72 [p=0.017]. A cut-off level of 100 was proposed to predict immune-mediated allograft injury. There was only one patient who had chronic antibody mediated rejection, and had high PIRCHE-II score (>100). This score could be especially of interest in management of recipients on non- CNI “difficult-to-monitor” immunosuppressive agents such as antimetabolites.

**O-055 Donor dominant one way HLA matching - a risk factor for lethal GVHD after LRLT**

***Peeyush Varshney, New Delhi, India***

Solid organ transplant from an HLA-homozygous donor resulting in donor-dominant one-way HLA matching significantly increases the risk of developing GVHD post-transplant. This study evaluated 7 LDLT cases of GVHD (out of >2500 LT’s in an Indian Center); 6 recipients had received a graft from 1st-degree blood relatives, and one from a 2nd-degree relative. Four had one way matching at all the 3 loci (HLA-A, B and DR), while the other 3 had matching in 2 loci only (HLA-A and -B). CNI and/or MMF were discontinued due to significant GI symptoms (diarrhea) and cytopenia in majority of the cases. All the 7 patients unfortunately died, mainly due to GVHD-driven sepsis and multiorgan failure. The authors proposed that a thorough pre-LT work up including HLA typing should be performed for living related donor LT cases, and utilization of such grafts should be restricted to very urgent cases only. It was emphasized that this could be a problem more often in Asian subcontinent where most of the donors are the family members and consanguineous marriages are also common. Confirmation of these findings, and feasibility of such investigation in all LDLT cases, needs larger studies from other centers as well.

**O-057 - An open-label proof-of-principle Phase 2a study to evaluate Autologous Hematopoietic Stem Cell Transplantation for Allogeneic Organ Transplant Tolerance (ASCOTT)**

***Andrzej Chruscinski, Toronto, Canada***

University of Toronto conducted this open label phase 2a study to evaluate autologous hematopoietic stem cell transplantation (aHSCT) for recurrent primary sclerosing cholangitis (rPSC) post-LT. It was stated that PSC was chosen because it is a sort of “immune related disease” and the prognosis after diagnosis is poor enough to consider any interventions. It was hypothesized that aHSCT can induce tolerance for such recipients against both allo- and auto antigens, by both deleted component (loss of T cells IgG/M autoantibodies) and regulatory component (expansion of Treg and transitional B cell through reconstitution of the immune system). 5 patients at a median of 98 (15-233) months post-LT with recurrent PSC received stem cell mobilization, stem cell collection/purification, and then aHSCT procedure: Busulfan, cyclophosphamide and rabbit antithymocyte globulin followed by autologous CD34 selected graft re-infusion. Of the 5 patients, two died (right heart failure and hemophagocytosis), one developed VOD and needed re-LT. The other two were alive, off immunosuppression at the end of the follow up. Compared to use of aHSCT in multiple myeloma patients (previous study with 95% 10-yr survival) the outcome was found to be inferior in rPSC LT recipients probably as they were much sicker and could have increased toxicity in them. A promising aspect was that, liver biopsy in the two patients who survived, and the other one who died due to heart failure after aHSCT, showed decreased fibrosis and inflammation.

**O-058 - Azathioprine or mycophenolic acid after liver transplantation: A tailored immunosuppression is key.**

***Marit Kalisvaart, Birmingham, United Kingdom***

This study from U.K. compared the use of azathioprine (AZA) and mycophenolic acid (MPA/MMF) in LT recipients. Although MMF is now more commonly used as a part of the triple IS regimen, AZA is less costly, and has a potential effect on IBD in PSC recipients (the cohort of the study included considerable proportion of PSC patient [12%]). In total 1009 LT recipients (2007-2015) were divided into 4 groups: TAC-AZA (74%), TAC-MMF (21%), MMF+ IL2 blocker+ delayed TAC (5%), other regimens (0.3%). The incidence of acute cellular rejection (ACR) was significantly higher in TAC-AZA (26%) than TAC-MMF (19%). Those who experienced ACR showed impaired survival (70% at 5 years) compared to those without (78%) [p<0.01]. Probably knowing or experiencing such difference, many of those who were initially on TAC-AZA were converted to TAC-MMF within 12 months (44%), while most of those who were initially on TAC-MMF remained on same regimen (87%). Importance of tailored immunosuppression according to underlying characteristics was suggested in their conclusion.

**O-059 - Comparable efficacy-safety and better renal function with everolimus and reduced-exposure tacrolimus versus standard-exposure tacrolimus in liver transplant recipients: H2304 and H2307 pooled analysis.**

***Gary Levy, Toronto, Canada***

The study showed the result of the 24-months pooled analysis from two multicenter RCT’s which evaluated the safety and efficacy of everolimus-based immunosuppressive regimen (H2304: deceased donor LT and H2307: living donor LT). They compared conventional tacrolimus group (target trough 8-12 ng/ml), to those with reduced-tacrolimus (3-5 ng/ml) and everolimus (3-8 ng/ml). The baseline characteristics were well balanced between the groups. Renal functions at 6 and 24 months were significantly better with everolimus+tacrolimus group, especially in those with lower MELD score reflecting better renal function at LT. In terms of HCC recurrence (authors suggested it was one of the main scopes of the study), those who received the regimen with everolimus showed a trend towards less recurrence rate than those with conventional tacrolimus group, especially those outside Milan criteria (5.9% vs. 23.1%), and those with AFP >400 (20% vs. 66.7%) at LT. Overall survival and safety profile were comparable among the studies / groups.

**O-074 - Clinical features and prognosis of DIHBS (diffuse intrahepatic biliary stricture) after adult ABO-incompatible living donor liver transplantation.**

***Jae Hyun Kwon et al., Seoul, Korea, Republic of***

Diffuse intrahepatic biliary stricture (DIHBS), an attenuated form of antibody mediated rejection (AMR), remains an unresolved problem in transplant recipients of ABO-incompatible (ABOi) living donor (LDLT). A retrospective study from Asan Medical Center included 497 patients between 2008 and 2017 who received an ABOi LDLT. Among them, 24 patients developed DIHBS at a median time of 2.8 months after transplant. The 3-year patient survival rate was 69.9% while graft survival rate was 40.6%. Both patient and graft survival rates were significantly lower than ABOi LDLT recipients without DIHBS (both p< 0.001). The authors found a decrease in incidence of DIHBS after year 2014 in their experience, and proposed further investigation into the role of prostaglandin E1 in this context. No risk factors for acute cellular rejection were found on multivariate analysis. In conclusion, DIHBS remains a severe complication of ABOi LDLT recipients as it significantly affects patient and graft survival.

**O-076 - Improvement of renal function with everolimus plus reduced tacrolimus in de novo liver transplant recipients - HEPHAISTOS study 12 month data.**

***Hans Juergen Schlitt, Study group, Germany***

The HEPHAISTOS study compared efficacy and safety of early use of everolimus [EVR] and reduced tacrolimus [rTAC], vs. standard tacrolimus [TAC-C) in *de novo* liver transplant [LTx] recipients and studied the impact on renal function at 1-year post *transplant.* In a 12 months [M] prospective, open-label, randomized study from 15 German centers, 642 patients were screened and 333 patients patients were randomized 1:1 between day 7 to 21 after LTx to either receive EVR (3-8ng/ml) + rTAC (< 5ng/ml) (n=169), or TAC-C (6-10ng/ml) (n=164), all with steroids until 6 months. Efficacy at M12 was demonstrated with similar incidence of renal insufficiency with EVR+rTAC or TAC-C, so the primary end point was not met. This maybe due to the fact that patients required good renal function at the outset to be randomized. About 30% of patients discontinued for adverse events. Among patients in the per protocol analysis (n=110 EVR+rTAC, n=101 TAC-C), eGFR was significantly higher with EVR+rTAC (+7.79 mL/min/1.73m²; p=0.0085) as compared to TAC-C, without compromising efficacy. This study confirmed that the early initiation of EVR is feasible.

**O-077 - Results of LITMUS (NCT 02541916): the liver immune tolerance bio marker utilization study**

***Andrzej Chruscinski, Toronto, Canada***

This Phase 2A single-center study, examined whether an 8 target and 5 housekeeping gene expression panel in peripheral blood mononuclear cells (PBMC) and liver allografts could identify operationally tolerant liver transplant recipients. The panel in PBMC was measured in 60 adult LT recipients at least at 3 months post-LT and without episodes of rejection. Patients with a putative tolerant gene profile in PBMC underwent a liver biopsy and were then weaned off immunosuppression (IS). Liver biopsy at 6 months and 1 year were performed after stopping IS. Overall 16 patients had the putative tolerance gene profile in their PBMC, and 12 agreed to enter the withdrawal phase of the study. 3 patients were excluded as their biopsies showed recurrent disease and/or rejection. Of the 9 remaining patients, 5 have now been weaned off of IS and are greater than 2 years post IS withdrawal, 2 are undergoing withdrawal and 2 developed acute cellular rejection, which was easily reversed. In patients who achieved tolerance, levels of fgl2 remained stable over time, foxp3 gene expression increased at 3 months and then returned to baseline, and tigit gene expression increased at 6 months post-IS withdrawal and remained elevated at 1 year. The authors concluded that a combination of gene expression monitoring in PBMC, and the liver allograft may identify operationally tolerant recipients.

**O-157 - A randomized controlled clinical trial of Thymoglobulin® and extended delay of calcineurin inhibitor therapy for renal protection after liver transplantation: A multicenter study**

***Bijan Eghtesad, Cleveland, United States***

This multicenter RCT from the U.S. investigated the use of thymoglobulin with delayed introduction of CNIs. The two arms were; r-ATG arm (Tymogloculin 1.5mg/kg at day 0, 2 and 4, in total 4.5 mg/kg along with steroid taper and MMF, without CNIs for 10 days post-LT) versus control arm (conventional steroid taper, MMF and CNIs). 55 patients were enrolled in both arms. Baseline characteristics in both groups were similar. Cumulative dose of CNI at the end of follow up was similar, and no difference in overall survival was seen on Kaplan-Meier analysis between two arms. During the first 10 days after LT, 2.9% (3/55) experienced acute rejection according to Banff criteria in r-ATG group, while none of the patients in control arm had rejection. Estimated GFR seemed somewhat better in r-ATG arm, but the significance was uneven over the follow up period. The median delta eGFR at 12 months after transplant seemed better in r-ATG arm, although it was not statistically significant (p=0.23). Rate of CMV infection and PTLD were similar between two arms. Authors suggested that renal protection could be more pronounced in patients with an initial degree of renal dysfunction.

**Viral hepatitis / ALD/ NASH / NAFLD**

**O-139 - Favorable waitlist outcomes in patients with alcoholic liver disease in the MELD-Na era *Mohamed Safwan, Detroit, United States***

Mohamed Dafwan et al. presented data showing that patients listed for alcoholic liver disease (ALD) had a higher chance of recovery from their listing disease severity than other causes of liver disease, especially those MELD 15-29 at listing.

**O-140 - The evolution of living donor liver transplantation for alcoholic liver cirrhosis in a high volume center: the Eastern perspective** ***Chih-Chi Wang, Kaohsiung, Taiwan, Republic of China***

Chih-Chi Wang et al. presented their experience in Taiwan for live donor liver transplantation for ALD. They reported equivalent survival for patients transplanted for ALD, even with a less than 6 months of sobriety. Interestingly they showed that despite a low recidivism rate (6.4%), patients who relapsed to alcohol abuse had a 31% 5-year survival vs. 95% in those who did not relapse.

**O-144 - Renal safety of entecavir and tenofovir with hepatitis B immunoglobulin in liver transplant patients *Dong Jin Joo, Seoul, Korea, Republic of***

Dong Jin Joo et al showed that renal damage due to entecavir and tenofovir were comparable as regards glomerular filtration rate in post-transplant patients, but that they discovered proximal tubular dysfunction was more common in the tenofovir group.

**O-145 - Patients treated for HCV and listed for LT in a French multicenter study: what happens at 3 years *Lucie Meunier, Montpellier, France***

Lucie Meunier et al. showed that 27% of patients treated with DAA’s had improvement in their disease status, and could be removed from that transplant list. This was most seen in patients with MELD< 20 and CTP score <7.

**O-146 - Psychosocial characteristics of patients with severe alcoholic hepatitis presenting for early liver transplantation evaluation** ***Ahmet Gurakar, Baltimore, United States***

Ahmet Gurakar et al presented the demographics of the patients who were both listed for acute alcoholic hepatitis, as well as those who were not listed at their program. They found that there was no clear difference, and called for criteria to define who has adequate psychosocial criteria for transplantation in acute alcoholic hepatitis.