

ADEFOVIR DIPIVOXIL FOR THE TREATMENT OF HBeAg - POSITIVE CHRONIC HEPATITIS B

Geoffrey Dusheiko, Royal Free and University College School of Medicine, London, UK



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Introduction

Adefovir dipivoxil is an orally bioavailable prodrug of adefovir, a phosphonate nucleotide analog of adenosine monophosphate. Adefovir has potent in vitro activity against hepadnaviruses, retroviruses and herpesviruses. The intracellular compound, adefovir diphosphate, acts as a competitive inhibitor and chain-terminator of hepatitis B virus (HBV) replication mediated by HBV DNA polymerase. A Marketing Authorization Application (MAA) has been submitted to the European agency for approval of adefovir dipivoxil 10 mg once daily for the treatment of chronic hepatitis B in adults with evidence of hepatitis B viral replication.

The efficacy of adefovir dipivoxil has been investigated in patients with compensated liver disease and evidence of HBV replication; in patients failing lamivudine therapy, including post-transplantation patients, patients with compensated and decompensated liver failure and patients co-infected with HIV. Two pivotal placebo-controlled clinical studies in patients with HBeAg or anti-HBe positive (pre-core mutant) chronic hepatitis B have been completed. An open-label study in liver transplantation patients with lamivudine-resistant HBV is continuing. The data in HBeAg positive patients is reviewed in this manuscript.

Approximately 400 million people have developed chronic hepatitis B infection, although the prevalence of chronic HBV infection varies widely between highly endemic, intermediate endemic and low endemic areas. The natural history of hepatitis B is variable, but approximately one third to 40% of patients develop progressive or severe liver disease including cirrhosis or hepatocellular carcinoma. Hepatitis B can be broadly subdivided into HBeAg- positive chronic hepatitis B, anti-HBe positive (pre-core mutant) hepatitis B and inactive carrier states. Young or adult patients with HBeAg positive chronic hepatitis B may have high levels of HBV DNA in serum but near normal or normal serum aminotransferases and minimal hepatitis during the early, immunotolerant phase of the disease. The disease may become more active in time however. HBeAg negative (presumed pre-core mutant) chronic hepatitis B is particularly common in Southern Europe and Asia. The disease is determined by the selection of HBeAg-negative variants of HBV (possessing mutations in the precore region of the hepatitis B genome that prevent the virus from producing HBeAg). However, the prototype precore mutation does not prevent packaging and replication of the HBV. The selection of these mutations is in part constrained by the predominant genotype of HBV. HBeAg negative chronic hepatitis B can be associated with wide fluctuations over time in viral replication and disease activity with exacerbations that are apparently injurious to the liver. Spontaneous remission to an inactive carrier state can also occur in chronic type B hepatitis.

Current treatments for chronic hepatitis B are limited: Hepatitis B replication can be inhibited, but a relatively small proportion of patients are successfully treated by finite courses of currently available antiviral agents. The immediate goals of treatment in chronic hepatitis B are to cause sustained suppression of HBV replication and thereby remission of liver disease to prevent progression to advanced hepatic fibrosis and cirrhosis, and other long term sequelae of cirrhosis including liver failure, portal hypertension (and sequelae of portal hypertension), HCC and death. Several extra-hepatic complications of hepatitis B virus infection, including membranoproliferative glomerulonephritis, and polyarteritis nodosa may also require antiviral treatment.

The recently introduced nucleoside analogue lamivudine results in improvement in liver histology, enhanced rates of HBeAg seroconversion, decreased serum HBV DNA levels and serum ALT normalisation. HBeAg seroconversion rates are improved in patients with raised serum aminotransferases. However, long term treatment with lamivudine will be required in patients who have not lost HBeAg or seroconverted to anti-HBe; the major disadvantage of this strategy is the selection of lamivudine-resistant (YMDD) HBV mutants in an increasing proportion of patients. While the outcome of resistance is variable, longer term follow-up of patients who develop YMDD mutants has demonstrated evidence of diminished therapeutic response. It is likely that long-term lamivudine therapy in either HBeAg positive or HBeAg negative patients will greatly increase the prevalence of lamivudine resistant chronic hepatitis B. Re-infection with HBV post transplantation has severe consequences in immunosuppressed liver transplant patients; 1 and 5 year survival rates of 73% and 44%, respectively, are reported for this group of patients. Limitations in current treatments have indicated the rationale for the development of additional antiviral treatments for hepatitis B, including adefovir dipivoxil.

Pharmacology of Adefovir Dipivoxil

Adefovir dipivoxil is a bis(pivaloyloxymethyl)ester prodrug of the synthetic nucleotide adefovir. The chemical name is 9-[2-[[bis(pivaloyloxy)methoxy]methoxy]ethyl]adenine. Following conversion to adefovir in the gastrointestinal tract, and transport into cells, adefovir is converted through two phosphorylation reactions, to adefovir diphosphate, the active molecule.

Adefovir dipivoxil, the oral prodrug of adefovir, enters cells more efficiently than adefovir. As adefovir is a monophosphorylated nucleoside, the conversion to the active form is achieved through only 2 of the 3 phosphorylation steps required for nucleoside analogs such as lamivudine. Adefovir diphosphate has a relatively long intracellular half life of 16-18 hours in T lymphocyte MT-4 cells. Adefovir has a long intracellular half-life of approximately 12 to 36 hours which makes it suitable for once daily oral dosing.

Adefovir diphosphate inhibits HBV polymerase by direct binding in competition with the endogenous substrate (deoxyadenosine triphosphate, dATP) and, after incorporation into viral DNA results in chain termination of DNA synthesis. Because adefovir diphosphate lacks a 3' hydroxyl group, the compound causes premature termination of viral DNA synthesis upon its incorporation into the nascent DNA chain. The active intracellular metabolite, adefovir diphosphate selectively inhibits HBV DNA polymerase (K_i value of 0.1 μM) at a concentration 10 - 700 fold lower than needed to inhibit human DNA polymerases α , β and γ . A low potential for resistance development with adefovir could be related to its close structural relationship with the natural substrate which limits the potential for steric hindrance as a mechanism of resistance. In addition, adefovir contains a flexible acyclic linker that may allow adefovir to bind to HBV polymerase with different conformations, and thus, further subvert steric hindrance. Adefovir also contains a phosphonate bond that is less susceptible to ATP-mediated chain terminator excision, which has been recognized as a mechanism of HIV resistance.

Clinical Pharmacology

Adefovir has activity against HBV, DHBV and WHV in cell culture models and against chronically infected animals. Adefovir is also a potent inhibitor of HIV and has activity against a range of herpes viruses including HCMV, HHV-6, HHV-8, HSV-1, HSV-2, varicella zoster and Epstein Barr virus. The inhibition constant (K_i) for adefovir diphosphate was 0.1 μM in an enzymatic assay using recombinant HBV polymerase. The IC_{50} of adefovir diphosphate for HBV polymerase in HBV core particles isolated from transfected HepG2 cells is 0.2 μM . Adefovir is active in vitro against all known lamivudine, emtricitabine, famciclovir and HBIG resistant HBV, using both cell culture and in vitro enzymatic assays.

Absorption, Distribution, Metabolism and Elimination Characteristics

Adefovir dipivoxil, a lipophilic prodrug of adefovir, was developed to provide improved intestinal permeability compared to the parent drug. Orally administered adefovir dipivoxil undergoes rapid enzymatic hydrolysis by nonspecific esterases yielding adefovir during or following the absorption process in the gastrointestinal

tract. Following oral administration of single doses of adefovir dipivoxil 10 mg to patients with chronic hepatitis B or healthy subjects, maximum observed adefovir concentrations (C_{max}) in plasma occur at a median 0.76-1.75 hours following dosing, with mean values ranging from 17.5 to 21.3 ng/ml. The mean adefovir area under the curve (AUC) ranged from 178 to 210 ng.hr/ml. The long terminal elimination half-life allows for once daily dosing. Good oral bioavailability of adefovir from adefovir dipivoxil 10 mg has been demonstrated (estimated to be approximately 60%), and plasma pharmacokinetics are not affected by food. Urinary recovery of unchanged drug is consistent with the estimated oral bioavailability derived from plasma data. Due to its short elimination half-life relative to a 24 hour dosing interval, there is no apparent accumulation of adefovir at steady state following 7 days of once daily dosing of adefovir dipivoxil 10 mg in patients with chronic hepatitis B.

In animals, adefovir is distributed to most tissues with the highest concentrations occurring in the intestinal tissues, kidneys and liver. The in vitro protein binding of adefovir to human plasma or serum proteins was negligible. Adefovir is not metabolised prior to elimination, and over 90% of an intravenous dose is recovered as unchanged drug in the urine over 24 hours following dosing. Adefovir renal clearance is approximately twice the calculated creatinine clearance, indicating that tubular secretion makes an important contribution to the elimination of adefovir. Adefovir dipivoxil is eliminated unchanged by the kidneys via glomerular filtration and active tubular secretion. A human organic anion transporter has been identified that rapidly transports adefovir and may be involved in the accumulation of adefovir in renal proximal tubule epithelium. Adefovir dipivoxil (10 mg) has not been studied in paediatric populations.

Preclinical toxicology

Studies have identified potential adefovir dipivoxil-associated hepatotoxicity (elevations in serum transaminases in mice and monkeys and dose-related histopathological changes in liver in mice only) and gastrointestinal toxicity (dose-related hyperplastic, degenerative, and inflammatory changes in rats and monkeys). (No clinical evidence of toxicity that could be related to these preclinical findings was observed in the pivotal studies of adefovir dipivoxil when administered at a dose of 10 mg once daily in chronic HBV-infected patients).

Nephrotoxicity

In preclinical studies, evidence for renal toxicity was noted in all species evaluated. This toxicity is characterised by a renal tubular nephropathy variably described as karyomegaly, cytomegaly, tubular dilatation, degeneration/regeneration, individual tubular epithelial cell necrosis, or elevations in blood urea nitrogen and/or creatinine. Nephrotoxicity was found to be the principal dose limiting toxicity associated with oral administration in of adefovir dipivoxil in rats or monkeys. Renal tubular kayomegaly is the most sensitive indicator of an effect on the renal tubular epithelium. Relevant changes have been observed at doses producing systemic exposures approximately 3 to 8 times that achieved in humans at the recommended therapeutic dose of 10 mg daily. The incidence and severity of renal tubular nephropathy was related to dose and duration of treatment. In clinical studies, nephrotoxicity has been confirmed as the most important dose-limiting toxicity of adefovir dipivoxil therapy, with doses 3 to 12 times higher than the recommended 10 mg daily dose.

Pharmacokinetics in Patient Populations

Adefovir pharmacokinetics are substantially altered in subjects with moderate and severe renal impairment (creatinine clearance < 50 mL/min) due to substantial reductions in the renal elimination of adefovir and, consequently, higher systemic adefovir exposure.

In patients with end stage renal disease (ESRD) requiring haemodialysis, adefovir concentrations in plasma reach high levels and no extra-renal route of elimination is observed. Since renal impairment or hepatorenal syndrome are common extra-hepatic manifestations that may be encountered in chronic hepatitis B, dose interval adjustments are required for patients with creatinine clearance of < 50 mL/min or those with ESRD requiring haemodialysis. However, no substantial alterations in the pharmacokinetics of adefovir have been

observed in subjects with moderate or severe hepatic impairment (Child-Pugh-Turcotte classifications B and C, respectively)

Resistance

In cell culture models, adefovir has demonstrated potent antiviral activity against HBV and a lack of cross-resistance against the lamivudine-resistant strains of HBV tested i.e. M552V, M522I and L528M/M552V1. These mutants remain sensitive to adefovir. This lack of cross-resistance may be explained by the fact that lamivudine-resistance is due to steric hindrance as a result of the unnatural L-sugar ring of lamivudine. In contrast, adefovir has a minimal acyclic linker in place of the sugar ring that closely matches the D-sugar ring of the natural nucleotide substrates, which allows adefovir to bind to lamivudine-resistant HBV polymerases without steric hindrance.

Clinical efficacy in chronic hepatitis B

As of February 28 2002 a total of 2084 subjects have been enrolled in clinical trials of adefovir dipivoxil. Doses of 5-125 mg/day have been assessed in the clinical development program. A full discussion of the overall experience in hepatitis B is beyond the scope of this manuscript. However these studies have included phase 1 and phase 2, open label safety studies, and phase 3 studies. Several patients have also been treated in investigator conducted studies, and enrolled in collaborative studies. Healthy volunteers have been enrolled in pharmacokinetic studies. An expanded access program has begun.

The initial Phase 1 and 2 clinical trials provided dose finding data to support the later pivotal studies. In Phase 1/2 clinical studies in both HBeAg positive and HBeAg negative patients with chronic hepatitis B, statistically significant decreases in serum HBV DNA concentrations were demonstrated within the first week of treatment, and were maintained for periods of treatment of up to 136 weeks. After 12 weeks of treatment, adefovir dipivoxil at doses of 30 mg and 60 mg once daily reduced serum HBV DNA levels by approximately 4 log₁₀ copies/mL (determined by Roche PCR, LLQ < 400 copies/mL) from baseline.

Study 404.

The first study was a randomised double blind placebo controlled phase 1/phase 2 study of the safety and efficacy of adefovir dipivoxil. Patients were randomised to receive either oral adefovir or placebo once daily for 4 weeks at 3 sequential dose levels: 125 mg, 250 mg and 500 mg. The study was however redesigned to evaluate only the 125 mg dose. The maintenance phase of this study was a pilot randomised double blind phase 1/phase 2 continued access study for patients who completed the first phase of the trial; this phase was designed to assess the longer term safety of 60 or 120 mg daily. HIV positive patients were included in this trial. The results showed that adefovir dipivoxil caused a statistically significant difference in the change from baseline to the week 4 efficacy endpoint in HBV DNA (-3.99 log₁₀ pg/ml) compared to the placebo group (0.001 log₁₀ pg/ml).

Study 404 maintenance phase

Patients who completed 4 weeks treatment and 12 weeks of post-treatment follow up during the first phase could be enrolled in the second phase of the study, during which they received treatment for 24 weeks with 24 weeks follow up. Patients were randomized to receive adefovir dipivoxil 60 or 120 mg daily. Fifteen patients were included in the efficacy analysis. Treatment with either dose resulted in, for the combined groups, a decrease in HBV DNA concentration from a mean at baseline of 9.94 log₁₀ meq/ml, by a mean of -3.02 log₁₀ meq/ml at the end of 24 weeks of treatment.

In both phases, serum HBV DNA concentrations had returned to near baseline levels of treatment. Serum ALT increases were reported as adverse events, but none of these events was associated with hepatic decompensation.

Study 412 First phase

Study 412 was a sequential cohort, randomised double blind placebo controlled dose escalation trial of 3 dose levels (5, 30 and 60 mg/day) of adefovir dipivoxil for 12 weeks for treatment of chronic hepatitis B. Both HBeAg- positive (53 patients) and anti-HBe positive (10 patients) were included. The median baseline HBV DNA concentration in the HBeAg positive cohort was 8.57 log₁₀ and the median baseline HBV DNA concentration in the anti-HBe positive cohort was 6.54 log₁₀ copies /ml. All patients had raised serum ALT at baseline.

Median HBV DNA concentrations declined in all treatment groups compared to placebo: - 1.82 log in the 5 mg group, -3.78 log in the 30 mg group and -3.34 log₁₀ in the 60 mg group, compared to -0.02 log₁₀ copies/ml in the placebo group (p < 0.001). Serum HBV DNA concentrations returned to baseline after treatment was discontinued. Six patients (15%) who received adefovir seroconverted from HBeAg. No dose related toxicities were observed.

Study 413

This was a phase 2 sequential cohort, randomised double blind placebo-controlled dose escalation trial of 3 dose levels (30, 60 and 120 mg daily) for the treatment of patients with chronic hepatitis B and normal ALT levels. Enrolment was stopped with 15 patients in the 30 mg dose group.

All patients were treated for 12 weeks. As in study 412, patients were eligible for study 412 extension phase, to receive another 12 months treatment. In this study there was a statistically significant difference in the change from baseline to week 12 in the log₁₀ serum HBV DNA (-2.03 vs -0.03 in placebo). No patient became HBeAg positive. HBV DNA was measured by the Chiron bDNA assay. No patients developed any nucleotide mutation in the HBV pol/RT domain during 12 weeks of adefovir dipivoxil therapy.

Study 412 extension and maintenance phases

Patients who completed the initial phase of study 96-412 and 96-413 including the 24 week off treatment follow up period, were eligible to receive open label adefovir dipivoxil at a dose of 30 mg per day for 52 weeks. Thirty nine patients were enrolled. The median baseline HBV DNA was 8.02 log₁₀ copies /ml.

Decreases in DNA were observed: the median time weighted average change from extension baseline was (in 38 patients) - 3.40 log₁₀ copies/ml up to week 100. Serum HBV DNA concentrations were less than 400 copies /ml in 63% of patients by week 96. 21% (6/28) patients who were HBeAg positive at extension baseline lost HBeAg and seroconverted to anti-HBe. No patients lost HBsAg.

Among 39 patients treated in this study, confirmed elevations of serum creatinine of >0.5 mg/dl above baseline occurred in 4 patients. All levels became normal after cessation of adefovir dipivoxil treatment. 28 of the 39 patients who participated in the extension/maintenance phase of the study 96-412 had dose reductions from 30 to 10 mg in accordance with protocol guidelines. There was no evidence of development of resistance with up to 60 weeks of treatment.

Study 435

Ongoing open label study evaluating the safety and efficacy of adefovir dipivoxil 10 mg daily in the treatment of chronic hepatitis B due to lamivudine resistant HBV in liver transplant patients and in patients wait-listed for liver transplantation. The analysis of this study, including resistance, nephrotoxicity and serious adverse events will be discussed by other authors in this symposium.

Phase 3 Studies of adefovir dipivoxil.

Study 437

The antiviral response seen in Phase 1/2 studies indicated a suboptimal antiviral effect with 5 mg and

maximal reductions in serum HBV DNA levels with doses of 30 mg and above. Data from previous studies indicated that daily dosing with 30 mg daily beyond 24 weeks is associated with the emergence of mild nephrotoxicity (seen at higher doses in HIV studies) that is reversible upon discontinuation of drug. Since patients who do not undergo HBeAg seroconversion after 48 weeks of therapy will require long-term treatment and HBeAg negative chronic hepatitis B patients may need indefinite treatment, long-term safety was a critical consideration in selecting an effective and safe dose. The selected dose had to have similar efficacy to 30 mg daily but without the toxicity. Study 437 is thus the pivotal trial; This was a phase 3 multicentre, multinational double blind randomised placebo controlled trial, in HBeAg positive patients with compensated liver disease, who were not undergoing current treatment and had evidence of HBV replication.

In study 437, HBeAg positive patients with chronic hepatitis B were enrolled while in study 438, the population comprised patients with HBeAg negative (presumed precore mutant) chronic hepatitis B. Both studies were designed with a two-year treatment duration. The use of a placebo control group in Studies 437 (and 438) was considered critical for the purpose of separating the effects of adefovir dipivoxil from the effects of the patients' possible HBV-related disease progression. Study 438, in anti-HBe positive patients will be discussed by other authors.

Study design Patients were randomised in the first year to 30 mg, 10 mg or placebo, with or without carnitine 250 mg /day. All patients were HBeAg positive (table 1) Table 2 gives the baseline disease characteristics.

The patient populations enrolled in Studies 437 and 438 comprise two major groups of patients with chronic hepatitis B i.e. HBeAg positive disease (which represents the majority of patients seen in Northern Europe) and HBeAg negative disease (which is of increasing importance in Southern European countries). In both studies, patients were required to have persistently elevated ALT levels at screening and evidence of hepatitis B viral replication. Both study populations had a median baseline Total Knodell score of 10. The median serum HBV DNA level was 8.36 log₁₀ copies/mL in Study 437 and 7.08 log₁₀ copies/mL in study 438. Nearly all patients (98% in Study 437 and 95% in Study 438) had ALT concentrations greater than the upper limit of normal.

Some patients in Study 437 had received prior antiviral medication: (24% IFN-alpha, 2% with lamivudine, and 5% with other anti-HBV medications).

515 patients were randomised in study 437. The intention to treat population was 511 patients.

Unfortunately, a total 91% of the patients who entered the second 48 weeks of Study 437 received at least one incorrect bottle of study medication. This randomisation error occurred as a result of the programming of an interactive voice assignment of blinded medication during the second year of study. Gilead Sciences were made aware of this on 12 July 2001. This error resulted in the termination of the blinded phase on 19 July 2001, and commencement of open-label therapy with 10 mg daily. Since the primary endpoint was at the end of the first 48-week period, the misallocation of study drug during the second year did not affect this determination. Data collected in the second year of Study 437 prior to the dosing error are also useful and interpretable.

End points

Histological change on liver biopsy is a direct measure of necro-inflammatory activity and provides an assessment of the cumulative degree of fibrosis in the liver at a specific time. Histological improvement has been identified as the preferred endpoint by regulatory authorities. Accordingly, changes in liver histology were assessed in the two pivotal placebo-controlled clinical trials (Studies 437 and 438). The primary endpoint of these studies was based on the quantitative assessment of histological improvement after 48 weeks of treatment using the Knodell HAI scoring score. Histological improvement was defined as a reduction from baseline of 2 points or more in the Knodell necro-inflammatory score with no concurrent worsening in the fibrosis score. A qualitative approach was also utilised based on a blinded ranked assessment in which the histopathologist had no knowledge of either the study treatment or biopsy

sequence. Secondary endpoints in the pivotal studies were based on established methods for determining the virological response (suppression of HBV replication as assessed by the decrease of serum HBV DNA) and biochemical response (as defined by reductions in ALT and rates of normalisation) to therapy. HBeAg seroconversion, defined as loss of HBeAg and appearance of anti-HBe was also a key secondary endpoint in Study 437. Loss of HBeAg has been correlated with clinical improvement.

The most sensitive polymerase chain reaction (PCR) assay available was utilised in the adefovir dipivoxil Phase 3 studies for the quantification of HBV DNA (Roche Amplicor PCR, lower limit of quantitation 400 copies/mL). The statistical methods applied for Studies 437 data utilised the intent-to-treat (ITT) population which included all patients who were randomised and received at least one dose of study medication. All patients with an assessable baseline liver biopsy result were included, and where 48 week histological results were missing or unassessable, the patients were analyzed as non-responders.

Efficacy

For the primary endpoint in Studies 437 and 438, adefovir dipivoxil 10 mg and 30 mg were significantly better compared with placebo in improving liver histology (Table 2).

Histological improvement

The primary endpoint was based on the assessment of necro-inflammation, a measure of disease severity as well as a dynamic measure of ongoing disease activity, which is the most-likely histological component to be responsive to therapy. In contrast, fibrosis reflects a cumulative structural change to the liver parenchyma. Nonetheless, on ranked assessment, both necro-inflammatory activity and fibrosis showed greater improvement in adefovir dipivoxil 10 mg and 30 mg compared to placebo recipients ($p < 0.001$). Worsening of necro-inflammatory activity and fibrosis was seen in a greater proportion of the placebo groups ($p < 0.001$) The outcome of the ranked Assessment of necroinflammatory and fibrosis scores before and after treatment are shown in table

Secondary efficacy

The significant clinical and virological effects of adefovir dipivoxil that were durable through 48 weeks are shown in Table 4.

Among the 20 patients in the adefovir dipivoxil 10 mg group who seroconverted, 15 patients (75%) had serum DNA levels < 1000 copies/ml at week 48, 16 patients (80%) had ALT $< \text{ULN}$ at week 48 and 13 (65%) had both. Among the 23 patients in the adefovir dipivoxil 30 mg group who seroconverted, 22 patients (96%) had serum DNA levels < 1000 copies/ml at week 48, 20 patients (87%) had ALT $< \text{ULN}$ at week 48 and 19 (83%) had both.

Continued treatment year 2

A gradual decline in serum HBV DNA during second 48 weeks among patients who remained on adefovir dipivoxil 10 mg with a median change from the second 48 week baseline of $-0.21 \log_{10}$ copies /ml at week 24.

Of the 390 patients who did not seroconvert during the first 48 weeks, 12/131 patients (9%) in the placebo to adefovir dipivoxil 10 mg group, 4/74 (5%) in the adefovir dipivoxil 10 mg to 10 mg group, 6/62 (10%) in the adefovir dipivoxil 10 mg to placebo group and 9/123 patients (7%) in the 30 mg to placebo group lost HBeAg over a median follow up of 16.1 weeks. No patient had a HBeAg seroconversion.

With continued treatment beyond 48 weeks (median additional follow-up of 16 weeks in Study 437), further reductions in serum HBV DNA levels occurred with an additional 21% of patients achieving levels < 400 copies/mL, 27% with ALT normalisation, 5% with HBeAg seroconversion and 16% with HBeAg loss.

Adverse Events

Overall, the observed adverse events were similar in nature and frequency between the active and placebo

groups.

Laboratory adverse events.

Mild increases in serum creatinine and decreases in serum phosphate levels were noted in study 437 (Table 5). Eight (5%) patients in adefovir dipivoxil 30 mg group, 9 (5%) in the adefovir dipivoxil 10 mg group and 8 (5%) in the placebo group had serious adverse events. No one type of serious adverse event was reported by more than one patient. Five patients in the adefovir dipivoxil 30 mg and four in the adefovir dipivoxil 10 mg and placebo group discontinued because of adverse events. One case of Fanconi syndrome was reported as being possibly related to adefovir dipivoxil in a patient treated with 30 mg daily for about 6 months. No deaths were reported in the study.

Other studies

Studies in Lamivudine-Resistant Patient Populations

Four clinical studies have been reported in populations of patients with chronic hepatitis B who were receiving long-term lamivudine therapy and had diminished therapeutic response as evidenced by increasing ALT and serum HBV DNA levels. Study 435 is a phase 3, open label study conducted in liver transplant patients (both pre- and post-transplant) with lamivudine-resistant HBV; Study 461 is a study of the combination of adefovir dipivoxil and lamivudine, as well as adefovir dipivoxil alone in patients with compensated liver disease and Study 460 is an open-label study in HIV co-infected patients with compensated liver disease. Data for patients with decompensated liver disease and lamivudine resistant chronic hepatitis B are also referenced from a GlaxoSmithKline-sponsored open-label study of combined adefovir dipivoxil and lamivudine therapy (Study 465).

The efficacy in post-liver transplant patients failing lamivudine therapy and the other studies of adefovir efficacy will be reviewed by other authors.

Resistance Surveillance Studies

In the resistance surveillance studies, HBV polymerase pol/RT domain was fully sequenced to identify any emerging amino acid substitutions. Virology sequencing studies were performed in conjunction with the phase 2 clinical studies as part of a prospective programme for resistance surveillance. No observed resistance site mutations were identified in patients treated with adefovir dipivoxil for up to 136 weeks in the phase 2 studies.

In study 437, of 511 patients, paired baseline and week 48 sequences were obtained for 381 patients. No HBV mutations associated with resistance to adefovir dipivoxil in patients treated for up to 48 weeks in this study in HBeAg positive (or in study 438) HBeAg negative chronic hepatitis B patients with up to 48 weeks of treatment with adefovir dipivoxil.

The antiviral efficacy and resistance testing in patients with lamivudine-resistant mutations at baseline (Studies 435 and 460i) will be reviewed by other authors. In patients co-infected with HIV and HBV, 48 weeks of treatment with adefovir dipivoxil 10 mg daily did not lead to the emergence of apparent adefovir resistance mutations, nor of K65R or K70E in the HIV reverse transcriptase of these patients.

Conclusions

There are currently two drugs licenced in Europe for chronic hepatitis B: Alpha interferon, a parenteral cytokine immune modulator with antiviral activity and lamivudine, an oral nucleoside analogue that inhibits HBV DNA synthesis by chain termination. Adefovir dipivoxil is an important new addition to current treatments for HBeAg (and anti-HBe) positive chronic hepatitis B.

Treatment with adefovir dipivoxil 10 mg and 30 mg daily results in significantly greater histological benefit (53%-59%) in patients with HBeAg positive chronic hepatitis B versus placebo (25%). HBeAg seroconversion rates, reduction in serum HBV DNA levels, rates of undetectable HBV DNA by PCR and ALT normalisation were also greater for adefovir dipivoxil when compared with placebo. As the sequelae of

chronic hepatitis B are due to progressive liver injury, it is reasonable to infer that agents which result in substantial histological improvement will alter the natural history of the disease. The 30 mg dose of adefovir dipivoxil is not considered the optimal therapeutic dose for treatment of chronic hepatitis B because of the emergence of mild nephrotoxicity with long-term dosing. In contrast, the safety and effectiveness of the 10 mg dose provides an acceptable risk benefit profile.

Several baseline characteristics were shown in the pivotal trials to be predictors of response to adefovir: Response occurred less often in patients with low ALT levels, high serum HBV DNA levels or low HAI score. However, DNA suppression occurred in patients with high HBV DNA levels. Interferon alpha is of limited use in patients with decompensated cirrhosis, or patients with HIV and immunosuppressed patients including patients who have undergone organ transplantation, who are also at risk of organ rejection. HBeAg positive patients with high levels of HBV DNA, normal ALT and minimal hepatitis respond poorly to treatment. These latter patients may respond to lamivudine, but the efficacy of lamivudine is restricted by the development of resistance. The ancillary adefovir studies to be reported by others show evidence of efficacy of adefovir in patients failing lamivudine therapy. Adefovir dipivoxil 10 mg has important antiviral activity, in this group, as demonstrated by reductions in serum HBV DNA levels, similar to that seen in patients with compensated liver disease with HBeAg positive or HBeAg negative chronic hepatitis B. Thus adefovir is an important, new necessity for the treatment of HBV infection.

In clinical use, mild nephrotoxicity is the most important dose-limiting toxicity of adefovir dipivoxil therapy. This toxicity has been characterised using data from studies in both HIV infected and chronic hepatitis B patients that evaluated doses 3 to 12 times higher (up to 120 mg daily), than the recommended dose of 10 mg proposed for chronic hepatitis B. Nephrotoxicity is primarily manifested by the onset of gradual, relatively increases in serum creatinine that generally occur after 24 weeks or more of therapy with doses of adefovir dipivoxil 30 mg or greater daily. There was no evidence of nephrotoxicity with adefovir dipivoxil 10 mg in the safety analysis of study 437. This is demonstrated firstly by the lack of any clinically relevant changes (as evidenced by median changes) in serum creatinine or serum phosphorus from baseline following 48 weeks of treatment with adefovir dipivoxil 10 mg. As of February 28 2002, safety data were available for 492 patients with chronic hepatitis B from the studies 98-437 and 98-438 for a median of 48 weeks and up to a maximum of 92 weeks. There was no evidence of a confirmed serum creatinine increase > 0.5 mg/dl from baseline or serum phosphorous < 1.5 mg/dl.

Nephrotoxicity was observed in up to 31% of patients wait-listed for transplantation and/or treated for lamivudine resistance post-transplant. Serum creatinine increases may be mild and patients may be able to continue treatment with adefovir. However, these patients are at risk of renal impairment, as a result of pre-existing renal insufficiency, decompensated liver disease, significant concurrent illnesses as well as concomitant agents particularly cyclosporine or tacrolimus which are known to be nephrotoxic. This category of patients will require careful monitoring for renal dysfunction while receiving these agents together with adefovir. Dose modifications may be required. A pharmacokinetic study of adefovir dipivoxil 10 mg in patients with varying degrees of renal impairment has led to proposed guidelines for dose interval adjustment for baseline creatinine clearance < 50 ml/min in this group of patients. In contrast, dose modifications are not required in patients with hepatic impairment.

ALT elevations can also be observed following treatment when adefovir dipivoxil 10 mg or other anti-HBV therapies are discontinued or indeed started, as a result of fluctuations in HBV DNA concentrations. Serum ALT elevations of > 10 x ULN were observed in approximately 24% of patients following discontinuation of adefovir dipivoxil 10 mg (i.e. in the second 48 weeks of Studies 437 and 438 in patients switching from adefovir dipivoxil to placebo). None of these episodes was associated with hepatic decompensation. However, as with all nucleoside analogues careful monitoring of patients after discontinuation of treatment with adefovir dipivoxil 10 mg is recommended.

The utility of adefovir dipivoxil as a first-line therapy in the management of patients with HBeAg (and anti-HBe-positive) chronic hepatitis B can be considered because of the high threshold of resistance. Whether this is optimal treatment for these patients requires comparison in controlled combination antiviral studies. The addition of other antiviral therapies may prove additive or synergistic. More profound and more rapid suppression of HBV DNA may improve HBeAg seroconversion rates. An improved understanding of the role

of pre-existing and residual cccDNA concentrations in infected hepatocytes, and immune tolerance to hepatitis B is required to devise optimal strategies for finite course of treatment of HBeAg-positive disease. However, the adefovir clinical programme is ongoing and continues to provide long-term efficacy and safety data in several populations of patients with chronic hepatitis B.

Table 1. Study Design Study 437 (Treatment HBeAg positive chronic hepatitis B)

Randomised	First 48 weeks		Second 48 weeks
1	Adefovir 30 mg n = 173		Placebo n = 153
2	Adefovir 10 mg n = 172	Re-randomised	Adefovir 10 mg n = 79
			Placebo n = 77
3	Placebo n = 170		Adefovir 10 mg n = 150

Table 2. Baseline Characteristics of patients in Study 437 (Treatment HBeAg positive)

	Placebo n = 167	Adefovir dipivoxil 10 mg n = 171	Adefovir dipivoxil 30 mg n = 173	All n = 511
Mean Age (years)	37	34.5	34	35
Male	71%	76%	75%	74%
White	36%	35%	37%	36%
Black	2%	5%	3%	3%
Asian	60%	60%	58%	59%
Median ALT (IU/L) ± SD	138.98 ± 131	138.78 ± 153	123.79 ± 96	133.77 ± 129
Median HBV DNA (log10 copies/ml)	8.33	8.40	8.34	8.36
HBeAg positive	96%	100%	95%	97%
HBsAg positive	100%	100%	100%	100%
Median Total Knodell Score	10	9.5	10	10
Median necro-inflammatory score	8	7	8	8
Median Fibrosis	1	1	1	1
Cirrhosis	8%	7%	4%	6%

Table 2. Patients with histological improvement (Study 437)

	Placebo (n = 167)	Adefovir dipivoxil 10 mg (n= 171)	Adefovir dipivoxil 30 mg (n= 173)
Assessable baseline biopsy	100%	100%	100%
Improvement	25%	53%	59%
No improvement	65%	36%	28%
Missing data	9%	10%	10%

Improvement defined as > 2 point decrease from baseline in Knodell necro-inflammatory score with no concurrent worsening in fibrosis at 48 weeks.

Table 3. Ranked Assessment of Necroinflammatory and fibrosis scores (Study 437 year 1)

	Placebo (n = 167)	Adefovir dipivoxil 10 mg (n= 171)	Adefovir dipivoxil 30 mg (n = 173)
Assessable baseline and week 48 biopsies	145	150	145
Necro-inflammatory			
Improved	41%	71%	77%
Same	26%	15%	12%
Worse	34%	13%	10%
p value		<0.001	<0.001
Fibrosis			
Improved	24%	41%	54%
Same	50%	45%	37%
Worse	26%	14%	10%
p value		< 0.001	< 0.001

Table 4: Secondary efficacy Parameters at week 48 (Study 437)

Efficacy Variable	Placebo (n= 167)	Adefovir dipivoxil 10 mg (n = 171)	Adefovir dipivoxil 30 mg (n = 173)
HBV DNA			
Serum HBV DNA < 400 copies/mL	0	21%	39%
Median change (log10 copies/mL)	-0.55	-3.52	-4.76
Loss of HBeAg	11%	24%	27%
HBeAg seroconversion*	6%	12%	14%
ALT			
Normalised	16%	48%	55%
Mean change ± SD	- 23.01 ± 140.7	- 92.0 ±167.1	- 74.44 ± 128.4
Median Change (IU/L)	- 17	- 51	- 54

Table 5. Laboratory abnormalities reported in patients Study 437

	Placebo	Adefovir 10 mg (n = 171)	Adefovir 30 mg (n = 173)
Creatinine increased	< 1%	4%	29%
ALT > 10 to 20 ULN	17%	9%	8%
Prothrombin time prolonged > 1.5 secs	0%	0%	0%
ALT > 20 ULN	2%	1%	1%
Prothrombin time prolonged > 1.5 secs	0%	0%	0%

Table 6. Histological Response by Baseline Disease Characteristic: Study 437 (ITT Population)

Baseline Characteristic	Study 437	
	ADV 10 mg	Placebo
ALT (multiples of ULN)		
< 2 x ULN	41%	23%
≥ 2 x ULN	62%	27%
HBV DNA (log10 copies/mL)		
< 7.6	60%	32%
≥ 7.6	51%	23%
Total Knodell Score		
< 10	31%	9%
≥ 10	75%	37%
Prior Interferon-alpha		
Yes	38%	26%
No	58%	25%