ELSEVIER

Advances in Hepatitis B Virus Infection

A.B. Jain and J.J. Fung

HEPATITIS B viral (HBV) infection is one of the most common persistent viral infections in humans. In the United States, 15,000 to 45,000 newly infected individuals are identified every year. However, the reported incidence has fortunately declined by 70% since 1987.

Hepatitis B virus is a partially double-stranded DNA virus, which replicates via an RNA intermediate, mainly in hepatocytes. There are six genotypes of the virus, A to F, which have a variable geographical distribution. These genotype differences may have clinical relevance to the natural history of the disease, the development of hepatocellular carcinoma (HCC), and the response to therapy.

HBV INFECTION

After HBV infection, the course of the disease is highly variable and unpredictable. The viral genotype and host immune response appear to play important roles in the clinical outcome. Patients with good immune defense mechanisms overcome the HBV infection and completely recover, with formation of HBsAb, which is protective for subsequent HBV infection. A small percentage of people present with acute fulminant liver failure, sometimes necessitating emergency liver transplantation. Approximately 15% of infected people acquire chronic HBV infection after an acute HBV infection. This incidence is much higher among cases of maternal transmission. These patients may become chronic carriers or may develop chronic hepatitis, which can lead to cirrhosis. Hepatocellular carcinoma may develop at any stage of the disease among the chronically infected population; however, its incidence is highest in patients with cirrhosis.

HBV SEROLOGY

Serum testing is extremely helpful to monitor the patient's response to HBV infection; however, more information, such as the genotype, serial assessment of viral load, liver function tests, and radiological imaging is necessary to understand the clinical course of the disease, which is highly variable.

HBsAb positivity alone implies immunity to subsequent HBV infection. The immunity lasts beyond 15 years, although booster HBV vaccination after 10 years is recommended. HBsAb positivity and HBcAb positivity is usually seen in individuals who have contracted and overcome HBV infection in the past. HBcAb is also thought to confer some protection against subsequent HBV infection. Patients with HBcAB positivity alone should be distinguished based upon IgM versus IgG responses, signifying recent infection versus recovery, respectively. The latter group should be vaccinated, with the hope of development of HBsAB. HBsAG positivity alone (without HBeAg or HbcAg) describes patients who have undetectable or low viral loads of HBV DNA and are chronic carriers. It is recommended that they be followed with AFP, LFTs, HBV DNA, and possibly ultrasound imaging of the liver every six

From the Thomas E. Starzl Transplantation Center (A.B.J., J.J.F.), Pittsburgh, Pennsylvania; and University of Rochester Medical Center (A.B.J.), Rochester, NY.

Address reprint requests to Dr Ashokkumar B. Jain, University of Rochester Medical Center, Box SURG, 601 Elmwood Ave, Rochester, NY 14642. E-mail: Ashok_Jain@URMC.Rochester.edu

0041-1345/03/$–see front matter
doi:10.1016/S0041-1345(02)03996-9

months. Some patients display periodic reactivation of the disease, with elevated ALT values and increased HBV DNA. Recurrent episodes can lead to significant liver injury. HBsAg-positive patients who are also HbcAg or HBeAg positive are often DNA positive. These individuals are actively infected and display viral replication. They should be treated with anti-HBV medications and followed serially with liver function tests, AFP levels, and ultrasound imaging for HCC. Serological testing of des-(γ)-carboxy-prothrombin (DCP) has also been proposed as a useful marker for HCC.

MUTATIONS AND THEIR IMPLICATIONS

HBV is prone to mutation because it replicates via a reverse transcription mechanism from an RNA intermediate. The three most common natural variants or mutants are the S gene mutant, the core promoter or precore mutant, and the P gene mutant. S gene mutants have been described to occur in babies born to HbsAg+ mothers who develop HBV infection despite vaccination and in liver transplant recipients who develop recurrent hepatitis B despite HBIG prophylaxis. This is a result of immune selection. The precore or core mutant inhibits HBeAg production and can lead to chronic hepatitis. These patients who can be HBV DNA positive and HbsAg negative,[1–5] appear to respond better to interferon. The P gene mutant is usually a drug (Lamivudine)-induced mutation, which affects the highly conserved $YM_{552}DD$ motif of the viral polymerase with substitution of amino acid valine or isoleucine with methionine. The YMDD motif, which lies in the nucleotide binding pocket of the viral polymerase, is necessary for the catalytic activity of the enzyme. This YMDD mutant reduces the susceptibility to Lamivudine but does not appear to affect Adefovir inhibition of the enzyme.[6–8]

PATHOLOGY

Chronic HBV infection leads to chronic periportal, portal, and spotty lobular inflammation, with gradual replacement of the parenchyma by fibrosis and scarring. B cells are found mainly in portal areas with primary lymphoid follicles. Inflammatory responses consist of cytotoxic T (CD8-positive) lymphocytes in spotty areas of lobular inflammation and at the edges of portal regions. Fibrosis begins around the edges of the portal areas until bridges are formed with scarring. Regenerative responses of hepatocytes are observed, disturbing the architecture of the liver, resulting in cirrhotic changes with portal hypertension. When patients clear the virus with the loss of HbsAg, there is a significant reduction in inflammation and thinning of fibrous bands to narrow the septae. Hepatitis activity index may fall by 50%; however, histologic improvement may lag behind the biochemical and serologic responses.

Hepatocellular carcinoma is one of the major complications of HBV infection. The incidence increases with the presence of cirrhotic changes. The disease is more common in the Far East and SubSahara Africa and less common in Western Europe and the United States. Spain, Italy, Greece, and Japan have an intermediate incidence of HCC. The mechanisms of development of HCC are not known.

TREATMENT OPTIONS

Interferon

Interferon is a naturally occurring cytokine, which has antiviral and immunoregulatory activity. It has been used to treat HCV and HBV infections. The response in HBV is much less than that in HCV infections. Treatment leads to loss of HBsAg in 6%, loss of HbeAg in 25%, and loss of HBV DNA in 20% of patients. However, sustained responses after INF are less common. Some trials suggest that Prednisone priming before INF treatment may result in a better response. However, withdrawal of steroids followed by INF therapy can result in hepatic decompensation. In addition, INF-induced flare-ups of the disease may be dangerous for patients with hepatic dysfunction. The drug may have limited use in highly selective cases with preserved hepatic function.

Lamivudine

Lamivudine (B-L-2^1, 3^1-dideoxy-3^1-thiacystidine; 3TC) is a nucleoside analog that has antiviral and anticancer activity. It inhibits HBV replication. It has been studied in phase III prospective clinical trials in the United States, Europe, and Asia in patients who are HbeAg positive and who have increased LFTs. Twelve months of therapy led to HbeAg loss in 30%, seroconversion in 18%, normalization of ALT in 45%, and histologic improvement in 50% of cases. Loss of HBsAg was, unfortunately, less common. The YMDD mutation rate on Lamivudine therapy continues to increase from 17% to 67% over 1 to 4 years.[4,6,10–15,16] The combined INF and Lamivudine (two trials: $n = 226, n = 238$) HBeAG seroconversion rate at 1 year was 29%, compared with 19% with INF alone and 18% with Lamivudine alone.

Adefovir Dipivoxil

Adefovir Dipivoxil (ADV) is a nucleotide analogue with antiviral properties *in vitro* and *in vivo* against herpes virus, retroviruses, and hepadna virus. It inhibits HBV DNA polymerase and has rare immunomodulatory properties. Gilson et al showed that up to 99% of the patients experienced a decrease in HBV DNA and improvement in ALT; 20% seroconverted from HBeAg to HbeAB positivity.[8,17] The drug was useful both for wild types and for viruses with the YMDD mutation. No polymerase mutations have been observed in the initial trials. The main side effect was dose-dependent nephrotoxicity.

Other Unapproved Drugs

This group includes various deoxynucleoside analogs and derivatives, most of which are in the final stages of clinical trials. They include Entecavir, Famciclovir, Clevundine (L-FMAU), Emtricitabine, Lobucavir (FTC), and diamin-

opurine dioxolane (DAPD). These agents appear to be associated with initial rapid reductions in viral load, but slow prolonged responses. It is also anticipated that, in the future, combinations of drug therapy may reduce the rate of mutation.[18–22]

HBV Infection and Liver Transplantation

Liver transplantation has been successfully performed in HBsAg-positive recipients. The short-term outcomes are similar to liver transplantation for other indications as long as prophylaxis is given. The ongoing problem has been the recurrence of HBV in the allograft, which is particularly high among patients with active replication at the time of liver transplantation.[23]

Intraoperative and postoperative passive immunization with HBIG has lowered the rate of recurrence. Long-term HBIG prophylaxis is more effective than short term. Most transplant centers administer a combination of HBIG for 1 to 2 years and long-term Lamivudine. However, some studies suggest that Lamivudine alone is just as effective as HBIG prophylaxis.[24–33] The duration of therapy with HBIG is still controversial. HBsAb concentrations >500 IU/L in the first month and >100 thereafter appear to be effective. Our practice is to administer HBIG (10,000 units) during the anhepatic phase and then daily for 7 days, monthly for 6 months, and then intramuscularly every 3 weeks for 2 years. There is some benefit to measure HBsAb titers. Lamivudine (150 mg daily) is prescribed as a lifelong prophylaxis.

HBV-Positive Donors

Donors who are HBsAg positive are not considered to be potential donors. Donors who are HBsAb positive only are considered completely safe; no prophylaxis needs to be administered to recipients. HBcAb-positive donors are investigated for their IgG and IgM status. IgM-positive donors are not used; however, IgG-positive HBcAb donor organs may be transplanted into HBsAg-positive recipients, naive patients who are critically ill, or HBcAb+ recipients. HBsAg+ recipients are treated with HBIG and Lamivudine prophylaxis (as described above) and thus are effectively prophylaxed when HBcAb+ donors are used.

CURRENT CONCERNS

The major concern at the present time with HBV infection is how to control the rate of mutation and how to treat patients who develop mutations. Current ongoing trials with Adefovir and Entacovir appear to be promising, but these agents are not yet approved by the FDA. The second recurrent question is how long HBIG should be continued after liver transplantation. The answer appear to be the longer the better, but the concerns with long-term use are the issues of cost and patient compliance. Fortunately, given the increasing rate of immunization, the overall incidence of HBV infection is decreasing worldwide.

REFERENCES

1. Hasegawa K, Huang JK, Wands JR, et al: Virology 185:460, 1991
2. Liang TJ, Hasegawa K, Rimon N, et al: N Engl J Med 324:1705, 1991
3. Zampino R, Marrone A, Cirillo G, et al: J Viral Hepat 9:183, 2002
4. Ben-Ari Z, Mor E, Shapira Z, et al: Liver Transplant 7:113, 2001
5. Liang TJ, Hasegawa K, Munoz SJ, et al: J Clin Invest 93:550, 1994
6. Kiyosawa K, Tanaka E: J Gastroenterol 36:139, 2001
7. Liaw YF: Antivir Chem Chemother 12(suppl 1):67, 2001
8. Locarni SA, Bartholomeusz A, Delaney WE: Expert Opin Invest Drugs 11:169, 2002
9. Benhamou Y, Bochet M, Thibault V, et al: Lancet 358:718, 2001
10. Lau DT, Khokhar MF, Doo E, et al: Hepatology 32(4 pt 1):828, 2000
11. Mazur W, Kr IF, Cianciara J, et al: Med Sci Monit 8:CR257, 2002
12. Multimer D: Liver Transplant 7:511, 2001
13. Saif MW, Little RF, Hamilton JM, et al: Ann Oncol 12:123, 2001
14. Sokal E: Expert Opin Pharmacother 3:329, 2002
15. Zoulim F: Drug Saf 25:497, 2002
16. Sokal E: Expert Opin Pharmacother 3:329, 2002
17. Gilson RJ, Chopra KB, Newell AM, et al: J Viral Hepat 6:387, 1999
18. Levine S, Hernandez D, Yamanaka G, et al: Antimicrob Agents Chemother 46:2525, 2002
19. Pramoolsinsup C: J Gastroenterol Hepatol 17(suppl 1):125, 2002
20. Galan MV, Boyce D, Gordon SC: Expert Opin Pharmacother 2:1289, 2001
21. Farrell GC: Drugs 60:701, 2000
22. Pramoolsinsup C: Management of Viral hepatitis B: J Gastroenterol Hepatol 7(Suppl 1):125, 2002
23. Cahlin C, Olausson M, Friman S: Transplant Proc 33:2467, 2001
24. Ben-Ari Z, Mor E, Manhaim V, et al: Transplant Proc 33:2895, 2001
25. Chu CJ, Fontana RJ, Moore C, et al: Liver Transplant 7:724, 2001
26. Han SH, Ofman J, Holt C, et al: Liver Transplant 6:741, 2000
27. Lee PH, Hu RH, Tsai MK, et al: Transplant Proc 32:2245, 2000
28. Lee KW, Lee SK, Joh JW, et al: Transplant Proc 33:3643, 2001
29. Lo CM, Cheung ST, Lai CL, et al: Ann Surg 233:276, 2001
30. Marzan A, Salizzoni M, Debernardi-Venon W, et al: J Hepatol 34:903, 2001
31. Naoumov NV, Lopes AR, Burra P, et al: J Hepatol 34:888, 2001
32. Perrillo RP, Wright T, Rakela J, et al: Hepatology 33:424, 2001
33. Rosenau J, Bahr MJ, Tillmann HL, et al: J Hepatol 34:895, 2001