The saga of entecavir

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*And the communication I have got to make is, that (it)
has great expectations.*

—Charles Dickens
Great Expectations

Chronic infection by hepatitis B virus (HBV) affects approximately 400 million people worldwide and is estimated to cause 1 million deaths annually [1]. The treatment of chronic hepatitis B has been radically altered in the past decade as a result of two developments. First, there are important new findings concerning its natural history. Second, the oral nucleoside/nucleotide analogues are now firmly established as an excellent alternative mode of therapy.

Studies of the natural history of chronic hepatitis B suggest that other than the traditional endpoint of hepatitis B e antigen (HBeAg) seroconversion, sustained suppression of HBV DNA to very low levels, preferably to below the detection limit of sensitive polymerase chain reaction (PCR) assays, is an even more important endpoint of treatment [2–5]. The availability of nucleoside/nucleotide analogues makes the ideal of sustained viral suppression a reality. The rate of HBeAg seroconversion is slower with nucleoside/nucleotide analogues than with interferon therapy because they lack the immunomodulatory effects of interferon. Unlike interferon, nucleoside/nucleotide analogues can be given orally, and, except for mild and reversible nephrotoxicity (approximately 3% in 5 years) with adefovir [6], are almost without side effects. Even a relatively short period of treatment with lamivudine has been shown to decrease the risk for the development of

cirrhosis complications and hepatocellular carcinoma (HCC) both in patients with established cirrhosis and in patients with precirrhotic disease [7, 8]. The problem with long-term nucleoside/nucleotide analogue therapy is of course the potential for the development of resistant mutants.

One of the most promising nucleoside analogues for long-term viral suppression with low rate of development of resistance is entecavir. Entecavir is a deoxyguanosine analogue that is rapidly phosphorylated intracellularly into its active 5'-triphosphate form. It inhibits HBV replication at three important steps: protein-linked priming of the HBV polymerase, synthesis of the first negative strand of the HBV DNA by reverse transcription, and synthesis of the second positive strand [9]. Its efficient phosphorylation and its triple action in the inhibition of HBV replication may explain its potency in the suppression of HBV DNA in small doses of 0.5–1 mg licensed for use. It has been approved for use in the treatment of chronic hepatitis B in the United States in 2005, and since then in the European Union, China, and several other countries worldwide.

In the current issue of the *journal*, Shindo et al. [10] report a randomized, double-blind phase II study of the antiviral activity of once-daily oral dose of entecavir 0.01, 0.1, or 0.5 mg, or lamivudine 100 mg, over 24 weeks in 137 nucleoside-naïve Japanese adults. This study confirmed the results of an international study of 169 patients including Asians and Westerners published in 2002 [11]. Both these studies indicate that entecavir 0.1 mg is non-inferior and entecavir 0.5 mg superior to lamivudine 100 mg in Japanese patients as well as in patients of other nationalities.

Entecavir has now been established as an excellent antiviral agent for chronic hepatitis B and is recommended as one of the first-line agents for nucleoside-naïve patients

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in various international treatment guidelines [12–14]. Two phase III pivotal trials of entecavir 0.5 mg daily versus lamivudine 100 mg daily in 715 HBeAg-positive patients and 648 HBeAg-negative patients have shown that entecavir is superior to lamivudine at week 48 of treatment [15, 16]. Entecavir has also been found to be superior to 10 mg of adefovir at week 48 of treatment in an open-label study of 69 treatment-naïve, HBeAg-positive patients [17]. The superiority of entecavir to lamivudine becomes even more apparent in comparative studies at week 96, partly because of its potency but, more important, because of its very low rate of resistance development [18, 19]. At week 96, 74% of entecavir-treated patients achieved HBV DNA of <300 copies/mL (~ 60 IU/mL) compared with only 37% of lamivudine-treated patients [19].

Follow-up studies for longer periods of treatment were marred by the initial protocols that mandated cessation of therapy when the patients achieved “complete response,” defined as HBV DNA of less than 0.7×10^6 copies/mL with HBeAg loss for the HBeAg-positive patients. Subsequently, it was found that a large proportion of both HBeAg-positive and HBeAg-negative patients with so-called “complete response” required recommencement of therapy. HBV DNA levels of 0.7×10^6 are moderately high levels. It is important to emphasize that the ideal aim of treatment should be *sustained* suppression of HBV DNA, preferably to levels *below* the detection limit by PCR assays [4, 5]. Although the initial large cohorts of patients were thus fragmented during follow-up, analysis has been performed for 98 HBeAg-positive patients who were on “continuous” entecavir (with a treatment gap of ≤ 35 days before recommencement of therapy) for 5 years [20]. The results are most encouraging: 94% of patients had HBV DNA of <300 copies/mL (~ 60 IU/mL), 80% had normal alanine transaminase (ALT) levels, and 41% had loss of HBeAg (17% with HBeAg seroconversion).

Even more encouraging are the long-term histologic assessment in 57 patients with biopsies at baseline, 48, and 280 weeks (median time for the third biopsy) [21]. Ninety-six percent of patients had histologic improvement and, very important, 88% had improvement in Ishak fibrosis score. These results are confirmed by an independent Japanese study with 37 nucleoside-naïve patients with biopsies at baseline, 48, and 148 weeks [22]. The reversal of fibrosis and cirrhosis carries great potential prognostic significance for the prevention of cirrhosis complications and, possibly, HCC.

Entecavir is also effective against lamivudine-resistant HBV, though the EC_{50} values of entecavir for five lamivudine-resistant mutant viruses tested by Ono et al. [23] are 2–778 times higher than those for wild-type HBV. A phase III, double-blind control trial in 286 lamivudine-refractory, HBeAg-positive patients showed that switching

to entecavir (141 patients) with a 1 mg daily dose (twice the dose for nucleoside-naïve patients) provided better histologic improvement, HBV DNA reduction, and ALT normalization than continuing lamivudine at week 48 [24]. However, the reduction of HBV DNA was less than in nucleoside-naïve patients; only 19% of lamivudine-refractory patients having HBV DNA of <300 copies/mL (~ 60 IU/mL) compared with the 67% of nucleoside-naïve patients [15]. By week 48, 1.4% of patients had virologic rebound due to the emergence of entecavir-resistant mutants, with seven other patients (of 134 tested) identified to have entecavir-resistant mutants at baseline without virologic rebound. By week 96, 23 of 77 entecavir-treated patients had developed genotypic resistance to entecavir [25]. The cumulative genotypic resistant rates for entecavir on lamivudine-resistant disease are 6%, 15%, 36%, 46%, and 51% from years 1 to 5 [26].

It must be emphasized that resistance to entecavir in nucleoside-naïve patients is a rare phenomenon. Resistance to entecavir requires three substitutions: the two lamivudine-resistant mutants M204 V/I and L180 M together with a “signature” mutations of T184G, S203I, or M250 V [27]. Molecular modeling suggests that the additional changes at T1874, S202, or M250 probably decrease access to the binding pocket in the reverse transcriptase domain of the mutants, which are still growth deficient relative to the wild-type HBV [28]. The high genetic barrier requiring three substitutions for resistance explains why the cumulative probability of genotypic resistance to entecavir after 5 years of therapy is only 1.2% ($n = 108$) [29]. However, this barrier is reduced to one substitution in patients who already have two lamivudine-resistant mutations. Hence, the high resistance rate with long-term entecavir treatment in lamivudine-resistant patients makes entecavir less than ideal for the management of lamivudine resistance.

For the treatment of resistance to lamivudine (a nucleoside analogue), nucleotide analogues such as adefovir and tenofovir are superior to entecavir, which is a nucleoside analogue like lamivudine. In general, HBV mutants resistant to nucleoside analogues tend to remain sensitive to nucleotide analogues, and vice versa [26]. However, preliminary studies have shown that lamivudine-resistant patients are more prone to develop mutations even with the potent nucleotide analogue tenofovir [30, 31].

Multiple cost-effective evaluation studies of entecavir versus lamivudine using mathematical models have been performed [32, 33]. In both the Asian and American populations, entecavir administered for up to 10 years has been shown to be highly cost-effective when the possible decrease in risks for the development of decompensated cirrhosis, and HCC is taken into consideration.

Finally, for treatment-naïve patients, is combination therapy necessary? Theoretically, the ideal combination for

maximal viral suppression and prevention of resistance is to combine a potent nucleoside with a potent nucleotide analogue. Such a study has not been performed. However, with potent agents such as entecavir and tenofovir, with resistance rates of 1.2% in 5 years [29] and 0% in 2 years [34–36], respectively, monotherapy with either of these two agents is a viable cost-effective option.

References

- Dienstag JL. Hepatitis B virus infection. *N Engl J Med* 2008;359:1486–1500
- Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA* 2006;295:65–73
- Iloeje UH, Yang HI, Su J, Jen CL, You SL, Chen CJ, et al. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. *Gastroenterology* 2006;130:678–686
- Lai CL, Yuen MF. Chronic hepatitis B—new goals, new treatment. *N Engl J Med* 2008;359:2488–2491
- Lai CL, Yuen MF. The natural history and treatment of chronic hepatitis B: a critical evaluation of standard treatment criteria and end points. *Ann Intern Med* 2007;147:58–61
- Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, et al. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B for up to 5 years. *Gastroenterology* 2006;131:1743–1751
- Liaw YF, Sung JJ, Chow WC, Farrell G, Lee CZ, Yuen H, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med* 2004;351:1521–1531
- Yuen MF, Seto WK, Chow DH, Tsui K, Wong DK, Ngai VW, et al. Long-term lamivudine therapy reduces the risk of long-term complications of chronic hepatitis B infection even in patients without advanced disease. *Antivir Ther* 2007;12:1295–1303
- Langley DR, Walsh AW, Baldick CJ, Eggers BJ, Rose RE, Levine SM, et al. Inhibition of hepatitis B virus polymerase by entecavir. *J Virol* 2007;81:3992–4001
- Shindo M, Chayama K, Mochida S, Toyota J, Tomita E, Kumada H, et al. Antiviral activity, dose–response relationship, and safety of entecavir following 24-week oral dosing in nucleoside-naïve Japanese adult patients with chronic hepatitis B: a randomized, double-blind, phase II clinical trial. *Hepatol Int* 2009;3: this issue. doi:10.1007/s12072-009-9135-0
- Lai CL, Rosmawati M, Lao J, Vlierberghe HV, Anderson FH, Thomas N, et al. Entecavir is superior to lamivudine in reducing HBV DNA in patients with chronic hepatitis B infection. *Gastroenterology* 2002;123(6):1831–1838
- Lok AS, McMahon BJ. Chronic hepatitis B. *Hepatology* 2007;45:507–539
- European Association for the Study of the Liver. EASL clinical practice guidelines: management of chronic hepatitis B. *J Hepatol* 2009;50:227–242
- Liaw YF, Suh DJ, Omata M. APASL guidelines for HBV management (provisional). 2008. Available from: <http://www.apasl.info/guidelinesHBV.html>
- Chang TT, Gish RG, de Man R, Gadano A, Sollano J, Chao YC, et al. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. *N Engl J Med* 2006;354:1001–1010
- Lai CL, Shouval D, Lok AS, Chang TT, Cheinquer H, Goodman Z, et al. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. *N Engl J Med* 2006;354:1011–1020
- Leung N, Peng CY, Hann HW, Sollano J, Lao-Tan J, Hsu CW, et al. Early hepatitis B virus DNA reduction in hepatitis B e antigen-positive patients with chronic hepatitis B: a randomized international study of entecavir versus adefovir. *Hepatology* 2009;49:72–79
- Gish RG, Lok AS, Chang TT, de Man RA, Gadano A, Sollano J, et al. Entecavir therapy for up to 96 weeks in patients with HBeAg-positive chronic hepatitis B. *Gastroenterology* 2007;133:1437–1444
- Yao GB, Chen CW, Lu WL, Ren H, Tan DM, Wang YM, et al. Virologic, serologic, and biochemical outcomes through 2 years of treatment with entecavir and lamivudine in nucleoside-naïve Chinese patients with chronic hepatitis B: a randomized, multi-center study. *Hepatol Int* 2008;2:486–493
- Chang TT, Yoon SK, Lai CL, Sievert W, Sollano J, Tan JL, et al. Five year of continuous entecavir (ETV) for nucleoside-naïve HBeAg (+) chronic hepatitis B (CHB): results from study ETV-901. *Hepatol Int* 2009;3:86–220, PE115
- Chang TT, Wu SS, Chao YC, Han KH, Yoon SK, Lai CL, et al. Long-term entecavir therapy results in reversal of fibrosis/cirrhosis and continuous histologic improvement in patients with HBeAg (+) and (–) chronic hepatitis B: results from studies ETV-022, -027 and -901. *Hepatol Int* 2009;3:86–220, PE119
- Imazeki F, Kage M, Moriyama M, Kumada H, Kobashi H, Toyota J, et al. Histologic assessment of long-term entecavir (ETV) treatment in chronic hepatitis B (CHB) patients. *Hepatol Int* 2009;3:86–220
- Ono SK, Kato N, Shiratori Y, Kato J, Goto T, Schinazi RF, et al. The polymerase L528 M mutation cooperates with nucleotide binding-site mutations, increasing hepatitis B virus replication and drug resistance. *J Clin Invest* 2001;107:449–455
- Sherman M, Yurdaydin C, Sollano J, Silva M, Liaw YF, Cianiara J, et al. Entecavir for treatment of lamivudine-refractory, HBeAg-positive chronic hepatitis B. *Gastroenterology* 2006;130:2039–2049
- Sherman M, Yurdaydin C, Simsek H, Silva M, Liaw YF, Rustgi VK, et al. Entecavir therapy for lamivudine-refractory chronic hepatitis B: improved virologic, biochemical, and serology outcomes through 96 weeks. *Hepatology* 2008;48:99–108
- Yuen MF, Fung J, Wong DK, Lai CL. Prevention and management of drug resistance for antihepatitis B treatment. *Lancet Infect Dis* 2009;9:256–264
- Tenney DJ, Rose RE, Baldick CJ, Levine SM, Pokornowski KA, Walsh AW, et al. Two-year assessment of entecavir resistance in lamivudine-refractory hepatitis B virus patients reveals different clinical outcomes depending on the resistance substitutions present. *Antimicrob Agents Chemother* 2007;51:902–911
- Baldick CJ, Tenney DJ, Mazzucco CE, Eggers BJ, Rose RE, Pokornowski KA, et al. Comprehensive evaluation of hepatitis B virus reverse transcriptase substitutions associated with entecavir resistance. *Hepatology* 2008;47:1473–1482
- Tenney DJ, Rose RE, Baldick CJ, Pokornowski KA, Eggers BJ, Fang J, et al. Long-term monitoring shows hepatitis B virus resistance to entecavir in nucleoside-naïve patients is rare through 5 years of therapy. *Hepatology*. Epub 2009 Feb 4
- Chauhan R, Hissar SS, Singh AK, Mishra SK, Kumar MD, Sarin SK. Higher frequency of selection of tenofovir resistant mutations in lamivudine exposed compared to naïve CHBV patients during tenofovir antiviral therapy. *Hepatology* 2008;48(Suppl): 719A
- van Boemmel F, Feucht HH, Schlosser B, Weich V, Schott E, Wiedenmann B, et al. Detection of mutations associated with resistance to nucleos(t)ide analogs in patients with HBV infection during treatment with tenofovir. *Hepatology* 2008;48(Suppl): 715A–716A

32. Yuan Y, Iloeje U, Li H, Hay J, Yao GB. Economic implications of entecavir treatment in suppressing viral replication in chronic hepatitis B (CHB) patients in China from a prospective of the Chinese Social Security program. *Value Health* 2008;11(Suppl 1):S11–S22
33. Veenstra DL, Sullivan SD, Clarke L, Iloeje UH, Tafesse E, Di Bisceglie A, et al. Cost effectiveness of entecavir versus lamivudine with adefovir salvage in HBeAg-positive chronic hepatitis B. *Pharmacoeconomics* 2007;25:963–977
34. Marcellin P, Heathcote EJ, Buti M, Gane E, de Man RA, Krastev Z, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. *N Engl J Med* 2008;359:2442–2455
35. Marcellin P, Buti M, Krastev Z, Gurel S, Balabanska RI, Dusheiko G, et al. Two year tenofovir disoproxil fumarate (TDF) treatment and adefovir dipivoxil (adv) switch data in HBeAg-negative patients with chronic hepatitis B (STUDY 102), preliminary analysis. *Hepatology* 2008;48(Suppl):370A
36. Heathcote EJ, Gane EJ, deMan RA, Chan S, Sievert W, Mauss S, et al. Two year tenofovir disoproxil fumarate (TDF) treatment and adefovir dipivoxil (adv) switch data in HBeAg-positive patients with chronic hepatitis B (study 103), preliminary analysis. *Hepatology* 2008;48(Suppl):376A