Research update

Chronic Hepatitis B in Asia—New Insights from the Past Decade
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Introduction

Chronic hepatitis B virus (HBV) infection is a major global health problem whose greatest impact is in the Asia-Pacific region. With the availability of sensitive HBV DNA assays and studies based on long-term longitudinal databases, the natural history of chronic HBV infection has become much better understood. The advances in antiviral therapy have also greatly improved the prognosis of this dreadful condition. Nonetheless, many challenges still remain. This review article summarizes the recent progress in the epidemiology, understanding of the natural history, and the challenges in management of chronic hepatitis B in the Asia-Pacific region.

Epidemiology of Chronic Hepatitis B

It is estimated that at least 2 billion people or one-third of the world population have been exposed to HBV infection. Approximately 400 million people worldwide or about 6% of the world population are chronically infected with HBV. Globally, 30% of cirrhosis and 53% of hepatocellular carcinoma (HCC) are caused by HBV infection. Each year, an estimated 500,000 people die because of HBV-related cirrhosis and HCC.

Chronic HBV infection in the Asia-Pacific region

The prevalence of HBV infection is highly endemic throughout the world, with much higher prevalence in Asia and the Pacific Islands, sub-Saharan Africa, the Amazon Basin, and Eastern Europe. About three-quarters of chronic HBV carriers live in the Asia-Pacific region and 15% to 25% of them will eventually die because of HBV-related liver disease.

Among Asian countries, the prevalence of chronic HBV infection varies greatly. High prevalence (>40%) regions include mainland China, Taiwan, Korea, Philippines, Thailand, Vietnam, and South Pacific island nations. Intermediate prevalence (2%–7%) regions include central Asia, Indian subcontinent, Indonesia, Malaysia, and Singapore. Australia and New Zealand belong to the low prevalence (<2%) countries, but the prevalence has increased in recent years due to immigrants from high prevalence countries.

Natural History of Chronic Hepatitis B

Phases of HBV infection in Asian patients

Perinatally acquired chronic hepatitis B is traditionally classified into three phases. The immune tolerance phase marks the initial two to three decades when hepatitis B e antigen (HBeAg) is positive. HBV DNA is very high, alanine aminotransferase (ALT) is normal, and histologic injury is minimal. It is followed by the immune clearance phase when host immune clearance leads to a reduction in HBV DNA and elevation in ALT levels. Patients who have prolonged, unsuccessful immune clearance will have progressive liver fibrosis, which eventually develops into liver cirrhosis. Successful immune clearance will lead to the third, low replicative phase, which is characterized by HBeAg seroconversion with positive anti-HBe antibodies, suppression of HBV DNA, and normalization of ALT.

In the low replicative phase are believed to have good prognosis. There is increasing evidence that a fourth phase—the immune escape phase—is also common in Asian patients in association with evolution of HBeAg-negative mutant forms of HBV. These patients have elevated HBV DNA with intermittent elevated ALT levels. HBeAg-negative patients with persistent viremia and biochemical activity have a higher risk of cirrhotic complications and HCC.
Clinical review

Safety and Efficacy of Oral HD-03/ES* Given for 6 Months in Patients with Chronic Hepatitis B Virus Infection

Rajkumar JS, et al.

Liver Function

Results of the study showed that 13 of the 25 patients (52%) who were treated with HD-03/ES had undetectable HBsAg at the end of treatment. This difference was statistically significant (P < 0.01) (Figure 1). HBsAg loss (60%, P < 0.01) and HBV DNA loss (60%, P < 0.05) also occurred during treatment with HD-03/ES in that 6 patients who were positive for both HBsAg and HBV DNA initially, but were negative for the same at the end of therapy (Figures 2 and 3).

Virological response

Clinical response

Six months of therapy with HD-03/ES capsules was markedly effective in majority of the patients as it resulted in disappearance or alleviation of clinical symptoms such as abdominal pain and poor appetite. Results showed that there was a trend toward normalization of liver function tests in all patients treated with HD-03/ES for 6 months (Table 1).

Introduction

Hepatitis B virus (HBV) is a hepatavirus that is noncytopathic and causes significant morbidity and mortality worldwide. Chronic hepatitis B (CHB) affects an estimated 400 million people worldwide with >50,000 fatalities each year. About 82% of the world's 530,000 cases of liver cancer per year are caused by viral hepatitis infection, with 316,000 cases associated with hepatitis B infection. According to a WHO report, India has intermediate endemicity of hepatitis B, with hepatitis B surface antigen (HBsAg) prevalence between 2% and 7% among populations studied. It has been estimated that, in India, of the 25 million infants born every year, over 1 million run the lifetime risk of developing chronic HBV infection. Every year more than 100,000 people in India die due to illnesses related to HBV infection.

A preliminary case study report indicated that there was significant reduction of HBeAg along with disappearance of viral DNA in a patient treated with HD-03/ES (a capsule formulation consisting of 125 mg each of hydroalcoholic extracts of the herbs Cypersus rotundus and Cypersus scariosus) as a dosage of two capsules twice daily for a period of 6 months. At the moment, there is no data to show whether HD-03/ES treatment is adequate for the treatment of HBV infection. Therefore, this clinical study was conducted to evaluate the safety and efficacy of HD-03/ES in patients with chronic hepatitis B infection.

Materials and Methods

Patients

An open prospective controlled clinical trial was conducted to evaluate the safety and efficacy of HD-03/ES capsules alone in the management of chronic hepatitis B infection. Patients, aged 18 to 60 years, with their serum alanine aminotransferase (ALT) level between 41 and 200 IU/L and who had positive serum HBsAg, were enrolled. Informed written consent was obtained from all study participants and the protocol of the study was approved by the ethical committee of the institute.

Treatment

Each patient was asked to take two capsules of HD-03/ES twice daily for a period of 6 months.

Etiological markers of hepatitis B

Serum samples collected from patients were stored at −20°C until analysis. Serum was assayed for HBsAg, hepatitis B e antigen (HBeAg), and HBV DNA at baseline and 4 and 6 months after therapy using commercially available enzyme-linked immunosorbent assay kits from Roche.

Liver function

Liver function examinations, including contents of serum proteins, total bilirubin (TB), and activities of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), were done every month during the treatment.

End points

The primary end point was HBsAg clearance. Secondary end points included HBV DNA levels and ALT normalization to 40 IU/L at the end of treatment.

Statistical analysis

The intention-to-treat analysis included all randomized patients who were HBeAg positive at baseline and received at least one dose of the study medication. Data were expressed as mean ± SD.

Results

Twentyfive patients (22 males and 3 females) aged between 20 and 45 years, with a mean age of 33.7 years, participated in this open study.
Hepatitis B Infection

What are the clinical case definitions for reportable hepatitis B virus infections?

According to the Centers for Disease Control and Prevention (CDC), acute hepatitis B is defined as an acute illness with discrete onset of symptoms and jaundice or serum aminotransferase (ALT) levels of >200 IU/L. Laboratory criteria for diagnosis of acute hepatitis B infection include the presence of hepatitis B surface antigen (HBsAg) or IgM antibody to hepatitis B core antigen (anti-HBc) and negative for IgG antibody to anti-hepatitis A virus. An acute case of hepatitis B is confirmed if it meets the clinical case definition, is laboratory confirmed, and is not known to have chronic hepatitis B.

Patients with chronic hepatitis B may be asymptomatic and have no evidence of liver disease or have a spectrum of diseases such as chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC). Laboratory criteria for diagnosis of chronic hepatitis B include negative result for IgM anti-HBc and positive result for one of these tests—HBsAg, hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), or hepatitis B virus (HBV) DNA or positive result for HBsAg, HBV DNA, or HBeAg two times at least 6 months apart.

A chronic case of hepatitis B is confirmed if it meets either of the above laboratory criteria for diagnosis. Chronic hepatitis B is probable if a person with a single HBsAg positive or HBV DNA positive or HBeAg positive lab result and does not meet the case definition for acute hepatitis B.

What are the major challenges in determining the treatment for an HBV-infected patient and optimal long-term management in clinical practice?

The primary goal of treatment for chronic hepatitis B is to reduce and maintain suppression of HBV replication to the lowest possible level, as evaluated by highly sensitive assays for HBV DNA, in order to prevent the progression of advanced liver diseases and failure. Although treatment is not required in patients in immune tolerance phase, it should be considered in those in immune clearance and reactivation phases of infection. Patients with HBeAg-negative chronic hepatitis B are treated long-term with the goal of durable and profound suppression of serum HBV DNA, as relapse is very common if treatment is stopped after serum HBV DNA becomes undetectable. However, development of resistance is possible with almost all currently available long-term therapies for hepatitis B.

Long-term therapy is commonly required and resistance is likely, with all agents in current use. For instance, pegylated interferon has comparable efficacy to antiviral agents, with the advantage of a shorter, fixed duration therapy without drug resistance, but the disadvantage of increased side effects. Therapy should be individualized. Regular monitoring is required to identify resistance, hepatitis flares, and response.

What is the role of currently available therapies for hepatitis B?

At present, the approved therapies for hepatitis B such as antivirals and interferons have relative advantages and disadvantages. Some of these disadvantages include parenteral administration and frequent dosing, with the advantage of a shorter, fixed duration therapy without drug resistance, but the disadvantage of increased side effects. Therapy should be individualized. Regular monitoring is required to identify resistance, hepatitis flares, and response.

Quantification of hepatitis B virus (HBV) DNA can be used for diagnosing HBV infection and monitoring the effect of antiviral therapy. However, probably because of mismatches between the template and primer/probe, HBV DNA in some HBV infections could not be detected using currently available commercial assays with single primer/probe. By aligning the HBV sequences, a duplex real-time polymerase chain reaction (PCR) assay was developed using two sets of primers/probes and a specific armored DNA as internal control (IC). The limit of the duplex real-time PCR assay was 29.5 IU/mL, whereas the specificity was 100%. The within-run precision coefficient of variation (CV) ranged from 1.02% to 2.73%, while the between-run CV ranged from 0.83% to 2.15%. The optimal concentration of armored DNA IC in the HBV DNA duplex real-time PCR assay was 1000 copies/mL. Data from 69 serum samples with HBV infection showed that the performance of the duplex real-time PCR assay was comparable to that of the COBAS Ampliprep/Cobas Taqman (CAP/CTM) HBV assay and was superior to those of the domestic commercial HBV assays. The duplex real-time PCR assay is sufficiently sensitive, specific, accurate, reproducible, and cost-effective for the detection of HBV DNA. It is suitable for high throughput screening and frequent HBV DNA level monitoring.

Comparison of Hepatitis B Surface Antibody Decay Rates after Vaccination between Hemodialysis and Peritoneal Dialysis Patients

The available information about maintaining effective immunity after hepatitis B virus (HBV) vaccination in dialysis patients is limited. The aim of this study was to determine whether a difference exists in the persistence of immunity between hemodialysis (HD) and peritoneal dialysis (PD) patients. The decay rate of hepatitis B surface antibody (anti-HBs) titers after HBV vaccination was compared between HD and PD patients. A total of 103 HD and 53 PD patients who were completely vaccinated were enrolled. The anti-HBs titers were examined at least one month after vaccination and then annually thereafter. Changes in the anti-HBs titers were assessed by comparing annual geometric mean titer (GMTs). Slopes of the anti-HBs titer decay rates plotted on a logarithmic scale for the HD and PD groups were −2.41 and −3.48, respectively. The decay rate of the PD group was significantly faster than that of the HD group (P = .0053). The decay rate of anti-HBs titers in the PD group was faster than that in the HD group. Hepatitis B vaccination could not offer long-term protection in HD or PD patients. Postvaccination testing every 6 to 12 months is necessary and revaccination may be protective in dialysis patients, especially in hyperendemic areas of hepatitis B infection.

Herb facts

Cyperus rotundus

Cyperus rotundus, a pcursor of herbal medicine, has been used against yellow fever in various countries and is considered safe and effective in the treatment of viral hepatitis and liver diseases. The extract of C. rotundus was found to be effective in improving liver function in experimental studies. It is known for its hepatoprotective and antiviral properties, particularly against hepatitis B virus (HBV) and hepatitis C virus (HCV). The mechanism of action of C. rotundus involves the inhibition of viral replication and the induction of antiviral cytokines.

Cyperus rotundus is used in Lk.52 HB

Drug resistance is a major challenge in viral hepatitis treatment, and progress has been made in developing new antiviral drugs. The emergence of drug resistance during virological response is a major concern in the treatment of hepatitis B infection. The development of new antiviral drugs is crucial to overcome the limitations of existing therapies and to improve treatment outcomes.
Management of Chronic Hepatitis B Patients

Patient selection for treatment

The improvement in the knowledge of natural history and the advances in antiviral therapies have great impact on the selection of patient for treatment. As cirrhotic patients have the highest risk of HCC and other liver-related complications, there has been little controversy to commence antiviral therapy as far as viral replication can be documented. In the 2003 European and Asian-Pacific consensus statements, ALT >2 times the upper limit of laboratory normal was taken as the indicator of significant hepatitis among noncirrhotic patients who may warrant antiviral therapy. Recent data have increasingly recognized that patients with normal or mildly elevated serum ALT are not guaranteed to be free from liver damage and liver-related mortality. In fact patients who have persistent active HBV viremia can have progressive liver damage despite normal or mildly elevated ALT levels, regardless of the HBeAg status. As a result, in the recent updated regional guidelines, liver biopsy is recommended among patients with normal or mild elevated ALT levels regardless of the HBeAg status. It is a result, in the recent updated regional guidelines, liver biopsy is recommended among patients with normal or mild elevated ALT levels regardless of the HBeAg status. As a result, in the recent updated regional guidelines, liver biopsy is recommended among patients with normal or mildly elevated ALT levels, regardless of the HBeAg status. A drug regimen is modified according to the on-treatment HBV DNA response. However, the emergence of lamivudine- or adefovir-resistant mutant forms of HBV, which rapidly develop tenofovir (but not tenofovir) resistance would be a concern with this approach.

Antiviral therapy

Conventional interferon-alfa was the only available antiviral therapy for chronic hepatitis B between 1985 and 1996. Since the registration of lamivudine in 1997 and onwards, there has been an explosion in the development of antiviral treatments for chronic hepatitis B. Clevudine is registered only in Korea and the Philippines, but not in other countries due to the risk of myopathy. In the Asia-Pacific consensus statement, no clear recommendation has been made on the choice of antiviral agents. The major reason is the vast difference in the economic situation and medical reimbursement arrangements between different Asia-Pacific countries. In fact, the estimated annual cost of antiviral drugs, if accepted across the affected population, might exceed the gross national income per capita in countries such as India, Indonesia, Philippines, and Papua New Guinea. Detailed cost-effective analysis is warranted to guide usage policies for HBV antiviral drugs in the Asia-Pacific region. One possibility is the roadmap approach in which an inexpensive antiviral drug is started as the first-line treatment, and the drug regimen is modified according to the on-treatment HBV DNA response. However, the emergence of lamivudine- or adefovir-resistant mutant forms of HBV, which rapidly develop entecavir but not tenofovir resistance, would be a concern with this approach.