

New therapies for chronic hepatitis B infection

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Abstract: Conventional pharmacotherapeutic approaches to the management of chronic hepatitis B virus (HBV) infection are compromised by drug resistance and a failure to achieve sustained HBV DNA suppression. Low rates of seroconversion to hepatitis B e antigen-negative status and loss of hepatitis B surface antigen, as well as the potential for the development of adverse effects, are additional problems. Two agents, entecavir and the pegylated interferon (peginterferon) α -2a, have recently been added to the therapeutic armamentarium for the management of chronic hepatitis B (CHB). Data from clinical trials indicate that these newly licensed drugs may offer advantages over conventional treatments such as lamivudine and, possibly, adefovir. In addition, several novel agents in late-stage clinical development, specifically telbivudine and clevudine, have also shown encouraging results in patients with CHB infection. This review summarizes the current clinical experience with these new agents, focusing on data in Asian populations, and discusses the implications of the data for CHB management.

T. T. Chang¹, Jidong D. Jia², Masao Omata³ and S. K. Yoon⁴

¹College of Medicine, National Cheng Kung University, Tainan, Taiwan, ²Beijing Friendship Hospital, Capital University of Medical Sciences, Beijing, China, ³Department of Gastroenterology, University of Tokyo, Tokyo, Japan, ⁴Division of Hepatogastroenterology, Department of Internal Medicine, The Catholic University of Korea Seoul, South Korea

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Prof. T. T. Chang, Department of Medicine, National Cheng Kung University Hospital, 138 Sheng-Li Road, Tainan 70428, Taiwan.
Tel: +886 6 2353535ext. 5389
e-mail: ttchang@mail.ncku.edu.tw

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Chronic hepatitis B virus (HBV) is a primary cause of liver disease in many parts of the world, particularly the Asia-Pacific region, contributing to sequelae such as cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC) (1). Conventional anti-HBV therapy with direct antiviral agents such as lamivudine and adefovir, and interferon α , has demonstrated a beneficial effect in reducing HBV replication and controlling HBV disease progression in patients with chronic hepatitis B (CHB) (2–9). However, the long-term efficacy of conventional therapy is less than satisfactory because of the rapid emergence of drug resistance to certain nucleoside and nucleotide analogs and the poor tolerability to interferon (10–12).

Several promising new anti-HBV agents, including entecavir and the pegylated interferon (peginterferon) α -2a and -2b, possess potent antiviral effects with less toxicity than standard agents and minimal or no risk of inducing drug resistance. In phase III randomized studies, entecavir and peginterferon α -2a have demonstrated clinical advantages over lamivudine (13–17).

More recently, entecavir has demonstrated greater suppression of HBV replication compared with adefovir (18). More recently, peginterferon α -2a and entecavir have been introduced in many of the countries in the Asia-Pacific region. In addition, several novel agents in late-stage clinical development, such as telbivudine and clevudine, have shown encouraging results in patients with chronic HBV infection (19–21). In this article, we review the recently reported clinical results with newly licensed agents and pharmacotherapies under development, which have demonstrated maintained suppression of viral replication with a limited emergence of drug resistance.

Anti-HBV agents licensed since 2005

Entecavir

Entecavir, a cyclopentyl guanosine analog that inhibits both the priming and elongation steps of viral replication, is a highly potent inhibitor of HBV polymerase (22–24). In phase III studies,

Table 1. Virologic, biochemical, and serologic end points from phase III studies of entecavir in patients with chronic hepatitis B (CHB)

	Histologic improvement (%)	ALT normalization (%)	HBV DNA <300 copies/ml (%)	Mean change in HBV DNA from baseline (log ₁₀ copies/ml)	Rate of HBeAg seroconversion (%)
<i>Nucleoside-naïve HBeAg-positive patients (Chang et al. (13))</i>					
Entecavir, 0.5 mg/day (n = 354)	72	68	67	-6.9	21
Lamivudine, 100 mg (n = 355)	62	60	36	-5.4	18
<i>P</i>	0.009	0.02	<0.001	<0.001	0.33
<i>Nucleoside-naïve HBeAg-negative patients (Lai et al (14))</i>					
Entecavir, 0.5 mg/day (n = 325)	70	78	90	-5.0	NA
Lamivudine, 100 mg/day (n = 313)	61	71	72	-4.5	NA
<i>P</i>	0.01	0.045	<0.001	<0.001	
<i>Lamivudine-refractory HBeAg-positive patients (Sherman et al (15))</i>					
Entecavir, 0.5 mg/day (n = 141)	55	61	19	-5.11	8
Lamivudine, 100 mg/day (n = 145)	28	15	1	-0.48	3
<i>P</i>	<0.001	<0.001	<0.001	<0.001	0.06

*Roche COBAS AmpliCor PCR assay (LLOQ = 300 copies/ml) ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; LLOQ, lower limit of quantification.

entecavir has demonstrated superior efficacy and an improved resistance profile to lamivudine in both hepatitis B e antigen (HBeAg)-positive and -negative nucleoside-naïve patients with CHB and patients who were lamivudine refractory (Table 1) (13–15). In these studies, 48 weeks of entecavir therapy resulted in superior histologic improvement, a greater mean reduction of HBV DNA viral load, with a larger proportion of patients demonstrating undetectable HBV DNA levels (<300 copies/ml by Roche COBAS AmpliCor PCR assay), and normalization of alanine aminotransferase (ALT) levels [$\leq 1 \times$ the upper limit of normal (ULN)] compared with an equal length of treatment with lamivudine. Moreover, among nucleoside-naïve HBeAg-positive and -negative patients who achieved a protocol-defined response (HBV DNA levels of <0.7 mEq/ml by bDNA assay, and HBeAg loss or ALT < $1.25 \times$ ULN) at week 48, a higher proportion of entecavir-treated patients than lamivudine-treated patients demonstrated a sustained response 24 weeks after the discontinuation of treatment (13, 14).

Data on the long-term efficacy of entecavir in HBeAg-positive and -negative nucleoside-naïve and lamivudine-refractory HBeAg-positive patients indicate that response to entecavir and suppression of viral replication is sustained for 96 weeks of therapy (25–27). In the phase III study of HBeAg-positive nucleoside-naïve patients, 243 patients treated with entecavir and 164 patients treated with lamivudine who achieved a virologic response (HBV DNA levels of <0.7 mEq/ml by bDNA assay, with HBeAg loss) at week 48 continued treatment until week 96 (25). During the second year of treatment, the proportion of entecavir-treated patients with undetectable HBV DNA (DNA levels of <300 copies/ml) increased from 64% to 81%, while the proportion of patients

with undetectable HBV DNA in the lamivudine group remained unchanged at 39%. At 96 weeks, a higher proportion of entecavir-treated patients than lamivudine-treated patients maintained HBV DNA levels of <300 copies/ml (80% vs 39%; $P < 0.0001$; Fig. 1A) (25). The cumulative rate of HBeAg seroconversion (31% vs 26%) and ALT normalization, defined as $\leq 1 \times$ ULN (87% vs 79%) over the 2 years of therapy was comparable between the entecavir and lamivudine groups, respectively (25). Similar findings were reported in a second study that compared long-term entecavir and lamivudine therapy in HBeAg-negative nucleoside-naïve patients (26). At week 96, a higher proportion of entecavir-treated than lamivudine-treated patients achieved HBV DNA levels of <300 copies/ml (94% vs 77%; $P < 0.0001$) and maintained ALT levels of $\leq 1 \times$ ULN (89% vs 84%; $P = 0.05$; Fig. 1B) (26). In patients with lamivudine-refractory CHB, prolonged treatment with entecavir was more effective than lamivudine in maintaining HBV DNA levels of <300 copies/ml (30% vs 1%; $P < 0.0001$), ALT normalization defined as $\leq 1 \times$ ULN (85% vs 29%; $P < 0.0001$), and HBeAg seroconversion rates (16% vs 4%; $P = 0.001$) (27).

Analysis of the safety data from the large, randomized, phase III studies of entecavir showed that the safety profile of entecavir was comparable with that of lamivudine in nucleoside-naïve and lamivudine-refractory patients (13–15). The resistance data for entecavir indicate no resistance in nucleoside-naïve, HBeAg-positive, and -negative patients after 2 years of therapy, and a low rate of resistance (1% at 1 year and 9% at 2 years) among lamivudine-resistant patients (28).

The efficacy of entecavir has also been studied in nucleoside-naïve and lamivudine-refractory

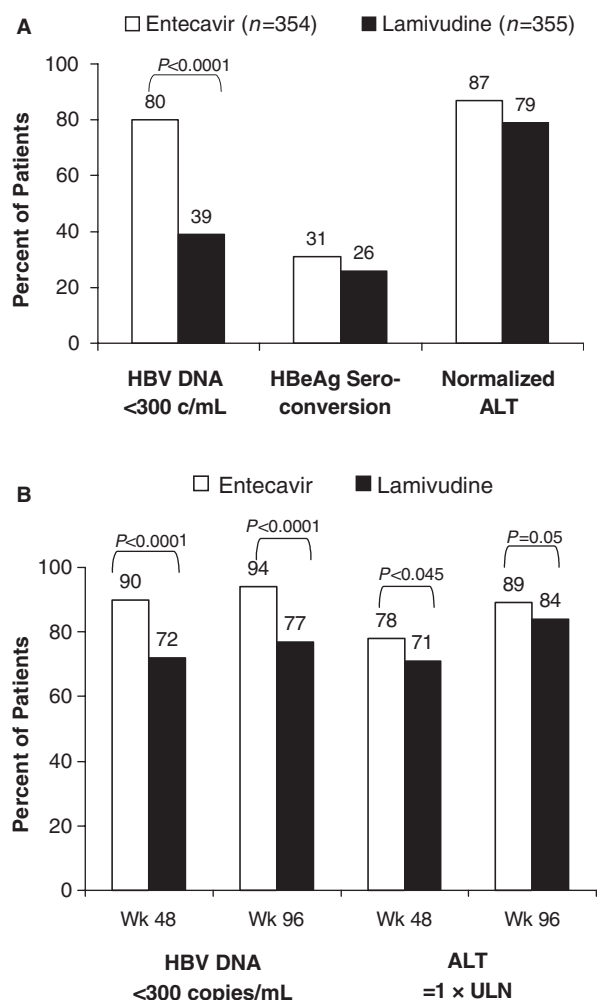


Fig. 1. Long-term efficacy of entecavir (at 96 weeks) in hepatitis B e antigen (HBeAg)-positive and -negative patients with chronic hepatitis B (CHB). (A) Long-term efficacy of entecavir (at 96 weeks) in HBeAg-positive patients with CHB (25). (B) The virologic and biochemical efficacy of entecavir at 48 and 96 weeks in HBeAg-negative patients with CHB (26).

Chinese patients with CHB. Data from a randomized, double-blind, multicenter, phase III study comparing entecavir and lamivudine in Chinese nucleoside-naïve patients were recently reported (29). In this study, patients were randomized to receive entecavir, 0.5 mg/day, plus placebo ($n = 261$) or lamivudine, 100 mg/day, plus placebo ($n = 258$) for 48 weeks. At week 48, a higher proportion of patients in the entecavir group than in the lamivudine group achieved the composite end point of HBV DNA level <0.7 mEq/ml by bDNA assay and an ALT level of $<1.25 \times$ ULN (90% vs 67%; $P < 0.0001$) (29). The overall mean reduction in HBV DNA level was greater in patients treated with entecavir than in patients treated with lamivudine (-5.9 vs $-4.3 \log_{10}$ copies/ml; $P < 0.0001$). A higher proportion of entecavir-treated patients than lamivudine-treated

patients achieved undetectable viral load, defined as an HBV DNA level of <300 copies/ml (76% vs 43%; $P < 0.0001$), and ALT normalization (90% vs 78%; $P = 0.0003$) at week 48 (29). The rate of HBeAg seroconversion by week 48 was comparable between the entecavir and lamivudine groups (15% vs 18%; $P = 0.39$) (Fig. 2).

A second placebo-controlled phase II study evaluated the efficacy of entecavir in 145 Chinese patients who have failed lamivudine therapy (30). Patients were randomized to receive either entecavir, 1.0 mg/day for 48 weeks, or placebo daily for 12 weeks, followed by entecavir, 1.0 mg/day for an additional 36 weeks. At week 12, patients in the entecavir group achieved a greater overall reduction in HBV DNA levels than did patients receiving lamivudine (-4.30 vs $-0.15 \log_{10}$ copies/ml) (30). Additionally, a higher proportion of entecavir-treated patients than lamivudine-treated patients had HBV DNA levels of <300 copies/ml (8% vs 0%; $P = 0.12$), and a significantly higher proportion of entecavir-treated patients than controls achieved ALT normalization ($\leq 1.0 \times$ ULN; 68% vs 6%; $P < 0.001$) (30).

The overall findings from phase III studies demonstrate the superior efficacy of entecavir compared with lamivudine reduction of HBV DNA levels (<300 copies/ml), normalization of ALT levels ($\leq 1 \times$ ULN), and improvement of liver histology in both nucleoside-naïve HBeAg-positive and -negative patients and in lamivudine-refractory HBeAg-positive patients. Additionally, the clinical benefits of entecavir are sustained for 96 weeks of therapy. No resistance to entecavir in treatment-naïve hepatitis B surface antigen (HBsAg)-positive and -negative patients has been observed after 96 weeks of therapy; in lamivudine-refractory patients, the rate of resistance has been found to be low (1% at 1 year and 9% at 2 years). Data from recent studies conducted in nucleoside-naïve and lamivudine-resistant Chinese patients confirm the effectiveness of entecavir in this patient population.

Peginterferons

Two peginterferons have been developed: peginterferon α -2a (Pegasys[®]; Hoffmann-La Roche; Nutley, NJ) and peginterferon α -2b (PEG-Intron[®]; Schering-Plough Corporation, Kenilworth, NJ). These agents differ in their pharmacokinetics, pharmacology, and receptor-binding properties. Peginterferon α -2b (molecular weight, 12 kDa) has a shorter half-life than peginterferon α -2a (molecular weight, 40 kDa) and is more of a prodrug, acting as a depot for interferon α with the release of free interferon α .

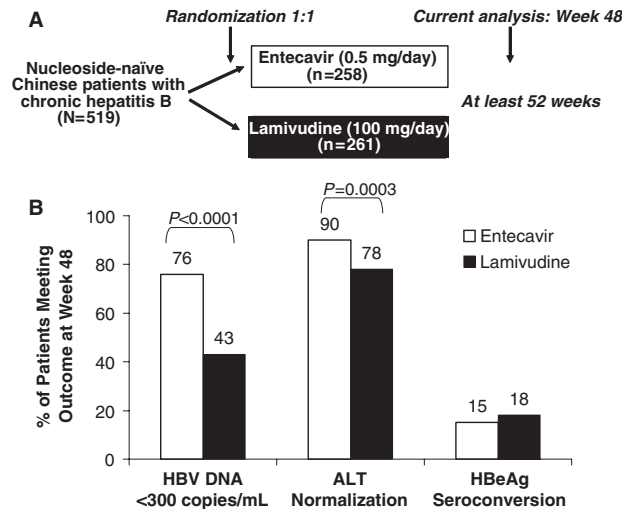


Fig. 2. Efficacy of entecavir and lamivudine in nucleoside-naïve Chinese patients. (A) Study scheme. (B) The virologic and biochemical efficacy of entecavir and lamivudine at 48 weeks (29).

In large phase III randomized trials, peginterferon α -2a with or without lamivudine demonstrated superior efficacy to lamivudine alone with respect to reduced HBV DNA levels from baseline, 48-week virologic response rates, and HBeAg and HBsAg seroconversion in patients with HBeAg-positive and -negative CHB (16, 17). More recently, the virologic response to peginterferon α -2a has been shown to be sustained after treatment in patients with HBeAg-positive (31) and HBeAg-negative CHB (32). Subanalysis of responses to peginterferon α -2a monotherapy in 150 Asian HBeAg-positive patients participating in a long-term follow-up study showed that HBeAg seroconversion occurred in 58 (39%) of patients at 6 months post-treatment (31). Of the 58 patients who seroconverted at 6 months, 48 (83%) maintained seroconversion at 12 months post-treatment, while three (5%) remained HBeAg negative but lost anti-HBe by the 1-year follow-up. Additionally, 15% of Asian patients who did not HBeAg seroconvert at 6 months post-treatment did undergo seroconversion by 12 months (31). In this analysis, sustained HBeAg seroconversion was associated with higher baseline ALT and lower baseline HBV DNA levels. Similar findings were reported in a second study involving 177 patients with HBeAg-negative CHB (32). Of the 144 patients who had a virologic response to peginterferon α -2a (HBV DNA levels of $<20\,000$ copies/ml), data were available on 89 patients at 48 weeks post-treatment. Of these patients, 49 (55%) showed sustained HBV DNA levels of $<10^5$ copies/ml during the 48-week follow-up period, including 22 (25%) with HBV DNA levels between 2×10^4 and 2×10^5 copies/ml and 27 (30%) with HBV DNA levels of $<20\,000$ copies/ml (33). Among the patients

achieving an ALT response, 72% maintained ALT levels at $<1.5 \times \text{ULN}$ at 6–12 months post-treatment. At the end of the initial 6 months of therapy, seven patients had achieved HBsAg loss or seroconversion, and one additional patient with a sustained virologic response had achieved HBsAg loss or seroconversion between 6 and 12 months (33).

The overall findings from this study demonstrate that biochemical and virologic responses to peginterferon α -2a were maintained in more than half of HBeAg-positive and -negative patients at 12 months after the end of treatment. Although no clear predictor of sustained virologic response was identified in either patient population, a trend toward a better response was associated with lower end-of-treatment levels of HBV DNA, higher baseline ALT levels, and HBV genotype C (32).

Oral antiviral agents in late-stage development

Telbivudine

Telbivudine (LdT, l- β thymidine; Idenix Pharmaceuticals, Cambridge, MA), an HBV-specific L-nucleoside analog of thymidine that preferentially inhibits HBV second-strand (DNA dependent) DNA synthesis, has demonstrated marked dose-related antiviral activity in initial studies of patients with CHB. In these studies, telbivudine at dosages of ≥ 400 mg/day was more effective than lamivudine, 100 mg/day, in the reduction of mean serum HBV DNA levels to <200 copies/ml (61% vs 32%; $P<0.05$), and normalization of ALT levels (63% vs 86%; $P<0.05$) in patients with HBeAg-positive CHB (33). Additionally, a greater proportion of telbivudine-treated patients

than lamivudine-treated patients experienced HBeAg seroconversion (31% vs 22%) and less viral breakthrough (4.5% vs 15.8%; $P = \text{NS}$ for both) (33).

These findings were confirmed by data from a large, randomized, phase III trial of telbivudine and lamivudine in 1367 patients with HBeAg-positive and -negative CHB (19). HBeAg-positive ($n = 921$) and HBeAg-negative ($n = 446$) patients were randomized to treatment with telbivudine, 600 mg/day, or lamivudine, 100 mg/day. At week 52, telbivudine was more effective than lamivudine in achieving all virologic efficacy end points in both HBeAg-positive and -negative patients ($P < 0.01$) (19). In the HBeAg-positive intent-to-treat (ITT) population, telbivudine was superior to lamivudine for the primary efficacy end point of therapeutic response (HBV DNA levels of $< 5 \log_{10}$ plus HBeAg loss or ALT normalization), both at weeks 52 and 76. In the HBeAg-negative ITT population, antiviral efficacy was greater with telbivudine than with lamivudine, as measured by reductions in HBV DNA levels from baseline and achievement of nondetectable HBV DNA levels at week 52. However, the therapeutic response (HBV DNA levels of $< 5 \log_{10}$ plus HBeAg loss or ALT normalization) at weeks 52 and 76 was similar between the treatment groups. Telbivudine demonstrated a safety profile comparable with that of lamivudine, and was associated with lower rates of primary treatment failure, lower rates of development of resistance, and fewer and less severe instances of ALT flares than lamivudine (19).

A multivariate subanalysis of the GLOBE study found that telbivudine provided better virologic responses than did lamivudine across nearly all patient subgroups. In this analysis, race, geographic region, and ALT levels were identified as key factors in determining virologic response to telbivudine (34). Greater HBV DNA suppression was observed with telbivudine in HBeAg-positive patients with baseline ALT levels of $> 2.5 \times \text{ULN}$ than in patients with baseline ALT levels of $< 2.5 \times \text{ULN}$ ($P < 0.0001$). In addition, HBeAg-positive Asian patients demonstrated greater HBV DNA suppression with telbivudine than did patients from North America ($P < 0.001$) or other regions ($P < 0.038$) (34). The subanalysis also showed that HBV DNA suppression with telbivudine was greater in HBeAg-positive and -negative Asians than in members of other ethnic groups ($P = 0.0145$). Patients with genotype C treated with telbivudine also attained significantly greater HBV DNA suppression than did telbivudine-treated patients with other genotypes ($P < 0.01$) (34).

Clevudine

Clevudine, a pyrimidine nucleoside analog, has also demonstrated potent activity *in vitro* and in HBV-infected patients (20, 21, 35, 36). In a multicenter, dose-escalation study, clevudine, 100 and 200 mg/day for 28 days, resulted in potent and durable posttreatment viral suppression (20). In a study that assessed the safety, tolerability, and antiviral response to 12 weeks of clevudine treatment in patients with HBeAg-positive CHB, clevudine showed potent antiviral activity during therapy and induced a sustained posttreatment antiviral effect for 6 months after a 12-week treatment period that was associated with a sustained normalization of ALT levels (21). This study involved a total of 98 patients who were randomized to placebo ($n = 32$), clevudine, 30 mg ($n = 32$), and clevudine, 50 mg ($n = 34$), for 12 weeks and followed up for 24 weeks off therapy. At week 12, the median serum HBV DNA reductions from baseline were 0.20, 4.49, and 4.45 \log_{10} copies/ml in the placebo, clevudine, 30 mg, and clevudine, 50 mg groups, respectively ($P < 0.0001$; Fig. 3) (21). Posttreatment antiviral activities were sustained at weeks 12 and 24 off therapy. Marked reductions in median serum ALT levels occurred during clevudine treatment and were maintained below the ULN throughout the 24 weeks off therapy in the two clevudine-treated groups. The incidences of adverse events and treatment-emergent grade 3 or 4 laboratory abnormalities were similar for the three groups.

Preliminary data from larger phase III studies evaluating the safety and efficacy of 24 weeks of clevudine, 30 mg/day in nucleoside analog-naïve patients with HBeAg-positive and -negative CHB show that clevudine has potent anti-HBV activity that can be sustained for up to 6 months after the discontinuation of therapy (37, 38). In the first study, 243 HBeAg-positive patients with CHB infection were randomized to receive clevudine, 30 mg/day ($n = 182$), or placebo ($n = 61$) for 24 weeks, with an additional 24 weeks of follow-up (37). In the second study, 83 HBeAg-negative patients with CHB infection were randomized to receive clevudine, 30 mg/day, or placebo for 24 weeks with 24 weeks of follow-up (38). In both HBeAg-positive and -negative patients, 24 weeks of clevudine therapy were associated with a substantial reduction in median serum HBV DNA levels, ALT normalization, and HBeAg loss. Reductions in serum HBV DNA and ALT levels were maintained at 24 weeks after the discontinuation of clevudine therapy. In these studies, no evidence of viral breakthrough or resistance was observed in HBeAg-positive and -negative patients.

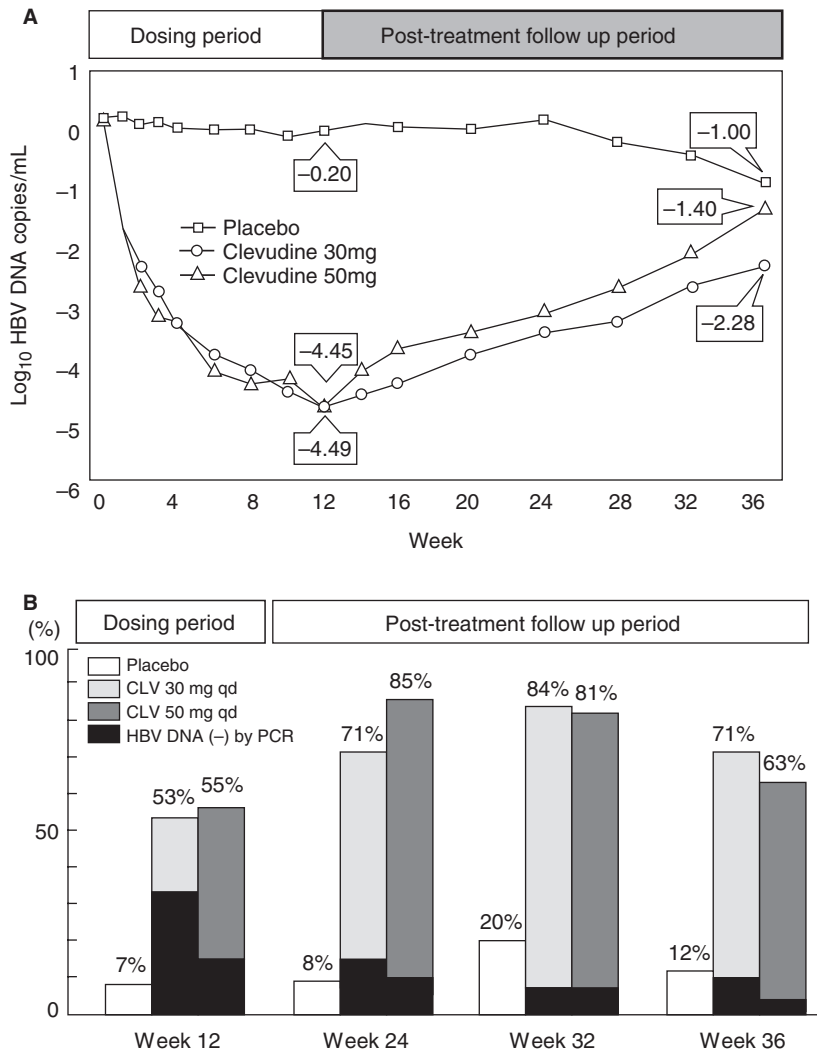


Fig. 3. Efficacy of clevidine (30 or 50 mg) in patients with hepatitis B e antigen (HBeAg)-positive chronic hepatitis B (CHB). (A) Changes in median log₁₀ HBV DNA from baseline. (B) Proportion of patients with normalized serum alanine aminotransferase (ALT) levels and undetectable serum HBV DNA by the Roche COBAS AmpliCor HBV monitor test at weeks 12, 24, 32, and 36 (21).

Tenofovir

Tenofovir disoproxil fumarate, an acyclic nucleotide reverse transcriptase inhibitor structurally related to adefovir, has demonstrated efficacy in patients with lamivudine-resistant HBV infection (39, 40) and in patients with CHB who are coinfecting with HIV (41–44). Preliminary data from studies comparing the efficacy of tenofovir and adefovir in patients with lamivudine-resistant CHB indicate that tenofovir is more effective than adefovir in reducing serum HBV DNA levels (39, 40). Thirty-five patients received tenofovir for 72–130 weeks, and 18 patients received adefovir for 60–80 weeks. At 48 weeks, 100% of the tenofovir-treated patients had HBV DNA levels of $<10^5$ copies/ml compared with only 44% of adefovir-treated patients ($P = 0.001$) (40). These findings need to be confirmed in large randomized trials. Tenofovir has also been shown

to be effective in HBV/HIV-coinfecting patients with lamivudine-resistant HBV (41–44); however, the use of tenofovir as monotherapy or in combination with lamivudine, emtricitabine, or entecavir needs to be defined.

Conclusion

Conventional antiviral and immunomodulatory drugs used for managing HBV infection indisputably provide clinical benefit, but their use can be limited by the lack of sustained reduction of HBV replication, the development of resistance, and poor tolerability. Newly approved anti-HBV therapies such as entecavir and the peginterferons have demonstrated increased antiviral potency and low-to-minimal levels of drug resistance, which will enable viral loads to be reduced even further, an effect that is expected to reduce significantly the morbidity and mortality asso-

ciated with CHB. In addition, clevudine, telbivudine, and tenofovir have also demonstrated potent efficacy and good safety profiles in patients with CHB infection. Ongoing clinical studies evaluating the use of these agents in combination with other anti-HBV therapies will help clarify their role in the management of CHB.

References

1. WORLD HEALTH ORGANIZATION. Hepatitis B – Surveillance and control. Available at <http://www.who.int/csr/disease/hepatitis/whocdscsrlyo20022/en/index1.html>. Accessed June 21, 2006.
2. LIN S M, TAI D I, CHIEN R N, SHEEN I S, CHU C M, LIAW Y F. Comparison of long-term effects of lymphoblastoid interferon alpha and recombinant interferon alpha-2a therapy in patients with chronic hepatitis B. *J Viral Hepatol* 2004; 11: 349–57.
3. VAN ZONNEVELD M, HONKOOP P, HANSEN B E, et al. Long-term follow-up of alpha-interferon treatment of patients with chronic hepatitis B. *Hepatology* 2004; 39: 804–10.
4. LIN S M, YU M L, LEE C M, et al. Interferon therapy in HBeAg positive chronic hepatitis reduces cirrhosis and hepatocellular carcinoma. *J Hepatol* 2006; in press.
5. GOODMAN Z, DHILLON A P, WU P C, et al. Lamivudine treatment reduces progression to cirrhosis in patients with chronic hepatitis B. *J Hepatol* 1999; 30(Suppl. 1): 59.
6. DIENSTAG J L, CIANCIARA J, KARAYALCIN S, et al. Durability of serologic response after lamivudine treatment of chronic hepatitis B. *Hepatology* 2003; 37: 748–55.
7. LIAW Y F, SUNG J J Y, on behalf of the CALM Study Group et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med* 2004; 351: 1521–31.
8. HADZIYANNIS S J, TASSOPOULOS N C, HEATHCOTE E J, et al. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B. *N Engl J Med* 2005; 352: 2673–81.
9. MARCELLIN P, CHANG T T, LIM S G, et al. For the Adefovir Dipivoxil 437 Study Group. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. *N Engl J Med* 2003; 348: 808–16.
10. LAI C L, RATZIU V, YUEN M F, POYNARD T. Viral hepatitis B. *Lancet* 2003; 362: 2089–94.
11. LOCARNINI S. Molecular virology and the development of resistant mutants: implications for therapy. *Semin Liver Dis* 2005; 25(Suppl. 1): 9–19.
12. LIAW Y F. The current management of HBV drug resistance. *J Clin Virol* 2005; 34(Suppl. 1): S143–6.
13. CHANG T T, GISH R G, DE MAN R, et al. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. *N Engl J Med* 2006; 354: 1001–10.
14. LAI C L, SHOVALD D, LOK A S, et al. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. *N Engl J Med* 2006; 354: 1011–20.
15. SHERMAN M, YURDAYDIN C, SOLLANO J, et al. Entecavir for treatment of lamivudine-refractory, HBeAg-positive chronic hepatitis B. *Gastroenterology* 2006; 130: 2039–49.
16. LAU G K, PIRATVISUTH T, LUO K X, et al. Peginterferon alpha-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. *N Engl J Med* 2005; 352: 2682–95.
17. MARCELLIN P, LAU G K, BONINO F, et al. Peginterferon alpha-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. *N Engl J Med* 2004; 351: 1206–17.
18. WILBER R, BRETT-SMITH H, ZHU J, et al. Entecavir (ETV) vs. adefovir (ADV): HBV DNA reduction in chronically infected HBeAg+ nucleoside-naive adults in a 12-week viral kinetics study. Presented at the NIH Management of Hepatitis B Conference, April 6, 2006, Bethesda, MD.
19. LAI C L, GANE E, LIAW Y F, et al. Telbivudine (LDT) vs. lamivudine for chronic hepatitis B: first-year results from the international phase III GLOBE trial, abstract LB1. *Hepatology* 2005; 42: 748A.
20. MARCELLIN P, MOMMEJA-MARIN H, SACKS S L, et al. A phase II dose-escalating trial of clevudine in patients with chronic hepatitis B. *Hepatology* 2004; 40: 140–8.
21. LEE H S, CHUNG Y H, LEE K, et al. A 12-week clevudine therapy showed potent and durable antiviral activity in HBeAg-positive chronic hepatitis B. *Hepatology* 2006; 43: 982–8.
22. COLONNO R J, GENOVESI E V, MEDINA I, et al. Long-term entecavir treatment results in sustained antiviral efficacy and prolonged life span in the woodchuck model of chronic hepatitis infection. *J Infect Dis* 2001; 184: 1236–45.
23. DE MAN R A, WOLTERS L M, NEVENS F, et al. Safety and efficacy of oral entecavir given for 28 days in patients with chronic hepatitis B virus infection. *Hepatology* 2001; 34: 578–82.
24. ONO-NITA S K, KATO N, SHIRATORI Y, et al. Susceptibility of lamivudine-resistant hepatitis B virus to other reverse transcriptase inhibitors. *J Clin Invest* 1999; 103: 1635–40.
25. CHANG T, CHAO Y-C, SOLLANO J. Entecavir (ETV) treatment through 96 weeks results in substantial virologic and biochemical improvement and HBeAg seroconversion in HBeAg+ chronic hepatitis B (CHB) patients (study ETV-022). Presented at the Shanghai-Hong Kong International Liver Congress, March 25–28, 2006, Shanghai, China.
26. SHOVALD D, AKARCA U, HATZIS G. Continued virologic and biochemical improvement through 96 weeks of entecavir treatment in HBeAg- chronic hepatitis B patients (study ETV-027). Program and abstracts of the 41st Annual Meeting of the European Association for the Study of the Liver, April 26–30, 2006, Vienna, Austria.
27. YURDAYDIN C, SOLLANO J. Entecavir results in continued virologic and biochemical improvement and HBeAg seroconversion through 96 weeks of treatment in lamivudine-refractory, HBeAg+ chronic hepatitis B patients (ETV-026). Presented at the 41st Annual Meeting of the European Association for the Study of the Liver; April 26–30, 2006, Vienna, Austria.
28. COLONNO R J, ROSE R E, LEVINE S M, et al. Entecavir (ETV) resistance is not observed in nucleoside-naive subjects and is observed infrequently by week 48 in lamivudine-refractory subjects with chronic HBV infection, abstract 478. *J Hepatol* 2005; 42(Suppl. 2): 573A.
29. YAO G B, CHEN C W, LU W L, et al. Entecavir is superior to lamivudine for the treatment of chronic hepatitis B: results of the phase 3 study ETV-023 in nucleoside-naive patients. Program and abstracts of the 2006 Shanghai-Hong Kong International Liver Congress; March 25–28, 2006, Shanghai, China, abstract 174.
30. YAO G B, REN H, WANG B E, ZHOU X Q. Randomized, placebo controlled phase II study of entecavir in patient who have failed lamivudine therapy (ETV-056). *Chinese Hepatol* 2005; 10: 2–4.
31. LAU G K, PIRATVISUTH T, THONGSAWAT S, et al. Durability of response to peginterferon alpha-2a (40 KD) (PEGASYS[®]) in Asian patients with HBeAg-positive chronic hepatitis B: 12 month follow-up data from a large, randomized study. Program and abstracts of the 2006 Shanghai-Hong Kong International Liver Congress, March 25–28, 2006, Shanghai, China, abstract 49.

32. MARCELLIN P, BONINO F, LAU G K, et al. Factors associated with sustained virologic response 1 year after treatment with peginterferon alfa-2a (40KD) (Pegasys®) monotherapy for HBeAg-negative chronic hepatitis B, abstract 976. *Hepatology* 2005; 42: 580A.
33. LAI C L, LEUNG N, TEO E K, et al. A 1-year trial of telbivudine, lamivudine, and the combination in patients with hepatitis B e antigen-positive chronic hepatitis B. *Gastroenterology* 2005; 129: 528–36.
34. LIM S G, LAI C L, GANE E, et al. The antiviral efficacy of telbivudine is consistent across hepatitis B patient subgroups: results from the GLOBE study. Shanghai-Hong Kong International Liver Congress, March 25–28, 2006.
35. BUTI M, ESTEBAN R. Entecavir, FTC, L-FMAU, LdT and others. *J Hepatol* 2003; 39(Suppl. 1): S139–42.
36. LOK A S. New treatment of chronic hepatitis B. *Semin Liver Dis* 2004; 24(Suppl. 1): 77–82.
37. YOO B C, KIM J H, LEE K S, et al. A 24-week clevudine monotherapy produced profound on-treatment viral suppression as well as sustained viral suppression and normalization of aminotransferase levels for 24 weeks off-treatment in HBeAg(+) chronic hepatitis B patients. *Hepatology* 2005; 42: 270A.
38. YOO B C, KIM J H, LEE K S, et al. Clevudine is highly efficacious in HBeAg(–) chronic hepatitis B patients with a sustained antiviral effect after cessation of therapy. *Hepatology* 2005; 42: 268A.
39. VAN BÖMMEL F, MAUSS S, ZOLLNER B, et al. Longterm effect of tenofovir in the treatment of lamivudine-resistant hepatitis B virus infections in comparison to adefovir. *Hepatology* 2005; 42(Suppl. 1): 269A.
40. VAN BÖMMEL F, WUNSCH T, MAUSS S, et al. Comparison of adefovir and tenofovir in the treatment of lamivudine-resistant hepatitis B virus infection. *Hepatology* 2004; 40: 1421–5.
41. BENHAMOU Y, BOCHET M, THIBAUT V, et al. Safety and efficacy of adefovir dipivoxil in patients co-infected with HIV-1 and lamivudine-resistant hepatitis B virus: an open-label pilot study. *Lancet* 2001; 358: 718–23.
42. BENHAMOU Y, THIBAUT V, VIG P, et al. Safety and efficacy of adefovir dipivoxil in patients infected with lamivudine-resistant hepatitis B and HIV-1. *J Hepatol* 2006; 44: 62–7.
43. BENHAMOU Y, FLEURY H, TRIMOULET P, et al. Anti-hepatitis B virus efficacy of tenofovir disoproxil fumarate in HIV-infected patients. *Hepatology* 2006; 43: 548–55.
44. DORE G J, COOPER D A, POZNIAK A L, et al. Efficacy of tenofovir disoproxil fumarate in antiretroviral therapy-naive and -experienced patients coinfecting with HIV-1 and hepatitis B virus. *J Infect Dis* 2004; 189: 1185–92.