

## Commented Summary from Current Medical Literature

### LONG-TERM THERAPY WITH ADEFOVIR DIPIVOXIL FOR HBeAg-NEGATIVE CHRONIC HEPATITIS B

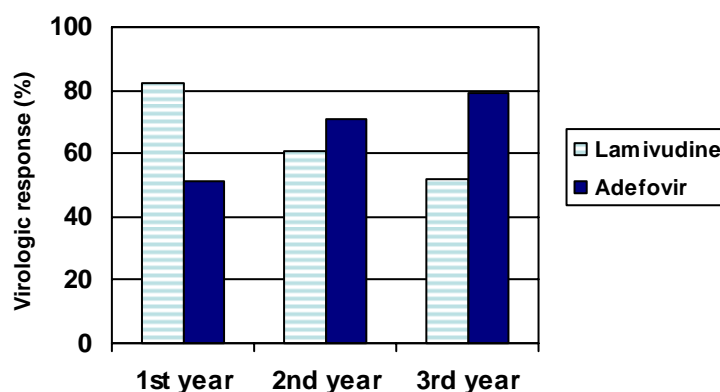
**Summary:** Treatment with adefovir dipivoxil for 48 weeks resulted in histologic, virologic, and biochemical improvement in patients with hepatitis B e antigen (HBeAg)-negative chronic hepatitis B. We evaluated the effect of continued therapy as compared with cessation of therapy. One hundred eighty-five HBeAg-negative patients with chronic hepatitis B were assigned to receive 10 mg of adefovir dipivoxil or placebo once daily for 48 weeks (ratio, 2:1). After week 48, patients receiving adefovir dipivoxil were again randomly assigned either to receive an additional 48 weeks of the drug or to switch to placebo. Patients originally assigned to placebo were switched to adefovir dipivoxil. Patients treated with adefovir dipivoxil during weeks 49 through 96 were subsequently offered continued therapy. The primary end points were changes in hepatitis B virus (HBV) DNA and alanine aminotransferase levels. Treatment with adefovir dipivoxil resulted in a median decrease in serum HBV DNA of 3.47 log copies per milliliter (on a base-10 scale) at 96 weeks and 3.63 log copies per milliliter at 144 weeks. HBV DNA levels were less than 1000 copies per milliliter in 71% of patients at week 96 and 79% at week 144. In the majority of patients who were switched from adefovir dipivoxil to placebo, the benefit of treatment was lost (median change in HBV DNA levels from baseline, -1.09 log copies per milliliter; only 8% of patients had levels below 1000 copies per milliliter at week 96). Side effects during weeks 49 through 144 were similar to those during the initial 48 weeks. Resistance mutations rtN236T and rtA181V were identified in 5.9% of patients after 144 weeks. In patients with HBeAg-negative chronic hepatitis B, the benefits achieved from 48 weeks of adefovir dipivoxil were lost when treatment was discontinued. In patients treated for 144 weeks, benefits were maintained, with infrequent emergence of viral resistance.

**Source:** Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, et al. *N Engl J Med*. 2005; **352**: 2673 – 2681.

**Comment:** An estimated 350 million persons worldwide are chronically infected with hepatitis B virus (HBV),<sup>1</sup> and approximately 1.7% of Iranian people are carriers of HBV.<sup>2</sup> While implementation of universal neonatal vaccination has significantly reduced the number of HBV carriers in the young population, its prevalence (about 2.8%) did not change in the Iranian adult population.<sup>2</sup> Presently, HBV is the most common cause of cirrhosis, hepatocellular carcinoma (HCC), and liver-related death in Iran.<sup>3,4</sup>

In Iran, the rate of HBeAg positivity is approximately 10% among chronically HBV-infected subjects.<sup>3</sup> However, among the subgroup of chronic hepatitis B (CHB) patients with high serum HBV DNA levels and significant liver fibrosis and inflammation, the rate of HBeAg positivity may be around 30 – 40%. Thus according to expert opinion, it is estimated that HBeAg-negative chronic hepatitis B constitutes 60 – 70% of the cases of CHB in Iran. HBeAg-negative CHB patients are more difficult to treat than their HBeAg-positive counterparts and relapse is more common after cessation of antiviral drugs.<sup>5</sup> The goal of treatment for CHB is to prevent cirrhosis and HCC. However, complete eradication of the virus from the patient's body is very difficult, even impossible, and rebound infection is common after drug withdrawal.<sup>6</sup>

Currently, there are five FDA approved drugs for the treatment of chronic hepatitis B: interferon alfa-2b, lamivudine, adefovir dipivoxil, entecavir, and peg-interferon alfa-2a. The last three drugs are relatively new, and long-term experience with these drugs is limited. In the present study, Hadziyannis et al reported the results of a controlled trial of adefovir in the treatment of HBeAg-negative CHB at weeks 96 and 144.<sup>7</sup> An earlier report of this trial showed that at week 48 there was a 51% virologic response (e.g. undetectable HBV DNA PCR).<sup>8</sup> Interestingly, continued treatment with adefovir increased virologic response to 71% and 79% at weeks 96 and 144, respectively. This important point is in a great contrast with lamivudine. Since, in HBeAg-negative CHB long-term lamivudine treatment leads to a progressive decrease in virologic response. In a study by Gaia et al<sup>9</sup> virologic response to lamivudine decreased from 82% at year 1, to 61% at year 2, 52% at year 3, and 39% at year 4. Figure 1 shows the great advantage of long-term administration of adefovir over that of lamivudine in HBeAg-negative CHB. This occurs because the rates of viral resistance differ significantly between these two drugs. During therapy with lamivudine, viral breakthrough occurred in 8% of



**Figure 1.** Comparison of ontherapy virologic response defined as undetectable HBV DNA level by PCR (e.g. HBV DNA < 1000 copies/mL) between lamivudine and adefovir on years 1, 2, and 3 of treatment. The figure is derived from references 7, 8, and 9 of this article.

patients at year 1, 34% at year 2, and 40% at year 3. However, virologic breakthrough on adefovir happened in no patients at year 1, 3% at year 2, and 5.9% at year 3.<sup>7,8</sup>

Is adefovir the end of the road? Certainly, the response is no. In a recent study published in abstract form, an 29% resistance rate to adefovir at five years was reported.<sup>10</sup> Also, the problem of both adefovir and lamivudine is that discontinuation of the drugs results in virologic and biochemical relapse (e.g. increasing HBV DNA levels, and increasing serum ALT) in nearly all patients.<sup>5,6</sup> Thus, one year treatment with either adefovir or lamivudine is not so beneficial in HBeAg-negative CHB and several years of treatment (or even indefinite therapy) with oral antiviral drugs which have low rates of viral resistance (e.g. adefovir, entecavir, etc) may be required in such patients.<sup>11</sup> The goal of treatment is long-term suppression of HBV DNA levels to less than 10,000 and, ideally, less than 1000 copies/mL.<sup>11</sup> Several trials of new antiviral drugs (e.g. entecavir, tenofovir, clevudine, etc) are underway in HBeAg-negative CHB patients throughout the world. Also, a combination of two nucleoside/nucleotide analogues may reduce the rate of viral resistance.<sup>10</sup> Thus, in the future, combination of two nucleoside/nucleotide analogues may become the standard treatment in patients requiring long term antiviral therapy. Undoubtedly, cost will be a significant problem when contemplating long-term therapy with nucleoside or nucleotide analogues.

What should we do with HBeAg-negative CHB patients in our country? While adefovir is one of the drugs of choice as first-line therapy in HBeAg-negative CHB, most Iranian patients can not pay for long-term (e.g. several years) treatment with adefovir. Presently, the price of adefovir is around 7 million Rials per month and insurance companies do not support the drug in Iran. Furthermore, according to the updated AASLD guidelines, long-term lamivudine therapy is not preferred as first-line treatment in HBeAg-negative CHB.<sup>12</sup> In my opinion, it may be better to start treatment with 12 to 24 months of interferon alfa (or 12 months of peg-interferon alpha). With this strategy, long-term and sustained viral suppression can be achieved in 20 – 40% of patients.<sup>13–15</sup> Obviously, interferon is contraindicated in decompensated cirrhotic patients.<sup>1</sup> In instances of relapse or nonresponse to interferon (or peg-interferon), treatment with lamivudine can be started (although drug resistance is a concern). In instances of resistance to lamivudine, combined adefovir and lamivudine should be considered in patients with advanced fibrosis and cirrhosis. Also, lamivudine-resistant patients with clinical deterioration should be considered for the above regimen. However, in stable patients with lesser degrees of liver fibrosis, options include withdrawal of lamivudine or adding adefovir to lamivudine.<sup>10,12</sup> It is hoped that newer antiviral drugs with lower prices become more readily available in the future in Iran. Certainly, if novel researches are completed and newer drug regimens become available, the above recommendations would be subject to modification. Also, multicenter controlled trials in HBeAg-negative CHB patients certainly need to be launched in the country.

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