Adefovir and pegylated interferon in treatment of chronic hepatitis B

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The approach used in my department at St Mary's is summarised below. Around 1000 patients with chronic HBV are in our long term care program and because many patients need viral suppression therapy for many years, perhaps even life long, the number is continually increasing.

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.

We do not initiate treatment in the immuno-tolerant phase because in the absence of inflammatory liver disease the chance of inducing durable HBe antigen/ antibody clearance is extremely low and drug resistance will develop particularly if starting levels of viraemia are high and monotherapy is used.

Second stage – the inflammatory process (hepatitis) becomes sufficiently intense to permit lysis of infected hepatocytes, and in some cases clearance of HBeAg and the development of anti-HBe. If the inflammation is sufficiently intense and pro-longed, patients may develop cirrhosis. .In the presence of elevated transaminases a liver biopsy is undertaken and if this reveals some fibrosis then therapy is offered. 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.

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 ml and liver biopsy evidence of significant fibrosis, therapy should be offered.

Two approaches to therapy of HBV infection are now open.

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.

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 (12%) at one year. The current pricing of pegylated interferon and its

convenience of administration – once weekly- has meant that most physicians are using it rather than standard interferon. The patients undergoing HBe antigen/ antibody conversion usually become inactive (HBV –DNA $<10^5$ with a normal ALT and minimal hepatitis) usually need no further therapy.

The 60-70% who do not undergo sero-conversion, 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 adefovir. Because of cost most physicians will use lamivudine first and then substitute adefovir, if lamivudine resistant virus emerges, which is the case in over 60% of cases after 3 years therapy. The resistance rate with adefovir 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. Entecavir is just being licensed and because of its greater potency and lower rate of emergence of resistance variants will be the drug of choice assuming that it is affordable.

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 a sufficiently rare occurrence to make this approach not clinically useful or cost effective. Long term viral suppressive therapy with orally administered drugs of low toxicity and with low rates of emergence of drug resistant virus are therefore the preferred approach. This usually entails treatment with nucleoside or nucleotide analogues such as lamivudine and now adefovir. Once again because of cost most physicians will use lamivudine first and then substitute adefovir only if lamivudine resistant virus emerges. This occurs less frequently than in HBe antigen positive infection probably because of the lower levels of viraemia initially. The resistance rate with adefovir 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 regenerating hepatocytes should be protected from infection. In this approach it seems likely that combination therapy, may be necessary. Pegylated interferons are not the preferred choice because they are parenterally administered and have more side effects than the nucleoside/nucleotide analogues.

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.

Current service provision and projection of future need.

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.

The HPA have calculated that about 260 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 c22, 000 cases, over and above are current patient population, by 2015. Currently viral suppressive therapy using a combination of Lamivudine and adefovir costs around £5000 per year and so for the new cases the cost would increase over the 10 years to £110 million per year.

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