Side Effects of Long-Term Oral Antiviral Therapy for Hepatitis B

Robert J. Fontana

The aim of this review is to summarize the safety profile of the five approved oral nucleoside analogs used to treat chronic hepatitis B virus (HBV) infection, focusing on both the class adverse effects and those that have been reported with individual agents, as well as their safety in pregnancy. All nucleoside analogs have a "Black Box" warning because of their potential for inhibition of human DNA polymerase gamma involved in mitochondrial DNA replication. A reduction in intracellular mitochondrial DNA levels can lead to varying clinical manifestations of mitochondrial toxicity (i.e., neuropathy, myopathy, lactic acidosis), but these side effects are rarely reported with the oral antiviral agents active against HBV. Adefovir and tenofovir are associated with a dose-dependent but usually reversible proximal renal tubular toxicity. For these reasons, patients receiving these agents should be monitored for renal toxicity and the dose modified for renal insufficiency. Prolonged use of tenofovir has also been reported to lead to reduced bone mineral density in patients with human immunodeficiency virus infection, but prospective studies in patients with HBV infection are lacking. Telbivudine treatment is associated with moderate serum creatine phosphokinase elevations in up to 12% of patients. There have been few prospective studies on the safety of nucleoside analogs during pregnancy. According to the Antiretroviral Pregnancy Registry, the incidence of birth defects associated with lamivudine and tenofovir use during pregnancy is not increased. Studies on the safety of long-term therapy with the nucleoside analogs, alone and in combination, are needed as are further studies of children, the elderly, pregnant women, and patients with renal insufficiency. (HEPATOLOGY 2009;49: S185-S195.)

Introduction

Prolonged treatment with oral nucleoside analogs is recommended for selected patients with chronic hepatitis B virus (HBV) infection until disease remission and/or serological endpoints have been achieved.[1,2] In addition, indefinite treatment is suggested for patients with chronic HBV infection with advanced liver disease or in some instances with chronic immunosuppressive therapy. The generally favorable side-effect profiles of the five approved agents during registration trials coupled with the low rates of antiviral drug resistance with the newer agents make them attractive for use beyond 1 year. However, infrequent but serious adverse events such as myopathy, neuropathy, and pancreatitis as well as reversible renal impairment have been reported during postmarketing surveillance.[1,2] The aim of this article is to review the safety profile of the oral nucleoside analogs approved for the treatment of hepatitis B. In addition, use of these agents in adults of reproductive age and during pregnancy will be reviewed.

Abbreviations: ATP, adenosine triphosphate; CPK, creatine phosphokinase; FIAU, fialuridine; GFR, glomerular filtration rate; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HIV, human immunodeficiency virus; mtDNA, mitochondrial DNA.

From the Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor, MI.

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Address reprint requests to: Robert J. Fontana, M.D., Associate Professor of Medicine, University of Michigan Medical Center, 3912 Taubman Center, Ann Arbor, MI 48109-0362. E-mail: rfontana@med.umich.edu; fax: 734-936-7392.

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Class Effects of Nucleoside Analogs

All five of the approved oral antiviral agents for treatment of HBV are chemically modified analogs of naturally occurring nucleosides or nucleotides that pharmacologically inhibit the polymerase activity of HBV leading to reduced viral replication and decreases in serum HBV DNA levels. Fortunately, most of the oral agents are weak inhibitors of human nuclear DNA polymerase beta, which is responsible for human gene replication and repair. However,

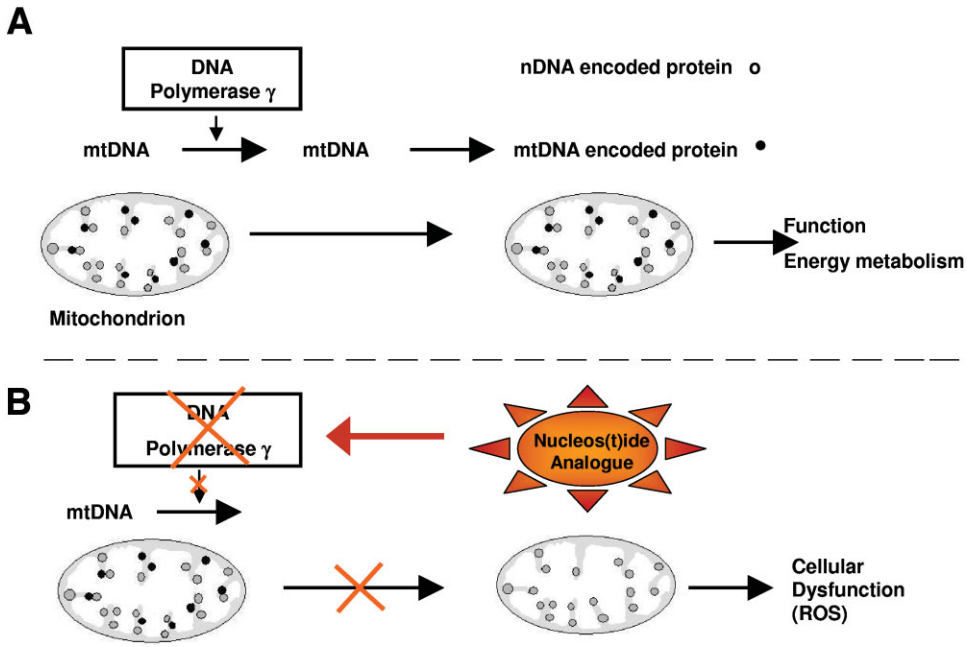

Fig. 1. Mechanism of mitochondrial toxicity associated with nucleoside analogs. (A) Proteins encoded by nuclear DNA (nDNA, ○) as well as those encoded by mitochondrial DNA (mtDNA, ●) are needed for mitochondria to carry out oxidative phosphorylation and energy metabolism. (B) When the intracellular concentration of a nucleoside analog exceeds a critical threshold, human mtDNA polymerase gamma activity can be inhibited. If mtDNA polymerase gamma activity is strongly inhibited or partially inhibited for prolonged periods of time, the level of intracellular mtDNA may decline due to impaired replication. This leads to mitochondrial dysfunction with impaired oxidative phosphorylation due to missing proteins involved in the respiratory chain and increased production of reactive oxygen species (ROS) that further damage intracellular proteins, lipids, and mtDNA eventually resulting in lactic acidosis and cell death.

some of these agents have a low level of activity against the human mitochondrial DNA (mtDNA) polymerase gamma and can lead to impaired mitochondrial replication with mitochondrial loss or dysfunction.

The main function of mitochondria in cells is to oxidize fatty acids and pyruvate to adenosine triphosphate (ATP). Under physiological circumstances, there is a tight coupling of oxidation and phosphorylation that is governed by mitochondrial enzymes such as cytochrome oxidases. Mitochondria also generate reactive oxygen species that can lead to oxidative stress if there is an imbalance between production and intracellular antioxidant defenses.[3,4] Inhibition of mtDNA polymerase gamma by nucleoside analogs can lead to depletion of intracellular mtDNA levels with resultant impairment of oxidative phosphorylation and cellular damage (Fig. 1). Clinical manifestations of mitochondrial toxicity vary based on the tissue affected but may include: myopathy, neuropathy, hepatic steatosis, pancreatitis, macrocytosis, hyperlactemia and lactic acidosis, and nephrotoxicity.[5] All nucleoside analogs have a "Black Box" warning regarding potential mitochondrial toxicity in their product labeling.

The most dramatic example of mitochondrial toxicity in patients treated for hepatitis B occurred with the now abandoned agent fialuridine (FIAU). Treatment with this nucleoside analog for more than 8-10 weeks led to a progressive clinical syndrome marked by lactic acidosis, hepatic steatosis, pancreatitis, neuropathy, myopathy, and irreversible liver failure.[6] Subsequent studies demonstrated that FIAU was efficiently and irreversibly incorporated into human mtDNA leading to mitochondrial failure.[7,8] Among the seven antiretroviral agents approved for treatment of human immunodeficiency virus (HIV) infection, the dideoxynucleosides appear to inhibit mtDNA polymerase gamma to the greatest extent both *in vitro* and *in vivo* and the relative activity of the antiretrovirals in mitochondrial toxicity is: zalcitabine (ddC) >> didanosine (ddI) > stavudine (d4T) > zidovudine >>>> tenofivir, lamivudine, emtricitabine, and abacavir.[9] In HIV-infected patients, the incidence of drug-related neuropathy has been correlated with the degree of mtDNA inhibition.[10]

Among the five nucleoside analogs approved for use in hepatitis B, the strength of inhibition of mtDNA polymerase gamma in an *in vitro* test system is substantially lower than that seen with zalcitabine and other antiretroviral agents[11,12] (Fig. 2). In particular, entecavir has demonstrated little evidence of mitochondrial toxicity compared to the other available agents at concentrations exceeding 100 times the maximum concentration seen in humans.[12] The impact of drug combinations in causing additive or synergistic mitochondrial toxicity *in vitro* has

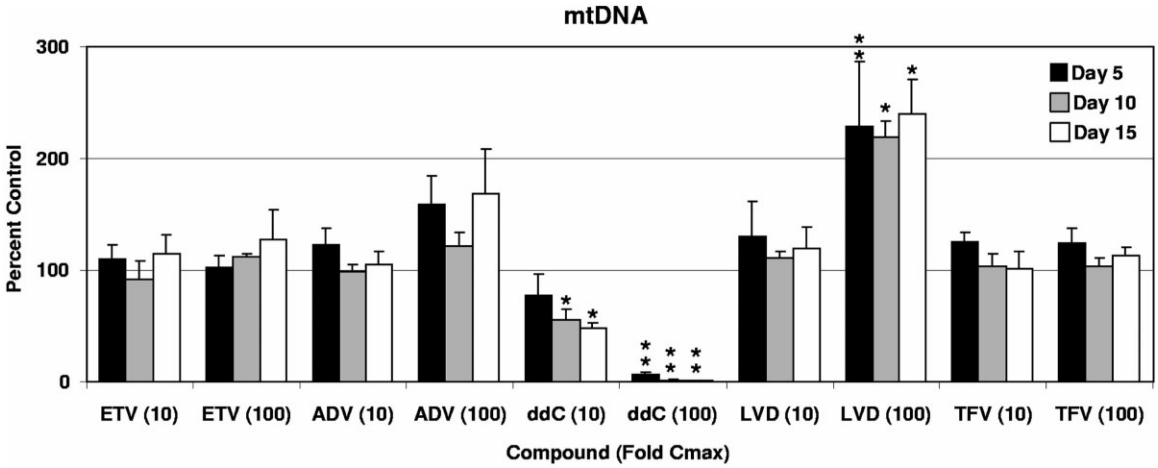

Fig. 2. Effect of supraphysiologic concentrations of nucleoside analogs on mtDNA levels. HepG2 cell cultures were exposed to 10-fold to 100-fold the maximum human concentration levels of the various antiviral agents. The levels of intracellular mtDNA and nuclear DNA were determined by real-time polymerase chain reaction and the ratios of mtDNA to nuclear DNA are presented after 5, 10, and 15 days of continuous exposure (*$P <$ 0.05, **$P <$ 0.001). Adapted from Mazzucco et al. with permission.[12] Abbreviations: ETV, entecavir; ADV, adefovir, ddC, dideoxycytidine; LVD, lamivudine; TFV, tenofovir.

not been well studied, and experience in patients with chronic hepatitis B without HIV infection is also largely unknown.[13] Furthermore, other host cofactors such as age, gender, genetics, medical comorbidities, and nutritional status may influence the risk and manifestations of mitochondrial toxicity as well as interindividual differences in the phosphorylation of nucleoside analogs.[14]

Nephrotoxicity

All of the oral antiviral agents for HBV are primarily excreted unchanged in the urine following ingestion (Table 1). As a result, either dose reductions or increased dosing intervals are recommended for patients with renal insufficiency. Adefovir dipivoxil and tenofovir disoproxil

Table 1. Approved Oral Antiviral Agents for HBV

	Lamivudine	Adefovir	Entecavir	Telbivudine	Tenofovir
Approval year	1998	2002	2005	2006	2008
Pediatric approval	2001 Age 2-17	2008 Age 12-17	No Age > 16	No Age ≥ 16	No Age ≥ 18
Clearance	Renal	Renal	Renal	Renal	Renal
Dose (mg/day) GFR > 50 mL/min	100 mg/day†	10 mg/day	0.5 mg/day*†	600 mg/day	300 mg/day
30–49 mL/min	50 mg/day	10 mg/day	0.25 mg/day or 0.50/every 2nd day	600 mg/every 2nd day	q 48 hours
10–29 mL/min	15–25 mg/day	10 mg/every 2nd day	0.15 mg/day or 0.50/every 3rd day	600 mg/every 3rd day	q 72–96 hrs
Dialysis	10 mg/day	10 mg/~week	0.05 mg/day or 0.50 mg/week	600 mg/week	weekly
Potential side effects		Nephrotoxicity at high doses	? Solid tumors in animal models		Nephrotoxicity in animal models
Side effects in licensing trials at 1 year	Similar to placebo	Similar to placebo	Similar to lamivudine	Grade 3/4 CPK 7% 1 year 12% 2 years	Similar to adefovir
Post-marketing Adverse events	Rare myopathy, neuropathy, pancreatitis	Nephrotoxicity in 3%-8% at 5 years	Negligible	Myopathy	Nephrotoxicity
Pregnancy category	C	C	C	B	B
Detection in human breast milk	Yes	Unknown	Unknown (Yes in rats)	Yes	Yes

*1.0 mg tablets of entecavir are approved for patients with lamivudine-resistant HBV.
†Oral elixir available. For lamivudine, use 15 mg/day if GFR is 5-14 mL/minute and 25 mg/day if GFR is 15-29 mL/minute.

fumarate are also associated with a dose-dependent renal toxicity in animal and human studies.[15] The clinical pattern of nephrotoxicity is characterized by slight rises in serum creatinine and decreases in serum phosphate levels occurring 4-12 months after starting these agents. The renal toxicity appears to be a proximal tubular injury and the clinical syndrome is a Fanconi-like renal tubular acidosis. The nephrotoxicity is usually reversible if therapy is stopped rapidly. If the agents are continued, frank renal insufficiency and troublesome renal tubular acidosis and hypophosphatemia can occur. When used in doses of 60-120 mg daily for treatment of HIV infection, adefovir was associated with some degree of nephrotoxicity in 22%-50% of patients.[16,17] In chronic hepatitis B, adefovir in doses of 30 mg/day was followed by development of milder degrees of nephrotoxicity in up to one-third of patients treated for more than 6 months.[18] The frequency of nephrotoxicity led to the evaluation and ultimate approval of lower doses of adefovir (10 mg daily). At this dose, adefovir has only rarely been associated with significant nephrotoxicity.

Nephrotoxicity appears to be less common with tenofovir than adefovir treatment, despite their similar molecular structure and the higher doses of tenofovir used (300 mg daily). In ongoing registration studies of tenofovir for chronic hepatitis B, renal toxicity has been rare. Nevertheless, instances of significant nephrotoxicity have been reported in patients with HIV who are treated for extended periods.[19-23] The incidence of nephrotoxicity, and particularly subclinical renal dysfunction, has not been adequately assessed during long-term tenofovir therapy.

The mechanism of nephrotoxicity associated with antiviral agents is not well understood but may involve alterations in renal tubular transporters, apoptosis, or mitochondrial toxicity.[24] The proximal renal tubule is most commonly affected presumably due to the high concentration of drug seen during glomerular filtration of these agents. In support of this, renal biopsies in patients with tenofovir nephrotoxicity demonstrated normal glomeruli but had marked proximal tubular damage with apoptosis of tubular epithelial cells.[24] Patients with isolated proximal renal tubular dysfunction may develop a Fanconi-like syndrome characterized by metabolic acidosis, hypophosphatemia, and glycosuria. Less common patterns of kidney injury include nephrogenic diabetes insipidus.[21] In addition, acute tubular necrosis with resultant acute renal failure may be seen with antiviral nephrotoxicity, particularly in patients with pre-existing renal insufficiency or those exposed to other nephrotoxic agents.

Overall, it appears that tenofovir is less nephrotoxic than adefovir in humans, but awareness and monitoring for this side effect in patients infected with HBV is needed. To minimize the risk of nephrotoxicity as well as other side effects with any of the oral nucleoside analogs, the dose or dosing interval should be modified in patients with HBV with renal insufficiency. Second, all patients infected with HBV with renal insufficiency receiving a modified dosing regimen of an oral antiviral agent should have regular monitoring of serum creatinine, phosphate, and urinalysis samples throughout treatment (every 2-3 months if mild impairment; monthly if moderate or severe impairment). Third, use of other nephrotoxic drugs should be avoided if possible and adequate hydration maintained. Finally, patients on long-term adefovir or tenofovir therapy should have regular monitoring of serum creatinine and phosphate levels and dose modifications carried out if creatinine levels rise by more than 0.5 mg/dL above baseline values or if serum phosphate levels fall below 2.0 mg/dL.

Lamivudine

Lamivudine at a dose of 100 mg/day was the first oral nucleoside analog approved for the treatment of chronic hepatitis B (approved in 1998; Table 1). Lamivudine has been the most widely used oral antiviral agent for HBV infection worldwide with an estimated 1.4 million patient-years of use as of 2008. Lamivudine was also approved for use in children ages 2-17 in 2001.[25,26] In the 1-year registration trials, lamivudine was generally well-tolerated and had a side effect profile similar to placebo.[27] The primary adverse event reported with prolonged lamivudine treatment over 4-5 years has been a liver disease flare of varying severity following the emergence of lamivudine-resistant HBV.[28,29] In addition, patients with chronic HBV infection can experience a potentially severe disease flare with discontinuation of lamivudine or any of the oral antiviral agents. Because the incidence of lamivudine-resistant HBV increases over time (i.e., 70% after 5 years), lamivudine is considered a second-line therapy for treatment-naïve patients.[1,2]

Over the years, rare reports of reversible myopathy, neuropathy, pancreatitis, and Fanconi syndrome have been reported with lamivudine treatment in patients with HBV and HIV coinfection.[30-34] In addition, patients with HIV infection receiving higher daily doses of lamivudine may develop lipoatrophy and asymptomatic macrocytosis.[35] Most of these complications have occurred in patients receiving multiple antiretroviral agents, and the specific role of lamivudine in causing these side effects is unclear. Lamivudine has been effective and well-tolerated in patients with decompensated cirrhosis due to HBV, solid-organ transplant recipients, and patients with cancer who are receiving chemotherapy.[36,37] However, the effi-

cacy and safety of reduced dosed lamivudine in patients with chronic hepatitis B and renal insufficiency is less well-established.

Adefovir Dipivoxil

Adefovir is an oral nucleotide analog which was approved for the treatment of chronic hepatitis B at a dose of 10 mg/day in 2002. Worldwide, there have been an estimated 410,000 patient-years of adefovir use through 2008 (Table 1). Adefovir was also approved in 2008 for use in children ages 12-17. Adefovir was initially developed as an antiretroviral agent for HIV but was abandoned due to the high rate of nephrotoxicity with higher doses.[16] In the 1-year registration trials for HBV infection, the frequency of grade I nephrotoxicity (i.e., serum creatinine $\geq$ 0.5 mg/dL above baseline values) was similar in adefovir-treated and placebo-treated patients (0% versus 0%).[38,39] However, in a cohort of 125 patients with chronic hepatitis B e antigen (HBeAg)-negative hepatitis B treated with adefovir for 5 years, the frequency of serum creatinine elevations that were 0.5 mg/dL above baseline was 3%.[40] Similarly, 8% of the 65 patients who were HBeAg-positive and receiving adefovir for 5 years had reversible creatinine elevations, 5% had albuminuria, and 3% developed hypophosphatemia.[41] In a large open-label study of adefovir in 226 liver transplant candidates with chronic hepatitis B and 241 recipients with lamivudine-resistant HBV, the frequency of nephrotoxicity was 6% and 21% after an average treatment duration of 39 and 99 weeks, respectively.[42] However, it was difficult to definitely attribute the creatinine elevations to adefovir therapy because these patients had severe underlying liver disease and were frequently receiving other nephrotoxic drugs.

Other potential adverse effects associated with prolonged adefovir therapy include the emergence of adefovir-resistant strains of HBV which can occur in 28% of treated patients after 5 years and lead to liver disease flares.[40,41] To minimize the risk of suboptimal response to adefovir in patients with lamivudine-resistant HBV, the manufacturer suggests that lamivudine be continued after adding on adefovir in this patient population (adefovir package insert). Adefovir should be used with caution in patients with HIV-HBV coinfection because HIV resistance may arise with an inadequate antiretroviral regimen.[16]

The mechanism of adefovir nephrotoxicity may involve alterations in multidrug resistance protein 4 expression and/or depletion of mtDNA from renal tubular epithelium.[43,44] Most patients experience mild reversible increases in serum creatinine levels without associated hypophosphatemia that improve with increasing the dosing interval or spontaneously resolve with continued dosing.[18] In one pilot study of 12 patients with lamivudine-resistant HBV and renal insufficiency, adefovir given at extended dosing intervals for a median of 15 months was effective but phosphate supplementation was required in some patients.[45]

Adefovir in Combination Regimens

There are a growing number of studies of adefovir and lamivudine combination therapy in both treatment-naïve and treatment-experienced patients with lamivudine-resistant HBV. In one study of 145 patients with lamivudine resistance, 8% of patients developed mild nephrotoxicity, but all were able to continue combination therapy after increasing the adefovir-dosing interval.[46] In another randomized controlled trial of lamivudine versus lamivudine plus adefovir in 115 treatment-naïve patients with chronic HBeAg-positive hepatitis, none of the patients receiving combination therapy developed nephrotoxicity.[47] In contrast, during a median follow-up of 32 months in 271 lamivudine-resistant patients treated with adefovir and lamivudine, 11% experienced nephrotoxicity leading to increased dosing intervals and 11% also developed de novo hypertension.[48] Adefovir has also been administered with emtricitabine for 2 years in 30 HBeAg-positive patients with improved antiviral efficacy and a similar safety profile to adefovir alone.[49] Finally, adefovir was given in combination with pegylated interferon α-2b in a pilot study of 26 patients with chronic hepatitis B with no evidence of nephrotoxicity but the duration of treatment was limited to 1 year.[50]

Entecavir

Entecavir is an oral nucleoside analog approved in 2005 at a dose of 0.5 mg/day for treatment-naïve patients and 1.0 mg/day for patients with lamivudine-resistant HBV (Table 1).[51,52] During preclinical development, prolonged administration of high-dose entecavir was associated with a higher incidence of solid tumors in animals compared to placebo. As a result, there is an ongoing study of clinical outcomes in more than 12,000 patients with chronic hepatitis B receiving long-term entecavir treatment versus other antiviral agents. However, there has been no evidence of an increased incidence of malignancy during 125,000 patient-years of worldwide entecavir use through 2008.

In the 1-year registration trials, the frequency and severity of clinical and laboratory adverse events were similar among entecavir-treated and lamivudine-treated patients.[51,21] In addition, there has been no evidence of mitochondrial or other serious adverse events in patients

treated with entecavir for up to 5 years.[53,54] In cell culture, entecavir demonstrated no evidence of mitochondrial toxicity and did not increase the likelihood of mitochondrial toxicity when combined with lamivudine, adefovir, or tenofovir.[12] However, patients with lamivudine-resistant HBV had an increasing risk of developing entecavir-resistant HBV during prolonged treatment (up to 37% at 4 years) which was occasionally associated with liver disease flares.[55,56] The safety and efficacy of entecavir combined with tenofovir is under evaluation, but small pilot studies appear promising.[57] A reduced dose of entecavir elixir or an increased dosing interval is recommended for patients with renal insufficiency (Table 1). However, the efficacy and safety of entecavir in patients with decompensated cirrhosis, transplant recipients, children, and patients with renal insufficiency is not well-described.[58] Entecavir should not be used in patients with HIV-HBV coinfection due to concerns of possible HIV-resistance.[59]

Telbivudine

Telbivudine is a potent oral nucleoside analog recently approved for treatment of chronic hepatitis B in 2006 at a dose of 600 mg/day. During the large, multinational registration trials, the side-effect profile of telbivudine was similar to lamivudine throughout the 2 years of treatment.[60,61] However, a significantly higher incidence of grade 3 to 4 serum creatine phosphokinase (CPK) elevations (i.e., $>$ 7 times upper limit of normal) was noted in telbivudine-treated compared to lamivudine-treated patients at 2 years (12.9% versus 4.1%).[60,61] In addition, two telbivudine-treated patients developed symptomatic myopathy that resolved with drug discontinuation. To date, there have been no published reports of lactic acidosis or neuropathy with telbivudine monotherapy. However, there are preliminary reports of moderately severe peripheral neuropathy in 17% of patients treated with the combination of telbivudine and peginterferon alfa-2a.[62] For this reason, telbivudine should not be used in combination with peginterferon at this time.

A 1-year pilot study of telbivudine combined with lamivudine demonstrated reduced antiviral efficacy compared to telbivudine alone but no evidence of increased toxicity.[63] There are several ongoing pilot studies exploring the safety and efficacy of telbivudine in combination with the nucleotide analogs adefovir and tenofovir. The safety and efficacy of telbivudine in patients with decompensated cirrhosis, transplant recipients, children, and renal insufficiency have not been adequately evaluated. In addition to extending the dosing interval in patients with renal insufficiency, all telbivudine-treated patients should be monitored for musculoskeletal symptoms. Serum creatinine and CPK levels should be tested before therapy and again at 3-month to 6-month intervals during treatment or if musculoskeletal symptoms develop.

Tenofovir

Tenofovir is an oral nucleotide analog approved for use in chronic hepatitis B in August 2008 at a dose of 300 mg/day.[64,65] Since its approval for HIV infection in 2001, there have been an estimated 1.7 million patient-years of tenofovir use, and tenofovir is currently a key component of most antiretroviral regimens in treatment-naïve patients with HIV infection. In the registration trials of tenofovir for HBV, the side-effect profile of tenofovir was generally favorable and similar to the comparator arm of adefovir. The frequency of serum creatinine elevations at 1 year was 0% in the tenofovir-treated and 0.4% adefovir-treated patients. In addition, phenotypic and genotypic HBV resistance to tenofovir has yet to be clearly described.[66] Tenofovir is also active against lamivudine-resistant HBV strains, both *in vitro* and *in vivo*.[67-69]

In the macaque simian immunodeficiency virus animal model, prolonged use of tenofovir led to a dose-dependent renal tubular toxicity.[15] In patients with HIV infection treated with tenofovir, the rate of adverse side effects was similar to that which occurred with other drugs combined with lamivudine after 3 years of continuous use.[70,71] Nephrotoxicity developed in 4% of HIV-infected patients, but most were able to continue tenofovir therapy at reduced doses. A total of 4% of patients developed hypophosphatemia, but few required phosphorous supplementation. Nevertheless, concerns regarding the potential nephrotoxicity of long-term tenofovir therapy remain with multiple cases of a Fanconi-like syndrome, nephrogenic diabetes insipidus, and even rare instances of acute renal failure having been reported in patients infected with HIV.[19-23] Although severe or symptomatic nephrotoxicity in patients with chronic hepatitis B treated with tenofovir has not been reported, the number of patients treated for more than 1-2 years is limited.

In clinical practice, it is appropriate to monitor serum creatinine and phosphate levels and urinalysis every 3 months during treatment with tenofovir particularly in patients with pre-existing or a predisposition to renal impairment.[72] Most instances of nephrotoxicity associated with tenofovir were reversible with early discontinuation. Recently, cases of reduced bone density as well as osteomalacia have been reported in patients with HIV infection receiving long-term tenofovir therapy.[73] However, reductions in bone mineral density during the first 48 weeks of treatment were nonprogressive and not associated with symptoms.[74,75] Regular bone density measurements and use of calcium with vitamin D is recommended in HIV-infected patients receiving pro-

Table 2. Antiviral Agents in Pregnant HBV Patients

Series	HBV DNA (copies/mL)	Antiviral Regimen	N (treated)/ N (untreated)	% HBsAg + Infants at 1 Year*
Retrospective series				
Rotterdam[84]	$> 1.2 \times 10^9$	Lamivudine 150 mg weeks 34 to 38	8	12.5%
			25 (historical controls)	28%
China[85]	NA	Lamivudine 100 mg week 0 to delivery	38 treated	0%
Prospective series				
China[86]	$> 1 \times 10^9$	Lamivudine 100 mg week 32 to 4 weeks postpartum	56 treated	18%
			52 placebo controls	39%

*All received peripartum HBIG and HBV vaccine except for some in prospective study.

longed tenofovir and the risk versus benefit of tenofovir treatment on bone metabolism in children should be considered.[76,77] Other side effects of tenofovir in patients infected with HIV have included fat redistribution but not frank lipoatrophy. To date, there is limited experience with tenofovir in patients with hepatitis B and decompensated cirrhosis, transplant recipients, children, and the elderly.[78] However, tenofovir has been effective in patients with HIV-HBV coinfection and associated with a low rate of renal impairment.[79,80]

Pregnancy

Vertical transmission of HBV from a viremic mother to their infant is a well-established means of disease transmission. Prior studies of postpartum hepatitis B immunoglobulin along with HBV vaccination of the infant have demonstrated a dramatic reduction in HBV transmission compared to untreated controls.[81] However, identified risk factors for transmission include poor compliance with the prophylaxis regimen and high serum levels of maternal HBV DNA during the third trimester of pregnancy.[82] Retrospective studies have suggested that lamivudine can be safely administered during the third trimester of pregnancy in highly selected hepatitis B surface antigen (HBsAg)-positive mothers with high HBV DNA levels in an attempt to reduce the risk of transmission[83-85] (Table 2). In one randomized controlled trial, the frequency of HBV transmission at 1 year from 56 lamivudine-treated mothers with high HBV DNA levels was 18% compared to 39% from the 52 untreated mothers, but compliance with hepatitis B immunoglobulin administration and vaccination was poor in both study arms.[86] Therefore, administration of antiviral agents in the third trimester of pregnancy cannot be recommended currently due to the potential untoward risk of these agents to the fetus coupled with their uncertain benefit and generally excellent outcomes with standard postpartum immunoprophylaxis.

All of the approved drugs for HBV have prominent warnings regarding the potential risk of adverse fetal outcomes with use immediately before and during pregnancy. As a result, it is recommended that men and women of child-bearing age receiving an oral nucleoside analog use contraception or practice abstinence. Of the five oral agents, telbivudine and tenofovir are Category B (i.e., not a known teratogen or embryotoxic in animals but inadequate human studies) whereas the other three drugs are all Category C (embryotoxic or teratogenic in animals but inadequate human studies). Therefore, avoidance of this medication class during the first trimester of pregnancy when organogenesis is occurring is advisable based on current evidence. Nonetheless, some women with HBV infection have conceived while taking nucleoside analogs and questions then arise regarding the risk of adverse fetal and maternal outcomes with continuing or stopping the agents.

In pregnant patients infected with HBV, there are no prospective studies comparing the efficacy or safety of any single antiviral agent to another. In general, it is advisable to use a Category B over a Category C drug during the first trimester whenever possible. However, the risk of switching a patient with a drug-resistant strain of HBV to an agent which may not be as effective must be weighed against the potential benefit to the fetus. Following delivery, the need for continued antiviral treatment in the mother also needs to be reassessed. Finally, most specialists suggest avoiding breast feeding if the mother remains on an oral nucleoside during the first year of life, but consultation with a qualified expert is recommended.

The Antiretroviral Pregnancy Registry

The Antiretroviral Pregnancy Registry has been tracking spontaneously reported maternal and fetal outcomes in women receiving oral nucleoside drugs since 1989. As of January 31, 2008, 9889 pregnancies wherein the mother had received an oral nucleoside analog were reported.[87] To date, 94.5% of the enrolled women had HIV infection and only 0.6%[61] were infected with HBV alone. The overall prevalence of birth defects in infants exposed to any antiretroviral agent during the first trimester of 3.0

per 100 live births (117 of 3951) or any trimester 2.8 per 100 live births (261 of 9400) was not significantly different from that reported in the general U.S. population of 2.72 per 100 live births. In addition, only infants exposed to didanosine had a significantly higher rate of birth defects than expected. The prevalence of birth defects with lamivudine exposure in the first trimester of 3.1% (85 of 2784) and with tenofovir of 2.2% (11 of 491) were similar to population controls. However, there are inadequate data regarding the risk of birth defects in the small number of pregnancies associated with entecavir, adefovir, and telbivudine use (5, 36, and 1, respectively).

There has been no overall increased risk of birth defects with lamivudine use in the first trimester of pregnant patients infected with HIV compared to the general population.[88] Therefore, lamivudine combined with zidovudine or other antiretrovirals is frequently recommended for pregnant HIV-infected women to reduce the risk of perinatal transmission from 25% to 2%.[89] However, due to reports of lactic acidosis and hepatic steatosis, liver biochemistries and electrolytes should be monitored monthly in all pregnant women receiving any nucleoside analog.[90] In addition, referral of HBV-infected patients to a high-risk obstetrical specialist is recommended for those patients contemplating or already having become pregnant and receiving or needing oral nucleoside analog therapy. Follow-up of all offspring exposed *in utero* to nucleoside analogs is also recommended.[91,92]

Needs for Future Research

It is anticipated that future studies will include prolonged use of the oral nucleoside analogs either alone or in combination in patients infected with HBV who are at risk for disease progression. Safety issues to address in future studies include:

What Is the Safety Profile of the Nucleoside Analogs when Given Alone or in Combination for Prolonged Periods of Time in Patients with Chronic Hepatitis B? Testing of drug combinations at pharmacologic as well as supratherapeutic doses in *in vitro* models, cell cultures, and animal models is needed to help identify potential safety concerns. In humans, short-term pharmacokinetic and pharmacodynamic studies of combination therapy are needed to determine if they provide incremental efficacy (i.e., rate of viral suppression), reduced likelihood of drug resistance, and potential drug-drug interactions. In addition, large, long-term prospective studies of HBV-infected patients with clinical, histological, and virological endpoints will be needed. During these studies, a minimum of every 2-3 months, study visits for assessment of adverse events and compliance are needed. In addition, prospective surveillance for mitochondrial toxicity and nephrotoxicity may be warranted when using some drugs alone or in combination. For example, serial assessment of serum CPK, creatinine, lipase, phosphate, and lactate levels as well as urinalysis is advisable with any combination therapy. In addition, assessment of bone mineral density and bone metabolite parameters in subjects receiving prolonged tenofovir would be prudent. Finally, collection of a baseline DNA sample and biological samples throughout the study would facilitate future mechanistic studies of adverse events.

What Is the Safety and Efficacy of the Nucleoside Analogs in HBV-Infected Patients with Renal Insufficiency? The safety and efficacy of the oral agents alone or in combination in patients with chronic hepatitis B and renal insufficiency or renal failure are largely unknown. Therefore, patients with chronic HBV infection and renal insufficiency should be treated with a single agent or combination regimen and prospectively assessed for efficacy, drug resistance, and safety. Collection of a baseline DNA sample and other biological samples during treatment is advisable. Additional studies using prophylactic phosphate supplementation or other agents to minimize nephrotoxicity may prove worthwhile in renally impaired patients.

What Are the Risk and Benefits of Nucleoside Analogs in Pregnant Patients with Chronic Hepatitis B, their Offspring, and Other High-Risk Patient Populations? Expansion of the existing Antiretroviral Pregnancy Registry to include more detail regarding the clinical, virological, and treatment characteristics of the mothers and their offspring through 1 year of follow-up would be worthwhile. If the voluntary registry will not be able to accrue sufficient incremental data, a prospective, multicenter, open-label protocol could be established to collect efficacy and safety data in mothers with HBV infection and their offspring. Finally, prospective studies of pediatric patients, the elderly, and decompensated patients with chronic hepatitis B are needed to better define the most effective and safe treatment regimen in these under-studied patient populations.

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