

a series of articles written by medical professionals about the management and treatment of hepatitis C

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## Overview of Treatment of Hepatitis B

### Introduction

Chronic hepatitis B (CHB) remains an important public health problem, with more than 2 million persons in the United States infected with the virus.<sup>1</sup> Without treatment, patients infected with CHB are at risk for development of cirrhosis and liver cancer.

Over the last 5 years, there has been an increased understanding of the treatment of CHB, and more medications have become available. There are now 7 drugs approved by the FDA for treatment of CHB: interferon alpha-2b, pegylated interferon alpha-2a, lamivudine, adefovir, entecavir, telbivudine, and tenofovir. Several other compounds are currently under investigation, including clevudine and emtricitabine.

The decision to start a patient on treatment for CHB can be complex and confusing. Persons infected with the hepatitis B virus with normal liver tests

(AST/ALT) may have no evidence of damage to the liver and therefore not require therapy, although this has been intensely questioned by a number of recent studies from Taiwan and Hong Kong.<sup>2-5</sup> Liver disease has been historically assessed by using a liver biopsy

to determine the extent of inflammation and scarring in the liver. If there is any evidence of damage to the liver on laboratory testing (ALT above the upper limits of "healthy" – 19 IU/mL for women and 25-30 IU/mL for men) or utilizing a liver biopsy, then experts recommend initiation of antiviral treatment with the goal

of suppression of the hepatitis B virus (HBV) DNA levels to undetectable, which has been shown to slow progression of liver disease and reverse fibrosis.<sup>6-9</sup> At the present time, the preferred first line agents are peginterferon alpha-2a, entecavir, and tenofovir because of their superior efficacy, and in the case

*HBsAg seroconversion is the best indicator of long term off-therapy viral suppression.*

of oral therapies, tolerability and resistance profiles over second and third line medications when compared in clinical trials.<sup>6-9</sup>

### Interferon/Pegylated Interferon

Pegylated interferon alpha-2a has essentially replaced standard interferon alpha-2b in clinical practice due to improved tolerability and efficacy with weekly dosing.<sup>7,9-10</sup> A large phase III randomized study compared peginterferon alpha-2a 180 mcg/wk, lamivudine 100 mg daily, and the combination of both drugs for 48 weeks in patients with HBeAg-positive CHB.<sup>11</sup> With peginterferon therapy for 48 weeks, 25-40% of patients have HBV DNA loss on therapy, and 22-32% of patients have HBeAg seroconversion (HBeAg + to - and antiHBe - to +) at 24 weeks after end of treatment. Importantly during long-term follow-up only 14% of patients remained HBV DNA undetectable. Improved survival, complication-free survival, and a reduction in the frequency of hepatocellular carcinoma have been documented or suggested in interferon responders. Interferon therapy is more effective in patients with low-level HBV DNA 20,000–10 million IU per mL, elevated ALT (esp if >90 IU/mL), immunocompetence, genotype A and B, normal liver function (albumin, bilirubin and coagulation), and acquisition of infection in adulthood.<sup>12</sup> The most common

side effect of interferon therapy is an influenza-like illness with fever, chills, headache, malaise, and muscle aches, as well as psychological side effects. Patients require careful monitoring during therapy for these and other side effects.

### Entecavir

In phase III studies, entecavir 0.5 mg/day demonstrated superior benefit to lamivudine 100 mg/day in nucleoside-naïve patients.<sup>13,14</sup> At 48 weeks of treatment, entecavir-treated patients had higher rates of histologic improvement (72% vs. 62%), HBV DNA reduction (-6.9 vs. -5.4 log<sub>10</sub> copies/mL), HBV DNA undetectability (67% vs. 36%), and ALT normalization (68% vs. 60%). Studies of entecavir therapy at 96 weeks show continued superiority over lamivudine therapy, with higher rates of HBV DNA undetectability (80% vs. 39%) and ALT normalization (87% vs. 79%).<sup>15</sup> Cumulative HBeAg seroconversion occurred in 31% of entecavir-treated patients compared to 25% of lamivudine-treated patients. Entecavir has also demonstrated superiority to adefovir, with a greater mean HBV DNA change from baseline (-6.23 vs. -4.42 log<sub>10</sub> copies/mL) and higher rates of HBV DNA undetectability (79% vs. 50% at 96 weeks of treatment).<sup>16,17</sup> HBeAg seroconversion rates are similar for entecavir and adefovir. Six-year data is now available dem-

onstrating marked reversal of liver fibrosis and liver inflammation.

Long-term resistance data for entecavir is also favorable, with 1.2% resistance rate at 5 years in nucleoside-naïve patients.<sup>18-20</sup> In patients with lamivudine-resistant CHB, resistance to entecavir is as high as 51% at 5 years.<sup>19,20</sup> Therefore entecavir should not be used as monotherapy in patients with suspected or documented resistance to lamivudine.

Entecavir demonstrates low toxicity, with few patients having major side effects. Entecavir dosing needs to be adjusted in patients with renal insufficiency.

### Tenofovir

Tenofovir is the most recently approved drug for the treatment of CHB. Recent studies have compared tenofovir to adefovir, and found that at 48 weeks, significantly more patients treated with tenofovir at 300 mg/day had completely suppressed HBV DNA levels than did patients treated with adefovir (100% vs. 44%).<sup>21-23</sup> In addition, patients who had an incomplete response to adefovir responded well to switching to tenofovir, with 82-100% achieving negative HBV DNA at week 96.<sup>24-25</sup> Perhaps most exciting, tenofovir is associated with the highest level of HBsAg seroconversion (HBsAg + to - and HBsAb - to +): 5% at 96 weeks of therapy.<sup>24</sup>

HBsAg seroconversion is the best indicator of long term off-therapy viral suppression. Five-year data demonstrated even more profound on-treatment suppression.

As of now, there have been no reported instances of tenofovir resistance after 2 years of therapy.<sup>24-25</sup> The majority of patients who experience viral breakthrough on tenofovir do so because of non-compliance with therapy. Decreased response rates to tenofovir have been documented when preexisting mutations associated with adefovir resistance have been documented.

Tenofovir is very well-tolerated. New or worsening renal dysfunction may occur with tenofovir, which is reversible with discontinuation of the drug. Patients should be screened with a baseline GFR prior to therapy using the MDRD formula, and creatinine clearance should be monitored during therapy in patients at risk. Tenofovir dosing also should be adjusted in patients with baseline renal dysfunction. Tenofovir has a category B rating in pregnancy, and has a long experience in pregnant women who have been treated with tenofovir for HIV infection. Tenofovir is the drug of choice in women of child-bearing age.

### Telbivudine

Telbivudine is a nucleoside analog that has been shown in phase

III studies to be superior to lamivudine at a daily dose of 600 mg/day.<sup>26-27</sup> Sixty per cent of patients after 1 year and 56% of patients after 2 years of treatment with telbivudine have undetectable HBV DNA, compared to 40% at 1 year and 39% at 2 years with lamivudine.<sup>28</sup> HBeAg seroconversion occurs in 22% of telbivudine treated patients after 1 year of treatment.<sup>26</sup> Telbivudine has also demonstrated superiority to adefovir with improved early virologic response and better outcomes at 1 year.<sup>29</sup> Telbivudine is not considered a first line agent due to unacceptably high resistance rates of 2.3-5% at 1 year and 11-25% at 2 years in treatment-naïve patients.<sup>26-28</sup> Resistance rates are lower if patients achieve undetectable HBV DNA by 24 weeks of therapy.<sup>30</sup>

Telbivudine is well-tolerated, with 7.5% of patients having reversible and mild muscle symptoms. Telbivudine has a category B rating in pregnancy, making it a drug of choice in women of child-bearing age, along with tenofovir.

### Adefovir

Placebo-controlled, randomized clinical trials of adefovir monotherapy (orally administered 10 mg/d) in patients with wild-type and pre-core-mutant chronic hepatitis B have demonstrated histologic, virologic, and biochemical improvements compa-

parable to those achieved with lamivudine monotherapy but with a much lower rate of resistance. In HBeAg-reactive patients, HBeAg seroconversions occurred during the first year of adefovir therapy (12%) – which is similar to lamivudine therapy (16-18%).<sup>31-32</sup> The HBeAg seroconversion rate continues to increase, and is 46% after 144 weeks of therapy.<sup>33</sup>

Adefovir was found to be safe and well-tolerated in clinical trials, and the treatment-limiting nephrotoxicity seen when this drug was used at higher doses for patients with HIV infection was not encountered among patients in HBV trials at 10mg per day. Dose adjustments of adefovir must take place if the patient has renal insufficiency.

Adefovir has been found to have increasing rates of resistance. Initial reports showed resistance to be low in the first year of therapy, but with subsequent follow-up, adefovir has been reported to have resistance rates as high as 30-42% at 5 years of treatment thus making adefovir a second line treatment.<sup>34</sup>

### Lamivudine

Lamivudine is associated with a 4-log suppression of HBV DNA at daily oral doses of 100 mg. In phase-III, prospective, controlled clinical trials among North American, European, and Asian

patients with HBeAg+ and elevated ALT, 12 months of lamivudine therapy was associated with 44% HBV DNA suppression, 17-32% HBeAg loss, approximately 16%-18% HBeAg seroconversion, sustained ALT normalization in approximately 40%-75%, and liver histologic improvement in approximately 50%.<sup>35-37</sup> Among those treated for two years, liver histology improved and fibrosis was reduced. Trials in which lamivudine and interferon were administered in combination (2-month lead-in period of lamivudine monotherapy, followed by a 4-month period of combination therapy) failed to show a benefit once treatment was discontinued.<sup>38</sup>

Although lamivudine is classified as category C in pregnancy, there is extensive experience with the safety and utility of lamivudine use during the third trimester of pregnancy to prevent perinatal transmission of hepatitis B in women with high HBV DNA levels. Because of this experience, lamivudine is the most commonly used antiviral medication for the treatment of pregnant women with CHB when high viral loads are present.

Clinical and laboratory side effects during lamivudine therapy cannot be distinguished from those during placebo treatment.

Mutations at the 204 site in the polymerase motif of HBV DNA emerge in approximately 20% of patients treated with lamivudine for a year, and the frequency of these mutations increases each year (>67% at 4 years).<sup>39-40</sup> Patients who develop resistance to lamivudine have a much higher rate of resistance to other antivirals; thus, lamivudine monotherapy should be avoided and is considered third line therapy.

### Summary

Interferon requires 24-48 weeks of therapy, achieved a 30+% HBeAg loss, 14-17% off treatment HBV DNA suppression and 7-11% HBsAg loss, and long-term improvements in natural history without HBV mutations, which are important issues to consider. However, interferon requires inconvenient injection therapy, is associated with side effects, is no better than lamivudine in head-to-head comparisons for HBeAg seroconversion, and is of limited value in certain subgroups. Entecavir and tenofovir are both safe and convenient to take, achieve a 30+% HBeAg loss at 2 years, histologic improvement in the majority of patients (not limited to HBeAg responders, as is the case for interferon), and achieve every benefit observed in interferon-treated patients. Telbivudine and adefovir are relegated to second-line therapy due to high rates of resistance. Lamivudine is now considered third-line therapy currently due to resistance concerns.

Oral antiviral agents generally need to be given for long-term due to risk of flaring HBV with cessation of therapy, which can result in significant liver enzyme abnormalities and in rare cases fulminant liver failure and death.



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