Background on viral hepatitis B and hepatitis C

Viral hepatitis is a major cause of chronic liver disease and a worldwide public health problem. It is estimated that over 350 million people are infected with hepatitis B virus and as for hepatitis C infections conservative estimates are at over 200 million persons. While in the developed countries the spread of hepatitis B has been all but controlled by sanitary measures and vaccination campaigns this is by far not been the case in developing countries where it represents a leading cause of death with cirrhosis and liver cancer. It is even more so the case for hepatitis C which is still a significant health issue in most countries where reported prevalence vary from 1.8% in the US to possibly more than 15% in Vietnam. If the 4 million Americans and the 5 million Europeans chronically infected with hepatitis C have access to potentially curative therapy, the remainder 95% of patients in the world are at risk of developing severe liver disease with significant mortality.

Hepatitis B: HBV

HBV is a DNA virus of the family of Hepadnaviridae identified more than 30 years ago which replicates in the hepatocyte where the viral genome is integrated into the nucleus. The markers of active infection are the hepatitis B surface antigen (HBsAg), the hepatitis B e antigen (HBeAg) and the hepatitis B core antigen (HBcAg). Chronic hepatitis B carriers have a 15-40% risk of developing serious complications such as cirrhosis and hepatocellular carcinoma (HCC) in their lifetime. The prevalence of HBV serologic markers in the US is 13% for persons born in high endemic areas such as South East Asia and China, 7% in injecting drug users, 6% in men who have sex with men, 8-11% in HIV infected patients, 3-10% in dialysis patients and 0.4-1.5% in pregnant females.

Laboratory tests: HBV can present as chronic hepatitis B (HBsAg +, HBV DNA > 10^5 copies, high ALT, high score on biopsy), as inactive HBsAg carrier state (HBsAg +, HBeAg -, HBV DNA < 10^5 copies, normal ALT, low score on biopsy), and as resolved hepatitis B (anti-HBc +/−, anti HBs positive, HBsAg negative, undetectable HBV DNA, normal ALT).

In South East Asia most of the chronic HBV infection results from perinatal transmission. There usually is a prolonged immune tolerant phase with positive HBeAg, high HBV DNA and normal ALT with later development of chronic hepatitis B with elevated ALT levels. When transmission of HBV occurs in adults through sexual activity or injections in drug users, seroconversion is commonly seen in a shorter period of time. High values of HBV DNA are associated with more severe liver disease.

Clinical issues: the incidence of cirrhosis in VHB is reported as 3% per year in HBeAg positive patients. The risk of primary liver cancer (HCC) increases in cirrhotic patients with age and alcohol consumption whether HBeAg has been cleared or not. Periodic screening is recommended in cirrhotic patients.
HBV replication is evaluated with HBeAg and HBV DNA. Screening for HCC requires determination of the AFP marker and an ultrasound. Liver biopsy allows definition of stage and grade of liver disease. Based on a thorough evaluation patients can be selected for antiviral therapy or included in a monitoring program. Whether treated or not carriers of hepatitis B should be given information as to the risk of sexual and perinatal transmission. As well household members should be given advice to be vaccinated if they are negative for HBV and newborns of HBV positive mothers should receive HB immunoglobulin and vaccine at delivery.

**Treatment:** the goal of treatment is to achieve sustained suppression of HBV replication which translates into remission of liver disease. End points include achieving normal ALT levels, undetectable HBV DNA and seroconversion of HBeAg into anti HBe. Efficacy of pharmacologic therapy is still disappointing to this date. Interferons are effective in suppressing HBV replication in some selected groups of patients. These agents (Pegasys ®, Peg-Intron ® ) with antiviral, antiproliferative, and immunomodulatory effects have to be administered as weekly subcutaneous injections for periods of 6 to 12 months or more which lead to substantial side effects such as fatigue, flu-like symptoms and depression as well as adverse events such as leucopenia. Long term outcome of treatment is largely unknown. Useful antiviral agents approved for HBV treatment include lamivudine (Zeffix ®) and adefovir dipivoxil (Hepsera ®). Several other agents are currently evaluated in clinical trials (telbuvidine, emtricitabine, entecavir, tenofovir). Although effective in suppressing viral replication these well tolerated antivirals have down sides because of the development of mutant forms of HBV and the frequent relapse after treatment is stopped.

**Hepatitis C: HCV**

HCV is an RNA virus belonging to the family of Flaviviridae recognized since the late eighties as the leading cause of transfusion associated chronic hepatitis. With blood screening measures transmission through blood products has been controlled to a large extent in most countries. There remain factors associated with infection such as injection-drug use and poor healthcare practices such as reusable syringes and needles. Sexual and maternal-fetal transmissions are inefficient means of infection. While the acute phase of hepatitis C is difficult to diagnose it is estimated that 75% of seropositive persons have circulating virus (viremia) and chronic liver disease. Severe complications with cirrhosis may develop in 20% of infected persons with a risk of carcinoma of 1-4% per year which makes hepatitis C the leading cause of liver transplantation in the US and EU.

**Laboratory tests:** HCV testing is recommended in persons with unexplained abnormal ALT and AST levels, in injected illicit drug users, in case of HIV, in case of blood transfusion prior to 1992, in hemodialysis patients, in hemophiliacs, in children born to HCV-infected mothers, in health care workers at risk of needle stick injury. HCV RNA is detected for a qualitative assay in the blood with PCR (polymerase chain reaction) and TMA (transcription-mediated amplification). A quantitative assay
is required when treatment is considered to predict and monitor response (Versant - Bayer Diagnostics).

There are 6 distinct genotypes of HCV which are relevant to predict response to therapy and define duration of treatment. Genotyping is performed by direct sequence analysis (Visible Genetics) or by reverse hybridization of PCR amplicons (Inno LiPA HCV II – Innogenetics).

Liver biopsy has been the gold standard to define degree of inflammation and stage of fibrosis in HCV. Several scoring systems are used to stage liver disease: Metavir, Ishak. Response to treatment is better in patients with milder degrees of fibrosis.

Clinical issues: after infection with HCV 3 out of 4 persons will remain infected and up to 20% will develop cirrhosis over a period of 20-30 years with a risk of liver cancer (HCC) of 2% per year. The indications for treatment take into account the genotype, the liver biopsy score, and other clinical factors such as alcohol intake, history of depression, compliance, presence of extrahepatic symptoms, co-infections with HIV, and so forth. In order to avoid transmission of HCV infected persons must be counselled not to share toothbrushes and razors, not to donate blood, to inform of their condition in case of wounds and dental care, and for those concerned to stop using illicit drugs or at least not to share material used for injections.

Treatment: with the goal to prevent liver complications treatment aims at achieving sustained virologic response (SVR) which is absence of HCV RNA 6 months after therapy. Over the last few years there have been significant improvements in the success of HCV treatment. After demonstrating that Interferons were useful in achieving response rates in a minority of patients a major breakthrough was the development of pegylated Interferons. These are produced by binding an inert PEG (polyethylene glycol) moiety to interferon molecules which increases the half life of the active agent (Pegasys®, Peg-Intron®). It can thus be given in weekly subcutaneous injections. Treatment protocols associate an antiviral agent ribavirin (Rebetol®, Copegus®). According to the genotype treatment duration can be 24 weeks or 48 weeks and response rates (SVR) are reported from 40-50% for genotype 1 and 70-80% for genotypes 2 and 3. Results are not as good in African-Americans and in co-infections with HIV. There are many adverse events during treatment such as depression, flu-like symptoms, irritability, fatigue, fever, neutropenia due to Interferon as well as haemolytic anemia, itching, rash due to ribavirin. Case to case decisions have to be made for special patient groups such as children, HIV co-infection, and renal disease. These events require strict selection criteria of patients and close follow-up with a substantial amount of laboratory work up by experienced providers.