Treatment of hepatitis B: the next five years

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ABSTRACT – The natural history of individuals chronically infected with hepatitis B typically fluctuates, with periods of active viral replication with or without an associated hepatitis and sometimes prolonged periods of spontaneous viral suppression and inactive liver disease. In the majority, this chronic infection is clinically silent unless either liver failure and/or hepatocellular carcinoma (HCC) supervenes. Thus proactive steps are needed to first identify those with hepatitis B infection and to then serially monitor those found to be chronically infected for both level of alanine aminotransferase (ALT) and hepatitis B virus DNA (HBV-DNA) (using sensitive polymerase chain reaction techniques. Antiviral therapy significantly reduces the risk of liver disease progression and HCC in those with ongoing viral replication $>10^5$ c/ml and advanced hepatic fibrosis. The decision of when to initiate (possibly lifelong) treatment has to be made judiciously. Before introducing therapy both patient and physician must recognise the need for compliance with both treatment and viral surveillance so as to minimise the development of drug resistance. Drug resistance needs to be identified prior to recurrence of hepatitis (rise in ALT) to prevent hepatic decompensation, this necessitates serial HBV-DNA testing.

KEY WORDS: antiviral therapy, chronic hepatitis B, drug resistance

Introduction

The goals of antiviral therapy are to induce sustained suppression of viral replication, clear hepatitis B surface antigen (HB_sAg) and eventually eliminate the chance of reactivation by clearing the template for viral infection, namely covalently closed circular DNA (cccDNA) from hepatocyte nuclei. One landmark study has already demonstrated that the nucleoside analogue lamivudine given to individuals with a baseline viral load ≥700,000 c/ml and significant hepatic fibrosis, both prevented liver disease progression and reduced the rate of hepatocellular carcinoma (HCC), most notably in those in whom viral suppression was maintained.[1] This study simultaneously highlighted the untoward consequences of drug resistance as the latter reduced the clinical benefit of treatment and so highlighted how

prolonged treatment in the face of viral resistance may potentially do more harm than good. The development of drug resistance may reduce the cost effectiveness of long-term antiviral therapy, hence the urgent need to clarify just who with chronic hepatitis B should receive treatment and with what agent(s).

Who to treat

This has been the topic of consensus statements from professional societies from several continents and a recent survey, sent to all members of the American Association for the Study of Liver Diseases and debated by a panel of international experts, has been published.[2] Although opinions differed, the majority opinion for the management of the two major forms of chronic hepatitis B, namely hepatitis e antigen (HB_eAg) positive and HB_eAg negative, was discussed. In terms of level of hepatitis B virus DNA (HBV-DNA) that would prompt consideration of the introduction of antiviral therapy, the levels decided upon were an HBV-DNA $≥10^5$ c/ml and $≥10^4$ c/ml respectively for HB_eAg-positive and HB_eAg-negative hepatitis. The goal of treatment in the former is seroconversion from HB_eAg to hepatitis B e antigen antibody (HB_eAb) and for the latter sustained undetectable HBV-DNA levels for >6 months. Despite discussion, definitive statements about what values for serum alanine aminotransferase (ALT) might prompt the initiation of therapy in those with the required HBV-DNA titre could not be made. There were also not enough published data to not recommend liver biopsy in those whose ALT values fell within the normal range despite ongoing viral replication, except in the individual who was HB_eAg positive in the immune tolerant phase of their infection.

The immune tolerant hepatitis B carrier is one who is HB_eAg positive with consistently very high levels of viral replication (usually $≥10^8$ c/ml) and absolutely normal ALT values. A liver biopsy performed in such an individual would show no evidence of progressive liver disease despite strong staining with both HB_sAg and HB_cAg in cytoplasm and large quantities of cccDNA in hepatocyte nuclei (all this in the absence of HIV co-infection). Such individuals are usually young (<30 years) and at present there is only pilot study evidence that a combination of immunostimulatory and viral suppressive treatment may induce viral clearance in some.[3] Although antiviral treatment

is not currently recommended for individuals in the immune tolerant phase of their disease, to eradicate infection prior to the initiation of any liver disease in all hepatitis B carriers is surely the eventual aim in the future management of chronic hepatitis B infection.

Can we predict who may require antiviral therapy?

Height of HBV-DNA

There have been a number of retrospective, but few prospective, reports of HBV-DNA titres which suggest the level of viral replication which puts an individual at risk of subsequent significant liver disease. All these reports indicate that those with high levels of viral replication at baseline, ie when first seen, have a worse outcome than those whose HBV-DNA titres are low at presentation. The equation is more complex, however, as baseline HBV-DNA values do not predict the subsequent fluctuations that may occur in some over time. These fluctuations reflect the role of the immune response to hepatitis B in the natural history of this disease. The level of immune control may range between there being too little (immune tolerant) to sufficient to initiate complete viral clearance (sometimes even too aggressive precipitating fulminant hepatic failure). At present we cannot reliably predict from the height of the serum of HBV-DNA at one point in time precisely who will develop cirrhosis and/or HCC. The report from Yang et al[4] indicated that the greatest risk of HCC was in those who at baseline were HB_eAg positive with high levels of viral replication. A subsequent study of serial HBV-DNA measurements indicated a gradient of risk for HCC according to baseline HBV-DNA titre – the risk increasing once HBV-DNA values of $\geq 10^4$ c/ml were detected. Such levels were present in 14% of those who were HB_eAg negative and in 98% of those who were HB_eAg positive. The size of the population studied was >4,000, 62% male and 67% >39 years old. Of those with HBV-DNA levels $\geq 10^6$ c/ml 13.5% developed HCC, whereas only 0.7% with undetectable HBV-DNA developed HCC over a 13-year follow up.[5]

Much earlier studies using a less sensitive measure for HBV-DNA had examined three at-risk populations – Chinese living in China, Chinese living in the USA and Africans living in Senegal – and noted that in the age groups 20–29, 30–39, 40–49 and 50–59 years there was a marked difference in rates of detectable HBV-DNA within these three populations which corresponded with the different rates of HCC.[6] These data suggested that both height and duration of viral replication, even within the same racial group, varied according to geographic region in accordance with the rate of HCC in these three groups of hepatitis B carriers.

Level of serum alanine aminotransferase

A study of liver histology in over 400 Chinese hepatitis B carriers, many with ALT values within the normal rage, indicated that the latter did not correlate well with severity of underlying liver damage.[7] A more recent and much larger study from

Korea (>180,000 subjects) indicated that values of ALT and AST once >20 IU/l were associated with an increased risk of liver death (more so in those with a family history of liver disease). This risk rose 10-fold once ALT values were >40 IU/l, ie the upper limit of the normal range (mean +2 SD).[8] Chen et al[5] documented the hazard ratio for HCC in those with baseline ALT values of <45 IU/l was 1, whereas for those with a baseline ALT ≥ 45 IU/l was 4.1 (p<001). Hence, whereas an elevation in ALT above the normal range profoundly increases the risk of HCC, an ALT value within the normal range at least at one point in time does not eliminate the risk of liver disease progression. Hence the need for serial monitoring of ALT in all hepatitis B carriers. Just how often measurement of both ALT and HBV-DNA should be performed simultaneously in all hepatitis B carriers is uncertain – but once to twice a year is probably appropriate.

Education of those identified as hepatitis B carriers

The reports of large-scale epidemiological/serological data published recently indicate the need for lifelong monitoring of all hepatitis B carriers. Thus patient education is an essential first step in the management of those with a chronic hepatitis B infection. Recent data indicate that measurement of ALT values is insufficient to identify those at risk of progressive disease and in need of antiviral therapy; rather HBV-DNA values need also to be measured serially. It is becoming increasingly common for there to be superimposed reasons for an elevation in ALT, most commonly due to fatty liver secondary to central obesity – now reported worldwide in epidemic proportions.[9] Serial monitoring of HBV-DNA using sensitive methods markedly increases the cost of patient management but the high risk of progressive disease among the hepatitis B carrier population (15–40%), occurring most often in men during their most productive years, means that even when HBV-DNA evaluation is included in a cost-effective analysis it is still likely to fall within the accepted range, although formal analyses are required.

Most individuals with chronic hepatitis B are entirely asymptomatic so it benefits the medical community at all levels to emphasise the need for lifelong monitoring and maintenance of preventative strategies in this population (Table 1). These are

Table 1. Education-identified hepatitis B virus carriers.

Prevention of transmission/vaccination of all contacts to HB_eAb

Inform all medical/dental/midwife contacts

Introduce screening for hepatocellular carcinoma (depends on race/age)

Management (prevention strategies) in cirrhotics

Understand vital importance of maintaining oral antiviral

Explain risk of immunosuppressive therapies precipitating a flare up of hepatitis B

Need for lifelong monitoring ALT/HBV-DNA status

ALT = alanine aminotransferase; HBV-DNA = hepatitis B virus DNA.

required to prevent transmission to family and household contacts, medical, dental and midwife contacts and all sexual partners. Once antiviral therapy is introduced, further education is required to avoid potentially fatal flare ups of disease which may occur with sudden withdrawal of antiviral and/or immunosuppressive therapy. The institution of preventative strategies is also necessary in the management of those with underlying cirrhosis.

'Ideal' treatment for chronic hepatitis B

Clearly the ideal therapy would be as it is for hepatitis C – a short-term therapy that offers cure without recurrence. Preferably the treatment should be oral and consist of a combination of antiviral agents which are able to completely suppress viral replication in the long term without the development of drug resistance or adverse side effects. It would be better still if they could be used safely during pregnancy, ie an equivalent to penicillin is needed.

Issues in the treatment of chronic hepatitis B that need to be addressed

Drug resistance

Inadequate drug-induced suppression of viral replication promotes drug resistance. Even in the face of highly effective drug therapy, however, drug resistance may develop. The clinician may suspect drug resistance to be present if a rise of ≥ 1 log in the serum HBV-DNA above the nadir (of that originally achieved with therapy) is observed and is sustained over the next month.[10] Once more than one oral agent has been employed, however, it becomes necessary to conduct genetic analyses to identify the precise mutation.[11]

Risk factors for drug resistance include both 'host' and 'viral' factors. Universally the most common is 'non compliance' which complicates of both short- and long-term therapy. Causes of non-compliance may be financial but 'drug fatigue' plays a large role in long-term therapy. In an individual who is asymptomatic it is particularly hard to maintain strict compliance unless perhaps they have witnessed a family member die as a consequence of hepatitis B. Little attention has been paid to inadequate dosing but the observation that high body mass index is one of the risk factors for lamivudine resistance would suggest that perhaps 100 mg daily is not always sufficient.[12] The recommended dose of adefovir dipivoxil (10 mg/d) is inadequate but larger doses are nephrotoxic. The 10 mg dose may explain why the rate of fall in HBV-DNA with adefovir dipivoxil may be very slow in some individuals but fortunately the genetic barrier is high for adefovir dipivoxil and so resistance to this drug is slow to develop. Other risk factors for drug resistance include high histological activity on liver biopsy. Not surprisingly, the greatest viral risk factor in the face of good compliance is a high baseline viral load, typically seen in those with HB_eAg positive infection, most notably in immune-tolerant persons. The initial virological response that takes place within the first six months of the introduction of oral antiviral therapy determines the subsequent likelihood of drug resistance. Pre-existing drug-induced mutations in the virus markedly limit the success of the introduction of a new oral antiviral agent. Hence, treating a nucleoside analogue naive individual is always more successful than when pre-existing drug-induced mutations are present. There is now a pool of individuals who are drug resistant to a number of different agents,[11] and who may transmit these resistant strains to non-immune individuals.[13] Thus we face a potential disaster which threatens the successful outcome of treatment of hepatitis B. There are many factors that need to be addressed to avoid such a disaster, the most important of which is patient and physician education.

Prevention of drug resistance (in the absence of human factors) relates both to the initial and subsequent level of drug-induced viral suppression (which needs to be to $<10^3$ c/ml by six months into therapy and is probably best achieved by using dual therapy from the start) and the genetic barrier of the particular therapy. Long-term data on the potential benefit of starting therapy with more than one agent rather than sequential therapy are currently lacking. When pegylated-interferon (IFN) is given with lamivudine,[14] the rate of resistance to lamivudine was less than with lamivudine monotherapy. When patients with lamivudine resistance are treated with adefovir dipivoxil and lamivudine is maintained, the rate of adefovir dipivoxil resistance is less.[15] Combination therapy is not always associated with a lower rate of resistance, however, as was observed when lamivudine was given together with telbivudine to treat naive patients, the resistance rate at the end of a year was 12% in those treated with this combination whereas the rate seen in those randomised to telbivudine monotherapy was only 4%.[16]

Consequences of drug resistance (Table 2)

Drug resistance impairs antiviral efficacy, so it reduces the chance of HB_eAg seroconversion. It may also induce a severe hepatitis – thus those most at risk of the consequences of drug resistance are patients with cirrhosis and those co-infected with HIV. The longer viral replication is allowed to continue in the face of resistance the more likely compensatory mutations will develop. A recently published clinical study illustrates well the risk of ignoring the presence of drug resistance.[17] Prior to the availability of adefovir dipivoxil there was no treatment for individuals with lamivudine resistance so if treatment was

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Table 2. Consequences of drug-resistant chronic hepatitis B.

Decreased rate of HB_e seroconversion to HB_eAb

Severe hepatitis (cirrhosis and HIV co-infection)

Massive ↑ viral replication post tx (↑ replication space) → fibrosing cholestatic hepatitis

'Priming' for compensatory mutations

Failure to secrete wild type HB_sAg thus anti-HB_s ineffective (effect on overlapping reading frame)

Transmission of drug resistance

HB_eAb = hepatitis B e antibody; HB_sAg = hepatitis B surface antigen.

continued in the face of resistance HBV-DNA levels rose higher and higher. Once adefovir dipivoxil was licensed patients with lamivudine resistance could be effectively treated. Lampertico and colleagues have shown that the earlier adefovir dipivoxil is introduced the quicker the HBV-DNA levels becomes suppressed once again.[17] If lamivudine resistance is ignored until ALT levels are seen to rise it may take over two years for their hepatitis to once again come under control and this may be too long for some with particularly severe disease. So at least in patients with cirrhosis the outcome is worse if drug resistance is not controlled as soon as the resistance occurs. Hence the need to screen patients (certainly those with cirrhosis) on oral antiviral agents for HBV-DNA levels rather than ALT as waiting for a rise in ALT before checking HBV-DNA may put the patient in jeopardy.

If drug resistance is present in a patient going for liver transplant it can be particularly hard to manage, as the new liver provides an enormous replication space, allowing massive viral multiplication which may be very difficult to bring under control. Therefore, in those patients who have severe liver disease and who may need a liver transplant either for HCC or liver failure, drug resistance must not be allowed to develop. For this reason it is recommended that patients on the liver transplant waiting list who are being treated with oral antiviral agents have their HBV-DNA values measured very frequently (monthly).

Viral markers needed for the future management of chronic hepatitis B

The epidemiological studies recently reported by Yang,[4] Chen,[5] Yuen,[18] and Iloeje[19] all indicate that it is essential that sensitive methods to detect HBV-DNA are available – without the ability to detect viral replication at low levels eg 10^3 c/ml (10^2 IU/ml) drug resistance cannot be identified in a timely fashion, nor can reactivation or low level grumbling hepatitis B in those with normal ALT values be recognised.

Once more than one therapy is introduced it will become necessary, just as it is for HIV, to be able to identify which mutation pattern is present once a sustained rise in HBV-DNA on therapy occurs. It is not entirely clear whether HB_sAg genotype is relevant to the risk of drug resistance but genotype is definitely important when it comes to choice of antiviral therapy. For patients requiring treatment for HB_eAg-positive hepatitis those with genotypes A and B respond much better to interferon therapy than do genotypes C and D.[20] Patients with genotype C infection appear to have an enhanced risk of HCC.[21]

The clinical value of identifying base core promoter and/or precore mutations is uncertain at present;[22] likewise the value of measuring cccDNA in liver tissue for the management of chronic hepatitis B is questionable.[23]

How drug resistance may be reduced: future treatments

Probably the optimal way to maintain viral suppression in the long term is to employ drug cocktails using a combination of agents which target multiple regions of the viral genome, other parts of the HBV life cycle and additional agents to exert immune control.[24]

RNA interference

RNA interference is a natural control mechanism in plants, it is a biological process by which dsRNA within the cell induces degradation of mRNA. Small interfering RNA (siRNA) can be used to target disease causing genes or virus specific sequences for degradation. To date, siRNA has been developed and shown to be effective in vitro against both HBV and HCV. Inhibition of both HB_sAg and HB_eAg has been shown both in cell culture and in the mouse model.[25,26] But there are several disadvantages to the employment of siRNA – firstly gaining access to the cell (specific vector) is problematic, and secondly, off-site targets may be deleterious. It is also a very expensive technique, particularly as rapid resistance develops unless a combination of siRNA are used.

Therapeutic vaccines

The concept of therapeutic vaccines is to overcome the tolerance of cytotoxic T-cells to hepatitis B epitopes by targeting dominant, highly conserved areas of the virus. This requires a potent adjuvant to stimulate cytotoxic T lymphocytes (CTL) and multiple epitopes need to be targeted simultaneously. The initial vaccine developed employed a single epitope and when given to healthy controls was able to induce measurable T-cell responses but when given to individuals chronically infected with hepatitis B, virtually no effect on CTL (or virus) was observed.[27] The best control of viral replication is immune control as is observed to occur spontaneously in at least 50% of hepatitis B carriers – without the hazards and expense of drug resistance. Thus the avenue of immune control in chronic hepatitis B is very desirable.

Other challenges facing the management of chronic hepatitis B

Chronic hepatitis B is a major cause of death worldwide, long recognised as such in the Far East and in sub-Saharan Africa. Changes in immigration patterns has meant that this potentially fatal yet treatable disease is now common everywhere. Mortality rates from hepatitis B are increasing in the Western world. But most hepatitis B carriers are asymptomatic and many have no knowledge that they are infected with a virus which could lead to their premature death. A recent study in New York, conducted among uninsured immigrants, showed that 22% of males (12.2% of females) were infected.[28] The carrier rate for hepatitis B was 18.8% in those under 18 years, 22.8% in those aged 26–59 years and 8.3% in those over 60 years old. The lower rate of hepatitis B in the over 60-year-old range suggests that chronic infection with hepatitis B kills prior to 60. This study indicates how important it is to identify those individuals who, for whatever reason, have not been tested for hepatitis B. A recent survey of endoscopy clinic patients in Sydney, Australia, indicated that those most likely to test positive for hepatitis B

were individuals with HIV, those who were Asian, or those from the Pacific Islands (adjusted odds ratio 36.3-fold and 12.4-fold respectively).[29] Now that we have effective therapies which can prevent both liver disease progression and liver cancer,[1] it is vital that we identify these silent carriers.

Primary prevention of hepatitis B

In 1986, Taiwan initiated universal infant vaccination against hepatitis B and by 1991 the carrier rate had been reduced from 9.8% to <1%.[30] The World Health Organization has recommended universal infant vaccination against hepatitis B, but to date this has been adopted by only 54% of the countries in the world. A recent meta-analysis highlights the overwhelming success of HBV vaccination when given to newborns of HB_eAg-positive mothers.[31] The challenge is to develop a vaccine which is so potent that only one, or at most two, injections are required. But the even larger challenge is to convince governments that primary prevention is a must; the most logical, most persuasive, argument is economic. But it is not the cost of the vaccine but the cost of the effective delivery which is the stumbling block, particularly in countries where women do not give birth in a medical facility.

Treatment of hepatitis B: the next five years

For those who are chronically infected, initial identification is a top priority as life-saving therapies are currently available but only for those who know they are infected. These therapies nevertheless need to be judiciously introduced and hence the need to regularly monitor all hepatitis B carriers for both ALT and level of HBV-DNA (using sensitive techniques). Patient (and physician) education is of paramount importance – so that both fully appreciate the value of virologic surveillance. Timely intervention with therapy and preventing drug resistance and more effective new therapies (such as the development of drug cocktails which attack the virus at several levels) are needed to achieve sustained suppression of detectable virus and eventually clearance of HB_sAg – the goal of any antiviral therapy.

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