8-2007

Time for an active antiviral therapy for hepatitis B: An update on the management of hepatitis B virus infection.

Hee Bok Chae
Chungbuk National University Hospital; Thomas Jefferson University

Hie-Won Hann
Thomas Jefferson University, Hie-Won.Hann@jefferson.edu

Time for an active antiviral therapy for hepatitis B: An update on the management of hepatitis B virus infection

Hee Bok Chae[1,2,3]
Hie-Won Hann[1]

[1]Liver Disease Prevention Center, Division of Gastroenterology and Hepatology, Department of Medicine; [2]Department of Pathology, Anatomy, and Cell Biology, Thomas Jefferson University, Philadelphia, PA, USA; [3]Department of Internal Medicine, Chungbuk National University Hospital, Cheongju, South Korea

Abstract: Significant advances in the management of chronic hepatitis B (CHB) have been made over the past decade. During this period we have witnessed improvements in survival as well as reduction of disease progression in CHB patients due to the introduction of effective antiviral therapy. The need for effective antiviral therapy is underscored by the results of the REVEAL-HBV study in which 3653 hepatitis B virus (HBV) carriers were followed over 12 year period. This study demonstrated that a persistently elevated serum HBV DNA level was the most important risk factor for the development of hepatocellular carcinoma (HCC). The ultimate goal of antiviral therapy for CHB patients should include halting the progression to cirrhosis and its life threatening complications and in preventing/reducing the development of HCC. An earlier study of 651 CHB patients with cirrhosis or advanced fibrosis from countries in Asia also demonstrated that treatment with lamivudine (LVD) not only delayed disease progression but also reduced the development of HCC. These landmark studies reaffirm the need for active antiviral therapy for CHB. Current treatment options for patients with CHB include interferon and nucleos(t)ide analogues. As we gain experience with these agents, it has become increasingly clear that long-term therapy benefits patients with CHB.

Keywords: pegylated interferon, lamivudine, adefovir, entecavir, tenofovir, telbivudine

Case reports

Since 1983, the author (HWH) has followed 6 families in which 16 children were identified as Hepatitis B surface antigen (HBsAg)-positive during high school or in college. Further investigation revealed all 16 children were born to HBsAg(+) mothers and were likely infected during childbirth. During subsequent years, HBsAg(+) members of 5 families were treated with antiviral agents, including LVD, adefovir (ADV), tenofovir (TDF) or entecavir (ETV) and they have remained well on therapy with normal liver function and liver imaging studies. Three children of the 6th family, however, did not receive therapy. Over the ensuing years, these children (now in their 40's) remained asymptomatic although their liver enzymes were occasionally elevated. Ultimately, one of the three children, after only two weeks of fatigue, was found to have an advanced HCC with cirrhosis and splenomegaly. He, at the age of 44, passed away within 6 months of his HCC diagnosis. Immediately, the two remaining children elected to start antiviral therapy.

In 2000, a 58 year-old Korean American man brought his older brother to Thomas Jefferson University Hospital for treatment of HCC. He himself had just completed interferon therapy for HBV and assumed he was cured. While his brother was undergoing cryosurgery he himself had an abdominal imaging and was found to have a 4 cm HCC in the right lobe of the liver. Laboratory studies revealed that he was Hepatitis B e antigen (HBeAg)-positive and had high levels of HBV DNA. He received radiofrequency tumor ablation and was started on LVD. He developed LVD resistance 4 years

Correspondence: Hie-Won Hann
Liver Disease Prevention Center, Division of Gastroenterology and Hepatology, Department of Medicine, Thomas Jefferson University, Philadelphia, PA 19107, USA
Tel +1 215 955 5806
Fax +1 215 955 0770
Email hie-won.hann@jefferson.edu

later, is currently on tenofovir (TDF) after suboptimal response to ADV. Now at the age of 64, he has remained a very successful businessman with normal liver function, undetectable serum HBV DNA and without recurrent or new HCC.

A 49 year-old Asian American man received IFN therapy for 4 months (3/94–7/94) but without HBeAg conversion. He received no therapy despite having ALT elevation until 5/96 when LVD (as Epivir) became available. LVD therapy was discontinued in 11/99 after HBeAg seroconversion and he relapsed in 9/02. Retreatment with LVD resulted in undetectable HBV DNA and LVD therapy was discontinued in 11/04. He is now 61 years old with normal liver function with undetectable HBV DNA and remains well.

The cases described above clearly illustrate how antiviral agents could successfully halt the progression of liver disease or development of new HCC in patients with CHB.

Introduction

There are nearly 350 million HBV carriers worldwide (Lee 1997). These carriers are at risk for development of cirrhosis, HCC and death. Recently, Chen et al (2006) in Taiwan reported the results of their 12 year follow-up study, the REVEAL-HBV study (Risk Evaluation of Viral load Elevation and Associated Liver disease/cancer). They found that elevated serum HBV DNA level ≥10,000 copies/mL was the most important risk factor for HCC independent of HBeAg, serum alanine aminotransferase (ALT) and liver cirrhosis. In this elegant study the authors followed 3653 HBsAg(+) carriers (aged 30–65 years) for a mean follow-up of 11.4 years and during this period 164 persons developed HCC. The incidence of HCC increased with serum HBV DNA level at study entry in a dose-response relationship ranging from 108/100,000 person-years for an HBV DNA level of <300 copies/mL to 1152/100,000 person-years for an HBV DNA level of ≥1,000,000 copies/mL.

Also, Liaw et al (2004), in a trial of 651 CHB patients with cirrhosis or advanced fibrosis from several countries in Asia, randomized 2/3 of patients to receive LVD and 1/3 of patients to receive placebo. In less than 3 years on study the authors observed that those who received LVD not only showed delayed disease progression but also had reduced incidence of HCC compared to those on placebo. These two landmark studies reaffirm the need for an active approach for patients with CHB with an antiviral therapy.

The aims of treatment of CHB are to achieve sustained suppression of HBV replication and remission of liver disease. The end points include normalization of serum ALT level, undetectable serum HBV DNA by an amplified assay, loss of HBeAg, with or without detection of anti-HBe, and improvement of liver histology (Lok and McMahon 2004). The ultimate long-term goal of therapy is to prevent hepatic decompensation, to reduce or prevent progression to cirrhosis and/or HCC, and to prolong survival (Liaw et al 2005).

In 1992, interferon alpha (IFN-α) was first introduced for the treatment of CHB. As of November 2006, there are six FDA approved drugs available for the treatment of CHB in the United States, including two formulations of interferon and four oral nucleos(t)ide agents.

With multiple therapeutic agents available, there is a great need for physicians to have sufficient knowledge to provide the best choice of treatment for their patients. While these drugs are all highly effective, there are differences in drug safety, cost, drug resistance and risks of disease flare from premature discontinuation of therapy or from poor compliance on the part of patients. In addition, the disease may recur even after treatment and therefore, close follow-up after the completion of therapy is important. Furthermore, close monitoring for early detection of HCC is essential during and after the treatment. As strong advocates for an active and earliest possible intervention for CHB with antiviral agents, the efficacy, the advantages and disadvantages of currently available therapeutic agents are being examined.

Interferon-α2b

Interferon-α2b (IFN-α2b) became available in 1992 and remained the only FDA approved agent for the treatment of CHB until 1998. IFN-α2b has direct effects on the immune system, including enhanced expression of HLA class I molecules and stimulation of CD8+ cytotoxic T-cell activity. The duration of treatment ranges between 4 to 6 months by subcutaneous injection of 5 million units daily or 10 million units three times weekly. This regimen results in HBeAg loss in 30%–40% of patients and clearance of HBsAg in 10% of patients. Studies from North America and Europe have shown HBeAg loss in 30%–35% of patients who are treated with 4 to 6 months of interferon-α2b (Perrillo et al 1990).

In HBeAg(–) CHB, the response has been defined as undetectable serum HBV DNA by unamplified assays and normalization of ALT level. Results of four randomized trials involving a total of 86 IFN-α2b treated patients and 84 controls showed that the end-of-treatment response ranged from 38 to 90% in treated patients compared with only 0% to 37% of controls. Longer duration of treatment up to 24 months may improve the rate of sustained response (Lok and McMahon 2001). A study from Taiwan showed that 6–10 months IFN therapy in HBeAg(–) CHB patients had an end-of-treatment

response of 57% (vs 18% of controls) and 6 months sustained response of 30% (vs 7%) (Lin et al 2001).

However, therapeutic effect of IFN-α2b in Asian patients has been far inferior to the results seen among European patients, possibly related to a longer duration of infection (Asians are often infected perinatally) and different HBV genotypes. Lok et al (1988) reported that IFN-α2b has little long-term effect in suppressing HBV replication in Chinese patients with CHB. Interestingly, Martin et al (1998), in their prospective controlled study with IFN-α2b comparing Caucasian and Asian-American patients with CHB, found no difference in clearance of HBeAg loss or HBV DNA (62% vs 60%) except for a shorter durability of response in Asian-American patients. The Asian American patients in this study were noted to have acquired HBV infection during adulthood. Side effect of IFN-α2b include flu-like symptoms, depression, renal failure, heart failure, and alopecia and others.

Pegylated interferon-α

Recently, pegylated forms of IFN-α2a (PegIFN-α2a) have been developed. Because of a decreased renal clearance rate, PegIFN-α2a is administered weekly. Studies suggest that PegIFN-α2a is more effective than standard IFN-α. The side effect profile of PegIFN-α2a is similar to that of standard IFN-α. PegIFN α2a in doses of 180 μg weekly has been used for 48 weeks in both HBeAg(–) (Lau et al 2005) and HBeAg(–) CHB (Marcellin et al 2004). The majority of 814 HBeAg(+) patients studied by Lau et al (2005) were Asian (87%). Most of them were infected with HBV genotype B or C. At the end of 48 week treatment, HBeAg seroconversion occurred in 27% of patients, and increased to 32% at the end of 6-month post-treatment observation period (Lau et al 2005). For HBeAg(–) 537 CHB patients, PegIFN-α2a in doses of 180 μg weekly for 48 weeks with or without LVD produced better results (HBV DNA decrease, ALT normalization) than LVD alone at the end of 6 months follow up off treatment (Marcellin et al 2004).

Nucleos(t)ide analogues

LVD, ADV, entecavir (ETV) and telbivudine (LdT) are all orally administered drugs currently available for treatment of CHB. In addition, several candidates, such as emtricitabine, clevudine, TDF, pradefovir and others are in the final stages of clinical trials.

Lamivudine (LVD)

LVD is a potent inhibitor of viral replication, convenient to administer, and has very few side effects. LVD is given in a dose of 100 mg (or 150 mg) daily. For HBeAg(+) CHB, a 2 year course of LVD has resulted in further increase of HBeAg seroconversion from 17% at 1 year to 27% at 2 years (Liaw et al 2000) and 47% after 4 years (Chang et al 2004). With LVD therapy, the majority of patients develop undetectable HBV DNA by PCR assay. However, LVD therapy should be continued until HBeAg seroconversion which may take months to years even after HBV DNA has become undetectable. The optimal duration of LVD administration following HBeAg seroconversion remains undetermined at present time. Nonetheless, it has generally been agreed that it needs to be longer than 6 months due to frequent relapses observed after cessation of therapy. The half-life of HBV-infected hepatocytes is reported to be 10–100 days with a mean of 16 days (Nowak et al 1996) and Zeuzem et al (1997) in their study with LVD described that the half life of HBV infected cells is longer than 100 days and 1 year treatment of LVD will not reduce the number of infected cells to less than 10% of its initial value. Ryu et al (2003) reported results of their study in which patients were continued on LVD therapy for 6, 12 and 24 months after the HBeAg conversion. They observed relapse rates 2 years after the cessation of LVD therapy to be 57%, 51% and 29% of patients who received 6, 12 and 24 months of additional LVD therapy respectively. More importantly, if LVD is stopped before HBeAg seroconversion even with undetectable HBV DNA, virus returns often accompanied with ALT flare which can be severe at times.

For HBeAg(–) patients, the length of continued therapy is determined from the time point when HBV DNA becomes undetectable by the available PCR assay. Currently, the recommendation is to continue treatment for minimum 2 more years after HBV DNA becomes undetectable. Despite this, there are relapses even after completion of the recommended length of therapy. Therefore, the efficacy of life-long treatment for the management of HBeAg(–) CHB is currently under investigation (Perrillo 2006).

Although it has been well established that HBeAg loss correlated positively with pretreatment ALT levels (Perrillo et al 2002) in LVD therapy, other studies with LVD (Hann et al 2005) and ETV (Rosmawati et al 2003), did not find significant correlation between pretherapy ALT and the virological response. Hann et al (2005) compared LVD therapy results for 317 HBeAg(+) and HBeAg(–) CHB patients with active viral replication with regard to different pretreatment ALT levels (upper normal limit of ALT 40 U/L). In this study, the loss of HBeAg were 40%, 57% and 61% for groups with pretreatment ALT <upper limit

of normal (ULN), 1–2 × ULN and >2 × ULN, respectively. However, these differences were not statistically significant. Also, in both HBeAg(+) and HBeAg(–) patients, there were no significant differences in the loss of HBV DNA among the three ALT groups.

Resistance to lamivudine (LVD)

Lamivudine (LVD) treatment of greater than 1 year has been associated with a steady increase in LVD resistance with reported rates of resistance of 38% and 65% at 2 and 5 years, respectively (Lok et al 2003) For LVD-resistant patients it is generally recommended to overlap ADV with LVD for some time during the switch to ADV. The role of continuing LVD treatment in patients with LVD-resistant HBV who are receiving adefovir is controversial. A pooled study of 467 patients with LVD resistant HBV demonstrated that resistance to ADV was seen only in those who stopped LVD (Snow et al 2005). Lee et al (2006) also found 18% ADV resistance in LVD resistant CHB patients who received ADV monotherapy. In recent reports on both HBeAg(+) and HBeAg(–) LVD-resistant CHB patients, the combination of LVD and ADV showed a superior virologic response when compared to ADV monotherapy (Barbon et al 2006; Lampertico et al 2006).

Prolonged treatment: benefits and limitations

Prolonged treatment with LVD is generally well tolerated. In patients with HBeAg(–) CHB. Prolonged LVD therapy (3.8 ± 1.4 years) has been associated with improved survival and reduction in the risk of liver related complications, seemingly equivalent to that observed in sustained responders to IFN-α therapy (Papatheodoridis et al 2005). A major problem complicating prolonged or long-term therapy with LVD, however, is the progressive increase in drug resistance. Recent study by Chae and Hann (2006), however, suggested that patients with a baseline HBV DNA level <6 $\log_{10}$ copies/mL have a much lower incidence of LVD resistance; 3% at 1 year, 9% at 2 years and 32% at 3 years of LVD therapy. In contrast, patients with a baseline HBV DNA >6 $\log_{10}$ copies developed LVD resistance at a rate of 10% at 1 year, 36% at 2 years and 74% at 3 years. Therefore, patients with low baseline HBV DNA may still benefit from long-term LVD therapy. LVD is also the least expensive among all antiviral drugs. The majority of HBV patients live in HBV endemic countries and these countries are also economically disadvantaged. Given that CHB management required long-term therapy, the cost of treatment can become an important personal and national issue (especially in hyperendemic regions).

Adefovir dipivoxil (ADV)

Adefovir dipivoxil (ADV) is the acyclic analogue of dAMP. In 2002, ADV received FDA approval for the treatment of patients with HBeAg(+) and HBeAg(–) CHB. It is a prodrug with enhanced oral availability. ADV has activity *in vitro* against both wild type and LVD-resistant HBV strains. For this reason, ADV has been used to treat patients with LVD resistance. Monotherapy with ADV 10 mg/day for HBeAg(+) patients leads to marked decrease in HBV DNA levels (by 3 to 4 $\log_{10}$ units), improvements in serum ALT and hepatic histology and increased rates of HBeAg seroconversion (Marcellin et al 2003). After 3 years of treatment HBeAg loss was 51%, HBeAg seroconversion 43% and 56% of patients had undetectable HBV DNA (Marcellin et al 2005). Similar trials have been carried out in patients with HBeAg(–) CHB, in whom improvements in serum ALT and liver histology occurred in more than 60% of patients (Hadziyannis et al 2005a).

Long-term treatment of adefovir (ADV)

Prolonged treatment with ADV has been reported to be associated with an increasing virologic response in HBeAg(+) and HBeAg(–) CHB and has been found to be generally safe. ADV treatment for 3 years results in an increase in HBeAg seroconversion (12 % at year 1, 29 % year 2, and 43% at year 3) (Marcellin et al 2005). Three years of continuous treatment also has been associated with a progressive decline in serum HBV DNA and an increase in the percentage of patients becoming HBV DNA negative by PCR in HBeAg(–) CHB (Hadziyannis et al 2005b). Serum creatinine should be monitored as slight elevations in serum creatinine have been observed in less than 2% of patients treated with 10 mg daily for 2 to 3 years and rarely require discontinuation of drug. (Hadziyannis et al 2005b). The resistance profile of ADV is better than that of LVD. Hadziyannis et al (2005a), in a study of 185 HBeAg(–) patients, reported ADV-resistance rates of 3% of patients at year 2, 11% at year 3, 18% at year 4 and 29% at year 5. However, others in a smaller study reported a higher cumulative probability of resistance to ADV of 22% after 2 years (Fung et al 2006). The N236T and A181V/T ADV resistant mutants have been reported, both of which are sensitive to LVD therapy.

Entecavir (ETV)

Entecavir (ETV) is a cyclopentyl guanine nucleoside analogue. ETV blocks HBV replication by inhibiting the

priming of HBV DNA polymerase as well as the synthesis of the first and second strand of HBV DNA. In a recent study of 715 patients with HBeAg(+)CHB, the mean reduction in serum HBV DNA from baseline to week 48 was greater with ETV 0.5 mg than with LVD 100 mg (6.9 vs. 5.4 $\log_{10}$ copies/mL, $p < 0.001$) (Chang et al 2006b). However, HBeAg seroconversion (or HBeAg loss) at 48 weeks between the two arms were similar; 21% (22%) for ETV and 18% (20%) for LVD. Histologic improvement after 48 weeks was observed more frequently in the ETV group (72%) and than in the LVD group (62%). Virological rebound during the first years of drug therapy was observed in 2% of the ETV group compared with 18% of LVD group. Genotype analysis of isolates obtained at week 48 from the six ETV-treated patients revealed no emerging substitutions compared with baseline samples. No resistance to ETV was reported 48 weeks in treatment naïve patients and less than 1% at year 3.

In a study of 648 patients with HBeAg(–) CHB, more patients in the ETV group than in the LVD group had undetectable HBV DNA at week 48 (90% vs. 72%). Patients treated with ETV had statistically significant improvements in the mean reduction of serum HBV DNA levels from baseline to week 48 when compared with patients on LVD therapy (5.0 vs 4.5 log10 copies/ml, $p < 0.001$) (Lai et al 2006).

ETV has also been shown to be effective against both LVD-resistant HBV and wild type. One mg is the most effective dose for patients who failed to respond to LVD as shown in a study with 182 subjects (Chang et al 2005). ETV resistance emergence in ETV-treated nucleoside naïve patients over a 4-year period was only 0.8%. However, the rate of ETV resistance increased to 1, 10, 32 and 39.5% at year 1, 2, 3, and 4 in lamivudine refractory patients (Colonno et al 2007). In a recent study patients with CHB were randomized to receive open label ETV 0.5 mg/day and ADV 10 mg/day and assessed for reductions in HBV DNA levels (Leung et al 2006). By week 24, ETV-treated patients achieved a mean log HBV DNA reduction of 6.97 compared to 4.84 for ADV treated patients. Undetectable HBV DNA (<300 copies/mL by PCR) was achieved by week 24 in 45% of ETV-treated and 13% of ADV-treated patients. A recent 3 year ETV study demonstrated that by week 144, 90% of 122 patients in the study showed undetectable HBV DNA (<300 copies/ml by PCR), 80% had normalization of ALT (ALT $\leq 1 \times$ ULN), 33% and 16% of patients achieved HBeAg loss and HBeAg seroconversion, respectively (Chang et al 2006a).

Telbivudine (LdT or TLV)

Telbivudine (LdT or TLV) is a beta -L-2'deoxythymidine which acts as a specific inhibitor of HBV polymerase. In a three-arm trial, LdT monotherapy was compared with LVD monotherapy and the combination of LdT and LVD in patients with HBeAg(+) CHB (Lai et al 2005). At week 52, LdT monotherapy produced a significantly greater mean log HBV DNA reduction (6.09 vs 4.57 $\log_{10}$ copies/ml), undetectable HBV DNA (61% vs 32%) and normalization of ALT (86% vs 63%) (all, $p < 0.05$) compared to LVD monotherapy. The combination treatment was not better than LdT alone. HBeAg seroconversion was 31% for LdT and 22% for LVD. Viral breakthrough was 4.5% compared to 15.8% for LVD. (Lai et al 2005). In the GLOBE Trial 1,367 patients with 921 HBeAg(+) and 446 HBeAg(–) CHB from 20 different countries were randomized to receive LdT or LVD (Lai et al 2006). Patients who received LdT had statistically significant HBV DNA reduction than those who received LVD regardless of HBeAg status. Drug resistance for HBeAg(+) group was 4.4% for LdT and 9.1% for LVD; for HBeAg(–) CHB patients, 2.7% of LdT and 9.8% of LVD developed drug resistance. Interestingly, LdT resistance mutations were solely M204I whereas LVD resistance mutations were a mixture of M204V, M204I and M204V + L180M double mutants.

The efficacy of LdT and ADV was studied in 135 patients with HBeAg(+) compensated CHB. The HBV DNA reduction at week 24 was far better for LdT than for ADV (Bzowej et al 2006). Another recent study which included both HBeAg(+) and (–) compensated CHB patients, investigated whether patients receiving LVD therapy would benefit from switching to LdT. Patients were randomized to either continue LVD (n = 124) or switch to LdT (n = 121) for 1 year. In patients with persistent viremia during LVD therapy, switching to LdT was associated with a significantly improved HBV suppression (Gane et al 2006).

Tenofovir disoproxil fumarate (TDF)

TDF is an acyclic nucleoside phosphonate (nucleotide) analogue of adenosine 5'-monophosphate. It inhibits HBV DNA polymerase and HIV reverse transcriptase, with close chemical similarity to ADV. At the present time, TDF is FDA-approved for the treatment of patients with HIV and not for those with HBV. The activity of TDF in LVD-resistant HBV has been observed in patients coinfected with HIV and HBV

who developed LVD resistance (Nunez et al 2002; Ristig et al 2002). Based on these experiences, TDF has been used off label for those with severe LVD resistance before the approval of ADV in 2002. Furthermore, TDF has recently been compared with ADV in 40 patients with CHB who became LVD resistant. Patients in the TDF group exhibited a more rapid decline in HBV DNA during the treatment period, with a mean reduction of –4.8 and –6.6 $\log_{10}$ copies/mL at 3 and 6 months, compared to a mean reduction of .97 and –1.72 $\log_{10}$ copies/mLat 3 and 6 months respectively in the ADV group. (Van Bommel et al 2003, 2004). Hann et al (2006) have also observed the similar differences. Of 109 patients who developed LVD resistance, 65 were placed on ADV and 44 on TDF. At 12 months on either therapy, the HBV DNA log reduction was 5.03 ± 1.64 for TDF and 2.36 ± 2.37 for ADV treated patients (p = 0.001). Furthermore, HBV DNA reduction >3 log at 12 month was observed in 63% and 28 % of the TDF and ADV arms, respectively (p = 0.013).

Characteristics of individual FDA approved drugs are listed in Table 1.

Combination therapy

With more antiviral agents becoming available, the future directions of CHB treatment may involve combination therapy, with the goals of reducing drug resistance, minimizing toxicities and maximizing efficacy. Ideal synergistic regimen may be combination of two drugs with different mechanism. Potential combinations need to be studied in large well designed clinical trials.

Although there were suggestions initially that the combination of LVD and IFN-α may have an additive benefit this has not yet been confirmed in a large scale study (Marcellin et al 2004). Also the combination of LdT and LVD was not shown to be more efficacious than LdT monotherapy (Lai et al 2005). The combination of emtricitabine and ADV showed more improved therapeutic effect and less frequent viral resistance

Table 1 Characteristics of FDA approved drugs for treatment of hepatitis B

Name	Trade name	Strong points	Weak points	Approved
Interferon alpha -2b	Intron A	• Finite duration of treatment • Durable response post-treatment (for responders) • No known resistance	• Significant side effects • 65%–70% fail to respond • Needle injection • High cost	1991
Lamivudine (LVD)	Epivir-HBV Zeffix (Asia)	• Oral • Safe with negligible side effects • Least expensive • Effective for ADV resistant HBV	• Long-term treatment may be needed • High incidence of resistance: 9.1%–20% at yr 1, 70% at yr 5 (esp. those with high baseline HBV DNA)	1998
Adefovir Dipivoxil (ADV)	Hepsera	• Oral • Effective against LVD-resistant HBV and ETV-resistant HBV • Low resistance: 0 at yr 1, 2% at yr 2, 7% at yr 3, 15% at yr 4	• Long-term treatment may be needed • Long-term renal toxicity unknown • 30% fail to respond • Less potent than LVD or ETV	2002
Entecavir (ETV)	Baraclude	• Oral • Potent viral suppression: greater than LVD or ADV • Effective for LVD-resistant HBV • Resistance: 0.8% at yr 4 for treatment-naïve patients, 39.5% at yr 4 for LVD-resistant HBV	• Long-term safety and efficacy unknown • Risk of carcinogenicity in rodents (in very high doses) • Cost >ADV >TLV >LVD	2005
Pegylated Interferon Alpha-2a	Pegasys	• Finite duration of treatment • Once weekly injection • Durable response post-treatment (for responders) • No known resistance	• Needle injection • Significant side effects • 65%–70% fail to respond • High cost	2005
Telbivudine (TLV or LdT))	Tyzeka	• Oral • Potent viral suppression • Resistance: 4% for HBeAg(+) CHB (cf. 9.1% for LVD), 2.7% for HBeAg(-) CHB (cf. 9.8% for LVD)	• Long-term safety and efficacy beyond 1 year unknown • Efficacy to LVD-resistant HBV unknown	2006

(Conjeevaram and Lok 2003; Marcellin et al 2004; Lau et al 2005; Chae and Hann 2006; Lai et al 2006; Colonno et al 2007)

than each drug (Lau et al 2004). An earlier study comparing LVD and ADV to LVD monotherapy showed no benefit of combination (Sung et al 2003). Nevertheless, Yuen et al (2001) showed that if patient's serum HBV DNA is $>10^3$ copies/ml at 6th month on LVD therapy, addition of adefovir could decrease the chance of LVD resistance which may occur in 64% of these patients at the end of the year.

Summary-practice guideline for HBeAg positive and negative patients

To date, several guidelines for the treatment CHB patients (AASLD (Lok and McMahon 2001 and 2004), EASL (The EASL Jury 2003), APASL (Liaw et al 2003) and others such as KASL guideline (Korean Association for the Study of Liver 2004), and Keeffe and his colleagues (Keeffe et al 2006) are presented. However, there are no uniform guidelines globally for the usage of antivirals in the treatment CHB at present. Ultimately the ideal antiviral therapy would be tailored for individual patients. Physicians may need to examine the various guidelines and determine which recommendations are most appropriate for the locale, availability of the drugs, and economic situations in which they practice. Keeffe et al recently suggested cut-off levels of HBV DNA as an indication of antiviral therapy of 20,000 IU/mL (100,000 copies/mL) for patients with HBeAg(+) CHB and 2,000 IU/mL (10,000 copies/mL) for HBeAg(–) CHB, both with abnormal ALT levels. The newly recommended upper normal level of ALT by Keeffe et al is 30 U/L for males and 19 U/L for females (Prati et al 2002).

At present, LVD, ADV, ETV, LDT or PegIFN can be considered as the first line option except the recent guideline proposed by Keeffe and his group in the US (Keeffe et al 2006). Despite issues with the development of resistance, LVD remains an affordable option for CHB therapy for patients with limited financial means. Based on the experience by Chae and Hann (2006), patients with low baseline HBV DNA ($\leq 6\log_{10}$ copies/ml) may still benefit from LVD as first line therapy. The ultimate goal of antiviral therapy for CHB patients lies in halting the progression of liver disease to liver cirrhosis and its life threatening complications and in preventing/reducing the development of HCC. We feel that this goal can be achieved with careful, well-informed decision making on antiviral therapy and close follow-up of CHB patients.

Acknowledgment

We thank Christine L. Hann, M.D., Ph.D. for her critical review and assistance with editing the manuscript. Supported by Chungbuk National University Grant in 2005 (HB.C.)

Note

Dr Hie-Won Hann is on the speaker's bureau for Gilead, Bristol-Myers Squibb and receives clinical research support from Gilead, Bristol-Myers Squibb, and Idenix.

References

Barbon V, Marzano A, Carenzi M, et al. 2006. Treatment with adefovir alone or in combination with lamivudine in chronic hepatitis B lamivudine-resistant patients: results after two years. *J Hepatol*, 44:S178.

Bzowej N, Chan HLY, Lai CL, et al. 2006. A randomized trial of telbivudine (LdT) vs adefovir for HBeAg-positive chronic hepatitis B: final week 52 results. *Hepatology*, 44:563A.

Chae HB, Hann HW. 2006. Baseline HBV DNA level is the most important factor associated with viral breakthrough (BT) during lamivudine (LVD) therapy for chronic hepatitis B (CHB). *Gastroenterology*, 130:A846.

Chang T-T, Chao Y-C, Kaymakoglu S, et al. 2006a. Entecavir maintained virologic suppression through 3 years of treatment in antiviral naïve HBeAg(+) patients. *Hepatology*, 44:229A.

Chang T-T, Gish RG, de Man R, et al. 2006b. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. *N Engl J Med*, 354:1001–10.

Chang TT, Gish RG, Hadziyannis SJ, et al. 2005. A dose-ranging study of the efficacy and tolerability of entecavir in lamivudine-refractory chronic hepatitis B patients. *Gastroenterology*, 129:1198–209.

Chang TT, Lai CL, Chien RN, et al 2004. Four years of lamivudine treatment in Chinese patients with chronic hepatitis B. *J Gastroenterol Hepatol*, 19:1276–82.

Chen CJ, Yang HI, Su J, et al. 2006. REVEAL–HBV Group. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA*, 295:65–73.

Colonno RJ, Rose R, Pokornowski K et al. 2007. Four year assessment of entecavir resistance in nucleoside-naïve and lamivudine refractory patients. *J Hepatol*, 46 (Suppl 1): S294.

Conjeevaram HS, Lok AS. 2003. Management of chronic hepatitis B. *J Hepatol*, 38 (Suppl 1):S90–103.

Fung SK, Chae HB, Fontana RJ, et al. 2006. Virologic response and resistance to adefovir in patients with chronic hepatitis B. *J Hepatol*, 44:283–90.

Gane E, Safadi R, Xie Q, et al. 2006. A randomized trial of telbivudine (LdT) versus lamivudine in lamivudine experienced patients-week 24 primary analysis. *Hepatology*, 44(Suppl 1):564A.

Hadziyannis SJ, Tassopoulos NC, Chan TT, et al. 2005a. Long-term adefovir dipivoxil treatment induces regression of liver fibrosis in patients with chronic hepatitis B: results after 5 years of therapy. *J Hepatol*, 42:754A.

Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, et al. 2005b. Adefovir Dipivoxil 438 study Group. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B. *N Engl J Med*, 352:2673–81.

Hann HW, Chae HB, Dunn S. 2006. Tenofovir (TDF) has stronger antiviral effect than adefovir dipivoxil (ADV) against lamivudine (LVD) resistant hepatitis B virus (HBV). *Gastroenterology*, 130 (Suppl 2):A846.

Hann HWL, Funk MLJ, Rosenberg DM, et al. 2005. Factors associated with response to lamivudine: a retrosepctive study in a tertiary care clinic serving patients with chronic hepatitis B. *J Gastroenterol and Hepatol*, 20:433–40.

Keeffe EB, Dieterich DT, Han SH et al. 2006. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: an update. *Clin Gastroenterol Hepatol*, 4:936–62.

Lai CL, Gane E, Hsu CW, et al 2006. Two year results from the GLOBE trial in patients with chronic hepatitis B: greater clinical and antiviral efficacy for telbivudine (LdT) Vs. Lamivudine. *Hepatology*, 44:222A.

Lai CL, Leung N, Teo EK, et al 2005. Telbivudine phase II investigator Group. 2005; A 1-year trial of telbivudine, lamivudine and the combination in patients with hepatitis Be Antigen-positive chronic hepatitis B. *Gastroenterology*, 129:528–36.

Lai CL, Shouval D, Lok AS, et al. 2006. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. *New Engl J Med*, 354:1011–20.

Lampertico P, Marzano A, Levrero M, et al. 2006. A multicenter Italian study of rescue adefovir dipivoxil therapy in lamivudine resistant patients: A 2 year analysis of 650 patients. *J Hepatol*, 44:S51.

Lau GK, Cooksley H, Ribiero RM, et al. 2004. Randomized double blind study comparing adefovir dipivoxil (ADV) plus emtricitabine (FTC) combination therapy versus ADV alone in HBeAg negative chronic hepatitis B: efficacy and mechanism of treatment response. *Hepatology*, 40:1155A.

Lau GK, Piratvisuth YT, Luo KX, et al. 2005. Peginterferon α-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. *N Engl J Med*, 352:2682–95.

Lee HJ, Suh JI, Jang BI. 1997. The therapeutic effect of recombinant interferon α in chronic hepatitis B patients. *Korean J of Gastroenterol*, 29:777–85.

Lee WM. 1997. Medical progress: hepatitis B virus infection. *N Engl J Med*, 337:1733–45.

Lee YS, Suh DJ, Lim YS, et al. 2006. Increased risk of adefovir resistance in patients with lamivudine-resistant chronic hepatitis B after 48 weeks of adefovir dipivoxil monotherapy. *Hepatology*, 43:1385–91.

Leung N, Peng CY, Sollano J, et al. 2006. Entecavir results in higher HBV DNA reduction VS adefovir in chronically infected HBeAg(+) antiviral-naïve adults: 24 week results (E.A.R.L.Y. Study). *Hepatology*, 44(Suppl 1):554A.

Liaw YF, Leung N, Guan R, et al. 2003. Asian-Pacific consensus statement on the management of chronic hepatitis B: an update. *J Gastroenterol hepatol*, 18:239–45.

Liaw YF, Leung N, Guan R, et al. 2005. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2005 update. *Liver international*, 25:472–89.

Liaw YF, Leung NW, Chang TT, et al. 2000. Effects of extended lamivudine therapy in Asian patients with chronic hepatitis B. Asian Hepatitis Lamivudine Study Group. *Gastroenterology*, 119:172–80.

Liaw YF, Sung JJ, Chow WC, et al. 2004, Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med*, 351:1521–31.

Lin CC, Wu JC, Chang TT, et al. 2001. Long-term evaluation of recombinant interferon alpha2b in the treatment of patients with hepatitis B e antigen-negative chronic hepatitis B in Taiwan. *J Viral Hepatitis*, 8:438–46.

Lok AS, Lai CL, Leung N, et al. 2003. Long-term safety of lamivudine treatment in patients with chronic hepatitis B. *Gastroenterology*, 125:1714–22.

Lok AS, Lai CL, Wu PC, et al. 1988. Long-term follow-up in a randomised controlled trial of recombinant alpha 2-interferon in Chinese patients with chronic hepatitis B infection. Lancet, 332:298–302.

Lok ASF, McMahon BJ. 2001. AASLD Practice guidelines: chronic hepatitis B. *Hepatology*, 34:1225–41.

Lok ASF, McMahon BJ. 2004. AASLD practice guidelines:chronic hepatitis B: update of recommendation. *Hepatology*, 39:857–61.

Marcellin P, Chang T, Lim S, et al. 2005. Increasing serologic, virologic and biochemical response over time to adefovir dipivoxil (ADV) 10 mg in HbeAg-positive chronic hepatitis B patients. *J Hepatol*, 42(Suppl 2):31.

Marcellin P, Chang T-T, Lim SG, et al. 2003. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. *N Engl J Med*, 348:808–16.

Marcellin P, Lau GKK, Bonino F, et al. 2004. Peginterferon α-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. *N Engl J Med*, 351:1206–17.

Martin P, Hann HW, Westerberg S, et al. 1998. Interferon-alpha2b therapy is efficacious in Asian-Americans with chronic hepatitis B infection: a prospective controlled trial. *Dig Dis Sci*, 43:875–9.

Nowak MA, Bonhoeffer S, Hill AM, et al. 1996. Viral dynamics in hepatitis B virus infection. *Proc Natl Acad Sci*, 93:4398–402.

Nunez M, Perez-Olimeda M, Diaz B, et al. 2002, Activity of tenofovir on hepatitis B virus replicaion in HIV–co-infected patients failing or partially responding to lamivudine. *AIDS*, 16:2352–4.

Papatheodoridis GV, Dimou E, Dimakopoulos K, et al. 2005. Outcome of hepatitis B e antigen-negative chronic hepatitis B on long-term nucleos(t)ide analog therapy starting with lamivudine. *Hepatology*, 42:121–9.

Perrillo RP. 2006. Therapy of hepatitis B-viral suppression or eradication? *Hepatology*, 43 (Suppl 1):S183–93.

Perrillo RP, Lai CL, Liaw YF, et al. 2002. Predictors of HBeAg loss after lamivudine treatment for chronic hepatitis B. *Hepatology*, 36:186–94.

Perrillo RP, Schiff ER, Davis GL, et al. 1990. A randomized, controlled trial of interferon α-2b alone and after prednisolone withdrawal for the treatment of chronic hepatitis B. The hepatitis interventional therapy group. *New Engl J Med*, 323:295–301.

Prati D, Taiolo E, Zanella A, et al. 2002. Updated definitions of healthy ranges for serum alanine aminotransferase levels. *Ann Intern Med*, 137:1–10.

Ristig MB, Crippin J, Aberg JA, et al. 2002. Tenofovir disoproxil fumarate therapy for chronic hepatitis B in human immunodeficiency virus/hepatitis B virus-coinfected individuals for whom interferon-alpha and lamivudine therapy have failed. *J Infect Dis*, 186:1844–7.

Rosmawati M, Lai CL, Lao L, et al. 2003. Baseline ALT level does not predict viral load reduction in response to entecavir therapy. *J of Hepatol* 38:166, Abstr 574.

Ryu SH, Chung YH, Choi MH, et al. 2003. Long term additional lamivudine therapy enhances durability of lamivudine-induced HBeAg loss: a prospective study. *J Hepatol*, 39:614–19.

Snow A, Thibault V, Qi X, et al. 2005. Combination of adefovir (ADV) and lamivudine (LVD) prevented emergence of adefovir resistance mutations in chronic hepatitis B patients with lamivudine-resistant HBV. *Gastroenterology*, 128:A745.

Sung JJY, Lai YF, Zeuzem S, et al. 2003. A randomized, double-blind phase II study of lamivudine (LVD) compared o lamivudine plus adefovir dipivoxil (ADV) for treatment if naïve patients with chronic hepatitis B (CHB) week 52 analysis. *J Hepatol*, 38 (Suppl 2):25.

The EASL Jury. 2003. EASL international consensus conference on hepatitis B. *J Hepatol*, 38:533–40.

Van Bommel F, Wunsche T, Mauss S, et al. 2004. Comparison of adefovir and tenofovir in the treatment of lamivudine resistant hepatitis B virus infection. *Hepatology*, 40:1421–5.

Van Bommel F, Wensche T, Schurmann D, et al. 2003. A comparison of adefovir and tenofovir in the treatment of lamivudine-resistant hepatitis B virus (HBV) infection. *Hepatology* 38(Suppl 1):A246.

Yuen MF, Sabion E, Hui CK, et al. 2001. Factors associated with hepatitis B virus DNA breakthrough in patients receiving prolonged lamivudine therapy. *Hepatology*, 34:785–91.

Zeuzem S, de Man RA, Honkoop P et al. 1997. Dynamics of hepatitis B virus infection in vivo. *J of Hepatol*, *27:431–6.*