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Hepatitis B and C in Asians

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Abstract

This review will focus on hepatitis B, because chronic hepatitis B virus (HBV) infection is by far the most important cause of chronic liver disease in Asians. In addition, there are significant differences in the epidemiology, natural history and response to treatment between Asians and Caucasians with chronic hepatitis B.

Hepatitis B

Epidemiology

It has been estimated there are approximately 350 million HBV carriers in the world, of whom 80% are Asians. The high prevalence of chronic HBV infection among Asians is related to a high frequency of maternal-infant transmission. Perinatally acquired hepatitis B leads to a very high (~90%) rate of chronic infection while the risks of progression to chronic infection are 20%-50% in early childhood infection and <5% in adult acquired infection. In the United States, HBV infection is predominantly acquired in adult life via heterosexual transmission.

Natural History

The natural course of chronic HBV infection is determined by the interplay between virus replication and host immune response. Chronic HBV infection generally consists of two phases: an early replicative phase with active liver disease and a late non-replicative phase with remission of liver disease. In patients with perinatally acquired HBV infection, there is an additional immune tolerance phase characterized by high levels of HBV replication (presence of hepatitis B e antigen [HBeAg] and HBV DNA in serum) but no evidence of active liver disease as manifested by lack of symptoms, normal serum aminotransferase (ALT) levels and minimal changes on liver biopsy. Immune tolerance is believed to be the major reason for the poor response to interferon therapy in HBeAg positive Asian patients who have normal ALT levels. The immune tolerance phase usually lasts 10 to 30 years, during which there is a very low rate of spontaneous HBeAg clearance. The low rate of viral clearance in children and adolescents accounts for a high prevalence of HBeAg among carrier women of reproductive age leading to a high frequency of maternal-infant transmission.

Transition from the immune tolerant to the immune clearance phase occurs during the second and third decades in patients with perinatally acquired HBV infection. During the

immune clearance phase, spontaneous HBeAg clearance occurs at an annual rate of 10%-20%. HBeAg seroconversion is frequently, but not always, accompanied by biochemical exacerbations (abrupt increase in serum ALT levels). Most exacerbations are asymptomatic. However, some are accompanied by symptoms of acute hepatitis and may lead to misdiagnosis of acute hepatitis B in patients who are not previously known to have chronic HBV infection. Exacerbations are more commonly observed in men than in women. The reason for the gender difference is not clear, but a higher frequency of exacerbations in men may at least in part account for a higher incidence of HBV-related cirrhosis and hepatocellular carcinoma among men. In a small percent of patients, exacerbations result in hepatic decompensation and rarely death from hepatic failure.

With time, patients enter into the low or non-replicative phase. During this phase, patients are HBeAg negative, anti-HBe positive. In some patients, virus replication has ceased and liver disease is in remission, although they remain HBsAg positive. Many patients continue to have very low levels of virus replication, but liver disease is usually inactive. Reactivation of HBV replication with reappearance of HBeAg and HBV DNA in serum and recrudescence of liver disease may occur when these patients are immunosuppressed. A small percent of patients continue to have moderate levels of HBV replication and active liver disease. These patients may have residual wild type virus or mutant HBV that cannot produce HBeAg due to mutations in the precore or core promoter region of the HBV genome.

The sequelae of chronic HBV infection vary from an asymptomatic earner state to the development of cirrhosis, hepatic decompensation, hepatocellular carcinoma and death. Among Chinese patients with chronic HBV infection, the life-time risk of a liver-related death has been estimated at 40%-SO% for men and 15% for women. Patients with a prolonged replicative phase have been shown to have worse prognosis. This may be related to a longer duration of necroinflammation, which in tum increases the risks of fibrosis, cirrhosis and perhaps carcinogenesis.

Prevention

Safe and effective vaccines are available for the prevention of HBV infection. Vaccination of newborns is the most effective prophylaxis, because of the high acceptance rate (especially if incorporated with other childhood vaccination) and its effect on reducing chronic HBV infection. In Taiwan, the HBsAg carrier rate among children has been reduced from 9.8% to 1.3% and the incidence of childhood hepatocellular carcinoma has decreased from 0.70 to 0.36 per 100,000 after 10 years of mass vaccination. The United States has adopted a broad approach to eliminate HBV transmission, including vaccination of all infants, catch-up vaccination of high-risk children and adolescents, and vaccination of high-risk adults.

Treatment

The main aim of treatment in chronic hepatitis B is to suppress HBV replication before there is significant, irreversible liver damage. The initial end-points of therapy are sustained clearance of HBeAg and serum HBV DNA (by hybridization assays) and improvement in liver disease, as indicated by normalization in serum ALT and decrease in necroinflammation on liver biopsy. Interferon-alfa (IFN-alpha)

Currently, IFN-a is the only approved treatment of chronic hepatitis B in most countries. IFN-a should be considered for patients with chronic HBV infection (HbsAg positive for more than 6 months), who have evidence of active virus replication (presence of HBeAg and serum HBV DNA by hybridization assay), and active liver disease (abnormal ALT and chronic hepatitis on liver biopsy). Interferon should be administered as subcutaneous or intramuscular injections in doses of S million units daily or 10 million units three times a week for 3-6 months. Response as defined by sustained clearance of HBeAg is generally observed in approximately 30%-40% of patients. However, the response appears to be lower in Asians. In an initial study, only 15% of Chinese adults treated with IFN-a had sustained clearance of HBeAg. In a subsequent study, HbeAg positive Chinese adults with elevated ALT were separately randomized from those with normal ALT levels. Sustained clearance of HBeAg was observed in 39% of patients who had elevated but in only 5% of those with nomal pre-treatment ALT levels. These findings confirmed that Asian patients who are HBeAg positive and have normal ALT levels (presumably still in the immune tolerant phase) respond poorly to IFN-a therapy.

However, the response was significantly better in patients with elevated ALT levels and comparable to that in Caucasian patients. These data suggest that the difference in response to IFN-a therapy between Asian and Caucasian patients is not related to genetic differences but to differences in age at infection and immune reactivity to HBV.

New antiviral agents

Many new antiviral agents have become available recently and have shown promise in the treatment of chronic hepatitis B. These include lamivudine, famciclovir, lobucavir and adefovir. These compounds are administered orally and are very well tolerated. They produce rapid and marked decrease in serum HBV DNA levels, but the effect is usually not maintained when treatment is stopped, thus necessitating long term treatment.

Of the new antiviral compounds, lamivudine or 3TC is the most extensively evaluated. It has been tested in two clinical trials in Asia. Preliminary data suggest that the overall efficacy of lamivudine in Asians is similar to that in Caucasians but the response in patients with normal ALT levels may be lower. In an initial study from Hong Kong, 42 Chinese patients were randomized to receive placebo or lamivudine for 4 weeks. Serum HBV DNA decreased by more than 90% in all the treated patients but none of the patients cleared HBeAg. In a subsequent ongoing study, 358 Chinese patients from Hong Kong, Taiwan and Singapore were randomized to receive placebo or lamivudine for one year. The responses in the treated patients vs. controls at the end of one year were respectively: HBeAg seroconversion - 16% vs. 4%, normalization in serum ALT - 72% vs. 24% and improvement in liver histology - 67% vs. 30%. However, 14% of the treated patients developed drug resistant HBV mutants. Recent data showed that the rate of HBeAg sero conversion increased to 25% at the end of the second year of therapy, but the rate of drug resistant mutants also increased to 38%. Although most patients with lamivudine resistant HBV mutants have mild liver disease, it is not clear if the pathogenicity of the mutants will increase with time. The role of lamivudine in the treatment of Asians with chronic hepatitis B depends on the rate of sustained response with longer duration (> 1 year) of treatment,

the incidence of drug resistant mutants and the long-term outcome of patients with these mutants.

Other treatment modalities

Other treatment that has been shown to have promise in Asian patients include thymosin: thymic derived peptides that may stimulate T cell function. In a recent study in Taiwan, patients who were treated with thymosin had a higher rate of HBeAg clearance and a higher rate of histologic improvement compared to controls. However, data on efficacy of thymosin in other studies have been conflicting.

Hepatitis C

Hepatitis C in Asians behaves very similarly to hepatitis C in Caucasians. Apart from Japan, chronic HBV infection is significantly more common than chronic HCV infection in Asian countries and is the predominant cause of cirrhosis and hepatocellular carcinoma. There is no indication that the natural history or response to treatment in Asians with chronic hepatitis C is different from that in Caucasians. Because of the high prevalence of chronic HBV infection in Asia, a small percent of Asian patients are dually infected with chronic HBV and HCV infection. In the majority of these patients, HCV appears to be the predominant cause of liver disease while HBV replication is suppressed. Despite the suppression of HBV replication, patients with dual infection tend to have more severe liver disease than patients infected with one virus only.