

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 adefovir, 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, rT184, rS202 or rM250 in addition to the amino acid mutations rM204V and rL180M 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 multi-agent 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

<p>Patient criteria</p> <ul style="list-style-type: none"> • 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 <p>Laboratory criteria</p> <ul style="list-style-type: none"> • 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-IFN α -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

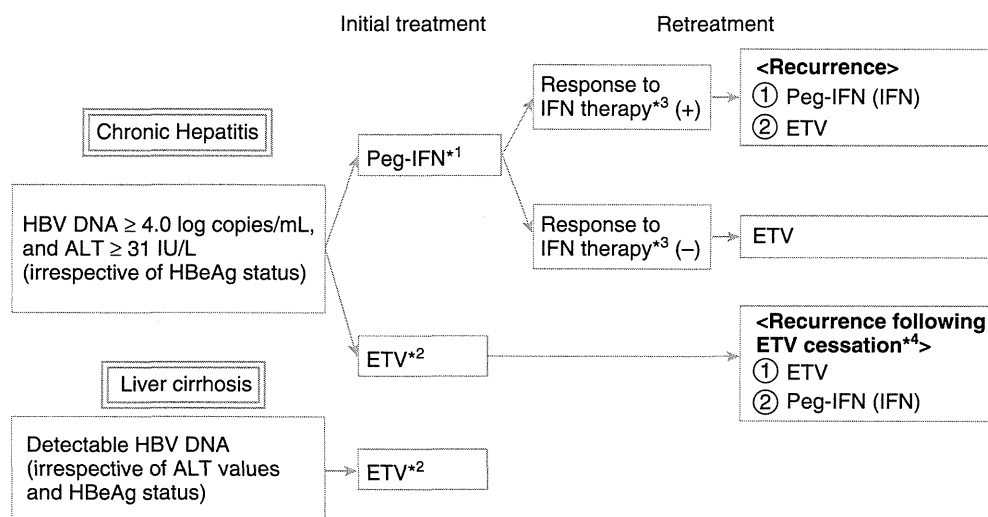
5.1 Basic principles of antiviral therapy (Fig. 6)

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, $\geq 95\%$ 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 $\geq 10\%$, and $\geq 70\%$ 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/

dL, PT-INR 1.4-1.6) found that early administration of lamivudine significantly reduced the incidence of hepatic failure and mortality.²⁷⁸ A retrospective study of lamivudine therapy for fulminant or severe hepatitis B with PT-INR ≥ 2.0 found that 82.4% (14/17) of patients in the treated group survived and cleared HBsAg within 6 months, whereas the survival rate in the historical control group not administered lamivudine was only 20% (4/20), with a significant difference seen between groups ($P < 0.001$).²⁷⁷ Other studies have demonstrated the efficacy of lamivudine in the treatment of fulminant hepatitis B, with no reports of problems with safety, such as adverse reactions.^{298,299} Although there are no clear guidelines for when to stop NA therapy, negative conversion of HBsAg is usually the indicator for treatment cessation.

Administration of NAs is the mainstay of treatment of acute exacerbation of the carrier state. The viral load is already high at the time of onset of fulminant hepatitis, by which stage a therapeutic response to NAs is unlikely, necessitating commencement of NA therapy before the onset of severe or fulminant hepatitis B. Although subject numbers were low, the "Prospective study of the efficacy of lamivudine" in patients with acute exacerbation of the carrier state, conducted by an MHLW study group, found that 71% (5/7) patients administered lamivudine when a prothrombin time declined to $\leq 40\%$ died, but all patients administered lamivudine when a prothrombin time was $\geq 60\%$ survived. They therefore recommended that lamivudine should be administered to patients with acute exacerbation of the carrier state without delay, before the prothrombin time goes below 60%.³⁰⁰ On the other hand, in patients with acute exacerbation of chronic hepatitis B, lamivudine should be administered before the total bilirubin level exceeds 5 mg/dL.³⁰⁰ The cessation criteria for NA therapy in patients with acute exacerbation of the carrier state are the same as for chronic hepatitis B.

Even when liver transplantation is indicated, early NA therapy is effective in preventing recurrent HBV infection following transplantation. Post-transplant HBsAg positive conversion is considered less common after transplantation for HBV-associated acute hepatic failure than for chronic liver disease, although it is difficult to predict post-transplant recurrence. At present, the standard prophylactic regimen in HBsAg positive recipients is to commence NA therapy prior to transplantation, then introduce high titer hepatitis B immunoglobulin (HBIG) intraoperatively, and continue NA + HBIG dual therapy postoperatively.^{301,302}

Of the NAs, a number of studies have demonstrated that lamivudine ameliorates acute liver failure.^{277,278,298,303} Although evidence is scarce, amelioration of acute liver failure has also been suggested for entecavir and tenofovir.³⁰⁴⁻³⁰⁶ Caution is required when administering entecavir to jaundiced patients with acute hepatic dysfunction, as a post-administration rise in transaminases may occur. Adefovir therapy is not recommended, as it has only weak antiviral activity, and is nephrotoxic. Caution is also required with the use of tenofovir, as latent nephrotoxicity has been reported.

6.2.4 IFN

IFN is occasionally administered in combination with a NA when treating fulminant hepatitis B in Japanese patients, because it often occurs in HBV carriers.³⁰⁷ There is, however, a dearth of evidence clearly demonstrating the usefulness of IFN in the treatment of fulminant hepatitis.^{308,309} Caution for adverse effects including worsening liver function and bone marrow suppression is required in administering IFN to these patients, either using a low dosage or using IFN- β in an intravenous formulation to avoid hemorrhagic complications. When fulminant hepatitis occurs in an HBV carrier, it is important to suppress persistent hepatic inflammation as quickly as possible, for which corticosteroids are administered in combination with antiviral therapy. A clinical trial of the usefulness of corticosteroid pulse therapy in combination with NA therapy in the treatment of fulminant hepatitis B is currently being conducted by an MHLW study group.

Recommendations

- *Antiviral therapy for fulminant hepatitis B should be commenced as soon as possible using NAs, whether it is a rapidly progressive acute infection or acute exacerbation of the carrier state.*
- *NAs should be administered immediately to patients with severe acute hepatitis B, aiming to commence therapy before the prothrombin time goes below 40% in patients with severe acute hepatitis B, and before the prothrombin time goes below 60% in patients with acute exacerbation of the carrier state.*
- *IFN may be administered in combination with NAs. However, careful attention should be paid to possible exacerbation of hepatic dysfunction or the development of decline of blood cell counts during treatment.*

6.3 HBV reactivation

Reactivation of HBV refers to a rise in the hepatitis B viral load caused by immunosuppression or chemo-

therapy in a patient with HBV infection. Reactivation of HBV is classified into reactivation from the carrier state and reactivation in a patient with resolved HBV infection (HBsAg negative, and anti-HBc antibody or anti-HBs antibody positive). Hepatitis associated with reactivation in a patient with resolved HBV infection is called “*de novo* hepatitis B”. Not only is severe disease common in cases of hepatitis associated with reactivation of HBV, but also treatment of concurrent conditions is made difficult by the onset of hepatitis, so it is extremely important to prevent the onset of hepatitis itself. The basic strategy for prevention and treatment of HBV reactivation associated with powerful immunosuppressant or chemotherapy regimens should follow the guidelines summarized below, based on the “Guidelines for the prevention of hepatitis B virus reactivation in patients receiving immunosuppressive therapy or chemotherapy (Revised version)”^{310,311} produced by an MHLW study group (Fig. 7). An MHLW study group currently conducting a multicenter nationwide prospective clinical trial of preemptive antiviral therapy to prevent HBV reactivation during treatment of malignant lymphoma with rituximab has published the results of interim analyses.³¹² As for HBV reactivation caused by immunosuppressive and anti-cancer therapies rather than rituximab, the MHLW “HBV Reactivation through Immunosuppressive and/or Anti-cancer Therapies” research group has also reported its results.³¹³ Furthermore, the Japan College of Rheumatology has published “A proposal for management of rheumatic disease patients with hepatitis B virus infection receiving immunosuppressive therapy”.³¹⁴

6.3.1 Risk of reactivation

The risk of reactivation of HBV is mainly governed by the HBV infection status and the degree of immunosuppression. The HBV infection status is classified into chronic active hepatitis, inactive carrier, and resolved infection. This corresponds to the risk of reactivation in descending order. There is no evidence available concerning asymptomatic carriers in the immune tolerance phase, the incidence of further activation of HBV, or whether NA therapy can prevent activation. The risks of HBV reactivation and the onset of hepatitis or fulminant hepatitis vary with the exact immunosuppressant or chemotherapy agents used, and the incidences of these events are unclear. When immunosuppressive therapy or chemotherapy including powerful agents such as rituximab is administered, careful attention should be paid to the possibility of reactivation in HBsAg positive patients

including inactive carriers, and patients with resolved infection. When standard immunosuppressive therapy or chemotherapy is administered, reactivation in HBsAg positive patients including inactive carriers is the main problem, but caution is also required with in patients with resolved HBV infection, as there have been reports of HBV reactivation in such patients with HBV DNA levels <2.1 log copies/mL, either administered corticosteroid monotherapy, or administered standard chemotherapy for the treatment of solid malignancies.³¹³ Risk factors for HBV reactivation in HBsAg positive patients are HBeAg positive status and high HBV DNA levels. Although most patients with resolved HBV infection are positive for both anti-HBc and anti-HBs antibody, some are either anti-HBc antibody positive or anti-HBs antibody positive alone. Although anti-HBs antibody act to suppress HBV reactivation, reactivation is still possible in patients positive for anti-HBs antibody alone.^{315–317}

HBV reactivation is commonly associated with hepatitis, which can vary from mild and transient hepatitis to severe and fatal. The onset of hepatitis associated with HBV reactivation is not always during immunosuppressive therapy or chemotherapy, but may occur after its interruption or cessation. In particular, severe hepatitis associated with HBV reactivation has been reported after cessation of corticosteroid and methotrexate therapy.^{318–321} Moreover, conditions such as fibrosing cholestatic hepatitis (FCH) may present when viral replication is increased in the immunosuppressed state.^{322,323}

6.3.2 Screening (Fig. 7)

Screening for HBV infection should be performed in all patients undergoing immunosuppressive therapy or chemotherapy, irrespective of whether abnormalities of hepatic function are evident or not. HBsAg levels should be measured in all patients prior to commencement of treatment. In HBsAg positive patients, HBeAg, anti-HBe antibody, and HBV DNA levels should also be measured. A real-time PCR should be used for measurement of HBV DNA levels. In HBsAg negative patients, anti-HBc antibody and anti-HBs antibody should also be measured. Patients positive for anti-HBc or anti-HBs antibody are diagnosed as patients with resolved HBV infection. However, this excludes those positive for anti-HBs antibody alone due to prior hepatitis B vaccination. The next step for patients with resolved HBV infection is measurement of HBV DNA levels. For measurement of HBsAg, anti-HBc antibody and anti-HBs antibody, a highly sensitive test such as the CLIA or CLEIA method should be used. If HBV infection is diagnosed, the past history of hepatitis should be elicited, and screening for

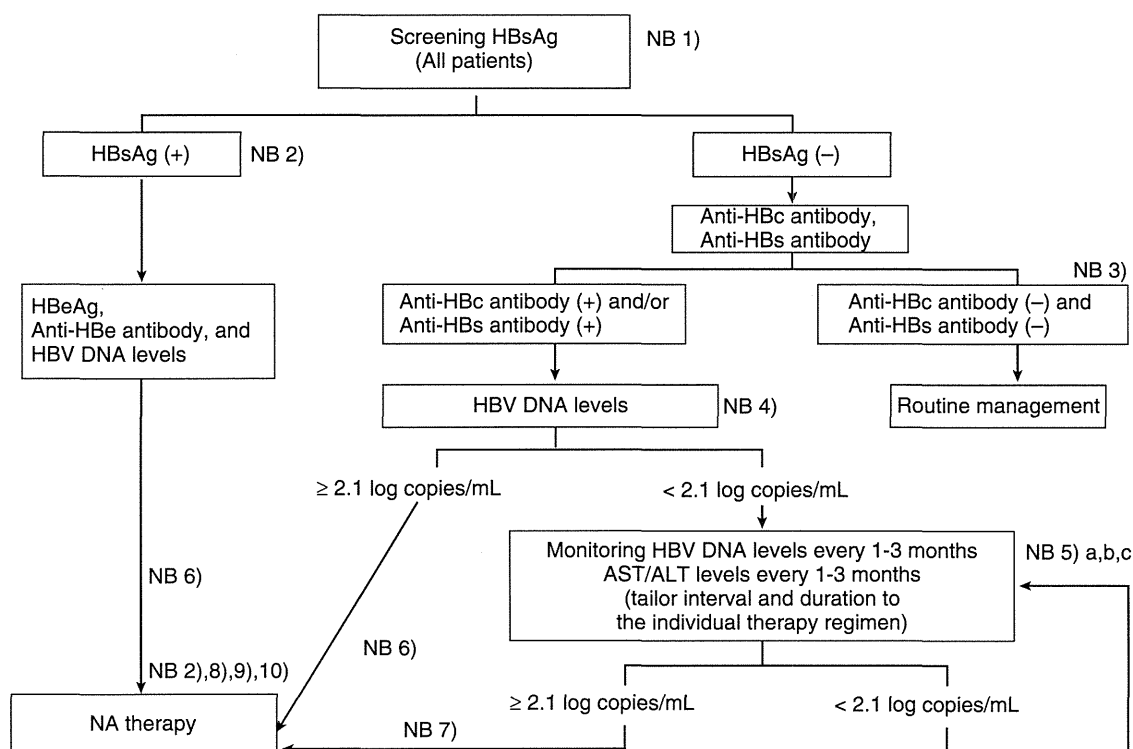


Figure 7 Guidelines for the prevention of hepatitis B virus reactivation in patients receiving immunosuppressive therapy or chemotherapy.

Addendum: Caution is required when administering powerful chemotherapeutic agents for hematological malignancies, as during or following completion of treatment some HBsAg positive or negative patients will develop hepatitis B due to reactivation of HBV, and some of these will go on to suffer fulminant hepatitis. Consideration should also be given to the possibility of HBV reactivation in association with standard chemotherapy for hematological malignancies or solid cancers, and immunosuppressive therapy for autoimmune diseases, such as rheumatic and collagen diseases. The incidences of HBV reactivation, hepatitis and fulminant hepatitis associated with standard chemotherapy and immunosuppressive therapy are not known, and there is a lack of evidence on which to base guidelines. Furthermore, prevention of fulminant hepatitis is not guaranteed with NA therapy.

NB 1) HBV carriers and patients with resolved hepatitis B should be screened prior to immunosuppressive therapy or chemotherapy. First HBsAg testing should be performed to determine whether they are an HBV carrier. HBsAg negative patients should be tested for anti-HBc antibody and anti-HBs antibody, to confirm past infection. Highly sensitive testing methods should be used for measurements of HBsAg, anti-HBc antibody and anti-HBs antibody.

NB 2) A hepatologist should be consulted concerning HBsAg positive patients. A hepatologist should preferably be consulted for all patients administered NAs.

NB 3) In some patients undergoing retreatment who did not undergo testing for anti-HBc or HBs antibody at the time of their initial chemotherapy, and in patients who have already commenced immunosuppressive therapy, antibody titers may be low, in which case measurement of HBV DNA levels is preferable.

NB 4) Patients with resolved HBV infection should be screened using real-time PCR measurement of HBV DNA levels.

NB 5)

a. Caution is required when treating patients with resolved HBV infection with rituximab + corticosteroid or fludarabine chemotherapy, or when they undergo hematopoietic stem cell transplantation, as these patients are at high risk of HBV reactivation. HBV DNA levels should be monitored on a monthly basis during treatment, and for at least 12 months afterward. Long-term monitoring is required for hematopoietic stem cell transplant recipients.

b. Although the incidence is low, there is a risk of HBV reactivation with standard chemotherapy regimens. HBV DNA levels should be measured every 1–3 months, with the interval and duration tailored to the individual therapy regimen. It is best to err on the side of caution with patients undergoing treatment for hematological malignancies.

Figure 7 Continued

c. There is also a risk of HBV reactivation associated with immunosuppressive therapy using corticosteroids, immunosuppressant agents, or molecular targeted therapy with immunosuppressant or immunomodulator activity. HBV DNA levels should be monitored on a monthly basis in patients on immunosuppressive therapy for at least 6 months after commencement or alteration (including cessation) of treatment. After 6 months, the interval and duration should be tailored to the individual therapy regimen.

NB 6) Administration should be commenced as soon as possible, before commencement of immunosuppressive therapy or chemotherapy.

NB 7) Administration should be commenced as soon as the HBV DNA levels exceed 2.1 log copies/mL, during or after immunosuppressive therapy or chemotherapy. If this occurs during treatment, it is preferable to consult with a hepatologist, and not immediately cease the immunosuppressant or antineoplastic agent with immunosuppressive activity.

NB 8) Entecavir is the recommended NA.

NB 9) Cessation of NA therapy can be considered if the following criteria are met.

In patients who were HBsAg positive at the time of screening, when the criteria for cessation of NA therapy in cases with chronic hepatitis B are met.

In patients who were anti-HBc antibody and/or anti-HBs antibody positive at the time of screening:

- 1 NA therapy has been continued for at least 12 months after completion of immunosuppressive therapy or chemotherapy.
- 2 ALT (GPT) levels have been normalized during this period (excluding causes of elevated ALT levels other than HBV).
- 3 negative conversion of HBV DNA has occurred during this period.

NB 10) Patients should be carefully monitored, including measurement of HBV DNA levels, for at least 12 months following completion of NA therapy. Monitoring methods depend on package inserts of each NA. NA therapy should be immediately resumed if HBV-DNA levels exceed 2.1 log copies/mL during monitoring period.

chronic liver disease performed, including abdominal ultrasonography. In HBV DNA positive patients, testing for HBV genotype, precore mutations and core promoter mutations is desirable.

Recommendations

- *Screening for HBV infection should be performed in all patients undergoing immunosuppressive therapy or chemotherapy, who are at risk of HBV reactivation.*
- *Screening for HBV infection should be performed in a systematic fashion, using a highly sensitive test, and include measurement of levels of HBsAg, anti-HBc and anti-HBs antibodies, and HBV DNA.*

6.3.3 Basic strategy for prevention and treatment of reactivation

When immunosuppressive therapy or chemotherapy, with the associated risk of HBV reactivation, is administered to patients with chronic active hepatitis, NA therapy should be commenced beforehand as possible. Immunosuppressive therapy is considered safe in patients with chronic hepatitis under cover of antiviral therapy.³²⁴ When immunosuppressive therapy or chemotherapy, with the associated risk of HBV reactivation, is administered to HBsAg positive inactive carriers, prophylactic NA therapy should be commenced without delay beforehand. Patients with resolved HBV infection and HBV DNA levels ≥ 2.1 log copies/mL on pretreatment screening should be administered prophylactic NA

therapy beforehand, as for inactive carriers. Patients with resolved HBV infection and HBV DNA levels < 2.1 log copies/mL on pretreatment testing should undergo regular monitoring of HBV DNA levels during and after their immunosuppressive therapy or chemotherapy. If HBV DNA levels exceed 2.1 log copies/mL during monitoring, preemptive NA therapy should be commenced immediately. The interval between tests should be of the order of 1–3 months, although the monitoring duration and intervals can be adjusted in accordance with the nature of the immunosuppressive therapy or chemotherapy.

A survey conducted by an MHLW study group found that increased HBV DNA levels were not necessarily detected in patients with resolved HBV infection, after HBV DNA levels (real-time PCR) were < 2.1 log copies/mL and amplification reaction signals were detected in pretreatment monitoring, or HBV DNA levels were < 2.1 log copies/mL and amplification reaction signals were detected in monitoring during treatment. They concluded that HBV reactivation can be diagnosed when HBV DNA levels exceed 2.1 log copies/mL, and it is reasonable to commence NA therapy at that point.³¹³

The usefulness of prophylactic lamivudine therapy prior to chemotherapy in HBV carriers has been demonstrated in prospective studies.^{325–328} Although few in number, some studies have shown prophylactic entecavir and tenofovir therapy to be useful.^{329–331} The

genetic barrier to resistance to lamivudine is low, so resistant strains are likely to appear if the virus has a high capacity to proliferate, or the period of administration is long, and at present entecavir therapy is recommended.

The criteria for cessation of NA therapy are the same as for cessation of NA therapy in HBsAg positive patients. For anti-HBc or anti-HBs antibody positive patients, NA therapy should be continued for at least 12 months after completion of immunosuppressive therapy or chemotherapy, although NAs may be ceased during this period if continued ALT normalization and HBV DNA negative conversion are seen. However, close follow-up including HBV DNA monitoring is necessary for at least 12 months after cessation of NA therapy.

Recommendations

- When immunosuppressive therapy or chemotherapy, with the associated risk of HBV reactivation, is administered to HBsAg positive inactive carriers, or patients with resolved HBV infection and HBV DNA levels ≥ 2.1 log copies/mL on pretreatment screening tests, NA therapy should be commenced without delay.
- Patients with resolved HBV infection and HBV DNA levels < 2.1 log copies/mL on pretreatment screening tests should undergo regular monitoring of HBV DNA levels during and after their immunosuppressive therapy or chemotherapy. If HBV DNA levels exceed 2.1 log copies/mL during monitoring, preemptive NA therapy should be commenced.
- Entecavir is the recommended NA.
- The criteria for cessation of NA therapy are the same as for cessation of NA therapy in HBsAg positive patients. For patients with resolved HBV infection, NA therapy should be continued for at least 12 months after completion of immunosuppressive therapy or chemotherapy, although cessation of NAs may be considered during this period if continued ALT normalization and HBV DNA negative conversion are seen.
- Close follow-up including HBV DNA monitoring is necessary for at least 12 months after cessation of NA therapy. If HBV DNA levels exceed 2.1 log copies/mL during the follow-up period, NA therapy should be recommenced immediately.

6.3.4 Liver transplantation

HBV reactivation is a potential problem in recipients of a liver transplant from an HBsAg negative and anti-HBc antibody positive donor. In a report from a time before prophylactic HBIG administration became standard, HBV reactivation occurred in 15 out of 16 recipients

of liver transplants from anti-HBc antibody positive donors, one of whom died from FCH.³³² It is preferable to exclude anti-HBc antibody positive donors, but a strategy is needed when transplantation of a liver from such a donor cannot be avoided. One such strategy is to administer HBIG during the transplantation procedure, and maintain anti-HBs antibody levels postoperatively. Postoperative administration of NA therapy, or NA+HBIG combination therapy, is also considered useful.^{333,334} Early commencement of NA therapy following HBV reactivation has also been reported to be effective.³³⁵

6.3.5 Transplantation of other organs

HBV reactivation is seen in a high proportion (50–94%) of HBsAg positive patients undergoing transplantation of kidneys and other organs.^{336–339} Following HBV reactivation, rapid progression is seen from chronic hepatitis B to liver cirrhosis, which becomes the cause of death. Prophylactic NA therapy is recommended for HBsAg positive and/or anti-HBc antibody positive patients, commencing prior to the transplantation procedure.

6.3.6 Hematopoietic stem cell transplantation

HBV reactivation is seen in a high proportion ($\geq 50\%$) of HBsAg positive patients undergoing of hematopoietic stem cell transplantation.³⁴⁰ The rate of HBV reactivation is 14–20% in patients with resolved HBV infection.^{341,342} The risk of HBV reactivation is higher with allogeneic bone marrow transplantation than with autologous bone marrow transplantation. This is thought to be due to the need for long term corticosteroid and immunosuppressant therapy for graft-versus-host disease (GVHD) with allogeneic transplantation. Characteristic of reactivation in patients with resolved HBV infection undergoing hematopoietic stem cell transplantation is the delayed onset of HBV reactivation, influenced by immunosuppressant therapy and delayed immune reconstitution.^{343,344} The median interval between transplantation and HBsAg positive conversion is long at 19 months (range 6–52 months),³⁴⁵ necessitating long term HBV DNA monitoring after transplantation.

6.3.7 Chemotherapy including rituximab

The risk of HBV reactivation is high with chemotherapy using rituximab or fludarabine for hematological malignancies, reported to be 20–50% in carriers and 12–23% in patients with resolved HBV infection.^{316,346} Prospective HBV DNA monitoring studies conducted in Japan and Taiwan found the risk of HBV reactivation to be

approximately 10% in patients with resolved HBV infection.^{312,347} For HBV reactivation associated with rituximab+corticosteroid combination therapy, the rate of fulminant hepatitis was high, and mortality also high in cases of fulminant hepatitis.^{288,348}

The Taiwanese group conducted a multicenter collaborative prospective clinical trial of monthly HBV DNA monitoring in patients with malignant lymphoma who underwent chemotherapy including rituximab.³⁴⁷ Using an HBV DNA cutoff value of 3.0 log copies/mL, they defined HBV reactivation as an increase in the HBV DNA levels at least 10 times greater than baseline. As a result, HBV reactivation was seen in 9.3% (14) of patients, in 5 of whom hepatic dysfunction was seen. Of these, serious hepatic dysfunction (ALT increase ≥ 10 times upper limit of normal) associated with HBV reactivation was seen in 2 patients, but it did not develop into fulminant hepatitis, and no deaths were reported.

In Japan, an MHLW study group is conducting a multicenter collaborative clinical trial with patients with malignant lymphoma who underwent rituximab+corticosteroid combination therapy with the aim of determining the usefulness of HBV DNA monitoring during treatment. They have published their interim analysis results.³¹² Using an HBV DNA cutoff value of 1.8 log copies/mL, they defined HBV reactivation as a HBV DNA levels above the cutoff value (greater than the signal detection sensitivity), and commenced NA therapy. HBV reactivation was seen in 16/187 patients, but there were no cases of hepatitis associated with HBV reactivation.

These results strongly suggest the necessity for highly sensitive HBV DNA monitoring and the immediate commencement of NA therapy as soon as HBV DNA becomes detectable. This supports the validity of the present MHLW guidelines for the management of HBV reactivation.

6.3.8 Standard chemotherapy

For standard chemotherapy regimens, the incidence of HBV reactivation is relatively high in inactive carriers, but only 1–3% in patients with resolved HBV infection.^{325,349,350} The incidence of HBV reactivation is higher for chemotherapy regimens that include corticosteroids or anthracycline anti-cancer agents.^{345,351,352} A prospective study conducted by an MHLW study group found that standard chemotherapy for solid cancers in patients with resolved HBV infection induced HBV reactivation (HBV DNA ≥ 2.1 log copies/mL) in 1 out of 36 patients. The HBV DNA levels in that patient was 2.4 log

copies/mL, and entecavir therapy was commenced immediately, with no evidence of the onset of hepatitis. Chemotherapy for hematological malignancies, not including rituximab, induced 1 case of hepatitis over the 3 month monitoring period.³¹³

In general, monitoring of HBV DNA levels in patients undergoing standard chemotherapy for solid cancers should be performed at intervals of 1–3 months, although the monitoring duration and intervals can be adjusted in accordance with the nature of the chemotherapy. More intensive surveillance is required for hematological malignancies. If reactivation occurs during chemotherapy, it is preferable to consult with a hepatologist, and not immediately cease the antineoplastic agent with immunosuppressive activity.

6.3.9 Immunosuppressive therapy for rheumatic and connective tissue diseases

It is characteristic of immunosuppressive therapy for autoimmune diseases, such as rheumatic and connective tissue diseases, that multiple immunosuppressant agents including methotrexate and corticosteroids are administered for long periods. Immunosuppressant agents known to be associated HBV reactivation include corticosteroids, immunosuppressant agents (azathioprine, cyclophosphamide, cyclosporine and mycophenolate mofetil), anti-rheumatic agents with immunosuppressive activity (methotrexate, tacrolimus, leflunomide and mizoribine), and biological agents such as anti-TNF- α agents.^{353,354} A prospective study conducted by an MHLW study group found that immunosuppressive therapy for rheumatic and connective tissue diseases in patients with resolved HBV infection induced HBV reactivation (HBV DNA ≥ 2.1 log copies/mL) in 6 out of 121 patients (2 patients with pretreatment HBV DNA < 2.1 log copies/mL, signal detected, 4 patients with pretreatment HBV DNA < 2.1 log copies/mL, signal not detected). The timing of reactivation was within 6 months after commencement of treatment in all cases.³¹³ Accordingly, HBV DNA monitoring at monthly intervals is desirable for at least 6 months after commencement or alteration of immunosuppressive therapy. There is insufficient evidence concerning monitoring more than 6 months after commencement or alteration of immunosuppressive therapy, so the monitoring duration and intervals can be adjusted in accordance with the nature of the treatment. If HBV reactivation occurs during immunosuppressive therapy, it is preferable to consult with hepatologist, and not immediately cease the immunosuppressant agent.

6.3.10 Novel molecular targeted therapies

Although evidence is lacking concerning the risk of HBV reactivation with novel molecular targeted therapies, there have been reports of hepatitis associated with several molecular targeted therapeutic agents.³⁵⁵⁻³⁵⁷ In particular, caution is required with molecular targeted therapeutic agents with immunosuppressive or immunomodulating activity, necessitating more intensive surveillance.

Recommendations

- Monthly HBV DNA monitoring should be performed for patients undergoing hematopoietic stem cell transplantation or chemotherapy including rituximab, corticosteroids or fludarabine, during treatment and for at least 12 months after its completion.
- HBV DNA monitoring should be performed every 1-3 months for patients undergoing chemotherapy for hematological malignancies, not including rituximab, and standard chemotherapy for solid malignancies, although the monitoring duration and intervals can be adjusted in accordance with the nature of the treatment.
- Monthly HBV DNA monitoring should be performed at monthly intervals for patients undergoing immunosuppressive therapy for rheumatic or connective tissue diseases, for at least 6 months after commencement or alteration of treatment. After 6 months, the monitoring duration and intervals should be decided in accordance with the nature of the treatment.

- If HBV reactivation occurs during chemotherapy or immunosuppressive therapy, it is preferable to consult with a hepatologist, and not immediately cease the anti-neoplastic agent with immunosuppressive activity or immunosuppressant agent.

6.4 Coinfection with HIV

6.4.1 Epidemiology

As we saw above in the section on acute HBV, coinfection with HBV and HIV infection may occur. HIV patients exhibit an HBsAg positive rate of 6.3%³⁵⁸ and anti-HBs antibody positive rate of around 60%.³⁵⁹ It has been reported that immunopathy associated with HIV can increase the likelihood of HBV infection becoming chronic by as much as 23%.³⁶⁰ Over 80% of HBsAg positive Japanese HIV-infected patients have HBV genotype A³⁶¹, which contributes to the higher HBsAg positive rates among HIV sufferers. Thus, coinfection with HIV can occur in patients with chronic hepatitis B as well as those with acute hepatitis B.

6.4.2 Basic principles

NAs are the mainstay of HBV therapy in patients coinfecting with HIV. Antiretroviral therapy (ART) for HIV infection involves a combination of three or more anti-HIV agents. Table 16 shows anti-HIV agents that are also active against HBV. Nucleoside analog reverse transcriptase inhibitors (NRTI) are generally used as two of the anti-HIV agents. They will normally have anti-HBV activity as well, to discourage the development of drug-resistant HBV.

Table 16 Anti-HIV drugs also active against HBV*

Common name	Product name	Code	Dosage	Remarks
Lamivudine	Epivir	3TC	300 mg once or twice daily	Reduce dosage for renal failure Different dosage to Zefix
Emtricitabine	Emtriva	FTC	200 mg	Reduce dosage for renal failure
Tenofovir disoproxil fumarate	Viread	TDF	300 mg	Reduce dosage for renal failure
Emtricitabine + tenofovir disoproxil fumarate	Truvada	TDF+FTC	One tablet	Reduce dosage for renal failure
Zidovudine + lamivudine	Combivir	AZT+3TC	Two tablets twice daily	Reduce dosage for renal failure Contraindicated if hemoglobin <7.5 g/dL Contraindicated in combination with ibuprofen
Abacavir + lamivudine	Epzicom	ABC+3TC	One tablet	Reduced dosage for renal failure Contraindicated in severe hepatic dysfunction

*All these of the above are classed as nucleoside analog reverse transcriptase inhibitors (NRTI). Other options include anti-HIV agents such as non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), integrase inhibitors and CCR-5 inhibitors.