Recommendations

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

5.4.2 Decompensated cirrhosis

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

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

Recommendations

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

5.5 Suppression of HCC by antiviral therapy

5.5.1 IFN

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

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

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

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

Recommendations

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

5.5.2 NAs

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

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

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

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

Recommendation

- *Lamivudine and entecavir therapy suppress carcinogenesis.*

6. TREATMENT OF OTHER CONDITIONS ASSOCIATED WITH HBV

6.1 Acute hepatitis

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

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

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

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

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

Recommendations

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

6.2 Fulminant hepatitis

6.2.1 Diagnosis and pathology

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

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

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

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

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

Recommendation

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

6.2.2 Principles of treatment

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

6.2.3 NAs

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

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 ≤40% died, but all patients administered lamivudine when a prothrombin time was ≥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

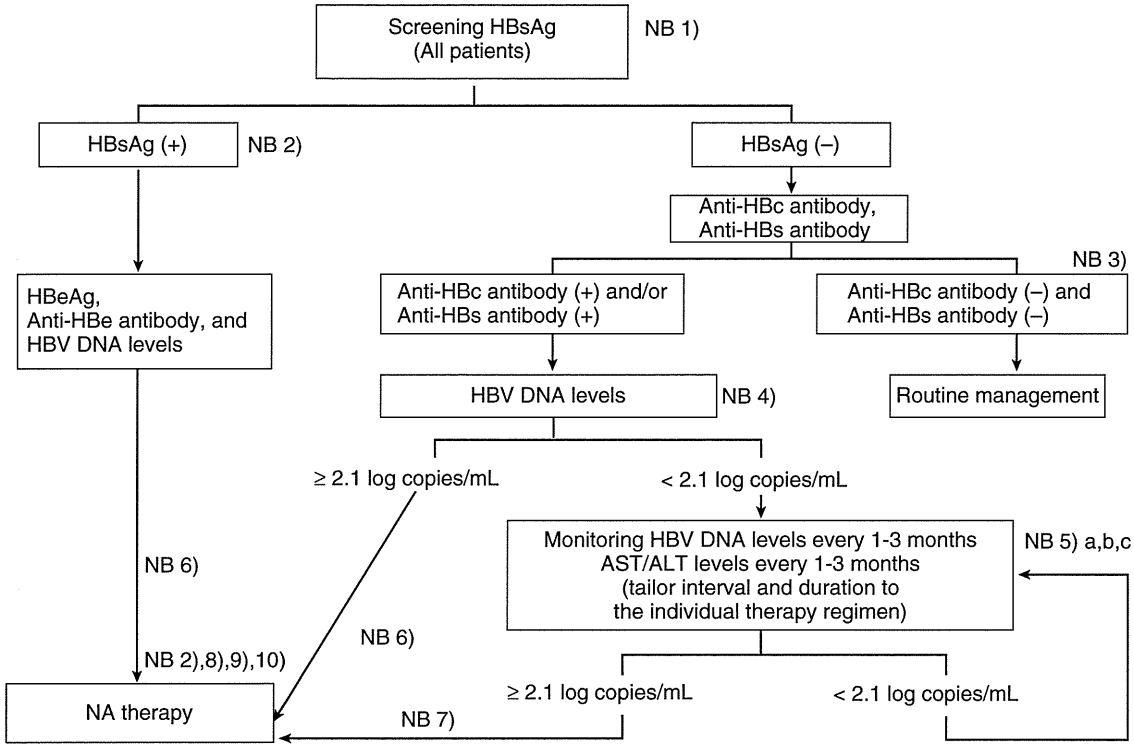

Figure 7 Guidelines for the prevention of hepatitis B virus reactivation in patients receiving immunosuppressive therapy or chemotherapy.

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 (≥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 A[361], 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 coinfected 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 + tenofivir 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.

In patients with very low CD4 counts (well below the normal range of 800–1200/μL), ART may cause exacerbation of hepatitis due to recovery of cellular immunity, in a phenomenon known as Immune Reconstitution Inflammatory Syndrome (IRIS). In the majority of cases, IRIS is observed within 16 weeks of starting ART. It can be difficult to distinguish between IRIS and drug-induced liver injury.

An issue with ART is the potential for drug-induced liver injury associated with the use of anti-HIV agents, particularly protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTI). The risk of liver injury generally decreases during ongoing ART;[362] it is however more likely in patients with advanced liver fibrosis, and particularly cirrhosis. Cessation of ART or a change in the agents used should be considered if liver injury is detected or hepatic function deteriorates.

Prolonged administration of tenofovir and/or adefovir can lead to renal damage.[363] In the case of tenofovir, this may be irreversible.[364] For this reason, changes in the drug regimen should be considered before the estimated glomerular filtration rate (eGFR) falls below 60% or phosphorus reabsorption falls below 70%.

6.4.3 Problems with treatment and responses

Before commencing ART including anti-HBV agents, it is important to check for a history of treatment with anti-HBV agents such as lamivudine, adefovir, entecavir or any of the anti-HIV drugs listed in Table 16. If any of these agents have been administered in the past, an infectious diseases specialist should be consulted regarding the choice of ART agents.

Functional hepatic reserve should also be evaluated prior to commencing ART including anti-HBV agents, given that IRIS can potentially exacerbate hepatitis in patients with a low hepatic reserve. Protease inhibitors and NNRTIs known to cause hepatic dysfunction should be avoided with these patients.

Entecavir is not recommended for patients coinfected with HIV and HBV not being administered anti-HIV agents, as it can lead to the emergence of drug-resistant HIV.

All the abovementioned factors should be considered in selecting the ART regimen. The ART regimen should consist of a backbone of either tenofovir (TDF) with emtricitabine (FTC), or tenofovir (TDF) with lamivudine (3TC), together with a key drug (integrase inhibitor, NNRTI or PI).

Where IRIS occurs during ART including anti-HBV agents, it is usually only transient in nature. Although it is generally held that cessation of ART should be considered when transaminase levels reach more than five to ten times the baseline level, it is preferable to address the problem without interrupting ART.

If it proves necessary to cease administration of an anti-HIV drug with anti-HBV activity (such as lamivudine, emtricitabine, tenofovir or Truvada (emtricitabine+tenofovir)) due to adverse reactions associated with ART, there is a danger of recurrence or aggravation of hepatitis. Where possible, two anti-HBV agents should be administered instead. Consideration should be given to entecavir+adefovir combination therapy.

It is rare for treatment to be indicated for HBV alone, and "treatment of HIV infection not indicated or not wanted". If this situation does arise, Peg-IFNα-2a therapy should be considered.

Specific directions regarding coinfections with HBV and HIV are set out in the HIV Guidelines.[365,366]

Recommendations

- *In patients with very low CD4 counts (well below the normal range of 800–1200/μL), ART may exacerbate hepatitis due to recovery of cellular immunity.*
- *When administering ART, we should take into consideration the potential for anti-HIV agents to cause drug-induced liver injury.*
- *Before commencing ART involving anti-HBV agents, it is important to check for a history of treatment with anti-HBV agents.*
- *Before commencing ART involving anti-HBV agents, it is important to evaluate functional hepatic reserve.*
- *The ART regimen should consist of a backbone of either tenofovir (TDF) with emtricitabine (FTC), or tenofovir (TDF) with lamivudine (3TC), together with a key drug (integrase inhibitor, non-nucleoside reverse transcriptase inhibitor or protease inhibitor).*
- *If it is necessary to cease administration of an anti-HIV drug with anti-HBV activity due to adverse reactions associated with ART, there is a danger of recurrence or aggravation of hepatitis. Where possible, two anti-HBV agents should be administered instead. Consideration should be given to entecavir+adefovir combination therapy.*

CONFLICTS OF INTEREST

THE MEMBERS OF Drafting Committee for Hepatitis Management Guidelines have received consultant

fees from GlaxoSmithKline, royalty from SRL, lecture fees from Ajinomoto Pharmaceuticals, MSD, Daiichi-Sankyo, Dainippon-Sumitomo Pharma, Mitsubishi Tanabe Pharma, Chugai Pharmaceutical, Bristol-Myers-Squibb, and research support from Eisai, MSD, Kan Research Institute, GlaxoSmithKline, Chugai Pharmaceutical, Bristol-Myers-Squibb, Daiichi-Sankyo, Mitsubishi Tanabe Pharma, Dainippon-Sumitomo Pharma, Toray, Minophagen Pharmaceutical.

REFERENCES

1 Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. *J Viral Hepat* 2004; **11**: 97–107.
2 Fattovich G, Bortolotti F, Donato F. Natural history of chronic hepatitis B: special emphasis on disease progression and prognostic factors. *J Hepatol* 2008; **48**: 335–52.
3 Ganem D, Prince AM. Hepatitis B virus infection-natural history and clinical consequences. *N Engl J Med* 2004; **350**: 1118–29.
4 McMahon BJ. Natural history of chronic hepatitis B. *Clin Liver Dis* 2010; **14**: 381–96.
5 Sugauchi F, Orito E, Ohno T *et al.* Spatial and chronological differences in hepatitis B virus genotypes from patients with acute hepatitis B in Japan. *Hepatol Res* 2006; **36**: 107–14.
6 EASL clinical practice guidelines: management of chronic hepatitis B virus infection. *J Hepatol* 2012; **57**: 167–85.
7 Liaw YF, Leung N, Kao JH *et al.* Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2008 update. *Hepatol Int* 2008; **2**: 263–83.
8 Lau GK, Piratvisuth T, Luo KX *et al.* Peginterferon Alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. *N Engl J Med* 2005; **352**: 2682–95.
9 Hayashi N, Kiyosawa K, Tsuboushi H *et al.* Efficacy and safety of treatment with peginterferon alfa-2a for chronic hepatitis B patients. *Kanzo* 2012; **53**: 135–46. (In Japanese.)
10 Liaw YF, Jia JD, Chan HL *et al.* Shorter durations and lower doses of peginterferon alfa-2a are associated with inferior hepatitis B e antigen seroconversion rates in hepatitis B virus genotypes B or C. *Hepatology* 2011; **54**: 1591–9.
11 Buster EH, Flink HJ, Cakaloglu Y *et al.* Sustained HBeAg and HBsAg loss after long-term follow-up of HBeAg-positive patients treated with peginterferon alpha-2b. *Gastroenterology* 2008; **135**: 459–67.
12 Piratvisuth T, Lau G, Chao YC *et al.* Sustained response to peginterferon alfa-2a (40 kD) with or without lamivudine in Asian patients with HBeAg-positive and HBeAg-negative chronic hepatitis B. *Hepatol Int* 2008; **2**: 102–10.
13 Wong VW, Wong GL, Yan KK *et al.* Durability of peginterferon alfa-2b treatment at 5 years in patients with hepatitis B e antigen-positive chronic hepatitis B. *Hepatology* 2010; **51**: 1945–53.
14 Chang TT, Gish RG, de Man R *et al.* A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. *N Engl J Med* 2006; **354**: 1001–10.
15 Ono A, Suzuki F, Kawamura Y *et al.* Long-term continuous entecavir therapy in nucleos(t)ide-naive chronic hepatitis B patients. *J Hepatol* 2012; **57**: 508–14.
16 Chang TT, Lai CL, Kew Yoon S *et al.* Entecavir treatment for up to 5 years in patients with hepatitis B e antigen-positive chronic hepatitis B. *Hepatology* 2010; **51**: 422–30.
17 Zoutendijk R, Reijnders JG, Brown A *et al.* Entecavir treatment for chronic hepatitis B: adaptation is not needed for the majority of naive patients with a partial virological response. *Hepatology* 2011; **54**: 443–51.
18 Yokosuka O, Takaguchi K, Fujioka S *et al.* Long-term use of entecavir in nucleoside-naive Japanese patients with chronic hepatitis B infection. *J Hepatol* 2010; **52**: 791–9.
19 Yuen MF, Seto WK, Fung J *et al.* Three years of continuous entecavir therapy in treatment-naive chronic hepatitis B patients: VIRAL suppression, viral resistance, and clinical safety. *Am J Gastroenterol* 2011; **106**: 1264–71.
20 Gish RG, Lok AS, Chang TT *et al.* Entecavir therapy for up to 96 weeks in patients with HBeAg-positive chronic hepatitis B. *Gastroenterology* 2007; **133**: 1437–44.
21 Gish RG, Chang TT, Lai CL *et al.* Loss of HBsAg antigen during treatment with entecavir or lamivudine in nucleoside-naive HBeAg-positive patients with chronic hepatitis B. *J Viral Hepat* 2010; **17**: 16–22.
22 Marcellin P, Lau GK, Bonino F *et al.* Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. *N Engl J Med* 2004; **351**: 1206–17.
23 Marcellin P, Bonino F, Lau GK *et al.* Sustained response of hepatitis B e antigen-negative patients 3 years after treatment with peginterferon alpha-2a. *Gastroenterology* 2009; **136**: 2169–79.
24 Lampertico P, Vigano M, Colombo M. Treatment of HBeAg-negative chronic hepatitis B with pegylated interferon. *Liver Int* 2011; **31** (Suppl 1): 90–4.
25 Lai CL, Shouval D, Lok AS *et al.* Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. *N Engl J Med* 2006; **354**: 1011–20.
26 Shouval D, Lai CL, Chang TT *et al.* Relapse of hepatitis B in HBeAg-negative chronic hepatitis B patients who discontinued successful entecavir treatment: the case for continuous antiviral therapy. *J Hepatol* 2009; **50**: 289–95.
27 Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology* 2009; **50**: 661–2.
28 Year 2012 Health and Science Research Grant from Ministry of Health, Labour and Welfare. Research on Hepatitis (Hepatitis Section). Emergency Comprehensive Measures against Hepatitis Study Group for Standardization of Latest Treatments for Viral Hepatitis. 2013 Guide-

lines for the treatment of hepatitis B, hepatitis C, and liver cirrhosis. 2013. (In Japanese.)
29 Tseng TC, Liu CJ, Yang HC *et al.* High levels of hepatitis B surface antigen increase risk of hepatocellular carcinoma in patients with low HBV load. *Gastroenterology* 2012; **142**: 1140–49.
30 Fattovich G, Rugge M, Brollo L *et al.* Clinical, virologic and histologic outcome following seroconversion from HBeAg to anti-HBe in chronic hepatitis type B. *Hepatology* 1986; **6**: 167–72.
31 Liaw YF, Chu CM, Huang MJ *et al.* Determinants for hepatitis B e antigen clearance in chronic type B hepatitis. *Liver* 1984; **4**: 301–6.
32 Lok AS, Lai CL, Wu PC *et al.* Spontaneous hepatitis B e antigen to antibody seroconversion and reversion in Chinese patients with chronic hepatitis B virus infection. *Gastroenterology* 1987; **92**: 1839–43.
33 Prati D, Taioli E, Zanella A *et al.* Updated definitions of healthy ranges for serum alanine aminotransferase levels. *Ann Intern Med* 2002; **137**: 1–10.
34 Chen CJ, Yang HI, Su J *et al.* Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA* 2006; **295**: 65–73.
35 Papatheodoridis GV, Manolakopoulos S, Liaw YF *et al.* Follow-up and indications for liver biopsy in HBeAg-negative chronic hepatitis B virus infection with persistently normal ALT: a systematic review. *J Hepatol* 2012; **57**: 196–202.
36 Chu CM, Liaw YF. Chronic hepatitis B virus infection acquired in childhood: special emphasis on prognostic and therapeutic implication of delayed HBeAg seroconversion. *J Viral Hepat* 2007; **14**: 147–52.
37 Yim HJ, Lok AS. Natural history of chronic hepatitis B virus infection: what we knew in 1981 and what we know in 2005. *Hepatology* 2006; **43**: S173–81.
38 Park CH, Jeong SH, Yim HW *et al.* Family history influences the early onset of hepatocellular carcinoma. *World J Gastroenterol* 2012; **18**: 2661–7.
39 Wan DW, Tzimas D, Smith JA *et al.* Risk factors for early-onset and late-onset hepatocellular carcinoma in Asian immigrants with hepatitis B in the United States. *Am J Gastroenterol* 2011; **106**: 1994–2000.
40 Castera L, Bernard PH, Le Bail B *et al.* Transient elastography and biomarkers for liver fibrosis assessment and follow-up of inactive hepatitis B carriers. *Aliment Pharmacol Ther* 2011; **33**: 455–65.
41 Goertz RS, Zopf Y, Jugl V *et al.* Measurement of liver elasticity with acoustic radiation force impulse (ARFI) technology: an alternative noninvasive method for staging liver fibrosis in viral hepatitis. *Ultraschall Med* 2010; **31**: 151–5.
42 Kim SU, Lee JH, Kim do Y *et al.* Prediction of liver-related events using fibroscan in chronic hepatitis B patients showing advanced liver fibrosis. *PLoS ONE* 2012; **7**: e36676.
43 Marcellin P, Ziol M, Bedossa P *et al.* Non-invasive assessment of liver fibrosis by stiffness measurement in patients with chronic hepatitis B. *Liver Int* 2009; **29**: 242–7.
44 Tsochatzis EA, Gurusamy KS, Ntaoula S *et al.* Elastography for the diagnosis of severity of fibrosis in chronic liver disease: a meta-analysis of diagnostic accuracy. *J Hepatol* 2011; **54**: 650–9.
45 Ikeda K, Izumi N, Tanaka E *et al.* Fibrosis score consisting of four serum markers successfully predicts pathological fibrotic stages of chronic hepatitis B. *Hepatol Res* 2012; **43**: 596–604.
46 Ahn SH, Park YN, Park JY *et al.* Long-term clinical and histological outcomes in patients with spontaneous hepatitis B surface antigen seroclearance. *J Hepatol* 2005; **42**: 188–94.
47 Chen YC, Sheen IS, Chu CM *et al.* Prognosis following spontaneous HBsAg seroclearance in chronic hepatitis B patients with or without concurrent infection. *Gastroenterology* 2002; **123**: 1084–9.
48 Huo TI, Wu JC, Lee PC *et al.* Sero-clearance of hepatitis B surface antigen in chronic carriers does not necessarily imply a good prognosis. *Hepatology* 1998; **28**: 231–6.
49 Liaw YF, Sheen IS, Chen TJ *et al.* Incidence, determinants and significance of delayed clearance of serum HBsAg in chronic hepatitis B virus infection: a prospective study. *Hepatology* 1991; **13**: 627–31.
50 McMahon BJ, Holck P, Bulkow L *et al.* Serologic and clinical outcomes of 1536 Alaska Natives chronically infected with hepatitis B virus. *Ann Intern Med* 2001; **135**: 759–68.
51 Simonetti J, Bulkow L, McMahon BJ *et al.* Clearance of hepatitis B surface antigen and risk of hepatocellular carcinoma in a cohort chronically infected with hepatitis B virus. *Hepatology* 2010; **51**: 1531–7.
52 Yuen MF, Wong DK, Fung J *et al.* HBsAg Seroclearance in chronic hepatitis B in Asian patients: replicative level and risk of hepatocellular carcinoma. *Gastroenterology* 2008; **135**: 1192–9.
53 Bonilla Guerrero R, Roberts LR. The role of hepatitis B virus integrations in the pathogenesis of human hepatocellular carcinoma. *J Hepatol* 2005; **42**: 760–77.
54 Brechot C. Pathogenesis of hepatitis B virus-related hepatocellular carcinoma: old and new paradigms. *Gastroenterology* 2004; **127**: S56–61.
55 Pollicino T, Saitta C, Raimondo G. Hepatocellular carcinoma: the point of view of the hepatitis B virus. *Carcinogenesis* 2011; **32**: 1122–32.
56 Orito E, Mizokami M, Ina Y *et al.* Host-independent evolution and a genetic classification of the hepadnavirus family based on nucleotide sequences. *Proc Natl Acad Sci U S A* 1989; **86**: 7059–62.
57 Usuda S, Okamoto H, Iwanari H *et al.* Serological detection of hepatitis B virus genotypes by ELISA with monoclonal antibodies to type-specific epitopes in the preS2-region product. *J Virol Methods* 1999; **80**: 97–112.

58 Miyakawa Y, Mizokami M. Classifying hepatitis B virus genotypes. *Intervirology* 2003; **46:** 329–38.
59 Matsuura K, Tanaka Y, Hige S *et al.* Distribution of hepatitis B virus genotypes among patients with chronic infection in Japan shifting toward an increase of genotype A. *J Clin Microbiol* 2009; **47:** 1476–83.
60 Ozasa A, Tanaka Y, Orito E *et al.* Influence of genotypes and precore mutations on fulminant or chronic outcome of acute hepatitis B virus infection. *Hepatology* 2006; **44:** 326–34.
61 Sugauchi F, Orito E, Ichida T *et al.* Epidemiologic and virologic characteristics of hepatitis B virus genotype B having the recombination with genotype C. *Gastroenterology* 2003; **124:** 925–32.
62 Sendi HM-MM, Zali MR, Norder H, Magnius LO. T1764G1766 core promoter double mutants are restricted to Hepatitis B virus strains with an A1757 and are common in genotype D. *J Gen Virol* 2005; **86** (Pt 9): 2451–8.
63 Erhardt A, Reineke U, Blondin D *et al.* Mutations of the core promoter and response to interferon treatment in chronic replicative hepatitis B. *Hepatology* 2000; **31:** 716–25.
64 Marcellin P, Liang J. A personalized approach to optimize hepatitis B treatment in treatment-naive patients. *Antivir Ther* 2010; **15** (Suppl 3): 53–9.
65 Wiegand J, van Bommel F, Berg T. Management of chronic hepatitis B: status and challenges beyond treatment guidelines. *Semin Liver Dis* 2010; **30:** 361–77.
66 Nakamura E, Kakuda H, Matsuura K *et al.* Quantitative analysis of hepatitis B surface antigen as a clinical marker. *Rinsho Byori* 2011; **59:** 838–43.
67 Piratvisuth T, Marcellin P, Popescu M *et al.* Hepatitis B surface antigen: association with sustained response to peginterferon alfa-2a in hepatitis B e antigen-positive patients. *Hepatol Int* 2013; **7:** 429–36.
68 Lau GMP, Brunetto M. On treatment monitoring of HBsAg levels to predict response to peginterferon alfa-2a in patients with HBeAg-positive chronic hepatitis B. *J Hepatol* 2009; **50:** S333.
69 Gane E, Jia J, Han K *et al.* NEPTUNE study: on-treatment HBsAg level analysis confirms prediction of response observed in phase 3 study of peginterferon alfa-2a in HBeAg-positive patients. *J Hepatol* 2011; **54:** abstract 69.
70 Chan HL, Wong VW, Chim AM *et al.* Serum HBsAg quantification to predict response to peginterferon therapy of e antigen positive chronic hepatitis B. *Aliment Pharmacol Ther* 2010; **32:** 1323–31.
71 Sonneveld MJ, Rijckborst V, Boucher CA *et al.* Prediction of sustained response to peginterferon alfa-2b for hepatitis B e antigen-positive chronic hepatitis B using on-treatment hepatitis B surface antigen decline. *Hepatology* 2010; **52:** 1251–7.
72 Brunetto MRBF, Marcellin P *et al.* Kinetic of HBsAg decline in patients with HBeAg-negative chronic hepatitis B treated with peginterferon alfa-2a according to genotype and its association with sustained HBsAg clearance 4 years post treatment. *Hepatology* 2008; **48:** 965A.
73 Takkenberg B, Zaaijer HL, De Niet A *et al.* Baseline HBsAg level and on-treatment HBsAg and HBV DNA decline predict sustained virological response in HBeAg-negative chronic hepatitis B patients treated with peginterferon alfa-2a (Pegasys) and Adefovir (Hepsera); an interim analysis. *Hepatology* 2009; **50:** abstract 491.
74 Kimura T, Rokuhara A, Sakamoto Y *et al.* Sensitive enzyme immunoassay for hepatitis B virus core-related antigens and their correlation to virus load. *J Clin Microbiol* 2002; **40:** 439–45.
75 Tanaka Y, Mizoguchi M. Fundamental and clinical evaluation of hepatitis B virus core-related antigen assay. *Mod Media* 2008; **54:** 347–52. (In Japanese.)
76 Rokuhara A, Tanaka E, Matsumoto A *et al.* Clinical evaluation of a new enzyme immunoassay for hepatitis B virus core-related antigen; a marker distinct from viral DNA for monitoring lamivudine treatment. *J Viral Hepat* 2003; **10:** 324–30.
77 Tanaka E, Matsumoto A, Suzuki F *et al.* HBV Core-Related Antigen Study Group. Measurement of hepatitis B virus core-related antigen is valuable for identifying patients who are at low risk of lamivudine resistance. *Liver Int* 2006; **26:** 90–6.
78 Shinkai N, Tanaka Y, Orito E *et al.* Measurement of hepatitis B virus core-related antigen as predicting factor for relapse after cessation of lamivudine therapy for chronic hepatitis B virus infection. *Hepatol Res* 2006; **36:** 272–6.
79 Haller O, Kochs G, Weber F. The interferon response circuit: induction and suppression by pathogenic viruses. *Virology* 2006; **344:** 119–30.
80 Sen GC. Viruses and interferons. *Annu Rev Microbiol* 2001; **55:** 255–81.
81 Stark GR, Kerr IM, Williams BR *et al.* How cells respond to interferons. *Annu Rev Biochem* 1998; **67:** 227–64.
82 Wills RJ. Clinical pharmacokinetics of interferons. *Clin Pharmacokinet* 1990; **19:** 390–9.
83 Bocci V. Administration of interferon at night may increase its therapeutic index. *Cancer Drug Deliv* 1985; **2:** 313–18.
84 Morgano A, Puppo F, Criscuolo D. Evening administration of alpha interferon: relationship with the circadian rhythm of cortisol. *Med Sci Res* 1984; **15:** 615–16.
85 Ito T, Hara A, Kodame H *et al.* QOL during IFN therapy in the patients with HCV positive-CAH. Effects of the injection in the evening. *Tama Symp J Gastroenterol* 1995; **9:** 46–9. (In Japanese.)
86 Wong DK, Cheung AM, O'Rourke K *et al.* Effect of alpha-interferon treatment in patients with hepatitis B e antigen-positive chronic hepatitis B. A meta-analysis. *Ann Intern Med* 1993; **119:** 312–23.
87 Lin SM, Tai DI, Chien RN *et al.* Comparison of long-term effects of lymphoblastoid interferon alpha and recombi-

nant interferon alpha-2a therapy in patients with chronic hepatitis B. *J Viral Hepat* 2004; **11**: 349–57.
88 Lok AS, Chung HT, Liu VW *et al.* Long-term follow-up of chronic hepatitis B patients treated with interferon alfa. *Gastroenterology* 1993; **105**: 1833–8.
89 Niederau C, Heintges T, Lange S *et al.* Long-term follow-up of HBeAg-positive patients treated with interferon alfa for chronic hepatitis B. *N Engl J Med* 1996; **334**: 1422–7.
90 Lin SM, Yu ML, Lee CM *et al.* Interferon therapy in HBeAg positive chronic hepatitis reduces progression to cirrhosis and hepatocellular carcinoma. *J Hepatol* 2007; **46**: 45–52.
91 Nishiguchi S. Hepatitis B IFN Treatment. In: Yano M, ed. *Liver Disease Consensus 2002 Diagnosis, Treatment and Pathology*. Tokyo: Japan Medical Centre, 2002; 71–7. (In Japanese.)
92 Fattovich G, Farci P, Rugge M *et al.* A randomized controlled trial of lymphoblastoid interferon-alpha in patients with chronic hepatitis B lacking HBeAg. *Hepatology* 1992; **15**: 584–9.
93 Hadziyannis S, Bramou T, Makris A *et al.* Interferon alfa-2b treatment of HBeAg negative/serum HBV DNA positive chronic active hepatitis type B. *J Hepatol* 1990; **11** (Suppl 1): S133–6.
94 Luo K, Mao Q, Karayiannis P *et al.* Tailored regimen of interferon alpha for HBeAg-positive chronic hepatitis B: a prospective controlled study. *J Viral Hepat* 2008; **15**: 684–9.
95 Lampertico P, Del Ninno E, Vigano M *et al.* Long-term suppression of hepatitis B e antigen-negative chronic hepatitis B by 24-month interferon therapy. *Hepatology* 2003; **37**: 756–63.
96 Papatheodoridis GV, Dimou E, Dimakopoulos K *et al.* Outcome of hepatitis B e antigen-negative chronic hepatitis B on long-term nucleos(t)ide analog therapy starting with lamivudine. *Hepatology* 2005; **42**: 121–9.
97 Zeuzem S, Welsch C, Herrmann E. Pharmacokinetics of peginterferons. *Semin Liver Dis* 2003; **23** (Suppl 1): 23–8.
98 Cooksley WG, Piratvisuth T, Lee SD *et al.* Peginterferon alpha-2a (40 kDa): an advance in the treatment of hepatitis B e antigen-positive chronic hepatitis B. *J Viral Hepat* 2003; **10**: 298–305.
99 Peginterferon α-2a formulation "Pegasys for subcutaneous injection" product information. Chugai Pharmaceutical Co, 2011. (In Japanese.)
100 Pegasys 90 μg for subcutaneous injection, Pegasys 180 μg for subcutaneous injection (Peginterferon α-2a (recombinant)) Patent Application Material. http://www.info.pmda.go.jp/shinyaku/P201100162/index.html, Chugai Pharmaceutical Co, 2011. (In Japanese.)
101 Chen JD, Yang HI, Iloeje UH *et al.* Carriers of inactive hepatitis B virus are still at risk for hepatocellular carcinoma and liver-related death. *Gastroenterology* 2010; **138**: 1747–54.
102 Buster EH, Hansen BE, Buti M *et al.* Peginterferon alpha-2b is safe and effective in HBeAg-positive chronic hepatitis B patients with advanced fibrosis. *Hepatology* 2007; **46**: 388–94.
103 Chen CF, Lee WC, Yang HI *et al.* Changes in serum levels of HBV DNA and alanine aminotransferase determine risk for hepatocellular carcinoma. *Gastroenterology* 2011; **141**: 1240–8.
104 Wai CT, Chu CJ, Hussain M *et al.* HBV genotype B is associated with better response to interferon therapy in HBeAg(+) chronic hepatitis than genotype C. *Hepatology* 2002; **36**: 1425–30.
105 Chien RN. Current therapy for hepatitis C or D or immunodeficiency virus concurrent infection with chronic hepatitis B. *Hepatol Int* 2008; **2**: 296–303.
106 Yang HI, Sherman M, Su J *et al.* Nomograms for risk of hepatocellular carcinoma in patients with chronic hepatitis B virus infection. *J Clin Oncol* 2010; **28**: 2437–44.
107 Piccolo P, Lenci I, Demelia L *et al.* A randomized controlled trial of pegylated interferon-alpha2a plus adefovir dipivoxil for hepatitis B e antigen-negative chronic hepatitis B. *Antivir Ther* 2009; **14**: 1165–74.
108 Takkenberg B, Terpstra V, Zaaijer H *et al.* Intrahepatic response markers in chronic hepatitis B patients treated with peginterferon alpha-2a and adefovir. *J Gastroenterol Hepatol* 2011; **26**: 1527–35.
109 Wursthorn K, Lutgehetmann M, Dandri M *et al.* Peginterferon alpha-2b plus adefovir induce strong cccDNA decline and HBsAg reduction in patients with chronic hepatitis B. *Hepatology* 2006; **44**: 675–84.
110 Erhardt A, Blondin D, Hauck K *et al.* Response to interferon alfa is hepatitis B virus genotype dependent: genotype A is more sensitive to interferon than genotype D. *Gut* 2005; **54**: 1009–13.
111 Kao JH, Wu NH, Chen PJ *et al.* Hepatitis B genotypes and the response to interferon therapy. *J Hepatol* 2000; **33**: 998–1002.
112 Suzuki F, Arase Y, Akuta N *et al.* Efficacy of 6-month interferon therapy in chronic hepatitis B virus infection in Japan. *J Gastroenterol* 2004; **39**: 969–74.
113 Shindo M, Hamada K, Nishioji K *et al.* The predictive value of liver fibrosis in determining the effectiveness of interferon and lamivudine therapies for chronic hepatitis B. *J Gastroenterol* 2004; **39**: 260–7.
114 Buster EH, Hansen BE, Lau GK *et al.* Factors that predict response of patients with hepatitis B e antigen-positive chronic hepatitis B to peginterferon-alfa. *Gastroenterology* 2009; **137**: 2002–9.
115 Janssen HL, van Zonneveld M, Senturk H *et al.* Pegylated interferon alfa-2b alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: a randomised trial. *Lancet* 2005; **365**: 123–9.
116 Sonneveld MJ, Wong VW, Woltman AM *et al.* Polymorphisms near IL28B and serologic response to

peginterferon in HBeAg-positive patients with chronic hepatitis B. *Gastroenterology* 2012; **142:** 513–20 e1.
117 Bonino F, Marcellin P, Lau GK *et al.* Predicting response to peginterferon alpha-2a, lamivudine and the two combined for HBeAg-negative chronic hepatitis B. *Gut* 2007; **56:** 699–705.
118 Rijckborst V, Hansen BE, Cakaloglu Y *et al.* Early on-treatment prediction of response to peginterferon alfa-2a for HBeAg-negative chronic hepatitis B using HBsAg and HBV DNA levels. *Hepatology* 2010; **52:** 454–61.
119 Moucari R, Mackiewicz V, Lada O *et al.* Early serum HBsAg drop: a strong predictor of sustained virological response to pegylated interferon alfa-2a in HBeAg-negative patients. *Hepatology* 2009; **49:** 1151–7.
120 Ma H, Yang RF, Wei L. Quantitative serum HBsAg and HBeAg are strong predictors of sustained HBeAg seroconversion to pegylated interferon alfa-2b in HBeAg-positive patients. *J Gastroenterol Hepatol* 2010; **25:** 1498–506.
121 Piratvisuth T, Lau G, Marcellin P *et al.* On-treatment decline in serum HBsAg levels predicts sustained immune control and HBsAg clearance 6 month posttreatment in HBsAg-positive hepatitis B virus-infected patients treated with peginterferon alfa-2a [40kD] (PEGASYS). *Hepatol Int* 2010; **4:** 152.
122 Brunetto MR, Moriconi F, Bonino F *et al.* Hepatitis B virus surface antigen levels: a guide to sustained response to peginterferon alfa-2a in HBeAg-negative chronic hepatitis B. *Hepatology* 2009; **49:** 1141–50.
123 Marcellin P, Piratvisuth T, Brunetto M *et al.* On-treatment decline in serum HBsAg levels predicts sustained immune control 1 year post-treatment and subsequent HBsAg clearance in HBsAg-negative hepatitis B virus-infected patients treated with peginterferon alfa [40kD] (PEGASYS). *Hepatol Int* 2010; **4:** 151.
124 Krogsgaard K, Bindslev N, Christensen E *et al.* The treatment effect of alpha interferon in chronic hepatitis B is independent of pre-treatment variables. Results based on individual patient data from 10 clinical controlled trials. European Concerted Action on Viral Hepatitis (Eurohep). *J Hepatol* 1994; **21:** 646–55.
125 Soza A, Everhart JE, Ghany MG *et al.* Neutropenia during combination therapy of interferon alfa and ribavirin for chronic hepatitis C. *Hepatology* 2002; **36:** 1273–9.
126 Capuron L, Gumnick JF, Musselman DL *et al.* Neurobehavioral effects of interferon-alpha in cancer patients: phenomenology and paroxetine responsiveness of symptom dimensions. *Neuropsychopharmacology* 2002; **26:** 643–52.
127 Cotler SJ, Wartelle CF, Larson AM *et al.* Pretreatment symptoms and dosing regimen predict side-effects of interferon therapy for hepatitis C. *J Viral Hepat* 2000; **7:** 211–17.
128 Raison CL, Miller AH. The neuroimmunology of stress and depression. *Semin Clin Neuropsychiatry* 2001; **6:** 277–94.
129 Sakai T, Omata M, Iino S *et al.* Phase II clinical trial of Ro25-8310 (Peginterferon α-2a) in the treatment of chronic hepatitis C. *Jpn J Med Pharm Sci* 2003; **50:** 655–72. (In Japanese.)
130 van Nunen AB, Hansen BE, Suh DJ *et al.* Durability of HBeAg seroconversion following antiviral therapy for chronic hepatitis B: relation to type of therapy and pretreatment serum hepatitis B virus DNA and alanine aminotransferase. *Gut* 2003; **52:** 420–4.
131 Dienstag JL, Schiff ER, Wright TL *et al.* Lamivudine as initial treatment for chronic hepatitis B in the United States. *N Engl J Med* 1999; **341:** 1256–63.
132 Ito K, Tanaka Y, Orito E *et al.* Predicting relapse after cessation of lamivudine monotherapy for chronic hepatitis B virus infection. *Clin Infect Dis* 2004; **38:** 490–5.
133 Nevens F, Main J, Honkoop P *et al.* Lamivudine therapy for chronic hepatitis B: a six-month randomized dose-ranging study. *Gastroenterology* 1997; **113:** 1258–63.
134 Santantonio T, Mazzola M, Iacovazzi T *et al.* Long-term follow-up of patients with anti-HBe/HBV DNA-positive chronic hepatitis B treated for 12 months with lamivudine. *J Hepatol* 2000; **32:** 300–6.
135 Lee CM, Ong GY, Lu SN *et al.* Durability of lamivudine-induced HBeAg seroconversion for chronic hepatitis B patients with acute exacerbation. *J Hepatol* 2002; **37:** 669–74.
136 Song BC, Suh DJ, Lee HC *et al.* Hepatitis B e antigen seroconversion after lamivudine therapy is not durable in patients with chronic hepatitis B in Korea. *Hepatology* 2000; **32:** 803–6.
137 Honkoop P, de Man RA, Niesters HG *et al.* Acute exacerbation of chronic hepatitis B virus infection after withdrawal of lamivudine therapy. *Hepatology* 2000; **32:** 635–9.
138 Lai CL, Chien RN, Leung NW *et al.* A one-year trial of lamivudine for chronic hepatitis B. Asia Hepatitis Lamivudine Study Group. *N Engl J Med* 1998; **339:** 61–8.
139 Suzuki F, Tsubota A, Arase Y *et al.* Efficacy of lamivudine therapy and factors associated with emergence of resistance in chronic hepatitis B virus infection in Japan. *Intervirology* 2003; **46:** 182–9.
140 Liaw YF, Leung NW, Chang TT *et al.* Effects of extended lamivudine therapy in Asian patients with chronic hepatitis B. Asia Hepatitis Lamivudine Study Group. *Gastroenterology* 2000; **119:** 172–80.
141 Lok AS, Lai CL, Leung N *et al.* Long-term safety of lamivudine treatment in patients with chronic hepatitis B. *Gastroenterology* 2003; **125:** 1714–22.
142 Suzuki Y, Kumada H, Ikeda K *et al.* Histological changes in liver biopsies after one year of lamivudine treatment in patients with chronic hepatitis B infection. *J Hepatol* 1999; **30:** 743–8.
143 Lok AS, Hussain M, Cursano C *et al.* Evolution of hepatitis B virus polymerase gene mutations in hepatitis B e

antigen-negative patients receiving lamivudine therapy. *Hepatology* 2000; **32**: 1145–53.
144 Tassopoulos NC, Volpes R, Pastore G *et al.* Efficacy of lamivudine in patients with hepatitis B e antigen-negative/hepatitis B virus DNA-positive (precore mutant) chronic hepatitis B. Lamivudine Precore Mutant Study Group. *Hepatology* 1999; **29**: 889–96.
145 Ono-Nita SK, Kato N, Shiratori Y *et al.* Susceptibility of lamivudine-resistant hepatitis B virus to other reverse transcriptase inhibitors. *J Clin Invest* 1999; **103**: 1635–40.
146 Ono-Nita SK, Kato N, Shiratori Y *et al.* YMDD motif in hepatitis B virus DNA polymerase influences on replication and lamivudine resistance: a study by in vitro full-length viral DNA transfection. *Hepatology* 1999; **29**: 939–45.
147 Akuta N, Suzuki F, Kobayashi M *et al.* The influence of hepatitis B virus genotype on the development of lamivudine resistance during long-term treatment. *J Hepatol* 2003; **38**: 315–21.
148 Chayama K, Suzuki Y, Kobayashi M *et al.* Emergence and takeover of YMDD motif mutant hepatitis B virus during long-term lamivudine therapy and re-takeover by wild type after cessation of therapy. *Hepatology* 1998; **27**: 1711–16.
149 Hashimoto Y, Suzuki F, Hirakawa M *et al.* Clinical and virological effects of long-term (over 5 years) lamivudine therapy. *J Med Virol* 2010; **82**: 684–91.
150 Kobayashi M, Suzuki F, Akuta N *et al.* Response to long-term lamivudine treatment in patients infected with hepatitis B virus genotypes A, B, and C. *J Med Virol* 2006; **78**: 1276–83.
151 Kurashige N, Hiramatsu N, Ohkawa K *et al.* Initial viral response is the most powerful predictor of the emergence of YMDD mutant virus in chronic hepatitis B patients treated with lamivudine. *Hepatol Res* 2008; **38**: 450–6.
152 Natsuizaka M, Hige S, Ono Y *et al.* Long-term follow-up of chronic hepatitis B after the emergence of mutations in the hepatitis B virus polymerase region. *J Viral Hepat* 2005; **12**: 154–9.
153 Nishida T, Kobashi H, Fujioka S *et al.* A prospective and comparative cohort study on efficacy and drug resistance during long-term lamivudine treatment for various stages of chronic hepatitis B and cirrhosis. *J Gastroenterol Hepatol* 2008; **23**: 794–803.
154 Suzuki F, Suzuki Y, Tsubota A *et al.* Mutations of polymerase, precore and core promoter gene in hepatitis B virus during 5-year lamivudine therapy. *J Hepatol* 2002; **37**: 824–30.
155 Ide T, Kumashiro R, Kuwahara R *et al.* Clinical course of patients with chronic hepatitis B with viral breakthrough during long-term lamivudine treatment. *J Gastroenterol* 2005; **40**: 625–30.
156 Kuwahara R, Kumashiro R, Ide T *et al.* Predictive factors associated with the progression to hepatic failure caused by lamivudine-resistant HBV. *Dig Dis Sci* 2008; **53**: 2999–3006.
157 Suzuki F, Akuta N, Suzuki Y *et al.* Clinical and virological features of non-breakthrough and severe exacerbation due to lamivudine-resistant hepatitis B virus mutants. *J Med Virol* 2006; **78**: 341–52.
158 Aizawa M, Tsubota A, Fujise K *et al.* Clinical course and predictive factors of virological response in long-term lamivudine plus adefovir dipivoxil combination therapy for lamivudine-resistant chronic hepatitis B patients. *J Med Virol* 2011; **83**: 953–61.
159 Hosaka T, Suzuki F, Suzuki Y *et al.* Factors associated with the virological response of lamivudine-resistant hepatitis B virus during combination therapy with adefovir dipivoxil plus lamivudine. *J Gastroenterol* 2007; **42**: 368–74.
160 Hosaka T, Suzuki F, Suzuki Y *et al.* Adefovir dipivoxil for treatment of breakthrough hepatitis caused by lamivudine-resistant mutants of hepatitis B virus. *Intervirology* 2004; **47**: 362–9.
161 Inoue J, Ueno Y, Wakui Y *et al.* Four-year study of lamivudine and adefovir combination therapy in lamivudine-resistant hepatitis B patients: influence of hepatitis B virus genotype and resistance mutation pattern. *J Viral Hepat* 2011; **18**: 206–15.
162 Kurashige N, Hiramatsu N, Ohkawa K *et al.* Factors contributing to antiviral effect of adefovir dipivoxil therapy added to ongoing lamivudine treatment in patients with lamivudine-resistant chronic hepatitis B. *J Gastroenterol* 2009; **44**: 601–7.
163 Ohkawa K, Takehara T, Kato M *et al.* Mutations associated with the therapeutic efficacy of adefovir dipivoxil added to lamivudine in patients resistant to lamivudine with type B chronic hepatitis. *J Med Virol* 2009; **81**: 798–806.
164 Shakado S, Watanabe H, Tanaka T *et al.* Combination therapy of lamivudine and adefovir in Japanese patients with chronic hepatitis B. *Hepatol Int* 2008; **2**: 361–9.
165 Tamori A, Enomoto M, Kobayashi S *et al.* Add-on combination therapy with adefovir dipivoxil induces renal impairment in patients with lamivudine-refractory hepatitis B virus. *J Viral Hepat* 2010; **17**: 123–9.
166 Toyama T, Ishida H, Ishibashi H *et al.* Long-term outcomes of add-on adefovir dipivoxil therapy to ongoing lamivudine in patients with lamivudine-resistant chronic hepatitis B. *Hepatol Res* 2012; **42**: 1168–74.
167 Wu S, Fukai K, Imazeki F *et al.* Initial virological response and viral mutation with adefovir dipivoxil added to ongoing lamivudine therapy in lamivudine-resistant chronic hepatitis B. *Dig Dis Sci* 2011; **56**: 1207–14.
168 Yatsuji H, Suzuki F, Sezaki H *et al.* Low risk of adefovir resistance in lamivudine-resistant chronic hepatitis B patients treated with adefovir plus lamivudine combination therapy: two-year follow-up. *J Hepatol* 2008; **48**: 923–31.

169 Marcellin P, Chang TT, Lim SG *et al.* Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. *N Engl J Med* 2003; **348**: 808–16.
170 Marcellin P, Chang TT, Lim SG *et al.* Long-term efficacy and safety of adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. *Hepatology* 2008; **48**: 750–8.
171 Hadziyannis SJ, Tassopoulos NC, Heathcote EJ *et al.* Adefovir dipivoxil for the treatment of hepatitis B e antigen-negative chronic hepatitis B. *N Engl J Med* 2003; **348**: 800–7.
172 Hadziyannis SJ, Tassopoulos NC, Heathcote EJ *et al.* Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B for up to 5 years. *Gastroenterology* 2006; **131**: 1743–51.
173 Fung SK, Chae HB, Fontana RJ *et al.* Virologic response and resistance to adefovir in patients with chronic hepatitis B. *J Hepatol* 2006; **44**: 283–90.
174 Lee YS, Suh DJ, Lim YS *et al.* Increased risk of adefovir resistance in patients with lamivudine-resistant chronic hepatitis B after 48 weeks of adefovir dipivoxil monotherapy. *Hepatology* 2006; **43**: 1385–91.
175 Kim YJ, Cho HC, Sinn DH *et al.* Frequency and risk factors of renal impairment during long-term adefovir dipivoxil treatment in chronic hepatitis B patients. *J Gastroenterol Hepatol* 2012; **27**: 306–12.
176 Ha NB, Garcia RT, Trinh HN *et al.* Renal dysfunction in chronic hepatitis B patients treated with adefovir dipivoxil. *Hepatology* 2009; **50**: 727–34.
177 Jung YK, Yeon JE, Choi JH *et al.* Fanconi's syndrome associated with prolonged adefovir dipivoxil therapy in a hepatitis B virus patient. *Gut Liver* 2010; **4**: 389–93.
178 Law ST, Li KK, Ho YY. Nephrotoxicity, including acquired Fanconi's syndrome, caused by adefovir dipivoxil – is there a safe dose? *J Clin Pharm Ther* 2012; **37**: 128–31.
179 Ono SK, Kato N, Shiratori Y *et al.* The polymerase L528M mutation cooperates with nucleotide binding-site mutations, increasing hepatitis B virus replication and drug resistance. *J Clin Invest* 2001; **107**: 449–55.
180 Colonno RJ, Rose R, Baldick CJ *et al.* Entecavir resistance is rare in nucleoside naive patients with hepatitis B. *Hepatology* 2006; **44**: 1656–65.
181 Tenney DJ, Levine SM, Rose RE *et al.* Clinical emergence of entecavir-resistant hepatitis B virus requires additional substitutions in virus already resistant to lamivudine. *Antimicrob Agents Chemother* 2004; **48**: 3498–507.
182 Tenney DJ, Rose RE, Baldick CJ *et al.* Long-term monitoring shows hepatitis B virus resistance to entecavir in nucleoside-naive patients is rare through 5 years of therapy. *Hepatology* 2009; **49**: 1503–14.
183 Kobashi H, Takaguchi K, Ikeda H *et al.* Efficacy and safety of entecavir in nucleoside-naive, chronic hepatitis B patients: phase II clinical study in Japan. *J Gastroenterol Hepatol* 2009; **24**: 255–61.
184 Kurashige N, Ohkawa K, Hiramatsu N *et al.* Lamivudine-to-entecavir switching treatment in type B chronic hepatitis patients without evidence of lamivudine resistance. *J Gastroenterol* 2009; **44**: 864–70.
185 Matsuura K, Tanaka Y, Kusakabe A *et al.* Recommendation of lamivudine-to-entecavir switching treatment in chronic hepatitis B responders: randomized controlled trial. *Hepatol Res* 2011; **41**: 505–11.
186 Suzuki F, Akuta N, Suzuki Y *et al.* Efficacy of switching to entecavir monotherapy in Japanese lamivudine-pretreated patients. *J Gastroenterol Hepatol* 2010; **25**: 892–8.
187 Liaw YF, Chien RN, Yeh CT *et al.* Acute exacerbation and hepatitis B virus clearance after emergence of YMDD motif mutation during lamivudine therapy. *Hepatology* 1999; **30**: 567–72.
188 Someya T, Suzuki Y, Arase Y *et al.* Interferon therapy for flare-up of hepatitis B virus infection after emergence of lamivudine-induced YMDD motif mutant. *J Gastroenterol* 2001; **36**: 133–6.
189 Suzuki F, Tsubota A, Akuta N *et al.* Interferon for treatment of breakthrough infection with hepatitis B virus mutants developing during long-term lamivudine therapy. *J Gastroenterol* 2002; **37**: 922–7.
190 Vassiliadis TG, Giouleme O, Koumerkeridis G *et al.* Adefovir plus lamivudine are more effective than adefovir alone in lamivudine-resistant HBeAg- chronic hepatitis B patients: a 4-year study. *J Gastroenterol Hepatol* 2010; **25**: 54–60.
191 Rapti I, Dimou E, Mitsoula P *et al.* Adding-on versus switching-to adefovir therapy in lamivudine-resistant HBeAg-negative chronic hepatitis B. *Hepatology* 2007; **45**: 307–13.
192 Sherman M, Yurdaydin C, Simsek H *et al.* Entecavir therapy for lamivudine-refractory chronic hepatitis B: improved virologic, biochemical, and serology outcomes through 96 weeks. *Hepatology* 2008; **48**: 99–108.
193 Tenney DJ, Rose RE, Baldick CJ *et al.* Two-year assessment of entecavir resistance in lamivudine-refractory hepatitis B virus patients reveals different clinical outcomes depending on the resistance substitutions present. *Antimicrob Agents Chemother* 2007; **51**: 902–11.
194 Suzuki F, Suzuki Y, Akuta N *et al.* Changes in viral loads of lamivudine-resistant mutants during entecavir therapy. *Hepatol Res* 2008; **38**: 132–40.
195 Suzuki F, Toyoda J, Katano Y *et al.* Efficacy and safety of entecavir in lamivudine-refractory patients with chronic hepatitis B: randomized controlled trial in Japanese patients. *J Gastroenterol Hepatol* 2008; **23**: 1320–6.
196 Suzuki Y, Suzuki F, Kawamura Y *et al.* Efficacy of entecavir treatment for lamivudine-resistant hepatitis B over 3 years: histological improvement or entecavir resistance? *J Gastroenterol Hepatol* 2009; **24**: 429–35.
197 Zoulim F, Locarnini S. Hepatitis B virus resistance to nucleos(t)ide analogues. *Gastroenterology* 2009; **137**: 1593–608. e1-2.

198 van Bommel F, de Man RA, Wedemeyer H *et al.* Long-term efficacy of tenofovir monotherapy for hepatitis B virus-monoinfected patients after failure of nucleoside/nucleotide analogues. *Hepatology* 2010; **51**: 73–80.
199 Patterson SJ, George J, Strasser SI *et al.* Tenofovir disoproxil fumarate rescue therapy following failure of both lamivudine and adefovir dipivoxil in chronic hepatitis B. *Gut* 2011; **60**: 247–54.
200 Kurashige N, Ohkawa K, Hiramatsu N *et al.* Two types of drug-resistant hepatitis B viral strains emerging alternately and their susceptibility to combination therapy with entecavir and adefovir. *Antivir Ther* 2009; **14**: 873–7.
201 Yatsuji H, Hiraga N, Mori N *et al.* Successful treatment of an entecavir-resistant hepatitis B virus variant. *J Med Virol* 2007; **79**: 1811–17.
202 Karatayli E, Idilman R, Karatayli SC *et al.* Clonal analysis of the quasispecies of antiviral-resistant HBV genomes in patients with entecavir resistance during rescue treatment and successful treatment of entecavir resistance with tenofovir. *Antivir Ther* 2013; **18**: 77–85.
203 Lok AS, Zoulim F, Locarnini S *et al.* Antiviral drug-resistant HBV: standardization of nomenclature and assays and recommendations for management. *Hepatology* 2007; **46**: 254–65.
204 Tanaka E, Matsumoto A, Yoshizawa K *et al.* Hepatitis B core-related antigen assay is useful for monitoring the antiviral effects of nucleoside analogue therapy. *Intervirology* 2008; **51** (Suppl 1): 3–6.
205 Suzuki F, Miyakoshi H, Kobayashi M *et al.* Correlation between serum hepatitis B virus core-related antigen and intrahepatic covalently closed circular DNA in chronic hepatitis B patients. *J Med Virol* 2009; **81**: 27–33.
206 Wong DK, Tanaka Y, Lai CL *et al.* Hepatitis B virus core-related antigens as markers for monitoring chronic hepatitis B infection. *J Clin Microbiol* 2007; **45**: 3942–7.
207 Matsumoto A, Tanaka E, Minami M *et al.* Low serum level of hepatitis B core-related antigen indicates unlikely reactivation of hepatitis after cessation of lamivudine therapy. *Hepatol Res* 2007; **37**: 661–6.
208 Matsumoto A, Tanaka E, Suzuki Y *et al.* Combination of hepatitis B viral antigens and DNA for prediction of relapse after discontinuation of nucleos(t)ide analogs in patients with chronic hepatitis B. *Hepatol Res* 2012; **42**: 139–49.
209 Tanaka E, Matsumoto M, Suzuki Y *et al.* Guidelines for avoiding risks resulting from discontinuation of nucleos(t)ide analogues in patients with chronic hepatitis B (2012). *Kanzo* 2012; **53**: 237–42. (In Japanese.)
210 Tanaka E, Matsumoto A. Guidelines for avoiding risks resulting from discontinuation of nucleos(t)ide analogues in patients with chronic hepatitis B. *Hepatol Res* 2013 Mar 8. doi: 10.1111/hepr.12108. [Epub ahead of print]
211 Iloeje UH, Yang HI, Su J *et al.* Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. *Gastroenterology* 2006; **130**: 678–86.
212 Serfaty L, Thabut D, Zoulim F *et al.* Sequential treatment with lamivudine and interferon monotherapies in patients with chronic hepatitis B not responding to interferon alone: results of a pilot study. *Hepatology* 2001; **34**: 573–7.
213 Shi M, Wang RS, Zhang H *et al.* Sequential treatment with lamivudine and interferon-alpha monotherapies in hepatitis B e antigen-negative Chinese patients and its suppression of lamivudine-resistant mutations. *J Antimicrob Chemother* 2006; **58**: 1031–5.
214 Manesis EK, Papatheodoridis GV, Hadziyannis SJ. A partially overlapping treatment course with lamivudine and interferon in hepatitis B e antigen-negative chronic hepatitis B. *Aliment Pharmacol Ther* 2006; **23**: 99–106.
215 Enomoto M, Nishiguchi S, Tamori A *et al.* Entecavir and interferon-alpha sequential therapy in Japanese patients with hepatitis B e antigen-positive chronic hepatitis B. *J Gastroenterol* 2013; **48**: 397–404.
216 Minami M, Okanoue T. Management of HBV infection in Japan. *Hepatol Res* 2007; **37**: S79–82.
217 Chien RN, Liaw YF, Atkins M. Pretherapy alanine transaminase level as a determinant for hepatitis B e antigen seroconversion during lamivudine therapy in patients with chronic hepatitis B. Asian Hepatitis Lamivudine Trial Group. *Hepatology* 1999; **30**: 770–4.
218 Lai CL, Lin HJ, Lau JN *et al.* Effect of recombinant alpha 2 interferon with or without prednisone in Chinese HBsAg carrier children. *Q J Med* 1991; **78**: 155–63.
219 Lai CL, Lok AS, Lin HJ *et al.* Placebo-controlled trial of recombinant alpha 2-interferon in Chinese HBsAg-carrier children. *Lancet* 1987; **2**: 877–80.
220 Lok AS, Lai CL, Wu PC *et al.* Long-term follow-up in a randomised controlled trial of recombinant alpha 2-interferon in Chinese patients with chronic hepatitis B infection. *Lancet* 1988; **2**: 298–302.
221 Lok AS, Wu PC, Lai CL *et al.* A controlled trial of interferon with or without prednisone priming for chronic hepatitis B. *Gastroenterology* 1992; **102**: 2091–7.
222 Perrillo RP, Lai CL, Liaw YF *et al.* Predictors of HBeAg loss after lamivudine treatment for chronic hepatitis B. *Hepatology* 2002; **36**: 186–94.
223 Han K, Kim D. Chronic HBV infection with persistently normal ALT b. not to treat. *Hepatol Int* 2008; **2**: 185–89.
224 Lai M, Hyatt BJ, Nasser I *et al.* The clinical significance of persistently normal ALT in chronic hepatitis B infection. *J Hepatol* 2007; **47**: 760–7.
225 Liaw YF, Chu CM, Su IJ *et al.* Clinical and histological events preceding hepatitis B e antigen seroconversion in chronic type B hepatitis. *Gastroenterology* 1983; **84**: 216–19.
226 Liaw YF, Tai DI, Chu CM *et al.* Acute exacerbation in chronic type B hepatitis: comparison between HBeAg and antibody-positive patients. *Hepatology* 1987; **7**: 20–3.