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REVIEW ARTICLE

Recent data on treatment of chronic hepatitis B with nucleos(t)ide analogues

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Abstract Forty years ago in 1967, Professor Blumberg discovered the Australian Antigen, later known as the hepatitis B surface antigen, and was awarded the Nobel Prize. This discovery enables the diagnosis of hepatitis B virus (HBV) infection and defines its epidemiology. Viral hepatitis B infection affects global health situation, and chronic hepatitis B (CHB) is particularly serious in the Asia-Pacific region. HBV vaccines created the first breakthrough in HBV prevention. Through universal HBV vaccination program for the newborns, promoted since the mid-1980s, the main route that perpetuates chronic infection from mother to child is curbed. Most children and young adults now have immunity against HBV infection. The next breakthrough comes with therapy for CHB. This prevents progression to cirrhosis and hepatocellular carcinoma. Standard interferon therapy with modest efficacy has been largely replaced by therapy with nuclos(t)ide analogues or pegylated interferons alfa-2a and -2b. Lamivudine was approved by the FDA USA in 1998, followed by adefovir dipivoxil in 2002, entecavir in 2005, and telbivudine in 2006. Clevudine, tenofovir, and many promising candidates are in different stages of development and clinical trial. This paper critically reviews recent data published or presented since the APASL Consensus and Guideline Update of 2005. Clinical efficacy mostly in patients with raised serum alanine aminotransferase will be analyzed.

Keywords Chronic hepatitis B · Therapy · Nucleos(t)ide analogues

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Introduction

Forty years ago in 1967, Professor Blumberg discovered the Australian Antigen, later known as the hepatitis B surface antigen (HBsAg), and was awarded the Nobel Prize [1]. This discovery enables the diagnosis of hepatitis B virus (HBV) infection and defines its epidemiology. Viral hepatitis B infection affects global health situation, and chronic hepatitis B (CHB) is particularly serious in the Asia-Pacific region [2, 3]. HBV vaccines created the first breakthrough in HBV prevention. Through universal HBV vaccination program for the newborns promoted since the mid-1980, the main route that perpetuates chronic infection from mother to child is curbed. Most children and young adults now have immunity against HBV infection. The next breakthrough comes with therapy for CHB. This prevents progression to cirrhosis and hepatocellular carcinoma (HCC) [4]. Standard interferon therapy with modest efficacy has been largely replaced by therapy with nucleos(t)ide analogues or pegylated interferons alfa-2a and -2b. Lamivudine was approved by the FDA USA in 1998, followed by adefovir dipivoxil in 2002, entecavir in 2005, and telbivudine in 2006. Clevudine, tenofovir, and many promising candidates are in different stages of development and clinical trial. This paper critically reviews recent data published or presented since the APASL Consensus and Guideline Update of 2005 [5]. Clinical efficacy mostly in patients with raised serum alanine

aminotransferase (ALT) will be analyzed. There has been increasing interest on early therapy for patients with normal ALT with the aim of preventing cirrhosis and HCC. However, this awaits data for evidence-based confirmation [6–9].

Lamivudine

Lamivudine (2′,3′-dideoxy-3′-thiacytidine), a reverse transcriptase inhibitor, was approved by the FDA in 1998 for the treatment of CHB infection in adult patients. Since the publication of results from pivotal clinical trials [10–12], many subsequent reports from different parts of the world confirmed results and explored predictors of response and risk of resistance.

HBeAg-positive CHB patients respond to lamivudine therapy with 4 to 5 $\log_{10}$ copies/ml reduction in serum HBV DNA level and 18–20% HBeAg seroconversion in the first year. Extended therapy increases response rate but at risk of continuous emergence of lamivudine-resistant mutants at the rate of 15–20% per year. HBeAg seroconversion is achieved in 35–65% after 5 years of therapy. Response is better among patients with higher baseline serum ALT level [13]. Viral suppression is associated with serum ALT normalization and histological improvement. Relapse of disease occurred in up to 50% of responders within 5 years of stopping therapy [14–16].

HBeAg-negative CHB patients have low pretreatment HBV DNA levels and achieve undetectable HBV DNA level more readily on lamivudine therapy. Treatment end point is difficult to define and durability of response is poor. In treatment-naïve, Chinese patients (pretreatment median HBV DNA of 6.1 $\log_{10}$ copies/ml), 24 months of the lamivudine resulted in 56% complete response with the reduction of HBV DNA below 10,000 copies/ml and ALT normalization. Twenty-six percent of lamivudine-treated group had undetectable HBV DNA by PCR assay vs 6% in placebo group ($P = 0.006$). However, majority of responders relapsed within 6 months of stopping treatment. Lamivudine-resistant mutants developed in 31% after 2 years [17]. Short course (6–12 month) of lamivudine therapy for patients with high pretreatment ALT-induced sustained response in one-third of the patients. This approach reduced the emergence of lamivudine-resistant mutants [18]. However, HBeAg-negative patients are often older and have more advanced liver disease that may not tolerate relapse hepatitis flare.

Lamivudine-resistant hepatitis B mutants (YMDD motif, rtM204I, and rtM204V with or without rtL180M) negate on-treatment clinical benefit. Often they require salvage therapy to prevent viral breakthrough and disease progression [19–21]. The overall benefit of long-term lamivudine therapy for patients with advanced fibrosis and cirrhosis is evident by the end of 3 years of treatment. In this study, disease progression and HCC development were significantly reduced by lamivudine therapy, but 49% of the treated patients harbored resistant mutants and derived less clinical benefit compared to those without resistant mutants [22]. The diagnosis and prompt management of lamivudine resistance is crucial to maintain therapeutic benefit and prevent a global epidemic of lamivudine-resistant liver disease. Genotypic confirmation of resistance is not available in most clinical settings. Close monitoring of serum HBV DNA to detect viral rebound is essential. Serum HBV DNA rise of 1 $\log_{10}$ copies/ml or more from nadir despite good drug compliance is indicative of lamivudine resistance and salvage therapy should be instituted before ALT elevation. Much controversy exists in the way the salvage therapy is delivered: addition, overlap, or switch to adefovir therapy have been shown to have variable degree of success in regaining viral suppression. More important, effective salvage strategy by the addition of combination of lamivudine and adefovir avoids the emergence of adefovir resistance. This will be reviewed in greater details in the session on adefovir dipivoxil.

Main areas that need critical appraisal for lamivudine therapy are

1. predictors of response,
2. predictors of durability of response,
3. predictors of resistance and management,
4. role in specific patient subgroups, and
5. role in combination with other agents.

Predictors of response

The Asian Lamivudine Trial on HBeAg-positive CHB patients showed high pretreatment ALT level significantly correlated with HBeAg seroconversion rate after 1 year of lamivudine 100 mg daily: the highest HBeAg seroconversion rate was observed in 100 mg lamivudine-treated patients with ALT levels greater than five times ULN (64%) compared with patients with ALT two to five times the ULN (26%, $P = 0.03$), and ALT less than two times the ULN (5%, $P < 0.001$). Baseline HBV DNA level and the presence of cirrhosis only marginally correlate with response [13]. Among the 58 patients on 5 years continuous lamivudine therapy, the annual cumulative HBeAg seroconversion rates were 22, 29, 40, 47, and 50%, respectively [16]. The best predictor of long-term response is again shown to be elevated pretreatment ALT. Patients with normal ALT given "lamivudine pulse" therapy resulted in ALT elevation and enhanced overall sustained HBeAg and HBV DNA loss [23]. Other predictors have been reported including female gender, negative HBV

DNA level by month 6 of therapy [6], younger age [18], high histological necroinflammatory grade [24], reduction in intrahepatic cccDNA and serum HBsAg level after lamivudine therapy with or without peginterferon [25, 26], and genotype D compared to A [27]. There was no difference in treatment response between patients with genotypes B and C [28]. In contrast, the presence of IgM anti-HBc in patients with acute exacerbation [29] and high body surface area were associated with poor response [30].

Predictors of durability of response post-treatment

In HBeAg-positive CHB patients, predictors of durable response are genotype B, age younger than 36 years, and additional lamivudine treatment for at least 8 months after HBeAg seroconversion [31]. Similarly, Korean study reported 58.8% HBeAg seroconversion after 5 years of lamivudine therapy, 44% durable 2 years post-treatment. Age and the duration of additional treatment were significant predictive factors for post-treatment relapse. Patients aged $\leq$40 who had additional treatment for >12 months after seroconversion had the lowest relapse rate ($P < 0.001$) [15]. On the other hand, level of HBV core-related antigen predicts relapse after cessation of lamivudine therapy [32]. Relapsers responded to retreatment promptly if they had prior HBeAg seroconversion rather than HBeAg loss alone [33, 34].

Predictors of lamivudine resistance and management

Emergence of lamivudine resistance negates response and should be avoided [19, 20, 22, 35–38]. Predictors of response also predict low risk for resistance emergence. Core promoter/precore mutations and HBV DNA <1,000 copies/ml at week 24 have also been reported to be associated with low risk of lamivudine resistance [30]. Three to six monthly monitor of serum HBV DNA is essential for early detection of lamivudine resistance and prompt salvage therapy. Adefovir monotherapy has initial response but not maintained in majority of patients [39]. In order to minimize viral breakthrough with rtN236T and reA181T mutations during adefovir therapy, longer duration of overlapping adefovir–lamivudine combination therapy can be considered. Long-term combination therapy for patients with high-resistance viral load is advisable and switch to higher adefovir dosage of 20 mg daily has been reported to benefit without added renal toxicity [40–46]. This will be discussed in greater details in the session on adefovir dipivoxil. Lamivudine-resistant CHB also showed initial response to entecavir therapy. However, the presence of lamivudine-resistant mutations (M204V and L180M) permits the rapid emergence of entecavir resistance (T184, S202, and/or M250 substitutions). Annual incidence of entecavir resistance was 1, 11, 22, and 29% by the end of year 1, 2, 3, and 4, respectively [47–49].

Role of lamivudine in specific patient subgroups

Lamivudine has been used successfully in patients with decompensated CHB and bridged them over the waiting time for orthotopic liver transplantation or spontaneous recovery. Lamivudine in combination with HBIG has resulted in good long-term survival without the recurrence of HBV infection among post-transplant patients [50, 51].

Lamivudine has an important role as prophylactic or preemptive therapy for HBsAg-positive patients undergoing chemotherapy. Lamivudine prophylaxis is more cost-effective compared with initiating lamivudine only when clinically overt hepatitis occurred. Both liver-related and cancer deaths are reduced presumably because need for cessation or modification of chemotherapy due to hepatitis B flares were avoided [52, 53].

The role of lamivudine therapy in children is not established because of low response and high resistance rates that may jeopardize future management. 21% of HBeAg-positive children treated with lamivudine achieved HBeAg loss and HBV DNA negativity at month 24. However, the incidence of YMDD mutations was high at 64%. The durability of response among the responders at year 1 was 89% at month 24 [54]. In a study of longer duration of therapy (median 33, range 14–66 months), response was achieved in the first 2 years and none thereafter. However, viral breakthrough reached 69.4% at the end of second year, increasing to 82.4% by the end of third year [55]. A small cohort of 33 immunoactive CHB children treated with different regimens of lamivudine and interferon-alfa combination therapy reported 66.7% response and 50% sustained response after completion of therapy [56].

Role for combination with other agents

Lamivudine in combination with adefovir, telbivudine, interferon, pegylated interferon in controlled trials has not demonstrated significant efficacy advantage compared with individual monotherapy. Combination therapy with telbivudine actually demonstrated antagonism [57]. The sequence of combination with pegylated interferon has been further evaluated showing inconsistent findings. One reported better virologic response with simultaneous therapy compared with either agents used as primer [58]. Another reported improved sustained virological response by decreasing HBV DNA level with nucleoside analogue before adding an immunomodulatory agent [59].

In summary, lamivudine is effective in both HBeAg-positive and -negative CHBs. The weakness of lamivudine

therapy is unsatisfactory maintained response because of high resistant emergence and low sustained response off therapy. The main strength is good safety profile, and low cost, at least initially, but one has to be aware of the escalating cost once resistance is developed.

Adefovir dipivoxil

Adefovir dipivoxil is an adenosine monophosphate analogue that acts as a chain terminator by inhibiting HBV DNA polymerase and reverse transcriptase activities. It is active against both wild-type and lamivudine-resistant HBV. The US FDA approved adefovir dipivoxil 10 mg daily for the treatment of CHB in adults in 2002. Higher dosage at 30 and 60 mg showed significant renal toxicity and were not investigated further.

In a phase III clinical trial, adefovir dipivoxil 10 mg daily for naïve HBeAg-positive CHB, 1-year therapy resulted in 53% histological improvement (25% in placebo), reduction in serum HBV DNA by 3.5 $\log_{10}$ copies/ml (0.55 $\log_{10}$ copies/ml in placebo), 12% HBeAg seroconversion (6% in placebo), and 48% ALT normalization (16% in placebo) [60]. There are few data on longer-term therapy but some reported up to 40% HBeAg loss/seroconversion after 3 years of therapy. HBeAg seroconversion was durable in 91% over a median 3-year follow-up after treatment discontinuation in a small cohort of 45 patients [61]. In an ongoing 5-year clinical trial in China, 240 HBeAg-positive Chinese patients have been randomized to receive adefovir. The baseline median HBV DNA 8.8 $\log_{10}$ copies/ml, ALT 2.7 × ULN, 22% with lamivudine-induced YMDD mutants. Preliminary data after 52 weeks showed median HBV DNA reduction of 4.5 $\log_{10}$ copies/ml, 28% HBV DNA undetectable (Roche COBAS Amplicor assay LOD 200–300 copies/ml), 13% HBeAg loss, 8% HBeAg seroconversion, and 79% ALT normalization. No adefovir-resistant mutations were identified and patients with YMDD mutants responded similarly. The study is currently ongoing to complete 5 years of therapy [62].

Naïve HBeAg-negative CHB patients (baseline median HBV DNA 7.08 $\log_{10}$ copies/ml, ALT 2.3 times the ULN, 11% cirrhosis) treated with adefovir dipivoxil for up to 192 or 240 weeks resulted in serum HBV DNA levels less than 1,000 copies/ml in 67% of patients, and ALT levels normalization in 69% after 240 weeks [63]. After 192 or 240 weeks of treatment, 83% showed improvement in necroinflammation, and 73% improvement in fibrosis. The cumulative improvement in Ishak fibrosis score was 35, 55, and 71% at weeks 48, 192, and 240, respectively. Adefovir resistance emerged at 3, 8, 18, 22, and 30% at the end of year 1, 2, 3, 4, and 5, respectively. Renal toxicity over 5 years was limited with only four (3%) patients developed slight elevations in serum creatinine over 0.5 mg/dl, and a maximum increase of 1.5 mg/dl [64]. Patients with maintained response were followed for median 18 months after stopping therapy. Serum HBV DNA became detectable again in all patients but at low levels of less than 50,000 copies/ml. A third of the patients had biochemical relapse and were retreated [65]. Long-term therapy resulted in the significant reduction, but not elimination, of intrahepatic cccDNA and impaired production of genomic HBV DNA. These parameters are being evaluated as predictors of outcome for discontinuing long-term antiviral therapy [66].

Review of international phase III data showed significant differences in the baseline serum HBV DNA levels with different HBV genotypes regardless of HBeAg serological status. Despite this, response to 48 weeks of adefovir dipivoxil 10 mg therapy showed no significant differences based on genotype, HBeAg status, or race [67]. There is also no significant difference in response was found between Asians and Caucasians [68].

Main areas that need critical appraisal for adefovir dipivoxil are

1. role as first-line therapy for treatment-naïve patients,
2. management strategy for lamivudine resistance,
3. management strategy of adefovir resistance,
4. role in specific subgroups, and
5. role for combination with other agents.

Role as first-line therapy for treatment-naïve patients

Adefovir dipivoxil is less potent than lamivudine and data for long-term efficacy for HBeAg-positive patients are lacking. The long-term response in HBeAg-negative patients is promising with less resistance emergence rate than lamivudine. Projecting this to HBeAg-positive patients, response is likely to increase with time but resistance profile is likely to be higher than the 30% observed among HBeAg-negative CHB therapy at year 5. Renal toxicity remains low especially among patients with normal renal function prior to therapy.

Management strategy for lamivudine resistance

Adefovir dipivoxil is effective in suppressing lamivudine-resistant HBV. Early clinical trials showed that adefovir alone or in combination with ongoing lamivudine therapy are both effective in patients with lamivudine-resistant HBV [40, 41]. Adefovir-resistant mutations were detected prior to adefovir use in 3.7% of patients with lamivudine resistance [69, 70]. Although adefovir resistance is not a problem initially in the treatment of lamivudine-resistant

CHB, virological, and biochemical breakthroughs due to adefovir resistance occurred in around 6–20% at the end of year 1, increasing to around 30% by the end of year 2. The strategy deployed to achieve best response and to avoid of emergence of adefovir resistance had been investigated by many groups. The findings are not consistent and sometimes contradictory. However, an overall perspective can be summarized as follows. First, lamivudine switched to adefovir with or without the interval of overlap is less effective when compared with lamivudine–adefovir combination therapy. This is especially so in patients with long-standing resistant HBV, high viral level, low ALT level, at either ends of the age spectrum, HBeAg positive, presence of cirrhosis, genotype non-D [42–46, 71–76]. Addition of adefovir to ongoing lamivudine therapy is now the recommended strategy to prevent emergence of adefovir-resistant mutants.

In compensated or decompensated liver cirrhosis associated with lamivudine resistance, both switch to adefovir monotherapy or adefovir add-on lamivudine therapy significantly improved Child-Pugh's score, serum ALT, and HBV DNA levels. The switch therapy was considered to be a reasonably safe and cost-effective approach [77].

In transplant candidates with lamivudine resistance, the combination of adefovir and lamivudine without HBIg use is safe and efficacious in preventing post-transplant graft reinfection [78]. Serum HBV DNA levels became undetectable in 59 and 65% at weeks 48 and 96, respectively, among wait-listed patients (<1,000 copies/ml), associated with improvement in liver function. Among post-transplantation patients, serum HBV DNA levels became undetectable in 40 and 65% at weeks 48 and 96, respectively. The cumulative probabilities of resistance were 0, 2, and 2% at weeks 48, 96, and 144, respectively. There were 4% of patients who discontinued adefovir for treatment-related adverse events [79].

The suboptimal virologic response to adefovir 10 mg among lamivudine-resistant HBeAg-positive CHB patients may be due to underdosing with 10 mg daily dosage. Increased dosage to 20 mg daily with careful monitoring of renal function achieved better efficacy and can be considered in patients with elevated ALT levels, severe, or rapidly progressive liver disease [80].

Management of adefovir resistance

There are reports of primary non-responders to adefovir therapy. Three cases of primary adefovir resistance were described, which involved a rare HBV variant with a valine at position 233 of the reverse-transcriptase domain instead of isoleucine (rtI233V), as in the wild-type virus. This HBV variant displayed resistance to adefovir, but sensitivity to tenofovir in vitro [69] and also sensitivity has been demonstrated with entecavir by both in vitro and in vivo studies [81]. There have been few reports on the management of adefovir resistance in the absence of lamivudine resistance, but this mutant is shown to be susceptible to lamivudine treatment.

On the other hand, the emergence of the adefovir-resistant mutation occurs earlier and more frequently during therapy for lamivudine resistance than in treatment-naïve patients. The cumulative incidence of adefovir-resistant mutations in treatment-naïve CHB was 0, 1–3%, and around 6% at year 1, 2, and 3, respectively; compared with around 6–20% and around 30% at year 1 and 2, respectively, in lamivudine-resistant patients. The restriction fragment mass polymorphism revealed 11 amino acid substitutions in the rt domain of the HBV polymerase leading to rtA181V, rtN236T, and rtA181T mutations associated with HBV DNA rebound. Alternative therapeutic strategy includes switch from adefovir to tenofovir, or a combination of tenofovir and emtricitabine therapy, which achieve efficacy without any renal toxicity [82].

Role in specific subgroups including children and transplant patients

A Phase 1–2 Open-Label study of the pharmacokinetics and safety of adefovir dipivoxil in 47 CHB children and adolescents (aged 2–17) showed that adefovir dipivoxil is generally well tolerated at 0.3 mg/kg for patients aged 2–6, 0.25 mg/kg for patients aged 7–11, and 10 mg for patients aged 12–17 years. Adefovir dipivoxil pediatric phase 3 study is ongoing [83].

Adefovir dipivoxil has also been reported to effectively treat chemotherapy-induced activation of HBV infection [84].

Role for combination with other agents

Few reports can be found on adefovir combination with other nucleos(t)ide analogues among treatment-naïve patients. A study of a small cohort of 26 patients, open-label single center pilot study showed the combination of pegylated interferon alfa-2b and adefovir for 48 weeks decreased serum HBV DNA by median 4.9 $\log_{10}$ copies/ml; 54% became HBV DNA undetectable. Paired liver biopsy showed intrahepatic total HBV DNA and cccDNA decreased by median 2.2 and 2.4 $\log_{10}$, respectively. Lower cccDNA levels before and at the end of therapy correlates with 8 of 15 HBeAg-positive responders [85].

In summary, adefovir dipivoxil is effective against both wild-type and lamivudine-resistant HBVs. Its efficacy in HBeAg-negative CHB is superior to lamivudine. Early detection of lamivudine resistance and prompt salvage treatment with addition of adefovir prevent emergence of

adefovir resistance and long-term results are pending but, so far, promising with little concern on renal toxicity.

Entecavir

Entecavir is a cyclopentyl guanosine analogue with potent selective inhibition of HBV replication. It does not inhibit human mitochondrial (gamma) polymerase. Entecavir inhibits the priming, the DNA-dependent synthesis, and the reverse transcription functions of HBV polymerase. It is phosphorylated intracellularly to the triphosphate active component and is potent against the wild-type HBV with EC50 of 40 nM. Three-dimensional homology models of the catalytic center of the HBV RT/DNA/dNTP complex were used with in vitro enzyme kinetic studies to examine the mechanism of action and demonstrated that entecavir halts HBV DNA elongation after incorporating a few additional bases. A novel hydrophobic pocket in the rear of the RT dNTP-binding site accommodates the exocyclic alkene moiety of entecavir. HBV DNA chain termination by entecavir is accomplished through disfavored energy requirements and steric constraints. In the woodchuck chronic infection model, entecavir therapy prolonged life span and decrease HCC rate. Sustained virologic reduction of up to 8 $\log_{10}$ copies/ml for 1–3 years was observed [86–88]. Rodent carcinogenicity lifetime studies revealed incident of lung adenoma and carcinoma, liver carcinoma, and hemangiomas in mice; and brain glioma, liver adenoma, and skin fibroma in rats at high dosages. However, these are species-specific and regarded as not likely to affect human subjects [89].

Viral dynamics in CHB patients treated with entecavir showed the median effectiveness in blocking viral production is 96%. Oral entecavir given for 28 days and 24 weeks in patients with CHB demonstrated efficacy and safety in 0.5 mg daily dose [90–92]. Pivotal phase III lamivudine-controlled clinical trials on treatment-naïve HBeAg-positive, and treatment-naïve HBeAg-negative CHB confirmed the significant improved efficacy compared with lamivudine [93, 94]. Entecavir also demonstrated efficacy in patients with lamivudine refractory HBeAg-positive CHB [95]. Study on the effect of 48 weeks of entecavir or lamivudine therapy on intrahepatic total HBV DNA and cccDNA levels showed both nucleoside analogues reduced serum viral load, intrahepatic total HBV DNA, and cccDNA by about 4.8, 2, and 1 log, respectively [96].

In a viral kinetic study (E.A.R.L.Y. Study) comparing entecavir to adefovir in HBeAg-positive CHB patients with high viral levels (mean baseline HBV DNA were 10.26 and 9.88 Log_{10} copies/ml in both groups, respectively), entecavir demonstrated significantly greater HBV DNA reduction as early as day 10. Reduction in HBV DNA at week 12 was -6.23 vs. -4.42 Log_{10} copies/ml in entecavir group versus adefovir group, respectively ($P < 0.0001$), and at week 48 was -7.28 vs. -5.08 Log_{10} copies/ml, respectively [difference (95% CI): -1.86 (-2.69, -1.03)]. At 48 weeks, 58 vs. 19% patients achieved undetectable HBV DNA (<300 copies/ml) by PCR, respectively [97].

Therapy in treatment-naïve CHB patients

In the phase 3, double-blind lamivudine-controlled trial of entecavir in treatment-naïve compensated HBeAg-positive CHB patients (Study 022), 715 patients were randomized to receive either entecavir 0.5 mg ($n = 354$) or lamivudine 100 mg ($n = 355$) once daily for a minimum of 52 weeks. The baseline demography of the entecavir-treated patients: HBV DNA 9.6 $\log_{10}$ copies/ml, ALT 140 IU/l; 50% genotype B or C; mean necroinflammatory score 7.8, Knodell fibrosis score 1.7, and 8% cirrhosis. Results at week 48 showed histologic improvement in 72 vs. 62% in the entecavir and lamivudine group, respectively ($P = 0.009$); undetectable serum HBV DNA levels by PCR assay in 67 vs. 36% ($P < 0.001$); ALT normalization in 68 vs. 60% ($P = 0.02$); mean reduction in serum HBV DNA from baseline was -6.9 vs. 5.4 $\log_{10}$ copies/ml ($P < 0.001$); HBeAg seroconversion 21 vs. 18% ($P = 0.33$). Patients with higher baseline serum ALT levels achieved higher HBeAg seroconversion (8.6% among those with baseline ALT less than two times the ULNl; 14.5% two to five times the ULN, and 68% greater than five times the ULN) (personnel communication). No viral resistance to entecavir was detected. Safety profile was good and similar in the two groups [93].

In the second year, 243 of 354 patients with virologic response (HBV DNA <0.7 MEq/ml but still HBeAg-positive) were rolled over to 96 weeks extended entecavir therapy. During this period, 37 patients achieved HBeAg seroconversion and discontinue therapy. A total of 119 of the 198 patients who remained HBeAg-positive but HBV DNA below 0.7 MEq/ml at week 96 were offered further extended entecavir therapy at dosage of 1.0 mg daily.

Since the design of this trial protocol does not yield intention-to-treat data on continuous 3 years of therapy, "Cumulative Confirmed Analysis" through 144 weeks was applied. Essentially, *cumulative* means the proportion of treated patients who ever achieved a confirmed end point on-treatment through week 144, and *confirmed* refers to two sequential measurements meeting the criteria or last observation. Thus, by week 144, 82% (292/354) of patients had cumulative confirmed HBV DNA <300 copies/ml, 49% (173/354) HBeAg loss and 39% (128/354) HBeAg seroconversion, and 90% (319/354) ALT normalization. However, among the original 354 patients, there were 27

non-responders, 14 withdrawals by week 96, 51 patients chose not to have third-year therapy, and 32 did not meet criteria for third-year therapy. This makes a total of 124 (35%) patients were not included in this analysis. One hundred eleven entecavir-treated patients achieved response (HBeAg loss and HBV DNA level <0.7 MEq/ml) by week 96, and discontinued therapy. Eighty-three (75%) patients had sustained response 24 weeks off therapy [98]. The results on 146 HBeAg-positive CHB after 192 weeks of entecavir therapy were presented in AASLD 2007. Ninety-eight of 108 (91%) achieved HBV DNA <300 copies/ml, 96 of 112 (86%) had ALT normalization, patients continued to experience HBeAg loss and seroconversion, reaching 39 of 96 (41%) and 15 of 96 (16%), respectively [99].

China reported on the efficacy of entecavir on 519 nucleoside naïve HBeAg-positive CHB patients in a randomized, double-blind lamivudine-controlled trial. At week 52, HBV DNA level decreased by 5.9 vs. 4.3 $\log_{10}$ copies/ml in entecavir and lamivudine groups, respectively ($P < 0.0001$); undetectable HBV DNA in 76 vs. 43% ($P < 0.0001$), HBeAg seroconversion rates 15 vs. 18% (NS). In another phases II and III trials in China involving 876 Chinese patients, efficacy, minimal drug resistance emergence, good safety profile, and good tolerability were reported [100–102].

In the phase III double-blind lamivudine-controlled trial of entecavir for treatment-naïve compensated HBeAg-negative CHB, 648 patients were randomized to entecavir 0.5 mg or lamivudine 100 mg once daily. At week 48, histologic improvement was obtained in 70 vs. 61% in the entecavir- and lamivudine-treated groups, respectively ($P = 0.01$); undetectable serum HBV DNA in 90 vs. 72% ($P < 0.001$) and ALT normalization in 78 vs. 71% ($P = 0.045$), respectively. The mean reduction in serum HBV DNA levels from baseline was 5.0 vs. 4.5 $\log_{10}$ copies/ml ($P < 0.001$). There was no evidence of resistance to entecavir. Safety and adverse-event profiles were similar in the two groups [95]. The cumulative confirmed response outcomes as defined earlier showed 88% achieved virologic response (HBV DNA <0.7 MEq/ml by Chiron bDNA assay and ALT <1.5 × ULN); 7% HBV DNA <0.7 MEq/ml but ALT >1.5 × ULN, and <1% HBV DNA >0.7 MEq/ml. After an off-treatment duration of over 60 days, patients with mean baseline HBV DNA level of 6.64 $\log_{10}$ copies/ml and ALT level of 222 IU/L were offered therapy with entecavir 1.0 mg daily. On retreatment, 93% achieved HBV DNA <300 copies/ml by week 48 [103].

Main areas that need critical appraisal for entecavir are

1. role as first-line therapy in treatment-naïve CHB patients,
2. de novo emergence of entecavir resistance,
3. role in lamivudine resistance, and
4. entecavir therapy in other patient subgroups.

Role as first-line therapy in treatment-naïve CHB patients

The efficacy of entecavir therapy is superior to lamivudine and adefovir dipivoxil in treatment-naïve HBeAg-positive and HBeAg-negative CHB patients. It is still early to comment on the durability of response to entecavir since few studies address this. There are no reported issues on safety profile. The main advantage is a significantly lower risk of entecavir resistance up to 4 year of therapy as discussed later.

De novo emergence of entecavir resistance in treatment-naïve patients

In the phase III clinical trial of treatment-naïve HBeAg-positive and HBeAg-negative CHB patients, HBV DNA levels were initially assayed with Chiron bDNA assay with lower detection limit of 5.14 $\log_{10}$ IU/ml. This was switched to PCR assay (LOD < 300 copies/ml or <57 IU/ml) that showed 91% became HBV DNA undetectable by week 96. The trial protocol as described earlier identified 22 patients as non-responders at week 48. Fifteen, seven, and five patients treated in the following 3 years were non-responders. Eighteen virologic rebounds were found during the first 96 weeks of therapy. Over a 2-year period, entecavir resistance was identified in two patients with lamivudine-resistant variants. Another three patients developed virologic rebound in the third year of therapy. They were attributable to lamivudine-resistant mutations present at baseline. Only one of them had an S202G entecavir resistance substitution which emerged at week 48. None of the other patients with viral rebound had genotypic resistance or in vitro loss of entecavir susceptibility. Genotyping all patients with PCR-detectable HBV DNA at weeks 48, 96, or end of dosing identified seven additional patients with lamivudine-resistant mutations, including one with simultaneous emergence of resistance to both lamivudine and entecavir. Eight of the ten patients had lamivudine resistance detectable at baseline, but seven of them subsequently achieved undetectable HBV DNA levels on ETV therapy. These findings suggest that the rapid, sustained suppression of HBV replication, combined with a requirement for multiple substitutions, creates a high genetic barrier to entecavir resistance in nucleoside-naïve patients. The cumulative probability of a virologic breakthrough due to entecavir resistance through 4 years is 0.8% in naïve and 39.5% in lamivudine-refractory patients [104–106].

Entecavir in the treatment of patients with lamivudine refractory CHB

In a dose-ranging study, HBeAg-positive and -negative patients ($n = 182$) who were viremic despite >24 weeks lamivudine treatment or harbored documented lamivudine-resistant substitutions were switched directly to entecavir (1.0, 0.5, or 0.1 mg daily) or continued on lamivudine (100 mg daily) for up to 76 weeks. At week 24, 79% patients receiving entecavir 1.0 mg and 51% on entecavir 0.5 mg had undetectable HBV DNA levels by bDNA assay compared with 13% in patients continued on lamivudine ($P < 0.0001$). By week 48, mean reductions in HBV DNA levels were 5.06, 4.46, and 2.85 $\log_{10}$ copies/ml on entecavir 1.0, 0.5, and 0.1 mg, respectively, and 68, 59, and 47%, respectively, normalized ALT. One virologic rebound due to resistance occurred (in the 0.5-mg group) [96].

In the phase III double-blind trial, HBeAg-positive patients refractory to lamivudine therapy were randomized to switch to entecavir 1 mg daily ($n = 141$) or to continue lamivudine 100 mg daily ($n = 145$) for a minimum of 52 weeks. Histologic improvement occurred in 55% of entecavir-treated vs. 28% of lamivudine-treated patients ($P < 0.0001$). Composite end point was achieved in 55 vs. 4%, respectively ($P < 0.0001$). Mean change in HBV DNA was -5.11 vs. -0.48 $\log_{10}$ copies/ml, respectively ($P < 0.0001$). Ten of the entecavir-treated patients developed genotypic resistance and two had virologic rebound with entecavir-resistance substitutions [107].

In a 2-year assessment of entecavir resistance in lamivudine-refractory CHB patients, available isolates from 192 entecavir-treated patients were sequenced, with phenotyping performed for all isolates with all emerging substitutions, in addition to isolates from all patients experiencing virologic rebounds. The T184, S202, or M250 substitution was found in lamivudine-resistant HBV at baseline in 6% of patients and emerged in isolates from another 11 of 187 (6%) and 12 of 151 (8%) of entecavir-treated patients by weeks 48 and 96, respectively. However, use of a more sensitive PCR assay detected many of the emerging changes at baseline, suggesting that they originated during lamivudine therapy. Only a subset of the changes in entecavir-resistant isolates altered their susceptibilities, and virtually all isolates were significantly replication impaired in vitro. Consequently, only 2 of 187 (1%) patients experienced entecavir-resistant rebounds in year 1. An additional 14 of 151 (9%) patients experienced entecavir-resistant rebounds in year 2. Isolates from all 16 patients with rebounds were lamivudine resistant and harbored the T184 and/or S202 change. Seventeen other novel substitutions emerged during entecavir therapy, but none reduced the susceptibility to ETV or resulted in a rebound [108].

In lamivudine refractory studies, virologic non-responders were identified in 52 of 187 patients at week 48, 46 of 146 treated in year 2, 21 of 30 treated in year 3, and 14 of 53 treated in year 4 [106]. Strong lamivudine resistance was associated with rtV173L + L180M + M204V dominant mutant and has the highest replication capacity. Following the switch to entecavir, the viral load rose again with a complex mixture of entecavir-resistant strains all harboring the lamivudine-resistant signature rtL180M + M204V and the rtS202G mutation. Although the rtL180M + S202G + M204V variant, that prevailed at the end of entecavir therapy, did not show the highest viral genome replication capacity, it conferred one of the strongest resistance levels to entecavir [49].

Entecavir therapy in other patient subgroups

In subgroup analysis from pivotal studies, response was compared between patients with advanced fibrosis/cirrhosis and the total patient group. Patients on entecavir were more likely than lamivudine to have undetectable HBV DNA, ALT normalization, and histologic improvement [109]. The role of entecavir in decompensated disease has not been reported but expected to have better results than other nucleos(t)ide analogues because of rapid viral suppression and low resistance rate. Its role in pre- and post-liver transplant patients, children, and patients with HCV, HDV, and HIV coinfection is likely to emerge with time as entecavir is being adopted in various clinical areas.

In summary, efficacy data on entecavir therapy up to 4 years is gaining superiority over lamivudine and adefovir dipivoxil in treatment-naïve HBeAg-positive and -negative CHB patients. It is safe and has a very low resistance rate among treatment-naïve patients as compared to relatively high rate in lamivudine-resistant patients and so warrant consideration for first-line therapy. However, it is much more costly, and the cost-effective analysis need to be systematically assessed [110, 111]. After initial data on the lack of activity against HIV, it is recently reported that it affects HIV-1 replication and resistance [112].

Telbivudine

Telbivudine, the prototype member of beta-L-2-deoxynucleosides, was approved by the FDA in October 2006 for the treatment of CHB.

Telbivudine daily dosing at 25, 50, 100, 200, 400, and 800 mg were studied and marked dose-related antiviral activity was evident, with a maximum at telbivudine doses of 400 mg/day or more. Correspondingly, post-treatment return of viral load was slowest in the high-dose groups

[113]. Pharmacokinetic studies in healthy subjects showed that concomitant lamivudine or adefovir dipivoxil did not appear to significantly alter the steady-state plasma pharmacokinetics of telbivudine and vice versa. Six hundred milligram telbivudine was well tolerated, and telbivudine plasma concentration-time profiles were similar across the four hepatic function groups [114]. The efficacy and safety profile of telbivudine 400 or 600 mg/day monotherapy or in combination with lamivudine 100 mg/day was compared with lamivudine monotherapy in a randomized, double-blind, multicenter trial in HBeAg-positive adults with compensated CHB. Median reductions in serum HBV DNA levels at week 52 ($\log_{10}$ copies/ml) were lamivudine, 4.66; telbivudine 400 mg, 6.43; telbivudine 600 mg, 6.09; combination 400, 6.40; and combination 600, 6.05. Telbivudine monotherapy is more effective than lamivudine monotherapy with greater HBeAg seroconversion (31 vs. 22%) and less viral breakthrough (4.5 vs. 15.8%) (P = NS for both). However, combination treatment was not better than telbivudine alone. In an exploratory scientific analysis, clinical efficacy at 1 year appeared related to reduction in HBV DNA levels in the first 6 months of treatment [115].

The international GLOBE trial included 1,367 adults with CHB (921 HBeAg-positive, 446 HBeAg-negative), conducted at 112 clinical centers in 20 countries worldwide. A total of 921 HBeAg-positive CHB patients (baseline HBV DNA >6 $\log_{10}$ copies/ml, ALT 1.3–10 × ULN, and compensated liver disease) were randomized to 2 years of telbivudine or lamivudine. Undetectable HBV DNA was achieved in 56% telbivudine vs. 39% of lamivudine-treated patients at year 1; 54 vs. 38% at year 2. ALT normalization was achieved in 77 vs. 75% (NS) at year 1, 67 vs. 61%, respectively, at year 2 ($P < 0.05$). However, HBeAg loss of 26 vs. 23% at year 1 and 34 vs. 29% at year 2 were of no significant difference. Sixty-three percent of the 921 HBeAg-positive patients had baseline ALT equal to or above 2 × ULN (ULN of 48 IU/l for males and 37 IU/l for females) that is generally regarded as one of the indicators for therapy. After 2 years, telbivudine reduced HBV DNA by 6.1 $\log_{10}$ copies/ml vs. lamivudine 5.0 $\log_{10}$ copies/ml ($P < 0.05$); PCR negativity 61 vs. 43% ($P < 0.05$); ALT normalization 72 vs. 63% ($P < 0.05$); HBeAg loss 42 vs. 32% ($P < 0.05$); HBeAg seroconversion 37 vs. 27% ($P < 0.05$); treatment failure (primary treatment failure with HBV DNA never attained level below 5 $\log_{10}$ copies/ml and resistance-related) 5 vs. 17% ($P < 0.05$) [116]. The GLOBE trial showed telbivudine genotypic resistance at YMDD motif being 4.4% at year 1 increasing to 21.6% at year 2 compared to 9.1 and 35.0% in lamivudine group.

In the 446 HBeAg-negative CHB patients, telbivudine resulted in a significantly higher percentage of undetectable HBV DNA than lamivudine, 88 vs. 71% at year 1 and 79 vs. 53% at year 2. ALT normalization was 74 vs. 79% (NS) at year 1 and 75 vs. 67% at year 2. Telbivudine genotypic resistance emergence was lower at 2.7 and 8.6%, respectively, at years 1 and 2 than to 9.8 and 21.9% in lamivudine group.

Initial report of adefovir salvage for telbibudine resistance, as monotherapy or combination therapy, resulted in viral suppression for 22 patients with viral breakthrough [117].

In the GLOBE trial, 134 of 458 patients (29%) receiving telbivudine and 123 of 463 patients receiving lamivudine (27%) were eligible to discontinue treatment after the first year if they achieved HBV DNA <5 $\log_{10}$ copies/ml and HBeAg loss for at least 24 weeks. Owing to investigator choice, only 59 of 257 (23%) did so and stopped treatment. At week 104, >80% of both telbivudine and lamivudine recipients exhibited sustained HBeAg responses. The median duration off-treatment was 35.2 weeks for telbivudine and 29.1 weeks for lamivudine [118].

In another 1-year randomized trial, 135 HBeAg-positive CHB adults (baseline HBV DNA >6 $\log_{10}$ copies/ml, ALT 1.3–10 × ULN) were initially randomized (2:1) to adefovir 10 mg daily or telbivudine 600 mg daily for 24 weeks. At week 24, mean HBV DNA reduction was −4.97 vs. −6.30 $\log_{10}$ copies/ml ($P < 0.01$). A secondary randomization (1:1) of adefovir recipients to continue adefovir or switch to telbivudine at week 24 showed viral load decreased sharply after telbivudine switch. Seventy-eight percent of patients with suboptimal response to adefovir, defined as HBV DNA remaining over 3 $\log_{10}$ copies/ml at week 24, experienced additional mean 2.1 $\log_{10}$ reduction between weeks 24 and 52 after switching to telbivudine [119]. Predictive analysis of response showed week 24 serum HBV DNA levels <3 $\log_{10}$ copies/ml (49% telbivudine vs. 22% adefovir; $P < 0.01$) correlated with undetectable HBV DNA at first year and an HBeAg seroconversion (44%). In all patients with viral breakthrough at first year (2 on telbivudine, 1 on adefovir), HBV DNA levels were >4 $\log_{10}$ copies/ml at week 24 [120].

Primary analysis at week 24 of a randomized trial of switching to telbivudine versus continued lamivudine in adults with CHB showed that patients with persistent viremia during lamivudine therapy experienced significant improvement in HBV suppression by switching to telbivudine [121].

Telbivudine was generally well tolerated with similar adverse event profile to lamivudine. However, creatinine kinase elevations were more frequent among subjects on telbivudine treatment. Grade 3 or 4 creatinine kinase elevations occurred in 9% of telbivudine-treated patients and 3% of lamivudine-treated patients. Cases of myopathy have been reported with telbivudine use several weeks to months after starting therapy.

The safety and efficacy of telbivudine in liver-transplant-recipient pediatric patients under the age of 16 years have not been established. The optimal duration of treatment with telbivudine has not been established [122]. Telbivudine is the only nucleos(t)ide analogue classified in pregnancy category B instead of C, indicating its relative safety for treating pregnant patients.

In summary, telbivuidne is more potent compared with lamivudine and adefovir. The resistant profile is not satisfactory. The concern over creatinine kinase elevation and number of histologic-documented myopathy is under investigation [123]. Whether telbivudine will be an important switch option for patients with suboptimal response to lamivudine or adefovir remains to be confirmed.

Emtricitabine

Emtricitabine (FTC) is a potent inhibitor of HBV and HIV. In a clinical trial of 248 patients (63% HBeAg positive), 48 weeks of emtricitabine 200 mg daily significantly improved histology (62 vs. 25% in placebo group), suppressed HBV DNA to undetectable level by PCR assay (54 vs. 2% placebo group), and induced biochemical response (65 vs. 25% placebo groups). HBeAg seroconversion rate was the same and 13% emtricitabine-treated patients developed resistant mutation at the YMDD motif [124].

Clevudine

Clevudine is a pyrimidine nucleoside analogue effective in suppressing woodchuck hepatitis virus replication by around 9 $\log_{10}$ copies/ml and causes a significant reduction of intrahepatic WHV RNA and cccWHV DNA levels. In humans, clevudine 10, 50, 100, or 200 mg/day for 28 days can reduce the median HBV DNA by −2.5, −2.7, −3, and −2.6 $\log_{10}$, respectively. More importantly, this suppression of antiviral activity is maintained at 12 and 24 weeks post-treatment [125–128].

The safety and efficacy of 30 mg clevudine once daily for 24 weeks was evaluated in 243 HBeAg-positive CHB patients (clevudine $n = 182$; placebo $n = 61$). Median serum HBV DNA reductions from baseline at week 24 were 5.10 and 0.27 $\log_{10}$ copies/ml in the clevudine and placebo groups, respectively ($P < 0.0001$), with ALT normalization in 68.2 and 17.5%, respectively ($P < 0.0001$). A total of 59% of patients in the clevudine group were PCR negative for HBV DNA [129]. Viral suppression in the clevudine group was sustained off therapy, with 2.02 $\log_{10}$ reduction at week 48 compared with baseline. In HBeAg-negative CHB, 86 patients (clevudine $n = 63$; placebo $n = 23$) were treated for 24 weeks. The median changes in HBV DNA from baseline were −4.25 and −0.48 $\log_{10}$ copies/ml at week 24 in the clevudine and placebo groups, respectively ($P < 0.0001$); ALT normalization was 74.6 and 33.3%, respectively ($P = 0.0006$). At weeks 24 and 48, 92.1 and 16.4%, respectively, of patients in the clevudine group had undetectable serum HBV DNA. Viral suppression in the clevudine group was sustained after withdrawal of therapy, with 3.11 $\log_{10}$ reduction at week 48. The incidence of adverse events was similar in clevudine and placebo groups. No resistance to clevudine was detected during treatment [130].

A double-blind, multicenter study of the combination of clevudine 10 mg and emtricitabine 200 mg once daily vs. or emtricitabine monotherapy for 24 weeks in 134 HBeAg-positive CHB patients showed 74 vs. 65% in combination therapy and monotherapy, respectively, achieved serum HBV DNA <4,700 copies/ml ($P = 0.114$). However, 24 weeks post-treatment, there was a significantly greater virologic and biochemical response in the clevudine and emtricitabine combination therapy [131].

Tenofovir

Tenofovir disoproxil fumarate (TDF) is licensed for the treatment of HIV-1. In order to evaluate the anti-HBV activity of TDF compared with ADV in HIV/HBV-coinfected subjects, patients were randomized, double-blind, placebo-controlled trial of daily 10 mg of ADV vs. 300 mg of TDF in 50 subjects with HBV and HIV coinfection on stable ART, with serum HBV DNA ≥100,000 copies/ml, and plasma HIV-1 RNA ≤10,000 copies/ml. This study closed early based on the results of a pre-specified interim review, as the primary non-inferiority end point had been met without safety issues. Over 48 weeks, treatment with either ADV or TDF resulted in clinically important suppression of serum HBV DNA. Both drugs are safe and efficacious for patients coinfected with HBV and HIV.

Before the availability of adefovir in some region, tenofovir has been used successfully for lamivudine resistance [132]. Subsequent switch back to adefovir resulted in viral relapse in 60% of patients. Tenofovir is a stronger antiviral agent than adefovir and retreatment with tenofovir regained viral suppression. The efficacy of tenofovir in patients who had been previously treated with lamivudine and consecutively with adefovir due to lamivudine resistance (patients with genotypic adefovir resistance excluded owing to potential cross-resistance) also demonstrated good efficacy [133].

In AASLD 2007, data on 1-year randomized double-blind comparison of tenofovir versus adefovir therapy for

treatment-naïve HBeAg-positive and -negative CHB patients were presented. In the HBeAg-positive CHB patients, 67% of the tenofovir-treated patients achieved the primary end point of clinical response (histologic improvement by two points or more in HAI score and serum HBV DNA below 400 copies/ml), significantly better than 12% achieved by the adefovir-treated group ($P < 0.001$). The main advantage of tenofovir was that 76% of the patients achieved serum HBV DNA below 400 copies/ml, compared to only 13% in the adefovir-treated group ($P < 0.001$). By week 48, 69% had normalized serum ALT levels in tenofovir group (54% in adefovir group, $P = 0.018$); HBeAg loss was 22.2 vs. 17.5%, respectively ($P < 0.05$) and HBeAg seroconversion 20.9 vs. 17.5%, respectively ($P > 0.07$). Five patients in the tenofovir group lost HBsAg, two underwent HBsAg seroconversion. No resistance was detected in either treatment group [134]. In the HBeAg-negative CHB patients, 71% of the tenofovir-treated patients achieved the primary end point of clinical response, significantly better than 49% achieved by the adefovir-treated group ($P < 0.001$). By week 48, similar serum ALT normalization rate was observed in both treatment groups. Mutations associated with tenofovir resistance were evaluated in eight samples with negative results [135].

Discussion

Treatment of CHB with nucleos(t)ide analogues has evolved in recent years to a stage with numerous choice and options available and a fine tune assessment for indication and selection. It is important to emphasize that the overall therapeutic goal being restoration of normal quality life. This can be achieved through viral eradication or persistent viral suppression, thereby resolving necroinflammation, and preventing progressive disease. The chance of success in therapy is dependent on two factors: first, the efficacy of the therapeutic agent, and second, the stage of disease when therapy is commenced. Published data are mostly of short-term evaluation of efficacy in 1–5 years on compensated CHB patients. The responders in these treated patients may benefit, yet in each study, there is significant proportion that did not even meet the short-term end point. The management plan of the partial responders, the relapsers post-therapy, and the breakthrough non-responders still require critical strategic thinking backed up by increasing knowledge on molecular virology. Extrapolation of efficacy among compensated CHB to other patient subgroups (such as patients with decompensated acute exacerbation, in advanced stage cirrhosis, in children or adult in immune tolerance phase, in HCV/HIV coinfected patients) is probably valid but data still need to be collected and analyzed.

The successive generation of nucleos(t)ide analogues has improved potency and raised genetic barrier to resistant mutation. Percentage of patients with undetectable HBV DNA on PCR assays has increased with corresponding increase in ALT normalization. Histologic improvement is a crucial proof of attainment of therapeutic goal. Documented regression of advanced fibrosis and cirrhosis among the responders of adefovir therapy is an exciting achievement. Slowed progression of disease and reduced emergence of HCC after 3 years of lamivudine therapy for CHB patients with advanced fibrosis is a proof for therapeutic aim. However, despite increased potency, corresponding increase in HBeAg loss or HBeAg seroconversion is not obvious. It may take longer in terms of years. The interaction between viral suppression and host immune activity may be the key to achieve the therapeutic milestone. It is an important area for further research and development. Therapy should aim for HBsAg loss or HBsAg seroconversion as an end point since durability of response, as defined by HBV DNA undetectable and HBeAg loss/seroconversion, is poor with most agents. The annual incidence of relapse is around 10–20%. Viral kinetic studies have identified additive or synergic efficacy with certain combination therapy such as emtricitabine + adefovir and telbivudine + Val-LdC. However, little clinical trial development follows due to various reasons. The combination of nucleos(t)ide analogue and immuno-modulators has also identified certain more effective combination regimen and requires formal controlled trials to substantiate the results.

At present, there are five nucleos(t)ide analogues approved by the FDA and other national/regional health authorities. Lamivudine remains the mainstay for many Asian regions because it is most economic. However, it is difficult and expensive to manage once the patient develops resistant mutants and requires salvage therapy with the addition of adefovir dipivoxil. This might be avoided by restricting patients with good predictors of response and low risk for resistance for lamivudine monotherapy, that is, younger HBeAg-positive patients with ALT over $5 \times$ ULN and low necroinflammatory grade, then considering alternative therapy if HBV DNA is still over 3 $\log_{10}$ copies/ml by week 24. Responders with HBeAg seroconversion and HBV DNA undetectable by PCR assay should have extra continuous therapy at least 1 year before stopping to consolidate response and enhance durable sustained response. Five years of adefovir therapy achieved satisfactory results for Caucasian HBeAg-negative patients. However, there is no sufficient data on natural history and treatment response on Asian HBeAg-negative patients and much work needs to be done in this area. The

lack of data on head-to-head comparison among these approved nucleos(t)ide analogues also hamper the analysis with regard to different predictive factors for response since all studies were either placebo or active-controlled with one other serum ALT level nucleos(t)ide analogue. The different characteristic of patient cohort, especially the baseline serum ALT levels, HBV DNA levels, and the different profile of genotypes and histologic staging may impact the clinical response.

The indication for therapy with nucleos(t)ide analogues has gradually been broadened since these agents are regarded as efficacious, safe, and more important, convenient to administer. It is an appealing proposition in the face of a third or so of the millions of CHB patients dying or being at risk of dying from liver-related diseases. Much debate surrounding the topic "who to treat" and "when to start" hinges on the unanswered question "when to stop." The view that oral nucleos(t)ide analogues therapy can be continued lifelong is based on good maintained response and little risk for resistance emergence among responders. This is a major undertaking of therapy for 10–50 or more years. Cost and long-term drug effect are the two main concerns against this proposal. Furthermore, these available data are only up to 4 or 5 years in selected patient cohort. Expenditure for medication, regular monitoring of serum HBV DNA by PCR assay, and physician consultation is substantial. There are patients who can afford such therapy personally. However, the majority of Asian CHB patients are in the low socioeconomic class or that the cost of their therapy is reimbursable by governmental agencies with strict criteria. Therefore, detailed cost-effective analysis stratified for age, gender, and disease stage should be performed to guide patients and health providers. The initial "road map" concept has been discussed in various forums. A vigorous and analytical discussion is needed to devise different "road maps" tailored for patients in different phases of CHB disease. This road map should aim to achieve a long-term goal in an affordable and feasible clinical practice.

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