Using natural history to guide management of chronic hepatitis B

Management strategies employed in chronic hepatitis B infection include observation, antiviral therapy and surveillance for complications, the choice of strategy depending on the stage of the infection.

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Chronic infection with the hepatitis B virus (HBV) is a global public health concern, affecting up to 400 million people worldwide. Between 20 and 40% of affected individuals will develop the most serious consequences of the chronic infection, namely cirrhosis, decompensated liver disease and hepatocellular carcinoma (HCC), and currently one million deaths per year worldwide are attributed to these HBV-related complications.[1] Current estimates suggest that in Australia between 90,000 and 160,000 individuals have chronic hepatitis B; of these, about half are immigrants from North-East (16.2%) and South-East Asia (33%).[2]

Age at initial exposure strongly influences the risk of developing chronic HBV infection, with 95% of perinatal infections but only 5 to 10% of adult-acquired infections leading to chronic disease. Primary prevention through immunisation is at the forefront of the global fight against HBV infection and vaccination programs have been implemented in over 100 countries, including Australia. This, along with other measures such as improved screening of blood products and programs for needle disposal and exchange, has led to significant falls in the incidences of acute and chronic infections in both high and low prevalence countries, as well as in the occurrence of HCC.[1]

Nevertheless, given the current disease burden,

IN SUMMARY

- **Screening for HBV infection should be carried out in individuals who are at high risk, such as those from high or intermediate prevalence countries, injection drug users and men who have sex with men.**
- **Primary prevention involves immunisation of high-risk individuals and education of infected patients to minimise transmission risk.**
- **It is reasonable to observe patients who are in the immunotolerant stage of infection or who have inactive infection. Liver function tests should be performed every six to 12 months, and patients referred when alanine aminotransferase (ALT) levels become elevated or there are concerns about the development of advanced liver disease.**
- **Antiviral therapy (pegylated alfa-interferon, lamivudine, adefovir or entecavir) is generally indicated in patients with evidence of active viral replication and associated hepatic inflammation and fibrosis. Most patients on antiviral therapy will be followed up in specialist clinics.**
- **HBV-infected patients with cirrhosis should always be treated to reduce the risk of developing liver failure and hepatocellular carcinoma (HCC), for which they have a 100-fold increased risk compared to non-infected individuals, and to improve mortality.**

antiviral treatment remains an important tool in attempting to reduce the incidence of cirrhosis and HCC in chronically infected patients.

Natural history of chronic hepatitis B

An acute infection with HBV may resolve with viral clearance and development of protective immunity or may persist as a chronic infection. The individual's age at exposure is the most important determinant of resolution or persistence. While 90% of infections in newborns and 30% of those in children under 5 years of age are likely to become chronic, only 5% of infections acquired in adulthood will do so.[3]

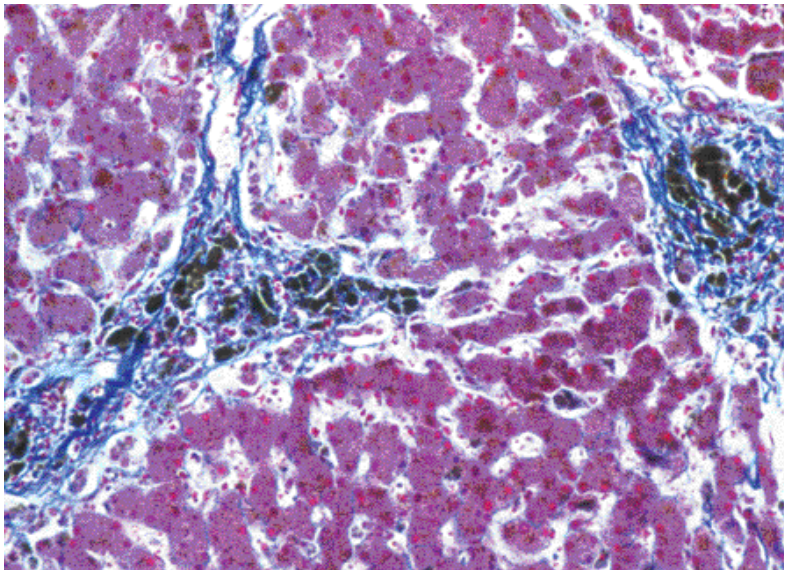
The clinical course of chronic HBV infection represents an ongoing and variable interaction between the virus and the host immune response. HBV does not directly damage the hepatocyte, rather inflammation and liver injury is a consequence of the host immune response against viral antigens displayed on infected hepatocytes.[4] One way to consider this complex process is as a progression through three phases: immune tolerance, immune clearance and inactive hepatitis B. These stages and the associated serology are described in the box and Table 1 on page 26.[3-6]

Regarding serology, the presence of hepatitis B surface antigen (HBsAg) is considered the hallmark of HBV infection, and hepatitis B e antigen (HBeAg) is a marker of HBV replication and infectivity. Antibody to hepatitis B core antigen (anti-HBc) is a marker of exposure to the virus and is not seen in patients who have acquired immunity to the virus through immunisation rather than infection.

Transmission of HBV

HBV can be transmitted in various ways. In endemic areas such as South-East Asia, it is commonly transmitted from mother to child around the time of birth. Transmission rates range from 90% in HBeAg positive mothers to 30% in HBeAg negative mothers.[7] Breastfeeding is not associated with increased transmission risk.

Horizontal transmission between young children via breaks in the skin or mucous membranes is the predominant mode of acquisition in areas with intermediate prevalence of HBV infection, such as the Mediterranean. In countries with a low prevalence of infection with the virus, such as Australia, sexual transmission and sharing of needles and equipment between injection drug users are the common means of acquisition.[1-3]



PHOTOLIBRARY

Figure. Light micrograph of liver section showing signs of cirrhosis. Fibrous bands (dark blue) are seen breaking up the structure of the liver, with healthy hepatocytes (pink) between the bands. HBV-infected patients with cirrhosis should be treated to reduce the risk of liver failure and cancer.

Limiting HBV transmission

Minimising the risk of transmission is a critical aspect of the overall management of HBV infection, and patients with chronic infection should be educated and counselled accordingly (Table 2). While the virus can be transmitted through a breach of a mucosal barrier, there is no firm evidence that it can be transmitted through simple contact of bodily fluids.

Postexposure prophylaxis is recommended for nonvaccinated individuals who are exposed to blood or infectious secretions. This entails a dose of the vaccine (Engerix-B, H-B-Vax II), which ideally should be given within 12 hours of exposure, and, depending on the source, a dose of hepatitis B immunoglobulin. Newborns of infected mothers are given hepatitis B immunoglobulin as well as vaccine immediately post-birth.

Other factors that may accelerate liver injury should be addressed (Table 2). Alcohol intake should be minimised, and obesity, diabetes and hypercholesterolaemia should be managed to reduce the risk of non-alcoholic fatty liver disease. Vaccination against hepatitis A is recommended (Avaxim, Havrix 1440, VAQTA Hepatitis A Vaccine).

continued

The stages of chronic HBV infection and their serological profiles

One way to consider the ongoing and variable interaction between the hepatitis B virus and the host immune response is as a progression through three phases: immune tolerance, immune clearance and inactive hepatitis B. Table 1 shows the serological, virological and relevant liver function test profiles associated with these stages.

Immune tolerance

The chronic infection that follows most neonatal and early childhood exposures is characterised by the presence of hepatitis B e antigen (HBeAg), very high levels of circulating virus (as indicated by high levels of HBV DNA) but minimal inflammation in the liver (as indicated by normal levels of serum alanine aminotransferase [ALT]) and no scarring. This phase of immune tolerance usually persists until the second to fourth decades of life, during which time tolerance wanes and the host immune system mounts a response against the virus, which is now recognised as foreign.

Immune clearance

Following loss of tolerance, most patients will experience a vigorous immune response at some time during the immune clearance phase, with active hepatitis, significant hepatic necroinflammation and high serum ALT levels. If this vigorous response is successful, there is suppression of viral replication and seroconversion of HBeAg (loss of HBeAg and production of antibodies to the e antigen [anti-HBe; also known as HBeAb]). This outcome is associated with reduced serum ALT, significant reduction in serum HBV DNA, regression of fibrosis, reduced risk of cirrhosis and HCC, and better overall survival. Unfortunately, a vigorous response is not always successful in controlling viral replication and, in some patients, a persistent but non-clearing immune response can lead to progressive scarring and cirrhosis. It is in this group of patients that antiviral therapy should be considered in order to achieve control of viral replication before severe liver damage occurs.[4,5]

Inactive hepatitis B

HBeAg seroconversion occurs in 60 to 85% of individuals,[3,4] following which patients remain hepatitis B surface antigen (HBsAg) positive but are considered to have inactive infection. Those who lose HBsAg and develop antibodies to it (anti-HBs; also known as HBsAb) are generally considered to have resolved hepatitis B.

A proportion of patients who successfully clear HBeAg with reduction in viral levels will later develop a mutant HBV, with reactivation of viral growth. The mutation in or near the precore region of the HBV genome commonly prevents the production of HBeAg, and HBeAg negative chronic hepatitis B (CHB) is often referred to as precore mutant CHB. HBeAg negative CHB is the predominant form seen in patients from the Mediterranean Basin and parts of the Far East. In comparison to patients with HBeAg positive CHB, patients with HBeAg negative CHB are usually older and tend to have more frequent fluctuations in liver function tests, despite generally lower levels of viraemia. This group of patients tends to have more severe histological changes, and have higher rates of progression to cirrhosis.[6] Treatment is challenging because the absence of an endpoint such as HBeAg seroconversion makes viral suppression the main goal and ongoing long-term therapy is usually required.

Table 1. Serological and ALT profiles associated with chronic HBV infection

Infection stage	HBsAg	Anti-HBs	Anti-HBc	HBeAg	Anti-HBe	HBV DNA	Serum ALT
Immunotolerant	+	-	+	+	-	High	Normal
HBeAg positive chronic hepatitis	+	-	+	+	-	Detectable (low to high)	Fluctuating
HBeAg negative chronic hepatitis*	+	-	+	-	+	Usually detectable, often low to moderate levels compared to HBeAg positive disease	Fluctuating (although may be normal)
Inactive infection*	+	-	+	-	+	Undetectable	Normal
Resolved infection	-	+	+	-	+	Undetectable	Normal
Previous immunisation†	-	+/-	-	-	-	Undetectable	Normal

* The serological profiles of HBeAg negative chronic hepatitis and inactive infection are identical but the stages can be differentiated by the presence of HBV DNA and/or elevated ALT in HBeAg negative chronic hepatitis. † Included for comparison.

Screening for and diagnosing HBV infection

Screening for HBV infection using HBsAg and anti-HBs testing should be carried out in individuals who are at high risk of HBV infection. High risk groups of people include those from areas of high and intermediate prevalence for HBV infection (HBsAg prevalence greater than 8% and between 2 and 7%, respectively), injection drug users and men who have sex with men (Table 3).[3]

Individuals at high risk (with the exception of pregnant women) who are negative for both HBsAg and anti-HBs should be vaccinated against HBV. Conversely, a positive HBsAg indicates chronic infection, and further testing for HBeAg, anti-HBe, HBV DNA levels and LFTs, and possibly a liver biopsy to determine liver injury, is indicated to further characterise the disease state (Table 1) and determine the need for therapy.

Treatment aims

Complete eradication of the virus does not occur, either spontaneously or following antiviral therapy, in HBV infection, unlike in hepatitis C virus infection, in which viral eradication occurs in 50% of patients following treatment. Loss of HBsAg and development of anti-HBs (surface antibody) is the best possible outcome, and represents a relative state of immunity although HBV DNA can still be detected in most patients using sensitive assays. However, even the best available treatments achieve HBsAg seroconversion rates of only 4 to 5%.[3,8-12]

Consequently, the main goal of treatment for hepatitis B is sustained suppression of viral replication in order to reduce necroinflammatory activity, prevent fibrosis and thereby prevent or delay cirrhosis and its associated complications such as HCC and hepatic decompensation.

Indications for treatment

Choosing patients who are likely to benefit from antiviral therapy remains one of the key challenges in HBV management. The difficulty in controlling viral growth, the frequent need for long term and sometimes indefinite therapy, variable response rates, increasing rates of antiviral resistance and treatment-related side effects are all factors that must be considered.

Understanding the natural history of HBV infection can inform treatment decisions. Patients in the immune clearance phase with evidence of active viral replication (detectable HBV DNA) and elevated ALT levels (indicating hepatic necroinflammation) who do not undergo spontaneous HBeAg seroconversion after several months of observation should be considered for therapy to prevent further liver injury. Patients with advanced fibrosis or cirrhosis are always candidates for treatment to prevent further disease progression.

In contrast, patients with inactive infection and those in the immunotolerant phase (who are HBeAg positive and have persistently normal ALT levels) are generally not treated as they usually have low levels of hepatic inflammation and

Table 2. Educating chronic hepatitis B patients

Precautions to minimise HBV transmission risk[3]

- Vaccination of sexual contacts and household members
- Use of barrier protection during sexual intercourse if partner not vaccinated or naturally immune
- Covering of open cuts and scratches
- Use of detergent or bleach to clean blood spills
- No sharing of toothbrushes or razors
- No donation of blood, organs or sperm

Unrestricted activities regarding transmission risk[3]

- Participation in all activities including contact sports
- Sharing of food and utensils
- Kissing
- Attendance at day care or school

Precautions to slow liver injury

- Minimisation of alcohol intake
- Management of obesity, diabetes and hypercholesterolemia
- Vaccination against hepatitis A

Table 3. Screening for HBV infection[3]

Screening is recommended in the following high risk groups:

- Individuals from areas of high and intermediate prevalence for HBV infection, including those from:
  - Asia (except Sri Lanka)
  - Africa
  - South Pacific Islands
  - Middle East (except Cyprus)
  - European Mediterranean (Greece, Italy, Malta, Portugal and Spain)
  - Spanish South America (Argentina, Bolivia, Brazil, Ecuador, Guyana, Suriname, Venezuela and the Amazon region of Colombia and Peru)
  - independent states of former Soviet Union
  - Eastern Europe (including Russia; excluding Hungary)
  - Caribbean
- Household and sexual contacts of HBsAg positive people
- Individuals who have ever injected drugs
- Individuals with multiple sexual partners or history of sexually transmitted disease
- Men who have sex with men
- Correctional facility inmates
- Individuals with chronically elevated ALT or AST*
- Hepatitis C virus- or HIV-infected individuals
- Patients undergoing renal dialysis
- All pregnant women

* AST = aspartate aminotransferase.

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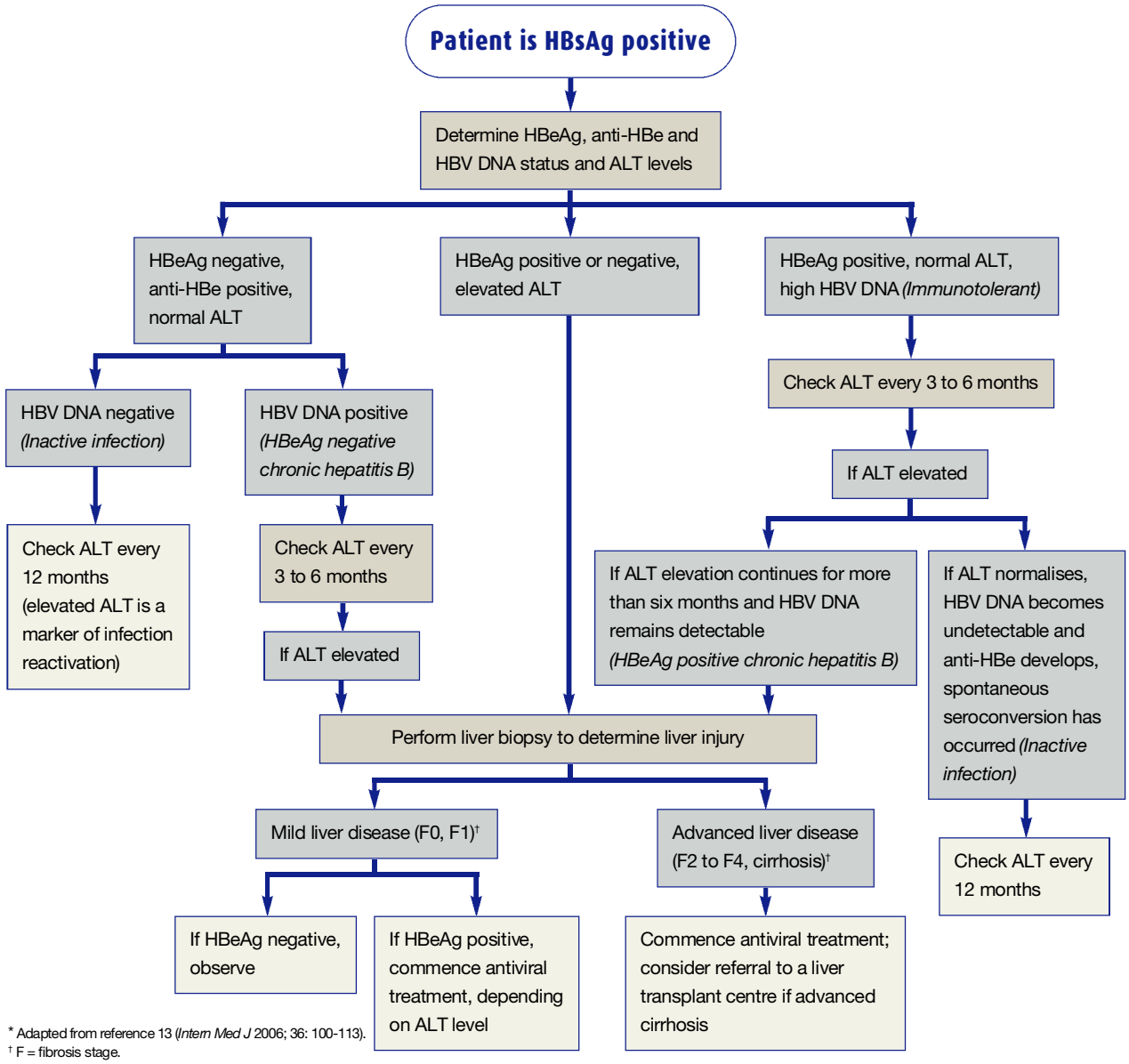
Management strategies for chronic hepatitis B based on stage of infection*



* Adapted from reference 13 (*Intern Med J* 2006; 36: 100-113).
† F = fibrosis stage.

lower treatment response rates than do patients with ALT levels elevated to at least twice the upper limit of normal.

The management of chronic hepatitis is summarised in the flowchart above.[13]

Follow up of untreated patients

Patients not being treated for HBV infection require regular follow up to identify changes such as the transition from immunotolerant to immunoclearance phases, reactivation of hepatitis, development of mutant viral strains as well as favourable outcomes such as HBeAg and HBsAg seroconversion. One study of 269 noncirrhotic patients who underwent spontaneous HBeAg seroconversion showed that over a nine-year period, 33% developed a raised ALT, 23% developed a precore mutant and 55% underwent HBeAg reversion to wild type virus.[5]

Most clinicians agree with the concept that cirrhosis risk is only significantly increased in patients with ongoing active hepatitis. However, a recent landmark natural history paper from Taiwan in a large cohort of patients aged over 30 years suggests that an elevated HBV viral load is a significant independent risk factor for the development of cirrhosis and HCC,

continued

Table 4. Screening for HCC[3]

Screening is recommended in the following HBV-infected individuals:

- Asian men aged over 40 years
- Asian women aged over 50 years
- Those with cirrhosis
- Those with a family history of HCC
- Africans aged over 20 years
- Those aged over 40 years with raised ALT and/or HBV DNA >2000 IU/mL

regardless of ALT level.[14] While this study was limited by its cross-sectional nature, it is likely to influence thinking about the way we treat chronic HBV infection in the future, and should be remembered in the context of ongoing follow up of untreated patients. Finally, untreated individuals who are considered high risk for HCC should undergo screening as outlined.

Treatment options

The treatments available in Australia for chronic HBV infection are the immunomodulator alfa-interferon (in standard or pegylated formulation) and the nucleotide/nucleoside analogues lamivudine (3TC, Zeffix), adefovir (Hepsera) and entecavir (Baraclude). For most patients, antiviral therapy will be initiated and followed-up in specialist clinics.

Alfa-interferon

Conventional alfa-interferon

Until just over 10 years ago, conventional interferon (interferon alfa-2a [Roferon-A] and -2b [Intron A, Intron A Redipen]) was the only proven therapy for chronic hepatitis B. As well as being an immunomodulator, interferon acts via direct antiviral and antiproliferative pathways. A meta-analysis of 15 controlled trials in HBeAg positive disease suggested that three to six months of therapy (twice or thrice weekly injections) led to loss of HBeAg and undetectable HBV DNA in 33% and 37% of patients respectively, both of which values were 20% greater than in the control group.[8] In HBeAg negative patients, in whom treatment response is usually defined as sustained viral suppression, five years after completion of treatment 18% of patients treated for six to 12 months and 30% of those treated for 24 months had continued viral suppression.[3]

Pegylated interferon

Having replaced conventional interferon as first line treatment for hepatitis C, pegylated alfa-interferon (peginterferon alfa-2a [Pegasys] is being increasingly used for chronic hepatitis B. Peginterferon is a long acting preparation that allows once weekly dosing while maintaining effective serum levels during the dosing interval. This has resulted in increased efficacy and tolerability in HCV treatment.

Large trials evaluating the use of peginterferon in HBeAg positive CHB have demonstrated HBeAg seroconversion rates of 29 to 36% and effective viral suppression rates of 32 to 34%, despite including patients with characteristics associated with poorer responses.[3,9] A large randomised study involving HBeAg negative patients found suppression of virus below detectable limits in 20% of peginterferon-treated patients compared to 7% of lamivudine-treated patients six months after completion of therapy. In all studies, the course of peginterferon was 48 weeks.[10]

Pros and cons of interferon therapy

Interferon-based therapies offer the major advantages of a finite period of therapy and lack of drug resistance development. Durability of the treatment response is also an important consideration; 70 to 90% of patients remain HBeAg negative up to eight years after conventional interferon-induced seroconversion.[3] A proportion of patients may have loss of surface antigen up to five years after the initial HBeAg loss. The response is less durable in HBeAg negative responders, with 70 to 85% relapsing over time.[3] There is little data to date regarding long-term outcomes with peginterferon.

The major disadvantage of the interferons is the adverse effects. Flu-like symptoms, fatigue, anorexia, weight loss, hair loss, emotional lability and mood disturbances are common. Although rare, suicide has been reported in patients on interferon therapy. Myelosuppression with neutropenia and thrombocytopenia can also occur, and regular monitoring is therefore required. Rarely, thyroid dysfunction and retinopathy have been reported. Furthermore, interferon therapy has been associated with dramatic ALT elevations ('ALT flares'), which in cirrhotic patients may cause decompensation (jaundice, ascites and encephalopathy). Hence, interferon therapy is relatively contraindicated in advanced cirrhosis.

The variable response rates and the potential for adverse events means patients should be carefully counselled regarding therapy with peginterferon. Features that predict favourable response rates include an elevated baseline ALT, moderate to low viral load, viral genotype A and B and increased inflammation on liver biopsy.

Nucleotide and nucleoside analogues

Of the three oral agents available in Australia for the treatment of hepatitis B, lamivudine and entecavir are used as first line therapy and adefovir is used for patients with lamivudine resistance. These drugs interrupt viral replication by inhibiting the enzymes necessary to produce HBV DNA. In general, they have a rapid onset of action in terms of suppressing viral replication and normalisation of ALT, and they can be used across a wide spectrum of clinical disease, including advanced cirrhosis. Patients also generally prefer them to the interferons because of the oral dosing, easy tolerability and minimal side effect profile. However, their significant

Consultant's comment

In Australia today, nearly as many people are infected with the hepatitis B virus as with the hepatitis C virus. A decade ago, the only available treatment for a select proportion of HBV-infected persons was interferon, administered on a thrice-weekly schedule. The current therapeutic arsenal includes pegylated interferon preparations and nucleoside and nucleotide analogues. Over the next decade, the range of options is likely to increase with immunomodulatory agents, newer nucleosides and nucleotides, combination therapies and, as well, drugs that target other parts of the hepatitis B virus replication cycle. This plethora of choices also suggests that the natural history of chronic hepatitis B virus infection is complex and that the available agents either are not suited for all patients or in fact are associated with problems that therefore mandate individualised therapy.

Primary care physicians diagnose most patients with chronic hepatitis B virus infection, and these practitioners triage individuals for either ongoing monitoring or antiviral therapy. Thus, an understanding of the natural history of chronic hepatitis B virus infection and its complications and available therapeutic options, and of decision making in its management, is paramount.

This article by Dr Ratnam and Dr Sievert has condensed what is a complex and rapidly changing field into a succinct account of the current management of patients with chronic hepatitis B. As the authors have attempted to demonstrate, therapeutic decisions are predicated on a sound understanding of the natural history and the phases of chronic hepatitis B virus infection. In turn, the therapeutic goal is to alter the natural history of chronic infection in order to reduce chronic hepatitis B-associated morbidity and mortality.

The principles outlined by in this article should take hepatitis B management in general practice out of the realms of mystery and into that of simple evidence-based guidelines.

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limitations include loss of efficacy due to the development of drug resistance and high relapse rates on stopping therapy, thus prolonged and often indefinite courses of therapy are required.

Lamivudine

The nucleoside analogue lamivudine has been widely used since it first became available in 1996. It is quick acting and effective, with significant reduction in the viral load beginning within the first week of treatment; 90% of patients receiving 100 mg daily show significant viral suppression by four weeks. Normalisation of ALT levels occurs in 60 to 70% of patients by six months.[3,9-12,15] Lamivudine has been shown to improve hepatic inflammation and fibrosis, and in a large trial of patients with advanced fibrosis or cirrhosis it reduced the incidence of hepatic decompensation and the development of hepatocellular carcinoma by 45% compared with untreated patients.[11]

The overall rate of HBeAg seroconversion ranges from 16% with 12 months of lamivudine therapy to up to 50% after five years of continuous treatment. The most important determinant of seroconversion is the pretreatment ALT level since, as previously mentioned, the higher the baseline ALT then the higher the HBeAg seroconversion rate.[3] Hence an elevated ALT prior to the initiation of therapy is an important factor to consider when deciding on therapy.

Lamivudine therapy can be ceased following HBeAg seroconversion but relapse rates can be as high as 23 to 40% in certain settings (such as short treatment duration, advanced disease and older age groups). Therefore, to minimise relapse, treatment is often continued for six to 12 months after seroconversion. In the absence of seroconversion, cessation of therapy is almost invariably associated with a recurrence of active hepatitis. Similarly, relapse rates of more than 90% are seen in HBeAg negative disease when therapy is stopped after one year;[3] consequently this group of patients is usually committed to an indefinite course of therapy.

The main shortcoming of lamivudine monotherapy is the high rate of drug resistant HBV mutants developing over time. Resistance can occur in up to 32% of cases after one year of lamivudine treatment and in up to 60 to 70% after five years of continuous therapy.[3,9-11,15] The length of time on treatment and suboptimal viral suppression are the main risk factors for the development of resistance. The clinical significance of resistance is that recurrent viral replication leads to increased disease activity, which in some cases can lead to acute exacerbations associated with hepatic decompensation and, rarely, death.

Adefovir

The nucleotide analogue adefovir works in a similar manner to lamivudine. In a large placebo controlled study, HBeAg positive patients who received adefovir dipivoxil 10 mg daily versus placebo for 48 weeks achieved undetectable levels of HBV DNA in 21% *v.* 0%, histological improvement in 53% *v.* 25%, and HBeAg seroconversion in 12% *v.* 6%.[15] Therapy in HBeAg negative patients resulted in undetectable DNA levels in 50% of patients at one year increasing to 70% at two years, which was maintained after five years of therapy.[12]

Compared with lamivudine, adefovir suppresses viral replication more slowly but development of resistance is not as

common. Early trials showed no resistance after one year of therapy, however long term follow-up data in HBeAg negative patients suggest rates as high as 20% after 4.5 years.[3,12]

Adefovir is effective against lamivudine-resistant strains and is currently only subsidised in Australia for this indication as monotherapy after an initial three-month overlap with lamivudine. There is increasing evidence, however, that a strategy of sequential monotherapy leads to higher rates of adefovir resistance when compared to using two agents that are not cross-resistant in combination (21% *v.* 0% resistance rates).[3]

Entecavir

The nucleoside analogue entecavir is the newest oral antiviral agent available for the treatment of hepatitis B. It is a highly potent inhibitor of HBV replication with low rates of resistance in previously untreated patients (less than 3% after two years). A large study comparing entecavir with lamivudine in over 700 HBeAg positive, treatment-naïve patients for one year showed undetectable HBV DNA in 67% *v.* 36% and histological improvement in 72% *v.* 62%; however, HBeAg seroconversion rates were similar at 21% *v.* 18%.[16] Another study in HBeAg negative disease showed effective virological suppression in 90% *v.* 72% and histological improvement in 70% *v.* 61%.[17]

Entecavir (0.5 mg/day) is available as a first-line therapy due to its efficacy and low rate of antiviral resistance. It is also used as a second-line agent at a higher dose of 1 mg/day due to its effectiveness against both lamivudine-resistant and adefovir-resistant strains. However, entecavir resistance is more likely to occur in patients with lamivudine resistance, and therefore it should not be used in such patients when adefovir is available.[16,18]

Newer nucleotide and nucleoside analogues

Tenofovir, telbivudine and clevudine are some of the newer agents that are currently in late stage clinical trials for the treatment of chronic hepatitis B. Of these, tenofovir appears to be the most promising, with evidence of good antiviral efficacy and low rates of resistance.

HBV and hepatocellular carcinoma

Chronic HBV infection confers a 100-fold increased risk of developing HCC compared to noninfected individuals. While the development of cirrhosis increases the risk of HCC significantly, between 30 and 50% of cases of HBV-related HCC develop in noncirrhotic livers, especially in Asian patients. While HBeAg and HBV viral load are significant independent risk factors for developing HCC, the presence of HBsAg alone confers a considerable increase in risk.[3,18]

Surveillance for HCC, using six- to 12-monthly ultrasound and measurement of serum -fetoprotein levels, is recommended for individuals at high risk (Table 4). In HBV-infected individuals without an additional risk factor as outlined, screening is not cost effective. Liver transplantation and surgical resection offer the best chance of long-term disease-free survival; transarterial chemoembolisation and radiofrequency ablation are commonly used palliative therapies.

Conclusion

The management strategy employed in a patient with chronic HBV infection depends on the natural history stage of the infection. The strategies include observation of patients who are in the immunotolerant stage of infection or who have inactive infection and antiviral therapies in patients with evidence of active viral replication and associated inflammation and fibrosis in the liver. Education of infected patients to minimise transmission risk is a cornerstone of management. Patients with cirrhosis should always be treated to reduce the risk of developing liver failure and HCC and to improve mortality.

Interferon-based therapies are effective in selected patients and provide durable responses but have significant side effects. Lamivudine can suppress viral replication and induce HBeAg seroconversion but is prone to development of antiviral resistance and loss of efficacy. The newer nucleotide/nucleoside analogues show considerable promise with effective viral suppression and lower rates of resistance but the long term outcomes are yet to be established. It is likely that in future, a combination therapy strategy may become the standard of care for chronic hepatitis B because of lower rates of resistance.

Patients with inactive disease, those in the immunotolerant phase or those with low level activity not on treatment require regular monitoring to identify a change in clinical stage that may require therapy.

Surveillance for HCC with six- to 12-monthly ultrasound and measurement of serum -fetoprotein levels is indicated in individuals at high risk. MT

A list of references is available on request to the editorial office

DECLARATION OF INTEREST: Dr Ratnam: None. Dr Sievert is serving on advisory boards for Bristol-Myers Squibb, Gilead, Schering-Plough, Roche, Novartis, Glaxo and Bayer and has received contract/grant funding from Schering-Plough, Roche, Gilead and Bristol-Myers Squibb.

Medicine Today 2007; 8(11): 24-35

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