

REGIONAL DRUG AND THERAPEUTICS CENTRE

**THE USE OF ADEFOVIR DIPIVOXIL FOR THE
TREATMENT OF CHRONIC HEPATITIS B
INFECTION**

**Wolfson Unit
Claremont Place
Newcastle upon Tyne
NE2 4HH**

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ABOUT THIS REPORT

This is one of a series of evaluations prepared by the Regional Drug and Therapeutics Centre. The aim is to give objective information and guidance to commissioners of health services, prescribers and others both on clinical aspects of the subject and on arrangements for prescribing. The reports are prepared by a multidisciplinary team within the Centre and reviewed by health authority personnel and appropriate external specialists. However, responsibility for the content and conclusions rests solely with the Regional Drug and Therapeutics Centre. We welcome comments on reports and suggestions for future topics. The following reports are available:

<i>Subject</i>	<i>Date issued</i>
Dornase alfa	December 1994
Paclitaxel in ovarian cancer	January 1995
Interferon beta-1b in MS	February 1995
	December 1995 (update)
Riluzole in ALS	October 1996
IV immunoglobulin therapy	January 1997
Abciximab in PTCA	February 1997
Recombinant FVIII	March 1997
Interferon alfa in hepatitis C	June 1997
Alglucerase for Gaucher's disease	July 1997
Taxanes in breast cancer	July 1997
Somatropin for GHD in adults	January 1998
New drugs for Alzheimer's disease	February 1998
Atypical antipsychotics	February 1998
Dornase alfa for cystic fibrosis	July 1998
Topotecan for ovarian cancer	July 1998
Irinotecan for colorectal cancer	July 1998
Interferon alfa for haematological malignancy	July 1998
Antiretroviral therapy	July 1998
Paclitaxel in ovarian cancer	December 1998 (update)
Interferon in MS	May 1999 (update)
Octreotide	July 1999
Drug treatment of obesity	July 1999
Low molecular weight heparins in venous thrombo-embolic disease	November 1999
Low molecular weight heparins in unstable coronary artery disease	November 1999
Ribavirin and interferon alfa for chronic hepatitis C	March 2000
Temozolomide for high grade gliomas	May 2000
New drugs for rheumatoid arthritis	May 2000
Verteporfin for age related macular degeneration	November 2000
Iloprost and epoprostenol in the management of pulmonary hypertension	February 2001
Atypical antipsychotics in the management of dementia	June 2001
Interferon alfa in the management of malignant melanoma	November 2001
Imatinib (Glivec [®] , STI-571), in the management of chronic myeloid leukaemia	November 2001
Agalsidase alfa and beta in the management of Fabry disease	July 2002
Carbaryl glutamate in the management of N-acetylglutamate synthetase deficiency	July 2002
Erythropoietin in the management of cancer related anaemia	July 2002
Drotrecogin alfa (activated) in the management of severe sepsis	December 2002
An update on newer agents for the treatment of pulmonary hypertension	February 2004

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SUMMARY

- **Hepatitis B is a serious liver infection caused by the hepatitis B virus (HBV) which claims the lives of approximately 1 million people worldwide per year.**
- **Chronic hepatitis B develops when the body fails to clear the virus following acute infection. In the UK up to 4% of the general population have serological evidence of previous exposure to the virus but only around 0.3 to 0.4% of the population have chronic infection. In the former Northern and Yorkshire region in 2002, there were 162 notifications of Hepatitis B to the Medical Officer for Environmental Health.**
- **Patients with chronic hepatitis B are at high risk of long-term liver complications; after 10 years 20% develop cirrhosis and 5% develop hepatocellular carcinoma. The purpose of treatment is to prevent or stop the progression of liver injury by suppressing viral replication or eliminating infection.**
- **Interferon alfa is currently licensed for the treatment of chronic hepatitis B. It has been associated with a decreased rate of hepatocellular carcinoma and death although it is only suitable for a minority of patients and a sustained response is seen in 30-40%. It is also associated with significant adverse effects and requires subcutaneous administration.**
- **More recently the oral antiviral agent lamivudine has been introduced. It is a nucleoside reverse transcriptase inhibitor that suppresses HBV replication. However most patients relapse once treatment stops and long-term treatment is associated with a high level of lamivudine resistance (up to 32% after 1 year).**
- **Adefovir dipivoxil is an oral nucleotide reverse transcriptase inhibitor licensed as a first-line agent for the treatment of chronic hepatitis B in adults. Two randomised placebo controlled studies have shown benefits in patients with chronic hepatitis B infection as measured by improvements in liver histology and other disease markers (HBV DNA levels etc.) after 48 weeks of treatment.**
- **The efficacy of adefovir compared with lamivudine, or in combination with lamivudine has been investigated in randomised, controlled trials in a limited number of patients. No studies have compared adefovir with interferon alfa. There is currently no conclusive evidence that adefovir has a beneficial effect on long-term complications of chronic hepatitis B such as cirrhosis, liver failure or hepatocellular carcinoma.**
- **At the licensed dose of 10 mg daily adefovir is well tolerated. Higher doses of 30 mg daily have been associated with reversible nephrotoxicity.**
- **Due to the limited comparative data it is not clear where adefovir fits into current treatment. It has been suggested that adefovir should be reserved for patients with HBeAg and/or >100,000 copies of HBV DNA, with ALT at least twice the normal value, who are lamivudine resistant and in whom interferon alfa has failed, is contraindicated or not tolerated. It may have a**

role as monotherapy for HIV/HBV co-infected patients where the HIV has not yet reached the stage of requiring treatment. The optimum duration of treatment has yet to be established.

- In view of the need for careful monitoring of clinical response and regular review, prescribing and monitoring of adefovir should be undertaken by hospital specialists only.
- Cost for 1 year's treatment is £3,833 +VAT. This is around three times the cost of lamivudine therapy.

BACKGROUND

EPIDEMIOLOGY

Hepatitis B is a serious liver infection caused by the hepatitis B virus (HBV) which claims the lives of approximately 1 million people worldwide per year.¹

The distribution of hepatitis B infection varies greatly throughout the world. In areas of high prevalence such as southeast Asia, China and Africa, approximately 10% of the population are chronic carriers of the virus.² In North America, Western Europe and Australia prevalence is much lower.² In the UK, as many as 4% of the general population have serological evidence of exposure to the virus but only around 0.3-0.4% have chronic infection.^{3,4} Worldwide it is estimated that more than 350 million people are chronically infected.¹ In the former Northern and Yorkshire region in 2002, there were 162 notifications of hepatitis B to the Medical Officer for Environmental Health. Although this was lower than in 2001 (n=193) it was higher than for any year between 1990 (n=37) and 1997 (n=130).⁵ These figures are likely to be an under-representation of the true numbers as HBV diagnoses are often not notified for a variety of reasons and also because many asymptomatic cases will remain undiagnosed.⁶

Hepatitis B virus is spread by contact with blood or other bodily fluids of an infected person. The main routes of transmission are perinatal, child-to-child transmission, unsafe injections and transfusions, and sexual contact.¹ Following infection, the incubation period for HBV ranges from 45 to 180 days, and symptoms include loss of appetite, nausea, vomiting, flu-like complaints, fatigue, abdominal pain, dark urine and jaundice.^{1,7} However an estimated 30% of people have no recognisable signs or symptoms.⁸

Chronic hepatitis B infection is defined as the presence of hepatitis B surface antigen (HBsAg) in the serum for at least six months.⁹ The risk of developing a chronic hepatitis B infection is related to the age when infected and may also be increased by immunosuppression (e.g., corticosteroid use, HIV).⁹ Ninety percent of infants exposed in the perinatal period will develop chronic infection, however less than 10% of adults will develop chronic infections.⁹ Patients with chronic hepatitis B are at high risk of long term liver complications as a result of viral replication causing progressive damage to the hepatocytes.¹⁰ After 10 years, about 20% of patients with chronic hepatitis B have developed cirrhosis and about 5% have progressed to hepatocellular carcinoma.¹¹

CURRENT OR CONVENTIONAL THERAPY

The purpose of treating chronic HBV infection is to prevent or stop the progression of liver injury by suppressing viral replication or eliminating infection.² Sustained loss of markers of active viral replication (hepatitis B e antigen (HBeAg) and HBV DNA) are the standard endpoints in clinical trials.^{2,12} In general, seroconversion from HBeAg to hepatitis B e antibody (anti-HBe) is associated with the disappearance of HBV DNA in serum and remission of liver disease.² However, some patients with anti-HBe continue to show signs of viral replication (i.e., have high levels of HBV DNA) and have active liver disease.² This group of patients were recently discovered to have a mutation in the precore region of the HBV genome which

decreases or prevents the production of HBeAg.^{2,9} These patients are said to have HBeAg - negative chronic hepatitis B.⁹

HbeAg - negative chronic hepatitis B is usually progressive and sustained spontaneous remission is rare. The disease is characterised by persistent or intermittent HBV replication, severe necroinflammation of the liver, and progressive fibrosis. Cirrhosis and hepatocellular carcinoma occur at a relatively high rate.¹³

Hepatitis B Vaccine / Immunoglobulin

There are two types of immunisation product; a vaccine and a specific immunoglobulin (which can provide passive immunity and can give an immediate but temporary response after accidental inoculation or contamination with antigen positive blood).¹⁴ In the UK immunisation is recommended for at risk groups including babies born to mothers with chronic hepatitis B, intravenous drug misusers, individuals who change sexual partners frequently, close family contacts of a case or carrier and health care workers who have direct contact with patients' blood.¹⁴

Interferon alfa

Interferon alfa is currently licensed for the treatment of chronic hepatitis B. Patients need to be carefully selected and a sustained response is seen in around 30-40%.² Predictors of a good response include high alanine aminotransferase (ALT) levels, low serum HBV DNA, active histologic changes and fibrosis on liver biopsy, short duration of illness before therapy, and absence of complicating illness such as renal failure or HIV.¹² Sustained biochemical remission has been associated with a decreased rate of hepatocellular carcinoma and death among patients treated with interferon alfa.⁹ Interferon alfa is associated with significant side effects and requires subcutaneous administration.² In patients with decompensated liver disease interferon alfa treatment is often not successful and may cause severe side effects.¹²

Lamivudine

More recently the oral antiviral treatment lamivudine was introduced for the treatment of chronic hepatitis B. In patients with chronic hepatitis B, lamivudine has been demonstrated to be effective in suppressing serum HBV DNA, in increasing the loss rate of serum HBeAg, in normalising aminotransferases activities and in decreasing necroinflammatory activity and fibrosis compared with placebo.² Similar responses have been observed in Asian patients, and patients with HBeAg - negative chronic hepatitis B.^{2,9}

Long-term treatment is associated with a high level of lamivudine resistance (up to 32% after 1 year).² Selection of lamivudine-resistant hepatitis B mutants is the main concern with lamivudine treatment.⁹ Resistance has been noted in the form of mutations at the tyrosine-methionine-aspartate-aspartate sequence (YMDD locus) of the DNA polymerase gene.² Lamivudine resistance usually results in a breakthrough of infection defined as the reappearance of HBV DNA in serum.⁹ The clinical course of patients with lamivudine-resistant mutants is variable and the long-term outcome remains to be determined.⁹ In some cases emergence of resistance is accompanied by acute exacerbations of liver disease and rarely decompensation. However, most patients who continue treatment have lower serum HBV DNA and ALT compared with pre-treatment levels.⁹ Concerns regarding resistance

associated exacerbations of liver disease mean that lamivudine is used with caution in patients with advanced cirrhosis.⁹

ADEFOVIR DIPIVOXIL

A new oral antiviral agent adefovir dipivoxil was launched in April 2003 for the treatment of chronic hepatitis B infection. The purpose of this report is to review its efficacy and place in treatment.

EFFICACY

Adefovir dipivoxil (Hepsera[®], Gilead Sciences Ltd) is an oral pro-drug of adefovir, an acyclic nucleotide phosphonate analogue of adenosine monophosphate, which is actively transported into cells where it is converted to adefovir diphosphate. Adefovir diphosphate inhibits viral polymerases by competing for direct binding with the natural substrate and, after incorporation into viral DNA, causes DNA chain termination.¹⁵

COMPARED WITH PLACEBO

The efficacy of adefovir compared with placebo has been evaluated in two, randomised, double-blind studies in treatment-naïve and previously treated patients with compensated chronic hepatitis B and without lamivudine resistance.^{16,17} Both studies had the same design and differed only in their inclusion criteria, the first study including HBeAg positive patients and the second study including HBeAg negative patients. The first study also included a high dose treatment arm. In both studies, treatment arms were well balanced with respect to demographic data and other baseline characteristics. Overall, enrolled patients had active viral replication (HBV DNA ≥ 5 log copies/ml, moderately elevated ALT (median of approximately 2.3 x upper limit of normal), and the majority had some hepatic fibrosis (Knodell fibrosis score of 1 to 4^a).¹⁶⁻¹⁸

The primary endpoint of both studies was the percentage of patients with improvement in liver histology at week 48. Improvement was defined as reduction from baseline of at least two points in the Knodell necroinflammatory score with no concurrent worsening of the Knodell fibrosis score and was assessed by a clinician blinded to patient treatment group. Secondary endpoints included changes from baseline in serum HBV DNA levels, the proportion of patients with undetectable levels of HBV DNA, the effect of treatment on ALT levels and, in the first study only, the proportion of patients with loss or seroconversion of HBeAg. In both studies, patients who received at least one dose of study medication were included in the analyses, however patients with missing or unassessable base-line liver biopsy specimens were prospectively excluded from the primary efficacy analysis. Patients with missing or unevaluable data at week 48 were considered to have had no response.^{16,17}

^a Knodell score¹⁹ - A Histology Activity Index for liver biopsy specimens. This is an accepted validated rating scale. Biopsies are graded in 4 categories: periportal necrosis (max score = 10), intralobular necrosis, portal inflammation, and fibrosis (max score for each = 4 e.g., fibrosis score of 0 = no fibrosis and a fibrosis score of 4 = cirrhosis). The first three categories are summated to produce the necroinflammatory score (max score =18)

In the first study, 515 patients who had HBeAg positive, compensated, chronic hepatitis B were randomised to either adefovir 10 mg (the licensed dose), adefovir 30 mg or placebo daily in a 1:1:1 ratio for 48 weeks.¹⁶ Twenty-four percent of patients had received previous interferon alfa treatment. A total of 494 patients (97%) had assessable pre-treatment liver biopsy specimens. The primary endpoint of histologic improvement was observed in 53% of patients treated with adefovir 10 mg compared with 25% of those in the placebo group ($p < 0.001$) (Absolute Risk Reduction (ARR) of 27.5%, 95% CI 17.4 - 37.6%) and 59% in the adefovir 30 mg group ($p < 0.001$ compared with placebo; ARR of 33.9%, 95% CI 23.9 – 44.0%).^{16,17} The median reduction in the Knodell necroinflammatory score was 2 points for the group treated with adefovir 10 mg daily, 3 points in the adefovir 30 mg group and no change in the placebo group ($p < 0.001$ for both treatment groups compared to placebo).¹⁶

Adefovir 10 mg or 30 mg also produced statistically significant improvements in secondary endpoints compared with placebo. Serum HBV DNA levels were reduced with a median change of 3.52 log copies/ml and 4.76 log copies/ml for 10 mg and 30 mg respectively vs 0.55 log copies/ml in the placebo group ($p < 0.001$). Twenty-one percent of patients receiving adefovir 10 mg and 39% in the 30 mg group had undetectable HBV DNA levels compared with none in the placebo group ($p < 0.001$). Loss of HBeAg occurred in significantly more patients in the adefovir groups than placebo (24%, 27% and 11% for adefovir 10 mg, 30 mg and placebo respectively, $p < 0.001$). HBeAg seroconversion also occurred in significantly more patients receiving adefovir compared with placebo (12%, 14% and 6% for adefovir 10 mg, 30 mg and placebo, respectively, $p = 0.049$ and $p = 0.011$). Normal ALT levels occurred in 48% of patients in the adefovir 10 mg group and 55% in the adefovir 30 mg group compared with 16% who received placebo ($p < 0.001$ compared with placebo).¹⁶

In the second study 185 patients who were negative for HBeAg were randomised to receive adefovir 10 mg or placebo daily in a 2:1 ratio.¹⁷ Forty-one percent of patients had previously received interferon alfa. A total of 178 patients (97%) had assessable pre-treatment liver biopsy specimens. Significantly more patients treated with adefovir reached the primary end point for histological improvement compared with the placebo group (64% vs 33%, $p < 0.001$; ARR of 30.3%, 95% CI 15.4 - 45.2%).¹⁷

Treatment with adefovir also resulted in significant decreases in the total Knodell score ($p < 0.001$), the necroinflammatory score ($p < 0.001$), and the fibrosis score ($p = 0.005$). Significantly more patients who received adefovir had normalised ALT levels at week 48 compared with the placebo group (72% vs 29%, $p < 0.001$). Serum HBV DNA levels were reduced (median of 3.91 log copies/ml vs 1.35 log copies/ml in the placebo group ($p < 0.001$)). Significantly more patients treated with adefovir had undetectable HBV DNA levels compared with the placebo group (51% vs 0%, $p < 0.001$).¹⁷

After 48 weeks patients in these 2 studies were reassigned to new groups for a further 48 weeks. Patients receiving placebo or adefovir 30 mg were re-randomised to receive adefovir 10 mg and patients previously receiving adefovir 10 mg were re-randomised to receive either 10 mg or placebo. However, study medication was misallocated in 91% of re-randomised patients. The blinded phase of the study was therefore terminated and patients could end the follow-up period or receive open-label adefovir 10 mg. The results from this follow up study are yet to be published in

full but interim results suggest that adefovir continued to improve virological, biochemical, serological, and virological parameters. At week 72, 23% of assessable patients (n = 66) had experienced HBeAg seroconversion compared with 14% at week 48.¹⁸ Treatment with adefovir for 144 weeks was associated with persistently normal ALT levels and HBV DNA <1000 copies/ml in 88% and 79% of patients (n=70), respectively.²⁰

There are unpublished data available which suggest that HBeAg seroconversion achieved on adefovir therapy is maintained following discontinuation of treatment.²¹ Sixty patients (91%) out of 66 previously treated with adefovir for a median of 48 weeks maintained seroconversion after a median duration off therapy of 55 weeks.

PRE- AND POST-LIVER TRANSPLANT

In an uncontrolled, open-label study the efficacy of adefovir was investigated in pre- and post-liver transplantation patients with chronic HBV infection associated with a reduced clinical and virologic response to lamivudine.²² The pre-liver transplantation group (n=128) and the post-liver transplant group (n=196) were treated with adefovir 10 mg daily for a median duration of 18.7 and 56.1 weeks, respectively. Patients with reduced renal function at study entry were initiated on a reduced dose of 5 mg daily. Concomitant hepatitis B immunoglobulin and ongoing lamivudine treatment were allowed at the discretion of the investigator. The primary endpoint of the study was the time-weighted average change in serum HBV DNA from baseline up to week 24. At 24 weeks, the median time-weighted average reduction in serum HBV DNA was 3.1 log copies/ml in both groups of patients, increasing further at week 48 to 3.4 log copies/ml in the pre-transplant group, and 3.3 log copies/ml in the post-transplant group. The absolute median reductions in HBV DNA were 4.1 log copies/ml or 4.3 log copies/ml for pre- or post-liver transplant patients respectively (p<0.001 compared with baseline). Improvements in ALT, bilirubin, and albumin levels and prothrombin times were also seen at week 48. Stable or improved Child-Pugh Scores^b were reported for 92% of the pre- liver transplant patients at week 24 and for 96% of the post-liver transplant patients at week 48. The 1-year survival rates of 84% in the pre-liver transplant group and 93% in the post-liver transplant group were similar to or better than survival rates reported in the literature for pre- and post-liver transplant patients with HBV (not resistant to lamivudine) treated with hepatitis B immunoglobulin or lamivudine.^{18,22}

IN COMBINATION WITH LAMIVUDINE

The efficacy of combination therapy with lamivudine and adefovir was evaluated in a 52 week, randomised placebo-controlled study involving patients with YMDD variant HBV infection with a reduced clinical and virologic response to lamivudine.²³ Ninety five patients with compensated disease received lamivudine 100 mg daily in combination with either adefovir 10 mg daily or placebo. The primary endpoint was the proportion of patients with either a HBV DNA level ≤ 5 log copies/ml or a reduction of ≥ 2 log copies/ml from baseline at both weeks 48 and 52 in patients with 5 log

^b Child-Pugh score (CP score) is a points system used to determine the severity of cirrhosis. Scores are given for the levels of ascites, encephalopathy, albumin, bilirubin and prothrombin times. Depending on the total score, a patient is classified as Class A (early cirrhosis) through Class C (advanced cirrhosis).

copies/ml at baseline. Significantly more patients taking adefovir and lamivudine fulfilled the primary endpoint compared with those on placebo and lamivudine (85% vs 11%, $p < 0.001$). Adefovir and lamivudine treatment was associated with a significantly higher reduction in HBV DNA levels compared with lamivudine and placebo (median change of -4.6 log copies/ml vs $+0.3$ log copies/ml, $p < 0.001$). Normalisation of ALT levels occurred in 31% of patients receiving adefovir in combination with lamivudine compared with 6% receiving lamivudine and placebo ($p = 0.002$).²³

In a small double-blind study, patients with compensated YMDD variant HBV infection were randomised to either adefovir 10 mg daily plus placebo ($n = 19$), a combination of adefovir 10 mg daily and lamivudine 100 mg daily ($n = 20$), or lamivudine 100 mg daily plus placebo ($n = 19$) for 48 weeks.²⁴ Patients enrolled in this study were HBeAg and HBsAg positive with HBV DNA ≥ 6 log copies/ml despite ongoing lamivudine therapy. Patients receiving adefovir monotherapy had been taking lamivudine for a median of 6-12 months longer than patients in the other 2 groups. The primary endpoint was the time-weighted average change from baseline in serum HBV DNA levels up to week 16 because patients experiencing a severe exacerbation of chronic hepatitis B were allowed open-label adefovir after this timepoint. Adefovir in combination with either placebo or lamivudine produced significantly greater reductions in the primary endpoint compared with lamivudine alone (-2.46 , -2.45 or -0.07 log copies/ml, respectively $p < 0.001$) at 16 weeks, and continued to produce significantly greater reductions up to 48 weeks.²⁴ The efficacy of combination therapy was similar to that of adefovir monotherapy.

The efficacy of combination therapy with lamivudine and adefovir was compared with lamivudine monotherapy in a randomised double-blind study in 115 treatment-naïve patients with chronic hepatitis B (published as an abstract only).²⁵ Patients were randomised to combination therapy with lamivudine 100 mg daily and adefovir 10 mg daily or lamivudine 100 mg daily and placebo for 104 weeks. The primary endpoint was the time-weighted average change in HBV DNA levels from baseline to week 16. After treatment for 16 weeks, the time-weighted average reduction in HBV DNA levels was 4.20 log copies/ml in both groups with median reductions in serum HBV DNA of 4.80 log copies/ml or 5.41 log copies/ml at 52 weeks in the lamivudine plus placebo or adefovir and lamivudine groups, respectively. Significantly more patients in the lamivudine plus placebo group had ALT normalisation at weeks 48 and 52 compared with the adefovir and lamivudine group (70% vs 48%, $p = 0.023$). An increased incidence of YMDD mutant HBV and viral breakthrough was observed in the lamivudine plus placebo group.

IN PATIENTS WITH HIV INFECTION

In an open-label, uncontrolled pilot study, 35 patients with YMDD variant HBV infection co-infected with HIV received adefovir 10 mg daily in addition to their anti-HIV therapy including lamivudine 150 mg twice daily. Treatment with adefovir resulted in a significant reduction in serum HBV DNA levels (mean change -4.01 log copies/mL from baseline, $p < 0.0001$) after 48 weeks.²⁶ Patients received adefovir for up to 144 weeks, although data beyond 48 weeks have not been fully published. At week 144, the mean reduction in HBV DNA levels was 5.5 log copies/mL and ALT normalisation occurred in 64% of patients.²⁷

An uncontrolled study, published as an abstract only, included 406 patients with lamivudine resistant HBV, 24% of whom were co-infected with HIV. Treatment with adefovir 10 mg daily for 3 months resulted in a reduction in HBV DNA levels (median change of 2 log copies/ml).²⁸

DECOMPENSATED LIVER DISEASE

The 52 week placebo-controlled study in patients with compensated YMDD variant hepatitis B included a cohort of 40 patients with decompensated disease or recurrent hepatitis B post-liver transplantation; this group of patients received open-label adefovir 10 mg daily in addition to their ongoing lamivudine therapy (100 mg daily).²³ After 52 weeks, 92% of patients had reached the primary endpoint (the proportion of patients with either a HBV DNA level ≤ 5 log copies/ml or a reduction of ≥ 2 log copies/ml from baseline at weeks 48 and 52), and the median reduction in HBV DNA was 4.6 log copies/ml ($p < 0.001$ compared with baseline). There were also significant improvements in the biochemical parameters of liver disease.²³

ADVERSE EFFECTS

In the first study that compared adefovir with placebo, the discontinuation rates due to adverse events were 2% in the adefovir 10 mg group and less than 1% for placebo.¹⁶ The incidence of all adverse effects reported was similar for adefovir 10 mg and placebo with the exception of asthenia (25% vs 19%) and diarrhoea (13% vs 8%). Adverse effects occurring more frequently in the 30 mg group compared with the 10 mg and placebo groups were anorexia (10% vs 4% vs 5%) and pharyngitis (40% vs 26% vs 32%).¹⁶ In the second placebo-controlled study, headache and abdominal pain occurred more often in the adefovir group than in the placebo group.¹⁷ In a pooled analysis of both studies ($n=522$) the incidence of severe adverse effects was similar for adefovir 10 mg (4%) and placebo (5%).¹⁸ The only adverse event type that occurred in more than one patient was chest pain, which was reported by two patients in the adefovir group. There were no deaths reported during the first 48 weeks of both studies. However three deaths, which were considered probably related to the underlying disease, have been reported during the follow up phase. One from sepsis and liver failure in a patient receiving adefovir 30 mg, one cardiac failure in a patient receiving adefovir 10 mg, and one mycosis septicaemia due to immunosuppressant treatment after liver transplant in a patient receiving adefovir 10 mg.¹⁸

HEPATIC FUNCTION

Exacerbations of hepatitis presenting as ALT elevations and increases in serum HBV DNA levels have occurred after withdrawal of adefovir, usually within 12 weeks of treatment discontinuation. It is recommended that patients are closely monitored following treatment withdrawal.^{15,18}

RENAL FUNCTION

Adefovir is excreted renally by a combination of glomerular filtration and active tubular secretion.¹⁵ There was no evidence of renal insufficiency in patients taking adefovir 10 mg daily for 48 weeks in the placebo-controlled studies.^{16,17} In contrast, the 30 mg dose was associated with nephrotoxicity.¹⁷ Two patients (0.4%) treated with adefovir 10 mg daily beyond 48 weeks had increases in serum creatinine >44

micromoles/L from baseline. Both cases resolved, one with continuation of treatment, the other following discontinuation of treatment.¹⁸ Patients with normal renal function should be monitored for changes in serum creatinine every 3 months and creatinine clearance calculated. Caution is advised in patients with creatinine clearance <50 ml/min and in patients receiving medicines that may affect renal function.^{15,18}

DOSAGE, ADMINISTRATION AND COST

Adefovir dipivoxil is currently licensed in the UK for the treatment of adults with chronic hepatitis B who have:

- compensated liver disease with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active liver inflammation and fibrosis
- decompensated liver disease

The recommended dose of adefovir is 10 mg once daily taken with or without food.¹⁵ Annual cost of treatment is £3,833 (+VAT).

Costs of current licensed treatments for chronic hepatitis B are summarised below:

Treatment	Dose	Annual cost (+VAT)*
Adefovir	10 mg daily	£3,833
Lamivudine	100 mg daily	£1,095
Interferon alfa	5 to 10 million IU three times per week	£4,212 to £8,424

* Costs from mims May 2004

There are no cost effectiveness data on the use of adefovir for the treatment of chronic HBV infection.

PLACE IN TREATMENT

Adefovir is more effective than placebo in reducing liver injury as well as biochemical, virological, and serological markers of hepatitis B in patients with compensated liver disease.^{16,17} In pre-and post-liver transplant patients with clinical evidence of lamivudine resistance and either compensated or decompensated liver disease there is limited evidence of efficacy from an open label study.²² In a small study, adefovir was reported to be as effective as the combination of adefovir and lamivudine and more effective than lamivudine alone.²⁴ However this study is too small to derive any reliable conclusions. Adefovir has not been compared with interferon therapy.

Limited data exists on sustained response rates and the optimum duration of therapy remains to be determined. In addition, the relationship between treatment response and long-term outcomes such as hepatocellular carcinoma or decompensated cirrhosis is not known. The cost-effectiveness of adefovir dipivoxil has yet to be established. The emergence of resistance to adefovir remains a possibility. No resistant mutations were seen in placebo-controlled trials after 48

weeks of adefovir treatment. Two cases of adefovir resistance occurred among 124 patients (1.6%) treated for 96 weeks that were not cross-resistant to lamivudine.²⁹ The overall incidence of resistance mutations in patients (n=70) from the second-placebo controlled study treated with adefovir for 48, 96 and 144 weeks was 0%, 3.0%, and 5.9%, respectively.²⁰

Due to the limited comparative data it is not clear where adefovir fits into current treatment. It may offer an alternative, convenient oral therapy for the treatment of chronic hepatitis B for patients with clinical evidence of lamivudine resistance. It has been suggested that adefovir should be offered as reserve therapy for patients with HBeAg and/or >100,000 copies of HBV DNA, who have twice the normal values for ALT and who are lamivudine resistant and in whom interferon has failed, is contraindicated or not tolerated.⁶ It may have a role as monotherapy for HIV/HBV co-infected patients where the HIV has not yet reached the stage of requiring treatment. However where the HIV does require treatment, HIV combination therapy should include at least two drugs which also have HBV activity (e.g.lamivudine plus tenofovir).⁶

The optimum duration of treatment with adefovir is unknown. Patients should be monitored every six months for hepatitis B biochemical, virological and serological markers. In HBeAg-positive patients, treatment should continue at least until HBeAg seroconversion or until HBsAg seroconversion, or there is loss of efficacy. In HBeAg-negative patients, treatment should continue at least until HbsAg seroconversion or there is evidence of loss of efficacy. In patients with decompensated liver disease or cirrhosis, treatment cessation is not recommended.¹⁵

NICE guidance on the use of adefovir and peglated interferon alpha-2a in the treatment of chronic hepatitis B is expected in February 2006.

ARRANGEMENTS FOR PRESCRIBING

Due to the need for careful monitoring of clinical response, prescribing and monitoring of adefovir should be undertaken by hospital specialists only.

FUTURE DEVELOPMENTS

Other nucleoside analogue antiviral agents are being investigated for the treatment of chronic hepatitis B including famciclovir, entecavir and emtricitabine. There are also studies ongoing/planned to investigate the effect of combination therapy for the treatment of chronic hepatitis B infection.³⁰

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APPENDIX 1. SUMMARY OF MAJOR CLINICAL TRIALS OF ADEFOVIR DIPIVOXIL IN THE TREATMENT OF HEPATITIS B.

Key: R – randomised controlled trial; DB – double blinded; PC – placebo-controlled; MC – multi centre; CI- confidence intervals; LT – liver transplant, DVAG– time-weighted average change in serum hepatitis B virus DNA, CPT – Child-Pugh-Turcotte, HBV – hepatitis B virus

Reference	Design	Intervention	Patient no.s	Inclusion Criteria	Exclusion Criteria	Primary outcome	Results	Adverse effects
Marcellin P et al, ¹⁶ 2003	R, PC, DB, MC	Adefovir 10 mg daily for 48 wks	172	Male and female 16-65 yrs who had HBeAg positive chronic hep B and compensated liver disease, presence of serum hep B surface antigen ≥ 6 months, serum HBV DNA ≥ 6 log copies/mL, ALT 1.2 – 10 x upper limit of normal, PT ≤ 1 second above normal, serum albumin ≥ 3 g/dL, total bilirubin ≤ 43 micromol/L, serum creatinine ≤ 133 micromol/L, adequate blood count	Serious medical or psychiatric illness, immunomodulatory therapy within the previous 6 months, recent treatment with corticosteroids, immunosuppressants or chemotherapeutic agents, organ or bone marrow transplant, serum AFP ≥ 50 ng/mL, evidence of hepatic mass, liver disease not due to hepatitis, prior therapy > 12 wks with a nucleoside or nucleotide with activity vs hep B, seropositivity for HIV, hep C or D	Historical improvement defined as a \downarrow of ≥ 2 pts in the Knodell necro-inflammatory score with no worsening of Knodell fibrosis score	More patients on adefovir 10mg or 30mg achieved the primary end point compared with placebo (53% vs 59% vs 25%, $p < 0.001$). Median reduction in Knodell necro-inflammatory score was 2 points for pts on adefovir 10mg vs 3 points for 30mg group or no change for placebo group ($p < 0.001$ for both compared with placebo)	Primary end point was amended before analysis and unblinding to compare the 10 mg dose only with placebo as, in a long-term phase 2 trial, the 30 mg dose was associated with reversible nephrotoxicity
		Adefovir 30 mg daily for 48 wks	173					Incidence of severe adverse events was 10% for adefovir 10mg, 9% for 30mg, 8% for placebo
	Placebo daily for 48 wks	170						

Adefovir dipivoxil for chronic hepatitis B

Reference	Design	Intervention	Patient no.s	Inclusion Criteria	Exclusion Criteria	Primary outcome	Results	Adverse effects
Hadziyanis SJ et al, 2003 ¹⁷	R, DB, PC, MC	Adefovir 10 mg daily for 48 wks	123	Age 16 – 65yrs, chronic hep B and compensated liver disease, detectable HBsAg for ≥6 months, undetectable HBeAg, detectable anti-HBe, serum HBV DNA ≥5 log copies/mL, ALT 1.5-15 x upper limit of normal range, total bilirubin ≤ 42.7micromol/L, PT ≤1sec above normal range, serum albumin ≥3g/dL, serum creatinine ≤133 micromol/L, adequate blood count	Serious medical or psychiatric illness, immunomodulatory therapy within the previous 6 months, recent treatment with corticosteroids, immunosuppressants or chemotherapeutic agents, organ or bone marrow transplant, serum AFP ≥50ng/mL, evidence of hepatic mass, liver disease not due to hepatitis B, prior therapy > 12wks with a nucleoside or nucleotide with activity vs hepatitis B, seropositivity for HIV, hep C or D	Histological improvement defined as a ↓ of ≥2 pts in the Knodell necro-inflammatory score with no worsening of Knodell fibrosis score	Significantly more pts on adefovir reached the primary endpoint (64% vs 33%, p< 0.001, 95% CI 15.4-45.2) Median reduction in Knodell necro-inflammatory score was 3 points for the adefovir group vs no change for the placebo group (p<0.001) Significantly more pts in the adefovir group than in the placebo group had normalisation of ALT (72% vs 29%, p<0.001)	76% of pts in adefovir group had at least 1 adverse event (6% had severe adverse events) compared with 74% (10% had severe adverse events) in the placebo group Headache and abdominal pain occurred more frequently in the adefovir group compared with the placebo group
		Placebo for 48 wks	62					

Adefovir dipivoxil for chronic hepatitis B

Reference	Design	Intervention	Patient no.s	Inclusion Criteria	Exclusion Criteria	Primary outcome	Results	Adverse effects
Schiff et al, 2003 ³²	MC, O,	Adefovir 10 mg daily for a median duration of 18.7 wks for pre-LT pts, 56.1 wks for post-LT pts. Pts with reduced renal function initiated on 5 mg daily	324	Pre-LT (n=128) and post-LT (n=196) pts with recurrent lamivudine-resistant hep B, serum HBV DNA ≥ 6 log copies/mL at least once in previous 2 months despite lamivudine treatment, ALT ≥ 1.2 x upper limit of normal, INR ≤ 1.3 , serum albumin ≥ 2.8 g/dL, serum total bilirubin ≤ 5 mg/dL, neutrophil count ≥ 750 mm ³ , platelet count $\geq 50,000$ mm ³ , haemoglobin > 7.5 g/dL, no history of variceal bleeding or hepatic encephalopathy and adequate renal function	Treatment with investigational agents with hep B activity, systemic agents with nephrotoxic potential (except immuno-suppressive agents or competitors of renal excretion), or chemotherapeutic agents. Active medical or psychiatric illness or alcohol or drug use which could interfere with treatment.	Time-weighted average change in serum hepatitis B virus DNA (DAVG) at wk 24	At week 24, median DAVG was -3.1 log copies/mL in both groups, increasing to -3.4 log copies/mL in the pre-LT group, and -3.3 log copies/ml in the post-LT group at week 48. Absolute median changes in HBV DNA of 4.1 log copies/mL or 4.3 log copies/mL for pre- or post-LT pts respectively (p<0.001 compared with baseline). At wk 48, ALT normalisation in 76% in pre-LT group, and 49% post-LT group	In the pre-LT group, 3 pts (2%) withdrew due to adverse events compared with 4 (2%) in the post-LT group. Most common ADRs were diarrhoea (3%), asthenia (2%), abdominal pain (2%), nausea (2%), creatinine increase (2%), kidney failure (2%) in the pre-LT group compared with asthenia (8%), creatinine increase (6%) in the post-LT group.

Adefovir dipivoxil for chronic hepatitis B

Reference	Design	Intervention	Patient no.s	Inclusion Criteria	Exclusion Criteria	Primary outcome	Results	Adverse effects
Perrillo et al, 2004 ²³	Group A: Pbo, R	Pts with compensated hep B were randomised to adefovir 10mg daily or placebo in addition to lamivudine 100mg daily for 52 wks	adefovir (46) placebo (49)	Compensated HBeAg positive, YMDD mutant hep B, serum HBV DNA ≥ 6 log copies/mL, ALT > 1.3 x upper limit of normal at least twice in previous 6mths	Coinfection with hep C, hep delta virus, or HIV, hepatocellular carcinoma, anaemia (Hb < 8 g/dL), leucopenia and granulocytopenia (WBC $< 1.0 \times 10^9/L$, neutrophil count $< 0.75 \times 10^9/L$, thrombocytopenia (platelet count $< 50 \times 10^9/L$), creatinine clearance < 50 mL/min or serum creatinine > 1.5 mg/dL, pancreatitis, or use of adefovir/other drug active against hep B within prior 3mths	Proportion of pts with either HBV DNA $\leq 10^5$ copies/mL or a ≥ 2 log reduction from baseline HBV DNA level at wks 48 and 52 in pts with > 5 log copies/mL at baseline	More pts in adefovir group with compensated disease met primary endpoint compared with those on placebo (85% vs 11%, $p < 0.001$). Reduction in HBV DNA levels was higher with adefovir than placebo (median change of -4.6 log copies/ml vs $+0.3$ log copies/ml, $p < 0.001$).	In compensated pts, no. of pts with 1 adverse event was similar in adefovir or placebo group (82% vs 83%) 95% of pts in decompensated group had an adverse event 1 pt in the decompensated group died due to respiratory failure
	Group B: O	Pts with decompensated hep B or recurrent hep B post-LT received adefovir 10mg daily in addition to lamivudine 100mg daily for 52 wks	40	Decompensated YMDD mutant hep B or recurrent YMDD mutant hep B post-LT Decompensation defined as presence of ≥ 1 of following: serum bilirubin > 2 x upper limit of normal, PT > 3 secs above normal range, serum albumin < 32 g/L, history of ascites, variceal haemorrhage or hepatic encephalopathy Serum HBV DNA ≥ 6 log copies/mL, ALT > 1.3 x upper limit of normal at least twice in previous 6 mths			92% of pts with decompensated disease reached primary endpoint with a median change in HBV DNA levels of -4.6 log copies/ml	

Adefovir dipivoxil for chronic hepatitis B

Reference	Design	Intervention	Patient no.s	Inclusion Criteria	Exclusion Criteria	Primary outcome	Results	Adverse effects
Peters et al, 2004 ²⁴	C, DB, MC, R	Adefovir 10mg daily plus placebo for 48 wks	19	Age 16 – 65 yrs, YMIDD mutant hep B, HBsAg present for at least 6mths, positive for HBeAg, ALT 1.2-10 x upper limit of normal, treatment with lamivudine for at least 6mths, HBV DNA ≥ 6 log copies/mL, CPT score ≤ 7 , PT < 1 sec above upper normal limit, serum albumin $> 3g/L$, total bilirubin ≤ 43 micromol/L, no history of variceal bleeding, ascites or encephalopathy	Serum phosphorous $\leq 2.4mg/dL$ (0.77mmol/L), serum creatinine ≥ 130 micromol/L, creatinine clearance $< 50mL/min$, absolute neutrophil count ≤ 1000 cells/mL, haemoglobin ≤ 10 or 9g/dL (males and females, respectively), serum α -fetoprotein $> 50ng/mL$, prior use of adefovir or interferon or other immunomodulatory therapies within previous 6mths, treatment with nephrotoxic drugs, competitors of renal excretion and/or hepatotoxic drugs in previous 2mths, prior organ transplantation, concurrent liver diseases, HIV, alcohol or substance use, pregnancy or lactation	DAVG up to 16 weeks After 16wks, pts with severe exacerbations of hep B could receive open-label adefovir	Adefovir alone or in combination significantly reduced the DAVG at 16 wks compared with lamivudine alone (-2.46, -2.45 or -0.07 log copies/ml $p < 0.001$), and continued to produce significantly greater reductions up to 48 wks. At 48 wks, ALT normalisation occurred in 47% of pts on adefovir, 53% on adefovir and lamivudine, and 5% on lamivudine ($p < 0.005$ compared with lamivudine)	No pt discontinued treatment due to an adverse event. Five serious adverse events were reported: 2 cases of HIV, and 1 case of renal colic in adefovir group, 1 case of cholelithiasis in the lamivudine group, and 1 pt on open-label adefovir after 48wks had diverticulitis
		Lamivudine 100mg daily plus placebo for 48 wks	19					
		Adefovir 10mg daily and lamivudine 100mg daily for 48 wks	20					

Adefovir dipivoxil for chronic hepatitis B

Reference	Design	Intervention	Patient no.s	Inclusion Criteria	Exclusion Criteria	Primary outcome	Results	Adverse effects
Benhamou et al., 2001 ²⁶	O	Adefovir 10mg daily plus existing anti-HIV treatments including lamivudine 150mg twice daily for 48 wks	35	HIV-1 infection, YMDD mutant hepatitis B with detectable HBV DNA in serum at least 6mths before inclusion, on lamivudine 150mg twice daily as part of antiretroviral regimen, HIV-1 viral load \leq log 2.6 copies/mL, serum creatinine <133micromol/L, serum phosphate >0.65mmol/L, serum amylase < 1.5 x upper limit of normal, neutrophil count >750 x 10 ⁶ , platelet count >50,000 x 10 ⁶ /L, haemoglobin >80g/L, negative serum pregnancy test, >18yrs	Prior use of adefovir, hep delta, active parasitic, bacterial or viral infections, AIDS-defining event < 1mth before entry, treatment with immunomodulators in previous 4wks, anti-HBV therapy other than lamivudine in previous 12wks, gi malabsorption or chronic nausea & vomiting, malignancy other than Kaposi's sarcoma treated with systemic drugs, decompensated cirrhosis, history of renal failure or heart failure, current alcohol or substance use, poor adherence to anti-retroviral therapy, history of clinically sig neuropathy, clinically sig renal dysfunction in previous 12mths, use of aminoglycosides, amphotericin B, didofovir, cisplatinum, IV pentamidine, vancomycin, systemic chemotherapy, D-carnitine or D, L-carnitine, pregnancy, breastfeeding	Not stated Change in serum HBV DNA levels from baseline	Adefovir resulted in a significant reduction in serum HBV DNA levels (mean change – 3.40 log copies/mL at wk 24, and – 4.01log copies/mL, p<0.0001) after 48 weeks Discontinuation of adefovir in 5 pts (temporarily in 1) resulted in rebound serum HBV DNA levels. Reintroduction of adefovir in 1 pt resulted in decrease in serum HBV DNA by –1.0 log copies/mL after 4wks 2 pts underwent HBeAg seroconversion	Transient increases in ALT levels >2 x baseline values in 15 pts, which declined over following 4-12wks despite continuation of adefovir 2 pts had increases in creatinine >44micromol/L above baseline. Resolved in both pts, in 1 pt after stopping adefovir and antiretroviral drugs and restarting adefovir with different antiretroviral drugs