Progress in the treatment of chronic hepatitis B: long-term experience with adefovir dipivoxil

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Most chronic hepatitis B patients do not undergo a curative response to interferon-α or nucleoside/nucleotide-based regimens and require long-term therapy. Long-term safety, efficacy and resistance profiles of hepatitis B virus (HBV) drugs are therefore crucial issues for patient management. Adefovir dipivoxil is a nucleotide prodrug indicated for the treatment of patients with hepatitis B e antigen positive or hepatitis B e antigen negative chronic hepatitis B, lamivudine-resistant HBV infection, HBV infection pre- or post-liver transplantation, or HIV co-infection. Long-term data from clinical trials of up to 5 years duration of adefovir dipivoxil have recently become available and are reviewed here. These data demonstrate that adefovir dipivoxil therapy results in sustained efficacy and safety in the majority of patients after multiple years of treatment. The efficacy of adefovir dipivoxil in treating lamivudine-resistant HBV and the delayed emergence of adefovir resistance are key factors contributing to the durable response achieved in broad groups of chronic hepatitis B patients.

Keywords: drug resistance, nucleoside, viral hepatitis, seroconversion, phosphonate

Introduction

The approval of nucleotide and nucleoside analogues marked a significant advance in the treatment of chronic hepatitis B. These agents, which include the nucleotide adefovir dipivoxil and the nucleosides lamivudine and entecavir, effectively suppress viral replication and ameliorate liver disease. However, nucleoside and nucleotide therapies usually require long-term administration to control disease because host control of viral replication [as evidenced by hepatitis B e antigen (HBeAg) and/or hepatitis B surface antigen (HBsAg) seroconversion] occurs in only modest numbers of patients. The requirement for chronic therapy necessitates long-term drug safety and the ability to delay or manage viral resistance to maintain antiviral suppression and clinical benefit.

Adefovir dipivoxil is an oral prodrug of the acyclic phosphonate nucleotide adefovir. Following absorption, adefovir dipivoxil is converted into adefovir and phosphorylated in hepatocytes to adefovir diphosphate, a competitive inhibitor of hepatitis B virus (HBV) polymerase. Safety and efficacy of a once daily 10 mg dose of adefovir dipivoxil was demonstrated in two pivotal Phase III trials that provided the basis for drug approval in the USA (September, 2002) and Europe (March, 2003).1,2 Adefovir dipivoxil is indicated for the treatment of chronic hepatitis B in adults with active viral replication and histological or biochemical [serum alanine aminotransferase (ALT) elevations] evidence of liver disease. This indication encompasses many patient populations including those with HBeAg+ or HBeAg− disease, those with treatment-naive or lamivudine-resistant HBV, those awaiting or post-liver transplant and HIV co-infected patients. This article will highlight key study results with adefovir dipivoxil and discuss its role in the treatment of chronic hepatitis B. Emphasis will be placed on recent long-term data that is particularly relevant because most patients require chronic therapy with this class of drugs.

Key clinical studies of adefovir dipivoxil

Four key studies will be discussed in this article (Table 1). Studies 437 and 438 were randomized, double-blind, placebo controlled Phase III trials that tested the efficacy of 10 mg of adefovir dipivoxil over a 2 year (96 week) period in patients with HBeAg+ or HBeAg− disease, those with treatment-naive or lamivudine-resistant HBV, those awaiting or post-liver transplant and HIV co-infected patients. This article will highlight key study results with adefovir dipivoxil and discuss its role in the treatment of chronic hepatitis B. Emphasis will be placed on recent long-term data that is particularly relevant because most patients require chronic therapy with this class of drugs.

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data from this study. Study 435 was an open-label Phase III compassionate use study designed to evaluate the safety and efficacy of 10 mg adefovir dipivoxil therapy in lamivudine-resistant chronic hepatitis B patients either pre- or post-liver transplantation. Depending on the time of enrolment, patients in study 435 received treatment for up to 3 years; patients left the study when adefovir dipivoxil became available commercially or through an early access programme. Study 460i was a small \( (n = 35) \) open-label investigator sponsored study conducted to determine the efficacy of 10 mg adefovir dipivoxil therapy in HBV/HIV co-infected patients with lamivudine-resistant HBV; patients in this study have now been followed for over 5 years.\(^3\)

### Long-term efficacy of adefovir dipivoxil

Several therapeutic endpoints can be measured for chronic hepatitis B. However, the primary goal of treatment is to suppress viral replication sufficiently to decrease hepatic necroinflammation and prevent severe liver sequelae (cirrhosis, liver failure and hepatocellular carcinoma). Accordingly, the primary endpoint in the Phase III pivotal studies 437 and 438 was improvement in liver histology. Secondary endpoints included biochemical improvement (serum ALT normalization) and virological suppression (reductions in serum HBV DNA).

In both pivotal Phase III studies (437 and 438), adefovir dipivoxil 10 mg was significantly better than placebo for the primary endpoint of histological improvement \( (P < 0.05) \), defined as at least a two point improvement in Knodell necroinflammatory score and no worsening of Knodell fibrosis score. After 1 year (48 weeks) of therapy 71\% (107/150) of HBeAg\( ^+ \) patients (study 437) had improvements in necroinflammation and 41\% (62/150) had improvements in fibrosis by ranked assessment. Similarly, 80\% (90/112) of HBeAg\( ^- \) patients (study 438) had improvements in necroinflammation and 48\% (54/112) had improvements in liver fibrosis after 1 year of therapy. Long-term data from study 438 indicated that 73\% (20/27) of patients with available biopsies after 5 years of therapy had improvements in necroinflammation and 75\% (18/24) had improvements in fibrosis when compared with baseline (Figure 1a). Importantly, long-term therapy produced further improvements in liver fibrosis as 70\% (16/23) of patients had improvements between year 1 and year 5 on adefovir dipivoxil 10 mg. Adefovir dipivoxil is therefore the first therapy to demonstrate that long-term administration and suppression of viral replication leads to continuing improvement in liver histology. Serum HBV DNA and normalization of ALT were secondary endpoints for these Phase III studies. In study 438, 64\% (79/123) of patients had serum HBV DNA levels suppressed below 1000 copies/mL and 72\% (84/116) achieved ALT normalization after 1 year. Over 5 years, 83\% (20/24) of patients had improvements in liver fibrosis and 75\% (18/24) had improvements in necroinflammation. The cumulative probability of genotypic resistance (emergence of rtN236T and/or rtA181V HBV polymerase mutations), virological resistance \( (>1 \log_{10} \text{copies/mL}) \), and clinical resistance (ALT elevations to >ULN after normalization plus virological resistance) over 5 years is shown in Figure 1b. ADV, adefovir dipivoxil.

### Table 1. Key clinical studies of adefovir dipivoxil

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient population ( (n)^a )</th>
<th>Length of study</th>
<th>Key references</th>
</tr>
</thead>
<tbody>
<tr>
<td>437</td>
<td>HBeAg( ^+ ) (511)</td>
<td>5 years (2 years placebo controlled with 3 year extension), dosing misallocation after 1 year</td>
<td>1</td>
</tr>
<tr>
<td>438</td>
<td>HBeAg( ^- ) (184)</td>
<td>5 years (2 years placebo controlled with 3 year extension)</td>
<td>2,28,29</td>
</tr>
<tr>
<td>435</td>
<td>Liver transplant, LAM-resistant ( (476) )</td>
<td>pre-OLT patients ( (n = 226) ) up to 2 years, post-OLT patients ( (n = 241) ) up to 3 years</td>
<td>30,31,8</td>
</tr>
<tr>
<td>460i</td>
<td>HIV co-infected, LAM-resistant (35)</td>
<td>5 year investigator study, ongoing</td>
<td>3,32,33</td>
</tr>
</tbody>
</table>

LAM, lamivudine.

\( a = \) number of patients who received treatment.
normalization after 1 year of therapy. Viral load suppression was greater in patients receiving 30 mg of adefovir dipivoxil in study 437, however, in contrast with the 10 mg dose, 30 mg was associated with an unfavourable safety profile (see below). After 5 years on 10 mg adefovir dipivoxil treatment, antiviral and biochemical responses were well-maintained: 67% (47/70) of patients had serum HBV DNA <1000 copies/mL and 66% (42/64) had normalized ALT.

The loss of HBeAg and seroconversion to anti-HBeAg antibody positive were also studied in patients in study 437 up to year 3. HBeAg loss occurred in 23%, 46% and 56% of patients after 1, 2 and 3 years of therapy, respectively. Full HBeAg seroconversion occurred in 14%, 33% and 46% of patients after 1, 2 and 3 years of therapy, respectively. Thus, similar to lamivudine, seroconversion rates increased as the duration of adefovir dipivoxil therapy increased. The durability of HBeAg seroconversion was also studied in patients that discontinued adefovir dipivoxil therapy after seroconverting during study 437. Ninety-one percent of patients that seroconverted during treatment with 10 mg of adefovir dipivoxil remained HBeAg negative and positive for anti-HBeAg after a median off-treatment follow-up of 3 years. Patients that seroreverted (lost anti-HBeAg and regained HBeAg) had a shorter median duration of adefovir dipivoxil therapy after the seroconversion than those that had a durable seroconversion.

In study 435, the long-term efficacy of adefovir was monitored for two groups of lamivudine-resistant liver transplant patients: those awaiting orthotopic liver transplantation (pre-OLT) and those having already received an orthotopic liver transplant (post-OLT). In pre-OLT patients, 59% (45/76) had HBV DNA <1000 copies/mL and 77% (49/64) normalized ALT after 1 year of adefovir dipivoxil therapy. After 2 years 65% (13/20) of patients had HBV DNA <1000 copies/mL and 77% (10/13) normalized ALT (Figure 2a). In the post-OLT group, 3 year data are available. The number of patients achieving HBV DNA <1000 copies/mL rose with each year of therapy: 40% (64/159), 65% (61/94) and 78% (35/45) of patients had serum HBV DNA <1000 copies/mL after 1, 2 and 3 years of treatment, respectively (Figure 2b). In post-OLT patients, ALT normalization was observed in 51% (56/110), 70% (46/66) and 58% (15/26) of patients after 1, 2 and 3 years of therapy, respectively. Study 435 represents the largest study in chronic hepatitis B patients with decompensated liver disease as approximately 60% of pre-OLT and 25% of post-OLT patients had a Child–Pugh Turcotte (CPT) class of B or C at the initiation of therapy. Pre-OLT patients with CPT class B or C had a median

![Figure 2](https://academic.oup.com/jac/article-abstract/59/5/827/727527)

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**Figure 2.** Efficacy (serum HBV DNA <1000 copies/mL and ALT normalization) of adefovir dipivoxil (ADV) therapy in pre-OLT patients over 2 years (a), in post-OLT patients over 3 years (b) and in HIV co-infected patients over 4 years (c).
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two-point improvement in their CPT score after 1 year (n = 32) of therapy, which was maintained at 2 years (n = 5). Post-OLT patients with CPT class B or C had a median improvement of three points in their CPT score after 1 (n = 20), 2 (n = 11) and 3 (n = 7) years of adefovir dipivoxil therapy. Adefovir dipivoxil is currently the only therapy approved for patients with decompensated liver disease and lamivudine-resistant HBV.

Long-term efficacy of adefovir dipivoxil against lamivudine-resistant HBV DNA has also been assessed in 35 HIV co-infected patients in study 460i. Patients in this trial initiated therapy with very high titres of serum HBV DNA (median 9.8 log10 copies/mL). After the first year of therapy 6% of patients had serum HBV DNA <1000 copies/mL and 35% normalized ALT. However increasing virological and biochemical efficacy was observed with each subsequent year of therapy and by 4 years, 58% of patients had achieved serum HBV DNA <1000 copies/mL and 70% normalized ALT (Figure 2c). HIV co-infected patients also saw improvements in liver fibrosis during therapy. Improvements in fibrosis were seen in 33% of patients (n = 15) after 1 year of therapy and 50% of patients (n = 12) had improvements after 4 years.6

Long-term safety of adefovir dipivoxil

During the development of adefovir dipivoxil for the treatment of HIV infection, high dose therapy was associated with reversible nephrotoxicity.7 Therefore, kidney function was closely monitored during the clinical development of lower doses for treatment of chronic hepatitis B. One year of treatment with 10 mg daily adefovir dipivoxil was not associated with significant increases in serum creatinine or decreases in serum phosphorus levels during either of the pivotal Phase III studies.1,2 In contrast, the 30 mg dose of adefovir that was tested in year 1 of study 437 was associated with increases in serum creatinine in 8% of patients after 48 weeks of therapy. Years 3–5 of studies 437 and 438 were not placebo controlled, however after 5 years of continuous 10 mg therapy in HBeAg− patients (study 438), no patient had a confirmed decrease in serum phosphorus to <2.0 mg/dL and 4/125 patients (3%) had confirmed increases in serum creatinine from baseline (≥0.5 mg/dL).

The safety of adefovir dipivoxil was also demonstrated in transplant patients (study 435). It is important to note that these patients take concurrent nephrotoxic medications (e.g. cyclosporine, tacrolimus) and frequently have pre-existing renal impairments. Because adefovir is cleared through the kidney, it is essential that the dose be adjusted based on patients’ renal function. Despite underlying renal impairment in this patient population, only 2% and 4% of patients discontinued adefovir dipivoxil therapy due to renal events after 1 and 3 years of therapy, respectively.8 A recent investigator sponsored study conducted in 42 pre- or post-OLT patients reported no discontinuations due to renal toxicity after 1 year of therapy.9 Adefovir has also been used successfully to treat kidney transplant recipients as well as those with other underlying renal insufficiencies10 and HIV co-infected patients who are at increased risk of renal dysfunction due to HIV, opportunistic infections, and multiple concomitant medications.11

Resistance to adefovir dipivoxil

Two adefovir resistance mutations were identified in the polymerase of HBV isolated from patients with viral load rebound during adefovir dipivoxil therapy: rtN236T and rtA181V. These mutations are distinct from those selected by lamivudine [rtM204V/I (YMDD) ± rtL180M ± rtV173L] or entecavir (lamivudine resistance mutations + rtA184G, rtS202I or rtM250V). The mutations rtN236T and rtA181V can occur independently or together in the same patients but are correlated with viral load rebound in either case. A third mutation, rtA181T, is associated with long-term adefovir therapy, but is not correlated with viral load breakthrough as a single mutation. However, rtA181T has been identified in combination with rtN236T in patients with viral load rebound.12

Study 438 provides the most extensive data for the frequency of genotypic resistance during adefovir dipivoxil monotherapy. During this study, no resistance mutations were observed during the first year of therapy. The cumulative probability of genotypic resistance emergence (rtN236T and/or rtA181V) was 3%, 11%, 18% and 29% after 2, 3, 4 and 5 years of therapy, respectively (Figure 1b and Table 2). Genotypic resistance was also infrequent in study 412, a small Phase II trial conducted in a mixed population of HBeAg+ and HBeAg− patients (probability of resistance was 5% after 3 years of therapy) (Table 2). Thus, the frequency of adefovir resistance during monotherapy is considerably less than that of lamivudine, which occurs in 23% of patients after 1 year and 71% of patients after 4 years.13 It is also important to note that genotypic resistance is associated with virological resistance (>1 log10 copies/mL confirmed increase in viral load from nadir) or clinical resistance [increase in ALT to greater than the upper limit of normal (>ULN) after normalization] in only a subset of patients (Figure 1b). After 5 years of adefovir therapy in study 438, 29% of patients had genotypic resistance, while 20% had virological resistance and 11% had clinical resistance.

Table 2. Cumulative probability of adefovir-associated genotypic resistance mutations (rtA181V and/or rtN236T) from year 1 to year 5

<table>
<thead>
<tr>
<th>Study</th>
<th>Year 1 (%)</th>
<th>Year 2 (%)</th>
<th>Year 3 (%)</th>
<th>Year 4 (%)</th>
<th>Year 5 (%)</th>
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<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>438</td>
<td>0</td>
<td>3</td>
<td>11</td>
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<td>29</td>
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<tr>
<td>412</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>–</td>
<td>–</td>
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<tr>
<td>435</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>–</td>
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<td>460i</td>
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<td>0</td>
<td>0</td>
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</tbody>
</table>

LAM-R, lamivudine-resistant.

*Study 437 included for year 1 only owing to the misallocation of dosing in year 2.
Multivariate analyses were carried out to determine if any baseline or post-therapy factors were significant predictors of adefovir resistance in the study 438 patient population. No baseline factors (including HBV DNA level, ALT, HBV genotype, necroinflammatory scores, age, race, BMI and gender) were found to be predictive of resistance. However, residual serum HBV DNA after 1 year of therapy was a positive predictor of resistance and, conversely, patients with viral titres below the limit of PCR quantification (<1000 copies/mL) had the lowest risk of developing resistance during long-term adefovir dipivoxil therapy.

Long-term adefovir resistance data in lamivudine-resistant patients are available from studies 435 and 460i (Table 2). During study 435, transplant patients received lamivudine at the treating physician’s discretion in addition to adefovir dipivoxil. Through 3 years of therapy, the cumulative probability of developing adefovir resistance was 2% after genotyping all patients with detectable serum HBV DNA (n = 47). It is noteworthy that adefovir resistance mutations only emerged in patients who had discontinued lamivudine, and therefore the rate of resistance emergence in patients receiving adefovir dipivoxil plus lamivudine was 0% at 3 years. In study 460i, all patients received lamivudine (as part of their HAART regimen) in addition to adefovir dipivoxil. After 5 years of therapy, no patient (n = 25) in study 460i developed an rtN236T or A181V resistance mutation. The very low resistance rates observed in studies 435 and 460i suggest that combination therapy with adefovir dipivoxil and lamivudine can further delay the emergence of adefovir resistance. A recent study conducted by Lampertico and colleagues supports this hypothesis. When lamivudine-resistant HBeAg+ patients were switched to adefovir dipivoxil plus lamivudine (n = 285) versus adefovir monotherapy (n = 303) genotypic resistance rates were significantly lower after a median 2 years of therapy in the combination arm (0.8% versus 5% respectively, P < 0.001).

Phenotypic analysis of adefovir-resistant HBV

In vitro analyses in cell-based HBV replication assays indicate that rtN236T confers a 7- to 14-fold reduction in adefovir susceptibility in vitro. The rtN236T mutation also confers a reduction in lamivudine susceptibility (2- to 13-fold) and tenofovir susceptibility (3- to 4-fold) but appears to remain susceptible to entecavir (no significant change in susceptibility in vitro). The rtA181V mutation confers a 4.3-fold reduction in adefovir susceptibility in vitro, a smaller reduction in tenofovir susceptibility (3.2-fold) as well as 12- to 15-fold changes in lamivudine and entecavir susceptibility. The rtA181T mutation does not cause significant changes in adefovir or tenofovir susceptibility in vitro (<2-fold increases in EC50), consistent with the observation that it does not cause viral load rebound as a single mutation in patients. rtA181T causes 12-fold and 8-fold decreases in lamivudine and entecavir susceptibility in vitro, respectively. rtA181V has also been selected by lamivudine in patients.

The clinical importance of the in vitro cross-resistance observed for adefovir-resistant HBV remains to be determined. In addition to susceptibility changes, drug doses and pharmacokinetic properties will significantly influence antiviral response in patients. Indeed, despite a small reduction in lamivudine susceptibility in vitro, preliminary evidence indicates that rtN236T patients have a favourable viral load response to lamivudine.
References


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