Therapeutic Options for Chronic Hepatitis B: Considerations and Controversies

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Five agents are currently approved for the treatment of chronic hepatitis B infection. This article will discuss the three agents for which the most extensive data are available; interferon (IFN), lamivudine, and adefovir, while the following article by Dr. Jules Dienstag will discuss the recently marketed agents, entecavir and peginterferon alfa-2a. The advantages of IFN are its finite duration of therapy (4–6 months), lack of emergence of resistance, and durability of response. On the negative side, response to IFN is less durable in patients with HBeAg-negative chronic hepatitis B virus (HBV). Also, use of IFN is limited by adverse effects and the mode of administration (daily to thrice-weekly subcutaneous injection). Lamivudine and adefovir are orally administered and have good tolerability and safety. Even in patients who experience a marked decrease in serum HBV DNA and loss of HBeAg, oral therapy needs to be continued for at least 6 months, to avoid the risk of reappearance of HBeAg and viremia. Rates of HBeAg seroconversion to anti-HBe-positivity increase with duration of lamivudine or adefovir therapy. The likelihood of development of resistance to lamivudine and associated viral breakthrough limits its long-term use. In patients with HBeAg-negative chronic hepatitis B, long-term therapy is usually required, as off-treatment relapse is common. The emergence of resistance to adefovir is delayed and infrequent, hence adefovir may be preferred in patients requiring long-term therapy.

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INTRODUCTION

The goals of treatment in chronic hepatitis B virus (HBV) infection are sustained viral suppression, normalization of serum alanine aminotransferase (ALT), and improvement in liver histology, leading to long-term reduction in the risk of cirrhosis and hepatocellular carcinoma (HCC). Interferon-α (IFN-α), lamivudine, and adefovir are all licensed for the treatment of chronic hepatitis B infection. Each has its particular advantages and disadvantages. Treatment outcomes differ between patient groups, and the histologic and serologic characteristics of a patient with chronic HBV infection are not the only important considerations in the therapeutic decision-making process.

IFN-α has broad antiviral and immunomodulatory activity. The effectiveness of IFN in patients with chronic HBV infection with ongoing viral replication, as evidenced by seropositivity for hepatitis B surface antigen (HBsAg) and hepatitis e antigen (HBeAg), was confirmed in a meta-analysis of 15 randomized, placebo-controlled trials (1). In comparison with placebo, significantly more patients treated with IFN (for at least 3 months) achieved HBeAg loss (33% vs 12%), reduction of HBV DNA to below the quantifiable limit (by hybridization technology) (37% vs 17%), and HBsAg loss (8% vs 2%). Significant effects on the rate of seroconversion to anti-HBe and anti-HBs were also evident. The effects of 4–6 months of IFN therapy translate into a meaningful clinical impact, with patients who have experienced HBeAg loss as a result of IFN therapy showing higher rates of cumulative survival and survival without clinical complications on long-term follow-up than those remaining HBeAg seropositive (2). Long-term benefit in reduction of HCC has also been reported (3). Asian patients with elevated serum ALT respond to IFN therapy as well as Caucasian patients, but those with normal or minimally elevated serum ALT, a relatively larger proportion of Asian patients, respond poorly (4–6). Moreover, in contrast to the study of Niederau et al. (2), a study in HBeAg-positive Chinese patients failed to show any benefit of IFN therapy in preventing long-term cirrhosis-related complications (7). Although this study found the rate of loss of HBeAg with IFN significantly greater than in the control group at 6 and 24 months, a significant proportion of the IFN-treated patients underwent HBeAg seroreversion, with the reemergence of HBV DNA.

A significant proportion of patients with chronic HBV infection have the HBeAg-negative form of the disease, owing to the presence of mutated virus that continues replicating but does not express the e antigen. Pooled results from trials in Greek and Italian patients indicate that HBeAg-negative patients can respond to IFN therapy (Table 1) (8–12). The response to IFN therapy is not, however, as durable as that in HBeAg-positive patients, particularly with the traditional
Table 1. Outcomes of IFN Therapy for HBeAg-Negative Chronic HBV

<table>
<thead>
<tr>
<th>Outcome Parameter</th>
<th>Patients (%)</th>
<th>Reference(s)</th>
</tr>
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<tbody>
<tr>
<td>Undetectable HBV DNA and ALT normalization at end of therapy</td>
<td>28–69</td>
<td>8–11</td>
</tr>
<tr>
<td>Sustained response at end of follow-up</td>
<td>6–33</td>
<td>8, 9, 11</td>
</tr>
<tr>
<td>Loss of HBsAg at end of follow-up</td>
<td>4.5–13</td>
<td>8, 11, 12</td>
</tr>
<tr>
<td>Long-term ALT normalization</td>
<td>27</td>
<td>12</td>
</tr>
</tbody>
</table>

4–6 months of therapy, and a prolonged treatment course may be needed to achieve the optimal response (8).

In both HBeAg-positive and HBeAg-negative patients, low serum HBV DNA level (<200 pg/mL), high serum ALT, high histologic activity, and more severe necroinflammation on liver biopsy are predictive of response to IFN (13–15). Patients infected with HBV genotype B or A are more likely to respond than those carrying genotype C or D (16, 17). Although HBV genotyping does not yet have a uniformly accepted role in practice, selection of candidates for IFN therapy may prove to be one such application.

The advantages of IFN are that it can be used for therapy of a short, finite course, with no emergence of resistance, response is durable, at least in HBeAg-positive chronic hepatitis B, and long-term survival benefit has been demonstrated. A small proportion of patients can achieve clearance of HBsAg by the end of treatment, and treated patients are more likely than controls to clear HBsAg in the subsequent years, particularly if they experienced successful HBeAg seroconversion on therapy (2, 18).

The disadvantages of IFN therapy are related to practicality and safety. Conventional IFN is administered by subcutaneous injection daily or three times weekly and the dose that can be given is limited by adverse reactions which include flu-like symptoms (headache, fevers, chills, myalgia, malaise), psychiatric effects (mood swings, irritability, depression), and bone marrow toxicity leading to neutropenia and thrombocytopenia. Therefore, in addition to drug costs, IFN therapy involves the cost of patient support and monitoring.

IFN-α is contraindicated in patients with decompensated cirrhosis because of the risk of exacerbation leading to liver failure (19), and caution is warranted even in patients with compensated cirrhosis because of the risk of decompensation with prolonged therapy (6, 20). It is also contraindicated in severe depression or psychiatric disorders and autoimmune disorders.

LAMIVUDINE

Lamivudine is an oral nucleoside analog that inhibits HBV DNA polymerase activity and hence viral replication. Lamivudine has good tolerability and safety. After short-term therapy (up to 6 months), serum HBV DNA, although markedly reduced in most patients, returns to pre-treatment levels when treatment is stopped (21). One year of therapy in HBeAg-positive patients is associated with HBeAg loss in 17–33% of patients and HBeAg seroconversion rates of 16–18% (21–24). Quantitation of viremia indicates that HBeAg seroconversion associated with lamivudine therapy is a reflection of profound suppression of viral replication: full HBeAg seroconversion was found to occur only in patients with a reduction in HBV DNA to <10^4 copies/mL (25). As with IFN, response is dependent on baseline serum ALT level. Patients with higher baseline serum ALT are more likely to undergo HBeAg seroconversion, irrespective of ethnicity (Fig. 1). Continuing lamivudine treatment until there is an HBeAg response is recommended, as maintaining therapy beyond 1 yr in patients who have failed to achieve HBeAg seroconversion yields increasing HBeAg seroconversion rates, despite the emergence of lamivudine-resistant YMDD viral strains (26). Most patients with HBeAg seroconversion following lamivudine therapy have a durable response that is maintained after discontinuation of treatment. Although there is a gradual increase in the likelihood of seroreversion ( reappearance of HBeAg) over the 3–4 yr following discontinuation, the majority of patients (in one study, 77% after a median follow-up period of 37 months) remain HBeAg-negative, and some also lose HBsAg (27).

Lamivudine is efficacious in chronic HBeAg-negative HBV infection, with short-term therapy (24 wk) achieving ALT/biochemical response rates similar to those in HBeAg-positive patients (28), but most HBeAg-negative patients relapse after treatment is stopped. Continued lamivudine therapy in HBeAg-negative patients leads to the emergence of YMDD mutants which is associated with increasing serum HBV DNA levels to those at least as high as baseline, usually followed by increases in serum ALT (29). Although 96% of HBeAg-negative patients have normal serum ALT after 12 months of lamivudine therapy, this drops to 60% by 24 months, and less than half maintain this biochemical remission beyond 30 months of therapy (29).

The proportion of patients in whom YMDD variants are detectable increases with time on lamivudine therapy, rising from around 15–25% after 1 yr to 70% by 4 yr (30).
Appearance of YMDD variants is associated with increases in serum HBV DNA and ALT toward pre-treatment levels, together with reversal of initial histologic improvement (6, 30). A 3-yr study in 63 patients continuing on lamivudine therapy after failing to undergo HBeAg seroconversion after 1 yr of lamivudine therapy found that histologic state was improved in 56%, remained stable in 33%, and worsened in only 11%; patients without YMDD variants were more likely to improve and less likely to deteriorate than those with a mutant strain, and the least improvement was evident in patients with long-standing YMDD mutation (31).

Lamivudine, unlike IFN, can be readily used in cirrhotic patients (6, 32). In Asian-Pacific patients with compensated cirrhosis (either HBeAg-positive or HBeAg-negative, but with detectable HBV DNA), lamivudine reduced the risk of liver complications, with a reduction of about 50% in disease progression (defined as hepatic decompensation, HCC, bacterial peritonitis, bleeding gastroesophageal varices, or death related to liver disease) during a median treatment duration of 32 months (32). It is noteworthy that this trial was terminated at the second interim analysis because of the clear benefit of therapy. Again, however, outcome was influenced by YMDD status; although untreated patients were the most likely to experience disease progression, treated patients with YMDD mutations experienced more endpoints resulting from decompensation than those who retained wild-type virus. This observation is an important affirmation of the principle that long-term viral suppression is critical to achieving optimal therapeutic outcomes. Lamivudine is also of benefit in comparison with historical controls in patients with decompensated cirrhosis, in whom IFN therapy is unsuitable (at conventional doses, at least), but the emergence of YMDD mutant strains may be particularly limiting in this patient group (6).

Patients on lamivudine should be followed periodically with quantitative HBV DNA assays and liver profiles for evidence of effective viral suppression and reduced hepatic necroinflammatory activity. In addition, HBeAg and anti-HBe should be evaluated prospectively in patients who are initially HBeAg-positive to determine if HBeAg loss or seroconversion has occurred. Laboratory assays should be performed at a minimum of once every 6 months, but many clinicians prefer to assess patient response every 3 months, frequent intervals may be justifiable for the first 2–3 yr, particularly when an excellent virologic response has been achieved, or liver transplants usually have confounding features such as systemic illness or other nephrotoxic drugs. Still, periodic follow-up of creatinine is recommended in all patients during treatment, particularly in individuals with pre-existing renal impairment or those taking nephrotoxic medications concomitantly. Patients with creatinine clearance below 50 mL/min require adjustment of the dosage interval (41).

**ADEFOVIR**

Adefovir dipivoxil is an oral nucleotide analog that is converted to the active metabolite, adefovir diphosphate. In clinical trials, 48 wk of adefovir therapy reduced HBV DNA by approximately 3.5 and 3.9 log_{10} copies/mL, in HBeAg-positive (33) and HBeAg-negative patients (34), respectively, with associated biochemical and histologic improvements. In HBeAg-positive patients, continued treatment leads to increasing proportions of patients showing ALT normalization (81% by 144 wk), reduction of HBV to undetectable levels (56% by 144 wk), and HBeAg loss (51% by 144 wk) (35). The rates of seroconversion increased from 21% at 48 wk (adefovir 10 mg), compared with 6% of patients given placebo, to 43% at 144 wk (35). Information regarding the durability of response after discontinuation of therapy is limited at present, but HBeAg seroconversion has been reported to be maintained in >90% of patients with a median follow-up of over a year (36). After 48 wk of therapy, HBV DNA was undetectable in 51% of HBeAg-negative patients (34); with continued therapy 71% became HBV DNA-negative by 96 wk (37).

In contrast to lamivudine, the emergence of resistance to adefovir seems to be relatively delayed and infrequent (Fig. 2) (30, 38, 39). Beyond 1 yr, two resistance mutations have been observed, N236T and A181V. When switching patients with lamivudine-resistant strains from lamivudine to adefovir a short (3-month) overlap period when the patient is treated with both agents before discontinuation of lamivudine is recommended to avoid the occurrence of ALT flares (40).

Guidelines for following patients on adefovir are similar to those for lamivudine (see above), but monitoring at less frequent intervals may be justifiable for the first 2–3 yr, particularly when an excellent virologic response has been achieved, because of the lower frequency of emergent resistance. Although nephrotoxic at higher doses, significant renal injury is rare in patients with normal renal function, and the occasional reports of rising creatinine in patients with advanced cirrhosis or liver transplants usually have confounding features such as systemic illness or other nephrotoxic drugs. Still, periodic follow-up of creatinine is recommended in all patients during treatment, particularly in individuals with pre-existing renal impairment or those taking nephrotoxic medications concomitantly. Patients with creatinine clearance below 50 mL/min require adjustment of the dosage interval (41).

**COMBINATION THERAPY**

Studies reporting the efficacy of combination therapy have appeared in the literature. To date, results have not suggested enhanced efficacy of such treatment. The rate of HBeAg
**Table 2. Summary of Licensed Agents for Chronic Hepatitis B Infection**

<table>
<thead>
<tr>
<th></th>
<th>Interferon</th>
<th>Lamivudine</th>
<th>Adefovir</th>
<th>Entecavir*</th>
<th>Peginterferon alfa-2a*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>5 MU qd or 10 MU tiw</td>
<td>100 mg qd</td>
<td>10 mg qd</td>
<td>Nucleoside naïve: 0.5 mg qd lamivudine-resistant patients 1.0 mg qd</td>
<td>180 μg qw</td>
</tr>
<tr>
<td><strong>Route</strong></td>
<td>Subcutaneous</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td><strong>Duration of treatment</strong></td>
<td>8 wk pretreatment with lamivudine followed by 16 wk of combination therapy</td>
<td>4–6 months</td>
<td>1 yr</td>
<td>8 wk</td>
<td>48 wk</td>
</tr>
<tr>
<td><strong>HBeAg-positive patients</strong></td>
<td>≥ 1 yr</td>
<td>≥ 1 yr</td>
<td>≥1 yr</td>
<td>≥1 yr</td>
<td>48 wk</td>
</tr>
<tr>
<td><strong>HBeAg-negative patients</strong></td>
<td>1 yr</td>
<td>1 yr</td>
<td>&gt;1 yr</td>
<td>&gt;1 yr</td>
<td>48 wk</td>
</tr>
<tr>
<td><strong>Drug resistance</strong></td>
<td>None</td>
<td>Year 1: ~20%</td>
<td>Year 1: 0%</td>
<td>Year 1: 0% in nucleos(t)ide naïve 7% in lamivudine-resistant cases</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Year 4: ~70%</td>
<td>Year 4: ~15%</td>
<td></td>
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</tbody>
</table>

*Refer to the article by Dr. Jules Dienstag for detailed discussion on entecavir and peginterferon alfa-2a.

séroconversion was reported in treatment naïve patients receiving lamivudine alone (100 mg qd for 52 wk), IFN monotherapy (10 MU thrice weekly for 16 wk) or the two in combination (8 wk pretreatment with lamivudine followed by 16 wk of combination therapy) (42). At week 52, the rate of HBeAg seroconversion was 29% in the combination arm compared to 19% and 18% in the IFN and lamivudine monotherapy groups, respectively. Although a higher rate of seroconversion was reported with combination therapy, this did not reach statistical significance.

In nucleos(t)ide naïve patients receiving either lamivudine alone (100 mg qd), or lamivudine and adefovir (10 mg qd) in combination there was no significant difference in serum HBV DNA level between the two groups following 52 wk of therapy. However, patients receiving lamivudine monotherapy had a higher rate of YMDD mutations compared to the combination group (20% vs 2%, respectively) (43). In patients with existing YMDD mutations, adefovir-lamivudine combination therapy is no more effective at reducing serum HBV DNA levels than adefovir alone (40). It may, however, result in a lower rate of long-term emergence of adefovir-associated mutations. Accordingly, although not approved, some clinicians have used a combination of lamivudine and adefovir in patients with cirrhosis to minimize the risk of resistance.

**AGENTS APPROVED FOR USE IN 2005**

Entecavir and peginterferon alfa-2a received FDA approval for the treatment of chronic hepatitis B infection in 2005 adding two important agents to our armamentarium. Table 2 provides a summary of the five agents currently approved by the FDA. In the following article Dr. Jules Dienstag will discuss the pivotal trial data concerning entecavir and peginterferon alfa-2a (44).

**CONCLUSIONS**

The advantages and disadvantages of IFN, lamivudine, and adefovir in the management of chronic HBV should be considered when deciding which therapy is appropriate for a particular patient, as should the serologic, virologic, and biochemical status of the patient. The advantages of IFN therapy, namely the finite duration of treatment and durable response with the low but real chance of HBeAg clearance, must be balanced against the risk of side effects and costs of administration. Although lamivudine is well tolerated and easily administered, the high risk of development of resistance limits its long-term use. Adefovir may be a better choice for patients lacking the factors predictive of a rapid response to oral therapy who are likely to require treatment beyond 1 yr.

Patients with serum HBV DNA >10⁵ copies/mL and elevated serum ALT are obvious candidates for therapy with IFN, lamivudine, or adefovir. Adefovir is preferred over lamivudine in HBeAg-negative patients as they are likely to require longer term, probably indefinite, therapy. However, patients with normal serum ALT or a serum HBV DNA level below 10⁵ copies/mL should not necessarily be excluded from consideration for therapy; excluding such patients without taking into account other parameters is likely to eliminate some patients who have disease or are at risk of progression and could benefit from therapy (45). One of the most important unanswered questions is whether long-term viral suppression will reduce the late incidence of HCC even in patients who have minimal liver disease. Novel agents with enhanced potency and, hopefully, low rates of long-term resistance will add to our therapeutic options as we continue to establish optimal treatment approaches.

**REFERENCES**

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