Hepatitis B: Treatment Strategies for Currently Available Drugs

Robert P. Perrillo, MD

Address
Section of Gastroenterology and Hepatology, Ochsner Clinic, 1514 Jefferson Highway, New Orleans, LA 70124, USA.
E-mail: rperrillo@ochsner.org

Current Hepatitis Reports 2003, **2**:63–70
Current Science Inc. ISSN 1540–3416

There are three licensed drugs for chronic hepatitis B at the current time: interferon alpha, and the nucleoside analogues, lamivudine and adefovir. The benefits as well as limitations of each of these agents are described in this article. Preliminary studies suggest that the combination of interferon and lamivudine is associated with an enhanced rate of virologic response when compared with either agent alone.

Introduction: Renewal of Interest in the Treatment of Chronic Hepatitis B

Antiviral therapy studies of hepatitis B were first published in the mid 1970s, nearly a decade before the first treatment trials were reported for hepatitis C. Yet much of the emphasis on antiviral therapy in the United States until very recently has been focused on the treatment of hepatitis C. This is due to a number of circumstances: 1) the excitement and clinical developments that followed the more recent discovery of the hepatitis C agent; 2) the extremely high frequency with which patients with hepatitis C become chronically infected (80% vs 5% for hepatitis B); 3) the far greater number of individuals (roughly 3 million vs 1.2 million for hepatitis B) who are chronically infected with the virus in the United States; and 4) an intense public and industry focus on the treatment of hepatitis C.

In the past 5 years, however, interest and excitement in the field of hepatitis B therapeutics has undergone a resurrection owing to the development of nucleoside analogue inhibitors of hepatitis B virus (HBV) replication. The newer drugs are not only better tolerated than interferon, they are also considerably less expensive. Somewhat ironically, recent studies have suggested that pegylated interferon may be more effective than traditional interferon for hepatitis B, and this has led to renewed interest in interferon therapy for this disorder. Emerging data suggest that a combination of interferon and nucleoside analogue therapy may be even more effective than either agent alone. It is possible that this approach will even exceed the therapeutic benefit provided by pegylated interferon used in combination with the nucleoside analogue ribavirin for patients with hepatitis C.

The majority of patients with chronic hepatitis B in the United States and Western Europe express hepatitis B early antigen (HBeAg) in blood. The current review is focused on the treatment of this type of patient. In contrast, more than 80% of cases in the Mediterranean region and as many as 30% to 40% of cases in Asia are of the HBeAg-negative variety. Although the same agents are used for HBeAg-negative chronic hepatitis B, responses tend not to be as sustained, and longer duration therapy is usually necessary.

Currently Available Agents

Interferon alpha

The currently recommended regimen for interferon in HBeAg-positive chronic hepatitis B is 5 million units (MU) daily or 10 MU three times a week for 4 to 6 months. This regimen results in long-term beneficial responses in approximately 33% of patients [1,2]. The optimal duration of treatment with interferon, however, has not been well established. A multicenter trial from Europe demonstrated added benefit of continuing therapy for 32 weeks in patients who remained HBeAg positive at week 16 but who had low levels of HBV DNA(< 10 pg/mL by nonpolymerase chain reaction (PCR)-based assay) [3]. Thus, continuation of treatment beyond 6 months is probably preferable to ensure the highest rate of response.

Interferon's mechanism of action is distinct from that of nucleoside analogues. It activates cellular ribonucleases, which degrade viral messenger RNA, and stimulates intracellular enzymatic pathways that suppress viral replication. Interferon also increases HLA class I antigen expression on the surface membranes of hepatocytes, making viral peptide recognition by cytolytic T-cells more effective, and it enhances macrophage and natural killer cell activity [4••]. These immunologic events are clinically recognizable by increments in alanine aminotransferase (ALT) during therapy, and they appear to be important in securing a virologic response [5••]. Stimulation of the immune response to HBV by interferon is known to be clinically important because the frequency of a virologic response correlates with the presence of an ALT flare (at least twice the baseline) during the second to third month of treatment [5••]. Although beneficial in clinically stable patients, these flares

of hepatitis can result in hepatic decompensation in patients with marginal hepatic reserve [6].

It has recently been demonstrated that the degree of flare during treatment has strong predictive value for achievement of a virologic response in patients with high baseline serum HBV DNA levels (> 100 pg/mL), a group that has been difficult to treat with conventional dosing regimens [7•]. The immunologically mediated destruction of infected hepatocytes can result in the disappearance of the covalently closed circular (ccc) HBV DNA that is the genomic template for replication; ultimately this event leads to hepatitis B surface antigen (HBsAg) seroclearance in some patients. Clearance of HBsAg is seldom observed with lamivudine and other nucleoside analogues during the first year of treatment, indicating that the virologic response to interferon and nucleoside derivatives is quantitatively similar but qualitatively different.

The use of pegylated or long-acting interferon presents new opportunities for the treatment of chronic hepatitis B. Pegylation involves the covalent binding of a linear or branched form of polyethylene glycol with interferon alfa-2b or alfa-2a, respectively, and this results in prolonged biological activity so that once-weekly dosing is possible. The pegylated interferons have been found to be more effective in the treatment of chronic hepatitis C [8]; clinical trials of pegylated interferon alfa-2a, alone or in combination with lamivudine, are underway in Europe in patients with HBeAg-positive chronic hepatitis B. Preliminary results look encouraging (Perrillo and Schalm, Personal communication). Recently, it has been shown that pegylated interferon is significantly more effective than standard interferon in enhancing $CD4^+$ T-helper 1 (Th1) responses in patients with chronic hepatitis C [9]. It could also prove to more effective in the immunoregulation of HBV and may be associated with a higher rate of virologic response than standard interferon.

Lamivudine

Lamivudine is a cytidine analogue that has been extensively studied and was the first drug in this class to be licensed as therapy for hepatitis B (1998). The excellent safety profile of lamivudine as well as its reduced cost (average retail price of $3.60 per vs $10/MU of interferon) led to reduced interest in interferon as a means of treatment.

The triphosphorylated form of the drug competitively inhibits HBV DNA polymerase and prematurely terminates HBV DNA chain elongation [10•]. Although in vitro experiments have shown that CD8 (*ie,* cytolytic T-cell) and CD4 (*ie,* helper T-cell) responses to viral peptides are enhanced during the early phase of treatment [11], conclusive evidence that the drug's efficacy is affected by reconstitution of the cellular immune response is lacking.

In a US multicenter trial involving 137 patients, a 52-week course of lamivudine resulted in HBeAg seroconversion in 17% of patients versus 6% in placebo-treated controls [12]. In the same study, 32% of treated patients versus 11% of controls demonstrated a loss of HBeAg. Lamivudine is extremely well tolerated, and ALT flares during therapy have not been shown to occur any more frequently than placebo-treated patients [12]. Treatment withdrawal has been reported to be associated with ALT flares (> 10 times the upper limit of normal and > three times baseline) in 17% to 19% of patients [5••,13]. These flares are thought to be due to rapid reemergence of wild-type HBV and are more likely to be associated with clinically detectable deterioration in patients with severe disease [5••,13]. To minimize the possibility of a clinically significant flare in cirrhotic patients, the author's practice is to use a step-down method of withdrawing lamivudine over several weeks so as to provide a more gradual reemergence of wild-type HBV.

In most instances (80%), virologic responses appear to be durable for at least 12 months after discontinuation. The rate of virologic relapse has varied widely in clinical trials. One European study found a significantly higher rate of relapse in lamivudine-treated patients (60%) as compared with those treated with interferon (28%) at the 2-year post-treatment interval [14]. The optimal duration of therapy remains unclear at the current time. A study conducted in Korea found that relapse occurred much more frequently (57% vs 20% at 1-year post-treatment) in patients who were treated for less than 3 months after HBeAg seroconversion [15]. Patients who have been maintained on lamivudine for 3 years have enhanced rates of HBeAg seroconversion and a more marked improvement in hepatic fibrosis [16•]. The best predictor of HBeAg seroconversion is the pretreatment ALT level [17•]. In a study involving more than 800 patients who had been treated with lamivudine for 52 weeks, HBeAg became nondetectable in 9% and 19%, respectively, of Asians and Caucasians with pretreatment ALT values between one and two times the upper limit. In contrast, HBeAg loss occurred in 26% and 30% of Asians and Caucasians, respectively, when the pretreatment ALT level was more than twice but less than five times the upper limit of normal. Unlike interferon, pretreatment serum HBV DNA level does not appear to predict a virologic response [1,17•].

The major downside of prolonged lamivudine monotherapy has been the tendency to develop resistance. This is clinically suggested by the reappearance of serum HBV DNA after two or more consecutive negative determinations in a patient who has been on treatment for at least 9 months. Resistance has been traced to one or more mutations in the YMDD motif of the polymerase gene (domains B and C of the viral polymerase) and occurs in a time-dependent manner [18]. YMDD mutants occur in 14% to 32% of patients after 1 year of treatment; this increases to approximately 37% at 2 years, 50% at 3 years, and 66% after 4 years of continuous dosing [19•,20]. Lamivudine-resistant variants have been found to have a decreased replication capacity when studied in vitro, and serum HBV DNA levels often remain below those observed prior to

treatment [21,22]. ALT levels remain elevated in patients infected with YMDD mutant HBV, but often these remain below pretreatment values [19•,22].

Patients with YMDD mutants are not as likely to have a subsequent virologic response as those individuals who maintain wild-type HBV. Occasionally, the emergence of YMDD mutants is followed by a pronounced ALT flare. In one study, HBeAg seroconversion was observed in 75% of patients who had an acute exacerbation linked to the mutant virus [23]. There is little systematic data on the natural history of infection with YMDD mutant HBV, but severe hepatitis has been observed, particularly in immunosuppressed patients [24,25]. Because of the uncertainty related to the long-term prognosis of YMDD mutant infection, concern has been voiced about the use of lamivudine monotherapy in patients with mild disease and prolonged use of this drug in individuals who may ultimately be in need of liver transplantation [4••].

Adefovir dipivoxil

Adefovir is an acyclic analogue of deoxyadenosine monophosphate that has broad-spectrum antiviral activity and is inhibitory to both HIV and HBV. This drug was recently licensed to treat hepatitis B based on phase III studies in HBeAg-positive and HBeAg-negative patients. The virologic response rate to 48 weeks of treatment was observed to be similar, although slightly less, than that seen with 1 year of lamivudine treatment (12% HBeAg seroconversion rate vs 17% for lamivudine) [26]. Unlike lamivudine, however, resistance to this drug has not been observed even when treatment is prolonged to 136 weeks. Moreover, in vivo as well as in vitro studies have demonstrated antiviral activity against the YMDD mutant as well as wild-type HBV [27,28]. One downside of the use of this drug that warrants particular attention if prolonged therapy is necessary is its higher cost. Current retail price is set at three to four times the price of lamivudine monotherapy.

In HIV infection, 60- and 120-mg doses given once daily have been associated with renal toxicity after 6 months of treatment. The 30-mg dose has been associated with a trend toward an increase in serum creatinine and depression of serum phosphorus levels (although both have tended to remain within normal range). No renal toxicity has been identified with the 10-mg dose during 1 year of treatment for chronic hepatitis B; this is the dose formulation that is likely to become licensed for treatment. Early data on extended therapy beyond 48 weeks look encouraging from the standpoint of safety. Owing to significantly greater cost when compared with lamivudine, however, it is uncertain whether this drug will be used as first-line therapy, and the optimal duration of treatment is currently unknown. It is likely to play a major role whenever clinically significant lamivudine resistance emerges. Many authorities feel that adefovir will also be used in combination with lamivudine to induce a more rapid decline in viral replication and to diminish the risk of YMDD mutant virus. Studies to evaluate these possibilities in treatment-naive patients are currently in process. An exploratory clinical trial in 40 patients with decompensated liver disease and confirmed YMDD mutant infection has demonstrated virologic and clinical improvement after 52 weeks of adefovir [29].

Table 1. Nucleoside analogues to treat chronic hepatitis B

Agent	Resistance demonstrated	Activity against YMDD mutant
Lamivudine	Yes	None
Famciclovir	Yes	Limited if any
Ganciclovir	No	Not known
Adefovir dipivoxil	No	Yes: in vitro and in vivo
Entecavir*	No	Yes: in vitro and in vivo
Emtricitabine*†	Yes	—
LdT*	Not known	Not known
Clevudine*	Not known	Not known

*Investigational at current time.
†Structurally similar to lamivudine.

Nucleoside Analogues Under Development

Other nucleoside agents, some of which are effective against the YMDD mutants as well as wild-type HBV, are currently being developed (Table 1). The following is a brief summary of the more promising agents.

Entecavir

Entecavir is an acyclic deoxyguanosine analogue with potent antiherpes and antihepadnaviral activity [30]. In woodchucks infected with woodchuck HBV, treatment with entecavir has produced 2 to 3 $\log_{10}$ reductions in viral load. This drug is of special interest because there is in vitro and in vivo evidence that it is inhibitory to both wild-type and lamivudine-resistant forms of HBV [31•,32]. A recent study has shown that therapy with entecavir is associated with a more profound fall in HBV DNA (≥ 1 log) when compared with lamivudine during a treatment period of 24 weeks [33••]. In clinical trials, entecavir has had an excellent safety profile. Phase III trials have recently been completed, and it is assumed that this drug will be licensed for use in hepatitis B sometime in the next year.

Emtricitabine

Emtricitabine (FTC) is a fluorinated derivative of lamivudine that is anticipated to have a similar resistance pattern. In vitro studies do not support that emtricitabine has antiviral activity against the YMDD mutant HBV [31•]. Ninety-eight patients with HBeAg-positive chronic hepatitis B were treated for 24 weeks in a dose-escalating study. HBV DNA levels were reduced by 3 logs at the higher doses [4••]. To date, this nucleoside has been well tolerated. Large-scale, placebo-controlled

trials of a 1-year course of emtricitabine in patients with HBeAg-positive chronic hepatitis B are in progress.

LdT

L-deoxythymidine (LdT) is a levo, or unnatural form of deoxythymidine, that has been shown to be a highly potent inhibitor of HBV DNA polymerase in vitro. Unlike other nucleoside analogues, the antiviral effect of LdT appears to be relatively specific for HBV. In subjects treated with 400 mg of LdT daily, there was a median 3.6 $\log_{10}$ copies/mL decrease from baseline in HBV DNA at 28 days [34]. To date, no clinically significant adverse effects have been observed. It is currently unknown if this drug is effective in treating the YMDD mutant HBV.

Clevudine

Clevudine (or L-FMAU) is a pyrimidine analogue with marked in vitro activity against human and woodchuck HBV [35]. The active triphosphate form inhibits HBV DNA polymerase but is not an obligate chain terminator. Single and multiple doses of clevudine have been administered to healthy human volunteers and the drug has been well tolerated. Recent cell culture studies have found that some but not all YMDD mutants are susceptible to this agent [31•]. Pilot studies in patients with chronic hepatitis B are being planned.

Multiple Nucleoside Analogues in Combination

Lamivudine and other nucleosides derivatives can induce a sustained suppression of HBV replication and improvement in ALT and liver histology. Unfortunately, these benefits only occur in a minority of treated patients, and a high rate of resistance will probably continue to be a major problem when nucleoside analogues are given as monotherapy for extended periods. As a result, many experts have postulated that more effective treatment may require the use of multiple nucleosides in combination. The aims of combination therapy would basically be twofold: first, to provide additive or synergistic benefit in the suppression of viral replication, and second, to discourage resistance to nucleoside monotherapy [36•]. By providing greater suppression of HBV replication, multidrug therapy could shorten the period of treatment necessary to induce a virologic response; as a result, this could diminish the rate of acquisition of drug-resistant mutants.

Combined nucleoside analogue treatment may have additive or synergistic antiviral effects if the nucleoside analogues use different pathways for intracellular activation, compete with different naturally occurring nucleotides for HBV polymerase, act on different viral subpopulations, or act at different sites in the replication cycle of HBV. At the current time, however, there are only limited in vitro and in vivo data to support that combination therapy is more effective. A combination of penciclovir, the active metabolite of famciclovir, a nucleoside derivative that is licensed for herpetic and varicella infection, and lamivudine has been shown to synergistically inhibit duck HBV replication [37]. Furthermore, a pilot study from Hong Kong has demonstrated that a 12-week course of famciclovir and lamivudine was significantly more inhibitory to HBV replication than lamivudine alone [38]. Although encouraging, there is reason to question the relevance of the duck experiments, because of species-dependent differences in the metabolic activation of nucleosides.

Moreover, it is conceivable that famciclovir given with lamivudine could shorten the time necessary for lamivudine resistance. This drug combination would be anticipated to be less potent than combinations using the newer nucleoside agents [31•,39]. At the time of this writing, clinical studies with adefovir used in combination with lamivudine are underway in treatment-naive patients. The preliminary results of trials in which adefovir has been used to treat already established YMDD mutant infection have demonstrated it to be clinically effective [28,29]. More definitive study of adefovir for the YMDD mutant infection will provide valuable insights for future therapy.

Interferon and Lamivudine in Combination

Mathematical modeling has shown that viral load typically decays in a biphasic manner during nucleoside analogue therapy. During the first 2 weeks of treatment, there is a rapid decline in HBV DNA, which has been interpreted as the clearance of virions produced before inhibition of viral replication. The second less steep phase is much more prolonged, occurring over many months, and is thought to reflect the decay of cccDNA or death of infected cells [40]. This latter event can be upregulated by targeted immune destruction of infected hepatocytes, which is stimulated by interferon and not the nucleoside analogue agents. This may explain why it has been difficult to show that treatment with nucleoside analogues results in elimination of the HBV cccDNA template for viral replication and why interferon results in more efficient clearance of HBsAg [41]. In light of these observations and in consideration of the fact that nucleoside analogues and interferon have different mechanisms of action, it is reasonable to evaluate combination therapy with one or more nucleosides in combination with interferon.

Using the woodchuck model, investigators have shown that a combination of 12 weeks of recombinant human alpha interferon and lamivudine was significantly more antiviral than either agent alone [42]. Clinical trials in humans have also suggested added benefit from this approach. In one study, 230 previously untreated patients with HBeAg-positive chronic hepatitis B were randomized to either lamivudine 100 mg daily for 52 weeks, interferon alpha 10 MU three times weekly for 16 weeks, or a combination of lamivudine and interferon for 16 weeks preceded by an 8-week course of lamivudine [43]. The HBeAg seroconversion rate at the end of 52 weeks was 29% for the combination regimen, 19% for the interferon monotherapy group, and 18% for those treated with lamivudine monotherapy.

This study has been criticized, however, because lamivudine was only given for 6 months in the combination group and interferon was started late, 2 months after initiating lamivudine. The reduction in ALT activity during the lamivudine lead-in period may have been associated with a less vigorous immune response to HBV. Theoretically, a rapid inhibition of viral peptide synthesis during lamivudine therapy may have led to a reduction in the efficiency with which viral peptides are displayed on the surface of infected hepatocytes in conjunction with HLA class I molecules. This would be anticipated to diminish the immunomodulatory activity of interferon. It is possible that an interferon lead-in phase or overlapping treatments would be more effective, and several such studies are currently underway (Perrillo, Unpublished data). Several small clinical trials in which famciclovir or lamivudine has been used in combination with interferon provide further support for potential additive or synergistic effects of combination therapy [44–46].

Corticosteroid Withdrawal Followed by Lamivudine

A number of studies have shown that corticosteroid withdrawal induces an immunologic rebound in patients with chronic hepatitis B. The combination of a short course of corticosteroids followed by interferon has been shown to be associated with a higher rate of virologic response in patients with mild disease [47]. Investigators in Taiwan have recently described a high rate of HBeAg seroconversion when patients were treated with a 4-week course of prednisolone followed by a 9-month course of lamivudine [48]. The response rate was 60% in the group of patients in whom withdrawal of corticosteroids was followed by an ALT flare (in excess of five times the upper range of normal) and only 10% in the subjects lacking a flare. Patients who responded were shown to have Th1-dominant responses according to the results of cytokine testing, which would be anticipated to lead to activation of cytotoxic T lymphocytes. More definitive study of this type of combination therapy appears warranted because this could become an alternative way of reducing the duration of treatment with lamivudine (or any other nucleoside) and by so doing, decreasing the frequency of drug resistance.

HBeAg-negative Chronic Hepatitis B

This condition is characterized by the absence of HBeAg, detectable serum HBV DNA (often of fluctuating nature and detectable only by PCR-based assay), and a worse long-term prognosis. Standard antiviral regimens used in patients with HBeAg-positive chronic hepatitis B often fail to provide lasting benefit in the HBeAg-negative form of chronic hepatitis B. Interferon therapy can result in sustained responses in 20% or more of patients when given for 12 months, and HBsAg seroconversion has even been documented, but the relapse rate continues to be higher than wild-type infection [49•].

Lamivudine as well as adefovir have also been tried in patients with HBeAg-negative chronic hepatitis B [50,51]. Several studies have reported end-of-treatment response rates of 60% to 70%. There is more data with regard to lamivudine at the current time, where it has been shown that treatment withdrawal after 52 weeks is associated with a high relapse rate (48% to 74%) within 6 months of discontinuation [50]. Studies using a longer treatment duration have shown a somewhat lower relapse rate, but the emergence of drug-resistant mutants in the second year of treatment continues to be a problem when lamivudine is used alone [52].

Conclusions

The treatment of chronic hepatitis B continues to evolve. The author's treatment recommendations with the currently available antiviral agents are listed in Table 2. Interferon is expensive and its use is associated with unpleasant adverse effects. Tolerability may be an important issue for some patients, but viral resistance to interferon has not been described and HBsAg seroclearance, a rare event with nucleoside analogue therapy, has been well documented in both HBeAg-positive and -negative forms of chronic hepatitis B. As with hepatitis C, longer-acting interferons may prove to be more effective than the nonpegylated forms used in the past.

Nucleoside analogues offer the advantage of reduced cost and minimal, if any, adverse effects. Virologic responses, however, are often incomplete with nucleoside analogues; these drugs have to be given for considerably longer periods of time (1 to 2 years) than interferon to induce a lasting virologic response. Now that both lamivudine and adefovir are licensed therapies, the major question is what drug to use as first-line therapy. A 52-week course of lamivudine has the advantage of greatly reduced cost when compared with adefovir and a well-established track record for safety. Continuation of lamivudine monotherapy beyond 1 year, however, results in a progressively higher rate of virologic resistance. In the author's opinion, therefore, prolongation of lamivudine treatment beyond the currently recommended 52-week course is particularly unsuitable for patients with histologically mild hepatitis B or in situations where the ALT level is consistently low (*eg*, < 1.3 times the upper limit of normal), because a very low response rate would be anticipated to occur in both situations. From a cost-utility standpoint, lamivudine is a particularly good choice as first-line therapy in patients with a pretreatment ALT of five or more times the upper limit of normal because it has been shown that more than 60% of patients responded to a 52-week course of treatment.

Both lamivudine and adefovir are far safer than interferon in patients with decompensated cirrhosis. Adefovir may have substantial clinical benefit in lamivudine-resistant patients before and after transplantation as long as

Table 2. Proposed current and future treatment regimens for HBeAg-positive chronic hepatitis B*

Using currently available drugs	First-line therapy	Second-line therapy	Not recommended
Clinically stable patient			
Normal ALT or < 1.3 × ULN	Observe†	—	—
ALT 1.3 to 2 × ULN	Lamivudine × 52 wk [12]‡ Adefovir × 48 wk [26]	4 to 6 wk of corticosteroids (PRED) prior to lamivudine × 36 to 52 wk [48]§	IFN alone
ALT 2 to 5 × ULN	Lamivudine × 52 wk + IFN × 32 wk [3]¶	Lamivudine × 52 wk, adefovir × 48 wk, or IFN × 32 wk	—
ALT > 5 × ULN	Lamivudine × 52 wk**	IFN × 32 wk	PRED and antiviral††
Decompensated patient			
Transplant candidate	Lamivudine, add adefovir if resistant‡‡	Adefovir§§	IFN [6]
Noncandidate for transplantation	Same as above	Adefovir‡‡	IFN [6]

*See text for further details on HBeAg-negative chronic hepatitis B.
†Should be treated in clinical trials only.
‡Numbers in brackets are literature references that support recommendation.
§PRED refers to either prednisone or prednisolone.
¶IFN may be of benefit by stimulation of cell-mediated immune response to hepatitis B virus.
**Based on studies indicating greater than 60% response rates to lamivudine alone.
††Patients with high ALT are not likely to require PRED-induced immunologic rebound.
‡‡Provided patient has normal renal function.
§§Many patients have renal dysfunction and may be at greater risk for adefovir nephrotoxicity.
ALT—alanine aminotransferase; HBeAg—hepatitis B early antigen; IFN—interferon; ULN—upper limit of normal.

renal function is intact. Undoubtedly, this drug will play a major role in the treatment of patients with clinically progressive liver disease owing to lamivudine-resistant HBV.

Many experts look to multiple nucleoside analogues as the future promise for hepatitis B therapy, in the way they have been for HIV. A question can be raised, however, as to whether combinations of this nature will have the same impact as they do in HIV infection, because the nucleoside derivatives used to treat hepatitis B have very similar mechanisms of action and they lack any direct immunologic effects. First and foremost, it should be remembered that hepatitis B is an immunologically mediated disease, and responses to antiviral therapy are more apt to occur in cases where the cellular immune response to HBV is more vigorous prior to treatment or where the cellular immune response can be successfully upregulated. For this reason, combinations of interferon and nucleosides may very well prove to be the most successful form of therapy for chronic hepatitis B in patients with moderate to severely active liver disease. There are preliminary data to support this, and more definitive assessments should become available in the next few years.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Perrillo RP, Schiff ER, Davis GL, *et al.*: **A randomized, controlled trial of interferon alfa-2b alone and after prednisone withdrawal, for the treatment of chronic hepatitis B.** *N Engl J Med* 1990, **323:**295–301.
2. Wong DKH, Cheung AM, O'Rourke K, *et al.*: **Effect of alpha interferon treatment in patients with hepatitis B e antigen-positive chronic hepatitis B: a meta-analysis.** *Ann Intern Med* 1993, **119:**312–323.
3. Janssen HLA, Gerken G, Carreno V, *et al.*: **Interferon alfa for chronic hepatitis B infection: increased efficacy of prolonged treatment. The European Concerted Action on Viral Hepatitis (EUROHEP).** *Hepatology* 1999, **30:**238–243.
4.•• Lok AS, Heathcote EJ, Hoofnagle JH: **Management of hepatitis B: 2000—summary of a workshop.** *Gastroenterology* 2001, **120:**1828–1853.

A concise review of the epidemiology, virology, natural history, immunopathogenesis, and treatment options for chronic hepatitis B. It assembled leading authorities in the field, and treatment recommendations as well as future directions for research are proposed.

5.•• Perrillo RP: **Acute flares in chronic hepatitis B: the natural and unnatural history of an immunologically mediated liver disease.** *Gastroenterology* 2001, **120:**1009–1022.

This is a well-referenced review of the clinical significance of serum ALT flares during chronic HBV infection, including those that occur in association with interferon and nucleoside analogues.

6. Perrillo R, Tamburro C, Regenstein F, *et al.*: **Low-dose, titratable interferon alfa in decompensated liver disease caused by chronic infection with hepatitis B virus.** *Gastroenterology* 1995, **109:**908–916.
7.• Nair S, Perrillo R: **Serum alanine aminotransferase flares during interferon treatment of chronic hepatitis B: is sustained clearance of HBV DNA dependent on levels of pretreatment viremia?** *Hepatology* 2001, **34:**1021–1026.

The authors examined the relationship between ALT flares during interferon therapy and virologic response in 163 patients. The degree of flare was an excellent predictor of response in patients with high-level (> 100 pg/mL) viremia at baseline.

8. Zeuzem S, Feinman SV, Rasenack J, *et al.*: **Peginterferon alfa-2a in patients with chronic hepatitis C.** *N Engl J Med* 2000, **343:**1666–1672.
9. Kamal SM, Fehr J, Roesler B, *et al.*: **Peginterferon alone or with ribavirin enhances HCV-specific CD4+ T-helper responses in patients with chronic hepatitis C.** *Gastroenterology* 2002, **123:**1070–1083.

10.• Torresi J, Locarnini S: **Antiviral chemotherapy for the treatment of hepatitis B virus infections.** *Gastroenterology* 2000, **118:**S83–S103.

An authoritative summary of the mechanisms of action of interferon and nucleosides. Each of the nucleoside analogues with activity against HBV is discussed, as is the problem of resistance to lamivudine.

11. Boni C, Penna A, Ocg GS, *et al.*: **Lamivudine treatment can overcome cytotoxic T-cell hyporesponsiveness in chronic hepatitis B: new perspectives for immune therapy.** *Hepatology* 2001, **33:**963–971.
12. Dienstag L, Schiff ER, Wright TL, *et al.*: **Lamivudine as initial treatment for chronic hepatitis B in the United States.** *N Engl J Med* 1999, **341:**1256–1263.
13. Honkoop P, De Man RA, Niesters HGM, *et al.*: **Acute exacerbation of chronic hepatitis B virus infection after withdrawal of lamivudine therapy.** *Hepatology* 2000, **32:**635–639.
14. Van Nunen AB, Hansen B, Suh D, *et al.*: **Durability of HBeAg seroconversion in chronic hepatitis B patients after lamivudine, alpha interferon, or lamivudine-alpha interferon -combination therapy [abstract].** *J Hepatol* 2001, **34(suppl 1):**155.
15. Song B-C, Suh DJ, Lee HC, *et al.*: **Hepatitis B e antigen seroconversion after lamivudine therapy is not durable in patients with chronic hepatitis B in Korea.** *Hepatology* 2000, **32:**803–806.
16.• Dienstag JL, Goldin RD, Heathcote EJ, *et al.*: **Histological outcome during long-term lamivudine therapy.** *Gastroenterology* 2003, **124:**105–117.

Demonstrates that 3 years of lamivudine monotherapy reduces necroinflammatory activity and reverses fibrosis (including cirrhosis) in 60% to 70% of patients, but the emergence of YMDD mutants blunts histologic responses.

17.• Perrillo RP, Lai CL, Liaw YF, *et al.*: **Predictors of HBeAg loss after lamivudine treatment for chronic hepatitis B.** *Hepatology* 2002, **36:**186–194.

Evaluated the relationship between HBeAg loss (and seroconversion) in approximately 800 patients who were treated in the phase III lamivudine trials. Using multivariate analysis, elevated pretreatment ALT levels or active histologic disease were the most important predictors of lamivudine-induced HBeAg loss. Asians and Caucasians had similar rates of response to lamivudine at comparable ALT levels.

18. Hunt CM, McGill JM, Allen MI, Condreay LD: **Clinical relevance of hepatitis B viral mutations.** *Hepatology* 2000, **31:**1037–1044.
19.• Leung NWY, Lai C-L, Chang T-T, *et al.*: **Extended lamivudine treatment in patients with chronic hepatitis B enhances hepatitis B e antigen seroconversion rates: results after 3 years of therapy.** *Hepatology* 2001, **33:**1527–1532.

After 3 years of treatment with lamivudine, 40% of 58 patients achieved HBeAg seroconversion, and response frequency was 65% in patients whose baseline ALT level exceeded two times the upper limit of normal. Unfortunately, lamivudine resistance was confirmed in 57% of patients at the 3-year mark.

20. Chang TT, Liaw YF, Guan R, *et al.*: **Incremental increases in HBeAg seroconversion and continued ALT normalization in Asian chronic HBV (CHB) patients treated with lamivudine for four years [abstract].** *Antivir Ther* 2000, **5(suppl 1):**44.
21. Melegari M, Scaglioni PP, Wands JR: **Hepatitis B virus mutants associated with 3TC and famciclovir administration are replication defective.** *Hepatology* 1997, **27:**628–633.
22. Perrillo R, Rakela J, Dienstag J, *et al.*: **Multicenter study of lamivudine therapy for hepatitis B after liver transplantation.** *Hepatology* 1999, **29:**1581–1586.
23. Liaw Y-F, Chien R-N, Yeh C-T, *et al.*: **Acute exacerbation and hepatitis B virus clearance after emergence of YMDD motif mutation during lamivudine therapy.** *Hepatology* 1999, **30:**567–572.
24. Mutimer D, Pillay D, Shields P, *et al.*: **Outcome of lamivudine resistant hepatitis B virus infection in the liver transplant recipient.** *Gut* 2000, **46:**107–113.
25. Peters MG, Singer G, Howard T, *et al.*: **Fulminant hepatic failure resulting from lamivudine-resistant hepatitis B virus in a renal transplant recipient.** *Transplantation* 2000, **68:**1912–1914.
26. Marcellin P, Chang T-T, Lim SG, *et al.*: **GS-98-437: a double-blind, randomized, placebo-controlled study of adefovir dipivoxil (ADV) for the treatment of patients with HBeAg (+) chronic hepatitis B infection: 48 week results [abstract].** *Hepatology* 2001, **34:**340A.
27. Xiong X, Flores C, Yang H, *et al.*: **Mutations in hepatitis B DNA polymerase associated with resistance to lamivudine do not confer resistance to adefovir in vitro.** *Hepatology* 1998, **28:**1669–1673.
28. Perrillo RP, Schiff E, Yoshida E, *et al.*: **Adefovir dipivoxil for the treatment of lamivudine-resistant hepatitis B mutants.** *Hepatology* 2000, **32:**129–134.
29. Mutimer D, Hann H-WL, Buti M, *et al.*: **Significant clinical improvement following the addition of adefovir dipivoxil to lamivudine in decompensated patients with YMDD v ariant HBV and a reduced response to lamivudine—1 year results [abstract].** *Hepatology* 2002, **36:**625A.
30. Innaimo SF, Seifer M, Bisacchi GS, *et al.*: **Identification of BMS-200475 as a potent and selective inhibitor of hepatitis B virus.** *Antimicrob Agents Chemother* 1997, **41:**1444–1448.
31.• Ono SK, Kato N, Shiratori Y, *et al.*: **The polymerase L528 mutation cooperates with nucleotide binding-site mutations, increasing hepatitis B virus replication and drug resistance.** *J Clin Invest* 2001, **107:**449–455.

Using a transfected human hepatoma cell line, the authors determined the replication fitness and susceptibility of wild-type HBV and five lamivudine-resistant mutants to 11 compounds. Only adefovir and entecavir were effective against all five mutants, although higher doses were needed against double mutants.

32. Tassopoulos N, Cianciara J, Rizzetto M, *et al.*: **Entecavir is effective in treating patients with chronic hepatitis B who have failed lamivudine therapy [abstract].** *Hepatology* 2001, **34:**340A.
33.•• Lai C-L, Rosmawati M, Lao J, *et al.*: **Entecavir is superior to lamivudine in reducing hepatitis B virus HBV DNA in patients with chronic hepatitis B virus infection.** *Gastroenterology* 2002, **123:**1831–1838.

In this 24-week trial, patients were either randomized to entecavir in one of two doses or lamivudine 100 mg daily for 24 weeks. In both treatment arms, very few patients achieved HBeAg loss, but both doses of entecavir were associated with significantly greater HBV DNA suppression and the drug was well tolerated.

34. Lai C-L, Lam PF, Myers MW, *et al.*: **Safe and potent suppression of hepatitis B virus (HBV) with L-deoxythymidine (LDT): results of a dose-escalation trial [abstract].** *Hepatology* 2001, **4:**321A.
35. Peek SF, Cote PJ, Jacob JR, *et al.*: **Antiviral activity of clevudine [L-FMAU, (1-(2-fluoro-5-methyl-beta, L-arabinofuranosyl) uracil)] against woodchuck hepatitis virus replication and gene expression in chronically infected woodchucks (marmota monax).** *Hepatology* 2001, **33:**254–266.
36.• Shaw T, Locarnini S: **Combination chemotherapy for hepatitis B virus: the final solution?** *Hepatology* 2000, **32:**430–432.

A concise review that focuses on the rationale for combinations of nucleoside analogues to treat chronic hepatitis B. The significance attached to viral load and viral dynamics is discussed. The authors point out that the second phase of viral clearance in which cccDNA is eliminated may require adjuvant therapy with immunomodulators.

37. Colledge D, Locarnini S, Shaw T: **Synergistic inhibition of hepadnaviral replication by lamivudine in combination with penciclovir in vitro.** *Hepatology* 1997, **26:**216–225.
38. Lau GK, Tsiang M, Hou J, *et al.*: **Combination therapy with lamivudine and famciclovir for chronic hepatitis B-infected Chinese patients: a viral dynamics study.** *Hepatology* 2000, **32:**394–399.
39. Tillmann HL, Trautwein C, Bock T, *et al.*: **Mutational pattern of hepatitis B virus on sequential therapy with famciclovir and lamivudine in patients with hepatitis B virus reinfection occurring under HBIg immunoglobulin after liver transplantation.** *Hepatology* 1999, **30:**244–256.
40. Tsiang M, Rooney JF, Toole JJ, Gibbs CS: **Biphasic clearance kinetics of hepatitis B virus from patients during adefovir dipivoxil therapy.** *Hepatology* 1999, **29:**1863–1869.

41. Dandri M, Burda MR, Will H, Petersen J: **Increased hepatocyte turnover and inhibition of woodchuck hepatitis B virus replication by adefovir in vitro do not lead to reduction of the closed circular DNA.** *Hepatology* 2000, **32:**139–146.
42. Korba BE, Cote P, Hornbuckle W, *et al.*: **Enhanced antiviral benefit of combination therapy with lamivudine and alpha interferon against WHV replication in chronic carrier woodchucks.** *Antivir Ther* 2000, **5:**95–104.
43. Schalm SW, Heathcote J, Cianciara J, *et al.*: **Lamivudine and alpha interferon combination treatment of patients with chronic hepatitis B infection: a randomised trial.** *Gut* 2000, **46:**562–568.
44. Marques AR, Lau DTY, McKenzie R, *et al.*: **Combination therapy with famciclovir and interferon-alpha for the treatment of chronic hepatitis B.** *J Infect Dis* 1998, **178:**1483–1487.
45. Seehofer D, Rayes N, Neuhaus R, *et al.*: **Antiviral combination therapy for lamivudine-resistant hepatitis B reinfection after liver transplantation.** *Transpl Int* 2000, **13(suppl 1):**S359–S362.
46. Mutimer D, Dowling D, Cane P, *et al.*: **Additive antiviral effects of lamivudine and alpha interferon in chronic hepatitis B infection.** *Antivir Ther* 2000, **5:**273–277.
47. Cohard M, Poynard T, Mathurin P, Zarski JP: **Prednisone-interferon combination in the treatment of chronic hepatitis B: direct and indirect meta-analysis.** *Hepatology* 1994, **20:**1390–1398.
48. Liaw YF, Tsai SL, Chien RN, *et al.*: **Prednisolone priming enhances Th1 response and efficacy of subsequent lamivudine therapy in patients with chronic hepatitis B.** *Hepatology* 2000, **32:**604–609.
49.• Hadziyannis SJ, Vassilopoulos D: **Hepatitis B e antigen-negative chronic hepatitis B.** *Hepatology* 2001, **34:**617–624.
Excellent review of the pathogenesis, clinical aspects, natural history, and treatment of this disorder.
50. Rizzetto M: **Efficacy of lamivudine in HbeAg-negative chronic hepatitis B.** *J Med Virol* 2002, **66:**435–451.
51. Hadziyannis S, Tassopoulos N, Heathcote J, *et al.*: **A double-blind, randomized, placebo controlled study of adefovir dipivoxil (ADV) for presumed precore mutant chronic hepatitis B: 48 week results [abstract].** *J Hepatol* 2002, **36(suppl 1):**4.
52. Hadziyannis SJ, Papatheodoridis GV, Dimou E, *et al.*: **Efficacy of long-term lamivudine monotherapy in patients with hepatitis B e antigen-negative chronic hepatitis B.** *Hepatology* 2000, **32:**847–851.