seroconversion. Overall, HBeAg seroconversion at five years after the end of treatment was seen in an impressive 60% of the total sample.[13]

Recommendation

- ***Clinical studies in Japan have found that 17% – 20% of patients with HBeAg positive chronic hepatitis B administered Peg-IFNα-2a at either 90 or 180 μg dosage for 48 weeks experience the target therapeutic benefits of HBeAg seroconversion, HBV-DNA <5.0 log copies/mL and ALT ≤40 U/L.***

3.3.2 Therapeutic effect in cases of HBeAg negative chronic hepatitis

An overseas comparative study of three treatment regimens for HBeAg negative patients (Peg-IFNα-2a for 48 weeks, Peg-IFNα-2a plus lamivudine for 48 weeks, and lamivudine only for 48 weeks) reported ALT normalization rates of 59%, 60% and 44% respectively, and HBV DNA negative conversion rates of 43%, 44% and 29% respectively at 24 weeks after finishing treatment.[22] Thus, the Peg-IFNα-2a groups demonstrated better results on both parameters. The long term benefits (negative HBV DNA and normal ALT levels at 72 weeks) were likewise stronger in the two Peg-IFNα-2a groups (15% and 16% compared to 6% for lamivudine only), although the effect tended to be less sustained overall compared to HBeAg positive patients. The HBV DNA levels <400 copies/mL were found in 19% of patients, and HBsAg elimination was observed in 3%.[22]

Meanwhile, a study of 61 patients with HBeAg negative chronic active hepatitis B in Japan compared the therapeutic effects from Peg-IFNα-2a dosages of 90 μg (32 patients) and 180 μg (29 patients). In terms of virological benefits, the target HBV DNA levels at finishing treatment (<4.3 log copies/mL) was achieved in 78.1% of the 90 μg group and 93.1% of the 180 μg group. After 24 weeks, these figures had fallen to 37.5% and 37.9% respectively, whereas the biochemical target (ALT ≤40 U/L) was achieved in 68.8% and 65.5% of patients respectively.[9] It should be noted that, as with the HBeAg positive study, the overwhelming majority of the patients in this study (58/61; 95%) were <50 years of age.

A long term follow-up study of 230 HBeAg negative patients treated with Peg-IFNα-2b (with or without lamivudine) reported HBV DNA negative conversion (DNA <4.0 log copies/m) in 21% of patients after five years, and HBsAg elimination in 5% after one year and 12% after five years.[23] Meanwhile, an Italian study of 128 genotype D HBeAg negative patients administered Peg-IFNα-2a over an extended period of 96 weeks (180 μg for 48 weeks then 135 μg for 48 weeks) reported 29% of cases reaching the virological target HBV DNA levels of <2000 IU/mL. It can be seen that this is considerably higher than the corresponding figure of 12% for the 48 week treatment regimen. HBsAg elimination rates were also better after 96 weeks (6%) compared to 48 weeks (0%).[24] Thus, the efficacy of Peg-IFNα-2a therapy on patients with HBeAg negative chronic hepatitis B can be considerably improved by extending the therapy period. In Japan however there is no national medical insurance approval for treatment regimens longer than 48 weeks.

Recommendation

- ***A clinical study in Japan reported that 38% of patients with HBeAg negative chronic hepatitis B administered Peg-IFNα-2a at either 90 or 180 μg dosage for 48 weeks achieved the virological target of a HBV DNA levels <4.3 log copies/mL 24 weeks after the end of treatment.***

3.4 IFN therapy for HBV-associated cirrhosis

It was demonstrated that IFN treatment of compensated HBV cirrhosis produced much the same outcomes and adverse effects to IFN therapy as in non-cirrhotic patients, and in Asian patients in whom HBeAg had been successfully eliminated the HBsAg elimination rate was boosted by a factor of 6.63 times, effectively suppressing progression of liver fibrosis and hepatocarcinogenesis.[101] A study of 24 patients with HBeAg positive compensated cirrhosis administered Peg-IFNα-2b (with or without lamivudine) for 52 weeks reported 30% efficacy (defined as HBeAg seroconversion and HBV DNA <4.0 log copies/mL) at 26 weeks after finishing treatment. This figure is significantly higher than the corresponding 14% for non-cirrhotic cases. Histological improvement was observed in 66% of cases, also significantly higher than the 22% for non-cirrhotic cases, with similar adverse reactions.[102] It should be noted however that IFN, unlike NAs, has an immunopotentiation effect that can increase the risk of acute exacerbation of hepatitis through immunological destruction of HBV infected cells. IFN therapy is contraindicated for HBV-associated decompensated cirrhosis patients in particular, who are at risk of potentially fatal adverse reactions such as deterioration of liver function.[103] In Japan there is insufficient evidence regarding the efficacy and safety of IFN therapy for HBV associated cirrhosis, and consequently this is not approved by

national medical insurance. Hence HBV-associated cirrhosis should be treated with NAs.

Recommendation

- ***There is insufficient evidence in Japan on the efficacy and safety of IFN therapy for HBV-associated compensated cirrhosis, and NA therapy is recommended instead. IFN treatment is contraindicated for patients with HBV decompensated cirrhosis.***

3.5 Should NAs be administered at the same time?

IFN administered in combination with lamivudine produces improved HBV DNA negative conversion and ALT normalization outcomes compared to lamivudine alone, for both HBeAg positive and negative patients. Meanwhile, studies comparing IFN plus lamivudine combination therapy with IFN monotherapy found similar therapeutic effects[8,22,104] and similar persistent benefits.[96,105,106] IFN in combination with adefovir was likewise found to have roughly the same therapeutic effect six months after treatment as IFN alone.[107] It has been reported that Peg-IFN in combination with entecavir or adefovir produces better negative conversion of HBsAg and reduction in cccDNA levels.[108,109] However in the absence of a broad consensus on this at the present point in time, there cannot be said to be sufficient evidence for improved therapeutic effects of IFN administered in combination with NAs.

Recommendation

- ***There is insufficient evidence for improved therapeutic effects of IFN administered in combination with NAs.***

3.6 Factors that determine therapeutic effect

Factors reported to determine the therapeutic effect of conventional IFN include HBV genotype,[104,110,111] age,[112] and the degree of fibrosis.[113] However, as shown below, Peg-IFN has a high therapeutic effect compared to conventional IFN, and has high efficacy against HBV genotype A, but its therapeutic effect is not influenced by other HBV genotypes or patient age. Currently, regardless of whether a patient is HBeAg positive or negative, there is no established method for predicting the treatment response prior to Peg-IFN treatment, with the exception of HBV genotype A (Tables 12,13).

3.6.1 HBV genotype

Concerning correlations between genotype and therapeutic effect, for conventional IFN therapeutic effect is

Table 12 Reports on favourable factors affecting Peg-IFN therapeutic effect for HBeAg positive cases

	Liaw[10]	Lau[8]	Buster[114]	Janssen[115]	Sonneveld[116]	Hayashi[9]
Dosage	α-2a 90/180 μg	α-2a 180 μg ± LAM 100 mg	α-2a 180 μg α-2b 100 μg	α-2b 100 μg ± LAM100 mg	α-2a/α-2b ± LAM100 mg	α-2a 90/180 μg
Administration period	24/48 weeks	48 weeks	α-2a: 48 weeks α-2b: 52 weeks	52 weeks	32–104 weeks	24/48 weeks
Cases	548	542	788	307	205	164
Race	NS			NS	NS	
Age	NS		Elderly	NS	Elderly	Young†
Gender	NS		Female	NS	NS	Female†
ALT	High†	NS	High	High	NS	NS
HBV DNA levels	Low	Low	Low	Low	Low	NS
HBsAg levels	Low					
Genotype	NS	NS	A (*vs* D)	A (*vs* D)	A (*vs* D)	
IL28B					Major	

†Tendency but not statistically significant.
LAM, lamivudine; NS, Not significant.

Table 13 Reports on favourable factors affecting Peg-IFN therapeutic effect for HBeAg negative cases

	Bonino[117]	Rijckborst[118]	Moucari[119]	Marcellin[23]	Hayashi[9]
Dosage	α-2a 180 μg ± LAM 100 mg	α-2a 180 μg ± RIB 1000/1200 mg	α-2a 180 μg	α-2a 180 μg ± LAM 100 mg	α-2a 90/180 μg
Administration period	48 weeks	48 weeks	48 weeks	48 weeks	24/48 weeks
Cases	518	107	48	230	61
Race	NS	NS		NS	
Age	Young	NS	NS	NS	NS
Gender	Female	NS	NS	NS	NS
ALT	High	NS	High	High	NS
HBV DNA levels	Low	NS	NS	NS	NS
HBsAg levels		NS	NS		
Genotype	B, C (vs. D)	NS	NS	NS	

LAM, lamivudine; NS, not significant; RIB, ribavirin.

reported to be high for genotypes A and B compared to genotypes C and D.[104,110,111] For treatment using the minimum dosage (90 μg) of Peg-IFNα-2a or short period (24 weeks), poorer therapeutic response has also been reported for genotypes C compared to genotype B.[98] However, the recent NEPTUNE study evaluated the therapeutic effect of Peg-IFNα-2a 180 μg/48 weeks, finding the response rate of antiviral therapy was the same for genotypes B and C, and genotype was not a predictive factor for therapeutic effect.[10] Possible reasons for this are that due to increased therapeutic effect from administration of Peg-IFNα-2a 180 μg for 48 weeks, any influence on the therapeutic effect from genotype C was lost. The results of other large scale clinical trials for HBeAg positive cases indicated strong Peg-IFN therapeutic effect for genotype A compared to genotype D,[114,115] but no difference in therapeutic effect between genotype B and genotype C was seen[8] (Table 12). In HBeAg negative cases also, no significant difference in response rate was found between genotype B and genotype C[23,117–119] (Table 13).

3.6.2 HBsAg levels

In recent years highly sensitive measurement of HBsAg levels has become possible, and it has been noted that HBsAg levels are useful in predicting IFN therapeutic effect. Although it is difficult to predict the therapeutic effect from the pretreatment HBsAg levels, the amount and rate of reduction in HBsAg levels during treatment are useful in predicting therapeutic effect.

A European study of 202 HBeAg positive patients administered Peg-IFNα±lamivudine for 52 weeks found that in cases where elimination of HBeAg and HBV DNA <10 000 copies/mL were achieved, the reduction of HBsAg levels at 12 weeks since treatment start correlated significantly with HBsAg elimination an average of 3 years after treatment completion.[71] In other reports, in patients administered Peg-IFNα, the HBsAg levels at 12 weeks after commencement of treatment is important for predicting therapeutic effect, and in cases where the HBsAg levels declined to 1500 IU/mL or less, the rate of elimination of HBeAg is high,[120,121] and subsequent elimination of HBsAg can be expected. In a Hong Kong study of 92 cases administered Peg-IFNα±lamivudine for 32–48 weeks, in cases where the HBsAg levels at 12 weeks after commencement of treatment was <1500 IU/mL, and declined to <300 IU/mL at 24 weeks, the therapeutic effect was high 1 year after treatment, and therapeutic effect was high particularly at 24 weeks in cases where the HBsAg levels declined ≥1 log IU/mL to ≤300 IU/mL.[70]

Even in HBeAg negative patients, when HBV DNA non-detection is defined as effective at 24 weeks after completion of 48 weeks administration of Peg-IFNα, the HBsAg levels at treatment completion is reduced to 2.1 ± 1.2 log IU/mL in effective cases, and if the HBsAg levels reduction at 12 weeks and 24 weeks treatment is ≥0.5 log IU/mL or ≥1.0 log IU/mL respectively, it has been reported as a highly effective response.[119] Furthermore, in a study by Brunetto *et al.*, in cases where the reduction in HBsAg during treatment is ≥1.1 log IU/mL, and the HBsAg at 48 weeks is ≤1.0 log IU/mL, the rate of decrease in the HBsAg levels at 3 years after completion of treatment was markedly high.[122] Furthermore, it has been reported that a decline of 10% or more in the HBsAg levels at the 12 week mark correlated with therapeutic effect 1 year after treatment, and HBsAg elimination after 5 years.[123] On the other hand, there is no way

to use the rate of decrease in HBV DNA levels to distinguish between responders and non-responders. From these results, HBsAg levels are more useful than HBV DNA levels in predicting the therapeutic effect of IFN treatment. However, these reports are all from overseas, and no Japanese evidence is yet available concerning IFN therapy and HBsAg levels.

3.6.3 Age and fibrosis

A Japanese study reported that with conventional IFN, therapeutic effect declines in patients aged ≥35 years,[112] but in a European study analyzing the therapeutic effect of conventional IFN in 496 HBeAg positive patients, based on 10 control trials, no correlation was seen between age and therapeutic effect.[124] A Japanese clinical trial of a 48 week course of Peg-IFNα-2a 180 μg found the combined efficacy rates (ALT ≤40 U/L, HBeAg seroconversion, HBV DNA <5.0 log copies/mL at 24 weeks after completion of treatment) were 15.0% and 23.8% respectively for ≥35 years and <35 years, with a tendency to greater efficacy in the younger group, but some effective cases also seen in the older age group.[9] In overseas trials, no correlation has been found between Peg-IFN therapeutic effect and patient age,[10,115] although there have been reports that in HBeAg positive cases, the therapeutic effect is better in older patients.[114,116] Regardless of whether HBeAg status, there is no clear consensus concerning the relationship between Peg-IFN therapeutic effect and patient age (Tables 12,13). Furthermore, for conventional IFN in patients with advanced fibrosis, the therapeutic effect declined,[113] but for Peg-IFN no correlation was seen between therapeutic effect and fibrosis.[102]

Taken together, due to the improved therapeutic effect seen with Peg-IFN, as with genotype C, factors such as age and advanced fibrosis which impair the therapeutic effect of conventional IFN are no longer significant prognostic factors for Peg-IFN therapy (Tables 12,13).

3.6.4 IL28B gene

In recent years it has been reported that for chronic hepatitis C, single nucleotide polymorphisms (SNPs) in proximity to the IL28B gene correlate extremely strongly with the therapeutic effect of Peg-IFNα+ribavirin combination therapy against genotype 1. A recent study of 205 HBeAg positive patients reported that, even in chronic hepatitis B, high HBeAg seroconversion and HBsAg elimination rates were seen in IL28B major homozygotes.[116] However, no conclusion has yet been reached about the correlation between IL28B genotype and IFN therapeutic effect in chronic hepatitis B, and further investigation and evaluation are required about the effect of host genome factors, including IL28B polymorphisms.

Recommendations

- ***HBV genotype, patient age and degree of fibrosis are factors reported to influence therapeutic effect of conventional IFN treatment. However, Peg-IFN has a greater therapeutic effect than conventional IFN, and high efficacy against HBV genotype A, but its therapeutic effect is not influenced by HBV genotypes B/C or patient age.***
- ***Currently, there is no established method for predicting the treatment response prior to Peg-IFN treatment, regardless of whether a patient is HBeAg positive or negative.***
- ***The amount and rate of reduction of HBsAg levels at 12 weeks and 24 weeks during Peg-IFNα therapy are useful for predicting therapeutic effect. However, no Japanese evidence is yet available concerning IFN therapy and HBsAg levels.***

3.7 Adverse reactions

Adverse reactions associated to IFN treatment are seen in almost all patients. The most common adverse reactions are influenza-like symptoms such as general malaise, fever, headache and joint pain, seen in 60–95% of patients. These influenza-like symptoms can be controlled in most cases by administering an antipyretic analgesic. Hematological testing often shows leukopenia, with white cell counts <1000/mm^3 in approximately 60% of cases. Leukopenia, neutropenia and thrombocytopenia often progress until the fourth week of administration, and then stabilize. However, with the exception of immunocompromised patients and those with cirrhosis, there is no increased risk of infection or hemorrhage associated with neutropenia or thrombocytopenia.[125]

ALT elevation is seen more frequently during IFN treatment for chronic hepatitis B than for chronic hepatitis C. This is considered to be due to the immunostimulatory action of IFN, and normally treatment can be continued, but caution is required in patients with decreased hepatic reserve to avoid liver failure. Neuropsychiatric symptoms such as depression and insomnia occur in 5–10% of patients, and are more common in those with pre-existent neuropsychiatric symptoms or a history of depression. Neuropsychiatric symptoms are classified into depression-specific symptoms and depression-related autonomic nervous

symptoms,[126–128] with selective serotonin reuptake inhibitors (SSRIs) reported to be useful in treating the former. IFN can also trigger or aggravate autoimmune conditions such as chronic thyroiditis, so the utmost caution is required when administering IFN to patients with autoimmune diseases. Interstitial pneumonitis, another reported adverse reaction to IFN therapy, can be serious and even life threatening. It usually occurs after two months of therapy, or in the latter stages of treatment. A rapid and appropriate response is required following the onset of respiratory symptoms such as a dry cough or dyspnea, including an immediate chest CT scan. Determination of serum KL-6 levels is also useful in the diagnosis of interstitial pneumonitis. Other reported adverse reactions to IFN therapy include cardiomyopathy, fundal hemorrhage, and cerebral hemorrhage.

The adverse reaction profile of Peg-IFN differs somewhat to that of non-pegylated IFN. In a Japanese clinical trial of Peg-IFNα-2a monotherapy, the adverse reactions with a higher reported frequency than non-pegylated Peg-IFNα-2a were skin reactions such as erythema at the injection site and hematological reactions such as decreases in the white cell or platelet counts. On the other hand, mild to moderate adverse reactions such as influenza-like symptoms, including fever and joint pains, or malaise and loss of appetite, were milder than with standard non-pegylated IFNα-2a.[129] The cessation rate due to adverse reactions to Peg-IFNα treatment is 2–8%.

Recommendations

- ***Reported adverse reactions to IFN therapy include influenza-like symptoms, reduction in blood cell counts, neuropsychiatric symptoms, autoimmune phenomena, interstitial pneumonitis, cardiomyopathy, fundal hemorrhage, and cerebral hemorrhage.***
- ***Pegylation stabilizes serum IFN levels, ameliorating influenza-like symptoms such as fever and joint pains.***
- ***Patients self-injecting at night minimizes influenza-like symptoms associated with natural IFN-α.***
- ***IFN-β should be considered in patients unable to tolerate IFN-α due to depression or other causes.***

4. PHARMACOTHERAPY (2) – NAs

NAS DIRECTLY SUPPRESS the HBV replication process. In particular, they specifically inhibit reverse transcriptase coded by the HBV itself, and powerfully inhibit negative and positive strand DNA synthesis in the HBV living environment (Fig. 2). As a result, HBV DNA levels in the blood quickly decline and ALT levels also improve. Effectiveness is achieved through continued administration, but if treatment stops the proliferation of virus reoccurs at high frequency causing recurrence of hepatitis.[130] The effect of eliminating HBV-infected hepatocytes is weak.

NAs currently approved by medical insurance system in Japan comprise 3 agents: lamivudine, adefovir and entecavir. In Japan, lamivudine, the first of the NAs, were approved by medical insurance in 2000, followed by adefovir in 2004 and entecavir in 2006 (Table 2).

If administration of the NAs is ceased, in many cases the HBV DNA levels rise again, returning to pre-treatment levels.[131–134] Even in cases where HBeAg seroconversion occurred during administration of a NA (lamivudine), it was found similarly that HBV DNA quantity rose again and HBeAg reappeared.[135,136] Furthermore, after treatment ceases, cases have been reported where ALT levels rose to ≥500 U/L, and total bilirubin rose to ≥2.0 mg/dL.[137] Accordingly, in order to achieve the aim of improved long term outcomes, in general it is necessary not to stop administration of the NAs, and provide continuous maintenance treatment to inhibit HBV reproduction.

4.1 Lamivudine

Lamivudine is a reverse transcriptase inhibitor, originally developed for treatment of human immunodeficiency virus (HIV). Like HIV, HBV passes through a transcriptase process in its lifecycle, so a reverse transcriptase inhibitor has therapeutic effect. Lamivudine has a structure (3TC-TP) similar to deoxycytidine triphosphate (dCTP), which is used as a foundation substance when reverse transcriptase synthesizes DNA using RNA as a template. For this reason lamivudine binds to reverse transcriptase during DNA synthesis and inhibits further DNA synthesis. This mechanism inhibits reproduction of the HBV virus and reduces HBV DNA levels. The dosage of lamivudine is 100 mg per day. Lamivudine has almost no adverse reactions and is very safe. Reported therapeutic results for lamivudine in HBeAg positive patients in Asian and other overseas countries are ALT normalization rates of 40–87% 1 year after commencement of treatment, 85% after 2 years, and HBV DNA negative conversion rates (solution-hybridization or branched chain DNA assays) of 44–87% after 1 year, and 74% after 2 years.[131,138,139] Reported HBeAg seroconversion rate are 17–28% after 1 year, 25–29% after 2 years, 40% after 3 years, and 50% after 5 years.[138–141] Furthermore, histological

improvement is also reported 1 year after commencement of treatment.[142]

The short term effects of lamivudine are also favorable in HBeAg negative patients.[134,143,144] In a Japanese study,[139] the HBV DNA negative conversion rate (HBV DNA <0.5 Meq/mL) was 94% after 1 year of treatment and 92% after 2 years, and the ALT normalization rate was 89% after 1 year, and 82% after 2 years. However, the HBV DNA negative conversion rate decreases over the long term.[96]

A major problem with lamivudine is the occurrence of drug resistance (YMDD motif mutation). In lamivudine-resistant viruses, mutation occurs in the amino acid sequence called the YMDD motif inside the RNA dependent DNA polymerase region. In other words, M (methionine) inside the YMDD motif mutates into V (valine) or I (isoleucine). As a result, changes occur in the polymerase structure, lamivudine bonding is reduced and its effectiveness declines. It has also been shown in *in vitro* tests that lamivudine resistance occurs due to YMDD motif mutation.[145,146]

In general, lamivudine-resistant viruses appear 6–9 months after treatment starts, and increase as treatment continues.[139,147–154] In Japanese studies, the incidence of lamivudine-resistant viruses was 13–15% at 1 year, 25–32% at 2 years, 29–45% at 3 years, 51–60% at 4 years, 63–65% at 5 years, and 70% at 6 years.[139,149–154] Past studies have identified HBeAg positive status at baseline, high HBV DNA load at baseline, cases where the HBV DNA load fails to fall below 3–4 log copies/mL after 3–6 months of treatment, persistent HBeAg positive status, cirrhosis, and genotype A as risk factors for the emergence of lamivudine-resistant viruses.[139,147,149–151,154]

Usually, no abnormalities are seen in blood tests immediately after the emergence of lamivudine-resistant viruses, but rising HBV DNA levels (breakthrough) and rising ALT levels (breakthrough hepatitis) are seen within 3–4 months of emergence of resistance in at least 70–80% or more of cases.[149,152,155] Great caution is required in these cases because breakthrough hepatitis can sometimes be more serious than hepatitis prior to lamivudine therapy.[156,157] Due to the high risk of emergence of lamivudine-resistant virus, currently lamivudine is not regarded as the first choice NA.

Recommendation

- ***Long-term lamivudine administration is associated with a high risk of emergence of resistant virus. Accordingly, lamivudine is not the first choice NA.***

4.2 Adefovir

Adefovir (adefovir dipivoxil) is an analog of adenine (dATP). Adefovir inhibits HBV reproduction not only through antagonistic competition with dATP, but by also acting as a chain terminator to stop the DNA extension process and inhibit HBV replication. *In vitro*, adefovir not only exhibits a similar antiviral effect to lamivudine against natural strains of HBV, but it has also been shown to be effective against lamivudine-resistant strains.[145] Its effectiveness against cases of exacerbated hepatitis due to lamivudine-resistant virus has been confirmed in actual clinical practice.[158–168] Adefovir therapy is officially approved by Japanese medical insurance system at a dosage of 10 mg daily.

Following 48 weeks of adefovir monotherapy in HBeAg positive patients, the HBV DNA negative conversion rate was 21%, and the HBeAg seroconversion rate 12%, with no resistant virus detected.[169] Following long term administration for 5 years, the HBV DNA levels declined an average of 4.05 log copies/mL, ALT levels declined by ≥50 U/L in 63% of cases, the DNA negative conversion rate was 39%, the HBeAg negative conversion rate was 58%, and seroconversion was reported in 48%. The incidence of adefovir-resistant virus was 21%.[170] In HBeAg negative patients, after 48 weeks of administration the HBV DNA negative conversion rate was 51% as expected, the ALT normalization rate was 72%, and resistant virus was not detected.[171] In another study, after 5 years of adefovir therapy, the HBV DNA negative conversion rate was 67%, the ALT normalization rate 69%, the histological improvement rate (Ishak fibrosis scores) 71%, whereas the incidence of resistant virus (rtA181T/V, rtN236T) was 0% at 1 year, 3% at 2 years, 11% at 3 years, 18% at 4 years and 29% at 5 years, and re-elevation of ALT was 11%.[172] Reported factors associated with adefovir-resistant virus are where treatment switched from lamivudine to adefovir monotherapy, advanced age, genotype D, and lamivudine-resistant virus.[173,174]

Important adverse reactions to adefovir are renal dysfunction and hypophosphatemia. After 4–5 years administration, creatinine levels increased to ≥0.5 mg/dL in 3–9% of patients,[170,172] and eGFR declined ≥20% in 2.6% at 1 year, 14.8% at 3 years, and 34.7% at 5 years.[175] Furthermore, treatment discontinuation due to renal dysfunction and decline in eGFR <50 mL/min was significantly more common in the group administered adefovir than in the non-treatment group (relative risk = 3.68). Renal dysfunction was more likely to occur in patients aged ≥50 years, patients

with mildly reduced eGFR at commencement of treatment (50–80 mL/min), and patients with hypertension or diabetes.[176] In a Japanese study, administration of adefovir for an average of 38 months caused elevated creatinine levels in 38% of cases, exceeding 1.4 mg/dL in 11% of cases. Factors associated with elevated creatinine levels were advanced age and long term therapy.[165] Elevated creatinine levels can be managed by reducing the dose of adefovir (such as alternate day administration). Hypophosphatemia (<2.0 or <2.5 mg/mL) was seen in 3–16% of cases,[165,170] and elevation of serum creatinine level was also observed in most of these cases.[165] Cases of Fanconi syndrome have also been reported,[165,177,178] indicating the need for careful monitoring.

Recommendations

- ***Adefovir long term monotherapy is moderately effective. However, resistant HBV may emerge with long term administration.***
- ***Care should be taken with long term administration of adefovir for the possible onset of renal dysfunction and hypophosphatemia (including Fanconi syndrome).***

4.3 Entecavir

Entecavir is a NA with a structure resembling that of guanosine (a guanine nucleoside), with a powerful and selective inhibitor effect against HBV DNA polymerase. The mechanism of its activity involves intracellular phosphorylation of entecavir and conversion into activated entecavir-triphosphate (ETV-TP). Through competition with the natural substrate deoxyguanosine triphosphate (dGTP), ETV-TP inhibits all 3 types of HBV polymerase activity during HBV DNA replication: (1) priming, (2) reverse transcription when the minus strand DNA is synthesized from mRNA, and (3) synthesis of plus strand DNA. *In vitro* experiments have demonstrated not only that entecavir has stronger antiviral activity than lamivudine or adefovir against HBV wild strains, but it is also effective against lamivudine-resistant strains.[179] Entecavir has had health insurance approval in Japan since 2006, for administration of 0.5 mg per day in treatment-naïve cases.

In Europe studies of entecavir therapy in patients naïve to NAs, in both HBeAg positive cases and negative patients, HBV DNA negative conversion rates and ALT normalization rates were higher for entecavir than for lamivudine.[14,25,180] The greatest characteristic of entecavir is that it has a lower incidence of viral resistance than lamivudine. For this reason entecavir is currently the treatment of first choice when using NAs. Resistance to entecavir is exhibited by amino acid mutation of either rtT184, rtS202 or rtM250, in addition to the lamivudine resistant amino acid mutations at rtM204V and rtL180M.[181] In the abovementioned study, increased HBV DNA levels were seen in 22 out of 679 patients until the 96th week of therapy. Only 1 case of entecavir-resistant HBV was confirmed at 1 year, and 1 more case at 96 weeks, in one of which lamivudine-resistant HBV had already been detected at the commencement of entecavir therapy.[180]

Long term results have been reported for entecavir administration for 5 years.[16,182] The HBV DNA negative conversion rate was 55–81% at 1 year, 83% at 2 years, 89% at 3 years, 91% at 4 years and 94% at 5 years, and the ALT normalization rate was 65% at 1 year, 78% at 2 years, 77% at 3 years, 86% at 4 years and 80% at 5 years, while the incidence of resistant HBV was 0.2% at 1 year, 0.5% at 2 years, and 1.2% at 3–5 years. However, in these studies, entecavir 0.5 mg daily was not continuously administered in all cases. On the other hand, in a report from Hong Kong of continuous entecavir therapy for 3 years, the HBV DNA negative conversion rate was 81% at 1 year, 90% at 2 years and 92% at 3 years; the ALT normalization rate was 84% at 1 year, 88% at 2 years and 90% at 3 years; and the HBeAg seroconversion rate was 22% at 1 year, 41% at 2 years and 44% at 3 years.[19] From of these cases, 1 case of resistant HBV was confirmed at 3 years.

In results from Japan concerning NAs naïve cases,[15,18,183] the HBV DNA negative conversion rate was 77–88% at year 1, 83–93% at year 2, 95% at year 3, and 96% at year 4. The ALT normalization rate was 83–87% at year 1, 88–89% at year 2, 92% at year 3, and 93% at year 4. The HBeAg seroconversion rate was 12–20% at year 1, 18–20% at year 2, 29% at year 3, and 38% at year 4. Histological evaluation also confirmed improvement in the Knodell necroinflammatory score and fibrosis score at 1 year and 3 years.[18] The incidence of entecavir-resistant HBV was 3.3% at 3 years.[18]

In consideration of the high risk of resistant HBV associated with long term administration of lamivudine, some studies have examined the results of a change from lamivudine to entecavir.[184–186] In cases where the HBV DNA levels during lamivudine therapy remained <2.6 log copies/mL, HBV DNA continued negative after switching to entecavir, and entecavir-resistant virus was not detected. On the other hand, when the HBV DNA levels is ≥2.6 log copies/mL at the time of switching, entecavir-resistant HBV may appear irrespective of whether lamivudine-resistant virus was already present.

Concerning problems with safety, almost no adverse reactions of clinical importance were reported. Points to keep in mind are that entecavir is not suitable for long term continuous therapy for women desiring to bear children due to the risk of teratogenesis, and the safety of long term administration has not been established.

Recommendations

- *Favourable results are obtained with entecavir in patients naïve to NAs, with a low incidence of resistant virus, currently making entecavir the first-choice NA.*
- *Switching to entecavir is recommended in patients in whom the HBV DNA negative conversion occurs with lamivudine therapy.*

4.4 Treatment of NA-resistant HBV

4.4.1 Lamivudine-resistant HBV

It has been reported that if lamivudine-resistant HBV appears and the viral load increases, onset of hepatitis is likely; furthermore, in some cases the hepatitis may become severe.[157,187] Accordingly, treatment with an antiviral agent is required if lamivudine-resistant HBV appears. IFN, adefovir and entecavir have been confirmed effective against lamivudine-resistant HBV, and are currently approved for Japanese medical insurance.

Although IFN can be used to a certain extent to treat hepatitis associated with lamivudine-resistant HBV, there are problems with adverse reactions and a limited treatment duration.[188,189] On the other hand, adefovir has good long term efficacy against lamivudine-resistant HBV, with mild adverse reactions and suitable for long term therapy, so currently adefovir is recommended. Rather than switch from lamivudine to adefovir, lamivudine and adefovir in combination provides a stronger antiviral effect.[190] The long term effect of lamivudine+adefovir combination therapy against lamivudine-resistant HBV has been reported as an HBV DNA negative conversion rate (<2.6 log copies/mL) using the Amplicor testing of 56–82% at 1 year, 74–84% at 2 years, 81–86% at 3 years, 80–92% at 4 years, and 85–86% at 5 years.[158,159,161,164,165,167] Reported factors relating to the antiviral effect of lamivudine+adefovir combination therapy include DNA load (low value), albumin level (low), ALT level (high), HBeAg (negative), and HBV DNA negative conversion during lamivudine therapy.[159,165,166,168] Reported ALT normalization rates were 67–81% at 1 year, 75–83% at 2 years, 80–92% at 3 years, 82–90% at 4 years, and 85% at 5 years.[158,159,161,164,165,167] HBeAg negative conversion rates for HBeAg positive cases at the time of commencement of combination therapy were 20–23% at 1 year, 17–25% at 2 years, 14–61% at 3 years; seroconversion rates were 5% at 1 year, 11% at 2 years, and 14% at 3 years.[159,161,166] Reported factors related to HBeAg negative conversion were ALT level (high), and the history of IFN therapy in the past.[159,166] If hepatitis associated with lamivudine-resistant HBV occurs, adefovir resistance develops if therapy is changed from lamivudine to adfovir, but if lamivudine+adefovir combination therapy is administered, the reported incidence of HBV resistant to both agents is low.[191]

Entecavir therapy is also administered to patients with lamivudine-resistant HBV (including cases unresponsive to lamivudine). The short-term results for entecavir therapy are good, and in some USA studies reported an HBV DNA negative conversion rate of 21% at 1 year, and 34–40% at 2 years, and an ALT normalization rate of 65% at 1 year, and 81% at 2 years.[192,193] However, the appearance of entecavir-resistant HBV associated with long term administration of entecavir has been confirmed. The incidence of entecavir-resistant HBV was 6% at 1 year and 8–13% at 2 years, and rebound of the HBV DNA load due to entecavir-resistant HBV was 1% at 1 year and 9% at 2 years. A Japanese study reported favorable results with a HBV DNA negative conversion rate of 16% at 6 months and 33% at 1 year, and ALT normalization rate of 78% at 6 months and 81% at 1 year,[194–196] although entecavir-resistant HBV was detected in 26% of cases up to year 3, in whom hepatitis rebounded in 40%.[196] In this way, entecavir therapy for lamivudine-resistant (or unresponsive) HBV may also produce viral strains resistant to entecavir.

Recommendations

- *Lamivudine+adefovir combination therapy is recommended for treatment of lamivudine-resistant HBV.*
- *Entecavir therapy of lamivudine-resistant HBV may also produce viral strains resistant to entecavir.*

4.4.2 Adefovir-resistant HBV

Reported adefovir-resistant mutations include rtA181V/T, rtI233V and rtN236T in the HBV polymerase reverse transcriptase (rt) region. Of these mutations, *in vitro* and *in vivo* testing has demonstrated sensitivity to both lamivudine and entecavir for the rtN236T mutation, but lamivudine resistance for the rtA181V mutation.[7,197] In 132 patients with lamivudine-resistant HBV treated with lamivudine+adefovir combination therapy, multiple resistant strains were seen in 3 cases before the commencement of adefovir therapy, and in 2 further

cases after therapy commenced (overall incidence 4%).[168]

Entecavir+adefovir combination therapy is administered to patients with HBV resistant to both lamivudine and adefovir, with undetermined results. On the other hand, in reports from Europe, in cases with resistance to lamivudine or adefovir monotherapy, or resistant/unresponsive to lamivudine+adefovir combination therapy, administration of the new agent tenofovir (median treatment period 23 months) yielded HBV DNA negative conversion in 79% of cases, HBeAg negative conversion in 24%, and HBsAg negative conversion in 3%.[198] In cases where lamivudine was ineffective and there was no response after at least 24 weeks of adefovir therapy, 12 weeks of tenofovir monotherapy or tenofovir+ lamivudine combination therapy reduced the HBV DNA load by a mean 2.19 log IU/mL, with HBV DNA negative conversion rates after 48 weeks and 96 weeks of 46% and 64% respectively.[199] Tenofovir is effective against multiresistant HBV strains, and it is hoped that it will be approved for use in clinical practice in Japan.

Recommendation

- ***Entecavir+adefovir combination therapy is administered to patients with HBV resistant to both lamivudine and adefovir, with undetermined results.***

4.4.3 Entecavir-resistant HBV

Entecavir-resistance involves one of the amino acid mutations, rtT184, rtS202 or rtM250 in addition to the amino acid mutations rtM204V and rtL180M that confer lamivudine resistance.[181] Efficacy has been reported for lamivudine+adefovir and for entecavir+adefovir combination therapy against entecavir-resistant HBV.[200,201] On the other hand, another study found that HBV DNA negative conversion was not achieved with lamivudine+adefovir combination therapy, but lamivudine+tenofovir combination therapy was effective.[202] At present the long term results for these combined therapy methods are unclear, and further studies including therapeutic results for tenofovir will be required.[7,203]

Recommendations

- ***Lamivudine+adefovir or entecavir+adefovir combination therapy is recommended for the treatment of entecavir-resistant HBV infection.***
- ***Tenofovir can be expected to be effective against multiagent resistant HBV strains.***

4.5 Towards a drug-free state

NA therapy for chronic hepatitis B produces a strong antiviral effect compared to IFN therapy, irrespective of HBV genotype, and has the added benefit of a low level of adverse reactions. On the other hand, with NA therapy, resistant mutations can appear with long term administration, the safety of long term administration has not been confirmed, and medical costs are high. Accordingly, when good therapeutic efficacy is achieved, cessation of NA therapy may be considered. However, there is a high likelihood of hepatitis recurrence following treatment cessation,[78] so it is important to identify cases unlikely to relapse and to cease NA therapy only in patients in whom treatment cessation is considered feasible. Sequential therapy is also being trialed, whereby the NAs are ceased after switching over to IFN, with the aim of continued therapeutic effect, or even achieving HBsAg negative conversion, after stopping NA therapy.

4.5.1 Cessation of NAs

NAs exert antiviral effects through inhibition of HBV DNA reverse transcriptase, but are unable to eliminate cccDNA present in hepatocyte nuclei. Accordingly, after cessation of NA therapy, even if HBV DNA negative conversion has occurred, this cccDNA becomes a template for HBV replication to resume, leading to recurrence of hepatitis.[204] Accordingly, HBV DNA negative conversion cannot be used as the sole criterion for cessation of NA therapy.

In such cases, HBcrAg and HBsAg become useful markers. A significant positive correlation has been reported between HBcrAg and cccDNA, even during NA therapy.[205,206] In fact, evaluation of cases of exacerbated hepatitis following cessation of NA therapy revealed significantly lower levels of HBcrAg (3.2 *vs* 4.9, $P = 0.009$) in the non-recurrence group compared to the recurrence group,[207] indicating that HBcrAg is a potential marker for cessation of NA therapy. Similarly to HBcrAg, HBsAg is thought to be little affected by NA transcriptase inhibition, and the retreatment rate after cessation of NA therapy was significantly lower for the group with low HBsAg levels (<1000 IU/mL) at the time of cessation (18% *vs* 63%, $P = 0.049$).[208]

Based on the above results, the MHLW research group produced a report titled "Studies concerning efficacy of IFN therapy aimed at creation of treatment discontinuation standards and treatment discontinuation in NAs therapy for hepatitis B", setting out policy regarding cessation of NA therapy.[209,210] A summary is shown in

Table 14 Conditions required for cessation of NA therapy

Patient criteria
• Both the treating physician and the patient fully understand that after cessation of NA therapy, there is a high incidence of recurrence of hepatitis, possibly severe
• Follow-up is possible after treatment cessation, and appropriate treatment is possible even if hepatitis recurs
• Even if recurrence of hepatitis occurs, it is unlikely to be severe if the degree of fibrosis is mild and the hepatic reserve is good
Laboratory criteria
• At least 2 years of administration of NAs
• Undetectable serum HBV DNA levels (using real time PCR) at the time of treatment cessation
• Negative serum HBeAg at the time of treatment cessation.

Table 14. To determine the criteria for therapy cessation, as shown below in Table 15, HBsAg and HBcrAg levels at therapy cessation were scored, the final score allocated to the following 3 categories of risk of relapse, and the success rate was predicted. Successful cessation was defined as "finally resulting in inactive carrier status, i.e. ALT ≤30 U/L and HBV DNA <4.0 log copies/mL". Studies have shown that if this inactive carrier status is achieved, there is no progression of liver disease, and risk of HCC also declines.[34,211]

Recommendations

- ***The following 3 patient criteria must be met for cessation of NA therapy: (1) Both the treating physician and the patient fully understand that after cessation of NA therapy, there is a high incidence of recurrence of hepatitis, possibly severe; (2) Follow-up is possible after treatment cessation, and appropriate treatment is possible even if hepatitis recurs, (3) Even if recurrence of hepatitis occurs, it is unlikely to be severe if the degree of fibrosis is mild and the hepatic reserve is good.***
- ***The 3 laboratory criteria for cessation of NA therapy are: (1) At least 2 years of administration of NAs; (2) undetectable serum HBV DNA levels (using real time PCR); (3) negative serum HBeAg at the time of treatment cessation.***
- ***When the above criteria are met, it is possible to predict the risk of relapse from HBsAg and HBcrAg levels at the time of cessation of therapy. NA therapy should be continued in the high risk group.***

4.5.2 Sequential therapy

As described earlier, although NAs inhibit replication of HBV DNA, they have no effect on cccDNA, whereas IFN has a weak effect on HBV reproduction inhibition, but

Table 15 Risk of relapse following cessation of NA therapy

HBsAg load at cessation (IU/mL)	Score	HBcrAg load at cessation (U/mL)	Score
<1.9 log (80)	0	<3.0 log	0
≥1.9 log (80), <2.9 log (800)	1	≥3.0 log, <4.0 log	1
≥2.9 log (800) IU/mL	2	≥4.0 log	2

Relapse risk	Total score	Predicted success rate	Evaluation
Low risk group	0	80~90%	Group for which cessation may be considered. However, even in the low risk group, recurrence of hepatitis can occur, so vigilance is required.
Moderate risk group	1~2	Approx. 50%	Group for which cessation may be considered depending on circumstances. This group requires further evaluation concerning cessation criteria and methods.
High risk group	3~4	10~20%	Continued treatment is recommended for this group. However, for patients aged <35, the cessation success rate is relatively high at 30~40%.

has immunomodulatory effects including increasing viral antigen presentation to host cells, with antiviral effects persisting after completion of administration. Accordingly, a number of clinical trials have been conducted using IFN in combination with NAs. Combination therapy regimens are either synchronous combination therapy or sequential combination therapy, where a NA is administered synchronously with IFN for a fixed period, then switched over to IFN monotherapy (or the switchover is from NA monotherapy to IFN monotherapy, with no synchronous administration period). Synchronous combined therapy was aimed to enhance therapeutic efficacy. However, the antiviral effects of synchronous Peg-IFN+lamivudine combination therapy may be higher than lamivudine monotherapy during treatment, but its therapeutic effect has been reported to be almost the same as Peg-IFN monotherapy.[8,22,115] Accordingly, at this time there is insufficient evidence that therapeutic effect improves with synchronous administration of IFN and NAs.

As with synchronous therapy, sequential therapy can be used with the aim of "enhanced therapeutic efficacy", or for "suppression of recurrence of hepatitis after cessation of NAs". Initially, Serfaty *et al.* conducted a sequential therapy study with 14 patients with HBeAg positive chronic hepatitis B in whom IFN treatment was ineffective. Lamivudine monotherapy was administered for 20 weeks, then IFN+lamivudine combination therapy for 4 weeks, followed by IFN monotherapy for 24 weeks, producing favorable therapeutic results with an HBeAg seroconversion rate of 45%, and HBV DNA negative conversion rate of 57%.[212] However, subsequent studies of sequential therapies following a variety of protocols have failed to demonstrate a significant enhancement of therapeutic efficacy.[213–215] A Japanese multicenter collaborative trial of sequential therapy following a similar method to Saferty *et al.* also found no significant enhancement of therapeutic efficacy in comparison to IFN monotherapy as a historical control.[216] However, this study did show that in almost all responders, HBeAg negative conversion occurred during initial lamivudine monotherapy. It has also been reported that in sequential entecavir+IFN combination therapy, a high rate of efficacy was demonstrated in patients where HBeAg negative conversion was seen during entecavir monotherapy.[215] Accordingly, in Japan the aim of sequential therapy is not to enhance therapeutic efficacy through addition of NAs, but rather as a method for safely discontinuing NAs, and currently is indicated in "patients who have undergone HBeAg negative conversion during NA therapy, or are HBeAg negative". Currently the MHLW research group is conducting prospective trials with the aim of evaluating the efficacy and safety of sequential therapy using Peg-IFN, with the following as the main entry criteria: (1) at least 2 years of NA therapy; and (2) HBeAg negative and HBV DNA load <3.0 log copies/mL (preferably undetectable HBV DNA using real time PCR). As evidence is accumulated, the indications for sequential therapy should become clearer.

Comprehensive studies are lacking concerning sequential therapy in cases where a favorable therapeutic response is maintained by NA therapy. Ning *et al.* conducted a randomized controlled study with 102 HBeAg positive patients without cirrhosis who were administered entecavir for 4 years, resulting in HBV DNA <3.0 log copies/mL and HBeAg <100 PEIU/mL. The sequential therapy group was administered entecavir+Peg-IFNα-2a synchronous combination therapy for 8 weeks, then Peg-IFN monotherapy for 40 weeks, and the entecavir monotherapy group was treated with entecavir alone. They reported that no difference between groups in the HBV DNA load, but a higher rate of HBsAg negative conversion during treatment for the sequential therapy group (27%, 4/15). As described above, in Japan sequential therapy is conducted with the aim of safely ceasing NAs, and there is no data concerning HBsAg negative conversion.

4.5.3 Retreatment following cessation of NAs or completion of sequential therapy

Recurrence of hepatitis following cessation of NA therapy (including sequential therapy) has the potential to become severe, and retreatment may be necessary. The abovementioned MHLW research group proposed criteria for retreatment after cessation of NA therapy. A retrospective analysis of patients who became inactive carriers found that approximately 2/3 experienced transient elevation of HBV DNA or ALT levels after cessation of NA therapy, clarifying that retreatment was not necessary for all cases of HBV DNA or ALT rebound.[208] However, a return to inactive carrier status is unlikely in cases with elevation of ALT ≥80 U/L or HBV DNA ≥5.8 log copies/mL, and retreatment should be considered.

Recommendations

- ***The aim of sequential therapy is not enhancement of the therapeutic efficacy of NAs, but as a method of safe cessation of NA therapy, and is currently indicated in "patients who have undergone HBeAg negative conversion during NA therapy, or are HBeAg negative".***

- ***Following cessation of NA therapy or completion of sequential therapy, a return to inactive carrier status is unlikely in cases with elevation of ALT ≥80 U/L or HBV DNA ≥5.8 log copies/mL, and retreatment should be considered.***

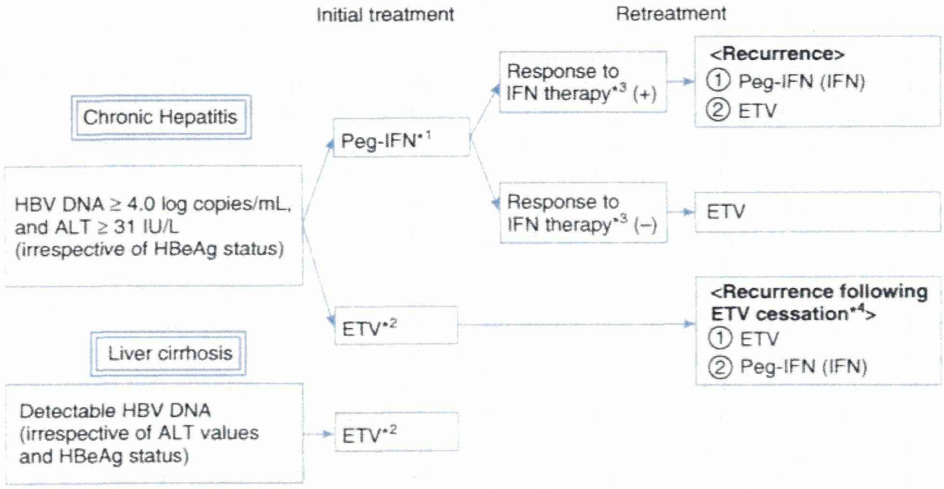
5. TREATMENT OF CHRONIC HEPATITIS AND LIVER CIRRHOSIS

5.1 Basic principles of antiviral therapy (Fig. 6)

5.1.1 Chronic hepatitis (initial treatment)

PEG-IFN THERAPY FOR a finite duration may provide drug-free, long-lasting HBeAg seroconversion, and also HBsAg negative conversion, with no development of drug resistance. For conventional IFN treatment, therapeutic efficacy fell for patients 35 years or older and for genotype C,[112] but in Peg-IFN clinical trials in Japan as well as overseas, there was no significant correlation between therapeutic efficacy and genotype or age.[8–10,115,124] Taking these characteristics into consideration, Peg-IFN monotherapy should be generally considered the first choice for initial treatment of chronic hepatitis, regardless of HBeAg status or HBV genotype. In cases where avoidance of long-term administration of NAs is preferable, particularly for young patients and women desiring to bear children, Peg-IFN is the treatment of first choice. It should be noted that, in Japanese clinical trials, ≥95% of subjects are aged <50 years, in both HBeAg positive and negative groups, and the efficacy of Peg-IFN therapy has not been adequately assessed in patients aged ≥50 years.[100] A full explanation may be warranted that the HBeAg seroconversion rate and HBV DNA negative conversion rate are not necessarily high, that it is difficult to efficacy in individual cases prior to treatment, and possible adverse reactions.

On the other hand, in cases where Peg-IFN is contraindicated for tolerability, or in cases with cirrhosis, entecavir therapy is administered initially with the aim of maintaining long term remission. However,



*1 Full explanation required that HBeAg seroconversion rate and HBV DNA negative conversion rate are not necessarily high, that effectiveness prediction for each case prior to treatment is difficult, and explanation of expected adverse reactions.
*2 After confirming no intention to produce children, explain fully the need for long-term continuous administration, and explain the risk of resistant mutations.
*3 Use ALT normalization, HBV DNA load decline (HBsAg load decline), and in HBeAg positive cases, use HBeAg negative conversion for reference, then make the judgment at 24-48 weeks after treatment completion.
*4 Retreatment standard for relapse after ETV cessation: HBV DNA ≥ 5.8 log copies/ml, or ALT ≥ 80 IU/L.

Figure 6 Basic protocol for antiviral treatment.

lamivudine therapy is recommended in cases of acute exacerbation of hepatitis associated with jaundice, because transaminases can rise in these patients following entecavir administration. When a prolonged treatment period is likely, a switch should be made to entecavir. Before commencing entecavir therapy, it is necessary to fully explain the need for long term continuous treatment, possible safety problem during pregnancy and the risk of resistant mutations, before obtaining informed consent.

5.1.2 Chronic hepatitis (retreatment)

In cases where the HBV DNA and ALT levels declined and hepatitis became quiescent following treatment with conventional IFN or Peg-IFN treatment, retreatment with Peg-IFN therapy should be considered if hepatitis recurs. Even in patients where quiescence of hepatitis was not obtained by conventional IFN therapy, retreatment with Peg-IFN is an option. However, in cases where tolerability of conventional IFN therapy is poor, and in cases where quiescence of the hepatitis is not obtained by the preceding Peg-IFN therapy, entecavir therapy is administered with the aim of maintaining long term remission. Even in cases of recurrence of hepatitis following cessation of entecavir therapy, retreatment with entecavir should be considered. The criteria for recurrence of hepatitis are HBV DNA levels ≥5.8 log copies/mL, or ALT levels ≥80 U/L.[209]

5.1.3 Liver cirrhosis

In Japan, there is insufficient evidence for the efficacy and safety of IFN treatment for HBV cirrhosis, and it is not officially approved. The initial treatment for liver cirrhosis is long term continuous entecavir therapy.

Recommendations

- *In general, Peg-IFN monotherapy should be considered the first choice treatment for chronic hepatitis, irrespective of HBeAg status or HBV genotype.*
- *Retreatment using Peg-IFN should be considered in patients with chronic hepatitis when recurrence of hepatitis occurs following treatment with conventional IFN or Peg-IFN. Entecavir therapy should be administered to IFN non-responders, with no efficacy from earlier IFN therapy. Even in cases of recurrence of hepatitis following cessation of entecavir therapy, retreatment with entecavir should be considered.*
- *The initial treatment for liver cirrhosis is long term continuous entecavir therapy.*

5.2 HBeAg positive chronic hepatitis

5.2.1 Timing of commencement of treatment

Even if they are HBeAg positive, asymptomatic carriers in the immune tolerance phase with ALTs consistently within the normal range present few abnormal histological findings. Furthermore, irrespective of the NAs or IFN, seroconversion rates from antiviral therapy are low at <10%.[217–222] For these reasons, treatment is not indicated in asymptomatic carriers.[223] HBV DNA, HBeAg and ALT levels should be monitored at 3–6 month intervals, and treatment considered if ALT levels rise.[32,224–227]

Treatment is indicated in patients with HBeAg positive chronic hepatitis B with HBV DNA levels ≥4.0 log copies/mL and ALT ≥31 U/L.[4,30–32] If there is no evidence of advanced fibrosis, and the patient is not considered at risk of fulminant hepatitis, it may be advisable to withhold treatment for another year while monitoring ALT, HBeAg and HBV DNA levels, anticipating natural HBeAg seroconversion, since the annual likelihood of natural HBeAg seroconversion is 7–16% per annum.[4,30–32] However, if HBeAg seroconversion does not occur, persistent hepatitis may cause progression of hepatic fibrosis,[2,4,228] necessitating treatment to prevent this. HBeAg positivity and elevated HBV DNA levels are independent risk factors for hepatocellular carcinogenesis and progression to liver cirrhosis,[2,34,37,211,229–231] and patient age (≥40 years) is also a risk factor for progression of liver cirrhosis and HCC.[2,36,37] The risk of HCC is also higher in patients with platelet counts <150 000, reflecting progression of hepatic fibrosis, or a family history of HCC.[38,39] Accordingly, treatment should be positively considered in patients with any of the abovementioned risk factors, even if they do not meet the criteria for commencement of treatment. Liver biopsy (or noninvasive alternative) should be performed as an optional investigation to determine the extent of fibrosis, and treatment is indicated if hepatic fibrosis is diagnosed.

Treatment should be commenced immediately, without a monitoring period, in patients with acute exacerbations of hepatitis associated with jaundice, or if there are concerns about liver failure.

Recommendations

- *Treatment is not indicated in HBeAg positive asymptomatic carriers.*
- *Treatment is indicated in patients with HBeAg positive chronic hepatitis cases with HBV DNA levels ≥4.0 log copies/mL and ALT ≥31 U/L.*
- *When ALT levels increase in patients with HBeAg positive chronic hepatitis, if there is no evidence of*

advanced fibrosis, and the patient is not considered at risk of fulminant hepatitis, one option is to defer treatment for approximately one year. However, if HBeAg seroconversion does not occur naturally, treatment is indicated to prevent progression of hepatic fibrosis due to persistent hepatitis.

- ***For patients who do not meet the criteria for commencement of treatment, in but have a high risk of HCC, liver biopsy (or noninvasive alternative) should be performed as an optional investigation to determine the extent of fibrosis, and treatment is indicated if hepatic fibrosis is diagnosed.***
- ***Treatment should be commenced immediately, without a monitoring period, in patients with acute exacerbations of hepatitis associated with jaundice, or if there are concerns about liver failure.***

5.2.2 Selection of therapeutic agent

In patients with HBeAg positive chronic hepatitis, the risk of liver failure is reduced by negative conversion of HBeAg, and life expectancy increased,[2,34,211,228–232] so the short term target of antiviral therapy is HBeAg seroconversion, and the ultimate long term target is negative conversion of HBsAg.

In general Peg-IFN monotherapy is considered the treatment of first choice for initial antiviral therapy, taking into consideration the absence of drug resistance, and relatively high probability that a prolonged HBeAg seroconversion, in a drug free state, can be achieved with treatment for a finite duration.

HBeAg seroconversion rates are no more than 24%–36% at 24 weeks after completion of 48 weeks of Peg-IFN therapy,[8–10] but in responders that achieved HBeAg seroconversion, HBeAg negative status was maintained in 77%–86% of patients in drug free status.[11–13] Even in cases who failed to achieve HBe seroconversion at the conclusion of treatment, delayed seroconversion occurs in 14% of cases 1 year later,[12] in 27% 3 years later,[11] and in 69% 5 years later.[13] The HBsAg negative conversion rate was low at 2.3%–3.0% of all patients 24 weeks after the conclusion of treatment,[8–10] but in responders who achieved HBeAg seroconversion, the HBsAg negative conversion rate was at an extremely high rate, 30% 3 years after treatment completion,[11] and 64% (with conventional IFN) 14 years after treatment completion.[233]

Entecavir is the first choice in patients at high risk of progression of hepatic fibrosis to liver cirrhosis. Furthermore, in cases where Peg-IFN is ineffective or contraindicated, entecavir therapy is administered with the aim of maintaining long term remission.

Higher rates of HBV DNA negative conversion and ALT normalization are achieved after 1 year of entecavir therapy than with Peg-IFN therapy.[14,25,183] Furthermore, after 4–5 years of long term continuous treatment, even higher levels of therapeutic efficacy are achieved, with HBV DNA negative conversion rates of 94%–96%, and ALT normalization rates of 80%–93%.[15,16] The HBeAg seroconversion rate was no better than 12%–22% after 1 year,[14,15,18,19,183] lower than for Peg-IFN, but the seroconversion rate increases with long term continuous treatment, and even if HBeAg seroconversion does not occur at the 2 year mark, after 5 years the seroconversion rate was 23%,[16] and a report from Japan indicated that the seroconversion rate was 38% after 4 years.[15] On the other hand, the HBsAg negative conversion rate is lower than for Peg-IFN, only 1.7% 48 weeks after commencement of treatment,[14] and 0.6%–5.1% after 3–5 years of treatment.[16,17,21]

In patients administered NA therapy that achieve HBeAg seroconversion and maintain HBV DNA negative status long term, cessation of NA therapy can be considered. The criteria established by the MHLW research group mentioned earlier should be referred to when considering stopping cessation of NA therapy, with less than 10% of patients meeting these criteria.[208] Sequential therapy with Peg-IFN, aiming at drug free status, can also be considered, although at present there is a lack of evidence supporting this method. HBeAg reappeared in 50% or more of cases where lamivudine therapy was ceased after seroconversion,[130] whereas seroconversion was maintained in 73%–77% of cases treated with entecavir.[20] There is little data available concerning HBeAg following cessation of entecavir, and more data needs to be gathered regarding this subject.

Low HBV DNA levels and high ALT levels are factors related to therapeutic efficacy that are common to both IFN and NA therapy, although both factors change along with natural course. These factors should be considered, in addition to the degree of necessity of treatment, in choosing the appropriate timing for commencement of treatment.

Recommendations

- ***In general, Peg-IFN monotherapy, with the aim of HBeAg seroconversion, is considered the treatment of first choice for initial antiviral therapy in patients with HBeAg positive chronic hepatitis.***
- ***Retreatment with Peg-IFN can be considered when required in responders to initial treatment with conventional IFN.***

- ***In patients with cirrhosis, and in cases where Peg-IFN is ineffective or contraindicated, entecavir is the first choice therapy with the aim of maintaining long term remission.***
- ***Lamivudine therapy is recommended in cases of acute exacerbation of hepatitis associated with jaundice.***

5.3 HBeAg negative chronic hepatitis

5.3.1 Timing of commencement of treatment

If HBeAg seroconversion occurs naturally or through treatment, in approximately 80% of cases HBV DNA levels remain low value, and ALT levels within the normal range, the patient becoming an HBeAg negative inactive carrier. HBeAg negative inactive carriers have a low risk of liver cirrhosis and HCC, with a good long-term prognosis,[4,30,32,50,234–239] and if HBV DNA negative conversion occurs, HBsAg also undergoes negative conversion in 1%–3% of patients per year.[240]

However, over the long term hepatitis recurrence is seen in 10%–20% of patients first diagnosed as HBeAg negative inactive carrier,[32,50,227,238,241] so accurate differentiation between the true inactive carrier state and HBeAg negative chronic hepatitis is difficult. In the current Guidelines, inactive carriers are defined as "patients in a drug free status (no antiviral therapy), and where three or more blood tests taken over the course of at least one year satisfy all the following conditions: (1) Persistently negative HBeAg; (2) Persistently normal ALT levels (≤30 U/L); and (3) HBV DNA <4.0 log copies/mL". Where advanced fibrosis is suspected on the basis of imaging studies or platelet counts, a liver biopsy should be conducted to assess the need for treatment.

Even after the diagnosis of inactive carrier status has been made, patients should be monitored every 6–12 months, and treatment is indicated if ALT levels increase. The incidence of hepatitic activity of at least moderate grade on liver biopsy in patients with ALT <40 U/L measured at least 3 times in 1 year is 7% if HBV DNA is 4–5 log copies/mL, 1.4% if HBV DNA is <4 log copies, and the incidence of hepatic fibrosis of at least moderate grade is 10% and 0.7%, respectively.[35] Accordingly, even if ALT levels remain within the normal range, liver biopsy is an option if HBV DNA is ≥4 log copies/mL, and treatment should also be considered.

It is common for patients with HBeAg negative chronic hepatitis to exhibit repeated transient increases in ALT and HBV DNA levels, and the likelihood of natural remission is low.[228,242–244] Progression of fibrosis at an advanced age is common compared to patients with HBeAg positive chronic hepatitis, so HBeAg negative chronic hepatitis should be considered a more advanced disease stage.[228,243,245] Even in patients with HBeAg negative chronic hepatitis, a high HBV DNA load, age ≥40 years, and a family history of HCC are independent risk factors for progression to liver cirrhosis and HCC,[2,34,36,37,211,229–231] so treatment should be actively considered if any of these factors are present. If hepatic fibrosis is confirmed by liver biopsy (or noninvasive alternative) as an optional investigation, treatment is indicated.

Recommendations

- ***In patients with HBeAg negative chronic hepatitis, progression of fibrosis at an advanced age is common compared to patients with HBeAg positive chronic hepatitis, so HBeAg negative chronic hepatitis should be considered a more advanced disease stage.***
- ***As for HBeAg positive chronic hepatitis, treatment is indicated in patients with HBeAg negative chronic hepatitis cases with HBV DNA ≥4.0 log copies/mL and ALT ≥31 U/L.***
- ***Even for cases fitting the criteria for inactive carrier status, if advanced fibrosis is suspected on the basis of imaging studies or platelet counts, a liver biopsy should be conducted. If hepatic fibrosis is confirmed, treatment is indicated.***
- ***Even after the diagnosis of inactive carrier status has been made, patients should be monitored every 6–12 months, and treatment is indicated if ALT levels increase.***

5.3.2 Selection of treatment

The initial aim of treatment of patients with HBeAg negative chronic hepatitis is to lead to inactive carrier status, with the additional aim of continued HBV DNA negative conversion in patients with advanced fibrosis. The ultimate aim is HBsAg negative conversion.

As for HBeAg positive patients, Peg-IFN is the therapy of first choice. Peg-IFN treatment of HBeAg negative patients decreases HBV DNA levels in 43%–44% of cases, with maintenance of HBV DNA levels <4.0 log copies/mL in 25%–28% of cases.[23] However, the HBV DNA negative conversion rate was 19% 24 weeks after the conclusion of treatment,[22] and long term was only 18%–21%,[23,24] with a lower probability of maintaining HBV DNA negative conversion compared to entecavir. On the other hand, the HBsAg negative conversion rate was 2.8%–4.0% 24 weeks after conclusion of treatment,[107] and 8.7%–12% 3 years after.[23,24] In responders

who achieved HBV DNA negative conversion, the HBsAg negative conversion rate is 44% at 3 years,[23] and in patients with HBsAg levels <10 IU/mL at conclusion of treatment, the rate is extremely high at 52%,[122] characteristics not seen with entecavir therapy. In this way, Peg-IFN monotherapy of HBeAg negative patients does not yield high overall rates of HBV DNA continuous negative conversion, but Peg-IFN is the treatment of first choice because in responders a drug free state and HBsAg negative conversion can be achieved with a finite duration of treatment. However, all these results are from overseas, and there is no Japanese data concerning elimination of HBsAg by Peg-IFN therapy.

On the other hand, as for HBeAg positive chronic hepatitis, patients at high risk of progression of hepatic fibrosis to liver cirrhosis, and in cases where Peg-IFN is ineffective or contraindicated, entecavir is the treatment of first choice.

With entecavir treatment, the HBV DNA negative conversion rate is 90% after 48 weeks of treatment,[25] and long term it is extremely high at 100%,[15] enabling certain achievement of HBV DNA negative conversion irrespective of pretreatment factors. However, the relapse rate after treatment cessation is high at 97%, so long term continuous treatment is the norm. The HBsAg negative conversion rate at 48 weeks after treatment commencement is reported as 0%.[25] Even with long term continuous treatment, HBsAg negative conversion is considered rare, but there have been reports of NA therapy with lamivudine yielding a HBsAg negative conversion rate of 6.9% at 9 years,[246] and for adefovir 5% at 3.8 years.[172] There are very few reports of the long term therapeutic results with entecavir, and further studies will be required to elucidate the HBsAg negative conversion rate with long term treatment.

Recommendations

- ***In patients with HBeAg negative chronic hepatitis, the overall rate of HBV DNA continuous negative conversion is not high with Peg-IFN therapy, but in responders we can expect high rates of drug free state and HBsAg negative conversion. Peg-IFN should also be considered the treatment of first choice for patients with HBeAg negative chronic hepatitis.***
- ***In patients at high risk of progression of hepatic fibrosis to liver cirrhosis, and in cases where Peg-IFN is ineffective or contraindicated, entecavir is the treatment of first choice with the aim of maintaining long term remission.***
- ***Lamivudine therapy is recommended in cases of acute exacerbation of hepatitis associated with jaundice.***

5.4 Liver cirrhosis

Compared to non-cirrhotic chronic hepatitis, patients with liver cirrhosis are at greater risk of chronic liver failure and HCC, necessitating more aggressive intervention, and the short term goal of treatment is not reduction in the HBV DNA load, but to keep HBV DNA persistently undetectable. IFN can cause acute exacerbation of hepatitis during treatment; particularly in patients with decompensated cirrhosis there is a risk of liver failure and serious infection, so IFN is contraindicated.[247,248] There are reports of efficacy for IFN and Peg-IFN therapy of compensated cirrhosis similar to that for chronic hepatitis,[102,221,249] but consideration of maintenance of continuous HBV DNA negative conversion, and safety issues, makes entecavir the first choice treatment.

5.4.1 Compensated cirrhosis

By suppressing HBV replication, NAs inhibit progression of fibrosis and progression of compensated cirrhosis to decompensated cirrhosis. In a randomized controlled clinical trial that randomly allocated lamivudine and a placebo to 651 patients with liver cirrhosis or advanced fibrosis, the proportion of patients with increased Child Pugh scores declined with lamivudine therapy (3.4% *vs* 8.8%), and the proportion of patients whose disease stage progressed also declined (7.8% *vs* 17.7%).[250] Long term continuous entecavir therapy ameliorates hepatic fibrosis, in 57% of all patients after 3 years of treatment, and in 85% of patients with advanced fibrosis, including liver cirrhosis.[18] With continuous treatment for an average of 6 years, hepatic fibrosis improved in 88% of all patients, and in 100% of cases of patients with advanced fibrosis, including liver cirrhosis.[251] In other words, liver cirrhosis is not an irreversible condition, and with long term continuous entecavir therapy it is possible to ameliorate fibrosis.

Relapse after cessation of NA therapy presents a risk of liver failure, so in general treatment continues for the rest of the patient's life. Cessation of treatment can be considered in cases of HBsAg negative conversion, but no results are available concerning long term outcomes following cessation of NA therapy. Even in patients exhibiting histological improvement of fibrosis, or patients meeting the criteria for cessation of treatment in chronic hepatitis, the lack of clear data regarding the pros and cons of treatment cessation means it cannot be recommended.

Recommendations

- *Entecavir is the treatment of first choice for compensated cirrhosis.*
- *Long term continuous entecavir therapy ameliorates hepatic fibrosis, including liver cirrhosis.*
- *Relapse after cessation of NA therapy presents a risk of liver failure, so in general treatment continues for the rest of the patient's life.*

5.4.2 Decompensated cirrhosis

The aim of treatment for decompensated cirrhosis is reversal of liver failure through improving hepatic function. Although several studies have reported improved hepatic function with lamivudine therapy,[249,252–254] fewer studies have evaluated the therapeutic efficacy in patients with decompensated cirrhosis of entecavir, which is currently the treatment of first choice.

In a report on 70 patients with decompensated cirrhosis administered entecavir, the therapeutic results after 1 year were 89% for undetectable HBV DNA, 22% for HBeAg seroconversion, and 76% for ALT normalization, similar to results for compensated cirrhosis. Albumin levels rose from 2.8 g/dL to 3.2 g/dL, total bilirubin fell from 3.0 mg/dL to 1.9 mg/dL, and the prothrombin time (PT) improved from 16.3 sec to 13.9 s. As a result, after treatment for 1 year in 49% of cases the Child-Turcotte-Pugh score improved by ≥2 points, declining from the pretreatment average 8.1 ± 1.7 to 6.6 ± 2.4, and 66% of cases improved to Child class A. Similarly, the MELD score decreased from 11.1 ± 3.8 to 8.8 ± 2.3.[255] In a trial where 191 cases of decompensated cirrhosis were allocated randomly to entecavir or adefovir for 96 weeks in a comparison of therapeutic efficacy, a higher rate of HBV DNA negative conversion was seen with entecavir (57% *vs* 20%), and in both groups the Child-Turcotte-Pugh score improved or was maintained in 2/3 of patients.[256] Although entecavir improves hepatic function in patients with decompensated cirrhosis in this way, in order to avoid relapse after cessation of treatment, lifelong continuation of treatment is recommended. On the other hand, the 1 year survival rate was 87% in the first study,[255] and the 6 month survival rate in the latter study was 88%,[256] indicating deaths from failure usually occur in the 3–6 months before the onset of therapeutic effect of NAs. We must recognize that a liver transplant is required to save such cases.[252] Also, for decompensated cirrhosis with a MELD score of ≥20, 5 cases were reported of entecavir therapy causing lactic acidosis, of whom one patient died.[257] Accordingly, careful monitoring is required during treatment of decompensated cirrhosis.

Recommendations

- *Entecavir is the treatment of first choice for decompensated cirrhosis. Although improvement of hepatic function can be expected, in order to avoid relapse after cessation of treatment, lifelong continuation of treatment is the norm.*
- *There is a report of lactic acidosis associated with entecavir therapy for decompensated cirrhosis, necessitating careful monitoring.*
- *IFN is contraindicated for decompensated cirrhosis, because of the risk of liver failure and serious infection.*

5.5 Suppression of HCC by antiviral therapy

5.5.1 IFN

Studies into the effects of IFN on carcinogenesis have all involved conventional IFN, and none Peg-IFN. Randomized controlled clinical trials evaluating the effects of IFN therapy on carcinogenesis comprise one study of 121 patients with HBeAg positive chronic hepatitis (liver cirrhosis; 10.3% of treated cases and 14.7% of controls),[258] and one small study evaluating 64 patients with HBeAg positive chronic hepatitis.[259] The results of the two trials differed; the former found a reduction in carcinogenesis (1.5% *vs* 11.8%, $P = 0.043$), whereas the latter trial found no carcinogenesis suppression effect (3.0% *vs* 6.4%). Even two comparatively large-scale case-controlled studies that matched the clinical backgrounds yielded contradictory results. One study observed HBeAg positive patients, 233 treated with IFN and 233 untreated for 6.8 years, with cancers detected in 2% of treated patients and 7% of untreated controls, showing carcinogenesis significantly reduced in the IFN therapy group ($P < 0.025$).[90] On the other hand, the other study of HBeAg positive patients, 208 treated with IFN and 203 untreated, found no significant difference in the rate of carcinogenesis (2.9% *vs* 0%).[260] Although many other studies have evaluated the relationship between IFN therapy and carcinogenesis,[261–266] they have all been cohort studies and their results do not consistently demonstrate a carcinogenesis suppressor effect for IFN. In these cohort studies, the carcinogenesis rate in the control group (untreated patients) varies greatly from 0% to 30.8%, and the rate including patients with cirrhosis also varies from 0% to 100%, with considerable differences in subject clinical backgrounds. These differences in the clinical background of applicable cases may be related to the variations in the reported carcinogenesis suppression effect of IFN.

A number of meta-analyses have examined the relationship between IFN therapy and carcinogenesis. One

analysis of 11 studies comprising 1006 patients treated with IFN and 1076 untreated controls found IFN therapy significantly reduced the carcinogenesis risk ratio to 0.59.[267] Another meta-analysis of 8 studies found that, although carcinogenesis was suppressed in IFN treated patients compared to untreated controls (risk difference 5.0%), the carcinogenesis suppression effect was found in a subgroup of ethnic Asians, where the carcinogenesis rate in the untreated controls was ≥10%, and ≥70% of subjects were HBeAg positive.[268] A third meta-analysis of 7 studies evaluated the therapeutic effect of IFN in patients with cirrhosis, 122 cases of HCC developed in 1505 patients with liver cirrhosis, and a carcinogenesis risk difference of 6.4% in IFN treated patients compared to untreated controls.[269] The authors discussed that, although all 7 studies indicated a tendency for IFN therapy to suppress carcinogenesis, only 3 studies showed a significant difference, of which 2 studies were results from Asia. Then they concluded that the overall significant difference disappeared with elimination of the last 2 Asian studies, and no firm conclusion was made concerning carcinogenesis suppression by IFN therapy. Another meta-analysis of 12 studies examining 1292 IFN treated patients and 1450 untreated controls, IFN therapy significantly reduced the carcinogenesis risk ratio to 0.66.[270] A sub-analysis indicated that carcinogenesis was suppressed by IFN therapy in liver cirrhosis patients (11.6% *vs* 21.5%, risk ratio 0.53, 95% CI: 0.36–0.78), whereas for non-cirrhosis patients the cancer rate was low, 0.9% in treated patients and 1.1% in untreated controls, showing no significant difference.

In this way, the carcinogenesis suppression effect of IFN therapy differs according to the patient's clinical background. For patients with liver cirrhosis and a high risk of carcinogenesis, a carcinogenesis suppression effect is obtained, but for patients with chronic hepatitis and a low risk of carcinogenesis, the results concerning carcinogenesis suppression effect are not consistent. Further large-scale studies will be required to draw any definite conclusions. In addition, there have been no studies that provide a detailed evaluation of the antiviral effects of IFN treatment, i.e. whether the carcinogenesis suppression effect differs according to HBV DNA suppression, HBeAg seroconversion or ALT normalization; this issue requires further evaluation.

Recommendations

- ***Suppression of carcinogenesis by IFN therapy has been confirmed by meta-analyses.***
- ***However, studies of carcinogenesis suppression by IFN have comprised a variety of clinical backgrounds, such as carcinogenesis rate and proportion of patients with liver cirrhosis, and the carcinogenesis suppression effect stratified for antiviral effect has not been evaluated, leading to contradictory results.***

5.5.2 NAs

Only one randomized controlled trial examining the effect of lamivudine therapy on carcinogenesis has evaluated patients with liver cirrhosis and advanced fibrosis, with a carcinogenesis rate of 3.9% for the lamivudine treated group, significantly lower than that of 7.4% for the untreated group.[250] In a Japanese case-controlled multicenter collaborative study, matching factors such as age, gender, liver fibrosis, family history, albumin levels and platelet counts, the carcinogenesis rate for the 377 lamivudine treated patients was 0.4% per year, and 2.5% for controls with matched clinical backgrounds, indicating that lamivudine therapy suppresses carcinogenesis.[271] In a comparison of 142 patients with HBeAg positive chronic hepatitis treated with lamivudine and 124 untreated controls, carcinogenesis was significantly suppressed (0.7% *vs* 2.4%).[272] In a cohort study comparing 872 lamivudine treated patients with 699 historical controls, the annual carcinogenesis rate was 0.95% in patients with liver cirrhosis where HBV replication was continuously suppressed by lamivudine therapy, compared to 4.10% in patients with liver cirrhosis not administered lamivudine, 2.18% where lamivudine resistance occurred, and 5.26% for the group in whom lamivudine could not adequately suppress HBV replication. These results indicated that the carcinogenesis rate declines in patients with liver cirrhosis if HBV replication is continuously suppressed by lamivudine treatment.[273]

The above results are from before introduction of adefovir against lamivudine resistant strains. In a cohort study where lamivudine therapy was administered to patients with HBeAg negative chronic hepatitis B, followed by adefovir therapy in lamivudine-resistant cases, the carcinogenesis rate was 7.7% in 195 patients not administered lamivudine, compared with 1.1% in 92 patients in whom remission was maintained out of a total 201 lamivudine treated patients, and 1.8% in the remaining 109 patients in whom lamivudine was ineffective or resistance developed. Furthermore, among patients with appearance of lamivudine resistance, the carcinogenesis rate was 0% in 79 patients administered adefovir, and 6.7% in patients not administered adefovir, indicating that even in lamivudine-resistant cases, if HBV replication was suppressed continuously by adefovir combination therapy, carcinogenesis was

suppressed.[96] In a meta-analysis of 5 studies, including the one above, of a total 2289 patients, carcinogenesis occurred in 32/1267 patients (2.5%) in the lamivudine treated group, and 120/1022 (11.7%) in the untreated group. Lamivudine therapy reduced the carcinogenesis risk ratio to 0.22 by; furthermore, in a sub-analysis of 753 patients with liver cirrhosis the carcinogenesis risk ratio was 0.17 with lamivudine therapy, and in a sub-analysis of patients without liver cirrhosis the carcinogenesis risk was 0.21, both sub-analyses indicating a significant suppression effect.[270]

The efficacy of entecavir therapy in suppressing carcinogenesis was evaluated in a cohort study that matched clinical backgrounds using propensity scores. The results showed a 5 year carcinogenesis rate of 3.7% for the entecavir treated group, significantly less than that of 13.7% for the untreated control group. Entecavir therapy reduced the carcinogenesis risk ratio to 0.37, and also suppressed carcinogenesis in patients with liver cirrhosis.[274] Furthermore, in a recent cohort study with patients with liver cirrhosis, the 5 year carcinogenesis rate was reduced to a risk ratio of 0.55 for the entecavir treated group compared to the historical control group.[275]

Recommendation

- ***Lamivudine and entecavir therapy suppress carcinogenesis.***

6. TREATMENT OF OTHER CONDITIONS ASSOCIATED WITH HBV

6.1 Acute hepatitis

ACUTE HEPATITIS B is a disease with a strong tendency to natural resolution, with more than 90% of sufferers becoming HBsAg negative, then anti-HBs antibody positive, without treatment. In essence, no treatment is necessary for these patients. Administration of corticosteroids or glycyrrhizin formulations, with the aim of ameliorating hepatic inflammation, may instead cause hepatitis to be prolonged or become chronic, and should be avoided.[276]

Lamivudine is effective in cases of severe (prothrombin time <40%) or fulminant (prothrombin time <40%, and grade 2 or worse hepatic encephalopathy) hepatitis. According to Tillman *et al.*, following administration of lamivudine to 20 patients with severe hepatitis, prothrombin time < 36%, 18 survived (of whom 3 received liver transplants).[277] Liu *et al.* investigated the efficacy of lamivudine therapy for fulminant hepatitis, reporting an improvement in the survival rate from 15.4% to 36.8%.[278] At present, administration of lamivudine is recommended to commence before the prothrombin time reaches 40%. Lamivudine therapy should be ceased when HBsAg negative conversion occurs.

There is insufficient evidence concerning entecavir therapy for severe acute hepatitis. A study comparing entecavir and lamivudine in the treatment of exacerbations of chronic hepatitis B found that entecavir was superior in antiviral effect to lamivudine, but a tendency to prolongation of jaundice was identified.[279] Caution is required in administering entecavir to acute hepatic dysfunction associated with jaundice.

At present, more than half of Japanese patients with acute hepatitis B are infected with HBV genotype A. Acute hepatitis B has been shown to be more likely to be prolonged or become chronic in patients with HBV genotype A.[280–282] The usefulness of NA therapy with the aim of preventing chronic disease has yet to be established, and is not recommended overseas either.

Acute hepatitis B, with sexual transmission as the main route of infection, can be a coinfection with HIV. To avoid drug resistance, treatment of HIV infection requires the use of at least 3 antiviral agents. Of the NAs approved for the treatment of hepatitis B in Japan, lamivudine has a strong anti-HIV effect, and adefovir and entecavir have weak anti-HIV effects.[283,284] It is therefore necessary to confirm whether coinfection with HIV is present before commencing NA therapy for acute hepatitis B, and take care to avoid HIV monotherapy. There has been some indication that entecavir monotherapy in patients with HBV/HIV coinfection, who are not receiving fully suppressive antiretroviral regimens, may lead to the emergence of drug resistant HIV strains.[283]

Recommendations

- ***Lamivudine therapy is recommended for patients with severe acute hepatitis B, commencing before the prothrombin time goes below 40%. Lamivudine should be ceased when HBsAg testing becomes negative.***
- ***Presence of coinfection with HIV should be determined before commencing lamivudine therapy.***

6.2 Fulminant hepatitis

6.2.1 Diagnosis and pathology

Approximately 40% of cases of fulminant hepatitis in Japan are caused by HBV.[285] The etiology of fulminant hepatitis B can be broadly divided into rapid progressive acute infection (transient infection) and acute exacerbation in an HBV carrier. A recently devised etiological

classification of acute liver failure further divides acute exacerbation in an HBV carrier into 3 categories: (1) asymptomatic or inactive carrier without drug exposure, (2) reactivation in asymptomatic or inactive carrier receiving immunosuppressive and/or anti-cancer drugs, and (3) reactivation by immunosuppressive and/or anti-cancer drugs in patients with resolved HBV infection (*de novo* hepatitis B).[286,287]

Both the pathological state and prognosis differ between patients with a rapidly progressive acute infection and those with acute exacerbation of the carrier state. The former is hepatitis in the process of clearing HBV, in which amelioration of the hepatitis can be expected as the viral load decreases. The latter, however, is hepatitis caused by HBV reactivation in a carrier with a persistent infection, and hepatitis will persist as long as viral proliferation continues. The survival rate is relatively favorable at 53% with medical therapy of acute infections, but only 16% in cases of acute exacerbation of the carrier state.[285] The prognosis is particularly poor in cases of fulminant hepatitis B occurring in patients with HBV reactivation.[288]

Differentiation between acute infection and acute on chronic infection can be difficult, even using HBV markers from before and after the onset of infection. For the etiological diagnosis of fulminant hepatitis B, we measure HBsAg, anti-HBs antibody, anti-IgM-HBc antibody, anti-HBc antibody, and HBV DNA levels. We can differentiate between acute infection and acute exacerbation of the carrier state through the presence of HBsAg prior to disease onset, and positive conversion of anti-HBs antibody during the disease course. If these markers are indeterminate, the anti-IgM-HBc antibody and anti-HBc antibody titers at the time of disease onset may be considered. In general, in acute infections anti-IgM-HBc antibody are positive with a high titer, whereas HBc antibody have a low titer. In carriers, the anti-IgM-HBc antibody titer is low, and the anti-HBc antibody titer is high. At present, anti-IgM-HBc antibody titers are usually measured using the CLIA (chemiluminescent immunoassay) method, with a cut-off titer of 10.0 for differentiation between acute infection and acute on chronic infection.[289] Determination of anti-HBc antibody titers using the CLIA method is becoming more common, although this has actually made differentiation between acute infection and acute on chronic infection more difficult in comparison with the earlier RIA (radioimmunoassay) and EIA (enzyme immunoassay) 1:200 dilution methods. HBV reactivation should be suspected in patients on immunosuppressive therapy or chemotherapy before or at the time of disease onset.

A variety of HBV variants have been reported in association with fulminant hepatitis B, and preferably the HBV genotype, and the presence of precore and core promoter mutations should be determined. The B1/Bj genotype is common in fulminant hepatitis associated with acute infections,[5] and high incidences of core promoter (A1762T/G1764A) and precore (G1896A/G1899A) mutations have also been reported.[5,60,290–293] An association has also been reported between preS2 variants, S antigen variants, and fulminant hepatitis B.[294–296] On the other hand, no specific variants have been identified in HBV carriers developing acute exacerbation.

Recommendation

- ***HBsAg, anti-HBs antibody, anti-IgM-HBc antibody, anti-HBc antibody, and HBV DNA levels should be determined in patients with fulminant hepatitis B to make the etiological diagnosis. Determination of HBV genotype and the presence of precore and core promoter mutations is also desirable.***

6.2.2 Principles of treatment

In general, acute hepatitis B is a condition that resolves naturally, with no need for treatment. NAs are indicated in cases where there is concern about possible rapid progression or severe hepatitis, although there are no clear indications for their use. The AASLD Guidelines state that treatment is indicated in prolonged hepatitis (>4 weeks of prolonged INR and hyperbilirubinemia).[297] It is important to commence antiviral therapy using NAs as soon as fulminant hepatitis B is suspected, whether it is a rapidly progressive acute infection or acute exacerbation of the carrier state. Even after commencement of NA therapy once fulminant hepatitis has been diagnosed, it takes some time for the antiviral effect to appear, and improved outcomes are not always achieved, so antiviral therapy should be commenced before the onset of fulminant hepatic failure. The treatment of fulminant hepatitis is not directed solely at the etiological cause, but is a multidisciplinary treatment encompassing protective therapy, artificial liver support, general care, and prevention of complications. Outcomes are generally poor for medical treatment of fulminant hepatitis B, so liver transplantation should be considered as soon as possible.

6.2.3 NAs

A randomized controlled clinical trial of lamivudine in the treatment of severe hepatitis B (bilirubin ≥10 mg/