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Review Article

Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2005 update

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Abstract *Background/Aims:* A large amount of new data on the treatment of chronic hepatitis B has become available such that the 2003 consensus statement requires revision and update. *Methods:* New data were presented, discussed and debated in an expert pre-meeting to draft a revision. The revised contents were finalized after discussion in a general meeting of APASL. *Results:* Conceptual background, including the efficacy and safety profile of currently available and emerging drugs, was reviewed. Nineteen recommendations were formed and unresolved issues and areas for further study were suggested. *Conclusion:* The current therapy of chronic hepatitis B is modestly effective but not satisfactory. The development of new drugs and new strategies is required to further improve the outcomes of treatment.

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Since the second version of Asian-Pacific consensus on the management of hepatitis B was finalized in September 2002 during the biennial meeting of APASL (1), adefovir dipivoxil has been approved globally, the EASL has published its consensus statement (2) and the AASLD has also updated its guidelines on chronic hepatitis B (3). In addition, large volume of new data on the treatment of chronic hepatitis B has become available. These include more studies on the events following the emergence of YMDD mutations, durability of response to lamivudine therapy, lamivudine therapy in patients with decompensated liver disease, in hepatitis B surface antigen (HBsAg) positive patients undergoing chemotherapy or organ (other than liver) trans-

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Table 1. Definition of frequently used terminology

Terminology	Definition
HBV markers	HBsAg, HBeAg, anti-HBe and HBV DNA
Minimally raised ALT	Serum ALT between upper limit and twice upper limit of normal
Hepatitis flare	Increase of serum ALT to $\geq$ 5 times ULN
Hepatic decompensation	Significant liver function abnormality as indicated by raised serum bilirubin and prolonged prothrombin time or occurrence of complications such as ascites
Inactive chronic HBV infection	HBsAg (+) anti-HBe (+) with undetectable serum HBV-DNA and normal ALT
Biochemical response	Normalization of serum ALT level
Undetectable serum HBV DNA	Serum HBV DNA below detection limit of assays (specially defined)
Virologic response	Undetectable serum HBV-DNA and HBeAg seroconversion, if appropriate
Sustained virologic response	Undetectable serum HBV-DNA and HBeAg seroconversion, if appropriate, for at least 6 months after stopping therapy
Viral breakthrough	Increase in serum HBV DNA by $\geq \log_{10}$ copies/ml during therapy

HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; ALT, alanine aminotransferase; ULN, upper limit of normal.

plantation and the role of hepatitis B virus (HBV) genotypes. The results of phase III clinical trial of adefovir, entecavir, pegylated interferon (IFN) and combination therapies are available or emerging. It is obvious that the guidelines or recommendations have to be updated. We have since monitored the progress and invited experts from the Asian-Pacific region to review relevant new data. A 2-day expert meeting was held in Taipei in October 2004 to discuss and debate the significance of the reported findings in order to institute an update of the 'consensus' again. The year 2003 'consensus' on the management of chronic hepatitis B (1) was revised accordingly. The key terms used in the statement were also defined (Table 1). Then, 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 APASL in New Delhi, India, on 14 December, 2004. The following is the finalized version of the updated consensus and recommendations on the management of chronic hepatitis B.

Conceptual background

HBV, 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, the majority of HBV infection is acquired perinatally or in early childhood. Some patients may be concurrently infected with other hepatotrophic viruses.

Previous studies revealed the presence of two replication pathways, namely episomal and integrated forms, and of reverse transcription process in HBV infection (4, 5). It has been suggested that covalently closed circular DNA plays a key role in the maintenance of chronic HBV infection (6). 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 in this geographic region can be divided into three phases: (i) immune tolerance, (ii) immune clearance and (iii) residual or inactive phase.

Immune tolerance phase is characterized by high HBV replication with little clinicopathological changes. During the immune clearance phase, hepatitis activity and even hepatitis flares with serum alanine aminotransferase (ALT) over five times upper limit of normal (ULN) may occur, and these may sometimes be complicated by hepatic decompensation. These ALT elevations and hepatitis flares are the results of the host's immune responses against HBV, such as HLA-class I antigen restricted, cytotoxic T lymphocyte (CTL)-mediated response against HBV antigen(s) expressed on hepatocytes with resultant apoptosis. Higher ALT levels, therefore, usually reflect more vigorous immune responses against HBV and more extensive hepatocyte damages. This is eventually followed by hepatitis B e antigen (HBeAg) seroconversion to its antibody (anti-HBe) and/or undetectable HBV-DNA (7). Up to 85% of HBeAg seroconversion is associated with clinical remission (inactive chronic HBV infection). However, reactivation or active hepatitis may occur because of HBeAg reversion or occurrence of HBeAg negative, HBV-DNA positive hepatitis (8, 9). The natural history of the HBeAg negative, HBV-DNA positive chronic hepatitis in the Asian-Pacific region has not been well studied, but it was demonstrated that hepatitis flares might also occur (8–10). A prospective study involving 684 patients with chronic hepatitis B showed that cirrhosis developed at an estimated annual incidence of 2.1%, and that the severity, extent, duration and frequency of hepatic lobular alterations during hepatitis flares tend to determine the disease outcome and clearance of HBV (11). One study

showed that 23% and 4.4% of patients with HBeAg negative hepatitis progressed to cirrhosis and hepatocellular carcinoma (HCC), respectively during a follow-up period of 9 (1–18.4) years (8). HCC may develop at an annual incidence of 3-6% in patients with cirrhosis and might also develop, but less frequently, in non-cirrhotic background (8, 12, 13). Even in incidentally identified asymptomatic subjects with chronic HBV infection, seropositivity for HBeAg and/or HBV-DNA are risk factors for cirrhosis and HCC (9, 14, 15). Spontaneous HBsAg seroclearance may occur and usually confers excellent prognosis (16). However, HCC may still occur though at a very low rate unless cirrhosis has already developed before HBsAg seroclearance (16, 17).

Based on an intergroup divergence of 8% or more in the complete genome nucleotide sequence, HBV has been classified into at least eight genotypes (18). Each genotype has its distinct geographical and ethnic distribution (18–20). Genotypes A and D occur frequently in Africa, Europe and India, while genotypes B and C are prevalent in Asia. Genotype E is restricted to West Africa, and F is found in Central and South America. Genotype G was reported in France, Germany and the United States. Recently, the eighth genotype H has been described in Central America. Even within the Asian-Pacific region, HBV genotype distribution varies. In addition, subtypes are identified within some genotypes (21, 22); however, their clinical significance remains to be examined (23).

Several studies have shown that compared with genotype C, genotype B is associated with spontaneous HBeAg seroconversion at a younger age (24–26), less active liver disease (27–29), slower progression to cirrhosis (30) and less frequent development of HCC (18, 27, 31, 32). A study from India indicated that genotype D is more often associated with HBeAg negative chronic hepatitis B, more severe diseases and may predict the occurrence of HCC in young patients (33).

Goals of treatment

It is clear that sustained viral suppression is the key to the reduction or prevention of hepatic injury and disease progression. Therefore, 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 ensure HBV-DNA sustained suppression, ALT normalization and prevent the development of decompensation (initial response), to reduce hepatic necroinflammation and fibrosis during and after therapy (maintained and sustained response). The ultimate long-term goal of therapy is to prevent hepatic decompensation, to reduce or prevent progression to cirrhosis and/or HCC, and to prolong survival (durable response).

Currently available treatments

Several potentially effective agents with different mechanisms of action have entered clinical practice or clinical trials. Several nucleoside analogues (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 showed that it had limited efficacy. Currently, interferon-α (IFN-α), lamivudine and adefovir have been licensed globally. Thymosin-α1 has also been approved in more than 30 countries, mainly in Asia. Peginterferon α-2a has been granted approval in some Asian and European countries and the approval process is underway in other countries.

IFN-α

Conventional IFN: IFN-α has been used for the treatment of chronic hepatitis B for over two decades. IFN-α has a dual mode of action: antiviral and immunomodulatory. Early controlled studies showed that a 4–6 month course of conventional IFN-α at a dose of 5 MU daily or 10 MU three times weekly achieved HBeAg loss in approximately 33% of HBeAg positive patients, compared with 12% of controls. A smaller dosage (5–6 MU three times weekly) has been used in Asian patients with similar efficacy (34, 35). 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 (36). Retreatment of relapsed patients with IFN-α showed a response rate of 20–40% (37). Children with chronic HBV infection and high ALT respond to IFN-α at rates similar to adults (38).

The HBeAg seroconversion rate is lower in patients with lower baseline ALT levels (1.3–3 × ULN). This rate may be improved by corticosteroid priming prior to IFN therapy (35). The recovery of immune function following steroid withdrawal may enhance the immunomodulatory effect of IFN. Severe side effects have been reported with this approach, particularly when used in patients with advanced liver disease (39, 40). When HBeAg seroconversion to anti–HBe is achieved, it is sustained in more than 80% of cases (41–43).

IFN therapy resulted in end of treatment biochemical and virological response in up to 90% of HBeAg negative, HBV-DNA positive

hepatitis patients. The sustained response, however, was disappointing: 10–15% with 4–6 months of treatment; 22% with 12 months of treatment and 30% with 24 months of treatment (44–47). A study from Taiwan showed that 6–10 months IFN therapy in HBeAg negative patients had an end of therapy response of 57% (vs 18% of controls) and 6 months sustained response of 30% (vs 7%) (48). IFN-α retreatment also resulted in a response rate of 20–40% for HBeAg negative patients (44).

A more recent meta-analysis of all studies utilizing conventional IFN-α for the treatment of chronic hepatitis B between 1987 and 1999 demonstrated that the probability of persistent ALT normalization, HBeAg clearance, sustained loss of HBV-DNA and HBsAg clearance was higher in the IFN treatment group compared with the no treatment group in both HBeAg positive and HBeAg negative patient subgroups (49).

Long-term follow-up studies suggest that IFN-induced HBeAg seroconversion is durable, could increase over time and results in better overall survival and survival free of hepatic decompensation (41, 42). The incidence of HCC is also lower in treated patients, especially in responders (42, 43, 46). However, whether the incidence of HCC is reduced in cirrhotic patients treated with IFN is less conclusive. Loss of HBsAg over time is rare in Asian patients (42).

The main advantage of IFN-α therapy is that a course of finite duration may achieve sustained off-therapy responses in a proportion of both HBeAg positive and HBeAg negative chronic hepatitis B patients. However, IFN treatment is usually associated with side effects, especially flu-like symptoms, fatigue, neutropenia, thrombocytopenia and depression. These are usually tolerable but may require dose modification and premature cessation of treatment (5%) (34, 50). IFN therapy-induced hepatitis flares may lead to decompensation in patients with cirrhosis and can be dangerous in patients with decompensated liver function despite dose reduction (40).

Pegylated IFN-α: Pegylated IFN-α (PegIFN-α) has replaced conventional IFN-α in the treatment of chronic hepatitis C because of its superior efficacy without increased toxicity and easier once-weekly administration. In an Asian study, a 24-week course of weekly PegIFN-α2a (40 KD) gave a higher HBeAg seroconversion rate (33%) 24 weeks after the end of treatment compared with conventional IFN-α2a (25%, $P > 0.05$). This benefit was noted even in patients with a rather low likelihood of response to conventional IFN (50). In a study of PegIFNα-2b (12 KD) involving mainly (79%) Caucasian patients, a 52-week course (100 μg once weekly for 32 weeks followed by 50 μg weekly for 20 weeks) was found to be well tolerated and gave a 6-month sustained HBeAg loss in 35% of patients and HBeAg seroconversion in 29% of patients (51). In a large-scale phase III international multicentre study involving 814 HBeAg positive patients (>85% were Asian), PegIFN-α2a (40 KD) monotherapy 180 μg once weekly for 48 weeks showed normal ALT in 41%, HBeAg seroconversion in 32%, HBV-DNA level $<10^5$ copies/ml in 32%, HBV-DNA levels <400 copies/ml in 14% and HBsAg seroclearance in 3% of the patients when assessed 6 months after the end of therapy (52). The sustained HBeAg seroconversion rate is similar to that after 6 months therapy though there is no head-to-head comparison between the 6 and 12 months therapy. PegIFN-α2a monotherapy in 564 HBeAg negative/anti-HBe positive chronic hepatitis B patients (>60% were Asian) showed normal serum ALT in 59%, HBV-DNA levels <20 000 copies/ml in 43%, HBV-DNA <400 copies/ml in 19% and HBsAg loss in 3% of the patients when assessed 6 months after the end of therapy (53). Similar efficacy was found in patients with ALT $<2 \times$ ULN. Peg IFN-α appeared superior to lamivudine in both HBeAg positive and HBeAg negative patients (52, 53).

Studies on conventional IFN therapy have shown that patients with genotype B HBV infection have a higher HBeAg seroconversion rate than genotype C patients (54, 55). Studies on Peg IFN have also shown that HBeAg seroconversion occurred more often in patients with genotypes B (33–44%) than in those with genotypes C HBV infection (21–28%) (50, 51), and more often in patients with genotype A (47%) than in those with genotype D HBV infection (25%) (51).

Combination with other agents: The role of IFN-α and lamivudine combination therapy in the treatment of chronic hepatitis B is not certain. In a large multinational study involving 230 HBeAg positive patients, HBeAg seroconversion on intention-to-treat analysis was not significantly better for patients on combination therapy, A per-protocol analysis, however, showed a significantly better benefit with combination therapy (36% vs 19%, $P = 0.02$), especially in patients with pretherapy ALT levels of 2–5 × ULN (56). IFN-α2b in combination with lamivudine for 24 weeks was found to give a sustained HBeAg seroconversion with undetectable levels of HBV-DNA (measured 48 weeks after the end of therapy) in 33% of patients compared with 11% of patients who took lamivudine monotherapy for 52 weeks (57). In HBeAg negative chronic hepatitis B, conventional IFN-lamivudine combination is no better than lamivudine monotherapy (58–59). There are also small studies on combination with other agents, including thymosin-α (60, 61) and ribavirin (62).

In a study in HBeAg positive Chinese patients, 8 weeks of PegIFN-α2b followed by 24 weeks of PegIFN-α2b and lamivudine combination and then by 28 weeks of lamivudine alone gave an end of treatment virological response of 60% compared with 28% with 52 weeks of lamivudine monotherapy. Sustained virological response (HBeAg seroconversion with HBV-DNA $<5 \times 10^5$ copies/ml 24 weeks after cessation of treatment) was 36% in the sequential combination group compared with 14% in the lamivudine monotherapy group. Patients were less likely to develop lamivudine-resistant mutants in the combination group (63). In an international multicentre study involving 266 HBeAg positive patients, 48 weeks with either PegIFN-α2b monotherapy or simultaneous PegIFN-α2b/lamivudine combination resulted in a similar rate of 24-week sustained HBeAg loss ($\sim$ 35%), ALT normalization ($\sim$ 33%) and HBV-DNA $<200\,000$ copies/ml ($\sim$ 30%) (51). PegIFN-α2a monotherapy and simultaneous PegIFN-α2a/lamivudine combination therapy had similar efficacy, which appeared to be superior to lamivudine monotherapy in both HBeAg positive and negative patients (52, 53). In addition, on-treatment HBV-DNA suppression was more profound with the combination regimen than monotherapy and rate of rtM204 V/I was reduced with combination therapy (52). Hence, there is a tendency for IFN or PegIFN and lamivudine combination to result in better sustained response than lamivudine monotherapy while PegIFN/lamivudine combination did not appear to be better than PegIFN monotherapy.

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, natural killer T cells and CD8+CTLs activity against HBV (64). One study showed that the response rate to subcutaneous $T\alpha_1$ 1.6 mg twice weekly for 6 months was 40% (vs 9% in controls) when assessed 12 months after the end of therapy (65). In keeping with these findings, a recent meta-analysis including 353 patients from five trials showed that the odds ratio for virological response to $T\alpha_1$ at the end of the treatment, 6 and 12 months posttreatment were 0.56 (0.2–1.52), 1.67 (0.83–3.37) and 2.67 (1.25–5.68), respectively, with a significantly increasing virological response over time after thymosin discontinuation (66). A meta-analysis of controlled trials also suggests that thymosin α_1 is effective in terms of delayed response after the end of therapy (44, 67). On the other hand, preliminary data on combination therapy with either IFN (60, 61) or nucleoside analogue (68) have shown promising results. However, the total number of patients ever included in the trials is relatively small, and more large-scale well-designed studies are needed to confirm its efficacy. The main advantages of thymosin α_1 are fixed duration of therapy and minimal side effects.

The concept that therapeutic restoration of antiviral immunity can lead to control of HBV replication and disease resolution in chronically infected patients has been directly demonstrated in chronic-HBV-infected patients undergoing bone marrow transplantation with marrow from donors with natural immunity to HBV. In this setting, the transplantation of a healthy immune system containing HBV-primed cellular and humoral immunity can lead to a resolution of HBV infection and HBsAg clearance. It has also been shown that HBsAg clearance is associated with the development of a strong HBV core-specific CD4 T-cell response and with the production of antienvelope antibodies (69). Thus, infusion of a healthy, HBV-primed, immune system can overcome chronic HBV infection, directly showing the therapeutic impact of the restoration of HBV-specific immunity. Other immunomodulating therapies, including therapeutic vaccines and IL-12, are still preliminary and await further study.

Direct antiviral agents
Lamuvidine and adefovir have been shown to be highly effective in inhibiting HBV replication. Lamivudine has been approved worldwide since 1998. Adefovir dipivoxil has also been approved by the US. FDA and then worldwide since September 2002. Entecavir has just been approved (in late March 2005). Emtricitabine, clevudine, telbivudine and other new nucleoside analogues are in various stages of appraisal.

Lamivudine: Lamivudine, a cyclic nucleoside analogue, is effective in terms of HBV-DNA suppression, ALT normalization and improvement in histology in both HBeAg positive and HBeAg negative/HBV-DNA positive patients (70–72). In HBeAg positive patients, HBeAg seroconversion correlates with pretreatment ALT level: 64% (vs 14% with placebo) in patients with ALT $>5 \times$ ULN, 26% (vs 5%) in patients with ALT 2–5 $\times$ ULN and only 5% (vs 2%) in those with ALT $<2 \times$ ULN at the end of 1-year therapy with lamivudine 100 mg daily (73). This indicates that patients with a more vigorous immune response to HBV respond better to the direct antiviral effect of lamivudine therapy (73, 74). Children treated for 1 year with lamivudine in dosages adjusted for body weight (3 mg/kg) showed similar response (75). In the absence of

HBeAg seroconversion, hepatitis flares may occur if lamivudine is stopped (76, 77).

Prolonged therapy increases the response rate (78, 79). More recent collective data based on a large database of almost 1000 patients documented modest overall rates of response in patients treated with long-term lamivudine. The rates of HBeAg seroconversion reported from this large cohort were 16%, 17%, 23%, 28% and 35% after 1, 2, 3, 4 and 5 years of lamivudine treatment, respectively (80). Uncontrolled studies in Asian patients with pretreatment ALT $\geq 2 \times$ ULN showed HBeAg seroconversion rate of 35–65% at the end of 3 years (81) and around two-third at the end of 5 years (78, 81). The response rate was even higher in patients with pretherapy ALT $> 5 \times$ ULN (79). The HBeAg seroconversion rate is similar between patients with genotype B or C HBV infection (77). When HBeAg seroconversion to anti-HBe is achieved, it is sustained in only 30–80% of cases after lamivudine is stopped (71, 81, 82). The durability of response is particularly low in patients with genotype C HBV infection, in older patients and if treatment is maintained for less than 4–8 months after HBeAg seroconversion (82, 83). Hepatitis flares may occur in patients with reappearance of HBeAg and detectable HBV-DNA (HBeAg reversion) (81, 82). 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 (72). It is difficult to define a treatment end point. Sustained antiviral response is obtained in only 15–20% of cases after 1 year of treatment. A study in 50 Chinese patients (78% with genotype C HBV) showed that a 2-year course of lamivudine therapy resulted in 74% viral response (PCR). In 37 patients who had had undetectable HBV-DNA by PCR and normal ALT on three separate occasions at least 3 months apart (at least 6 months), lamivudine therapy was stopped. The 1-year relapse rate was 50%, mostly (86%) in patients with genotype C infection (84).

Lamivudine is well tolerated with few serious adverse events and is safe, even in patients with decompensated cirrhosis (78, 80, 85). Long-term therapy in viremic patients with advanced fibrosis or cirrhosis delays clinical progression by reducing the rate of hepatic decompensation and HCC development, even in patients with low or normal ALT (86).

After 6–9 months of lamivudine therapy, breakthrough may start to occur because of HBV mutations that are resistant to lamivudine. These HBV variant species have mutations in the YMDD motif of the polymerase gene (rtM204I and rtM204V with or without rtL180M). The incidence increases with increasing duration of therapy and up to 70% among patients treated with lamivudine continuously for 5 years (78–80). Other important factors associated with the emergence of rtM204 I/V include baseline HBV-DNA, ALT and/or hepatitis activity (87). The emergence of genotypic rtM204 I/V detected by PCR is followed by phenotypic reappearance of HBV-DNA (this must be distinguished from viral rebound because of noncompliance) and ALT elevation in over 90% of patients during continuing lamivudine therapy (88). Hepatitis flares may develop and are sometimes severe and may be associated with hepatic decompensation (88, 89). One study showed that new and distinct YMDD mutants may be selected during continuing lamivudine therapy and elicit another hepatitis flare (90). The initial histologic improvement may be reversed in patients who were harbouring rtM204 I/V (91, 92). The benefit of long-term therapy in preventing disease progression in patients with advanced fibrosis or cirrhosis also decreased after emergence of rtM204 I/V (86, 93). The pros and cons of long-term lamivudine therapy must therefore be balanced taking into account the potential clinical benefit, possible risk associated with YMDD and other mutations and the durability of response after stopping therapy.

Combination therapy with lamivudine and adefovir or lamivudine and telbivudine showed better response and lower rates of resistant mutations than lamivudine monotherapy, but the efficacy was similar to adefovir or telbivudine monotherapy (94, 95). A pilot study in 30 Taiwanese patients showed that a short course of prednisolone priming enhanced Th1 response and efficacy of subsequent lamivudine therapy (96). A recent study from India has shown that 'lamivudine pulse' therapy is effective in patients with chronic hepatitis B who have normal ALT (97). Further studies need to be undertaken for this group of immune tolerant patients. Obviously, such an approach may be dangerous in patients with advanced fibrosis or cirrhosis.

Adefovir dipivoxil: Adefovir dipivoxil is a synthetic acyclic adenine nucleotide analogue. It is a potent inhibitor of HBV reverse transcriptase of the wild-type HBV, famciclovir-resistant and lamivudine-resistant mutants.

Two large international multicentre double-blinded, placebo-controlled studies have shown that 10 mg oral adefovir dipivoxil daily for 48 weeks is effective in terms of histologic improvement, HBV-DNA suppression, ALT normalization and HBsAg loss (1.6–2% vs 0%) in both

HBeAg positive and HBeAg negative CHB (98, 99). In HBeAg positive patients, HBeAg loss and HBeAg seroconversion also increased as compared with controls (12% vs 6%) (98). In patients with compensated chronic hepatitis B, the safety profile of adefovir dipivoxil 10 mg was similar to placebo. Renal laboratory abnormalities reported with adefovir dipivoxil 30 mg were not observed with 10 mg dosage in the 1-year study. Increase in serum creatinine was reported in 2.5% when therapy was extended to 3 years, but was reversible on stopping adefovir (100). Majority of patients with decompensated chronic hepatitis B, including pre- and postliver transplantation patients, have some degree of underlying renal insufficiency. Studies on these patients showed increases by ≥ 0.5 mg/dl from baseline in serum creatinine in 16% by week 48 and 31% by week 96, and 1% required discontinuation because of renal failure. The response observed among Asian and Caucasian patients was similar. Integrated analysis from all phase III clinical trials showed that HBV genotype does not influence virologic response, but a correlation with HBeAg seroconversion or durability of sustained response has not been determined (101). Patients who completed 144 weeks continuous adefovir dipivoxil therapy showed increased virologic, biochemical and histological response (100).

Sequenced RT domain of HBV-DNA polymerase identified rtN236T and A181 V mutations with decreased susceptibility to adefovir dipivoxil in patients on adefovir therapy longer than 1 year. The overall incidence of adefovir-resistance mutation is low. Integrated incidence rate was 0%, 3.0% and 5.9% at the end of each successive year of therapy. Adefovir-dipivoxil-resistant rtN236T mutant remains susceptible to cyclic nucleoside analogues lamivudine, emtricitabine, telbivudine and entecavir *in vitro* and may argue for their combination in therapy (102, 103).

In patients with lamivudine-resistant mutants, adefovir dipivoxil monotherapy or in combination with lamivudine induced serum HBV-DNA response in majority of the patients with a median reduction of 3.6–4.6 $\log_{10}$ copies/ml after 1 year (104). Normalization of ALT was achieved in 31–53%. Extending combination therapy for 2 years led to significantly more patients achieving HBV-DNA levels of <200 copies/ml by PCR. HBeAg seroconversion was 6–8% after 1 year of combination therapy, compared with 0–2% in lamivudine monotherapy and 11% in adefovir dipivoxil monotherapy. At week 104, HBeAg seroconversion increased to 12% on combination therapy (105). Although switching patients to adefovir dipivoxil monotherapy appeared to achieve good response, unexplained transient ALT flare occurred without associated increase in serum HBV-DNA level or reversion to wild-type HBV (106). A control study in 42 Korean patients with decompensated liver disease showed that switching to adefovir monotherapy was effective and safe (107). A cohort study on 18 Taiwanese patients with cirrhosis also demonstrated that switching to adefovir monotherapy was effective and safe in patients with cirrhosis, even in those with decompensation (Liaw YF 2005). A few patients who stopped adefovir dipivoxil after HBeAg loss or seroconversion tended to relapse (105).

The overall result with adevofir dipivoxil is promising. The main advantage over lamivudine is the low incidence of drug resistance and ability to suppress lamivudine-resistant mutants. Initial concern on renal toxicity appeared rare with 10 mg dosage and no patient had significant elevation of serum creatinine greater than 0.5 mg/dl in the clinical trial. Caution must be taken in treating patients with renal impairment. Studies on long-term therapy should be performed to address efficacy and durability of response, and to establish a safety profile. The cost effectiveness and risk-benefit of long-term adefovir dipivoxil should be addressed properly.

Other emerging direct antivirals: A number of promising oral nucleoside analogues is in the process of clinical assessment. Phase III clinical trials have shown that 1-year Entecavir is superior to lamivudine in reducing HBV-DNA in both HBeAg positive (6.98 vs 5.46 log, $P<0.0001$) (108) and negative patients (5.20 vs 4.66 log, $P<0.001$) (109). Switching to entecavir monotherapy is also effective in lamivudine-resistant patients (5.14 vs 0.48 log, $P<0.001$) and safe without the risk of ALT flare (110, 111). In HBeAg positive patients, HBeAg loss was documented in 27% of lamivudine-naive patients (vs 20% lamivudine treated, $P=0.045$) (108) and 10% in lamivudine-resistant patients (vs 3% lamivudine treated, $P=0.028$) (110). Entecavir resistance only developed in lamivudine-resistant patients in the 1-year studies (108–110).

Telbivudine suppresses wild-type HBV by 5–8 $\log_{10}$ and is more potent than lamivudine in a phase II 1-year study (94). The phase III clinical trial is ongoing. A dose finding study of clevudine showed an end of 4-week treatment HBV-DNA reduction of 2.5–3.0 $\log_{10}$ and notably a 6 month off therapy reduction up to 2.7 $\log_{10}$ (112). Clevudine 30 mg/day for 24 weeks resulted in HBV-DNA reduction of 4.64 $\log_{10}$, undetectable by PCR in 59%, HBeAg loss in 24% and ALT normalization in 76% (113). Tenofovir disoproxil fumarate exerts a strong and early suppression of

HBV with YMDD mutations and has a good safety profile (114).

Complementary/alternative 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. However, the quality of existing studies was poor (115). Further, large-scale randomized control trials are needed to confirm their efficacy.

Special groups of patients

Pregnancy

In pregnant mothers, no firm recommendation can be made on the use of nucleoside analogues in the prevention of transmission because of the lack of sufficient data and conflicting results with regard to efficacy and adverse events (116, 117). Women with chronic hepatitis B who become pregnant while on therapy can continue treatment, but the stage of the mother's liver disease and potential benefit of treatment must be weighed against the small risk to the fetus.

Patients with concurrent infection

Patients with concurrent infection, such as hepatitis C virus (HCV), hepatitis delta virus (HDV) infections and human immunodeficiency virus (HIV), tend to have a higher incidence of cirrhosis, HCC and mortality (118–120). There is insufficient data to reach firm conclusions on the management of patients with HCV and/or HDV infection. However, it is generally agreed that it is important to determine which virus is dominant in patients with concurrent HCV infection. If HBV is dominant, lamivudine or adefovir can be used while conventional IFN is of limited efficacy and suppression of HBV may result in HCV hepatitis (121). Higher dose (9 MU, trice weekly) IFN-α for 12 months may inhibit HDV RNA, normalize ALT and improve histology in 50% of the patients with chronic HDV infection, with ALT response sustained in 50% and significantly improved in the long-term outcome and survival (122).

Data on the effect of IFN-α against HBV in HIV coinfected patients are scarce. The available data showed that IFN-α 5 MU/day or 10 MU tiw for 16–24 weeks for HBeAg positive or >48 weeks for HBeAg negative patients were used (123, 124). Lamivudine 150 mg twice daily has been shown to be effective and well tolerated in CHB patients co-infected with HIV resulting in significant reductions in serum HBV-DNA levels (125). However, prolonged therapy with lamivudine is associated with a higher incidence of YMDD mutations (50% after 2 years and 90% after 4 years) (126). Patients may have hepatitis flares when lamivudine therapy is discontinued or when lamivudine resistance emerges (126, 127). Adefovir 10 mg daily is effective in HIV/HBV coinfected patients with lamivudine-resistant HBV, resulting in a 4 $\log_{10}$ drop in HBV-DNA and ALT normalization by 48 weeks (128, 129). Adefovir is generally well tolerated with no significant changes in HIV RNA levels or CD4 cell count (127). Tenofovir, a nucleotide reverse transcriptase inhibitor has been approved for the treatment of HIV infection and at the recommended dose has been shown to be active against wild-type and lamivudine-resistant HBV (114, 130). However, nephrotoxicity associated with the use of tenofovir has been reported.

Decompensated patients

Patients with hepatic decompensation should be considered for treatment as it may improve their overall health status and may even remove them from the liver transplant list. IFN has shown no benefit in patients with Child's B or C cirrhosis. Moreover, significant side effects because of serious bacterial infections and exacerbation of liver disease have occurred even with low doses (40). Lamivudine is well tolerated and results in clinical improvement especially in patients who completed a minimum of 6 months treatment (85, 131–137). Since improvement or stabilization usually takes 3–6 months, early treatment is recommended. An analysis of 154 patients confirmed the benefit of lamivudine only in patients who survived the first 6 months of treatment with estimated actuarial 3-year survival of 88% (136). The major concern with early treatment is selection of resistant mutants that may be associated with biochemical dysfunction, reduction in efficacy and rapid clinical deterioration, especially in patients with cirrhosis (86, 137). Adefovir has not been evaluated as primary treatment in patients with decompensated cirrhosis. A study of compassionate use of adefovir in 128 patients with decompensated cirrhosis and 196 patients with recurrent hepatitis B after liver transplantation showed that the addition of adefovir is associated with 3–4 log reduction in serum HBV-DNA levels throughout treatment (138). However, nephrotoxicity has been reported in 28% of patients with decompensated cirrhosis who received 1-year adefovir 10 mg (139). Close monitoring of renal function is required if this drug is being used for such patients.

Paediatric patients

Children with elevated ALT respond to IFN and lamivudine in a manner similar to adults (38, 75).

Newer agents such as Peg IFN and other nucleoside analogues including adefovir have not yet been studied in children with chronic HBV infection.

Patients on immunosuppression or chemotherapy
Reactivation of HBV replication with decompensation has been reported in 20–50% of CHB patients undergoing cancer chemotherapy or immunosuppressive therapy, especially therapies containing high-dose steroids (140–142). There is insufficient information on patients who are HBsAg negative but anti-HBc and/or anti-HBs positive. Lamivudine is effective in the treatment of HBV reactivation particularly if it is used preemptively in HBsAg positive organ transplantation recipients and cancer patients undergoing chemotherapy (143, 144). Prophylactic use of lamivudine within 1 week before start and 6 weeks after end of chemotherapy can reduce HBV reactivation frequency and severity of flares and improve survival (145–147).

Liver transplantation for chronic HBV infection
Advances in immunosuppression, organ preservation, surgical techniques and intensive care have improved the long-term outcome after liver transplantation, with 5-year survival now exceeding 85% (148). Excellent results are also achieved after transplantation for HCC provided that the tumour was within the so-called 'Milan' criteria associated with low risk of recurrence posttransplant (single tumour <5 cm or up to three tumours <3 cm). Most recipients regain excellent health within 3–6 months and return to productive lives, with full employment and family life (149, 150). Liver transplantation has become a cost-effective treatment of liver failure and HCC and is comparable to other medical and surgical interventions (151–153). Improving economies and live-related liver donation have allowed a rapid expansion of liver transplantation within the Asia-Pacific region. Hepatitis B is the most common indication for both acute and chronic liver failure in Asian-Pacific countries. Acute chronic hepatitis B accounts for most cases of acute liver failure in this region, while more than 80% of cases of chronic liver failure and HCC in Asia-Pacific is caused by chronic hepatitis B. Until recently, however, liver transplantation was contraindicated in CHB because of the high risk of HBV recurrence rapidly leading to graft loss and death. Although HBV recurrence can be prevented in 60% of cases by high-dose (10 000 IU/month) intravenous hepatitis B immunoglobulin (HBIG) (154), this therapy is prohibitively expensive (US $50 000 per annum, life-long) and is ineffective in HBV-DNA+transplant candidates. Suppression of pretransplant viral replication will significantly reduce the risk of posttransplant recurrence. In addition, viral suppression will rescue some patients with decompensated cirrhosis, thereby removing the need for future transplant (84, 133), unless the patient has poor prognostic index at baseline, which include HBV-DNA level, serum bilirubin and renal function (136). Posttransplant HBV recurrence may still occur despite antiviral prophylaxis and is usually because of lamivudine resistance. Antiviral therapy should be commenced in all potential liver transplant candidates with decompensated HBV-cirrhosis and detectable HBV-DNA (by PCR) – lamivudine in treatment-naïve candidates and adefovir in those with lamivudine resistance.

Posttransplant prophylaxis with lamivudine is associated with increased rate of virologic breakthrough, which reached 40% by 3 years. In these circumstances, adefovir therapy has been shown to be effective in reducing viral loads, resulting in excellent outcomes (103). Combination lamivudine/HBIG prophylaxis reduces recurrence rates to less than 5% and is associated with 5-year patient and graft survival rates of 85% and 80%, respectively. Lamivudine plus low-dose intramuscular HBIG (800 IU daily for 1 week then monthly) appears as effective as lamivudine plus high-dose intravenous HBIG, but is less than 10% the cost (US $4000). In recipients of live-related graft from an HBV-immune donor, adoptive immune transfer may result in *de novo* anti-HBs production. This is thought to explain the low rates of HBV recurrence with lamivudine prophylaxis reported in Hong Kong. However, levels of anti-HBs fell after 1 year and longer term follow-up is needed to determine duration of protection in such cases (155).

A liver from an anti-HBc(+) donor carries a significant risk of *de novo* HBV infection if transplanted into an HBV-naïve recipient. This risk is negligible in the following groups: (a) the transplant candidate is HBsAg(−) but anti-HBs(+) (i.e. HBV-immune) through either vaccination or previous exposure; (b) the transplant candidate is both HBsAg(−) and anti-HBs(−) (i.e. HBV-naïve) but receives long-term prophylaxis with either lamivudine or HBIG.

Recommendations and issues

Based on the above-mentioned background information, the following issues and recommendations for management of chronic HBV infection are listed. The recommendations were graded as I (at least 1 well-designed, randomized, control trial), II (well-designed cohort or case-controlled studies), III (case series, case reports or flawed

clinical trials) and IV (opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees) (157).

General management

Before active therapy, thorough evaluation of the patients is essential. Complete biochemical tests, blood counts and HBV replication status are parts of the initial evaluation. Besides drug therapy directed at liver disease, counselling of the patient is also very important and even crucial for a successful antiviral therapy. This should include information on the infectivity/transmission of HBV and preventive measures for family members; advice on lifestyle such as activity, diet, alcohol use, risk behaviours and factors that predispose to superinfection with other hepatitis virus(es) and its prevention; and the importance and need for careful follow-up and long-term monitoring and possible therapy. The indications, risks/benefits, advantages/disadvantages, cost and possible problems of each therapeutic option should be explained in detail. Careful assessment on an individual basis is absolutely essential before starting therapy.

Recommendation 1. Thorough evaluation and counselling are mandatory before considering drug therapy (IV).

Indications for treatment

Available information suggests that patients with normal ALT respond poorly to these drugs. Therefore, no drug treatment is recommended for this group of patients. However, they should be followed-up every 3 months for the first year and then 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 (male, age >40, cirrhotics, positive family history of serious liver disease) (158). 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 ALTs as a guide to the indication for antiviral treatment.

Recommendation 2. Patients with persistently normal or minimally elevated ALT should not be treated except in cirrhotic patients, but need adequate follow-up and HCC surveillance every 3–6 months (I).

Recommendation 3. Liver biopsy is recommended in viremic patients with raised ALT prior to therapy (IV).

When to start treatment?

Treatment may be started if patients have persistently elevated ALT level $\geq 2 \times$ ULN (at least 1 month between observations).

Patients with ALT in a rising trend (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 measurement. Treatment must be initiated in time to prevent the development or deterioration of hepatic decompensation. On the other hand, such exacerbations may also precede spontaneous HBeAg seroconversion and may be followed by disease remission. Because of this, it is reasonable to delay treatment for an observation period of 3 months if there is no concern about hepatic decompensation.

Recommendation 4. HBV-DNA seropositive ($>10^5$ copies/ml) patients with ALT $>2 \times$ ULN should be considered for treatment (I). Start treatment as early as possible in case of impending or overt hepatic decompensation (II). Otherwise, 3–6 months observation is recommended (II).

Which drugs or strategy?

At the moment, drugs approved for the treatment of chronic hepatitis B have relatively limited sustained long-term efficacy. Therefore, careful balance of the probability of response, patient's age, severity of liver disease, the likelihood of adverse events and complications is necessary. The rates of sustained response seem to be higher with IFN-α and Peg IFN-α2a than with lamivudine or adefovir and can be achieved with a defined duration of treatment. However, IFN and Peg IFN have more side effects and require closer monitoring. Except for patients with hepatic decompensation, conventional-IFN or Peg IFN-α2a, lamivudine or adefovir can all be considered as initial therapy. The decision as to which agent to use should be an individual one based on disease severity, hepatic function, rapidity of action, side effects, cost of the drugs and patient choice.

For viremic patients (both HBeAg positive and HBeAg negative, adults and children) with an ALT level $>5 \times$ ULN, lamivudine is recommended, particularly if there is a concern about hepatic decompensation because of its rapidity of action.

Adefovir is an alternative though its suppressive effect is less and slower than lamivudine. Although IFN therapy is also more effective in patients with higher ALT, it is generally not recommended in such circumstances because its therapeutic effect is not immediate and the patient may become decompensated. Cirrhotic patients can become decompensated during an IFN-induced flare.

For HBeAg positive patients with an ALT level between 2 and 5 × ULN, the choice among conventional IFN, pegylated IFN-α2a, lamivudine and adefovir is less clear and either agent may be used. In making the choice, patients and their doctors should consider the differences in duration, cost of treatment and profile of adverse effects of each agent.

Corticosteroid priming before IFN or lamivudine therapy is not generally recommended and should be used cautiously and only in expert centres and not in patients with more advanced disease.

For HBeAg negative patients with intermittent or persistent increase in ALT, moderate-to-severe inflammation and fibrosis on biopsy and serum HBV-DNA levels $>10^5$ copies/ml, a 12-month course of IFN or Peg IFN-α2a induces higher sustained response rate than a similar course of lamivudine (19, 51, 159). Lamivudine or adefovir are other options, but long-term therapy is required and the benefits of treatment must be weighed against the consequences of resistant mutants when lamivudine is used. The long-term effect of IFN therapy is better known than lamivudine or adefovir. The decision as to which agent to use should be an individual one based on disease severity, history of flares, hepatic function, side effects, cost of the drugs and patient choice. (Fig. 1).

Recommendation 5. Patients can be treated with conventional or Pegylated IFN (I), lamivudine (I), adefovir (I). Thymosin-α can also be used (II). Lamivudine is recommended if there is a concern about hepatic decompensation (II).

However, Peg-IFN-α2b has not been well studied in HBeAg negative patients and has not yet been approved for the treatment of chronic hepatitis B.

How to monitor?

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

Recommendation 6. During therapy, ALT, HBeAg and/or HBV-DNA should be monitored at least every 3 months (I). Renal function should be monitored if adefovir is used (I). During IFN therapy, monitoring of adverse effects is mandatory (I).

Recommendation 7. After the end of therapy, ALT and HBV markers (including HBV-DNA) should be monitored monthly for the first 3 months to detect early relapse and then every 3 months (for cirrhotic patients and those who remain HBeAg/HBV-DNA positive) to 6 months (for responders) (II). For non-responders, further monitoring is required to recognize a delayed response and to plan retreatment when indicated (II).

When to stop therapy?

The recommended duration of IFN therapy for HBeAg positive hepatitis is 4–6 months irrespective of whether or not response has occurred. For HBeAg negative patients, 12 months therapy is more beneficial. A 6–12 months observation period after the end of IFN 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. The recommended duration of thymosin α_1 therapy is 6 months with 12 months observation after the end of therapy.

Since the incidence of YMDD mutants increases with increasing duration of lamivudine therapy, it is suggested to stop lamivudine therapy if the patient has undergone HBeAg

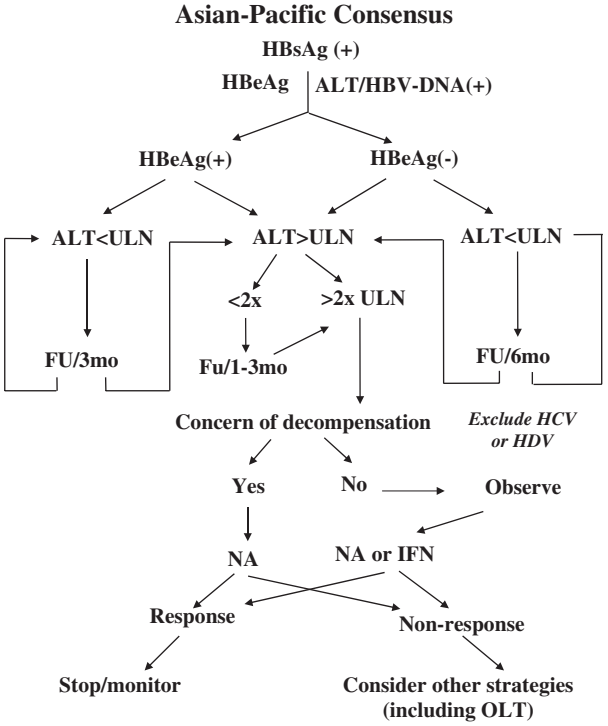

Fig. 1. Summary of the Asian-Pacific consensus on the management of chronic hepatitis B. NA, nucleoside or nucleotide analogues; IFN, interferon-α based therapy; Fu, follow-up; ULN, upper limit of normal.

seroconversion with HBV-DNA loss (by sensitive quantitative PCR methods and at least $<10^5$ copies/ml) measured in two consecutive occasions at least 6 months apart. For those who remain HBeAg positive after 1 year of lamivudine therapy, the decision to continue or stop therapy should be evaluated individually on the basis of clinical/virological response and disease severity. Lamivudine therapy may continue till end point or shift to adefovir if YMDD mutations emerge. For HBeAg negative patients, the optimal duration of treatment is unknown and the decision to stop therapy should be determined on clinical response and severity of underlying liver disease.

Recommendation 8. For IFN, the current recommended duration of therapy is 4–6 months for HBeAg positive patients and at least a year for HBeAg negative patients (I). For Peg IFN, the recommended duration is 6 months for HBeAg positive patients (II) and 12 months for HBeAg negative patients (I). For thymosin α_1, the recommended duration of therapy is 6 months for both HBeAg positive (I) and negative patients (II).

Recommendation 9. The recommended duration of lamivudine or adefovir therapy is a minimum of 1 year (I). In HBeAg positive patients, treatment can be stopped when HBeAg seroconversion with undetectable HBV-DNA has been documented on two separate occasions at least 6 months apart (II). In HBeAg negative patients, treatment can be stopped if undetectable HBV-DNA (PCR) and normal ALT have been documented on three occasions in a minimum of 6 months (II).

What to do for patients in special circumstances?

All HIV patients with active HBV replication and elevated serum aminotransferases may be considered for treatment. Treatment needs to be individualized according to the patient's HIV status. If the patient's HIV infection does not fulfil treatment criteria, adefovir monotherapy at 10 mg is preferred as it is active against HBV but not HIV. Lamivudine or tenofovir monotherapy is not recommended in this setting because of the risk of HIV resistance. If patient's HIV infection is being treated, highly active antiretroviral therapy containing either tenofovir or lamivudine/tenofovir combination is recommended.

Recommendation 10. Adefovir or IFN (if $CD_4 > 400$) is preferred if patients' HIV infection does not require treatment. If patient's HIV infection is being treated, tenofovir or lamivudine/tenofovir combination should be included in the active antiretroviral therapy (II).

In patients with decompensated liver disease, IFN is usually contraindicated or requires dose modification because it may be associated with severe side effects.

Recommendation 11. Lamivudine is the agent of choice for patients with obvious or impending hepatic decompensation (II).

HBV reactivation is well recognized as a serious complication in immunosuppressed patients, including those undergoing immunosuppressive therapy or chemotherapy. Reactivation commonly occurs after the first two to three cycles of chemotherapy. Lamivudine therapy is effective when instituted early before there is obvious jaundice and decompensation. Prophylactic suppression of HBV during the course of chemotherapy is a feasible approach. Prophylactic treatment using adefovir has not been reported.

Recommendation 12. Before receiving immunosuppression or chemotherapy, patients should be screened for HBsAg (III). If HBsAg is positive, prophylactic lamivudine therapy before the start and at least 6 weeks after the end of immunosuppression or chemotherapy is recommended (II).

For those patients being treated with lamivudine in whom YMDD mutants have emerged, the general practice usually is to continue lamivudine in order to further suppress or prevent the return of wild-type HBV. In view of the adverse effects of YMDD mutants (85–91) and the finding that the defective replication of some YMDD mutants is restored completely after addition of lamivudine (89), two Asian studies attempted to stop lamivudine therapy. The results suggest that there is no benefit to continue lamivudine therapy (160) and it is safe to stop lamivudine (161) after the emergence of YMDD mutants. In case adefovir dipivoxil is available, switch to adefovir therapy is indicated. If these 'rescue' drugs are not available, stopping lamivudine therapy with close monitoring may be an option in patients who develop YMDD mutants.

Recommendation 13. For patients who developed drug resistance while on lamivudine, switching to adefovir monotherapy is indicated (I). If 'rescue' drugs are not available, stopping lamivudine therapy with close monitoring may be an option (II).

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

What to do in the setting of liver transplantation?

There are criteria for listing patients for liver transplantation.

Recommendation 14. If any of the following are present, it may be appropriate to list the patient for liver transplantation (IV):

1. Child–Pugh score ≥ 10.
2. Diuretic-resistant ascites.
3. Portal hypertensive bleeding not controlled by endoscopic therapy or TIPSS.
4. Episode of spontaneous bacterial peritonitis.
5. Intractable hepatic encephalopathy.
6. Potentially reversible life-threatening extrahepatic manifestations, including hepatopulmonary syndrome, portopulmonary hypertension and protein–calorie malnutrition.
7. Unresectable HCC, provided the lesion is less than 5 cm in maximum diameter, or up to three lesions less than 3 cm and without extrahepatic or vascular invasion.

Recent advances in the therapy of chronic hepatitis B using nucleos(t)ide analogues have allowed the option of liver transplantation. These agents are effective in pretransplant treatment, prevention (in combination with HBIG) of posttransplant HBV recurrence and treatment of posttransplant HBV-related allograft infection.

Recommendation 15. Lamivudine (100 mg/day) (or ADV if lamivudine resistant) should be commenced in all patients with HBV-associated liver failure (acute and chronic) who are listed for transplantation and are PCR (+) for HBV-DNA. In the elective candidate, transplantation should ideally be delayed until serum HBV-DNA titre has fallen by at least 2 logs or is undetectable by PCR (III).

Recommendation 16. Lamivudine plus low dose HBIG (400–800 U, i.m. daily for 1 week, followed by 400–800 U monthly long term) provide safe and effective prophylaxis against HBV reinfection of the allograft. There is no target through serum anti-HBs level (III).

Recommendation 17. Lamivudine (or adefovir if already receiving lamivudine) should be commenced if there is HBV-related allograft injury (II), and corticosteroid therapy should be minimized and HBIG stopped (III).

There is also emerging data that HBIG $\pm$ lamiivudine prophylaxis can be replaced by lamivudine monotherapy after 12 months posttransplant in certain 'low-risk' patient groups. These include patients who were HBV-DNA negative (hybridization assay) before lamivudine therapy was started pretransplant (154), and also those patients with sustained protective levels of anti-HBs production following posttrannsplant vaccination (155).

Recommendation 18. Late conversion (at least 12 months posttransplant) from HBIG $\pm$ Lamivudine to Lamivudine monotherapy may be considered in 'low-risk' patients (I).

Recommendation 19. An HBV-naïve patient receiving a liver from an anti-HBc (+) donor should receive long-term prophylaxis with either Lamivudine or HBIG (III).

Unresolved issues and areas for further study

The treatment of chronic hepatitis B has advanced into the era of nucleos(t)ide analogues. However, the results are still unsatisfactory. In particular, the following issues remain unsettled:

(1) Should patients with an ALT level of $<2 \times$ ULN be treated, and if so when and how?
(2) What is the role of HBV genotypes in therapy?
(3) Which is the first (line) choice among the currently available direct antiviral agents?
(4) Is there effective therapy for patients with concurrent HCV and/or HDV infection?
(5) What is the role for corticosteroid withdrawal, lamivudine pulse therapy or other immunomodulating agents and modes of immunomodulation?
(6) What is the role of combination therapy?
(7) Cost-effectiveness of each therapeutic strategies.
(8) Do traditional Chinese medicines or other herbal medicines have a role in 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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