Management of Hepatitis B: Recent Advances

PHILIP ABRAHAM

The treatment of hepatitis B virus (HBV) infection continues to evolve rapidly. The US Food and Drug Administration approved interferon alpha-2b in 1992 for the treatment of hepatitis B. Subsequently, four oral agents (lamivudine, adefovir, entecavir, telbivudine) and pegylated interferon alpha have received approval.

PRINCIPLES OF THERAPY

Eradication of the virus is nearly impossible due to extrahepatic reservoirs of HBV, integration of HBV DNA into the host genome, and because of protected intracellular covalently closed circular (ccc) DNA, which is likely responsible for viral rebound after therapy is discontinued. Over the last decade there has been a shift in the treatment focus for chronic HBV infection from finite treatment to long-term viral suppression, along the lines followed for HIV infection. This is a result of availability of well-tolerated oral agents as well as data suggesting that viral suppression decreases the risk of complications, including hepatocellular carcinoma.

Patients with mild chronic hepatitis (ALT less than twice upper limit of normal, HBV DNA < 10^5/ml, histologic activity index ≤ 3 if biopsy is done) should be monitored; therapy should be considered if there is evidence of moderate to severe activity during follow-up. Patients with moderate to severe chronic hepatitis should be treated if there is active HBV replication (HBV DNA > 10^5 copies/ml) and persistent elevation of aminotransferases (more than twice upper limit of normal) after 3-6 months of observation.

In HBeAg-positive patients, the endpoint of treatment is the disappearance of HBeAg and, ideally, development of hepatitis B e antibody (anti-HBe). Loss of HBeAg is generally accompanied by loss of HBV replication. Treating for at least an additional 3-6 months – preferably even up to a year – yields better-sustained response rates. In HBeAg-negative patients, the endpoint is reduction of viral load, and this generally takes over a year. In both cases, normalization of liver enzymes and arrest of histologic progression or even regression are ideal accompaniments.

Unlike in HCV infection, where viral genotype has a well-established role in treatment, genotype may not influence treatment decisions in hepatitis B. Some data suggest that the use of interferon in genotype A patients may result in increased seroconversion compared with other genotypes. On the other hand, a recent Japanese study concluded that response to lamivudine is strongest among HBeAg-positive patients with genotype B virus and poorest among those with genotype A. In other words, the clinical utility of genotyping is not yet established.

TREATMENT GROUPS

Acute HBV Infection

The efficacy of antiviral therapy in the setting of acute hepatitis B is not established; such therapy is not currently recommended. Earlier studies suggested that treatment with lamivudine may improve the clinical course of patients with severe acute hepatitis B, but this has been contradicted by recent findings. Thus, at present, antiviral therapy is not considered standard of care even for severe acute hepatitis B.

Inactive (“Asymptomatic”, “Healthy”) Carrier (Table 1)

These individuals, who are HBeAg-negative with normal serum ALT and low-level viremia, have a more
favorable prognosis. However, it must be borne in mind that viral replication may continue in this population, with inflammation or fibrosis on liver biopsy. Such subjects may therefore be at risk for significant liver disease even after prolonged periods of quiescence, and should be monitored with liver biochemistries every 6-12 months. Although no therapy is routinely recommended at present, studies focusing on reducing viral load (in those with high load) in order to decrease future risk of liver disease are in progress.

**Chronic Hepatitis B (Tables 2 and 3)**

**Interferon**

The main advantages of interferon are the finite treatment course of 4 months (in HBeAg-positive patients) to 12 months (in HBeAg-negative patients), the low relapse rates, effectiveness even at low viral loads, and lack of resistant mutants. The drug – in a dose of 5 million units (MIU) daily or 10 MIU thrice a week – has been effectively used in both HBeAg-positive and −negative patients. Its main disadvantages are the cost and side-effect profile. The drug should be used with caution in patients with cirrhosis, in view of the risk of decomposition on therapy; it is contraindicated in those with existing decomposition. HBeAg clearance occurs in approximately one-third of patients and loss of hepatitis B surface antigen (HBsAg) in 5 to 10% of patients. Current data suggest that pegylated interferon-alpha may be more effective than standard interferon (and lamivudine) in HBeAg-positive patients.

**Antiviral Therapies**

**Lamivudine:** Although this drug is of low cost and is very effective in decreasing viral load, it is associated with a high incidence of mutations in the YMDD motif of the HBV DNA polymerase. Mutation occurs in approximately 25% of patients at year 1 and approaches 60 to 70% by year 4 of therapy. Its dose is 100 mg daily (3 mg/kg/day up to maximum of 100 mg daily in children), and it should be continued for at least 1 year. Patients in whom HBeAg seroconversion has occurred should be maintained on treatment for 3 to 6 months after HBeAg seroconversion is confirmed (two occasions at least 2 months apart), to reduce post-treatment relapse. Treatment may be continued in patients who have not developed HBeAg seroconversion. The recommended treatment duration for HBeAg-negative chronic hepatitis B is longer than 1 year, but the optimal duration has not been established. In patients who have breakthrough infection due to lamivudine-resistant mutants, treatment with the drug may be continued as long as benefit to the patient is maintained.

The drug has also been used in patients with severe acute HBV infection (although this is not standard) and
those with acute decompensation of chronic disease. Its safety, along with that of the other currently available oral therapies, in decompensated chronic liver disease has been established.

**Adefovir:** Adefovir dipivoxil is a nucleotide analog of adenosine monophosphate, and so does not share cross-resistance with nucleoside compounds such as lamivudine and entecavir. This makes it an optimal choice for patients with resistance to any of the other drugs, and it is currently the drug of choice as salvage therapy in patients who develop mutations on lamivudine.

It appears that each additional year on therapy (daily dose 10 mg) yields better results. Current data suggest a high rate of seroconversion and HBeAg loss with extension of therapy with adefovir. Unlike with lamivudine, the likelihood of development of mutation and consequent resistance is very low. Beyond the first 48 weeks of adefovir therapy, during which the resistance rate may be as low as 0%, the yearly incidence of adefovir resistance may be 4 to 5%. Even in patients receiving combination therapy (lamivudine plus adefovir), no resistance was observed. The earlier fear of nephrotoxicity with the drug has been contradicted by more recent reports that show no significant rise in creatinine levels in the large numbers of patients treated with the drug. Caution is however recommended during its use in patients with renal dysfunction.

**Entecavir:** Entecavir is a nucleoside analog of 2'-deoxyguanosine. It has been found to be equivalent to lamivudine in terms of HBeAg seroconversion, and comparable or superior with respect to viral suppression and histologic improvement. The daily dose of entecavir is 1 mg; the drug is predominantly eliminated by the kidney. There is some concern regarding its use in patients with renal impairment, but further studies are awaited. Entecavir resistance was not observed in the registration studies, but genotypic mutations may eventually lead to clinical resistance and viral rebound.

**Telbivudine:** Telbivudine is the most recent drug to be approved by the US FDA (2006) for the treatment of chronic hepatitis B. The drug (daily dose 600 mg) has been found to be effective against lamivudine-resistant HBV strains. A large trial, however, showed significant resistance rates at 2 years and a likelihood of cross-resistance with lamivudine. Adefovir-resistant strains conferred a 3- to 4.6-fold reduced susceptibility to telbivudine in vitro. Long-term results are awaited.

### Other Therapies

A number of other agents are currently under study for the treatment of hepatitis B. Tenofovir and valtorcitabine are at the forefront presently and awaiting data prior to approval.

### Antiviral Prophylaxis

HBsAg should be tested in persons who are at high risk of HBV infection, prior to initiation of chemotherapy or immunosuppressive therapy. Prophylactic antiviral therapy with lamivudine is recommended for HBV carriers at the onset of cancer chemotherapy or of a finite course of immunosuppressive therapy, and maintained for 6 months after completion of chemotherapy or immunosuppressive therapy. The role of the newer oral agents has not been established.

### CONCLUSIONS

Currently, there is no clear-cut first-line therapy for treatment-naïve individuals. The subset of patients who prefer interferon therapy and have no contraindication to its use varies by region; pegylated interferon may become an option in future.

In HBeAg-positive patients, lamivudine, adefovir and entecavir are all viable options. However, lamivudine is being used less often due to the high associated resistance rates. Adefovir has demonstrated excellent seroconversion rates beyond 1 year, with relatively low resistance. Entecavir demonstrated excellent viral suppression and moderate HBeAg seroconversion in clinical studies; data on whether long-term treatment provides still higher seroconversion rates are awaited. Telbivudine is a promising newer nucleoside agent, but needs long-term evaluation.

Future studies will need to focus on combination therapy regimens in an effort to reduce the development of resistance. The lamivudine-resistant population is currently eligible for treatment with adefovir or entecavir. The low seroconversion rates associated with entecavir in this patient population and the potential for cross-resistance with lamivudine make adefovir a more likely choice in this setting. Combination therapy perhaps makes clinical sense in terms of decreasing resistance to either class of drug, although at higher cost of therapy.

### SUGGESTED READING

1. Cooksley G, Manns M, Lau GKK, et al. Effect of genotype and other baseline factors on response to peginterferon alfa-2a (40-


