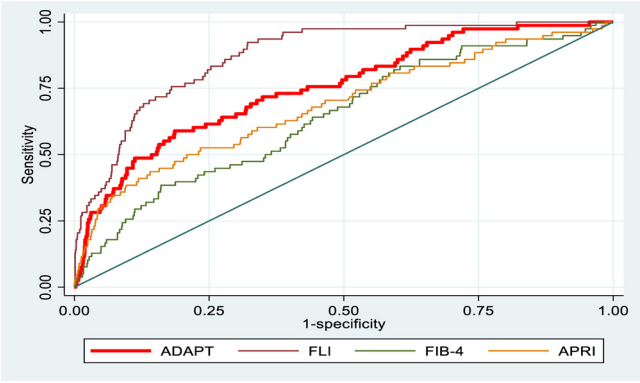

Figure: ROC curves of non-invasive fibrosis scores for prediction of significant fibrosis.

Conclusion: In this population-based study, the ADAPT composite score that includes PRO-C3 offers superior predictive accuracy for the diagnosis of significant liver fibrosis as compared to other recommended screening tools such as FIB-4 and APRI. The individual components of ADAPT are easily accessible clinical parameters and as such could be used as a tool for the early detection of liver fibrosis in the general population, particularly in a sequential-type approach.

Immune-mediated and cholestatic: Experimental and pathophysiology

OS019

Novel anti-cholestatic treatment strategies by combining inhibition of the Apical sodium-dependent bile acid transporter with stimulation of urinary bile salt excretion or lowering bile salt synthesis

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Background and aims: The apical sodium-dependent bile acid transporter (ASBT) is primarily expressed in the small intestine and kidney, where it prevents bile salts from being excreted in respectively feces and urine. Intestine-restricted drugs that inhibit ASBT are currently clinically explored to reduce toxic accumulation of bile acids during cholestasis. Intestine-restricted ASBT inhibitors (ASBTi) may be less effective in severe cholestasis and also yield gastrointestinal side-effects in case of high bile salt load in the colon. Here, we test two ASBT-targeting treatment strategies in pre-clinical models with cholestasis-induced liver injury. First, systemic ASBT inhibition, to increase renal bile acid excretion and second a combination treatment with obeticholic acid (OCA) to limit bile salt synthesis and reduce colonic bile acid load.
Method: Systemic ASBT inhibition was tested by performing a bile duct ligation (BDL) in adult ASBT knock-out (KO) mice (129P2/OlaHsd background, Jackson) and wild-type littermates to induce severe cholestasis. In our second strategy, BDL was performed in adult wild-type C57Bl/6 mice after 2 days oral gavage pre-treatment with OCA and ASBTi. In a different model, wild-type C57Bl/6 mice were fed a 0.1% 3, 5-diethoxycarbonyl-1, 4-dihydrocollidine (DDC) diet while receiving daily treatment with either placebo, OCA, ASBTi or both (OCA + ASBTi). After sacrifice, liver injury was determined by plasma liver enzymes, RT-qPCR and liver histology, while HPLC analysis was used to quantify bile salt concentrations in plasma, liver, small intestine and feces.
Results: ASBT KO mice had reduced liver necrosis, reduced bilirubin and alkaline phosphatase (ALP) levels compared to wild-type mice after BDL. ASBT KO mice also showed a trend to reduced bile salt pool size, and increased urinary bile salt excretion. OCA + ASBTi treatment reduced the total bile salt pool size before cholestasis-onset and resulted in reduced bilirubin, ALP and a ~60% reduction in liver necrosis compared to placebo control in a BDL model. Besides, OCA + ASBTi treatment decreased fecal bile salt excretion compared to monotherapy with ASBTi.
Conclusion: Systemic ASBT inhibition effectively reduces BDL-induced liver damage. Combined OCA + ASBTi treatment lowers the bile salt pool size and improves liver health after BDL-induced cholestasis, while it also shows therapeutic potential by reducing fecal bile salt excretion.

OS020

Low-dose IL-2 alleviates drug-induced primary biliary cholangitis in mice by improving Treg and Th17 balance

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Background and aims: The imbalance of regulatory T (Treg) and T helper 17 (Th17) cells correlates with increased risk of autoimmune diseases. Their imbalance was also reported in primary biliary cholangitis (PBC) patients. Previous studies have suggested that low-dose IL-2 can alleviate disease severity through modulating $CD4^+$T cell subsets in patients with autoimmune diseases. However, the efficacy of low-dose IL-2 in PBC remains unexplored. Hence, the present study aimed to examine effects of low-dose IL-2 in PBC mouse models.
Method: PBC was induced in female C57BL/6 mice by two immunizations with 2-nonynoic acid (2OA-BSA) at two-week intervals. Besides, polyinosinic polycytidylic acid (poly I:C) was injected i.p. every three days. The control group was injected with PBS instead of 2OA-BSA and poly I:C. PBC mice were divided into the treated and untreated groups, and low-dose IL-2 was injected s.c. every three days after four weeks from modeling in the treated group (Fig. A)and the untreated group was replaced with saline. The serum was isolated from blood sampled by eyeball extirpating for biochemical detection. Th17 and Tregs were analyzed by flow cytometry, and the related cytokines were analyzed by ELISA. Liver histopathology was examined by HandE and immunohistochemical staining. The experimental data were analyzed by SPSS 24.0 software. $P < 0.05$ indicated statistical significance.
Results: Eight weeks after modeling, the serum AMA was positive and the ALP was significantly increased in PBC mice compared with control group. The pathology showed lymphocyte infiltration in the portal area, and damage and reactive proliferation of small bile duct, and $CD4^+$ and $CD8^+$ T cells were infiltrated around the bile duct. Flow cytometric examination of spleen cells revealed recovery of reduced Tregs and increased Th17 after low-dose IL-2 treatment (Treg/CD4%:9.26 ± 0.50 vs 6.10 ± 0.14 vs 8.24 ± 0.04; Th17/CD4%: 0.29 ± 0.20 vs 1.00 ± 0.17 vs 0.33 ± 0.09) ($p < 0.05$) (Fig. B). Low-dose IL-2 treatment inhibited IL-17A levels (0 vs 4549 ± 597.5 vs 1928 ± 387) ($p < 0.05$) and improved serum biochemical index (ALP: 119.1 ± 6.20 vs 82.36 ± 12.6 U/L) (Fig. C). Histopathological examination of liver revealed the improvement of portal area inflammation and reactive bile duct hyperplasia and damage after low-dose IL-2 treatment (Fig. D).