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Dear Ms Miller

NICE Health Technology Appraisal: Adefovir dipivoxil and peginterferon alfa-2a for chronic hepatitis B

Please find attached a review of the above as the submission from the Royal College of Physicians, in association with the British Society for Gastroenterology and the British Association for the Study of the Liver. This may duplicate your Technology Appraisal document. However, as the authors are both international experts and the document has been reviewed by Professor Humphrey Hodgson, President BASL, I felt that you would like to have the full details of their deliberations.

Best wishes.

Yours sincerely

Dr W R Burnham
Consultant Physician & Gastroenterologist
Registrar. Royal College of Physicians
President, European Board of Gastroenterology

The use of pegylated Interferon alpha and Adefovir dipivoxil in the treatment of Hepatitis B Infection

A joint submission prepared on behalf of The Royal College of Physicians of London, The British Association for the Study of the Liver, and The British Society of Gastroenterology.

Professional Advisers Prof H C Thomas and Prof G Dusheiko

Document Summary

Pegylated Interferon alpha and Adefovir dipivoxil may be regarded as substitutions and/or supplements for currently more widely used drugs – standard interferon, and lamivudine respectively. For ease of consideration, this document therefore initially outlines the different circumstances and approaches to treatment of the various forms of HBV disease, but then discusses separately the role of pegylated interferon and the role of adefovir.

Pegylated alpha 2a interferon offers advantages over standard interferon for the treatment of chronic hepatitis B infection, with greater patient acceptability and more favourable pharmacokinetics being the major advantages. Adefovir dipivoxil does not share cross resistance with lamivudine, and thus fulfils a need for patients who have developed resistance to lamivudine. Adefovir can be also be considered as a first line therapy for chronic hepatitis B, used either singly or in combination with lamivudine, thus reducing the incidence of viral resistance. These agents are useful resources, but several dilemmas remain in decision making for the treatment of hepatitis B. The clinical care of hepatitis B is still evolving. Combination treatments may become necessary but may not be required for all patients. The need for combination therapy and the accurate prediction of patients for whom finite or circumscribed courses of treatment will be effective, rather than indefinite courses of suppressive therapy, remain key unknown elements of the management of hepatitis B.

Introduction and description of underlying problem

Current service provision and projection of future need.

The HPA have calculated that about 350 cases of chronic hepatitis B arise per year as a result of acute infections acquired in the UK and around 7000 are imported in immigrant groups coming to the UK from high prevalence areas of the world such as South Asia and Africa. Assuming 30% of these are identified and need treatment and that therapy must be continued for at least 10 years, we will be treating c 22, 000 cases, over and above the current patient population, by 2015.

The UK still has substantial inequalities in the provision of services for liver disease, and cost has often been a major consideration slowing or preventing the provision of antiviral treatment. Service could be provided in the developing national system of **Managed Clinical Networks in Hepatology,** which have been recommended as part of the **Action Plan for Hepatitis C** and are currently increasing capacity to deliver anti-viral therapy for this condition. The capacity will need to be further expanded to accommodate this therapy and the need to vaccinate family and other contacts – this will require additional nursing capacity.

HBV Disease

HBV infection is parenterally transmitted; it is seen in babies born to HBV-infected mothers, after transfusion of blood and blood products, after intravenous drug use and after sexual contact. It is not transmitted through intact skin.

The outcome of HBV infection depends on the age of the patient and genetic factors determining the efficiency of the host immune response. Thus, almost 100% of children infected at birth but only 2–10% of those infected in adult life, develop persistent infection. Persistence of infection following acquisition of the virus in adulthood is most common in men and in patients with immunodeficiencies. In Africans and Europeans, the major histocompatibility class II genotype has been shown to influence outcome; DRB1:1302 is more often associated with viral clearance than other

genotypes. The severity of the hepatitis in both transient and persistent infections is variable depending on the nature of the host response.

Acute HBV infection – the incubation period is 3–6 months. In the week before icterus appears, some patients develop a serum sickness-like syndrome including arthralgia, fever and urticaria. The clinical picture varies from asymptomatic anicteric infection to protracted icterus and, in some patients (< 1%), liver failure (fulminant hepatitis). The severity of the hepatitis increases with age.

The acute infection is self-limiting and does not need anti-viral therapy. Most patients recover within 1–2 months after the onset of icterus. Patients who are symptomatic may require bed-rest but this probably does not accelerate recovery. Sexual contacts should be offered hyperimmune globulin and then immunised with the vaccine. Fulminant hepatitis B may benefit from antiviral therapy.

Chronic HBV infection – chronic hepatitis B is defined as viraemia and hepatic inflammation continuing for more than 6 months following HBV infection. Most patients are infected at birth or have a subclinical infection as an adult, so are unaware that they have been infected.

In a patient with chronic viraemia, the need for treatment is decided on the basis of whether there is evidence of chronic hepatitis with fibrosis. The presence of fibrosis indicates that the patient is at risk of developing cirrhosis and hepatocellular carcinoma and therefore, dependent on their age and other health risks, may require treatment.

Histology

The histological appearance may range from almost complete normality to various inflammatory states with variable fibrosis (previously classified as chronic active hepatitis, chronic persistent hepatitis and chronic lobular hepatitis but now quantitated as an inflammatory grade (out of 18) and a fibrosis stage (out of 6))

- Liver biopsy reveals the severity of the disease, but the histological appearances are not specific for hepatitis B (except when viral markers are detected in the tissues, using specific techniques).
- When a biopsy is performed within 6 months of an episode of acute hepatitis, chronic hepatitis cannot be distinguished histologically from resolving acute disease.

Course of chronic disease

Chronic HBV infection generally passes through a series of stages, both clinically and in terms of virological markers.

'HBe-positive virus' infection is the form most commonly encountered in Northern Europe and North America. The virus replicates and encodes infected liver cells to synthesise and secrete hepatitis B e antigen (HBeAg). As a result, HBeAg can be detected in the serum. Later, viral DNA can become integrated into the cellular DNA. At this stage, production of HBsAg can occur without viral replication and HBe antigenaemia.

'HBe-negative virus' infection has recently been recognised (Carman et al 1989). This is a variant form of HBV, which can lead to productive viral infection without secretion of HBeAg. HBe-negative virus is also known as the 'pre-core mutant', reflecting the most common mutation identified in the viral genome.

This form of the virus can emerge late in the course of infection in individuals initially infected with HBe-positive virus or can occur *ab initio* (particularly in patients from Mediterranean countries and the Far East).

Stages of infection.

In patients infected with HBe-positive virus, up to four stages of chronic infection (each of which may last for many years) may be described (Chu et al 1985).

First stage – after an initial period of several years, when there is often no evidence of hepatitis (immuno-tolerant phase), there is a period of increasing inflammatory necrosis of hepatocytes with viraemia and HBeAg in the serum. HBV DNA is detectable usually at levels $>10^5$ genomes per ml serum.

Second stage – the inflammatory process (hepatitis) becomes sufficiently intense to permit lysis of infected hepatocytes, clearance of HBeAg and the development of anti-HBe. If the inflammation is sufficiently intense and prolonged, patients may develop cirrhosis. The phenomenon of loss of HBeAg

and conversion to anti-HBe positivity is referred to as ‘seroconversion’. When this has run its course and the patient is HBe antigen negative, there is a reduction of inflammation accompanied by histological change from active to inactive hepatitis, or active cirrhosis to inactive cirrhosis in patients in whom seroconversion has been prolonged. The spontaneous seroconversion rate is 5–10%/year, though this varies between populations.

Third stage follows seroconversion; patients continue to produce HBsAg because of integrated sequences of viral DNA within host cell DNA. The liver may show minimal hepatitis, normal histology or inactive cirrhosis, and the blood biochemistry may be almost normal or normal with HBV DNA levels $<10^5$ genomes per ml serum.

Fourth stage – increasing viraemia and hepatitis in the absence of HBe antigenaemia may follow, reflecting emergence of the HBe-negative (pre-core mutant) strain of the virus. During this stage, transaminases become elevated and HBV DNA increases to $>10^5$ genomes per ml., but HBeAg is not present in the serum. Further hepatitis in this phase may lead to cirrhosis.

Prognosis: In terms of the potential to develop cirrhosis, prognosis is worse in active than in inactive chronic infection.

Clinical features

The clinical picture in individuals with chronic HBV infection varies widely, and the histological picture cannot always be predicted from the symptoms. Patients with chronic hepatitis are often asymptomatic, though they may suffer from malaise, and well-compensated cirrhosis can be asymptomatic. Compared with patients with autoimmune liver disease, patients with chronic HBV-induced hepatitis are less likely to have florid liver disease, particularly at the stage of active inflammation; they also have lower globulin levels.

Presenting features

Incidental presentation – patients are most commonly asymptomatic and are recognised following blood donation, or blood or other routine medical screening.

Following recognised HBV infection – after an episode of acute HBV infection, patients should be followed up until HBsAg disappears, anti-HBs appears and liver function tests become normal. If this does not occur within 6 months, the patient is chronically infected with HBV and specialist referral is required.

Negative IgM antibody to hepatitis B core antigen (HBcAg) at presentation suggests a patient is not in an episode of acute hepatitis, but already has chronic HBV infection.

Symptomatic presentation – symptoms include general malaise, fatigue, arthralgia and right hypochondrial discomfort. At later stages, patients may present with hepatic decompensation or during acute flares of hepatitis.

Complications

Cirrhosis – the complications of cirrhosis include portal hypertension with variceal bleeding, ascites with spontaneous bacterial peritonitis, and a tendency towards hepatic decompensation with encephalopathy and death.

Hepatocellular carcinoma is common in regions with a high prevalence of hepatitis B infection. The risk of hepatocellular carcinoma in an HBsAg-positive male in the Far East is almost 300 times greater than that in HBsAg-negative controls. In 80% of patients, there is a background of cirrhosis with the chronic HBs antigenaemia. The risk in a chronic HBsAg carrier who is HBe antigen negative with normal liver histology, is very low.

Treatment

Antiviral therapy is indicated in patients with progressive liver disease (histological evidence of active inflammation and evidence of developing fibrosis). This requires liver biopsy. Biochemical tests will identify those with significant necro-inflammatory activity but only liver biopsy will allow assessment

of hepatic fibrosis. Tests reflecting collagen synthesis such as pro-collagen peptides only reflect part of the story in that they do not reflect collagen breakdown. Imaging test are measures of cumulative collagen deposition but are insensitive.

In patients with continuing viral replication with serum HBV-DNA concentrations greater than 10^5 genomes per m and liver biopsy evidence of significant fibrosis, therapy should be offered.

Two approaches to therapy of HBV infection are now open.

1 ***Circumscribed (or finite) therapy***

2 ***Long term viral suppressive therapy.***

As already noted this document discusses separately the role of pegylated interferon and the role of adefovir.

PEGYLATED INTERFERON

Circumscribed therapy:

This involves relatively short term therapy with either interferons or nucleoside analogues, allowing recovery of the immune response to an extent which then allows control of the infection in the absence of further anti-viral drug administration. The immunostimulant properties of the interferons may offer advantage over the nucleoside analogues, in this respect. Standard (non-pegylated interferon) provides fluctuating plasma levels of the immunostimulant and requires frequent dosing by subcutaneous injection; pegylated interferons allow more sustained levels with less frequent administration.

In **HBe antigen positive infection**, recovery of the immune response is marked by HBe antigen/antibody seroconversion and occurs in up to a third of patients (33% in a recent meta-analysis by Lok and McMahon) with active inflammatory liver disease when treated with standard alpha

interferon for 3-6 months usually at dosages of 5 megaunits daily or 9-10 megaunits thrice weekly. The results with pegylated alpha 2a and 2b when given for 12 months are slightly (but not significantly) better (36-37%) than standard interferon (33%) and statistically better than lamivudine (18%) and adefovir dipivoxil(ADF) (12%) at one year. The current pricing of pegylated interferon and its convenience of administration – once weekly - has meant that many physicians are using it rather than standard interferon, but there are regional differences in the UK depending on local policies. The patients undergoing HBe antigen/ antibody conversion usually become inactive (HBV –DNA $<10^5$ with a normal ALT and minimal hepatitis) and usually need no further therapy.

The 60-70% who do not undergo seroconversion, need long term viral suppressive therapy with, ideally, orally administered drugs of low toxicity and with low rates of emergence of drug resistant virus. No ideal drug exists currently. The best current approach usually entails treatment with nucleoside or nucleotide analogues such as lamivudine and now ADF. Because of cost most physicians will use lamivudine first and then substitute ADF, if lamivudine resistant virus emerges, which is the case in over 60% of cases after 3 years therapy. The resistance rate with ADF is much lower and it would be the drug of first choice for maintenance viral suppression were it not for the fact that it costs 4 times as much as lamivudine – see discussion below.

In **HBe antigen negative infection**, long term control of the infection after a limited period of anti-viral therapy with interferon or nucleoside or nucleotide analogues, is difficult to attain. Long term viral suppressive therapy with orally administered drugs of low toxicity and with low rates of emergence of drug resistant virus is therefore frequently a necessity. This usually entails treatment with nucleoside or nucleotide analogues such as lamivudine and now ADF. Once again because of cost most physicians will use lamivudine first and then substitute ADF only if lamivudine resistant virus emerges. This may occur less frequently in patients with lower levels of viraemia. The resistance rate with ADF is much lower and it would be the drug of first choice for maintenance viral suppression were it not for the fact that it costs 4 times as much as lamivudine.

Long term viral suppressive therapy.

The second approach recognises that, in some patients, the immune system is unable to recover to the extent of then being able to control re-emergence of HBV. This is the case in two thirds of patients with HBe antigen positive disease and the majority of HBe antigen negative viraemic subjects. In these patients long term suppression of HBV replication with either nucleoside or nucleotide analogues, will be necessary until the infected cells containing cccDNA, have been eliminated. The half-life of these cells may be 10 or more years (Nowak et al., 1996) and therefore therapy must be protracted. In such circumstances suppression of HBV levels to very low levels is essential to stop or reduce the chance of emergence of drug resistant variants and to protect regenerating hepatocytes from infection. In this approach it seems likely that combination therapy, may be necessary. Pegylated interferons can be considered, but are parenterally administered and have more side effects than the nucleoside/nucleotide analogues. Thus at the present time, orally administered nucleoside or nucleotide analogues are the treatment of choice (see later).

Treatment of HBV-induced cirrhosis and hepatocellular cancer by liver transplantation has achieved significant success, particularly when HBV replication is controlled with lamivudine before transplantation and hyperimmune globulin and lamivudine are continued indefinitely afterwards. Only patients with early-stage hepatocellular carcinoma (one or two lesions < 2–3 cm in diameter) are offered transplantation; in these, 5-year survival is 50–70%. Interferons are contra-indicated in decompensated cirrhosis and after liver transplantation.

Conclusions re pegylated interferons

The use of pegylated rather than standard alpha interferons has substantial advantages in respect of convenience and patient acceptability

ADEFOVIR

Introduction

Adefovir dipivoxil (ADF), a novel acyclic nucleoside analogue was initially developed for the treatment of HIV infection, but has now been licensed as therapy for HBV. A major objective of the treatment of hepatitis B is sustained suppression of HBV replication to prevent progressive liver disease. Permanent inactivation of active HBV replication without the requisite for further antiviral treatment is attainable in only a minority of HBeAg and anti-HBe positive patients.

Pharmacology of ADF

ADF dipivoxil (ADF) is an orally bioavailable prodrug of adefovir, a phosphonate acyclic nucleotide analogue of adenosine monophosphate.[1] The chemical name is 9-[2-[[bis[pivaloyloxy)methoxy]methoxy]ethyl]adenine. ADF has potent in vitro activity against hepadnaviruses, retroviruses and herpesviruses.[2-5] ADF diphosphate acts by selectively inhibiting the reverse transcriptase (RT) of HIV, the reverse transcriptase-DNA polymerase of HBV and the DNA polymerase of the herpesviruses by direct binding to the enzyme in competition with the endogenous substrate deoxyadenosine triphosphate (dATP).[6] ADF diphosphate lacks a 3' hydroxyl group and, after incorporation into the nascent viral DNA, results in premature termination of viral DNA synthesis.[7] The active intracellular metabolite, ADF diphosphate selectively inhibits HBV DNA polymerase at a concentration 10-700 fold lower than needed to inhibit human DNA polymerases. Enzymatic assays using recombinant HBV polymerase have shown that the inhibition constant (Ki) for ADF diphosphate is 0.1 um.[1] The IC_{50} of ADF diphosphate for HBV polymerase in HBV core particles isolated from transfected HepG2 cells is 0.2 um.

Pharmacokinetics:

Adefovir is not well absorbed orally because of limited intestinal permeability of the phosphonate.[8] The bioavailability has been significantly improved with the development of the prodrug adefovir dipivoxil (ADF). Orally administered ADF undergoes rapid enzymatic hydrolysis by nonspecific esterases yielding ADF which is transported into cells, where it is converted through two phosphorylation reactions, to ADF diphosphate, the active molecule.[9] Unlike other nucleoside analogues such as lamivudine, ADF is monophosphorylated and is not dependent on initial phosphorylation by viral nucleoside kinases to exert its antiviral effect. ADF has a long intracellular half-life of approximately 16 to 18 hours and can be given once daily. [10] Following oral administration of single doses of ADF 10mg to patients with chronic hepatitis B or healthy subjects, the maximum observed ADF concentrations (Cmax) in plasma occur at a median 0.76-1.75 hours following dosing, with mean values ranging from 17.5 to 21.3 ng/ml. The mean ADF area under the curve (AUC) ranged from 178 to 210 ng/hr/ml. The oral bioavailability of ADF from ADF 10 mg has been estimated to be approximately 60% and this is not affected by food.

The in vitro protein binding of ADF to human plasma or serum proteins is negligible and the clearance of ADF is entirely attributable to renal excretion. ADF is not metabolised prior to elimination, with over 90% of an intravenous dose being recovered as unchanged drug in the urine over 24 hours following dosing.[11] In addition to passive filtration, tubular secretion contributes to the elimination of ADF.[11-13] A renal human organic anion transporter (hOAT1) at the basolateral membrane of the proximal convoluted tubules has recently been identified that rapidly transports ADF into the cells and may be implicated in the nephrotoxicity of ADF.[14] Due to its short elimination half-life relative to a 24 hour dosing interval, there is no apparent accumulation of ADF at steady state following 7 days of once daily dosing of ADF 10 mg in patients with chronic hepatitis B. However, ADF pharmacokinetics are substantially altered in subjects with moderate and severe renal impairment (creatinine clearance < 50 mL/min).[8;11] In patients with end stage renal disease (ESRD), ADF concentrations in plasma reach high levels. Dose interval adjustments are required for patients with creatinine clearances of less than 50 mL/min or those with ESRD requiring haemodialysis. However, no substantial alterations in the pharmacokinetics of ADF

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

Toxicity:

Nephrotoxicity is the major side effect of higher doses of ADF. ADF causes a proximal convoluted tubule lesion characterised biochemically by a rise in urea and creatinine and histologically by karyomegaly, cytomegaly, tubular dilatation, degeneration and regeneration, and individual tubular epithelial cell necrosis in experimental animals. The incidence and severity of renal tubular nephropathy is related to the dose and duration of treatment. In animal and human studies, nephrotoxicity has been confirmed as the most important dose-limiting toxicity of ADF therapy, with doses 3 to 12 times higher than the recommended 10 mg daily dose for hepatitis B. In the large HIV trials an incidence of nephrotoxicty between 17% and 60% was reported. However, in the two largest hepatitis B phase three trials involving 695 patients, no clinically significant renal toxicity was found at the 10mg dose. While the mechanism of the nephrotoxicity remains unclear, the human renal organic anion transporter 1 (hOAT1) probably plays a crucial role.[15;16] There is now good in vitro evidence that ADF does not affect the mtDNA content or level of mitochondrial enzyme function.[17]

In the two large phase three clinical studies, the ADF 10 mg groups differed from the placebo group only in asthenia, diarrhoea, headache and abdominal pain, and none of these led to cessation of the ADF.[18;19] Serum aminotransferase elevations can also be observed during antiviral treatment when antiviral agents are discontinued or indeed started, as a result of fluctuations in HBV DNA concentrations. Serum ALT elevations of greater than 10 x ULN were observed in approximately 24% of patients following discontinuation of ADF 10 mg. None of these episodes was associated with hepatic decompensation.

Antiviral resistant HBV infection

The selection of antiviral resistance remains a disadvantage of treatment with nucleoside analogues and is a fundamental disadvantage of treatment with long-term lamivudine therapy. There are a number of structural differences between lamivudine and ADF that predict lower rates of resistance with ADF.[20] Firstly, ADF diphosphate, the active metabolite of adefovir, more closely resembles its natural substrate deoxyadenosine triphosphate (dATP) than lamivudine, which contains an L-sugar ring.[21] In contrast to lamivudine, ADF diphosphate has a minimal acyclic linker in place of the L-sugar ring that closely matches the D-sugar ring of dATP. This similarity between ADF diphosphate and dATP means that a mutation in HBV DNA polymerase not binding ADF diphosphate would also impair dATP binding. It also results in more flexibility, allowing the ADF to bind lamivudine-resistant HBV DNA polymerase without steric hindrance.[20;22] Secondly, because ADF is monophosphorylated, it requires only two phosphorylation steps compared with three for lamivudine. It has been suggested that this results in ADF action in cell types that may be reservoirs for HBV, such as bile duct epithelium.[23] ADF may decrease the load of covalently closed circular DNA (cccDNA).[24] In the two largest studies of HBeAg-positive and HBeAg-negative patients, involving 695 patients, no resistance was reported.

However, following 96 weeks of treatment with ADF and rising HBV DNA levels suggesting resistance, a mutation in the HBV DNA polymerase (a rtN236T substitution) was identified in a patient, which conferred resistance to ADF.[25] Interestingly, this patient responded clinically and virologically to lamivudine therapy. Sequencing of the RT domain of the HBV polymerase has suggested that two mutations, i.e. rtN236T and rtA181V confer resistance to ADF. These mutants remain sensitive to lamivudine, emtricitabine, telbuvidine, and entecavir.[26;27] Life table analysis has suggested a cumulative incidence of 3.9% to 5.9% (in naïve patients) after three years of treatment within clinical trials, but further data outside of clinical trials are required to establish the “true” rate of resistance in the clinic.

Clinical efficacy in Chronic HBV infection:

HBeAg-positive Infection:

After the evidence of nephrotoxicity with high dose ADF in HIV positive patients emerged, lower doses of ADF were investigated for chronic HBV infection. The initial phase 1 and 2 clinical trials provided dose-finding data in both HBeAg-positive and HBeAg-negative patients. Short courses (4 to 12 weeks) of ADF evaluated doses between 30-125mg daily, and were shown to reduce HBV DNA by between 1.8 - 4 $\log^{10}$ copies/ml at the end of treatment. [28]

The pivotal phase III studies examined both ADF 10mg and 30mg to determine the dose with the most favourable risk-benefit profile. These studies were multinational, double blind randomised placebo controlled trials, in HBeAg-positive and HBeAg-negative patients with compensated liver disease, with evidence of active HBV replication, who were not undergoing current treatment.[18;19] In the HBeAg-positive trial, 515 patients were randomised to one of three arms: ADF 30 mg daily, ADF 10 mg daily or placebo. The primary endpoint of this study was based on the quantitative assessment of histological improvement after 48 weeks of treatment using the Knodell Histologic Activity Index (HAI) score.[29] Histological improvement was defined as a reduction from baseline of 2 points or more in the Knodell HAI, with no concurrent worsening in the fibrosis score. Secondary endpoints in the study were based on established methods for determining the virological response (suppresssion of HBV replication as assessed by the decrease of serum HBV DNA) and biochemical response (as defined by reductions and normalisation in ALT during therapy). HBeAg seroconversion, defined as loss of HBeAg and appearance of anti-HBe, was also a key secondary endpoint. Loss of HBeAg has been correlated with long-term clinical improvement.[30] ADF 10mg daily emerged with the more favourable risk-benefit profile for long-term treatment. This dose resulted in significant improvement when compared with placebo: improvement in liver histology (53% vs 25%, $p<0.001$), reductions in HBV DNA (3.52 verus 0.55 log copies/ml, $p<0.001$), normalisation of ALT (48% vs 16%, $p<0.001$), and HBeAg seroconversion (12% vs 6%, $p=0.049$). There were no significant side-effects and no resistance was found. As a result, ADF 10mg daily is the recommended and approved dose.

HBeAg -Negative (Precore-mutant) Infection:

The liver injury is more severe and more rapidly progressive in patients with chronic HBV who are negative for HBeAg and positive for antibodies to HBeAg, with active viral replication (more than 5 log copies/ml).[31] These patients require long-term treatment to suppress viraemia. The pivotal anti-HBe positive ADF study was a double blind randomised controlled study.[18] One hundred and eighty five patients were randomised to placebo or ADF 10mg daily for 48 weeks. The primary and secondary endpoints were the same as the HBeAg positive study of ADF. At 48 weeks the ADF treated group had significant improvement when compared with placebo: improvement in liver histology (64% vs 33%, $p<0.001$), reduction in HBV DNA (3.91 vs 1.35 log copies per ml, $p<0.001$), an undetectable HBV DNA (<400 copies/ml) (51% vs 0%, $p<0.001$), normalisation of ALT (72% vs 29%, $p<0.001$). No significant side effects compared to placebo were reported and no genotypic resistance was found. Thus ADF is an agent that has low rates of resistance and good long-term viral suppression, which is of particular benefit in precore-mutant HBV infection.

ADF in lamivudine-resistant patients

Lamivudine-resistance is conferred through acquired selection of HBV with mutations of the YMDD motif of the HBV DNA polymerase gene.[32] Four major patterns have been observed: L18OM + M204V; M204I; L180M + M204I; V173L + L180M + M204V; and occasionally L180M + M204V/I. The L18OM + M204V occurs most frequently. Although viral "fitness" may be reduced, as lower levels of HBV DNA occur, recent studies have suggested that the disease may progress.[33] ADF has been shown in vitro to be active against lamivudine-resistant HBV,[34;35] and there are a number of reports of successful treatment of lamivudine-resistant patients with ADF, particularly for post –transplant recurrence of hepatitis B.[36,37;38,39] From one study, there did not appear to be an advantage in continuing long term lamivudine in the face of lamivudine resistance after starting ADF in patients with compensated liver disease. [40] Rapid reductions in HBV DNA were observed by 4 weeks in all recipients of ADF, but the median changes from baseline were not greater in those who continued lamivudine, suggesting that ADF alone was effective. Thus treatment with ADF alone was suggested to suffice in these patients, and there was thought to be no long term advantage of continuing lamivudine therapy in patients with YMDD mutations. [40;41]

HBV/HIV co-infection:

Approximately 10% of HIV infected individuals are also infected with HBV.[42;43] ADF has been assessed in HIV/HBV co-infection in those with lamivudine resistant HBV, which is common in this group. A study of lamivudine–resistance in HIV/HBV co-infected patients found a rate of 20% per year developed resistant HBV, all with prototype mutations.[44;45] In an open-labelled trial of 35 HBV/HIV co-infected individuals with lamivudine-resistant HBV, patients were given ADF 10mg daily for 48 weeks.[46;47] The mean decrease in HBV DNA was 3.4 log at week 24 and 4.01 log at week 48. This reduction is similar to non-HIV infected individuals. This trial indicated that ADF has sustained antiviral activity against lamivudine-resistant HBV in HIV co-infected individuals. However, there may be advantages to choosing tenofovir in HIV coinfected patients.

Orthotopic liver transplantation.

Recurrent HBV infection in the transplanted liver has been a major problem. A retrospective study of liver transplantation in Europe before lamivudine showed that patients with low levels of hepatitis B replication at the time of transplantation and those given long-term immunoprophylaxis with HBIG had a reduced risk of recurrent HBV infection and reduced mortality.[48] With the advent of lamivudine outcomes have improved further. Pre-transplant treatment with lamivudine resulted in suppression of HBV DNA levels in 12 of 19 treated patients.[49;50] Currently both HBIG and lamivudine are used prophylactically and recurrent HBV is now rare.[51-53] However, cases associated with lamivudine-resistance are problematic, as patients with recurrent hepatitis B post-transplant may develop fibrosing cholestatic hepatitis a manifestation of high levels of viral replication in immunosuppressed patients.[54;55] A study of 10 patients treated with lamivudine pre-liver transplantation for HBV revealed the risk of lamivudine-resistant strains following transplant. [56] In a study post liver transplant lamivudine-resistant patients, all developed liver failure with liver dysfunction.[57] ADF has proved to be an important antiviral drug to salvage patients with lamivudine resistance post-transplant. In an open label study 127 liver transplant patients with lamivudine-resistant HBV were treated with ADF 10mg.[58]

Treatment resulted in a median 4 log10 drop in HBV DNA concentrations at 48 weeks indicating the important role of ADF as second-line therapy in those patients who develop lamivudine-resistance in the peri-transplant setting.

Discussion:

Indications for treatment

The precise indications for treatment of hepatitis B are still evolving, and the ongoing development of other potentially useful agents means that the optimal treatment is not yet certain. In broad terms, therapy should be considered for patients if there is evidence of moderate or severe hepatitis or fibrosis and evidence of viral replication, with concentrations of HBV DNA > 10^5 copies/ml. The general consensus is that patients with progressive disease should be treated, whereas patients with mild chronic hepatitis should be monitored, and treated at an appropriate time. A proportion of patients desire treatment to reduce infectivity. Treatment of the inactive carrier state is not indicated, except perhaps as part of a strategy to reduce infectivity for operating surgeons if government policy allows this. Virological response rates in HBeAg positive patients are higher for all currently licensed agents for those patients with higher baseline serum ALT, and indeed HBeAg seroconverion rates remain low for HBeAg patients with low serum aminotransferases. Histological improvement has been documented with HBV DNA suppression. These statements have been reviewed in detail elsewhere.[59]

First line treatments

A full discussion of the management of chronic hepatitis B is beyond the scope of this report for NICE. However a few general comments to place the use of ADF in context can be made for the purpose of the NICE evaluation. Interferon alpha (and pegylated interferon alpha), lamivudine and ADF Interferon alpha, and pegylated interferon alpha can be considered for finite courses of therapy (treatment courses of approximately one year). Relatively high rates of HBeAg seroconversion (30-35%), or durable suppression of HBV DNA in anti-HBe positive patients (approximately 40%) have been reported recently in phase III trials for pegylated alpha interferons. HBeAg positive patients with high levels of

HBV DNA, normal ALT and minimal hepatitis respond poorly to interferon treatment. Alpha interferon requires injection, and has a side effect profile that deters some patients, making it less useful for long term suppression. Interferon alpha is of limited use in patients with decompensated cirrhosis, fulminant hepatitis, patients with HIV co-infection and immunosuppressed patients including patients who have undergone organ transplantation, who are at risk of organ rejection.

Finite course of treatment are possible with lamivudine; approximately 15-20% of HBeAg positive patients seroconvert to anti-HBe after one year. Lamivudine is an oral agent with a low rate of adverse events, but the efficacy of lamivudine monotherapy for long term HBV suppression in both HBeAg and anti-HBe positive patients with high levels of HBV DNA is restricted by the high incidence of resistance. The incidence of lamivudine resistance in chronic hepatitis rises from 24% after one year of treatment to 66% after 4 years.

HBeAg seroconversion rates of 12% after one year of treatment have been reported for ADF, as has effective suppression of HBV DNA in anti-HBe positive patients. Longer term treatment with ADF may lead to increments in HBeAg loss with low rates of resistance.

There are advantages and disadvantages to each of these potential first line licenced therapies. However, each of these agents used as monotherapy in HBeAg positive patients and to some extent in HBeAg negative hepatitis B may be disadvantageous. Unfortunately the ideal combination or sequential therapy has yet to be determined, and must still be explored in future clinical trials. However, to date there is evidence that although there is no evidence for synergism with the combination of either ADF or lamivudine, or PEG IFN and lamivudine, resistance may be lowered, and further strategies for treatment require evaluation. More profound and more rapid suppression of HBV DNA in the first year of treatment may improve HBeAg subsequent seroconversion rates. An improved understanding of the role of pre-existing and residual cccDNA concentrations in infected hepatocytes, and immune tolerance to HBV is required to devise optimal strategies for finite course of treatment of HBeAg-positive disease.[60;61] In this way the useful life of these important drugs can be extended, with societal benefits if

resistance can be reduced. Monotherapy with the drugs under consideration or with newer drugs in development (entecavir and emtricitabine) which are highly potent inhibitors of HBV (up to 6 log suppression) and lower rates of resistance may be feasible, but possibly not ideal for the majority of patients who require maintenance suppression. Whether this is optimal treatment for HBeAg-positive and negative patients requires comparison in controlled combination antiviral studies, and future consideration by NICE.

ADF for Lamivudine resistance

There is clear evidence of the efficacy of ADF in patients failing lamivudine therapy. ADF 10 mg has important antiviral activity for this group, as demonstrated by reductions in serum HBV DNA levels. Thus ADF is an important new drug in this context for the treatment of HBV infection. Although it is safe to change to ADF in patients with compensated liver disease, an overlapping period before discontinuing lamivudine seems advisable in patients with cirrhosis or decompensated liver disease. Although the available evidence suggests that ADF monotherapy suffices for the treatment of lamivudine resistance, [40] the wisdom of continuing ADF alone could be challenged, given the rates of resistance or non response observed in some centers (G Dusheiko, data in progress). Lamivudine suppression of wild type HBV DNA may be important to reduce the risk of breakthrough. This requires further assessment.

Efficacy of ADF

This report requires an examination of the effectiveness of ADF "in isolation." The utility of ADF as a first-line therapy in the management of patients with HBeAg positive or negative chronic hepatitis B can be considered because of the high threshold of resistance. ALT elevations can be observed during treatment when ADF 10 mg or other anti-HBV therapies are discontinued or indeed started, as a result of fluctuations in HBV DNA concentrations. As with all nucleoside analogues, careful monitoring of patients after commencing and discontinuing treatment with ADF 10 mg is recommended. There was no

clinically relevant evidence of nephrotoxicity with ADF 10 mg in the safety analysis of the large pivotal hepatitis B studies after two years and up to a maximum of 92 weeks. For HBeAg positive patients, ADF can be given at a dose of 10 mg daily for at least one year with seroconversion of HBeAg was in 12% of patients. While this is a comparable rate to lamivudine, these rates still remain low. As with all nucleoside analogues careful monitoring of patients after discontinuation of treatment with ADF 10 mg is recommended.

Recent data suggests that three years of ADF treatment for HBeAg positive patients results in HBV DNA suppression (<1000 copies/ml) in 56%, ALT normalisation in 81%, and 43% seroconversion. (Marcellin et al). Resistance was delayed and infrequent in this study. However, these data must be viewed somewhat circumspectly, as the key inclusion criteria for the patients in this study are not detailed: these patients have apparently been "rolled over" from the original pivotal 437 study but only 65 of the original 171 patients randomised to ADF 10 mg have been included. Also, due to a randomisation error, patients received significant periods of intermittent dosing in year two of the study. Resistance evaluation and DNA measurements have apparently been restricted to the 65 patients on follow up.

Therapy remains useful while HBV DNA is suppressed. Long term use of ADF monotherapy (> 3 years) will require monitoring for resistance and nephrotoxicity as these data are not available, but the risk of nephrotoxicity is low at three years. Serum creatinine concentrations require monitoring throughout the period of treatment.

Although the data do not yet adequately define stopping points, ADF could be maintained for 6 months or longer after HBeAg seroconversion is achieved. The durability of HBeAg seroconversion responses with this policy is currently being ascertained, but appears to be encouragingly high. Although HBeAg seroconversion rates for HBeAg positive patients are modest, the likelihood that continuation of treatment will produce a virological response is not greatly offset by the cumulative risk of developing

drug resistance to ADF over the first years of treatment. Thus high rates of continued suppression of HBV DNA (70% > 3 log) and ALT normalisation are maintained.

However, the rate of suppression of HBV DNA on ADF is variable and can be slow in a percentage of patients, (perhaps 15-20%) and physicians need to evaluate DNA responses after 3- 6 months of treatment to detect poor primary responders. Several baseline characteristics were shown in the pivotal trials to be predictors of lower response rates to ADF: low ALT levels, high serum HBV DNA levels or low HAI score on liver biopsy. However, DNA suppression occurred in patients with high HBV DNA levels.

Most evidence suggest that long term treatment will be necessary for anti-HBe positive patients treated with ADF. Relapse rates are high with all nucleosides and nucleotides antiviral agents. As these patients are already HBeAg negative, the goal of treatment is suppression of viral replication to reduce histological progression. A high threshold of resistance is the major advantage of ADF monotherapy in anti-HBe positive disease, and monotherapy with the drug can be considered. Treatment should be continued while HBV DNA is suppressed. Loss of HBsAg is highly unusual in these patients during or after treatment, but may be the required end point for cessation of therapy.

Nephrotoxicity was observed in up to 31% of patients wait-listed for transplantation and/or treated for lamivudine resistance post-transplant. Serum creatinine increases may be mild and patients may be able to continue treatment with ADF. However, these patients are at risk of renal impairment, as a result of pre-existing renal insufficiency, decompensated liver disease, significant concurrent illnesses as well as concomitant medications, particularly cyclosporine or tacrolimus which are known to be nephrotoxic. This category of patients will require careful monitoring for renal dysfunction while receiving these agents together with ADF. Dose modifications for ADF are required.

ADF in the context of treatment for chronic hepatitis B

There are now three drugs licensed in Europe and North America and parts of Asia for chronic hepatitis B: alpha interferon, lamivudine, and ADF. As stated above there is no established consensus as to which patients should be treated, but HBeAg positive and anti-HBe positive patients with progressive and active disease are more likely to benefit. In general, treatment of chronic hepatitis B should be targeted at patients with active disease and viral replication, preferably at a stage before signs and symptoms of cirrhosis or significant injury have occurred. Current treatments of chronic hepatitis B have limited long-term efficacy. Eradication of the infection is possible in only a minority of patients. However, if HBV replication can be suppressed, the accompanying reduction in histological chronic active hepatitis lessens the risk of cirrhosis and hepatocellular carcinoma.

HBeAg positive patients should be followed for a few months to ascertain their status, and antiviral therapy should be considered if there is active HBV replication (HBV DNA above 10^5 copies/mL) and persistent elevation of aminotransferases after 3-6 months of observation. HBeAg negative patients should be considered for antiviral therapy when the serum aminotransferases are raised, and there is active viral replication (HBV DNA above 10^5 copies/mL). Many clinicians would consider a liver biopsy helpful for ascertaining the degree of necroinflammation and fibrosis.

If a virological response is not achieved within 1 year, the likelihood that continuation of treatment will produce a response is offset by the cumulative risk of developing drug resistance over time. Therapy remains useful if HBV DNA is suppressed (histological improvement has been documented). Unlike lamivudine, the likelihood that continuation of treatment will produce a virological response is not greatly offset by the cumulative risk of developing drug resistance over time. HBeAg seroconversion rates (12%) are low in the first year, but increase with time. Therapy likewise remains useful if HBV DNA is suppressed (histological improvement has been documented), and therefore ADF monotherapy can be considered for anti-HBe positive patients with active disease.

ADF remains an important salvage drug for patients with lamivudine resistance. Long term use of ADF monotherapy (more than 2 years) will require monitoring for resistance, primary non response and

possible nephrotoxicity. Although it is safe to change to ADF in patients with compensated liver disease, an overlapping period before discontinuing lamivudine, or perhaps not discontinuing lamivudine seems advisable. However the effect of this strategy on subsequent emergence of ADF resistance needs assessment.

There is little or no role for ADF in self limited acute hepatitis, and no data on the role of ADF for fulminant hepatitis B. Preliminary uncontrolled data suggests that antiviral therapy with a nucleoside may reduce the risk of death or the need for liver transplantation. Nucleoside analogues or nucleotide analogues are useful in preventing reactivation of disease or an exacerbation of disease in patients with haematological malignancies receiving chemotherapy or bone marrow transplant, but there is less information for ADF than for lamivudine. Similarly ADF may have a role in reducing morbidity from extrahepatic HBV disease. Paediatric studies are in progress. The comparative efficacy of Tenofovir vs ADF for HBeAg positive and negative disease is the subject of some interest and head to head trials are in place.

Patients with chronic type B hepatitis disease will require relatively long courses of treatment, and viral resistance may emerge. The end points of treatment will require careful evaluation. Several dilemmas remain in decision making for the treatment of hepatitis B. These include the cost effectiveness for using ADF as a first line therapy, (as monotherapy or together with lamivudine), versus the utility and cost effectiveness of using ADF for lamivudine resistance. These evaluations will be the subject of NICE review. The clinical care of hepatitis B is still evolving. Combination treatment may become necessary for most, but may not be required for all patients. The evaluation of patients for whom monotherapies and finite courses rather than indefinite courses of suppressive therapy will suffice remain key unknown elements of the management of hepatitis B. New drugs for hepatitis B remain of value to the individual and to society for reducing the future burden of disease. The development of antiviral resistance is the converse of effectiveness, however, and their unwise use leading to an increased population with resistant strains of HBV represents an opportunity cost.

Coclusions re adefovier

Adefovir dipivixol (ADF) is a novel acyclic nucleoside analogue that has recently been approved for the treatment of chronic hepatitis B (HBV). Large randomised controlled studies have recently shown that ADF results in histological, virological and biochemical improvement in both HBeAg-positive and HBeAg-negative chronic HBV. These clinical improvements occur without serious side effects and at relatively low rates of resistance at the dose of 10mg daily, in treatment trials of up to three years, although resistance has now been observed. In addition, the drug is efficacious in hepatitis B infected liver transplant recipients, particularly in those who have developed lamivudine-resistance, and in patients with decompensated cirrhosis. ADF can be added as a treatment option to existing treatment options (alpha-interferons and lamivudine) and has a role in the ongoing management of chronic HBV. The optimal use of ADF as either a monotherapy or as part of combination therapy requires further assessment. Most patients with chronic type B hepatitis disease will require relatively long courses of treatment, and viral resistance may emerge.

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This is to confirm the imprimatur of the British Association for the Study of the Liver on the attached joint submission to NICE concerning HBV therapy with pegylated interferon alpha and adefovir dipivoxil.

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11/2/2005