NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Overview

Hepatitis B (chronic): adefovir dipivoxil and peginterferon alfa

The overview is written by members of the Institute's team of technical analysts. It forms part of the information received by the Appraisal Committee members prior to the first committee meeting. The overview summarises the evidence and views that have been submitted by consultees and evaluated by the Assessment Group, and highlights key issues and uncertainties. In order to allow sufficient time for the overview to be circulated to Appraisal Committee members prior to the first Appraisal Committee meeting, it is prepared before the Institute receives Consultees' comments on the Assessment Report. These comments are therefore not addressed in the Overview.

A list of the sources of evidence used in the preparation of this document is given in Appendix A.

Background

The condition

Hepatitis B is an infectious disease of the liver caused by one or other form of the hepatitis B virus (eight genotypes, A–H, can be distinguished). The virus is transmitted by sexual contact, through the use of infected blood and blood products, by re-use of contaminated needles and syringes, and by vertical transmission from mother to child during, or soon after, birth.

In most people, the initial infection with hepatitis B virus (acute phase) is either asymptomatic or associated with mild, non-specific symptoms which are self-limiting. There is no need for antiviral treatment in the acute phase. However, a small proportion of patients (less than 2%) develop fulminant hepatic failure; these patients might benefit from antiviral therapy, although neither of the drugs under consideration in this appraisal is licensed for the treatment of acute hepatitis B.

Chronic hepatitis B is defined as viraemia and hepatic inflammation that persists for more than 6 months after the acute infection. Chronic disease is the result of the failure of the host immune system to eliminate the virus in the acute phase. The risk of becoming chronically infected with hepatitis B virus varies according to the age at which the infection is acquired. Almost 100% of neonates, and about 50% of young children, develop chronic hepatitis B if infected with hepatitis B virus. In contrast, only about 2–10% of people who are infected as adults go on to develop chronic hepatitis B.

The Department of Health estimates that about 180,000 people in the UK have chronic hepatitis B. There are about 7,700 new cases of chronic hepatitis B each year. Of these, around 300 people were infected within the UK, while the remainder (mainly immigrants to the UK) were infected abroad, generally in areas of high prevalence where the virus is frequently transmitted from mother to child.

The pathogenesis and clinical manifestations of chronic hepatitis B infection are the result of a complex interaction between the virus and the host immune system. The hepatitis B virus does not directly damage the liver cells itself. The symptoms and complications of the disease arise when the host's immune system attempts to remove the infection by killing infected hepatocytes. The course of the infection can be described in terms of virological markers and clinical progression.

Virological markers

HBeAg-positive (HBeAg+) infection is the most common form of the disease in Northern Europe. Hepatocytes infected with the HBeAg+ form of the virus synthesise and secrete the hepatitis B e antigen (HBeAg), which can be detected in serum. This is sometimes called the 'wild-type' strain. HBeAg is an important marker of active viral replication and until the discovery of the HBeAg-negative form of the virus (see below), people positive for hepatitis B surface antigen (HBsAg) and negative for HBeAg were considered to have non-replicative infection.

HBeAg-negative (HBeAg–) infection involves a variant form of the virus in which active viral infection is not accompanied by secretion of HBeAg. HBeAg– virus is also known as 'pre-core mutant' virus. The viral mutation can emerge late in the course of infection in people initially infected with HBeAg+ virus or can occur from the beginning. The frequency of pre-core mutation is primarily determined by the genotype of the infecting hepatitis B virus. It is rarely associated with genotypes A, F and H, but is more frequent in genotypes B to E. All known isolates of genotype G do not express HBeAg. The genotypes have distinct geographical distributions; for example, genotype A is prevalent in North West Europe and the USA, genotype D is prevalent South-Eastern Europe and the Middle East, while genotypes B and C are prevalent in South East Asia. Consequently, the prevalence of HBeAg– chronic hepatitis varies geographically.

Clinical progression

The natural history of the disease can be divided into phases, each of which may last many years.

Immunotolerant phase

People who are affected at birth or in early childhood initially enter an 'immunotolerant' phase during which the immune system does not actively fight the virus. The virus is highly replicative during this phase, but the child is usually asymptomatic. High levels of viral DNA are detectable, and the child is HBeAg seropositive (if infected with HBeAg+ virus). The child is highly infectious, and may be a source of infection within the family and community. This phase can last for many years before progressing to active disease. In those who acquire

the infection as adults, the immunotolerant phase is very short (about 2–4 weeks) and represents the incubation phase of the infection.

Active chronic hepatitis B

The first stage of active disease involves a period of increasing inflammatory hepatic necrosis as the immune system begins to fight the virus. This stage of the disease is characterised by elevated levels of viral DNA in the blood, persistently raised levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and evidence of hepatic necrosis and inflammation on biopsy. In HBeAg-positive chronic hepatitis B, progression to cirrhosis occurs at an annual rate of 2–5.5%, with a cumulative 5-year rate of progression of 8–20%.

HBeAg seroconversion

In people infected with HBeAg+ virus, the next stage of the infection occurs when inflammation becomes sufficiently intense to permit lysis of infected hepatocytes. This produces a ‘flare’ of the disease with symptoms resembling acute hepatitis B, and leads to the development of antibodies against the ‘e’ antigen (anti-HBe).

This is referred to as ‘seroconversion’. In most patients the development of anti-HBe coincides with a reduction in viral load, undetectable HBeAg, and persistently normal AST and ALT. Hepatitis B viral DNA is undetectable using classical hybridisation techniques, although very sensitive techniques such as PCR can detect residual viral DNA in most seroconverted patients. On biopsy, there is histological change from active to inactive hepatitis, or active cirrhosis to inactive cirrhosis. The seroconverted disease state is associated with good quality of life and a relatively low risk of disease progression. It is sometimes referred to as the ’inactive HBsAg carrier state’ because patients continue to express HBsAg.

The spontaneous seroconversion rate is 5–10% per year, though this varies between populations. Once seroconversion has taken place, most people remain in the inactive HBsAg carrier state. However, increasing viraemia and recurrent hepatitis after seroconversion is indicative of the emergence of the HBeAg– (pre-core mutant) strain of the virus.

HBeAg-negative chronic hepatitis B

HBeAg-negative chronic hepatitis is associated with a fluctuating course and a poor prognosis. Few patients with HBeAg– chronic hepatitis achieve a lasting remission. Active disease is associated with either persistent elevation of ALT or an erratic pattern of ALT changes with flare-ups that resemble acute hepatitis B and can be severe or even fatal. Progression to cirrhosis of he liver has been estimated to occur in 8–10% of people with HBeAg– chronic hepatitis B each year.

HBsAg seroconversion

The development of antibodies against hepatitis B surface antigen with clearance of HBsAg occurs spontaneously in about 0.5–2% of people with chronic

hepatitis B each year in western countries. In countries where hepatitis B is endemic, the rate is much lower – between 0.05 and 0.08% per year. This is most likely to occur in the year following HBeAg seroconversion. Clearance of HBsAg signifies resolution of the chronic infection.

Complications

People with active chronic hepatitis B are at increased risk of liver cirrhosis and hepatocellular carcinoma. It has been estimated that between 25 and 40% of people with chronic hepatitis B will die prematurely from one these conditions.

Cirrhosis

Chronic infection and inflammation of the liver may eventually lead to the replacement of functional liver tissue with fibrotic scar tissue. These changes in liver composition are called cirrhosis. In the early stages, there is sufficient healthy tissue to provide adequate liver function and most patients do not have any overt symptoms. This is termed compensated cirrhosis. However, cirrhosis often progresses to the point where functional tissue can no longer compensate for the cirrhotic lesions. Decompensated cirrhosis is irreversible liver failure and has a poor prognosis. The complications of liver failure include jaundice, a tendency to bruise or bleed, ascites (abnormal fluid in the abdomen), hepatic encephalopathy (neuropsychiatric abnormalities ranging from mild confusion to coma), portal hypertension and oesophageal varices (with the potential for catastrophic bleeding). Only 14–28% of patients with decompensated cirrhosis survive for 5 years. Decompensated cirrhosis due to hepatitis B is a major indication for liver transplantation.

Hepatocellular carcinoma

People with chronic hepatitis B are a hundred times more likely to develop hepatocellular carcinoma than people who resolve the acute infection. This cancer generally emerges 25–30 years after the acute infection. The risk is greatest in those with cirrhosis. There are several treatment options, including surgical resection, injecting the tumours with alcohol or acetic acid, and destroying them with lasers, ultrasound, liquid nitrogen or radiation. Partial hepatectomy, in which up to 80% of the liver is removed, offers a potential cure but has poorer survival than transplantation. Transplantation is potentially curative for small tumours that have not metastasised. However, in general the outcome for people with hepatocellular carcinoma is poor: most die within 12 months of diagnosis, and only 5–6% will be alive 5 years after diagnosis.

Current management

The aim of treatment is to prevent liver disease (cirrhosis, hepatic failure and hepatocellular carcinoma) which is best achieved by eradication or sustained suppression of replication of the hepatitis B virus. Treatment may be given as a finite course (circumscribed therapy) – with the intention of allowing the immune system to respond and control the infection without the need for further drug treatment – or as

long-term viral suppressive therapy. The latter is required if short-term therapy is unsuccessful.

The first drugs to be licensed for the treatment of chronic hepatitis B were **alfa interferons**. Interferons are natural proteins that activate the immune system in response to viral infection. There are three recombinant interferon products licensed for the treatment of chronic hepatitis B: IntronA (interferon alfa-2b, Schering-Plough), Roferon-A (interferon alfa-2a, Roche) and Viraferon (interferon alfa-2b, Schering-Plough). Interferon alfa-2a is usually given at a dose of 2.5 to 5 million units per square metre of body surface area by subcutaneous injection three times a week for 4 to 6 months. Interferon alfa-2b is given at a dose of 5 million units/m^2 three times a week for 4 to 6 months. The side-effects of interferons can be severe and this means that they are not suitable for long-term treatment in chronic hepatitis B. There are no data on long-term maintenance therapy with interferon and the treatment is not licensed for this.

In HBeAg+ chronic hepatitis B, the effectiveness of treatment is normally evaluated in terms of HBeAg seroconversion (that is, transition to the inactive carrier state). According to the joint submission from the professional organisations[1], HBeAg loss/seroconversion occurs in 33% of people with HBeAg-positive chronic hepatitis B after a course of treatment with standard interferon alfa. Long-term treatment with an alternative antiviral is required for those who do not undergo seroconversion.

In HBeAg– chronic hepatitis B response is usually defined as undetectable serum HBV DNA by hybridisation assays. People with HBeAg– chronic hepatitis B do not often have a sustained response to a course of interferon. A consensus statement from the European Association for the Study of the Liver (EASL)suggests that interferon produces a response in between 50 and 75% of people during a course of 4–12 months of interferon, but this response is maintained for 12 months after stopping treatment in less than half of them.

There have been no reports of viral resistance to interferon.

Lamivudine (Zeffix, GlaxoSmithKine) is a nucleoside reverse transcriptase inhibitor antiviral drug. The dose in adults is 100 mg per day. It can be given both as a circumscribed course of treatment or as long-term viral suppressive therapy. In HBeAg+ chronic hepatitis B, treatment is usually given for a year. According to the joint professional organisations' submission, this results in HBeAg seroconversion in 15–20% of cases.

In HBeAg– chronic hepatitis B, long-term control of the infection is difficult to attain after circumscribed therapy and long-term treatment with antiviral drugs is often needed. The main problem with long-term antiviral treatment is the emergence of

[1] Joint submission from The Royal College of Physicians of London, The British Association for the Study of the Liver, and The British Society of Gastroenterology.

resistance. Resistance to lamivudine occurs in more than 60% of cases after 3 years' treatment.

The technology

Table 1 Summary description of technology

Generic Name	Pegylated interferon alfa-2a	Adefovir dipivoxil
Proprietary name	Pegasys	Hepsera
Manufacturer	Roche	Gilead Sciences
Dose	180 micrograms once weekly by subcutaneous injection	10 mg once daily by mouth
Acquisition cost excl VAT (BNF 49th edition)		

Pegylated interferons are formed by attaching strands of polyethylene glycol (PEG) to the interferon molecules. This prolongs the rate of absorption and excretion of interferon, reducing the fluctuations in serum level that occur with unmodified interferon. Pegylated interferon may be administered less frequently than the unmodified form (once a week compared with three or more times a week). There are several pegylated interferons on the market but only one is licensed for the treatment of chronic hepatitis B. Pegylated interferon alfa-2a (Pegasys, Roche) is licensed for the treatment of HBeAg+ or HBeAg– chronic hepatitis B in adults with compensated liver disease and evidence of viral replication, increased ALT and histologically verified liver inflammation and/or fibrosis.

Adefovir is structurally related to the purine base adenine. It is converted intracellularly to the diphosphate which inhibits the synthesis of hepatitis B virus DNA through competition for the enzyme reverse transcriptase and incorporation into the viral DNA. Adefovir is not well absorbed after oral administration and is given by mouth as the prodrug adefovir dipivoxil. It is licensed for the treatment of chronic hepatitis B in adults with:

- 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 evidence

Clinical effectiveness

The Assessment Report included systematic reviews of randomised controlled trials (RCTs) and RCTs comparing pegylated interferon alfa or adepovir dipvoxil with other

antiviral drugs, placebo or best supportive care. A total of six RCTs and one systematic review met the criteria for inclusion in the review of clinical effectiveness.

Pegylated interferon alfa

The Assessment Group found three RCTs investigating pegylated interferon alfa in chronic hepatitis B.

Pegylated interferon alfa in HBeAg-positive chronic hepatitis B

In HBeAg+ chronic hepatitis B, HBeAg seroconversion marks recovery of the immune response. Both studies of pegylated interferon alfa in HBeAg+ chronic hepatitis B reported HBeAg seroconversion.

The comparison of pegylated with standard interferon alfa was open an open-label study in 194 people. The participants were randomised to one of three doses of pegylated interferon alfa or standard interferon. Treatment was for 24 weeks followed by a 24-week treatment-free follow up period. The study was conducted in 18 centres in Taiwan, Thailand, China, Australia and New Zealand. The rates of HBeAg seroconversion and ALT normalisation were higher in the patients treated with pegylated interferon alfa (see Table 2), but the differences were not statistically significant. Viral response rates (measured as HBV DNA levels < 500,000 copies/ml) were higher for patients treated with pegylated interferon alfa-2a (36% for all three doses combined) when compared with standard interferon (25%), but the difference was not statistically significant.

The comparison of pegylated interferon alfa with lamivudine was a larger study in which 814 patients with HBeAg-positive chronic hepatitis B received either pegylated interferon alfa plus placebo, pegylated interferon alfa plus lamivudine, or lamivudine alone. The study was partially double blind in that those who were receiving pegylated interferon alfa were blinded as to whether they were receiving lamivudine. This study was available only as an abstract at the time the assessment report was finalised, but it has recently been published in full. The majority of patients in the study were Asian and most were infected with genotype B or C hepatitis B virus. Treatment was for 48 weeks followed by a 24-week treatment-free follow up period. In the intention to treat analysis, patients with missing values at week 72 were classified as having no response. The fully published version indicates that withdrawal rates were low in all three groups (6%, 7% and 5% in the pegylated interferon alfa plus placebo, pegylated interferon alfa plus lamivudine, and lamivudine groups, respectively).

In this study, the rates of HBeAg seroconversion were higher in the patients treated with pegylated interferon plus placebo than in those treated with lamivudine alone (see.Table 2). The addition of lamivudine to pegylated interferon alfa did not improve the HBeAg seroconversion rate.

A statistically significantly larger percentage of trial participants using pegylated interferon alfa alone (32%) or in combination with lamivudine (34%) showed a HBV DNA ‘response’ (< 100,000 copies/ml) when compared with lamivudine alone (22%) at week 72 ($p = 0.012$ and $p = 0.003$, respectively).

The proportion of patients with an ALT response (normalisation) at week 72 was higher in the groups taking pegylated interferon alfa-2a than in the group taking lamivudine alone (see Table 2). The difference between pegylated interferon monotherapy and lamivudine alone was statistically significant (p = 0.002), as was the difference between the combination and lamivudine alone (p = 0.006).

At the end of treatment, lamivudine-resistant mutations were seen more frequently in the patients who received lamivudine alone than in those who received lamivudine plus pegylated interferon alfa (< 1% versus 18% of patients). This difference did not reach statistical significance.

HBsAg seroconversion was seen in 8 (3%) trial participants using pegylated interferon alfa-2a alone and in 8 (3%) using pegylated interferon alfa-2a in combination with lamivudine at the end of follow up (72 weeks); this is more than the HBsAg seroconversion rate of participants using lamivudine alone (0%), and the difference was statistically significant (p = 0.004).

Table 2 Studies of pegylated interferon alfa in HBeAg+ chronic hepatitis B

Author	Intervention	Duration of treatment	Follow up (including treatment)	HBeAg seroconversion	ALT normalisation
Cooksley et al (2004)	Pegylated interferon alfa 90 mcg/week (n = 49)	24 weeks	48 weeks	37%	43%
	Pegylated interferon alfa 180 mcg/week (n = 46)			33% (34%)	35% (36%)
	Pegylated interferon alfa 270 mcg/week (n = 48)			27%	31%
	Interferon alfa 4.5 million units 3x per week (n = 51)			25%	25%
Lau et al (2005)	Pegylated interferon alfa 180 mcg/week + placebo (n = 271)	48 weeks	72 weeks	32%	41%
	Pegylated interferon alfa 180 mcg/week + lamivudine 100 mg daily (n = 271)			27%	39%
	Lamivudine 100 mg daily (n = 272)			19%	28%

Pegylated interferon alfa in HBeAg– chronic hepatitis B

In HBeAg– chronic hepatitis B, HBeAg seroconversion[2] is not a relevant outcome, and effectiveness is generally measured in terms of HBV DNA suppression and liver histology and function.

[2] HBsAg seroconversion can be included as an outcome in clinical studies, but this is a very rare event and so RCTs are unlikely to have sufficient power to detect differences between treatments for this outcome.

The only study of pegylated interferon alfa in HBeAg– chronic hepatitis B was a comparison of pegylated interferon alfa plus placebo, pegylated interferon alfa plus lamivudine, and lamivudine alone. Treatment was for 48 weeks followed by a 24-week treatment-free follow up period. Of 552 patients who were randomised 537 were included in the intention-to-treat analyses (those who were randomised but did not receive medication were excluded, and all nine patients from one centre were excluded because of irregularities in study conduct). In the intention-to-treat analysis, patients with missing values at week 72 were classified as having no response. The discontinuation rates were 8%, 6% and 2% in the pegylated interferon alfa plus placebo, pegylated interferon alfa plus lamivudine, and lamivudine groups respectively.

The study had two predetermined primary measures of efficacy: the normalisation of ALT levels and the suppression of HBV DNA levels to below 20,000 copies/ml. At the end of treatment (week 48) the proportion of patients with normalised ALT was highest in the lamivudine monotherapy group. At week 72 the percentage with normalised ALT was significantly higher in the groups treated with pegylated interferon alfa than in the lamivudine group (59% with pegylated interferon alfa monotherapy and 60% for pegylated interferon alfa plus lamivudine, versus 44% for lamivudine; $p = 0.004$ and $p = 0.003$ respectively).

For the primary outcome of virological response (HBV < 20,000 copies/ml) at week 48, the percentage of responders was 81% in the pegylated interferon alfa plus placebo group, 92% in the pegylated interferon alfa plus lamivudine group, and 85% in the lamivudine group. At week 72, the percentage of responders was significantly higher in the groups treated with pegylated interferon alfa than in the lamivudine group (43% for pegylated interferon alfa monotherapy and 44% for pegylated interferon alfa plus lamivudine, versus 29% for lamivudine; $p = 0.007$ and $p = 0.003$ respectively).

HBsAg loss occurred in seven (4%) patients receiving pegylated interferon alfa plus placebo and in five (3%) patients receiving pegylated interferon alfa plus lamivudine. HBsAg seroconversion (HBsAg loss and the presence of anti-HBs antibody) occurred in five (3%) patients receiving pegylated interferon alfa plus placebo, and in three (2%) patients receiving combination therapy. HBsAg loss or seroconversion did not occur in any of the patients receiving lamivudine monotherapy.

There was no statistically significant difference in histological improvement between the pegylated interferon alfa-2a group, the lamivudine group and the pegylated interferon alfa-2a with lamivudine group.

Treatment resistance mutations were detected in 32 people in the lamivudine group (18%) and one person in the pegylated interferon plus lamivudine group ($p < 0.001$).

Adefovir dipivoxil

The assessment report included five studies of adefovir dipivoxil in chronic hepatitis B.

Adefovir dipivoxil in HBeAg-positive chronic hepatitis B

Four of the five studies of adefovir dipivoxil were conduced in patients with HBeAg-positive chronic hepatitis B. All four reported HBeAg loss and/or seroconversion as an outcome (Table 3), but this was not a primary endpoint in any of the studies.

The pivotal study by Marcellin et al. was a comparison of two doses of adefovir dipivoxil (10 mg and 30 mg) with placebo in 515 people with HBeAg+ chronic hepatitis B and compensated liver disease. The primary endpoint was histological improvement (defined in terms of a reduction in Knodell necroinflammatory score) for the comparison between the adefovir dipivoxil 10 mg group and the placebo group. This analysis was based on 329 patients (97%), randomised to adefovir dipivoxil 10 mg or placebo, for whom base-line liver-biopsy specimens were available. Histological improvement was seen in 53% percent of patients in the adefovir dipivoxil 10 mg group and 25% of patients in the placebo group ($p < 0.001$). The results for HBeAg seroconversion are shown in Table 3 below. HBV DNA 'response' (< 400 copies/ml at week 48) was established in a statistically significant greater proportion of patients in both adefovir groups when compared with the placebo group ($p < 0.001$ for both comparisons), as was ALT normalisation (see Table 3 below, $p < 0.001$ for both comparisons).

In the study by Peters et al., 59 people with HBeAg+ chronic hepatitis B and genotypic evidence of lamivudine-resistance, raised ALT, and serum HBV DNA level > 10^6 copies/ml despite ongoing treatment with lamivudine were randomised to adefovir dipivoxil 10 mg, lamivudine 100 mg, or addition of adefovir dipivoxil to ongoing lamivudine treatment. The primary endpoint was time-weighted change from baseline in serum HBV DNA level. Reductions in this endpoint were seen in all recipients of adefovir dipivoxil. HBV DNA levels were 'undetectable' (< 1000 copies/ml) in 26% of patients receiving adefovir plus placebo and 35% of patients receiving adefovir plus lamivudine versus none receiving lamivudine plus placebo ($p < 0.05$). ALT was normalised in 53% and 47% of the adefovir dipivoxil plus lamivudine and adefovir dipivoxil groups respectively, compared with 5% (1/19) of the lamivudine group ($p = 0.001$ and $p = 0.004$, respectively).

The other two studies investigated the combination of adefovir dipivoxil with lamivudine compared with lamivudine alone. One was in treatment naïve patients and the other was in people with lamivudine resistance. In the study of treatment naïve patients there was no advantage in adding adefovir dipivoxil to lamivudine. However, in people with lamivudine resistance, adefovir dipivoxil plus lamivudine was more effective than lamivudine alone in terms of both virological response – 85% of those using adefovir dipivoxil plus lamivudine reached a HBV DNA level of ≤ 10^5 copies/ml compared with 11% using lamivudine alone ($p < 0.001$) and in 37% ALT was normalised compared with 9% in the lamivudine group ($p = 0.003$)

– and HBeAg seroconversion (see Table 3 below). By week 52 a significantly lower proportion of people in the adefovir plus lamivudine group had detectable YMDD mutations than in the lamivudine group alone (62% versus 96%, $p < 0.001$).

Table 3 Studies of adefovir dipivoxil in HBeAg+ chronic hepatitis B

Author	Intervention	Duration of treatment	Follow-up	HBeAg loss	HBeAg seroconversion	ALT normalisation
Marcellin et al (2003) *treatment naïve*	Adefovir dipivoxil 10 mg daily (n = 172)	48 weeks	48 weeks	24%	12%	48%
	Adefovir dipivoxil 30 mg daily (n = 173)			27%	14%	55%
	Placebo (n = 170)			11%	6%	16%
Peters et al (2004) *lamivudine resistant*	Adefovir dipivoxil 10 mg daily + placebo (n = 19)	52 weeks	52 weeks	16%	11%	47%
	Adefovir dipivoxil 10 mg daily + lamivudine 100mg daily (n = 18)			17%	6%	53%
	Lamivudine 100mg daily + placebo (n = 19)			0	0	5%
Sung et al (2003) *abstract treatment naïve*	Adefovir dipivoxil 10 mg daily + lamivudine 100mg daily (n = 55)	52 weeks	52 weeks	19%	—	48%
	Lamivudine 100mg daily + placebo (n = 57)			20%	—	70%
Perrillo et al (2004) *lamivudine resistant*	Adefovir dipivoxil 10 mg daily + lamivudine 100mg daily (n = 46)	52 weeks	52 weeks	15%	8%	37%
	Lamivudine 100mg daily + placebo (n = 48)			2%	2%	9%

Adefovir dipivoxil in HBeAg– chronic hepatitis B

One study compared adefovir dipivoxil with placebo in people with HBeAg– chronic hepatitis B. This was a double-blind study in which 185 people were randomised in a 2:1 ratio to adefovir dipivoxil or placebo for 48 weeks. The primary endpoint was histological improvement defined in terms of a reduction in Knodell necroinflammatory score with no worsening of fibrosis. A total of 167 patients (91%) had assessable pre-treatment and post-treatment liver biopsy specimens. Significantly more patients in the adefovir dipivoxil group had histological improvement than in the placebo group (64% versus 33%, $p < 0.001$). At week 48, 51% of the adefovir dipivoxil group had undetectable HBV DNA levels (< 400 copies/ml), compared with no one in the placebo group ($p < 0.001$) and 72% showed normalised ALT levels compared with 29% in the placebo group ($p < 0.001$).

Long-term follow-up data from this study were available as abstracts, and have been published since the assessment report was completed. After week 48, 123 people who had been assigned to adefovir dipivoxil in the initial study were randomised to continue adefovir dipivoxil at a dose of 10 mg daily or to switch to placebo. Of the 61 patients who had initially been randomised to placebo, 60 switched to treatment with adefovir dipivoxil 10 mg daily. At week 96, undetectable levels of HBV DNA were found in 71% of the continued-adefovir dipivoxil group, compared with 8% of the placebo group. In the group who received adefovir dipivoxil for 48 weeks having previously received placebo for 48 weeks, undetectable levels of HBV DNA were found in 76% of patients.

The cumulative incidence of resistance to adefovir dipivoxil among all patients was 3% at 96 weeks and 5.9% at 144 weeks. This trial will continue until all patients have completed 5 years follow-up.

Cost effectiveness

Several models populate the literature. All involve either lamivudine (LAM), interferon alfa (IFN), or both, but none of the available analyses involve either pegylated interferon alfa (PEG) or adefovir dipivoxil (ADV).[3] The only available models that consider the treatments of interest are the two manufacturers' models and the Assessment Group's (AG) model. All three models have a similar structure, and given that the inputs of the three models are also similar, the results from one model to another do not vary much.

All three models are Markov models with a number of health states. Simulated patients begin in one health state and move successively to different health states over time with probabilities determined from various trials, and with health-related quality of life in each state determined from studies of actual patients. Simulated patients gain health benefits from treatment by going into remission (with a higher associated quality of life) more often than those not on treatment, and by delayed entry (on average) to poor health states. Patients on treatment on average also live longer than those not on treatment. As they proceed through the model, simulated patients incur treatment costs that differ depending on the particular health state they are in at the time.

The Assessment Group model

This model has a lifetime horizon to estimate the cost effectiveness of the two drugs of interest from an NHS plus personal social services perspective.

3 A cost effectiveness analyses that includes strategies with adefovir dipivoxil has been published recently, but this was not available at the time the Assessment Report was produced. Kanwal F, Gralnek IM, Martin P, et al. Treatment alternatives for chronic hepatitis B virus infection: a cost-effectiveness analysis. Ann Intern Med. 2005;142(10):821-31

It is assumed that patients begin with a treatment involving either IFN or PEG. This treatment lasts either 24 or 48 weeks, as appropriate for the patient group according to HBeAg positive or negative status. If this treatment fails to seroconvert the patient, the following alternative care pathways are explored.

- No further treatment (best supportive care, BSC).
- Patient begins LAM to be continued indefinitely, or until seroconversion or LAM resistance emerges.
    - If LAM resistance emerges:
        - no further treatment
        - treatment with ADV.
- Patient begins ADV to be continued indefinitely, or until seroconversion or ADV resistance emerges.
    - If ADV resistance emerges:
        - no further treatment
        - treatment with LAM.

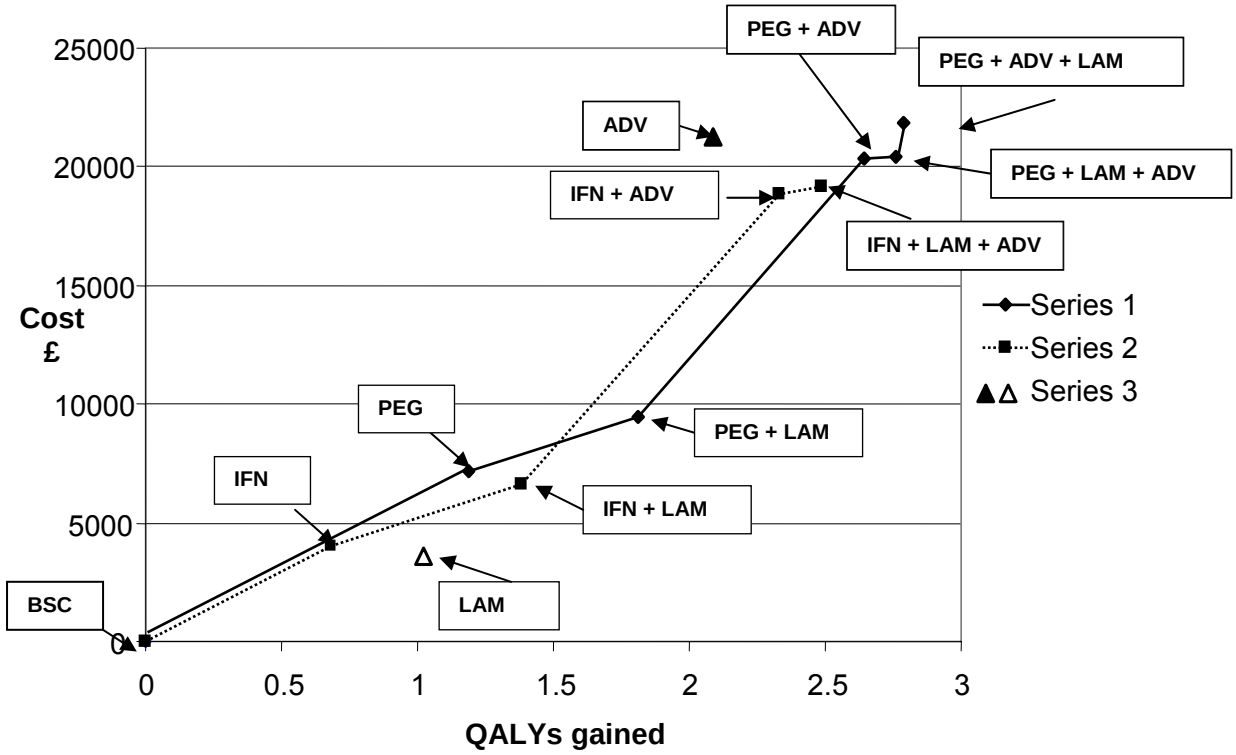
A further analysis assumes that there is no initial treatment with IFN or PEG, and the patient begins either with LAM or ADV, and goes through the same pathways as above (LAM alone; LAM followed by ADV [LAM +ADV]; ADV alone; ADV followed by LAM [ADV + LAM]).

In each pathway, the total number of QALYs gained is estimated by running the simulated patient through the model 10,000 times with repeated sampling of variables drawn randomly from distributions on each run, and the average total cost of each pathway is estimated in the same way.

The results of these analyses are illustrated on the cost-effectiveness plane in Figures 1-6 below. Series 1 (solid line) shows strategies based on PEG and Series 2 (dotted line) shows strategies based on IFN. Best supportive care (BSC) is at the origin. In the figures, the “+” sign indicates sequential use in the order specified, not combination use. Combinations of drugs have not been considered, as there is no evidence for combination use being better than one of the drugs on its own. The cost effectiveness of LAM and ADV are shown as single points (or Series 3) in the figures

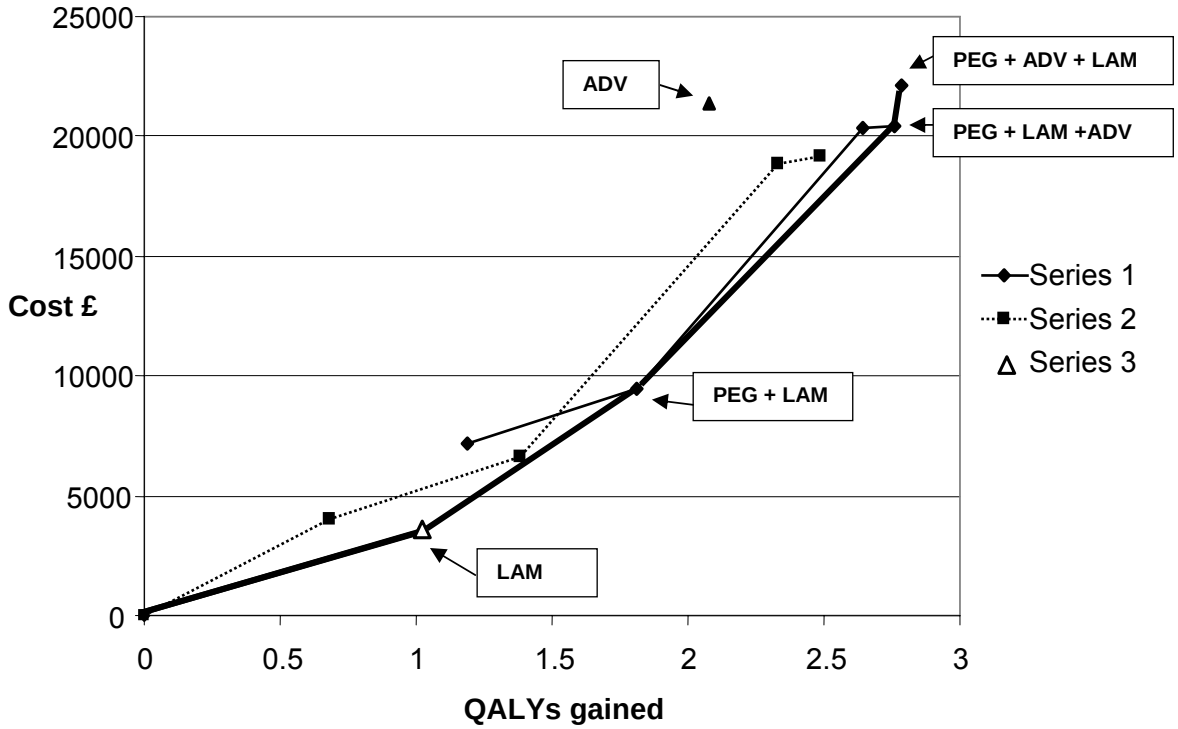
Note that the sequences LAM followed by ADV, ADV followed by LAM, and IFN followed by ADV then LAM are not represented in the figures, but these will almost certainly be dominated strategies.

Figure 1: Cost per QALY for all patients



In the diagram, any points that are to the northwest of a line joining two alternative strategies are dominated or extendedly dominated. All treatments that are not dominated appear on the "outer envelope" as illustrated in Figure 2 below.

Figure 2: Cost effectiveness plane showing the "outer envelope" for all patients



The only treatment sequences that are not dominated and appear on the outer envelope are LAM, IFN + LAM, PEG + LAM, PEG + LAM + ADV, PEG + ADV + LAM. The treatments that are on the outer envelope are called "admissible".

Of these admissible treatment sequences, PEG + LAM + ADV is likely to be cost effective versus PEG + LAM (ICER £11,400 per QALY), as illustrated by the slope of the line joining the two treatment options in Figure 1, but PEG + ADV + LAM is unlikely to be considered cost effective versus PEG + LAM + ADV because the ICER is estimated to be £160,000 per QALY.

Subanalyses for HBeAg+ and HBeAg– chronic hepatitis B separately

This is the same analysis as that carried out above, but for HBeAg+ and HBeAg– patients separately. The conclusions are unchanged. The model shows a greater advantage of PEG over IFN in people with HBeAg– chronic hepatitis B (the PEG and IFN lines are reversed in the two diagrams below). Nevertheless, PEG is estimated to be cost effective over IFN in both groups.

Figure 3 Cost/QALY for HBeAg+ chronic hepatitis B

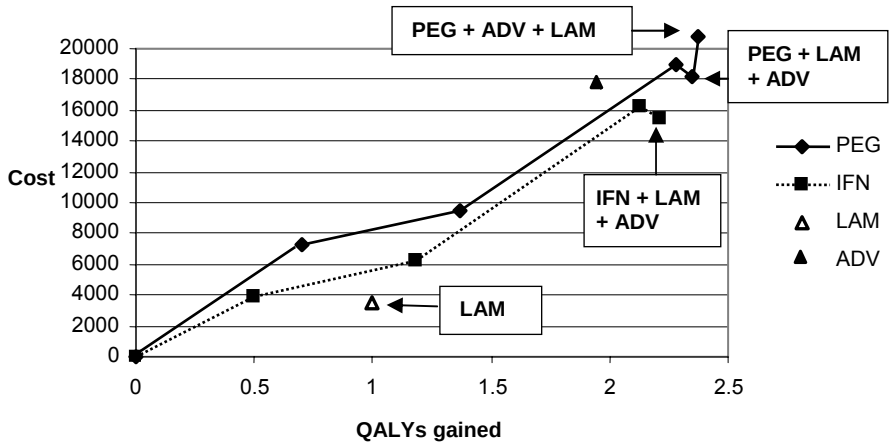
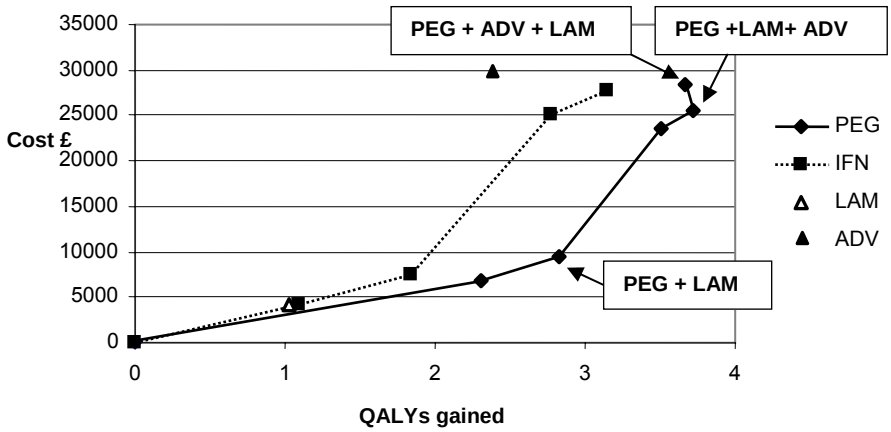


Figure 4 Cost/QALY for HBeAg– chronic hepatitis B



The admissible sequences for each group are shown in Figures 5 and 6.

Figure 5 Cost/QALY for HBeAg+ chronic hepatitis B

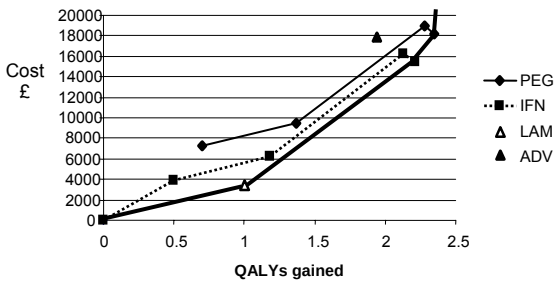
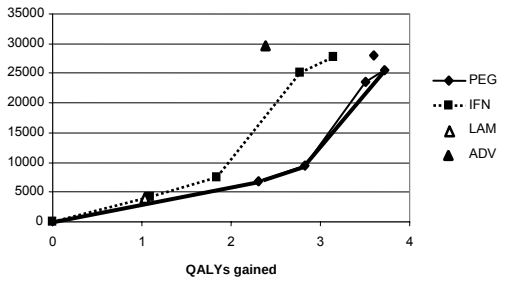


Figure 6 Cost/QALY for HBeAg– chronic hepatitis B



For HBeAg+ chronic hepatitis B (Figure 5) the admissible sequences are LAM, IFN + LAM + ADV, PEG + LAM + ADV and PEG + ADV + LAM. All ICERs are less than £25,000 per QALY except PEG + ADV + LAM vs PEG + LAM + ADV, which is estimated to be £57,000. For HBeAg– chronic hepatitis B (Figure 6) the admissible sequences are PEG, PEG + LAM, PEG + LAM + ADV, and the last of these is likely to be cost effective compared with PEG + LAM (ICER £18,000). All other strategies are estimated to be dominated. As before, the strategies LAM + ADV, ADV + LAM have not been shown.

One-way sensitivity analyses

The results are relatively insensitive to changing the assumptions, one at a time. What appears to change results the most is the change in discount rates from those currently used (1.5% annual discount on benefits but 6% discount on costs), to the rate required by the Treasury Green Book of 3.5% discount for both costs and benefits, which will be used by NICE when the Institute's *Guide to the Methods of Technology Appraisals* starts being used in the near future (11th wave). In a model where, on average, the simulated people live for an average of some 20 years, the new rates of discount would place more emphasis on future costs and would value future benefits less than with the present discount rates used. Thus the costs per QALY with the new discount rates rise.

None of the sensitivity analyses reported in the Assessment Report for admissible strategies have high ICERs, but not all are reported. The Appraisal Committee will be appraised, at the first meeting, of any further sensitivity analyses that might change the above results in any significant manner.

Probabilistic sensitivity analysis

Here, all variables are allowed to change. The results of this analysis are reported in the Assessment Report on pages 143 to 149, and essentially do not add a great deal to the conclusions that are likely to be reached from the analysis so far reported.

Transmission of drug resistant strains

What has not been reported is any rudimentary economic analysis of drug resistance. There are about 350 new cases of chronic hepatitis B originating in England and Wales and about 7000 cases coming into the country each year. In that case, since the transmission rate within England and Wales is relatively low, the transmission of lamivudine-resistant hepatitis B may not pose a great problem. Since the incidence of adefovir resistance appears to be much lower than that of lamivudine resistance, the same consideration applies for adefovir dipivoxil.

Independence

The results reported above assume that a person's reactions to IFN or PEG are independent of those to LAM and/or ADV. If, for example, there exists a strain of the disease that makes it difficult to control with IFN or PEG, it may also be more difficult than average to control it with LAM or ADV. If such a correlation were strong, then it could substantially change the results of the sequential analysis reported above,

because it would mean that later strategies would be less effective. However, the available evidence does not support the existence of high correlations.

Notes on technical aspects

- **Transition probabilities**

  Tables 32 and 33 on pages 126 and 127 of the Assessment Report show the sources for the transition probabilities for the natural progression of the disease, and Tables 34 and 35 on pages 127–8 of the Report show the assumptions made about the effect of the drugs used. The latter are generally congruent with the Assessment Group's review of clinical effectiveness. Some specific considerations are noteworthy:

  - For the effect of lamivudine on ALT normalisation in HBeAg– patients the 48 week (end of treatment) data were used from the pivotal trial versus pegylated interferon alfa-2a while for pegylated interferon the 72 week data were taken from this trial.
  - Data on adefovir dipivoxil in HBeAg– patients on the same outcome were taken from the group that were randomised to continue on adefovir to reach a total of 96 weeks active treatment.
  - It was assumed that the same seroconversion rate applied for patients with and without compensated cirrhosis within the natural history model.
  - Relapse rates were only applied to patients who underwent seroconversion while on treatment and are only applied in the year immediately following seroconversion, after which the relapse risk reverts to the spontaneous reactivation rate.

- **Utilities**

  Paragraph 6.1.5.2 on page 129 of the Assessment Report shows the source of utility data for the model.

The Gilead model

The Gilead model does not consider IFN or PEG, but assumes either that patients bypass IFN or PEG, or that they present for LAM or ADV treatment after having been unsuccessfully treated with IFN or PEG.

The costs per QALY gained from this analysis are compared with the costs per QALY gained (where calculated) from the above Assessment Report analysis, and are given in the Table 4.

Table 4 Comparison of costs per QALY

Treatment	Cost/QALY (Gilead)	Cost/QALY (Assessment Report)
LAM vs BSC	3100	3700
LAM +ADV vs BSC	6700	-
LAM + ADV vs LAM	8200	-
ADV + LAM vs LAM	11,400	-
ADV + LAM vs LAM + ADV	29,000	160,000 (PEG+ADV+LAM vs PEG+LAM+ADV)

Note that the results do not report the cost effectiveness of ADV versus BSC.

The Roche model

This model reports a number of cost effectiveness results, all involving either IFN or PEG, for HBeAg+ and HBeAg– disease separately. The results establish PEG as the cost effective treatment of choice at first line over LAM, ADV and IFN. Nothing is said about later choices for those people for whom PEG has not been clinically effective.

Table 5 For HBeAg+ patients: outcome HBeAg seroconversion

Comparison	Incremental cost/QALY (Roche)	Incremental cost/QALY (Assessment Report)
1. PEG 24 (weeks) vs IFN 24 (weeks)	2,700	-
2. PEG 48 vs IFN 24	13,900	16, 700 for PEG 48 vs IFN 48
3. PEG 48 vs LAM 48	5,300	-
4. PEG 48 vs LAM 208	5,900	LAM dominates PEG, but may be different comparison. Also LAM alone is likely not to be the treatment of choice when sequential therapy is considered (see graphical analysis above).
5. PEG 48 vs ADV 48	1,400	-
6. PEG 48 vs ADV 208	Cost saving / dominant	ADV vs PEG: 8,500, so favours ADV, but (a) must be seen in context, because ADV (alone) is likely to be dominated by sequential therapy (see graphs above) and (b) it may not be same comparison.
7. PEG 48 vs no treatment	2,800	16,200

Table 6 For HBeAg– patients: outcomes combined ALT and HBV DNA response

Comparison	Incremental cost/QALY (£)(Roche)	Incremental cost/QALY(Assessment Report)
8. PEG 48 vs LAM 48	3,200	400, but may be different comparison
9. PEG 48 vs LAM 208	1,900	
10. PEG 48 vs no treatment	1,500	2,200

Overall, the Roche analysis, which ignores the sequential nature of treatment options, appears to be of limited usefulness in the totality of this appraisal.

Issues for consideration

- The clinical experts at the Appraisal Committee meeting should be asked to discuss lamivudine and adefovir dipivoxil resistance, particularly in relation to the risk of transmission of resistant forms of the virus.
- The Assessment Group model uses the assumption that response (seroconversion) is independent of previous therapy. This might not be true.
- One way sensitivity analyses show that the ICER is increased by discounting costs and benefits at 3.5%. This is particularly pronounced for adefovir dipivoxil (see table 41 of the Assessment Report).
- In the Assessment Group model, adefovir dipivoxil and lamivudine are assumed to be taken indefinitely or until seroconversion or resistance occurs. The clinical experts at the Appraisal Committee may have a view as to whether this reflects clinical practice.

Ongoing Research

Further follow-up from the study of adefovir dipivoxil in HBeAg-negative chronic hepatitis B will be available when all patients have completed 5-years follow-up. This was expected to occur in June this year.

Authors

Janet Robertson

Technical Advisor, NICE Appraisal Team

Alastair Fischer
Health Technology Analyst, NICE Appraisal Team
July 2005

Appendix A. Sources of evidence considered in the preparation of the overview

A J Shepherd, J Jones, A Takeda, P Davidson, A Price. Southampton Health Technology Assessment Center (SHTAC). *Adefovir dipivoxil and pegylated interferon alfa-2a for the treatment of chronic hepatitis B – a systematic review and economic evaluation.* May 2005

B Submissions from the following organisations:

I Manufacturer/sponsors:

- Gilead Sciences
- Roche

II Professional/specialist and patient/carer groups:

- Royal College of Nursing
- Royal College of Physicians
- British Association for the Study of the Liver
- British Society of Gastroenterology.

} Joint submission

C Details of any additional references used:

- Hepatitis B: Out of the shadows. A report into the impact of hepatitis B on the nation's health. Foundation for Liver Research. Available from URL http://www.britishlivertrust.org.uk/content/diseases/hepatitis_b.asp
- Proceedings of the European Association for the Study of the Liver (EASL) International Consensus Conference on Hepatitis B. September 14-16, 2002. Geneva, Switzerland. Hepatol. 2003; 39 (Suppl 1): S1-235.