EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Focus

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Role of regulatory T cells and control of NK cell activation in experimental biliary atresia – a further clue for deciphering the pathogenesis of this neonatal cholangiopathy

Extra hepatic biliary atresia is a relatively common cholestatic liver disease affecting one in 10–20,000 newborns which develop an obstructive cholangiopathy. The etio-pathogenesis of this entity is not fully understood. A number of mechanisms have been proposed to explain the rapid development of the characteristic destructive cholangiopathy which requires immediate surgical intervention, preferably within 4–8 weeks after birth. These include among others, an infectious etiology, i.e., by group C Rota virus, cytomegalic virus infection, immune mediated injury as a result of immune dysregulation, a graft versus host induced cholangiocyte injury by maternal chimeric lymphocytes, and a genetic etiology which leads to an undefined susceptibility to environmental infectious agents or toxins.

In this issue of the journal, Miethke and co-workers have used an experimental mouse model of rhesus Rota virus (RRV) infection in which intraperitoneal injection of RRV within 3 days of birth leads to a natural killer cell (NK) mediated inflammatory cholangiopathy in neonatal balb/c mice by day 7. Previously, these investigators have elucidated the role of interferon γ, $CD8^+$, and NK cells in the initiation of neonatal cholangiopathy in this model. In a set of elegant and exhaustive *in vivo* and *in vitro* experiments, the authors now provide evidence for the role of T regulatory cells (Tregs) in the development of biliary atresia in the mouse model. Data obtained suggest that early, postnatal absence of T regulatory cells (Tregs) is a key factor in development of a cholangiopathy, allowing hepatic dendritic cells (DC) to activate NK cells, leading to the initiation of bile duct injury characteristic for biliary atresia. It is not yet known whether a similar mechanism of immaturity of the immune system (and decreased or absence of Treg activity) is also present in the early neonatal period in human neonates with biliary atresia. Confirmation of these results in babies with biliary atresia is difficult and probably impossible. However, indirect support for a similar mechanism in humans is provided in this paper by the increased expression of Tregs signature genes in liver tissue obtained from nine babies with biliary atresia. In summary, this report adds further important information on the mechanism of immune mediated biliary injury in experimental biliary atresia.

Impact of anti-viral therapy on incidence of hepatocellular carcinoma and survival of hepatitis C patients with advanced fibrosis

A 2008 US NIH consensus statement regarding the impact of anti-viral treatment against hepatitis B on the incidence of complications and outcome of chronic HBV included the following statement: "*The major goals of anti-HBV therapy are to prevent the development of progressive disease, specifically cirrhosis and liver failure, as well as hepatocellular carcinoma development and subsequent death. To date, no RCTs of anti-HBV therapies have demonstrated a beneficial impact on overall mortality, liver-specific mortality, or development of hepatocellular carcinoma*" (http://consensus.nih.gov/2008/statementhep).

A similar question mark has been raised regarding the impact of anti-viral therapy in hepatitis C virus (HCV) infection on the incidence of hepatocellular carcinoma (HCC) and other long-term complications of chronic hepatitis C.

In the absence of prospective controlled trials, it is still difficult to assess the long-term beneficial effect of anti-viral therapy and sustained anti-viral response (SVR) on the natural course and complications of chronic HCV infection in general and HCC in particular. Previous reports have demonstrated only a marginal beneficial impact of interferon therapy on the incidence of HCC as concluded by a meta-analysis by Craxi and Camma (*Clin Liver Dis 2005;9:329*). In this issue of the journal, Cardoso and co-workers report their single center retrospective analysis on the impact of anti-viral therapy (primarily by combined peginterferon and ribavirin) on the incidence of HCV associated HCC in a cohort of 127 patients with bridging fibrosis (F3) and 180 patients with cirrhosis (F4). The main finding of this report is a significantly lower incidence rate of HCC in patients who achieved an SVR as compared to non-SVR patients. Multi-variate analysis confirmed that non-SVR was an independent predictor of HCC, of liver related complications (ascites, bleeding esophageal varices) and liver related mortality. Surprisingly, the overall SVR rate of 33% is lower than expected in a population of patients which includes also genotype 2 and 3 subjects with chronic HCV. This result may however explain the relatively higher rate of HCC in the present study population as compared to another study performed in Italy (*Bruno S et al. Hepatology 2007:45:579*). Although these results which report a relatively short mean follow-up of 3.5 years may seem obvious to the practicing hepatologist, the data provided add important information. The conclusions derived from this study deliver a message emphasizing the importance of anti-viral therapy in patients with advanced fibrosis and compensated cirrhosis despite the clinical experience that such patients may not tolerate this treatment very well.

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