

EDITORIALS



Hepatitis B — Preventable and Now Treatable

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Chronic infection with hepatitis B virus (HBV) accounts for an enormous burden of disease worldwide, including up to half of all cases of cirrhosis, end-stage liver disease, and hepatocellular carcinoma.¹ With the development of a safe and effective vaccine in the early 1980s, hepatitis B became a preventable disease. Routine HBV vaccination of newborns in Taiwan and China, areas of the world with high rates of hepatitis B, was followed by significant declines in rates of chronic hepatitis B and hepatocellular carcinoma.² In the United States, where the disease is uncommon, the incidence of new cases is currently 75 percent lower than before introduction of the vaccine.³

More recently, hepatitis B has become a treatable disease. Five agents are now approved for therapy of chronic hepatitis B in the United States, with several more available for other indications or in the pipeline. Current choices include interferon alfa (standard⁴ and pegylated^{5,6}) and three oral antiviral agents (lamivudine,⁷ adefovir dipivoxil,^{8,9} and most recently, entecavir^{10,11}). The importance of therapy for chronic hepatitis B was demonstrated dramatically in a landmark clinical trial from Asia, in which long-term treatment with lamivudine improved survival and decreased hepatocellular carcinoma in patients with chronic hepatitis B and advanced fibrosis or cirrhosis.¹²

Entecavir is the newest of the antiviral agents approved for chronic hepatitis B. It is a guanosine analogue with marked activity against HBV DNA polymerase in vitro and in vivo. In the woodchuck model of hepatitis, long-term use of entecavir led to maintained suppression of virus replication and decreased rates of hepatocellular carcinoma.¹³ As described by Chang et al.¹⁰ and Lai

et al.¹¹ in this issue of the *Journal*, trials in humans show that entecavir has few side effects and potent activity against HBV. After 48 weeks of treatment, 67 percent of patients with chronic hepatitis B who were positive for hepatitis B e antigen (HBeAg) and 90 percent of those who were negative for HBeAg had undetectable serum HBV DNA levels, with the use of sensitive assays. For comparison, in similarly designed controlled trials of other agents, rates of suppression of HBV DNA to undetectable levels among patients with chronic hepatitis B who were positive for HBeAg were 36 percent with the use of lamivudine, 21 percent with the use of adefovir, 25 percent with the use of peginterferon, and none with the use of placebo.^{5,8,10} Among patients with HBeAg-negative chronic hepatitis B, suppression of HBV DNA to undetectable levels was reported in 72 percent of patients treated with lamivudine, 51 percent treated with adefovir, 63 percent treated with peginterferon, and none treated with placebo.^{6,9,11} Just as impressive were findings that entecavir was associated with little or no antiviral resistance.^{10,11}

Unfortunately, the availability of agents such as entecavir for patients with chronic hepatitis B does not make therapy of this disease simple. All five licensed agents are effective in suppressing HBV DNA levels and improving serum alanine aminotransferase levels and hepatic histology, but it is still unclear who should be treated, with which agent (or combination of agents), for how long, with what monitoring, and with the use of which end points to measure the success or failure of treatment.

The central problem is that current therapies do not eradicate HBV, nor do they cure the infec-

tion, which does occur with successful treatment of hepatitis C.⁴ With oral antiviral treatment, only a small proportion of patients (<2 percent) become negative for hepatitis B surface antigen (HBsAg). A higher proportion (16 to 24 percent) may become HBeAg-negative and have a sustained remission even after therapy is stopped. But in the majority of patients, particularly those with HBeAg-negative disease, HBV is suppressed but not eradicated by treatment, and relapse occurs when the drug is stopped. Furthermore, relapse can be associated with severe exacerbation of disease, which may cause hepatic decompensation and death.^{4,5,10} Once treatment with oral antiviral agents has begun, it is difficult to stop.

Of course, a reasonable alternative is long-term treatment. The safety profile and side effects of the oral agents used for the treatment of chronic hepatitis B support this approach. The challenge is the markedly increased expense. Furthermore, the safety and efficacy of long-term therapy have yet to be proved.

Safety issues are largely theoretical. Nucleoside analogues can cause lactic acidosis, pancreatitis, and acute fatty liver, but monotherapy with current anti-HBV agents has not been linked to these syndromes. During more than a decade of use in patients with chronic hepatitis B, lamivudine has had an excellent record of safety. Adefovir can cause renal dysfunction, which necessitates monitoring of creatinine levels, but this toxicity is uncommon with use of the recommended dose. Entecavir has the shortest track record, but its safety has been excellent in short-term studies. It is of concern, however, that high doses of entecavir have been linked to development of cancer in mice, so its long-term safety warrants further monitoring.

A more critical issue is the long-term efficacy of oral antiviral agents in patients with chronic hepatitis B. The major problem is antiviral resistance. Antiviral resistance develops slowly (after months or years) in patients with chronic hepatitis B but is usually followed by reversal of clinical improvement. Resistance to lamivudine develops at a rate of 15 to 25 percent of patients a year, reaching 70 to 80 percent after four years.^{4,14} Resistance to adefovir is rare before two years of therapy have been completed but reaches 15 to 20 percent by four years.¹⁴ Fortunately, lamivudine-resistant HBV is fully susceptible to adefovir and partially susceptible to entecavir, either

of which can be used in cases of lamivudine resistance. Perhaps the most promising aspect of entecavir therapy has been the low rate of antiviral resistance. To date, resistance to entecavir has been described only in patients with preexisting lamivudine resistance.¹⁵ However, there is limited information on long-term use.

What, then, can be recommended? Primarily, therapy should be reserved for patients who need to be treated — those with active disease exemplified by raised serum alanine aminotransferase levels, by clinical or histologic evidence of progressive disease, or both. The decision to start therapy should not be made on the basis of HBV DNA levels alone, which can be high in persons with mild or minimal disease. Peginterferon therapy is appropriate for some patients, but its applicability is limited by its expense, side effects, frequent contraindications, and lack of efficacy in two thirds of patients.

In contrast, the oral antiviral agents are attractive because they are easy to administer, have minimal side effects, and are effective in the full spectrum of patients with chronic hepatitis B, including those with liver decompensation or other coexisting conditions. **Either adefovir or entecavir is an appropriate first-line agent.** Treatment probably should be continued indefinitely. Patients who become HBsAg-negative and selected patients who become HBeAg-negative on treatment may be able to stop therapy if they are subsequently monitored carefully. Combination therapy, which is important in treating HIV infection, has not been shown to be advantageous in chronic hepatitis B, although more long-term studies are needed.⁴⁻⁶

With its excellent potency and low rate of resistance, entecavir seems to be an outstanding agent for treating chronic hepatitis B. Its use at present, however, should be tempered with the knowledge that this chronic liver disease is likely to require long-term therapy, and that this drug is easy to start but difficult to stop.

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The Changing Landscape of Myeloma Therapy

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The introduction of melphalan and prednisone for the treatment of multiple myeloma was followed by only minor advances in the management of the disease for almost 20 years.¹ The failure of other agents, alone or in combination, to extend survival beyond three years prompted a new treatment strategy in the early 1980s: myeloablative doses of melphalan supported by an infusion of autologous hematopoietic stem cells. After this approach was found to be superior to conventional chemotherapy for the initial treatment of myeloma, the efficacy of two sequential courses of high-dose therapy, each supported by an infusion of autologous stem cells, was tested. As compared with a single infusion of stem cells, two infusions significantly prolonged both overall and event-free survival, particularly among patients who did not enter remission after receiving the first transplant.^{2,3} The benefit of melphalan-based double autologous transplantations was greatest in patients whose myeloma cells had a normal karyotype: these patients had an estimated probability of remaining in remission at 10 years of nearly 20 percent, suggesting that long-term control and even cure of myeloma are possible with double autologous stem-cell transplantation.⁴

More recent advances in the management of

myeloma include the identification of new ways to overcome drug resistance.¹ Also important is recognition of the pivotal role of the bone marrow microenvironment in promoting the growth, survival, and resistance of myeloma cells to conventional chemotherapy. As a result of this work, new classes of agents for the treatment of myeloma have been introduced. These include thalidomide; lenalidomide, a potent analogue of thalidomide; and the proteasome inhibitor bortezomib. Once the activity of these drugs in advanced and refractory myeloma was confirmed,⁵ studies of their efficacy in earlier phases of the disease were initiated. Meanwhile, the concept of targeting the bone marrow microenvironment (the “soil”) in a way that interferes with the growth of the myeloma “seed” emerged as the rationale for trials of new agents in combination with established therapies in an attempt to enhance cytotoxicity, reverse drug resistance, and increase the probability of curing myeloma.

Thalidomide, an old drug with an infamous past, has been redeemed as a treatment for not only relapsed or refractory myeloma but also newly diagnosed disease. As an initial treatment to prepare patients for autologous stem-cell transplantation, thalidomide in combination with dex-