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Clinical and molecular features of chronic hepatitis C infection and advanced liver disease

AKADEMISK AVHANDLING

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GENERAL SUMMARY

The aim of this thesis was to study molecular and clinical aspects of hepatitis C infection (HCV), especially in patients with advanced liver disease.

In the first study we investigated whether the use of a second generation contrast agent in ultrasound (US) examinations can improve detection of hepatocellular carcinoma (HCC) and characterisation of focal liver lesions in 49 HCV-infected patients with liver cirrhosis. In total 96 examinations with conventional US followed by a contrast-enhanced ultrasound (CEUS) examination were analysed retrospectively. The number of diagnosed malignant liver lesions increased from one to ten after CEUS.

In the second study we analysed the efficacy and tolerability of combination therapy with pegylated interferon (peg-IFN) and ribavirin in 104 patients with HCV-associated Child-Pugh class A liver cirrhosis at a Swedish university clinic. Sustained virological response (SVR) was achieved in 13% of genotype 1-, 60% of genotype 2-, and 31% of genotype 3-infected patients. In treatment-naïve patients, the corresponding rates were 13%, 82% and 38% respectively. In 46% of patients, treatment was discontinued prematurely owing to a lack of virological response in the majority. SVR rates found in our study, in particular for genotype 1 patients, were lower than those generally found in randomised controlled studies.

In the third study we evaluated the long-term impact of SVR to antiviral therapy on the risks of developing HCC, liver complications and death in 351 HCV-infected patients with compensated Child-Pugh class A liver cirrhosis. They were followed prospectively for a mean of 5.3 years, up to 8.6 years. Among patients with SVR (n=110), 5.0% developed HCC, 3.6% ascites, 0.9% liver encephalopathy and none variceal bleeding. The incidences of HCC, any liver complication, liver-related and overall death per 100 person-years were 1.0, 0.9, 0.7 and 1.8% among patients with SVR versus 1.9, 2.5, 2.4 and 3.1% respectively among patients without SVR (n=241). Risks of HCC, liver decompensation and death were markedly reduced in patients with SVR, but the risk of developing HCC was remaining at 1% per year.

In the fourth study we investigated whether there is an association between levels of the HCV NS3 protein in liver biopsies, T cell protein tyrosine phosphatase (TCPTP) cleavage and clinical parameters in patients with chronic HCV infection. Hepatic NS3 and TCPTP protein levels were determined in liver biopsies from 69 HCV RNA-positive patients and 16 control patients. Levels were correlated to viral load or clinical parameters for the severity of liver disease. We found that intrahepatic NS3 expression and the viral load were inversely correlated with intrahepatic TCPTP protein levels. Detection of NS3 did not associate with any other clinical parameters. The clear link demonstrated suggests that TCPTP cleavage may have important consequences for the HCV life-cycle and HCV-induced liver diseases.

Conclusions: In HCV-infected patients, TCPTP cleavage may play an important role for the viral life-cycle and progress of HCV-induced liver disease. Patients with HCV-induced liver cirrhosis who receive standard of care therapy in clinical settings achieve SVR at lower rates than those generally found in randomised controlled studies, in particular genotype 1 patients. If SVR is achieved, risks of HCC, liver decompensation and death are markedly reduced in these patients, but the risk of HCC remains at a non-negligible level, warranting a continued surveillance for HCC. Diagnostic confidence may be improved with CEUS in surveillance for HCC. Patients with HCV-induced liver cirrhosis constitute a clinically challenging group of patients. Additional studies are needed to further understand the pathogenesis of HCV and how it establishes a chronic infection, in order to improve the rate of eradication by treatment and to identify prognostic factors for liver complications after achieving SVR, along with optimising surveillance in patients with chronic HCV infection, so that survival may be increased.