New antiviral agents are currently being developed to treat patients with chronic hepatitis B. Both pegylated interferon alfa-2a and entecavir are now approved for the treatment of hepatitis B while telbivudine, tenofovir, emtricitabine, and pegylated interferon alfa-2b are in clinical development. Successive advances have resulted in more profound suppression of hepatitis B replication, a reduction in breakthrough resistance, and an increase in the frequency of attainment of virologic, serologic, biochemical, and histologic clinical endpoints.

(Am J Gastroenterol 2006;101:S19–S25)

INTRODUCTION

Although several therapies are approved for the management of patients with chronic hepatitis B, each of the approved drugs has its limitations. On the horizon, however, are several new antiviral agents that promise improved efficacy. Although an analysis of all potential agents is beyond the scope of this review, we will focus on those agents that have been recently introduced or are likely to be introduced in the near future. In parallel with the development of direct antiviral agents, others are pursuing immunomodulatory drugs and therapeutic vaccines; however, these approaches are less likely to compete successfully with potent, safe, direct antiviral agents.

ENTECAVIR

Unlike the other agents, entecavir inhibits hepatitis B virus (HBV) replication at three steps, priming, negative strand synthesis, and positive strand synthesis (1), which may account for the marked antiviral activity of this new agent. Just completed were two randomized, controlled, Phase III, registration trials of entecavir in patients with chronic hepatitis B previously untreated with nucleos(t)ide analogs, one in a hepatitis B e-antigen (HBeAg)-reactive group, the other in an HBeAg-negative cohort (presumed to have precore or core promoter mutations). These were sizeable studies involving 709 and 638 patients, respectively. Like the trials of lamivudine and adefovir, the primary endpoint in the entecavir trials was histologic improvement (≥2-point reduction in the histologic activity index [HAI] and no worsening of fibrosis), but unlike trials of the earlier agents, the entecavir trials were not placebo-controlled; instead, the control group received lamivudine. The entecavir dose selected for these Phase III studies was 0.5 mg daily, which in Phase II, dose-ranging studies achieved maximal reduction of HBV DNA replication by approximately five orders of magnitude (2). In the Phase III trial involving HBeAg-reactive patients (one third of whom had failed the previous interferon treatment), in the entecavir group, histology was improved in 72% (vs 62% in the lamivudine group, \( p = 0.0085 \)), HBV DNA was rendered undetectable (<400 copies per mL) by polymerase chain reaction (PCR) in 69% (vs 38% for lamivudine, \( p < 0.0001 \)), alanine aminotransferase (ALT) improved to <1.25 times the upper limit of normal (ULN) in 78% (vs 70% for lamivudine, \( p = 0.0136 \)), but HBeAg seroconversion occurred in 21%, indistinguishable from the 18% seroconversion rate in the lamivudine group (3).

In a companion study among HBeAg-negative patients, histologic improvement was substantial, occurring in 70% (vs 61% for lamivudine, \( p = 0.0143 \)), HBV DNA became undetectable by PCR in 91% (vs 73% for lamivudine, \( p < 0.0001 \)), and ALT fell below the 1.25 × ULN threshold in 86% of patients (indistinguishable from the 81% in the lamivudine group) (4). No resistance mutations were encountered in the entecavir group, in either the HBeAg-reactive or the HBeAg-negative chronic hepatitis B group, during these 48-wk trials. In addition, the level of HBV DNA suppression achieved by entecavir was approximately 1.5 log\(_{10}\) more profound than that achieved by lamivudine in the HBeAg-reactive group, a median of 7 log\(_{10}\) copies/mL compared with 5.5 log\(_{10}\) copies/mL (\( p < 0.0001 \)); and 0.5 log\(_{10}\) more profound in the HBeAg-negative group (as expected, the baseline HBV DNA was lower in the HBeAg-negative group), a median of 5.2 log\(_{10}\) copies/mL compared with 4.7 log\(_{10}\) copies/mL (\( p < 0.0001 \)) (3, 4). In previous studies, lamivudine had reduced HBV DNA by only a median of 4 log\(_{10}\) copies/mL (5), and entecavir by a median of 5 log\(_{10}\) copies/mL (2); the apparent “improvement” in HBV DNA suppression by both lamivudine and entecavir is likely a reflection of the increasing sensitivity of PCR assays for HBV DNA over time. Given that assays for HBV DNA have changed over time, comparing HBV DNA suppression in any trial to that achieved in historical trials can be misleading; however, the inclusion of a lamivudine comparator arm in the entecavir trials provides confidence in the conclusion that entecavir is more effective at suppressing HBV DNA...
Entecavir has activity against lamivudine-resistant HBV, and a third lamivudine-controlled entecavir trial was carried out in a cohort of 286 lamivudine-refractory patients with YMDD-mutant HBV infection. The primary, histologic endpoint for this study, defined as a 2-point improvement in necroinflammatory HAI and no worsening of fibrosis, occurred twice as frequently in the entecavir group (55%) as in the lamivudine group (28%, \( p < 0.0001 \)). For this trial, the secondary endpoint was somewhat novel, a composite of undetectable HBV DNA as determined by the less stringent branched DNA (bDNA) assay (threshold of \( \sim 7 \times 10^5 \) copies/mL) and normal ALT. Entecavir was dramatically better than lamivudine in reaching the composite endpoint, 55% versus 4% (\( p < 0.0001 \)). Furthermore, entecavir reduced HBV DNA by a median of 5.14 \( \log_{10} \) copies/mL compared with lamivudine, which, as anticipated in this group, reduced HBV DNA by a median of only 0.48 \( \log_{10} \) copies/mL (\( p < 0.0001 \)). Clearly, entecavir is very effective against YMDD-mutant chronic hepatitis B and represents another choice beyond adefovir and tenofovir in the management of lamivudine-resistant hepatitis B (6).

In patients with lamivudine-resistant hepatitis B, switching from lamivudine to adefovir is associated with hepatitis-like ALT flares in one third of patients (7). A recent report suggests that switching from lamivudine to entecavir does not result in such hepatitis-like flares (8), but in that study, the definition of a flare was confined to patients with ALT elevations that were \( > 2 \times \) baseline and \( > 10 \times \) ULN; thus, flares \( \leq 10 \times \) ULN were not counted, although they were included in the adefovir trial cited above. Similarly, in the registration trials of lamivudine, posttreatment flares were defined as 2-fold and 3-fold ALT elevations over baseline; in short, posttreatment flares, defined differently in different trials, are not readily comparable. On the other hand, the data presented suggest that severe posttreatment flares are uncommon when entecavir replaces lamivudine in lamivudine-refractory hepatitis B.

As noted above, no resistance emerged to entecavir during the 48-wk trials in patients who were nucleos(t)ide-naive. Very rarely, entecavir resistance has been observed in a small number of highly lamivudine-experienced patients with long-standing lamivudine resistance prior to the introduction of entecavir, primarily in immunosuppressed liver allograft recipients. The frequency of entecavir resistance during a year of therapy, however, remains very low, occurring in approximately 1% of patients with preexisting lamivudine resistance (9).

These three studies represent a substantial body of data that, in conjunction with a highly favorable safety drug profile, recently resulted in Food and Drug Administration (FDA) approval of entecavir.

**TELBIVUDINE**

In a Phase II trial, the L-nucleoside telbivudine (LdT) appeared to be approximately 1.5 \( \log_{10} \) more potent than lamivudine in suppressing HBV DNA (10, 11). This 52-wk, randomized, controlled trial involved 104 patients distributed among five treatment arms, telbivudine 400 mg daily, telbivudine 600 mg daily, lamivudine 100 mg daily, and two combination arms in which lamivudine was paired with telbivudine at 400 and 600 mg daily. Lamivudine monotherapy suppressed HBV DNA by a median of 4.6 \( \log_{10} \) copies/mL. The other four arms, telbivudine at 400 or 600 mg daily alone or a combination of telbivudine at either dose administered with lamivudine, all achieved a median HBV DNA reduction of 6 \( \log_{10} \) copies/mL. Disappointing observations included the absence of additive efficacy or synergy between telbivudine and lamivudine, and a slight degradation in effect toward the end of therapy that might represent potential competition for phosphorylation between the two drugs or reflect the late emergence of resistance. Although telbivudine is associated with much less resistance than lamivudine, resistance emerged during the 1-yr trial in 5% of the patients in the two telbivudine monotherapy arms (vs 21% in the lamivudine monotherapy arm and 12% in the two lamivudine–telbivudine combination therapy arms).

In addition, in the Phase II trial, telbivudine monotherapy was superior to lamivudine or to lamivudine–telbivudine combination therapy in inhibiting HBV DNA to <200 copies/mL by PCR (61% vs 32% and 49%, respectively), in reducing ALT to normal (86% vs 63% and 78%), and in achieving HBeAg seroconversion (31% vs 22% and 15%). Again, the fact that combination therapy was less effective than either drug alone in these virologic, biochemical, and serologic endpoints raised the specter of competition between the two drugs.

Large-scale, randomized, controlled, Phase III trials of telbivudine are now in progress; like entecavir, telbivudine therapy is being compared with a lamivudine control arm. Unlike previously approved nucleos(t)ide analogs, however, telbivudine is the first of these antiviral agents in which histology will not be the primary endpoint; instead, the primary endpoints will be serologic and virologic. Whether, with contemporary assays for HBV DNA, telbivudine will be shown in Phase III trials to be virologically equivalent or superior to entecavir remains to be seen. Fortunately, both drugs have been compared to concomitant lamivudine control arms; based on data generated to date, both achieve a median reduction of HBV DNA, that is 1.5 \( \log_{10} \) better than lamivudine. Telbivudine is expected to be associated with some, albeit low-level, resistance; whether Phase III data will demonstrate an advantage for telbivudine in virologic or serologic endpoints will help determine the role for telbivudine in the armamentarium of therapeutic choices for hepatitis B. We will have to wait for the Phase III data, now being generated in a very sizable patient population, before reaching conclusions about the relative benefits of this new drug.

**TENOFOVIR**

Tenofovir, approved for HIV, is also highly active against HBV, and many of us had an opportunity to use it in our
lamivudine-resistant patients during the window of time before adefovir was approved. The dose utilized in patients with chronic hepatitis B infection is 300 mg daily. Of the dozen studies that have been described in the literature, all are relatively small and not necessarily randomized, in which tenofovir appeared to be effective in the treatment of lamivudine-resistant chronic hepatitis B, both in HBV mono-infected and HBV/HIV co-infected patients. One example is a non-randomized trial of tenofovir versus adefovir in 40 patients with lamivudine-resistant chronic hepatitis B (12). In the 25 patients treated with tenofovir, the median 6-month reduction in HBV DNA was 6.6 log10 versus only 1.72 log10 for the 15 patients treated with adefovir. HBV DNA was undetectable by PCR in 57% of the tenofovir group versus only 7% of the adefovir group, and ALT was normal in 44% versus 20%, respectively. Although most of the reported experience on the use of tenofovir in hepatitis B has been in patients with lamivudine resistance, the data presented to date support the superior potency of tenofovir over that of adefovir. An anecdotal case is illustrative. In an HBeAg-reactive patient with lamivudine-resistant hepatitis B, we added adefovir for 52 wk as part of a clinical trial. During adefovir therapy, the patient’s HBV DNA fell from 106 copies/mL to a nadir of 103 copies/mL at week 40, culminating at a level of 102 copies/mL at week 52, the end of therapy in the trial. At week 60, after his HBV DNA had rebounded to 106 copies/mL, tenofovir 300 mg/day was added. Thereafter, the level of HBV DNA fell to 103 copies/mL within 1 wk, HBeAg seroconversion occurred within 4 wk, and HBV DNA became undetectable (<103 copies/mL) within 5 wk. Although this is a single, anecdotal case, many investigators have observed similar improvements for tenofovir over adefovir in potency and rapidity of inhibition of HBV DNA, and reports continue to appear in the literature (13). Currently, there are clinical trials planned in which tenofovir and adefovir will be compared head-to-head; observations generated to date would predict that tenofovir will be shown in randomized, controlled trials to be superior to adefovir.

EMTRICITABINE

Emtricitabine (FTC) is similar in structure and activity to lamivudine (3TC), and a dose of 200 mg/day was selected based on early dose-finding trials. Results of a Phase III, placebo-controlled 48-wk trial were presented recently in which 167 HBeAg-reactive patients were randomized to emtricitabine and 81 to placebo; the primary endpoint was histology (≥2-point improvement in HAI). Histologic improvement occurred in 62% of the treated patients versus 25% of the placebo group (p < 0.001), very similar to histologic outcomes in clinical trials of both lamivudine and adefovir (14). HBV DNA <400 copies/mL was recorded in 56% of the treated patients (10–20% higher frequency than with lamivudine in previous reports) versus 7% of the placebo group (p < 0.001), and emtricitabine was superior in the biochemical endpoint of normal ALT, 65% versus 25% of the placebo group (p < 0.001). Considering serology, however, HBeAg seroconversion occurred in a disappointing, indistinguishable 12% of the emtricitabine-treated and the placebo control groups. Resistance at 48 wk was recorded in 12.6% of the emtricitabine group, lower than the incidence of resistance recorded in lamivudine trials. Ultimately, this drug appears to be relatively similar to lamivudine, and the likelihood is high that the new generation of more potent antiviral agents, including entecavir and télbivudine, will prove superior to both lamivudine and emtricitabine.

A potential role for emtricitabine would be in combination with a nucleotide analog, such as adefovir. Recently, a trial of adefovir monotherapy versus adefovir plus emtricitabine—a combination approved for HIV—was described in 30 HBeAg-positive patients (15). In this trial, at 48 wk, the combination suppressed HBV DNA by a median of 3.48 log10 copies/mL compared with only 2.22 log10 copies/mL reduction in the adefovir monotherapy group (p < 0.01). What remains difficult to explain is the very limited 2 log10 reduction in HBV DNA achieved in the adefovir monotherapy arm, well below the 3.5 log10 reduction reported among HBeAg-reactive patients in registration trials (16). The difficulty in interpreting these data is largely due to the very small sample size and the earlier observation that a combination of lamivudine plus adefovir offers no advantage in HBV DNA inhibition over lamivudine monotherapy (17).

PEGYLATED INTERFERONS

The development of long-acting pegylated interferons for the treatment of chronic hepatitis C has rekindled interest in interferon-based therapy of chronic hepatitis B. Results of large, randomized, controlled trials of pegylated interferon (PEG IFN) alfa-2a and alfa-2b in both HBeAg-reactive and HBeAg-negative chronic hepatitis B have been reported.

PEG IFN Alfa-2b in HBeAg-Reactive Chronic Hepatitis B

Jansséen et al. undertook a prospective trial among 307 predominantly European (21% Asian) patients who were randomized to be treated for 52 wk with either PEG IFN alfa-2b (weekly injections of 100 µg × 32 wk followed by 50 µg for the final 22 wk) plus lamivudine 100 mg daily, or PEG IFN monotherapy (plus placebo); this trial did not include a lamivudine monotherapy arm (18). At the end of the 52-wk treatment period, combination therapy was superior to monotherapy in achieving HBeAg loss (44% vs 29%; p = 0.01), and in suppression of HBV DNA to undetectable levels (<400 copies/mL as determined by PCR) (33% vs 10%; p < 0.001). However, at week 78 (6 months after completion of therapy), the two treatment arms were indistinguishable (HBeAg loss in 35% vs 36%, and undetectable HBV DNA in 9% vs 7% of the combination therapy and monotherapy arms, respectively). Despite the addition of PEG IFN to lamivudine, lamivudine resistance continued to occur in the cohort receiving the PEG IFN–lamivudine
combination (present in 5% of the cohort at baseline and 11% at the end of therapy), suggesting that PEG IFN would not necessarily prevent the emergence of resistance to lamivudine when the two drugs are used together. In this trial, HBsAg seroconversion occurred in 6% of study subjects, evenly distributed between the two treatment arms. Based on these results, the investigators concluded that adding lamivudine to PEG IFN provides no advantage over PEG IFN monotherapy, and that PEG IFN alone should be the standard therapy.

These findings are reminiscent of the results of an earlier trial of lamivudine combined with standard IFN reported in 2000 (19). That original trial was based on the hypothesis that reducing the level of HBV DNA with an initial 8 wk of lamivudine would render patients more responsive to a 16-wk course of IFN, which had been shown to be more effective in patients with low HBV DNA levels (20). In that trial, the combination was superior (in achieving HBeAg seroconversion) to therapy with either drug alone (52 wk of lamivudine or 16 wk of IFN) at the end of therapy (week 52), but that advantage was lost at week 64, 4 months after the end of the longest treatment arm (lamivudine monotherapy), at which time all three groups were indistinguishable. In both the previous IFN–lamivudine and contemporary PEG IFN–lamivudine trials, the apparent superiority of combination therapy at the end of therapy was not durable and did not predict the ultimate outcome measured 4–6 months later.

PEG IFN Alfa-2a in HBeAg-Reactive Chronic Hepatitis B

Peginterferon alfa-2a has recently received FDA approval for the treatment of patients with chronic hepatitis B infection. In a large, randomized, controlled trial of PEG IFN among 814 patients with HBeAg-positive chronic hepatitis B, monotherapy with PEG IFN alfa-2a (180 μg once a week) was compared with lamivudine monotherapy (100 mg/day) and a combination arm of PEG IFN plus lamivudine; treatment lasted 48 wk, and clinical outcomes were assessed at week 72. The 72-wk results of this study, i.e., 24 wk after the completion of therapy, were reported recently (21). At this time point, 6 months after therapy, the frequency of HBeAg seroconversion (32% vs 27%) and HBeAg loss (34% vs 28%) were similar in the PEG IFN monotherapy and PEG IFN–lamivudine combination therapy groups, respectively; both PEG IFN arms were superior to the lamivudine monotherapy arm, in which HBeAg seroconversion and loss occurred in 19% and 21% of patients, respectively. The criterion for undetectable HBV DNA was not very stringent, $<10^5$ copies/mL; at week 72, this endpoint was met by 32% of the PEG IFN monotherapy group, 34% of the combination group, and only 22% of the lamivudine monotherapy group; similarly, a return to normal ALT was observed at week 72 in 41%, 39%, and 28% of the three groups, respectively. The differences in these endpoints between the PEG IFN arms and the lamivudine monotherapy arm were all statistically significant ($p = 0.043$ to $<0.001$). These observations led the investigators of this study to conclude that adding lamivudine to PEG IFN did not confer any additional benefit and that the most efficacious treatment arm was PEG IFN monotherapy. Although HBsAg seroconversion was observed in the two PEG IFN arms, this endpoint was met in only 3% of the study patients. HBsAg seroconversion did not occur in the lamivudine monotherapy arm in this trial, but among lamivudine-treated subjects in registration trials of lamivudine, HBsAg seroconversion did occur in a comparable proportion.

At week 48, i.e., at end of therapy, both PEG IFN–lamivudine combination therapy and lamivudine monotherapy suppressed HBV DNA more profoundly, by a mean of 7.2 log10 copies/mL and 5.8 log10 copies/mL, respectively, than PEG IFN monotherapy (4.5 log10 copies/mL). Evaluated in this way, lamivudine does appear to add benefit.

One of the difficulties in comparing lamivudine to PEG IFN at week 72 is that assessing the impact of lamivudine 6 months after its discontinuation subjects lamivudine to a new standard for a nucleos(t)ide analog. Six months after discontinuation of lamivudine, all but those with HBeAg responses will have reverted back to baseline. In assessing the results of this trial, those who advocate PEG IFN therapy tend to focus on the value of treating for a finite period of 1 yr—an approximate 10% increment in HBeAg response and a 3% frequency of HBsAg seroconversion. In contrast, those who advocate for nucleoside analogs such as lamivudine tend to focus on the more profound suppression achieved with these antiviral agents, an effect that can be maintained by extending therapy beyond a year. The frequency of lamivudine–associated HBeAg responses increases with the duration of treatment, which, when extended beyond a year, equals or exceeds HBeAg response rates observed with PEG IFN. Lamivudine advocates ask whether the marginal benefit of a year of PEG IFN, as measured at 18 months, including the trivial HBsAg seroconversion rate, justifies subjecting 100% of the patients to a year of injection therapy associated with morbid side effects.

Returning to the issue of HBsAg seroconversion during antiviral therapy, interferon protagonists focus on the expectation that IFN-based treatment can achieve HBsAg seroconversion, while nucleos(t)ide-based treatment does not. In fact, the 10% HBsAg seroconversion rates reported in the past for IFN-treated patients are no longer being observed (22). One possible explanation is that the data observed in the 1980s and early 1990s may have included a higher frequency of patients with HBV genotype A, who are more likely to lose HBeAg and HBsAg, but who are becoming vanishingly rare. As the data for entecavir and telbivudine demonstrate, new nucleosides suppress HBV replication more profoundly than PEG IFN, and nucleos(t)ide treatment is much more likely than IFN treatment to result in demonstrable histologic improvement, now being reported in up to 70% of nucleoside-treated patients.

PEG IFN Alfa-2a in HBeAg-Negative Chronic Hepatitis B

In a recently published report, Marcellin et al., described a three-arm, prospective, randomized trial of PEG IFN
alfa-2a (180 μg injected once a week), versus a combination of PEG IFN–lamivudine, versus lamivudine monotherapy (100 mg a day), each administered for 48 wk to a total cohort of 537 patients with HBeAg-negative chronic hepatitis B (23). At week 48, the end of therapy, while all subjects were still receiving treatment, HBV DNA was undetectable (<400 copies/mL as measured by PCR) in 73% of the lamivudine monotherapy group, which was better than in the PEG IFN monotherapy group (63%), but the combination group results were even better at 87%. Moreover, at week 48, a return to normal ALT was achieved more frequently in the lamivudine monotherapy group (73%), than in the combination therapy group (49%) or the PEG IFN monotherapy group (only 38%). At week 72, i.e., 6 months after discontinuation of therapy, the two PEG IFN arms outperform the lamivudine monotherapy arm. Whether patients received PEG IFN with or without lamivudine, approximately 60% maintained a normal ALT, and approximately 20% maintained undetectable levels of HBV DNA (<400 copies/mL); in the lamivudine monotherapy group, 6 months after discontinuation of therapy, ALT was normal in 44% of patients and HBV DNA was <400 copies/mL in only 7%. Unlike the trial reported by Janssen et al. in HBeAg-reactive patients (18), the emergence of YMDD mutations was confined to the lamivudine monotherapy group, occurring in 15% of patients at the end of therapy.

One advantage of the combination therapy was an extra log₁₀ reduction in HBV DNA at week 48 compared with the PEG IFN monotherapy group or the lamivudine monotherapy group. At week 48, lamivudine and PEG IFN monotherapies reduced HBV DNA by a mean of 4.1 and 4.2 log₁₀ copies/mL, compared to a mean reduction of 5.0 log₁₀ copies/mL in the combination arm. Six months after therapy was discontinued, HBV DNA inhibition was degraded in all three arms, down to a mean of 2.3, 2.4, and 1.6 log₁₀ copies/mL in the PEG IFN, PEG IFN–lamivudine, and lamivudine arms, respectively. With such low levels of HBV DNA suppression maintained 6 months after completion of therapy, further loss of virologic response is inevitable. In fact, in HBeAg-negative chronic hepatitis B, a 6-month posttreatment endpoint is not a faithful reflection of ultimate treatment efficacy, as discussed below.

In this trial of PEG IFN alfa-2a for HBeAg-negative chronic hepatitis B, as reported for other PEG IFN trials in patients with chronic hepatitis B, PEG IFN was said to be better tolerated than PEG IFN for chronic hepatitis C (23). Depression, rigors, and myalgias were substantially less frequent in this trial among patients with hepatitis B than in the three pivotal trials of PEG IFN alfa-2a for chronic hepatitis C (24–26). In fact, drug discontinuation, fatigue, and fever were reported at similar or even higher frequencies in the hepatitis B trial, and dose reduction was actually more frequent in the hepatitis B trial than in any of the three hepatitis C trials. Certainly, depression is common among patients with chronic hepatitis C, even without antiviral therapy, but the notion that PEG IFN is any more tolerable in hepatitis B than in hepatitis C is difficult to accept.

Regarding the durability of treatment response in patients with HBeAg-negative chronic hepatitis B, data for standard IFN treatment illustrate the limitations of early posttreatment observations. Among the 216 patients treated with standard IFN alpha-2b for 5–12 months, 54% had levels of HBV DNA below the sensitivity threshold of hybridization assays (≈ 10⁵ viral copies/mL); however, a year later, the virologic response was degraded to only 24%, and after long-term follow-up monitoring for a median of 7 yr, the response was durable in only 18% (27). Similarly, in the trial of PEG IFN in HBeAg-negative chronic hepatitis B (Marcellin et al.), suppression of HBV DNA to the more stringent threshold of <400 copies/mL fell in the PEG IFN monotherapy group from 63% at the end of 48 wk of therapy to only 19% 24 wk later; inevitably this trend will continue, and durability will continue to decline with duration of follow-up monitoring (23).

In addition, some investigators have suggested that durable responses in HBeAg-negative chronic hepatitis B are confined to patients treated with interferons. On the contrary, Fung et al. have shown, in a very small study involving 50 Chinese patients with HBeAg-negative chronic hepatitis B, that the 18-month durability of a virologic response (<10⁵ viral copies/mL) can be maintained in 50% of patients after 2 yr of lamivudine therapy (28). Thus, observations in patients with HBeAg-negative chronic hepatitis B support the need for protracted therapy, regardless of whether the treatment is with a nucleos(t)ide analog or an IFN preparation. Whichever treatment approach is chosen, sustained virologic responses can be achieved in HBeAg-negative patients, but only if treatment is over an extended period. Moreover, 6 months after completion of treatment is too soon for a confident assessment of response durability in this patient population.

Although limited data on histologic benefit are available in clinical trials of interferon for chronic hepatitis B, each of the registration trials of nucleotide and nucleoside analogs in patients with hepatitis B have shown convincing histologic benefit in the majority of treated patients.

THE IMPORTANCE OF SUPPRESSING VIRAL REPLICATION

An important observation derived from the lamivudine trial and telbivudine trial databases is that suppression of HBV DNA has a dramatic impact on clinical endpoints. Among patients treated in Phase II trials of telbivudine, including those in the comparator lamivudine arms, patients in whom HBV DNA was suppressed to <200 copies/mL at week 24 achieved an end-treatment HBeAg response of 47% at week 52; in contrast, patients in whom the level of HBV DNA was not suppressed adequately and remained >4 log₁₀ copies/mL at week 24 achieved end-treatment HBeAg responses of only 7% at week 52. Conversely, if the level of HBV DNA was suppressed to below the level of quantification (<200 copies) or even to below 3 log₁₀ copies/mL, no YMDD resistance/viral
breakthrough occurred. Viral breakthrough was confined to the subgroup in whom HBV DNA could not be adequately suppressed and remained >3 log_{10} copies/mL, and viral breakthroughs were especially more likely if the level of HBV DNA exceeded 4 log_{10} copies/mL (10).

The important lesson derived from these observations is that the more profound the level of HBV DNA suppression realized, the more likely a treated patient is to achieve a serologic endpoint and the less likely they are to experience resistance. In addition, data collected during the development of oral nucleos(t)ide antiviral agents have shown a direct correlation between the level of HBV DNA inhibition and histologic benefit. For example, in a review of 26 prospective studies of antiviral therapy in 3,428 patients with chronic hepatitis B, Mommeja-Marin et al. showed that the median level of improvement in HAI between baseline and the end of treatment is directly proportional to the median log_{10} reduction achieved in HBV DNA (t = 0.06, p = 10^{-6}) (29). Data such as these have now influenced the FDA to allow new trials of antiviral drug development for hepatitis B to rely on virologic primary endpoints instead of histology.

In conclusion, the degree of HBV DNA suppression correlates with meaningful clinical endpoints and is inversely related to the emergence of resistance. Therefore, the more profound the level of HBV DNA suppression the better. Ultimately, chronic hepatitis B is a viral disease, and viral suppression is the primary endpoint that will be reflected by all other clinical endpoints. From this observation follows the assumption that the antivirals that suppress HBV DNA most profoundly will emerge as first-line therapy. In all likelihood, combination therapy will be required to maintain viral suppression profoundly and to preempt the emergence of any resistance. For the majority of patients with chronic hepatitis B (almost all of those with HBeAg-negative disease and, among those with HBeAg-reactive disease, all but the proportion who experience HBeAg responses during treatment), potent, safe, and low-resistance oral regimens will ultimately emerge that will permit long-term oral treatment. Although several decades of observation may be required to prove the point, a reasonable prediction is that limiting the duration of high HBV DNA replication with antiviral therapy is very likely to be shown to improve the natural history of chronic hepatitis B and to limit its often dire clinical consequences.

Reprint requests and correspondence: Jules L. Dienstag, M.D., GI Unit – GRJ-825, Massachusetts General Hospital, Blake 4, 55 Fruit Street, Boston, MA 02114

Received July 15, 2005; accepted August 24, 2005.

REFERENCES

17. Sung JY, Lai JY, Zeuzem S, et al. A randomized double-blind phase II study of lamivudine (LAM) compared to lamivudine plus adefovir dipivoxil (ADV) for treatment