Personal statement
G Dusheiko
Royal Free and University College School of Medicine
Royal Free Hospital

Introduction

A great deal of evidence will be before the assessment committee. This personal statement concentrates on a few issues. We have entered a new age of treatment for hepatitis B. At a time when we have gained an improved understanding of the characteristics hepatitis B, particularly the distinction between HBeAg positive and negative disease, orally administered antiviral agents and new interferons with greater antiviral activity are being introduced. These promise to improve the outcome of chronic hepatitis B but will make new demands on disease ascertainment and monitoring including measurement of antiviral drug resistance and polymerase chain reaction (PCR)- based HBV DNA testing.

The clinical problem

Hepatitis B has a complex natural history and causes a spectrum of disease. Treatment by and large is indicated for chronic disease. There may be a role for rapidly acting nucleoside analogues in fulminant acute hepatitis. Treatment of chronic hepatitis B is complex.

HBeAg positive patients: These patients may or may not have active hepatitis. HBeAg positive patients are generally younger, with predominantly wild type HBV in serum. Hepatitis B in these patients is often acquired in childhood, and high levels of HBV DNA (usually > 10^{7-9} copies/ml) are present. Patients may have normal or near normal ALT and are in the "immunotolerant phase" of the disease. Immunological tolerance in these patients has been verified by experimental evidence as it difficult to discern antigen-specific T cell responses in such patients. Progression of HBeAg positive disease in patients with normal serum ALT and minimal hepatitis is slow, and generally these patients should not be treated as response rates are low in this group. Infectivity may be a consideration, but vaccination can prevent transmission of disease.

A proportion of HBeAg positive patients have raised ALT in the active phase of the disease (immuno-active phase). If active disease is present, the disease is more likely to respond to interferon and nucleos(t)ide therapy. Spontaneous seroconversion rates are higher in patients with raised serum ALT and genotype B (vs C) and genotype D (vs A) infection.

Anti_HBe positive disease. (also mistakenly called pre-core mutant disease). These patients are HBsAg and anti-HBe positive. HBV DNA circulates at typically > 10^5 copies/ml, but < 10^8 copies/ml. There are genotypic explanations for absent HBeAg expression. The immunological basis for the disease is being defined. Serum ALT are elevated, but the disease is characterised by a variable course, with fluctuating ALT and HBV DNA concentrations and a mixture of wild type and HBeAg negative virus. Liver biopsy shows necro-inflammation and varying fibrosis. Rates of progression are more rapid than in HBeAg positive disease with mild disease. Different patterns of HBeAg negative disease can be determined by the presence of core promoter vs pre-core mutations.

Inactive carrier state. Spontaneous remission in disease activity occurs in a proportion of HBeAg positive patients, who seroconvert to anti-HBe. Lower HBV DNA levels are found ($<10^5$ copies/ml). Little or no necroinflammation or fibrosis is present (depending on the timing of seroconversion). There is a propensity to reactivation in some. It is important to understand the biological basis for spontaneous control of hepatitis B to improve response rates of antiviral therapy

Goals of therapy of hepatitis B

The goals of therapy of hepatitis B are to prevent progression of the disease. The immediate objectives depend upon the stage of disease. If the disease has not progressed to cirrhosis then prevention of progression to advanced fibrosis or cirrhosis is desirable. If cirrhosis has developed then preventing decompensation or HCC or death is important. There is data to suggest that if HBV replication is suppressed, the accompanying reduction in histological activity lessens the risk of progression. Patients may request treatment to reduce infectivity, but primarily treatment of HBV should be targeted to alter the outcome of the disease. Progression of disease in hepatitis B is not linear, but is punctuated by episodes of activity which are injurious to the liver.

The end points of treatment differ in HBeAg positive and negative disease. In HBeAg positive disease reduction in HBV replication leads to an accompanying reduction in ALT. Loss of HBeAg and seroconversion to anti-HBe is a potential stopping point (depending upon factors). Loss of HBeAg may lead to loss of HBsAg. Histological improvement occurs and loss of cccDNA within cells has been documented. Unfortunately a variable T cell response suggests that finite courses with a circumscribed response occur in only a minority. Categorical analysis has not clarified what relative or absolute reduction in ALT and DNA predicts histological improvement and HBeAg seroconversion, although there are some pointers. Thus is it not clear whether profound reductions in DNA (for example 7 $\log_{10}$) are critical for long term therapy, although DNA reduction clearly has implications for rates of resistance.

In anti-HBe positive disease, as such patients are already HBeAg negative, reduction in ALT, and HBV DNA and the accompanying reduction in ccc DNA and histological improvement are the end points. Stopping points and finite courses of treatment are less commonly achieved, but progression can be halted if resistance or relapse does not occur.

Diagnosis

Serological markers, HBV DNA and serum ALT distinguish HBeAg positive from anti-HBe positive disease. Liver biopsy has informed us in the past, and some utility will be lost in the future if liver biopsies are not performed. The biopsy provides a unique source of information, but its value in routine diagnosis is being questioned. Activity and stage are dynamic and cumulative records respectively of disease status. There are problems with liver biopsy including a low finite risk to patients, and within the NHS, costs and delays are barriers to treatment. Nonetheless liver biopsy remains the standard for interpretation of disease. Disease with mild activity contains only rare piecemeal necrosis Patients with high level of viraemia may have only minimal hepatitis. Lobular hepatitis is more common in patients with active viral replication and raised ALT. Advanced disease is characterised by bridging fibrosis or

cirrhosis. Technological advances may change the need for biopsy, so that its role in practice will be refined. However, at present biopsy still provides recommendations and is a guidepost to treatment. The biopsy remains a research tool for assessing intra-hepatic T cell responsiveness. ccc DNA measurement, micro-array and proteomics for example.

Approaches to therapy of hepatitis B.

Therapy can theoretically involve a finite course of therapy, continuous, long-term therapy (indefinite therapy) or for many patients, a treatment course that is undefined and is dependent upon response. There are major uncertainties in predicting whether a monotherapy will suffice, or whether combination therapies are more beneficial. Thus several treatment options exist for individual patients, making rational choices for first line and second line treatment somewhat difficult. Recent evidence has not greatly helped to reduce the uncertainty of outcome for treatment. Genotypes of hepatitis B do not have the predictive power of response to treatment as genotypes of hepatitis C. In Far Eastern patients genotype B is usually associated with less active disease than genotype C; there is a lower prevalence of HBeAg in genotype B. Genotype B patients have higher rates of spontaneous seroconversion, and there is evidence that genotype B infection is associated with higher rates of response to interferon. In European patients genotype A has a higher rates of response than genotype D to interferon. HBeAg seroconversion rates are higher in genotype D infection. There are probably little or no difference in response to nucleos(t)ide analogues. However, genotypes may affect the rate development of lamivudine resistant mutants and durability of response to nucleosides.

A. Adefovir

The Clinical problem

Patients who may be treated with adefovir dipivoxil

The efficacy of adefovir has been assessed in patients with HBeAg positive (wild type) and HBeAg negative disease, and it is possible to define health outcome measures based on short and medium term results. Adefovir has been appropriately evaluated in different settings for the spectrum of chronic hepatitis B infection. No evidence has been gained to indicate that adefovir dipovoxil is effective in fulminant acute hepatitis. Similarly, although there may be role for adefovir in subacute hepatic necrosis, the efficacy of this agent in this disease is unknown.

Measures of clinical effectiveness have been obtained, but the measures of response have not been standardised across trials of different agents. There remain a number of uncertainties because measures of response have not been standardised and because HBV DNA measurements suffer from differing sensitivity, standardisation and thresholds used to assess response

Analyses of trials

HBeAg positive and negative disease

The adefovir studies have been well conducted, but it is not certain whether treatment responses in clinical trials can be replicated in clinical practice. The efficacy of adefovir has been assessed in HBeAg positive patients. An increment in HBeAg loss and ALT normalisation occur over time. At first glance 46% HBeAg seroconversion rates after three years of treatment appear satisfactory. These treatment responses

imply that continued treatment of HBeAg positive patients with an antiviral drug with a low rate of resistance leads to satisfactory HBeAg seroconversion rates that increment with time.[1] However, a high proportion of patients in this analysis received a misallocation of drug, with interrupted therapy associated with flares in serum aminotransferases after the first year of treatment, and the presented data refer to a subset of 65 HBeAg- positive patients who continued long term treatment. A dose effect of 10 mg vs 30 mg in the pivotal phase III trial was apparent. 10 mg resulted in 3.5 log suppression of HBV DNA versus 4.5 log suppression by 30 mg at 48 weeks.

The 10 mg dose chosen has been chosen because of the more favourable risk benefit ratio, but this may not be optimal for a proportion of patients. A variable proportion of patients, particularly HBeAg positive with higher body mass index (BMI) and high viral load have slower and poor primary responses; In one analysis the bottom quartile 25% of patients had less than 2.2 $\log_{10}$ reduction ; the third quartile had a 2.2 - 3.5 $\log_{10}$ reduction. These effects may be seen in routine clinical practice where worse compliance, and a higher BMI may affect susceptibility to ADV resulting in poor primary responses. [2]

Adefovir in HBeAg negative chronic hepatitis B.

A more consistent effect has been noted in this group. Three year safety and efficacy data have just been published. [3] At week 192 (3.6 calender years) HBV DNA levels of <1000 copies/ml were note in 77% of patients. A similar decrement was observed at 96 weeks of treatment. ALT normalisation was noted in 91%. Fibrosis improved in 63% at week 144 (defined as greater than 1 point reduction).

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. The drug improves outcomes for lamivudine resistant patients awaiting transplantation. [4] 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 seemed advisable in patients with cirrhosis or decompensated liver disease. Although the available evidence suggests that ADF monotherapy suffices for the treatment of lamivudine resistance, (1) the wisdom of continuing ADF monotherapy must be challenged, given the rates of resistance or non response observed with adefovir monotherapy in some centers. This assessor considers that continued lamivudine suppression of wild type HBV DNA may be important to reduce the risk of adefovir breakthrough or slow primary response, and therefore treatment for lamivudine resistance should include lamivudine and adefovir.

Adefovir is a useful agent for the treatment of hepatitis B in HIV co-infected patients where treatment of HIV is not deemed necessary as the drug has no effect on HIV at a dose of 10 mg per day. Longer term follow up of a cohort of infected patients has shown that by week 192, 58% of patients had HBV DNA levels of < 1000 copies/ml

[1] Marcellin et al EASL 2005 abstract 73
[2] Durantel Abstract AASLD 2004
[3] Hadziyannis et al NEJM July 2005
[4] Schiff EASL 2005 Abstract 7

and 70% had normal ALT normal. However, it should be pointed out the the cohort of patients followed in this study circulated lamivudine resistant HBV but continued HAART and lamivudine therapy. For HIV HBV co-infection where treatment of HIV is necessary, tenofovir is the better option as it is active against both viruses.

Costs and cost effectiveness.
A full perspective on costs has been provided independently. It would be helpful in the future to compare the costs of **combination therapies** with a nucleoside and nucleotide versus sequential monotherapies.

Special considerations
It is important to identify particular patients for whom adefovir monotherapy will suffice. This assessor's viewpoint is that anti-HBe positive patients could be treated with adefovir monotherapy. First line treatment is effective in this group. Long term therapy is required, and resistance has been reported, but at lower rates than with lamivudine therapy. In other groups such as HBeAg-positive patients, or anti-HBe positive patients with decompensated cirrhosis, rapid suppression of HBV DNA replication with a low risk of primary non response or resistance is important, and combination therapies will be advantageous. Although there is no proof of principal that combination therapy will be synergistic, the proof of principle that resistance to lamivudine and adefovir are reduced when used in combination has been established. There is some urgency to establish the time horizons for the availability of combination therapies in the latter patients to avoid the opportunity costs incurred by engendering multidrug resistant hepatitis B infection.

Development of resistant mutations has reported with adefovir monotherapy treatment in both HBeAg positive and HBeAg negative patients. Patients from five studies have been included in interim analyses. These studies have been based on careful genotypic analysis of entire reverse transcriptase region of the HBV genome. The reported mutations correlate with HBV DNA rebounds of > 1 log above nadir, suggesting phenotypic resistance. A figure of 18% at 4 years of therapy has been reported. Life table methods have been used to analyse risk but these do not represent true incidence figures. Two adefovir mutations have been identified: N236T and A181V. All patients who have shown resistance mutations received adefovir monotherapy. HBV DNA levels at week 48 predicts rate of resistance: Suppression to $< 3 \log_{10}$ was associated with a 4% rate of ADV resistance at week 144 (2.7 years) A level of 3-6 $\log_{10}$ copies/ml resulted in 26% resistance, but an HBV DNA concentration of > 6 log was associated with 67% resistance at week 144. Also the A181V mutation has a greater effect on subsequent sensitivity to lamivudine than N236T; this compares with observed in vitro effects on fold sensitivity. [5][6][7] No ADV resistance has been observed to date in treatment-naïve patients treated with adefovir and emtricitabine (FTC) or adefovir and lamivudine. No adefovir resistance has been observed to date when adefovir is added to on-going lamivudine therapy.

[5] Peters M et al CROI
[6] Safdar et al AASLD 2004 Abstract 64
[7] Locarnini EASL 2005 abstract 36

Comparator technologies
The heterogeneity of responses to adefovir and poor primary responses (a feature of several new agents), and the risk of resistance in some subgroups of patients may become an issue. Tenofovir and entecavir are licenced drugs in the USA. There is emerging evidence of the efficacy of tenofovir in chronic hepatitis B. Small studies in HBV mono-infected and HIV – HBV coinfected patients have shown a greater log suppression of HBV with tenofovir 300 mg (5.5 log vs 2.8 log compared to adefovir 10 mg). However , comparisons in this study were historical rather than head to head. (2) In the ACTG 51272 study, tenofovir 300 mg caused a 4.8 log suppression at 48 weeks vs 3.9 log suppression in patients receiving adefovir 10 mg (n = 52). Other small reports have suggested an efficacy for tenofovir in lamivudine resistance patients when adefovir 10 mg has been suboptimal. There is an urgent need to more fully evaluate tenofovir (and tenofovir in combination). A randomized phase III controlled trial comparing the efficacy of adefovir dipivoxil and tenofovir disoproxil is underway in HBeAg positive and negative patients. The licensure of tenofovir would expand the HBV therapy armamentarium.

Entecavir is a potent inhibitor of hepatitis B. In randomized controlled trials a mean of - 7 $\log_{10}$ suppression of HBV DNA with 0.5 mg daily at 48 weeks was observed, compared to – 5.5 $\log_{10}$ with lamivudine. Seventy two percent of patients had < 400 copies/ml compared to 42% with lamivudine after 48 weeks of therapy. However, the HBeAg seroconversion rate remained relatively low at 48 weeks (21 and 18% respectively) in study 022. _ No resistance was detected in treatment - naïve subjects after 1 year of therapy. A rate of 7.4% resistance in patients in lamivudine resistant hepatitis B was observed at 48 weeks. Significantly slower median declines in HBV DNA have been reported with adefovir than with entecavir, lamivudine or TDF (and other unlicenced agents such as LdT) . We require further information required on the relative speed of action of adefovir in decompensated cirrhosis, as well as the safety of long term use of entecavir.

Pegylated alpha2a interferon
Pegylated alpha interferons are displacing standard interferons for the treatment of chronic hepatitis C infection, and are likely to similarly replace standard interferons for the treatment of chronic hepatitis B infection. The clinical problem and spectrum of disease treatable by interferon are similar to that described above for oral nucleosid(t)es. However the role of interferon in patients with decompensated hepatitis B is more problematic, given the effect on platelets and neutrophils in patients with portal hypertension and hypersplenism. There is no role for alpha interferon in the treatment of acute or fulminant hepatitis B.

The efficacy of pegylated alpha2a interferon in HBeAg positive and negative chronic hepatitis B has been established in two large pivotal trials.

HBeAg positive patients
Pegylated alpha 2a interferon (PEG IFN) has recently been shown to be active against HBeAg and anti-HBe positive chronic hepatitis. Higher HBeAg (and HBsAg) seroconversion rates in HBeAg-positive patients enhance the possibility of a finite course of treatment which remains an important objective of treatment.

To date the highest HBeAg seroconversion rates in HBeAg-positive patients have been reported with standard and pegylated interferon alpha. The addition of lamivudine to pegylated alpha2a interferon has not improved seroconversion rates compared to pegylated alpha2a interferon alone. Strikingly, in HBeAg positive patients, a -7.2 log suppression of HBV DNA at the end of 48 weeks in patients with lamivudine plus pegylated alpha2a interferon was found, compared to a – 4.5 log suppression of HBV DNA in patients treated with pegylated alpha2a interferon. Thus to summarise, combination therapy with the combination of pegylated alpha 2a treatment and a nucleoside (lamivudine) was superior to monotherapy at end of treatment but combination therapy failed to be superior when evaluated at the end of follow up. HBeAg seroconversion at the end of follow up in these studies could not be related to the rate of viral suppression observed at the end of treatment. Lower rates of lamivudine resistance were observed however, and other studies should follow this initial report. Other studies have reported a possible superior efficacy of the combination of lamivudine and pegylated interferon. [8]

These data suggest an interesting additive effect during treatment.[9] Resistance to the nucleoside analogue used in these studies, in this case lamivudine, was reduced. These on treatment results have not translated into higher rates of seroconversion in follow up, but suggest that the possibility that prolongation of treatment in these groups with an oral agent, for example a nucleotide such as tenofovir, could consolidate the gains that are otherwise foregone when treatment with PEG IFN monotherapy or combination is stopped. The molecular or immunological mechanisms for this effect requires further study, but reduction in HBV cccDNA, an enhanced non cytolytic or cytolytic or T cell response could explain these findings. It is important to determine whether a higher percentage of HBeAg patients would seroconvert from HBeAg to anti-HBe within the first one to three years of treatment with PEG IFN and TDF. Indeed preliminary evidence from small trials suggests that this may be the case. This information, together with the emerging efficacy of TDF provides a rationale for assessing the efficacy of nucleotides with PEG IFN. Future trial designs for example a study of TDF + PEG IFN could provide an opportunity to examination continuation of an oral nucleotide to maintain low levels of virus, in particularly intracellular ccc DNA) to enhance seroconversion or prolong suppression beyond the point of stopping the combination. There may be an important rationale for continuing suppression of HBV DNA from a low base.

Anti-HBe positive patients Relapse rates remain high after stopping 48 weeks of treatment of anti-HBe positive patients. The combination of pegylated alpha2a interferon and lamivudine resulted in -5 log suppression of HBV DNA after 48 weeks of treatment compared to -4.1 log suppression on treatment with pegylated alpha2a interferon alone, suggesting a degree of synergism between these agents during treatment, despite the fact that no sustained difference in suppression of HBV was observed within 6 weeks of stopping treatment, or after 24 weeks of follow up. [10] Lower rates of lamivudine resistant YMDD mutants 1% vs. 18% at the end of therapy were found in this study.

---

[8] Chan et al Hepatology 41 1357 2005
[9] Lau et al NEJM July 2005
[10] Marcellin P et al NEJM 2004

Conclusions

The clinical care of hepatitis B is still evolving. Treatment is being influenced by introduction of new nucleoside and nucleotides, some still in development. Short term studies show effectiveness and the ability of these new drugs, as well as pegylated interferon to decrease viral replication. Suppression of viral replication reduces histological progression and reduces the incidence of HCC. The efficacy of combinations has not been fully explored. Synergisms have not been easy to demonstrate, particularly because similar classes of drugs have been assessed. However, reduced resistance with combination therapy has been shown, and this should lead to new clinical and theoretical paradigms for treatment and the assessment of cost effectiveness. There are disadvantages to using a monotherapy with high rates of resistance. These include the fact that treatment failure is likely, and that failure is associated with and exacerbation of disease.

Is use of a cheaper drug with high rates of resistance as monotherapy short sighted? Use of a single drug as first line agent will place great selection pressure on HBV, and will reduce the benefit of the drug in a total treatment approach and future effectiveness. Such a strategy incurs a future cost of increasing resistance and reduces the cycle of useful life. Should we be indifferent to the negative externality of resistance? We are likely to increase the population with resistant strains, and to increase the precedent for resistance or deleterious mutations with other agents. Thus resistance is an opportunity cost, which makes useful drugs unusable. Direct collective treatment costs may diverge from individual costs, and NICE will need to consider a population- wide treatment strategy. Will we place reliance on phenotypic testing rather than rational use to reduce the stock of disease? What incentives can we put in place to avoid overuse and minimise the negative impact?

At the present time clinicians, patients and public health authorities must make choices on basis of data that is not fully matured. Decisions are made at this time pending the arrival of new combination data. The prospect of resistance must be thought of as a key parameter in decision making and NICE will have to take this into account. Questions remain regarding optimal combinations and criteria for initiating therapy with different agents. For adefovir, there are questions regarding individual unresponsiveness to first line therapy in some patients with high viral loads and advanced disease.

Thus it will be important to consider policy guidelines, and to develop appropriate algorithms for the treatment of hepatitis B so that appropriate monotherapies can be used where monotherapies suffice, but combination and comcomitant therapies where a monotherapy is inappropriate. These strategies could include measurement of baseline parameters that predict response and DNA decline during the first weeks of treatment to predict the likelihood of HBeAg seroconversion and the risk of resistance. Resistance suppression may become the key attribute of combination therapy, particularly for HBeAg positive patients, but may be difficult and expensive to be statistically demonstrable in the short term.

A number of NHS resources will need to be made available for HBV sequencing, resistance testing, the testing of HBV genotypes, pre-core mutation, and core

promoter changes, and for liver biopsies. There will need to be appropriate support for infrastructures, training of staff to provide support services, and management of side effects.

Reference List (see footnotes)

1. Peters MG, Hann HH, Martin P, Heathcote EJ, Buggisch P, Rubin R et al. Adefovir dipivoxil alone or in combination with lamivudine in patients with lamivudine-resistant chronic hepatitis B. Gastroenterology 2004; 126(1):91-101.

2. Van Bommel F, Wunsche T, Mauss S, Reinke P, Bergk A, Schurmann D et al. Comparison of adefovir and tenofovir in the treatment of lamivudine-resistant hepatitis B virus infection. Hepatology 2004; 40(6):1421-1425.