REVIEW

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Current Nucleos(t)ide Analogue Therapy for Chronic Hepatitis B

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Although the prevalence of chronic hepatitis B has decreased considerably in recent years due to widespread use of the hepatitis B virus (HBV) vaccine, its prevalence still remains high in adults, and this can place a significant burden on health care in areas with endemic HBV. Since the introduction of nucleos(t)ide analogues (NUCs), there has been marked improvement in the care of patients with chronic hepatitis B, resulting in increased survival. However, the emergence of drug resistance in patients treated with NUCs is a major concern. The number of multi-drug resistant patients is increasing, and many patients may not respond to the currently available drugs. In this review, we describe the current status of NUC therapy for antiviral-naïve and -resistant patients. **(Gut Liver 2011;5:278-287)**

Key Words: Chronic hepatitis B; Nucleos(t)ide analogue; Drug resistance; Hepatitis B virus

INTRODUCTION

Chronic hepatitis B virus (HBV) infection is an important health problem affecting approximately 400 million people worldwide. Chronic HBV infection can progress to cirrhosis, decompensated cirrhosis, hepatocellular carcinoma (HCC), and death. The prevalence of HBV infection has decreased dramatically following widespread use of HBV vaccine in Korea, an endemic area. However, chronic HBV infection is still prevalent in the population in their 20s in Korea,[1] and has remained a significant burden to the health care system. The circulating level of HBV DNA has been proved as the most important correlating factor in the development of cirrhosis and HCC. The suppression of HBV replication can reduce necroinflammatory activity and prevent progression to cirrhosis and HCC. Several nucleos(t)ide analogues (NUCs) have been developed over the past decade, and the administration of NUCs has played a crucial role in the treatment of chronic HBV infection. Despite their potent anti-HBV effects, NUCs cannot eradicate HBV infection, and for this reason, long-term therapy is necessary. The major drawback of long-term monotherapy with NUCs is the emergence of drug resistance. The emergence of resistance limits the efficacy of the antiviral drugs, raising a serious concern in clinical practice. The prevention of drug resistance and selection of appropriate treatment options in the face of drug resistance are important for reducing morbidity and mortality of patients with chronic HBV infection.

GOALS OF TREATMENT

The goal of therapy is to improve survival by preventing progression of chronic hepatitis to cirrhosis, end-stage liver disease or HCC. Short-term goals include reduction in HBV DNA levels, persistent alanine aminotransferase (ALT) normalization, and hepatitis B e antigen (HBeAg) seroconversion. Loss of hepatitis B surface antigen (HBsAg) is an ideal end point, but this rarely occurs. NUCs can not completely eradicate HBV infection as they show little effectiveness in eliminating covalently closed circular DNA in the nucleus of infected hepatocytes. Long-term administration on NUCs is required in order to effectively treat patients with chronic HBV infection.

The European Association for the Study of the Liver (EASL) guidelines suggest that therapy must reduce HBV DNA to as low a level as possible, ideally below the lower limit of detection by the real-time PCR assay.[2] Persistent viremia has been associated with frequent development of antiviral resistance.

DEFINITION OF FAILED RESPONSE AND VIRAL RESISTANCE

1. Primary non-response

Primary non-response is defined as less than a 1 $\log_{10}$IU/mL

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decrease in HBV DNA level from baseline after 3 months of therapy based on the EASL guidelines.[2] The American Association for the Study of Liver Disease (AASLD) guidelines define primary non-response as failure to achieve a 2 $\log_{10}$IU/mL decrease in HBV DNA after at least 6 months of therapy (Table 1).[3] It may be due to poor compliance or low antiviral activity. A switch to a more potent drug is recommended for patients with primary non-response.

2. Partial response

The EASL guidelines propose that partial virologic response is defined as a decrease in HBV DNA of more than 1 $\log_{10}$IU/mL but detectable HBV DNA by real time PCR at week 24 or 48, depending on the genetic barrier of anti-viral drugs (Table 1).[2] If drugs with a high genetic barrier such as entecavir (ETV) or tenofovir (TDF) are being administered, antiviral response can be assessed at week 48. Adefovir (ADV) has delayed antiviral effect. Thus, these patients can also be assessed at week 48. A partial virologic response to antiviral drugs correlates with the risk of promoting antiviral resistance. The serum HBV DNA level at week 24 of therapy was found to be associated with the emergence of antiviral resistance in patients treated with telbivudine (LdT) or lamivudine (LAM).[4] Patients with HBV DNA level >1,000 copies/mL at week 24 of therapy correlated with high rates of resistance when compared to those with a low HBV DNA level. A prospective cohort study of untreated hepatitis B patients showed that the risk for cirrhosis and HCC was higher in patients with HBV DNA levels >10,000 copies/mL than those with HBV DNA <10,000 copies/mL.[5,6] International practice guidelines recommend treating chronic hepatitis B patients with HBV DNA levels >10,000 copies/mL using antiviral drugs. When partial virologic response is identified, antiviral treatment should be modified.

3. Virologic breakthrough

Virologic breakthrough is defined as an increase in serum HBV DNA by >1 $\log_{10}$copies/mL above nadir after achieving a virologic response during treatment (Table 1).[2,3] Drug-noncompliance is frequently associated with virologic breakthrough. Therefore compliance should be confirmed at the time of virologic breakthrough. If virologic breakthrough occurs, serum HBV DNA increases progressively despite continuous treatment followed by an elevation in ALT level. A test for genotypic resistance is needed to confirm the diagnosis and select appropriate treatment options. For patients presenting with mild elevation in HBV DNA and normal ALT, additional tests for HBV DNA are also necessary.

NUCLEOS(T)IDE ANALOGUES

A number of NUCs have been developed and used for the treatment of patients with chronic HBV infection. NUCs inhibit viral polymerase activity, thus affecting negative strand and positive strand DNA synthesis.[7] LAM, an analogue of dideoxycytidine, was the first approved HBV polymerase inhibitor. LAM is the prototype of the L-nucleoside family. The triphosphate form of LAM inhibits nascent viral DNA synthesis. Other NUCs belonging to the L-nucleoside family are emtricitabine, LdT, and clevudine. ADV and TDF belong to the acyclic D-nucleotide, while ETV to the cyclic D-nucleoside. ADV and TDF are phosphorylated forms of nucleotide analogues. Long-term administration of drugs belonging to the L-nucleoside family is associated with the frequent development of antiviral resistance, when compared to drugs belonging to D-nucleos(t)ide analogues (Table 2).

Table 1. Definition of a Response to Antiviral Therapy for Chronic Hepatitis B

	AASLD*	EASL†	APASL‡
Primary non-response	Decrease in serum HBV DNA by <2 $\log_{10}$IU/mL after at least 24 weeks of therapy	Decrease in serum HBV DNA less than 1 $\log_{10}$IU/mL from baseline at 3 months of therapy	Reduction of serum HBV-DNA <1 log IU/mL at 12 weeks of oral antiviral therapy in a compliant patient
Partial virological response		Decrease in serum HBV DNA of more than 1 $\log_{10}$IU/mL but detectable HBV DNA by real-time PCR assay§	
Virological breakthrough	Increase in serum HBV DNA by >1 $\log_{10}$ (10-fold) above nadir after achieving virologic response, during continued treatment	Increase in serum HBV DNA level of more than 1 log $\log_{10}$IU/mL compared to nadir (lowest level) HBV DNA level on therapy	>1 log IU/mL increase in serum HBV-DNA from nadir of initial response during therapy as confirmed 1 month later

HBV, hepatitis B virus.
*American Association for the Study of Liver Disease guidelines, Hepatology 2009;50:661-662;[3] †European Association for the Study of the Liver guidelines, J Hepatol 2009;50:227-242;[2] ‡Asian-Pacific Association for Study of the Liver recommendations, Hepatol Int 2008;2:263-283; §Partial virologic response should be assessed at 24 weeks of treatment for lamivudine and telbivudine and 48 weeks of treatment for entecavir, adefovir and tenofovir.

Table 2. Potency and Resistance of Currently Available Nucleos(t)ide Analogues

	Antiviral potency	Genetic barrier	Resistant pattern
Pyrimidine analogues			
L-nucleosides			
Lamivudine	Moderate	Low	rtM204V/I±rtL180M
Emtricitaine	Low	Low	rtM204V/I±rtL180M
Telbivudine	High	Low	rtM204I
Clevudine	High	Low	rtM204I
Purine analogues			
Cyclic D-nucleoside			
Entecavir	High	High	rtM204V/I±rtL180M plus rtT184, rtS202, rtM250
Acyclic D-nucleotides			
Adefovir	Low	Moderate	rtA181T/V, rtN236T
Tenofovir	High	High	rtA181T/V, rtN236T

1. Lamivudine

Lamivudine (LAM), the (-) enantiomer of 3'-thiacytidine, is an oral 2', 3'-dideoxynucleoside that inhibits DNA synthesis by terminating the nascent proviral DNA chain. Unlike other dideoxynucleosides, LAM does not inhibit mitochondrial DNA or bone marrow progenitor cells at concentrations that block the synthesis of HBV DNA, and it is not incorporated into mitochondrial DNA.[8] The recommended dose of LAM for adults with normal renal function (creatinine clearance >50 mL/min) and no HIV co-infection is 100 mg orally once daily. Dose reduction is necessary for patients with renal insufficiency (Table 3).

In HBeAg-positive chronic hepatitis B patients, HBeAg seroconversion at 1 year was seen in 16-18% of patients who received LAM compared with 4-6% of untreated controls. Undetectable serum HBV DNA was noted in 44-60% of patients, and ALT normalization was observed in 41-72%. Histologic improvement defined as a reduction in the necroinflamma-

Table 3. Adjustment of Adult Dosage of Nucleos(t)ide Analogues in Accordance with Creatinine Clearance

Creatinine clearance (mL/min)	Recommended dose	
Lamivudine		
≥50	100 mg qd	
30-49	100 mg first dose, then 50 mg qd	
15-29	35 mg first dose, then 25 mg qd	
5-14	35 mg first dose, then 15 mg qd	
<5	35 mg first dose, then 10 mg qd	
Adefovir		
≥50	10 mg qd	
20-49	10 mg every other day	
10-19	10 mg every third day	
Hemodialysis patients	10 mg every week following dialysis	
Entecavir	NA naïve	Lamivudine refractory/resistant
≥50	0.5 mg qd	1 mg qd
20-49	0.25 mg qd or 0.5 mg q48 hr	0.5 mg qd or 1 mg q 48 hr
10-19	0.15 mg qd or 0.5 mg q 72 hr	0.2 mg qd or 1 mg q 72 hr
<10 or Hemodialysis* or CAPD	0.05 mg qd or 0.5mg q 7 days	0.1 mg qd or 1 mg q 7 days
Telbivudine		
≥50	600 mg qd	
30-49	600 mg q 48 hr	
<30 (not requiring dialysis)	600 mg q 72 hr	
End-stage renal disease	600 mg q 96 hr*	
Tenofovir		
≥50	300 mg q 24 hr	
30-49	300 mg q 48 hr	
10-29	300 mg q 72-96 hr	
<10 with dialysis	300 mg q 7 days or after a total of approximately 12 hr of dialysis	
<10 without dialysis	No recommendation	

This table was adapted from AASLD guidelines (Hepatology 2009;50:661-662).[3]
CAPD, continuous ambulatory peritoneal dialysis.
*Administer after hemodialysis.

tory score by ≥2 points was reported in 49-56% of patients.[9-11] The proportion of patients achieving HBeAg seroconversion increased substantially with continued LAM treatment to 50% after 5 years. The incidence of HBeAg seroconversion was greater in patients with higher baseline ALT concentrations.[12,13] In HBeAg-negative chronic hepatitis B patients, undetectable serum HBV DNA at one year is observed in 60-70% of patients who received LAM.[14-16] In patients with bridging fibrosis or compensated cirrhosis, LAM can improve clinical outcomes.[17,18] LAM significantly delayed overall disease progression and reduced the incidence and the risk of HCC compared to a placebo control group (7.8% vs 17.7%, and 3.9% vs 7.4%, respectively).[18] LAM is also beneficial in patients with decompensated cirrhosis caused by actively replicating HBV. Significant clinical improvement, defined as a decrease in the Child-Pugh-Turcotte score by ≥2 points, was observed in 55% of patients.[19] However, it takes 3 to 6 months to show clinical benefit, and HCC can occur even among patients with clinical improvement. Studies from Asia reported lower rates of durability of improvement (50-60%) than those from non-Asian countries (77%).[20-22] Factors associated with increased durability of LAM-induced HBeAg seroconversion were: longer duration of therapy after HBeAg seroconversion, younger age, a lower HBV DNA level when treatment was stopped, and genotype B versus C.

Mutations in the YMDD motif (rtM204V, rtM204I) are the primary mutants responsible for LAM resistance. The other mutations such as rtL180M, rtL80I/V, and rtV173L are frequently found in LAM-resistant patients. The rtA181T/S and rtT184S mutations are rarely found. A study of 67 LAM-resistant Korean patients showed that the rtL180M, rtL80I and rtV173L mutations were present in 78%, 43%, and 11% of patients, respectively.[23] The rtM204V mutation accompanied rtL180M, and rtL80I was always observed in conjunction with rtM204I. Genotypic resistance was detected in 14-32% after 1 year of LAM treatment, and the frequency increased with each year of therapy, reaching 60-70% after 5 years of treatment.[9-12,24] Factors associated with increase in the rate of LAM resistance include longer duration of treatment, higher pretreatment serum HBV DNA levels, and higher level of residual virus after initiation of treatment.[24,25]

2. Adefovir

Adefovir dipivoxil (ADV) is an orally bioavailable pro-drug of adefovir, a nucleotide analog of adenosine monophosphate. It can inhibit both reverse transcriptase and DNA polymerase activity and is incorporated into HBV DNA causing chain termination. The recommended dose of ADV for adults with normal renal function (creatinine clearance >50 mL/mim) is 10 mg orally daily. The dosing interval should be increased in patients with renal insufficiency (Table 3).

In HBeAg-positive chronic hepatitis B patients, the HBeAg seroconversion rates at 1 year were 12% and 14% for patients who received ADV 10 mg and 30 mg compared with 6% for the placebo group. Mean reduction of serum HBV DNA level was 3.5 and 4.8 $\log_{10}$copies/mL, and ALT normalization was observed in 48% and 55% of patients who received 10 mg and 30 mg ADV for 48 weeks, respectively. Histologic improvement was observed in 53% and 59% of patients who received 10 mg and 30 mg ADV. But 8% of patients in the ADV 30 mg dose group had nephrotoxicity.[26] Cumulative HBeAg seroconversion was estimated to be 48% after 5 years of treatment.[27] In HBeAg-negative chronic hepatitis B patients, undetectable serum HBV DNA at 1 year was observed in 51% of patients who received ADV 10 mg, and this increased to 71% after 2 years.[28,29] Another study has reported that serum HBV DNA was undetectable in 53% after 5 years of continuous ADV treatment.[30] ALT normalization was observed in 72% of patients, and histologic response was observed in 64% of patients at 1 year of ADV treatment.[29] Comparable results were observed at 1 year of ADV treatment in Asian chronic hepatitis B patients. Undetectable serum HBV DNA was observed in 39% of patients, and mean reduction of serum HBV DNA was 3.7 $\log_{10}$copies/mL. ALT normalization was observed in 63% and histologic improvement was observed in 56% of Asian patients.[31]

The rtA181T/V and rtN236T mutations are associated with ADV resistance. *In vitro* studies have shown that ADV-resistant mutations decrease susceptibility to treatment by 3 to 15 folds.[32,33] A phase III trial showed no ADV-resistant mutations were found after 1 year of treatment,[34] but cumulative probabilities of genotypic resistance to ADV at 1, 2, 3, 4, and 5 years were 0%, 3%, 11%, 18%, and 29%, respectively in HBeAg-negative patients.[30] The cumulative rate of genotypic resistance to ADV was estimated to be 20% after 5 years of treatment in HBeAg-positive patients.[26] Risk factors for ADV resistance include suboptimal viral suppression and sequential ADV monotherapy in LAM-resistant patients.[35,36] In LAM-resistant patients, the cumulative genotypic resistance and virologic breakthrough at 5 years of sequential ADV monotherapy were reported to be 65.6% and 61.8%, respectively.[37]

3. Entecavir

Entecavir (ETV) is a carbocyclic analogue of 2'-deoxyguanosine. It can inhibit HBV replication at three different steps: the priming of HBV DNA polymerase, the reverse transcription of the negative strand HBV DNA from the pregenomic RNA, and the synthesis of the positive strand HBV DNA. The approved dose of ETV for nucleoside-naïve patients is an oral dose of 0.5 mg daily and 1.0 mg for LAM-refractory/resistant patients. The dose should be adjusted for patients with an estimated creatinine clearance <50 mL/min (Table 3).

In HBeAg-positive patients, ETV resulted in significantly higher rates of virologic, histologic, and biochemical responses compared to LAM. In a Phase III clinical trial, serum HBV DNA was undetectable at 1 year in 67% of patients who received ETV 0.5 mg compared to 36% of patients who received LAM 100

mg. Histologic improvement was observed in 72% and 62% of patients and ALT normalization was observed in 68% and 60% of patients, respectively. HBeAg seroconversion rates were also seen in 21% of patients who received ETV compared to 18% of patients who received LAM.[38] ETV resulted in earlier and more marked viral suppression than ADV.[39] In HBeAg-negative patients, ETV resulted in significantly higher rates of virologic, histologic and biochemical responses compared to LAM. More patients in the ETV group had undetectable serum HBV DNA levels (90% vs 72%) and normalization of ALT levels (78% vs 71%) compared to that of the LAM group. Histologic improvement after 48 weeks of treatment occurred in 70% as compared with 61% of patients in the LAM group. The mean reduction in serum HBV DNA levels from baseline to week 48 was greater with ETV than with LAM (5.0 vs 4.5 $\log_{10}$copies/mL).[40] In decompensated cirrhosis, a recent study showed that ETV resulted in virologic and biochemical responses similar to the compensated liver disease group. Undetectable serum HBV DNA was observed in 89.1% of the decompensated group compared to 78.5% of the compensated group. HBeAg seroconversion rate (48.1% vs 41.1%) and normalization of ALT (76.4% vs 75.0%) were also similar between the two groups.[41]

In HBeAg-positive patients who lost HBeAg and discontinued ETV therapy after 48 weeks, undetectable HBV DNA, normalization of ALT and HBeAg seroconversion were sustained in 39%, 79%, and 77%, respectively, at 24 weeks off-treatment.[42] However in HBeAg-negative patients, only 3% sustained suppression of serum HBV DNA to undetectable levels at 24 weeks after cessation of treatment.[43]

Resistance to ETV appears to occur through a two-hit mechanism with initial selection of the rtM204V/I mutation, followed by amino acid substitutions at rtT184, rtS202, or rtM250. In NUCs-naïve patients, the 5-year cumulative probability of genotypic ETV resistance and genotypic ETV resistance associated with virologic breakthrough was only 1.2% and 0.8%, respectively. In contrast, the 5-year cumulative probability of genotypic ETV resistance and genotypic ETV resistance associated with virologic breakthrough was 51% and 43%, respectively, in LAM-resistant patients.[44] *In vitro* studies showed that ETV-resistant mutations are susceptible to ADV and TDF.[45]

4. Telbivudine

Telbivudine (LdT), a synthetic thymidine nucleoside analogue (L-enantiomer of thymidine), is phosphorylated intracellularly to the active triphosphate form, which competes with the natural substrate thymidine 5'-triphosphate to inhibit hepatitis B viral DNA polymerase; this enzyme inhibition blocks reverse transcriptase activity, thereby reducing viral DNA replication. The approved dose of LdT is 600 mg daily. Doses should be adjusted for patients with estimated creatinine clearance <50 mL/min (Table 3).

In HBeAg-positive patients, LdT resulted in significantly higher rate of virologic and histologic responses compared to LAM. In a phase III clinical trial, undetectable serum HBV DNA at 1 year was observed in 60.0% of patients who received LdT 600 mg compared to 40.4% of patients who received LAM 100 mg. Histologic improvement was observed in 64.7% and 56.3% of patients, respectively. However, there was no significant difference in biochemical and serologic response rates. ALT normalization was observed in 77.2% of patients who received LdT compared to 74.9% of patients who received LAM, and similar results were observed in HBeAg seroconversion rates, 22.5% for LdT group and 21.5% for LAM group.[46] After 2 years of treatment, LdT resulted in higher rate of sustained undetectable serum HBV DNA rates (55.6% vs 38.5%) and ALT normalization (69.5% vs 61.7%) compared to LAM. The HBeAg seroconversion rate was similar in two groups (29.6% vs 24.7%).[47] In HBeAg-negative patients, LdT showed a significantly higher rate of virologic response when compared to LAM. Undetectable serum HBV DNA levels at 1 year were observed in 88.3% of patients who received LdT, compared with 71.4% of patients treated with LAM. Results of histologic improvement and ALT normalization were similar in two groups: 66.6% vs 60.0% and 74.4% vs 79.3% after 1 year of LdT and LAM treatment, respectively.[46] After 2 years of treatment, LdT sustained a higher rate of undetectable serum HBV DNA (82.0% vs 56.7%) and similar ALT normalization rate (77.8% vs 70.1%) compared to LAM.[47] Non-detectable serum HBV DNA at treatment week 24 was the strongest predictor for better outcomes for both HBeAg-positive and HBeAg-negative patients.[48] In Korean patients, similar antiviral effectiveness of LdT was observed in a subgroup analysis of GLOBE phase III clinical trial.[49]

LdT selects for mutations in the YMDD motif. The rtM204I signature mutation was the primary basis for LdT resistance, with secondary mutations detected at the rtL80, rtL180, and other codons. The rtA181T mutation was detected in several LdT recipients but was not associated with viral breakthrough and it was replaced by wild type with continued LdT treatment in most patients.[47] In the phase III clinical trial, genotypic resistance after 1 and 2 years of treatment was observed in 5.0% and 25.1% of HBeAg-positive and in 2.3% and 10.8% of HBeAg-negative patients who received LdT, compared to 11.0% and 39.5% of HBeAg-positive and 10.7% and 25.9% of HBeAg-negative patients who received LAM, respectively.[46,47] *In vitro* studies have shown that HBV with the rtM204I mutation remains sensitive to the nucleotide analogues, ADV and TDF.[50] This is supported by the fact that switch or add-on ADV treatment reduced serum HBV DNA levels by 3.7 to 4.3 logs in 16 weeks, indicating that viral suppression can be restored by switch-to or add-on ADV.[47]

5. Tenofovir

Tenofovir disoproxil fumarate (TDF), an oral prodrug of tenofovir, is a nucleotide analogue with potent activity against HBV DNA polymerase. It is similar to ADV in structure and *in vitro*

studies have shown that TDF and ADV are equipotent. Since TDF appears to be less nephrotoxic, the approved dose is much higher than ADV; 300 mg vs 10 mg daily. The dose should be adjusted for patients with estimated creatinine clearance <50 mL/min (Table 3).

In HBeAg-positive patients, TDF 300 mg resulted in significantly higher rate of undetectable serum HBV DNA (76% vs 13%), ALT normalization (68% vs 54%), and HBsAg loss (3% vs 0%) compare to ADV 10 mg at 1 year. TDF showed similar rate of histologic response (74% vs 68%) and HBeAg seroconversion (21% vs 18%) compared to ADV.[51] After 3 years of TDF treatment, including some patients who received 1-year ADV treatment followed by 2-year TDF treatment, 72% of HBeAg-positive patients had undetectable serum HBV DNA levels. ALT normalization was seen in 81%, HBeAg loss occurred in 34% and HBeAg seroconversion was observed in 26% of patients. HBsAg loss over 3 years was 8%.[52] In HBeAg-negative patients, TDF resulted in higher rate of undetectable serum HBV DNA than ADV (93% vs 63%). Histologic improvement and ALT normalization were similarly observed in two groups (72% vs 69% and 76% vs 77%, respectively).[51] After 3 years of TDF treatment, including some patients who received 1 year of ADV treatment followed by 2 years of TDF treatment, 87% of HBeAg-negative patients had undetectable serum HBV DNA levels. ALT normalization was observed in 74% of patients. No patient achieved HBsAg loss up to 3 years.[52] In patients with decompensated liver disease, a phase II study showed tolerability failure was as infrequent as 6.7% in the TDF group, 4.4% in the TDF plus emtricitabine group, compared to 9.1% in ETV group (p=0.622). At week 48, serum HBV DNA <400 copies/mL was observed in 70.5% of the TDF group, 87.8% of the TDF plus emtricitabine group, and 72.7% of the ETV group. ALT normalization was observed in 57%, 76%, and 55% of patients and HBeAg seroconversion occurred in 21%, 13%, and 0% of patients, respectively. Child-Turcotte-Pugh and Modification for End-stage Liver Disease scores improved in all groups.[53] TDF monotherapy was found to induce potent and long lasting antiviral response in NUCs-experienced patients with previous treatment failure (LAM, ADV, LAM plus ADV).[54]

One study reported that alanine to threonine substitution at rtA194 was associated with resistance to TDF in patients with HBV and HIV co-infection.[55] A recent study has found that the rtA194T polymerase mutation is associated with partial TDF drug resistance and negatively impacts the replication competence of HBV constructs. However, viral replication can be restored to wild type levels if these polymerase mutations occur together with precore or basic core promoter substitutions, as found in HBeAg-negative hepatitis B.[56] A phase III clinical trial reported that none of the amino acid substitutions in HBV DNA polymerase/reverse transcriptase that developed through 3 years of treatment were associated with decreased phenotypic sensitivity to TDF.[57]

6. Clevudine

Clevudine [1-(2-deoxy-2-fluoro-b-Larabinofuranosyl) thyminine, L-FMAU] is a nucleoside analog with an unnatural β-L configuration and has shown potent effect against HBV and some activity against Epstein-Barr virus *in vitro*. Clevudine inhibits the DNA-dependent DNA activity of HBV polymerase, as well as reverse transcription and priming. Clevudine has no effect on mitochondrial DNA metabolism at concentrations ranging from 0.1 to 200 μM, as measured by lactic acid production, mitochondrial DNA content and structural effects.[57-59] The approved dose of clevudine is 30 mg daily orally.

In HBeAg-positive patients, 59.0% in the clevudine group had undetectable serum HBV DNA levels (less than 300 copies/mL) at week 24. The proportion of patients who achieved normalization of ALT levels was 68.2% in the clevudine group and 17.5% in the placebo group. HBeAg loss and seroconversion occurred in 15.3% and 10.0% of patients in the clevudine group at week 48. These rates were similar to those in the placebo group (12.0% and 12.0%, respectively).[60] Compared with LAM, clevudine demonstrated greater virologic, serologic, and biochemical responses. Median reduction in serum HBV DNA at week 48 was 4.27-5.2 $\log_{10}$copies/mL compared to 3.17-4.2 $\log_{10}$copies/mL in the LAM group. Undetectable serum HBV DNA was observed in 60-73% and 38-40% in the clevudine and LAM group, respectively. HBeAg seroconversion occurred in 11-18% of patients in the clevudine group compared with 11-12% in the LAM group at week 48.[61,62] In HBeAg-negative patients, 92.1% in the clevudine group had undetectable serum HBV DNA levels at week 24. The proportion of patients who achieved ALT normalization was 74.6% and 33.3% in clevudine and placebo groups at week 24, respectively.[63]

However, in contrast to published data on the safety profile of clevudine based on short-term clinical trials, several studies reported relatively frequent chances of developing myopathy in patients who received longer therapy with clevudine. A recent study reported the emergence of myopathy in 32 patients (8.8%) out of 363 chronic hepatitis B patients receiving clevudine therapy for more than 6 months.[64] Myopathy associated with clevudine is characterized by a weakness in proximal muscles of the lower extremities with elevated muscle enzymes, presumably caused by mitochondrial toxicities.[64]

Virologic breakthrough occurred in 0-5.5% up to 1 year treatment with clevudine.[60,63,65,66] *In vitro* phenotypic analysis showed that the mutation rtM204I was predominantly associated with clevudine resistance, whereas rtL229V was a compensatory mutation for the impaired replication of the rtM204I mutant. A study of 14 clevudine-resistant patients showed rtM204I in 85% of the patients, and rtA181V and rtA181T were each observed in 1 patient.[67] All of the clevudine-resistant clones were resistant to LAM .[66]

TREATMENT OF NAÏVE PATIENTS

Drugs with potent antiviral activity and a high genetic barrier (ETV or TDF) should be used for NUCs-naïve patients. The rate of partial response assessed at week 48 was 45% in HBeAg-positive naïve patients receiving ETV. However, 83% and 89% of HBeAg-positive patients achieved HBV DNA levels <300 copies/mL at week 96 and 144, showing long-lasting antiviral effect of ETV.[68]

LAM was widely prescribed for patients with chronic hepatitis B owing to its antiviral efficacy and safety profile. Nonetheless, since LAM induces high rate of resistance, it is not recommended as first-line therapy. Switching from LAM to ETV monotherapy may be considerable. A study about the efficacy of ETV monotherapy in LAM-pretreated patients showed that HBV DNA suppression (<2.6 $\log_{10}$copies/mL) was achieved in 100% and 92% of patients after 2 years of ETV switching therapy according to baseline HBV DNA levels (less than 2.6 and 2.6-5.0 $\log_{10}$copies/mL, respectively).[69] Thus, switching to ETV should be considered in LAM-pretreated patients. Switching to TDF may have similar effects in this setting of patients.

A favorable long- term response was found in some patients receiving LAM or LdT. A 5-year follow-up study showed that 90% of patients with two baseline factors (HBV DNA levels <9 $\log_{10}$copies/mL, ALT ≥2xULN) and with week 24 HBV DNA of <3 $\log_{10}$copies/mL achieved HBeAg seroconversion, and 10% of them had YMDD mutations.[70] The GLOBE trial showed that HBeAg-positive patients with baseline HBV DNA of <9 $\log_{10}$copies/mL, ALT ≥2xULN and non-detectable HBV DNA at 24 weeks of LdT therapy achieved HBeAg seroconversion in 52%, and LdT resistance in 1.8% at 2 years of therapy.[48] These results suggest that patients with non-detectable HBV DNA at 24 weeks of LAM or LdT therapy would have a good response to long term treatment with those drugs.

TREATMENT OF DRUG RESISTANT PATIENTS

In the past, LAM was widely used for the treatment of chronic hepatitis B patients, and resistance to LAM developed in many patients. The development of LAM resistance limits future treatment options. Sequential monotherapy with ADV or ETV for LAM resistance was associated with the frequent development of dual resistance to LAM and ADV or ETV. To avoid development of multi-drug resistance, add-on therapy has been recommended for anti-viral drug resistance. Drugs that are not cross-resistant should be used for add-on therapy. It was reported that virologic breakthrough developed in 8 of 80 (10%) NUCs-naïve and 12 of 27 (44%) LAM-pretreated patients after 12 months of clevudine therapy.[67] Thus, clevudine therapy should not be considered for LAM pretreated patients.

ADV add-on to ongoing LAM is the standard therapy for patients with LAM resistance. An Italian cohort study showed that none developed ADV resistance during a median of 40 months of treatment duration in patients with ADV added to LAM, whereas virologic breakthrough due to mutations developed in 21% of patients receiving ADV monotherapy.[71] Add-on therapy was found to be more efficacious in patients receiving early treatment with ADV than in patients receiving treatment later at the time of high viremia levels.[72]

ADV monotherapy is still used in some patients with LAM resistance because of the high cost of add-on therapy. In patients with LAM-resistant HBV, ADV monotherapy had been an established treatment modality for several years, but recent studies have reported that it carries a significant risk for resistance in the long term.[71,73] Virologic and biochemical breakthrough with the emergence of ADV-resistant mutations occurred in 21% of patient who received ADV monotherapy at 15 to 18 months of treatment.[71] Another study has reported that ADV resistance reached 6% at week 192 in patients with HBV DNA <3 $\log_{10}$copies/mL at week 48 of ADV monotherapy, compared with 49% at same time point in patients with HBV DNA >3 $\log_{10}$copies/mL at week 48 of ADV monotherapy. These were HBeAg-negative patients with LAM resistance.[30] Thus, continuation of ADV monotherapy may maintain undetectable HBV DNA levels in patients with a complete response to ADV monotherapy. However, LAM should be added to ongoing ADV therapy in patients with only a partial virologic response to ADV monotherapy. Later addition of LAM to ADV monotherapy was found to effectively prevent the development of ADV resistance in patients with LAM resistance, comparable to the ADV addition to ongoing LAM therapy.[74] LAM-resistant mutants remain susceptible to TDF, and TDF has a more effective anti-HBV effect than ADV. TDF add on therapy may be more effective in preventing the development of resistance than ADV add-on in LAM-resistant patients.

Sequential ADV monotherapy for LAM resistance increases the development of multi-drug resistance to LAM and ADV, and resistance to LAM and ADV occurs even in LAM-resistant patients receiving combination therapy with LAM and ADV. ADV-resistant mutants remain sensitive to TDF or ETV. Sequential TDF monotherapy was report to completely suppress HBV DNA only in a minority of patients with dual drug resistance to LAM and ADV.[75] Recently, a prospective study showing efficacy of TDF rescue therapy for patients with failure of both LAM and ADV has been reported. Forty-six percent and 64% of patients with failure of both LAM and ADV (suboptimal response or genotypic resistance) achieve an undetectable HBV DNA at 48 and 96 weeks of TDF therapy, suggesting that TDF is the preferred drug in patients with prior failure or resistance to LAM and ADV. However, antiviral activity of TDF was found to be inferior to that observed in naïve-patients and in previous studies.[76] Combination therapy with ETV and TDF has been recommended for the treatment of patients with resistance to LAM and ADV.[50] The efficacy of sequential ETV monotherapy was found to be

suboptimal in these patients.[77,78] ETV monotherapy selected YMDD mutants in all patients within 48 weeks of therapy, resulting in early development of ETV resistance.[77] The efficacy of combination therapy with LAM and ADV was compared with ETV monotherapy in these patients. Combination therapy with LAM and ADV was shown to be inferior to ETV monotherapy in suppressing HBV DNA.[79] However, drug resistance developed more frequently in patients receiving ETV monotherapy than patients receiving LAM plus ADV at 18 months of therapy.[80]

ETV-resistant mutations are susceptible to TDF and ADV. TDF add-on therapy is recommended for ETV resistance by EASL and AASLD guidelines. ADV add-on therapy should be considered in ETV-resistant patients. However, the efficacy of ADV add-on therapy may be limited in ETV-resistant patients.

CONCLUSIONS

The development of NUCs represents a significant advance in the treatment of chronic hepatitis B. Long-term treatment with NUCs has improved liver function and increased survival of patients. However, their major action is to suppress HBV replication, rather than eliminate HBV completely. The limitations are a higher chance of relapse after discontinuation of treatment and emergence of anti-viral resistance. Drugs with strong antiviral effect and a high genetic barrier to mutation, such as ETV and TDF, are recommended for the treatment of naïve-patients. The emergence of antiviral resistance limits treatment options. Add-on therapy with drugs without cross-resistance is a rule for drug resistance. Treatment options may be limited due to the unavailability and high cost of antiviral drugs. It is important that physicians make a judicious treatment plan based on individual properties of each antiviral drug and the host's immune status.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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