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SPECIAL REPORT

Asian-Pacific consensus statement on the management of chronic hepatitis B: An update*

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For the Asian-Pacific Consensus Working Parties on Hepatitis B

INTRODUCTION

Since the Asian-Pacific consensus on the management of hepatitis B was published in 2000[1], large volumes of new data on the treatment of chronic hepatitis B have become available. These include events following the emergence of YMDD mutations; durability of response to lamivudine therapy; lamivudine therapy in pediatric patients, patients with decompensated liver disease and hepatitis B surface antigen (HBsAg) positive organ (other than liver) transplantation recipients. In addition, the results of phase III clinical trials of adefovir dipivoxil and phase II studies of entecavir, pegylated interferon and combination therapy are emerging. The American Association for the Study of Liver Diseases (AASLD) has published its guidelines on chronic hepatitis B[2]. The European Association for the Study of the Liver (EASL) also held its own consensus conference on hepatitis B in September 2002 (unpubl.). In addition, issues related to hepatitis B virus (HBV) genotypes have attracted much attention. It was anticipated that relevant new data and new insights on the management of chronic hepatitis B would emerge and thus, the guidelines or recommendations may have to be updated periodically.

We have since monitored the progress and invited experts from the Asian-Pacific region to meet in Bangkok in February 2002 to review relevant new data and debate the significance of the reported findings in order to institute an update of the 'consensus'. The year 2000 'consensus on the management of chronic hepatitis B' was revised accordingly. The revision was circulated for further comments and it was refined through electronic communications among the experts. The revised contents were presented and discussed at the biennial meeting of the Asian Pacific Association for the Study of the Liver (APASL) in Taipei on 27 September 2002. Recommendations were also circulated to several international experts for wider comment and input. The following is the finalized version of the updated consensus and recommendations for the management of chronic hepatitis B.

CONCEPTUAL BACKGROUND

Hepatitis B virus pathogenesis and natural course

Chronic HBV infection is a serious clinical problem because of its worldwide distribution and potential adverse sequelae. It is particularly important in the Asian-Pacific region where the prevalence is high. In this part of the world, HBV infection is usually acquired perinatally or in early childhood. Some patients may be concurrently infected with other hepatotrophic viruses.

Better understanding of the molecular biology and pathogenesis of HBV has revealed that covalently closed circular DNA (cccDNA) plays a key role in the maintenance of chronic HBV infection. As HBV is not usually cytopathogenic by itself, chronic HBV infection is a dynamic state of interactions between the virus, hepatocytes and the host immune system. Accordingly, the natural course of chronic HBV infection can be divided into three consecutive phases: (i) immune tolerance; (ii) immune clearance and; (iii) the residual phase.

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During the immune clearance phase, hepatitis flares may occur, and these may be complicated by hepatic decompensation. These flares or exacerbations are the result of a class I histocompatibility antigen (HLA)-restricted, cytotoxic T lymphocyte (CTL) mediated response against HBV antigen(s) expressed on hepatocytes with resultant apoptosis. This is eventually followed by hepatitis B e antigen (HBeAg) seroconversion to its antibody (anti-HBe). Seroconversion is associated with clinical remission, although reactivation may occur due to HBeAg reversion or the occurrence of HBeAg negative HBV-DNA positive hepatitis[3]. The natural history of HBeAg negative HBV-DNA positive chronic hepatitis in the Asian-Pacific region is not well studied, but hepatitis flares and disease progression do occur[4]. The severity, extent, duration and frequency of hepatic lobular alterations during hepatitis flares tend to determine the disease outcome and clearance of HBV[3].

HBV genotype distribution varies within the Asian-Pacific region and there are remarkable differences in the clinical and virological characteristics (including response to therapy) between patients with different genotypes[5]. In spite of the above, viral clearance is the key to the reduction or prevention of hepatic injury and disease progression.

Goals of treatment

The primary goal of treatment for chronic hepatitis B is to eliminate or permanently suppress HBV. This will decrease pathogenicity and infectivity, and thereby stop or reduce hepatic necroinflammation. In clinical terms, the short-term goal of treatment is to reduce hepatic inflammation, to prevent the development of hepatic fibrosis and/or decompensation, to ensure a sustained loss of HBV-DNA and alanine aminotransferase (ALT) normalization. The long-term goal is to prevent ALT flares that may lead to hepatic decompensation, to prevent progression to cirrhosis and/or hepatocellular carcinoma (HCC), and ultimately prolong survival.

Currently available treatments

Several potentially effective agents with different mechanisms of action have entered clinical practice or clinical trials. Among these, alfa-interferon and lamivudine have been widely studied, and their use has been licensed in many countries. As a result, substantial experience in the use of these agents has been accumulated. Adefovir dipivoxil has also been approved by the US Food and Drug Administration (FDA) since September 2002 and will soon be commercially available in Europe, Asia and other parts of the world.

Interferon α

In HBeAg positive patients with ALT greater than three times the upper limit of normal (ULN), the response rate assessed 6–12 months after the end of interferon therapy is approximately 30–40% compared to 10–20% in matched controls. In this group of patients, interferon 5 MU tiw for 4–6 months can be effective in Asian patients, but the response rate is slightly lower than that in Caucasian patients due to relative immune tolerance subsequent to early life exposure. However, the response rate is comparable in Asian patients with abnormal ALT[6]. There is emerging evidence that treatment for longer than 12 months may improve the rate of HBeAg seroconversion, particularly in those with lower HBV-DNA levels (< 10 pg/mL) after 16 weeks of treatment[6]. Children with chronic HBV infection and high ALT respond to interferon α (IFN-α) at rates similar to adults[7]. A preliminary study has shown that Pegylated IFN-α_{2a} monotherapy causes a rapid and profound reduction in HBeAg, resulting in a higher HBeAg seroconversion rate as compared with conventional IFN-α_{2a}[8]. This needs to be confirmed by further phase III studies. In patients with a lower pretherapy ALT level (1.3–3 × ULN) the HBeAg seroconversion rate is lower. This rate may be improved by corticosteroid priming prior to interferon therapy[9]. However, severe side-effects have been reported with this approach, particularly when used in patients with advanced liver disease[10,11].

When HBeAg seroconversion to anti-HBe is achieved, it is sustained in more than 80% of cases[12,13]. It may also be followed by HBsAg loss during long-term follow-up, although this is very rare in Asian patients.

Patients with HBeAg negative HBV-DNA positive active hepatitis also respond during interferon therapy but usually relapse after the end of therapy. Retreatment of patients who relapsed with IFN-α showed a response rate of 20–40% in both HBeAg positive and negative patients[14].

Spontaneous HBeAg seroconversion is usually associated with excellent prognosis, although HBeAg negative HBV-DNA positive hepatitis may occur[4]. Long-term follow-up studies suggest that interferon-induced HBeAg seroconversion confers similar benefits in terms of survival, liver failure and HCC[12,13]. However, interferon treatment is usually associated with side-effects, especially flu-like symptoms, neutropenia and thrombocytopenia, which are usually tolerable but may require dose modification[6]. Interferon therapy induced hepatitis flares may lead to decompensation in patients with cirrhosis. It may be dangerous in patients with decompensated liver function despite dose reduction[15].

Thymosin α_1 and other immunomodulating agents

A few studies have evaluated the efficacy of thymosin α_1, which is an immunomodulating agent able to enhance the Th_1 immune response. One study showed that the sustained response rate to subcutaneous thymosin α_1 (1.6 mg twice weekly for 6 months) was 40% (compared to 9% in controls) when assessed 12 months after the end of therapy[16]. A meta-analysis of controlled trials also suggests that thymosin α_1 works by inducing a delayed response 6–12 months after the end of therapy.

However, more studies are needed for confirmation. Other immunomodulating therapies, including therapeutic vaccines and IL-12 are being investigated[17].

Direct antiviral agents

Several nucleoside analogs (e.g. adenine arabinoside, fialuridine, and lobucavir) were found to be effective but significant toxicity precluded their further evaluation. Famciclovir is able to suppress HBV replication but phase III trials show that it has limited efficacy. Lamuvidine has been shown to be highly effective in inhibiting HBV replication. Adefovir dipivoxil and entecavir are also effective. Emtricitabine, clevudine, LdT and other new nucleoside analogs are in various stages of appraisal[18]. Lamivudine has been approved worldwide since 1998 and adefovir dipivoxil has also been approved by the US FDA since September 2002.

Lamivudine

Lamivudine has been shown to be effective in terms of HBV-DNA suppression, ALT normalization and improvement in histology in both HBeAg positive and HBeAg negative/HBV DNA positive patients[19–21]. In those with HBeAg, one year of therapy with lamivudine (100 mg daily) produces HBeAg seroconversion in proportion to pretreatment ALT level: 64% (compared to 14% with placebo) in patients with ALT > 5 × ULN, 26% (compared to 5%) in patients with ALT 2–5 × ULN and only 5% (compared to 2%) in those with ALT < 2 × ULN[22]. This indicates that patients with a more vigorous immune response to HBV respond better to the direct antiviral effect of lamivudine therapy. Children treated for one year with lamivudine in dosages adjusted for body weight (3 mg/kg) showed a similar response[23]. Hepatitis flares, sometimes severe, may occur if lamivudine is stopped before HBeAg seroconversion[24].

Prolonged therapy increases the proportion of HBV-DNA loss and HBeAg seroconversion. In patients with pretreatment ALT ≥ 2 × ULN, the rate of HBeAg seroconversion is 65% at 3 years and 77% at 5 years[25]. When HBeAg seroconversion to anti-HBe is achieved, it is sustained in 30–80% of cases[20,26]. The durability of response is particularly low if treatment is maintained for less than 4 months after HBeAg seroconversion[26]. Hepatitis flares may occur in patients whose response is not durable, and these are usually associated with the reappearance of HBeAg (HBeAg reversion)[26]. In HBeAg negative/HBV-DNA positive hepatitis B, the antiviral and therapeutic impact of lamivudine is similar to that in patients with HBeAg positive chronic hepatitis[21]. It is, however, difficult to define a treatment end-point and a sustained antiviral response is obtained in only 15–20% of cases after one year of treatment. Longer treatment duration studies are in progress.

Lamivudine is well tolerated with few serious adverse effects and is safe in patients with decompensated cirrhosis[27].

After 6–9 months of lamivudine therapy, HBV mutants that are resistant to lamivudine start to emerge. These HBV variant species have mutations in the YMDD motif of the polymerase gene. The incidence increases with increasing duration of therapy (approximately 70% among patients treated with lamivudine continuously for 5 years)[18,25].

The emergence of YMDD mutations is associated with the reappearance of HBV-DNA (this must be distinguished from viral rebound due to non-compliance) and frequently with ALT elevation. Although ALT values usually do not reach pretreatment levels, hepatitis flares may develop and this is sometimes associated with hepatic decompensation[28]. The benefit of long-term lamivudine therapy must therefore be balanced against concerns about any possible harm or risk associated with YMDD mutations and the durability of treatment response.

The combination of lamivudine and interferon appeared to increase the HBeAg serocnversion rate, particularly in patients with pretherapy ALT levels of 2–5 × ULN[29,30]. Pegylated IFN and lamivudine combination trials are in progress and preliminary results are very encouraging.

Adefovir dipivoxil and entecavir

Recent studies have shown that adefovir dipivoxil (ADV) and entecavir are effective in suppressing both wild type HBV and HBV with YMDD mutations[31,32]. ADV was not associated with any viral resistance after one year of therapy in both HBeAg-positive and negative patients[33]. However, well-controlled comparative data between lamivudine and ADV are still not available. ADV in high dosages causes renal damage and must be used with caution in patients with impaired renal function.

Traditional Chinese medicines and other herbal medicines

Traditional Chinese medicines and other herbal medicines (complementary/alternative medicine) have been reported as having some therapeutic potential in the treatment of chronic HBV infection, but require further large scale randomized control trials to confirm their efficacy[34].

Special groups of patients

There is insufficient data to reach firm conclusions on the management of pregnant patients, patients with concurrent hepatitis C virus (HCV) and/or hepatitis D virus (HDV) infections, human immunodeficiency virus (HIV) positive patients, immunosuppressed patients and patients with extrahepatic manifestations[14]. Recent studies have shown that patients with decompensated liver disease respond well to lamivudine

therapy[27,35,36]. As mentioned earlier, children with elevated ALT respond to IFN and lamivudine in a similar manner to adults[7,23]. For HBsAg positive organ transplantation recipients and HBsAg positive cancer patients undergoing chemotherapy, lamivudine is effective in the treatment of HBV reactivation, particularly if it is used pre-emptively[37–40]. For HIV positive patients with chronic hepatitis B, lamivudine included in triple therapy is effective in the suppression of HBV, but prolonged therapy is associated with a higher incidence of YMDD mutations. This may induce more severe liver disease in post-transplant settings, than in HIV negative patients.

General management

Besides drug therapy directed at liver disease, counseling of the patient is also very important. This should include information on the infectivity/transmission of HBV and preventive measures such as vaccination for family members, advice on alcohol use, risk behaviors and factors that predispose to superinfection with other hepatitis viruses and their prevention, the importance and need for careful follow-up and long-term monitoring, and possible therapy. The indications, the risks/benefits and advantages/disadvantages of each therapeutic option should be explained in detail. Careful assessment on an individual basis is absolutely essential before starting therapy.

ISSUES AND RECOMMENDATIONS

Indications for treatment

Currently, interferon and lamivudine are the two drugs licensed worldwide. Available information suggests that patients with normal ALT respond poorly to both interferon and lamivudine. Therefore, no drug treatment is recommended for them. However, they should be followed-up and monitored every 3 months if HBeAg is positive and every 6 months if HBeAg negative. Surveillance for HCC using ultrasonography and serum alphafetoprotein every 3–6 months is also important for high risk HBV infected persons (e.g. male, age > 40, cirrhotics, positive family history of serious liver disease)[41]. In contrast, patients with active HBV replication (HBeAg and/or HBV-DNA positive) and raised ALT are candidates for treatment. Liver biopsy is recommended before therapy to determine the fibrotic stage, to assess the necroinflammatory grade, and to exclude other possible causes of raised ALT as a guide to the indication for antiviral treatment.

Recommendation 2.1

Patients with persistently normal ALT should not be treated but need adequate follow-up and HCC surveillance every 3–6 months.

Recommendation 2.2

Liver biopsy is recommended in viraemic patients with raised ALT prior to therapy.

When to start treatment?

For patients with an ALT level $\geq 2 \times$ ULN, treatment may be started if ALT is persistently elevated (at least 1 month between observations).

Recommendation 2.3

HBV-DNA seropositive patients with ALT $> 2 \times$ ULN should be considered for treatment.

Patients with rising ALT (from normal or minimally elevated levels) or with ALT $> 5 \times$ ULN may be developing an exacerbation and severe hepatitis or hepatic decompensation may follow, particularly in patients with advanced fibrosis. Therefore, they should be monitored closely with weekly or biweekly serum bilirubin level and prothrombin time measurements. Treatment must be initiated in time to prevent the development or deterioration of hepatic decompensation. Conversely, such exacerbations may also precede spontaneous HBeAg seroconversion and may be followed by disease remission. Because of this, it is acceptable to delay treatment for an observation period of 3 months if there is no concern about hepatic decompensation.

Which drugs or strategy?

For viraemic patients (both HBeAg positive and HBeAg negative adults and children) with an ALT level $> 5 \times$ ULN, lamivudine is recommended if there is a concern about hepatic decompensation because of its rapidity of action. Interferon therapy is also more effective in patients with higher ALT. However, interferon therapy is not generally recommended under such conditions because its therapeutic effect is not immediate and the patient may become decompensated. Interferon may carry the potential to precipitate decompensation in patients with cirrhosis.

For HBeAg positive patients with an ALT level between 2 and $5 \times$ ULN, the choice between interferon and lamivudine is less clear and either agent may be used. In making the choice between lamuvidine and IFN, patients and their doctors should consider the differences in duration, cost of treatment and profile of adverse effects of each agent.

Corticosteroid priming before interferon or lamivudine therapy is not generally recommended and should be used cautiously and only in expert centers and in patients with suspected mild disease. Other combinations or strategies should be evaluated.

For HBeAg negative patients with intermittent or persistent increase in ALT, moderate to severe inflammation and fibrosis on biopsy, and high serum HBV

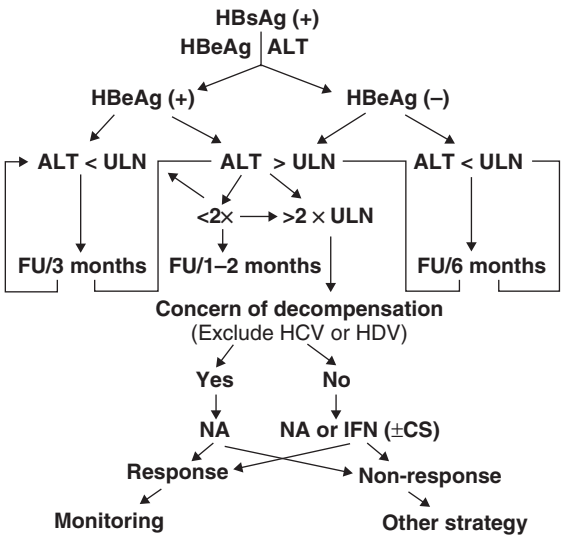

Figure 1 Summary of the Asian-Pacific consensus on the management of chronic hepatitis B. ALT, alanine aminotransferase; CS, corticosteroid; Fu, follow-up; HCV, hepatitis C virus; HDV, hepatitis D virus; HBeAg, hepatitis B early antigen; HBsAg, hepatitis B surface antigen; IFN, interferon; NA, nucleoside or nucleotide analogs; ULN, upper limit of normal.

DNA levels ($>10^5$ copies/mL), a 12-month course of interferon induces a higher rate (24%) of sustained response than a similar course of lamivudine (13%)[14,42]. Lamivudine could be an option but long-term treatment is required and the benefits of treatment must be weighed against the consequences of resistant mutations. In addition, the long-term effect of interferon therapy are better known than that for lamivudine. The decision to treat should be an individual one based on disease severity, history of flares, hepatic function, side-effects and the cost of drugs, and patient choice. (Fig. 1)

Recommendation 2.4

Patients can be treated with either lamivudine or interferon. Lamivudine is recommended if there is a concern about hepatic decompensation.

How to monitor therapy?

To achieve the most cost-effective treatment, adequate monitoring during and after treatment is important.

Recommendation 2.5

During therapy, ALT, HBeAg and/or HBV-DNA (quantitative method) should be monitored at least every 3 months. During interferon therapy, the monitoring of adverse effects is mandatory.

Recommendation 2.6

After the end of therapy, ALT and HBV markers (including HBV DNA) should be monitored monthly for the first 3 months for early relapse and then every 3 months (for cirrhotic patients and those who remain HBeAg/HBV-DNA positive) to 6 months (for responders). For non-responders, further monitoring is required to recognize a delayed response and to plan retreatment when indicated.

When to stop therapy?

The recommended duration of interferon therapy for HBeAg positive hepatitis is 4–6 months irrespective of whether or not a response has occurred. For HBeAg positive non-responders and HBeAg negative patients, 12 months therapy is more beneficial. A 6–12 months observation period after the end of interferon therapy is also recommended to detect delayed response, and to establish whether a response is sustained and thus, whether retreatment or other therapy is required.

In lamivudine therapy, in view of the fact that YMDD mutants may emerge during prolonged therapy, it is suggested therapy stop if the patient has undergone HBeAg seroconversion with HBV-DNA loss (by sensitive quantitative PCR methods and at least $<10^5$ copies/mL) in two consecutive measurements at least 6 months apart. For those who remain HBeAg positive after one year of lamivudine therapy, the decision to continue or to stop therapy should be evaluated individually on the basis of clinical/virological response and disease severity. For HBeAg negative patients, the optimal duration of treatment is unknown and the decision to stop therapy should be determined by clinical response and severity of underlying liver disease.

Recommendation 2.7

For interferon, the current recommended duration of therapy is 4–6 months.

Recommendation 2.8

For lamivudine in HBeAg positive patients, treatment can be stopped when HBV DNA loss with HBeAg seroconversion is documented on two separate occasions 6 months apart.

What to do for patients in special circumstances?

Interferon is usually contraindicated or requires dose modification because it may be associated with severe side-effects in patients with decompensated liver disease.

Recommendation 2.9

Lamivudine is the agent of choice for patients with impending or obvious features of hepatic decompensation.

HBV reactivation is well recognized as a serious complication in immunosuppressed patients, including those undergoing chemotherapy and taking immunosuppressives. It commonly occurs after the first 2–3 cycles of chemotherapy. Lamivudine therapy is effective when instituted early before there is obvious jaundice and decompensatation. Prophylactic suppression of HBV during the course of chemotherapy is a feasible approach[37–39].

Recommendation 2.10

For immunosuppressed patients, lamivudine is the preferred treatment and interferon is usually ineffective or even contraindicated in the setting of organ transplantation. HBsAg positive patients undertaking immunosuppressives or chemotherapy need close monitoring for reactivation and must start lamivudine therapy promptly before decompensation develops.

For the treatment of those with concurrent HCV and/or HDV infection, data are limited and further studies are required.

For those patients being treated with lamivudine in whom YMDD mutants have emerged, current practice is usually to continue lamivudine therapy in order to further suppress or prevent the return of wild type HBV. However, recent studies indicate that this practice does not always seem to benefit patients. Studies have shown that adefovir dipivoxil and entecavir are effective for patients with YMDD mutants. Adefovir dipivoxil will be available shortly and can be used to 'rescue' such patients. If these 'rescue' drugs are not available, stopping lamivudine therapy with close monitoring may be an option in patients who develop YMDD mutants[43,44]. Further studies of the long-term outcome of such cases and the efficacy of adding a second antiviral agent are ongoing.

Unresolved issues and areas for further study

The treatment of chronic hepatitis B has advanced into the era of nucleoside analogs. However, the results are still unsatisfactory. In particular, the following issues remain unsettled:

- Should patients with an ALT level of 1–2×ULN be treated, and if so when and how?
- What is the role of HBV genotypes in therapy?
- What are the indications and duration of treatment with direct antiviral agents for patients with HBeAg negative HBV-DNA positive chronic hepatitis B?
- Which is the first choice among the currently available direct antiviral agents?
- Will any treatment strategy be shown to reduce the risk of HCC?
- Is there effective therapy for patients with concurrent HCV and/or HDV infection?
- What is the best strategy when YMDD mutants emerge during lamivudine therapy?
- What is the role for corticosteroid withdrawal or other immunomodulating agents?
- Do traditional Chinese medicines or other herbal medicines have a role in the treatment of hepatitis B?

The development of new drugs and new strategies, especially combination or sequential antiviral therapy, is the highest priority in further improving the outcomes of treatment.

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