Benefits and Risks of Nucleoside Analog Therapy for Hepatitis B

Jules L. Dienstag

Five oral agents have been approved for the treatment of chronic hepatitis B, ranging in virological potency, clinical efficacy, barrier to resistance, and side-effect profile. The degree of histological, biochemical, and serological improvement with therapy generally corresponds to the degree of suppression of serum hepatitis B virus (HBV) DNA achieved with therapy. Conversely, for agents with a low barrier to resistance, the profundity of HBV DNA suppression in individual patients correlates inversely with the likelihood of resistance. The durability of hepatitis B e antigen (HBeAg) responses after a consolidation period of an additional 6-12 months of therapy is ~80% in western populations, lower in Asian populations. Loss of hepatitis B surface antigen (HBsAg) during a year of oral-agent therapy is limited, except with the most potent agents, but extending therapy for a second year and beyond can yield frequencies of HBsAg responses close to those reported in trials of interferon-based therapy. The oral agents are approved for 1-2 years of therapy, but treatment is continued indefinitely in the majority of patients (except for the ~20% of patients who are HBeAg-reactive who achieve a durable HBeAg response). HBeAg responses and virological/biochemical benefit continue to be maintained and to increase with continued therapy beyond the first year. Data continue to accumulate supporting the link between long-term HBV DNA suppression and reduction in hepatic fibrosis, hepatic decompensation, and liver-related mortality. All the benefits of a single year of injectable peginterferon therapy can be achieved with the newer, low-resistance oral agents continued beyond the first year, without interferon side effects. Future studies are needed to develop drug regimens that are even more effective in achieving clinical endpoints, that are not hampered by resistance, and that are more confined in treatment duration but are more durable. (Hepatology 2009;49: S112-S121.)

Introduction

Oral nucleoside and nucleotide analogs have revolutionized the management of chronic hepatitis B. Five such antiviral agents have been approved, ranging in profundity and rapidity of hepatitis B virus DNA (HBV DNA) suppression, in barrier to resistance, and in side-effect profile. In registration trials, among nucleoside-treatment-naïve patients treated for a year with oral agents, the level of HBV DNA suppression correlated with the degree of histological, biochemical, and serological improvement with therapy generally corresponds to the degree of suppression of serum hepatitis B virus (HBV) DNA achieved with therapy. Conversely, for agents with a low barrier to resistance, the profundity of HBV DNA suppression in individual patients correlates inversely with the likelihood of resistance. The durability of hepatitis B e antigen (HBeAg) responses after a consolidation period of an additional 6-12 months of therapy is ~80% in western populations, lower in Asian populations. Loss of hepatitis B surface antigen (HBsAg) during a year of oral-agent therapy is limited, except with the most potent agents, but extending therapy for a second year and beyond can yield frequencies of HBsAg responses close to those reported in trials of interferon-based therapy. The oral agents are approved for 1-2 years of therapy, but treatment is continued indefinitely in the majority of patients (except for the ~20% of patients who are HBeAg-reactive who achieve a durable HBeAg response). HBeAg responses and virological/biochemical benefit continue to be maintained and to increase with continued therapy beyond the first year. Data continue to accumulate supporting the link between long-term HBV DNA suppression and reduction in hepatic fibrosis, hepatic decompensation, and liver-related mortality. All the benefits of a single year of injectable peginterferon therapy can be achieved with the newer, low-resistance oral agents continued beyond the first year, without interferon side effects. Future studies are needed to develop drug regimens that are even more effective in achieving clinical endpoints, that are not hampered by resistance, and that are more confined in treatment duration but are more durable. (Hepatology 2009;49: S112-S121.)

Abbreviations: ALT, alanine aminotransferase; anti-HBe, antibody to HBeAg; cccDNA, covalently closed circular DNA; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HIV, human immunodeficiency virus.

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of histological and biochemical improvement and the proportion of treated patients in whom HBV DNA can be suppressed to below an undetectable threshold; however, hepatitis B e antigen (HBeAg) loss or seroconversion to antibody to HBeAg (anti-HBe) is relatively uniform (~20%) in these trial cohorts over a range of average HBV DNA suppression from 4 to 7 log10 IU/mL. On the other hand, when trial subjects are stratified according to relative suppression of HBV DNA, those with the most profound suppression and lowest residual HBV DNA experienced a substantially higher frequency of HBeAg loss or seroconversion than those whose HBV DNA was not suppressed as well.7,9

Durability of HBeAg seroconversion after a consolidation period of 6-12 months (~80% in western patients, lower in Asian patients) is also uniform across oral agents over a range of HBV DNA suppression from 4 to 7 log10 IU/mL.10-12 Loss of hepatitis B surface antigen (HBsAg) during a year of oral-agent therapy is limited, except with the most potent agents, but extending therapy for a second year and beyond can yield frequencies of HBsAg responses close to those reported in trials of interferon-based therapy.8,13 Although the oral agents are approved for 1-2 years of therapy, treatment is continued indefinitely in the majority of patients (except for the ~20% of patients who are HBeAg-reactive who achieve a durable HBeAg response). Data continue to accumulate supporting the link between profound, durable HBV DNA suppression and retardation, and even reversal, of both hepatic fibrosis and hepatic decompensation.14-17

**Nucleoside Analogs**

In registration trials for the oral antiviral nucleoside analogs, clinical endpoints were measured at 1 year (48 or 52 weeks); lamivudine and adefovir dipivoxil were compared to placebo,1-4,18 whereas the other approved agents were compared to an active agent—entecavir and telbivudine against lamivudine5-7 and tenofovir disoproxil fumarate against adefovir.8 For the year of observation against placebo, the oral agents were statistically superior, improving serological, virological, biochemical, and histological endpoints. For the first agents to be approved, lamivudine and adefovir, histological improvement at 1 year was the primary clinical endpoint used in the registration trials, which was achieved in more than half of treated subjects, compared to approximately a quarter of placebo recipients. Furthermore, antiviral therapy retarded progression of fibrosis. In the registration trials for entecavir, tenbuvudine, and tenofovir, these agents were superior to the active comparator (lamivudine, adefovir) in virological, biochemical, and histological, but not serological, endpoints. The rates of achieving these endpoints during therapy with these five oral agents and, for comparison, peginterferon are shown in Fig. 1A-D.

Treatment with these oral agents (see details below) has been shown to be life-saving. Such therapy can not only retard the progression of fibrosis and reverse both fibrosis and cirrhosis,2-4,14-19-21 but also salvage patients with decompensated chronic hepatitis B,15,17,22 and prevent hepatic decompensation in patients with advanced fibrosis and cirrhosis.16 Since the adoption of widespread nucleoside analog therapy at the beginning of this decade, the number of patients per year registered in the United States as candidates for liver transplantation has fallen by a third.23 In addition, in a model of the simulated impact of long-term nucleoside therapy with a low-resistance agent on the 20-year progression of viremic (HBV DNA >10^5 copies/mL) chronic hepatitis B, treatment is predicted to reduce liver-disease mortality by 80% in patients both without (from 17% to 2%) and with (from 77% to 26%) cirrhosis.24

**Lamivudine**

Lamivudine or 3-thiocytidine is an L-nucleoside analog that interferes with HBV DNA polymerase activity by chain termination and was the first oral agent licensed for treatment of hepatitis B. At a daily dose of 100 mg, lamivudine treatment for 52 weeks results in suppression of HBV DNA by an average of 5.5 log_{10} copies/mL in HBeAg-positive and 4.7 log_{10} copies/mL in HBeAg-negative patients. Treatment results in a 1-year HBeAg seroconversion rate of approximately 20%, renders HBV DNA undetectable (<10^3 copies/mL) in 36%-44% (HBeAg-positive) to 60%-73% (HBeAg-negative) of patients, and improves hepatic histology in 50%-65% of patients.1-5,7,18 Lamivudine is as well tolerated as placebo but is associated, as are other antivirals, with instances of marked alanine aminotransferase (ALT) elevations during therapy and after discontinuation of therapy. Although lamivudine has the most extensive safety record, its current use is limited by the high frequency of lamivudine resistance (up to 50% in year 1 and up to 70% by the end of 5 years)25 and the availability of more potent agents with superior efficacy and markedly improved resistance profiles.

With increasing duration of lamivudine therapy, the frequency of HBsAg serological responses continues to increase,26-28 reaching ~50% at 5 years. Lamivudine therapy has been shown in clinical trials to retard the progression of fibrosis, reduce progression to and reverse cirrhosis, salvage and stabilize patients with hepatic decompensation (delaying or averting liver transplantation), and, in patients with advanced fibrosis and cirrhosis, to prevent hepatic decompensation.2,14-17 During therapy, HBsAg seroconversion is rare; however, after successful HBeAg seroconversion and cessation of therapy in western (not Asian) patients, lamivudine-
treated patients can experience HBsAg seroconversion rates (~20% at 3 years in one small study) similar to those achieved after interferon therapy.\textsuperscript{11}

The emergence of lamivudine-resistant mutant HBV, however, limits lamivudine’s clinical impact.\textsuperscript{14,16} Such resistance occurs in 15%-30% of patients treated for 1 year.

Fig. 1. Comparisons of the virological, biochemical, histological, and serological endpoints achieved during 1 year (48-52 weeks) of antiviral therapy in patients with HBeAg-positive and HBeAg-negative chronic hepatitis B. These data were derived from individual reports of registration trials and, therefore, do not represent direct comparisons; the trials summarized were conducted at different times, in different populations, and with different HBV DNA assays (A) Median log\textsubscript{10} HBV DNA reduction. (B) Percent of patients with suppression of HBV DNA to undetectable levels (<300-400 copies/mL, except for adefovir, <1000 copies/mL). (C) Percent of patients with normalization of alanine aminotransferase activity (biochemical response). (D) Percent of patients with a histological response, defined as a ≥ 2-point improvement in the histology activity index (HAI). All patients in these trials underwent liver biopsy prior to or at baseline and at the end of a year of therapy; peginterferon-treated subjects underwent liver biopsy 24 weeks after completing therapy (week 72). (E) Percent of patients with HBeAg-positive chronic hepatitis B who achieved an HBeAg seroconversion and who experienced HBsAg loss (serological responses). ADV, adefovir dipivoxil; ALT, alanine aminotransferase; CLV, clevudine; ETV, entecavir; HAI, histology activity index; LVM, lamivudine; PEG, peginterferon; TBV, telbivudine; TDF, tenofovir disoproxil fumarate.
and in up to 70% of patients treated for 5 years. Although patients with lamivudine-resistant HBV may continue to demonstrate clinical benefit initially, ultimately compensatory mutations emerge that result in a loss of effectiveness, which can be especially devastating for patients with advanced liver disease and among immunosuppressed patients after liver transplantation who may experience hepatic decompensation. As is true for the other oral agents, lamivudine is as effective in prior interferon non-responders as in treatment-naïve patients.

**Adefovir**

Adefovir, an acyclic phosphonate nucleotide analog that inhibits DNA polymerase by chain termination, was the second oral drug approved for the treatment of hepatitis B. Adefovir is less potent than lamivudine and the other more recently introduced oral agents. In 48-week registration trials, adefovir suppressed HBV DNA by 3.5-4 log10; lowered HBV DNA to undetectable (<10^2 copies/mL) in only 13%-21% (HBeAg-positive) to ~50%-65% (HBeAg-negative) patients; suppressed HBV DNA relatively slowly; and was less likely to induce a 1-year (48-week) HBeAg seroconversion (12%). The advantages of adefovir are its limited resistance during years 1-2, the absence of cross-resistance with lamivudine and other L-nucleosides and, therefore, its value as treatment for lamivudine-resistant chronic hepatitis B and for hepatic decompensation associated with lamivudine resistance prior to and after liver transplantation. Used for several years, as demonstrated primarily in HBeAg-negative patients, adefovir tends to maintain clinical effectiveness during protracted treatment; HBsAg loss has been recorded in 5% of patients treated for 4-5 years. Durability of HBeAg seroconversion is compa-
rable to that of the other oral agents. Limiting the appeal of adefovir, a sizable proportion (20%-50%) of patients fail to achieve even a 2-log_{10} reduction in HBV DNA (primary nonresponse). Moreover, although resistance to adefovir is slow to emerge, resistant variants increase progressively after the first year, reaching almost 30% by the end of 4 years. At a daily oral dose of 10 mg, adefovir has an excellent safety profile, almost indistinguishable from placebo in side effects; however, studies with higher doses demonstrated the potential renal toxicity of adefovir (renal tubular acidosis reflected by hypophosphatemia and elevated creatinine levels), usually not appearing during the first 6-8 months of therapy. Even at a daily dose of 10 mg of adefovir, a small subset of patients (3% treated for 4-5 years) experience a ≥0.5 mg/dL elevation in creatinine; therefore, periodic creatinine monitoring is advisable.

**Entecavir**

Entecavir is a cyclopentyl guanosine analog that inhibits HBV DNA priming, reverse transcription of negative-stranded HBV DNA and synthesis of positive-strand HBV DNA and has profound activity against HBV. In large registration trials, both in patients who are HBeAg-positive and HBeAg-negative with chronic hepatitis B and including patients with previous interferon failure, a daily dose of 0.5 mg of entecavir was compared to 100 mg of lamivudine. Entecavir was found to be superior to lamivudine in degree of suppression of HBV DNA, by 6.9 versus 5.5 log_{10} copies/mL in HBeAg-positive patients and 5.0 versus 4.5 log_{10} copies/mL in HBeAg-negative patients. Therapy with entecavir was associated with a more frequent fall of HBV DNA to undetectable levels (≤10^2 copies/mL (60% versus 40%; 6.4 log_{10} versus 5.5 log_{10} reduction), and in achieving histological improvement (65% versus 56%) but not in biochemical (77% versus 75%) or serological responses (HBeAg seroconversion in 23% versus 22%). In HBeAg-negative patients, telbivudine (600 mg/day) was superior to lamivudine (100 mg/day) in suppressing HBV DNA to undetectable levels, <10^2 copies/mL (60% versus 40%; 6.4 log_{10} versus 5.5 log_{10} reduction), and in achieving histological improvement (65% versus 56%) but not in biochemical (77% versus 75%) or serological responses (HBeAg seroconversion in 23% versus 22%).

**Telbivudine**

Telbivudine is a potent L-nucleoside that is believed to cause chain termination and is highly potent against HBV in cell culture. Telbivudine was tested against lamivudine in a large (1367 subjects) multicenter trial of patients who were HBeAg-positive and HBeAg-negative. In HBeAg-positive patients, at the end of year 1, telbivudine (600 mg/day) was superior to lamivudine (100 mg/day) in suppressing HBV DNA to undetectable levels, <10^2 copies/mL (60% versus 40%; 6.4 log_{10} versus 5.5 log_{10} reduction), and in achieving histological improvement (65% versus 56%) but not in biochemical (77% versus 75%) or serological responses (HBeAg seroconversion in 23% versus 22%). In HBeAg-negative patients, telbivudine was superior to lamivudine in suppressing HBV DNA to undetectable levels (88% versus 71%; 5.2 log_{10} versus 4.4 log_{10} reduction) but not in achieving histological (67% versus 66%) or biochemical improvement (74% versus 79%). These responses were well-maintained during the second year of therapy, and HBeAg seroconversion increased to 30% by the end of year 2.

Telbivudine is tolerated as well as lamivudine and appears to be quite safe, although mostly asymptomatic grade 3-4 creatine kinase elevations were more common in telbivudine-treated than in lamivudine-treated patients after 2 years of therapy. Durability of HBeAg responses was similar to that achieved with the other oral agents; relapse was common after discontinuation of therapy in HBeAg-negative patients. In this registration trial, the frequency of antiviral resistance to telbivudine at 1 year was 5% (versus an uncharacteristically low level of 11% for lamivudine) in HBeAg-positive and only 2% (versus 11% for lamivudine) in HBeAg-negative patients. By the
end of year 2, however, resistance emerged in 25% of telbivudine-treated HBeAg-positive patients, two-thirds of the 40% frequency observed in the lamivudine arm, and in 11% of the telbivudine-treated HBeAg-negative group. Because of its cross-resistance with lamivudine and its high rate of treatment-emergent resistance, telbivudine has limited appeal, and its potential virological and clinical benefit is outweighed and overshadowed by its high resistance profile. For these reasons, telbivudine has not been embraced as a treatment choice for patients with chronic hepatitis B.

**Tenofovir**

Tenofovir disoproxil fumarate, the most recently approved (in August 2008) drug for hepatitis B, is a promising new antiviral agent for the treatment of patients with chronic hepatitis B. Like adefovir, tenofovir is an oral acyclic nucleotide analog; however, tenofovir at recommended oral doses is more potent, more rapidly acting, and has a better resistance profile and an excellent safety profile. Licensed initially for the treatment of human immunodeficiency virus (HIV), either as monotherapy or in a single-pill combination with emtricitabine, tenofovir has excellent antiviral activity against hepatitis B in patients with HIV/HBV coinfection as well as in patients with HBV monoinfection. In two recently completed, 48-week, randomized, controlled trials, oral tenofovir (300 mg/day) was compared to adefovir (10 mg/day) in treatment-naive patients with HBeAg-positive and HBeAg-negative chronic hepatitis B. In HBeAg-positive patients, tenofovir reduced HBV DNA levels by an average of 6.2 log_{10} IU/mL and suppressed HBV DNA to undetectable levels (<10^2 IU/mL) in 80% of patients versus only 13% in the adefovir group. Tenofovir and adefovir treatment resulted in similar rates of histological benefit (74% versus 68%) and HBeAg seroconversion (21% versus 18%). An important finding was HBsAg seroconversion in 3% of patients during the first 48 weeks of therapy in the tenofovir group. In the HBeAg-positive group, at the end of year 2 of continuous tenofovir treatment, HBeAg seroconversion increased to 27% and HBsAg loss increased to 6%. In HBeAg-negative patients, at the end of year 1 of therapy, tenofovir reduced HBV DNA by an average of 4.6 log_{10} IU/mL and suppressed HBV DNA to <10^2 IU/mL in 95% of patients, compared to 64% in the adefovir group. Histological improvement occurred in 72% and normalization of ALT in 79% of the tenofovir-treated subjects. No evidence of tenofovir resistance was found during the 2 years of this trial.

In addition to having a very favorable resistance profile, tenofovir, like adefovir, has been reported to be effective in treating patients with lamivudine-resistant HBV. Importantly, the high frequency of primary nonresponse to adefovir has not been observed in tenofovir-treated patients. Otherwise well tolerated, tenofovir has the potential to be associated with renal toxicity, although the rate appears to be less than with adefovir. Isolated cases of Fanconi’s syndrome and creatinine elevations have been reported in patients with HIV infection treated with tenofovir, but this complication has been rare in patients with hepatitis B monoinfection. In tenofovir-treated patients, periodic creatinine monitoring is advisable. Because of its superiority to adefovir in so many domains, now that tenofovir is approved, it should supplant the use of adefovir in clinical practice.

**Other Oral Agents**

Emtricitabine and clevudine are oral L-nucleoside analogs with activity against HBV; neither has been approved as therapy of hepatitis B in the United States or Europe. Emtricitabine is approved as therapy for HIV infection and is available as monotherapy or as a single-pill combination with tenofovir. Similar to lamivudine in structure, emtricitabine has both an efficacy and a resistance profile similar to those of lamivudine. As monotherapy, emtricitabine appears to offer no advantage over lamivudine; however, the combination of resistance-profile-complementary tenofovir and emtricitabine has been studied in patients with chronic hepatitis B and in those with HBV-HIV coinfection (see the report by Terrault elsewhere in these proceedings).

Clevudine, approved for use in Korea, is a pyrimidine analog that is very potent in inhibiting woodchuck hepatitis virus, an animal model for human HBV; a distinguishing characteristic of clevudine over other oral agents is the long delay in return of baseline HBV DNA levels after cessation of therapy. On the other hand, in a phase III trial of daily oral doses of 30 mg of clevudine for 24 weeks in HBeAg-positive patients, HBV DNA was suppressed by only 5.1 log_{10}, and HBeAg seroconversion occurred in only 8% (versus 9% in placebo recipients). Based on studies in woodchucks, clevudine has been predicted to eradicate HBV covalently closed circular DNA (cccDNA) and to yield sustained virologic responses. To date, however, clevudine has not been observed to achieve improvements over already approved antivirals in the traditional clinical endpoints measured during clinical trials; in addition, neither eradication of cccDNA nor clearance of HBsAg has been documented. In fact, reductions of cccDNA occur, paralleling declines in serum HBV DNA, during treatment with all antiviral drugs and during spontaneous reductions in HBV replication (e.g., during spontaneous HBeAg responses); to date, no antiviral agent...
has been documented to be superior to others in lowering cccDNA, and none has eradicated cccDNA. Resistance to clevudine has not been observed in some trials, whereas in others, resistance has emerged in up to 10% during a year of clevudine therapy. Clinical trials in which clevudine is being compared to adefovir, the least potent of the oral agents, are in progress.

Durability of Response

In HBeAg-reactive patients, “consolidation” treatment with oral agents for at least 6 months after HBeAg seroconversion leads to a durable response in ~80% of western patients.10,11; durability of HBeAg responses has been reported to be substantially lower in Asian populations.12 In a recent report, Hsu et al.46 found that the level of pretreatment baseline HBV DNA was predictive of relapse versus durability after lamivudine treatment. In 71 Asian subjects with lamivudine-associated HBeAg seroconversion, relapse after treatment occurred in only 11% (durability 89%) in patients with a baseline HBV DNA of \( \leq 10^8 \) copies/mL but in as many as 44% (durability 56%) in those with baseline HBV DNA levels of \( >10^8 \) copies/mL. Potentially, this observed dichotomy in durability based on baseline HBV DNA could account for some of the differences in reported durability of posttreatment HBeAg seroconversion between some western and some Asian populations.

In contrast to HBeAg-positive patients, in whom a durable response can be sustained after therapy, in HBeAg-negative chronic hepatitis B, a year of treatment almost always results in a posttreatment relapse after withdrawal of therapy.3,18,33,34 Thus, durable responses are the exception rather than the rule in the majority of patients treated with oral agents; almost all HBeAg-negative patients and ~80% of HBeAg-positive patients who do not achieve HBeAg seroconversion do not sustain their responses when treatment is discontinued. Therefore, patients should be monitored closely after stopping therapy, and therapy should be re instituted promptly for relapse. Such monitoring is especially imperative in patients with cirrhosis, in whom posttreatment relapses can precipitate hepatic decompensation. Because a year of oral-agent therapy achieves a durable response in so few, therapy is continued beyond the first 48-52 weeks. Although the duration of nucleoside analog therapy has not been defined, in clinical trials of all the approved oral agents, long-term treatment has proven to be safe, to maintain and enhance clinical endpoints,13,26-28,33,34,38,47 and, for at least some of the agents (entecavir, tenofovir) but not the others (lamivudine, adefovir, telbivudine), to maintain an excellent, negligible-resistance profile.

Choice of Agents

Among the five oral agents, entecavir and telbivudine have both been shown to be superior to lamivudine3-7 and tenofovir has been shown to be superior to adefovir.8 Based on superiority in efficacy and resistance profiled in clinical trials, entecavir and tenofovir have been recognized as the best agents to use as first-line therapy, eclipsing lamivudine, telbivudine, and adefovir.

Oral Agents Versus Interferon-Based Therapy

Compared to a finite, 48-week course of peginterferon, therapy with oral agents is usually longer, often indefinite in duration. Although after a year peginterferon is more likely than oral therapy to result in durable HBeAg and HBsAg responses,48,49 the advantage accrues to a very small proportion of patients and comes with a substantial cost—cumbersome injection therapy, difficult-to-tolerate side effects, the laboratory/clinical monitoring to manage drug toxicity, and increased direct and indirect medical expense. Although depression during peginterferon therapy has been reported to be less likely in patients with hepatitis B than hepatitis C,48,50 other peginterferon side effects, dose reductions, and drug discontinuations are comparable between these two types of viral hepatitis. Moreover, the advantage in serological responses to a 48-week course of peginterferon therapy is balanced and, according to many authorities, is negated by a “catching up” and even surpassing in HBeAg and HBsAg responses that can be accomplished with continuation of oral side-effect-free therapy beyond a year.13,27,28,38,47 Extending oral-agent therapy by 6-12 months, which is without the side effects of injectable peginterferon, achieves the same rate, ~30%, of durable serological outcomes as a year of peginterferon, and continuing oral-agent therapy beyond a year continues to increase the frequency of HBeAg seroconversion, ~50% at 5 years. Moreover, HBsAg responses continue to occur after HBeAg seroconversion during the years following antiviral therapy, both in interferon-treated51,52 and oral agent–treated patients.11 Although antiviral resistance, which does not occur during peginterferon therapy, complicates oral agent therapy, rescue therapy with a non-cross resistant oral agent is almost always successful, and the new generation of antivirals (entecavir, tenofovir) has such a favorable resistance profile that interferon-based therapy no longer has a measurable resistance advantage.

Oral agents have other unique benefits not shared by interferon-based therapy, including efficacy in prior interferon nonresponders and patients with high-level HBV DNA; demonstrated activity in reversing fibrosis, cirrho-
sis, and hepatic decompensation; an indication after liver transplantation and during cytotoxic chemotherapy; and documented efficacy in preventing hepatic decompensation in patients with advanced fibrosis and cirrhosis. In addition, the oral agents, especially the more recently introduced antivirals, suppress HBV DNA substantially more profoundly than interferon-based therapy. Because of the convincing relation emerging between sustained, high-level HBV DNA and the late, life-threatening outcomes of chronic hepatitis B (cirrhosis and hepatocellular carcinoma), more profound HBV DNA suppression represents a worthy treatment objective, more likely to be achieved by the newer oral agents than by interferon-based therapy. Even over the short term, the lower the level of HBV DNA achieved with antiviral therapy (i.e., the lower the level of residual viremia during antiviral therapy), the more likely to occur are the beneficial serological, biochemical, and histological endpoints measured in clinical trials and the less likely is drug resistance to occur. Finally, even for younger patients with modest levels of HBV DNA, substantial ALT elevations, and favorable genotypes (A and B versus C and D [at least for peginterferon alfa-2b, not statistically for peginterferon alfa-2a]), who have been identified as more likely to benefit from peginterferon therapy and for whom peginterferon has been suggested by some authorities as first-line therapy, the relative advantages of oral agent therapy persist. The relative advantages and disadvantages of the oral agents and peginterferon are summarized in Table 1. Potential risks of long-term nucleoside analog therapy are summarized elsewhere in these proceedings.

**Conclusions**

The current generation of oral antiviral nucleoside and nucleotide analogs are safe, well tolerated, highly potent, with negligible resistance (entecavir and tenofovir). Although a finite 48-week period of peginterferon therapy results in a higher frequency of durable HBeAg and HBsAg responses during therapy than can be achieved with a year of oral agent therapy, almost all of the oral agents are superior to interferon-based therapy in achieving other clinical endpoints, i.e., in suppressing the level of HBV DNA (log₁₀ reduction and rate of undetectable HBV DNA) and in achieving biochemical and histological improvement. In addition, with longer use, oral agents can equal and exceed the level of peginterferon-associated HBeAg and HBsAg serologic responses without the need for injections, side effects, and the extra direct and indirect medical costs of monitoring patients being treated with peginterferon. Based on observations across all the oral agents, we can conclude with confidence that found, durable therapeutic HBV DNA suppression can slow and reverse the progression of chronic hepatitis B.

In general, the degree of HBV DNA suppression correlates with meaningful clinical endpoints; the more profound the suppression of HBV DNA the better. Ultimately, chronic hepatitis B is a viral disease, the immunologic responses to HBV and the role of the immune system in liver injury notwithstanding. Therefore, suppression of viral replication can be viewed as the primary clinical endpoint, which, once achieved, leads to improvement in all other clinical endpoints, both as shown over the short term, as measured in clinical trials, and as predicted over the long term, provided that the virological response can be maintained.

**Needs for Future Research**

Future studies are needed to develop antiviral drug regimens that are even more effective in achieving clinical endpoints, that are not hampered by resistance, and that are more confined in treatment duration but are more durable. Achieving these ends may require identification and exploitation of novel treatment targets or creative combination therapy. Current treatment guidelines are based on data that demonstrate the efficacy of treatment for viremic patients with elevated ALT levels but are less

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**Table 1. Relative Features of Treatment with Oral Agents and Pegylated Interferon for Chronic Hepatitis B**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Peginterferon</th>
<th>Oral agents</th>
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<tr>
<td>Route</td>
<td>Injection, once weekly</td>
<td>Oral, once daily</td>
</tr>
<tr>
<td>Tolerability</td>
<td>Poor</td>
<td>Excellent</td>
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<tr>
<td>Clinical monitoring</td>
<td>Intensive, Costly</td>
<td>Minimal to Moderate</td>
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<tr>
<td>Duration of therapy</td>
<td>1 year</td>
<td>Indefinite in &gt;-80%</td>
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<tr>
<td>Maximum log₁₀ HBV DNA suppression</td>
<td>Rarely</td>
<td>Usually</td>
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<tr>
<td>Effective in high HBV DNA (&gt;10⁶ IU/mL)</td>
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<td>~20%</td>
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<tr>
<td>1-year HBeAg seroconversion</td>
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<td>~80%</td>
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<tr>
<td>&gt;1-year HBeAg seroconversion</td>
<td>Not available</td>
<td>30%-50%</td>
</tr>
<tr>
<td>Durability of HBeAg seroconversion</td>
<td>3%-4%</td>
<td>0%-3% (3-5%)</td>
</tr>
<tr>
<td>HBsAg loss year 1 (year 2)</td>
<td>None</td>
<td>LVM++++++, TBV++, ADV++</td>
</tr>
<tr>
<td>Resistance</td>
<td>Not Recommended</td>
<td>ETV, TDF Negligible</td>
</tr>
<tr>
<td>Compensated cirrhosis</td>
<td>Contraindicated</td>
<td>Delays Decompensation</td>
</tr>
<tr>
<td>Decompensated cirrhosis</td>
<td>Potentially Lifesaving</td>
<td></td>
</tr>
<tr>
<td>Cost of 1 year of therapy</td>
<td>$18,000</td>
<td>$2500–$8700</td>
</tr>
</tbody>
</table>

ADV, adefovir; ETV, entecavir; LVM, lamivudine; NA, not applicable; TBV, telbivudine; TDF, tenofovir.
secure for those with normal to near-normal ALT levels\(^5\); for patients with neonatally acquired, life-long HBV infection who have high-level HBV replication but insubstantial necroinflammatory activity, additional research should help define the optimal time during the course of chronic hepatitis B to intervene—when the most substantial, consequential, injurious disease activity occurs—and to prevent the dreaded late outcomes of infection. For all categories of patients, predictors of responsiveness need to be refined to aid in patient selection for antiviral therapy and its timing (when to start and when to stop). Future studies will be necessary to determine whether, with the new generation of rapid-acting, high-potency antivirals that have a very high barrier to resistance, combination therapy can be shown in practical clinical trials to be superior to monotherapy. Finally, treatment recommendations should be refined to reflect evolving changes in therapy and in the understanding of the pathophysiology of chronic hepatitis B.

**References**


