*some drugs is contraindicated. The package insert should be referred to before administrating SMV.*

## 2.4 Drug resistance

The CONCERTO-2 and CONCERTO-3 trials,[10] conducted with non-responders and relapsers, investigated gene mutations in the NS3 protease region in cases of treatment failure, including breakthrough, meeting the discontinuation criteria due to insufficient antiviral effect, HCV RNA positive at completion of treatment, and relapse following completion. Testing for genetic mutations was possible in 59 out of 61 cases of treatment failure, in 54 (92%) of whom mutations conferring SMV resistance were detected. Almost all of these were amino acid 168 substitutions (52/54), with 42 cases of substitution including D168V (35 single D168V substitutions, 7 mixed or multiple substitutions), and 10 single or mixed D168A/H/T/E/X substitutions. For the two cases with no D168 substitutions detected, a single Q80L substitution was seen in one, and mixed Q80K and R155K substitutions in the other. Genotype 1b was present in 97% of the subjects of these studies, and the overseas ASPIRE study also reported that D168V substitutions are responsible for almost all SMV resistance in genotype 1b, whereas R155K substitutions are mainly responsible for SMV resistance in genotype 1a.[17]

Overseas clinical trials have reported that the presence of Q80K polymorphism pretreatment in patients with genotype 1a may reduce the SVR rate.[8,12,13] As Q80K polymorphism is detected in 23–41% of patients with genotype 1a, this may be a predictive factor for therapeutic efficacy. Q80K polymorphism is rare in patients with genotype 1b.[8]

*Recommendations*

- *Resistant mutations are found in a high proportion of patients in whom SMV + Peg-IFN + RBV triple therapy is ineffective. Almost all of these mutations were D168V substitutions in genotype 1b.*
- *SVR rates may be reduced in patients with genotype 1a and Q80K polymorphism pretreatment. Q80K polymorphism is rare in patients with genotype 1b.*

# 3. TREATMENT-NAÏVE PATIENTS

A NUMBER OF new agents are under development for the treatment of HCV genotype 1 and high viral load (≥5.0 log IU/mL using real-time PCR, HCV core antigen ≥300 fmol/L) infections. These include HCV selective antiviral agents (protease inhibitors, polymerase inhibitors, NS5A inhibitors), new IFN preparations, RBV prodrugs, and agents with immunostimulant effects. At present, however, what we have available for general clinical use are antiviral therapies based on IFN preparations, in other words Peg-IFN (IFN) ± RBV ± protease inhibitors (SMV, TVR). In 2011 TVR + Peg-IFN + RBV triple therapy became available for use in Japan. Use of this combination reduced the duration of treatment for 48 or 72 weeks to 24 weeks, and provided a marked improvement in therapeutic efficacy, albeit some problems with adverse reactions. In December 2013, national medical insurance coverage approved the use of SMV,[9–11] a second generation protease inhibitor, for the treatment of genotype 1 high viral load infections. The duration of treatment for SMV + Peg-IFN + RBV triple therapy is 24 weeks, the same as for TVR-based triple therapy. However, once daily dosing for the former, as well as high SVR rates of 80–90% in Japanese clinical trials with treatment naïve subjects (DRAGON,[6] CONCERTO-1,[9] and CONCERTO-4[11]), and similar rates of adverse reactions to the control Peg-IFN + RBV dual therapy group, make SMV + Peg-IFN + RBV triple therapy the present treatment of first choice.

There are no clear discontinuation criteria for SMV-based triple therapy, and very few patients in whom this regimen is contraindicated, so in general the discontinuation criteria for TVR-based triple therapy should be followed.

In some patients, however, in whom adverse reactions are a concern, and the risk of carcinogenesis is considered low, it may be possible to await the introduction of the new agents with more favorable safety profiles.

## 3.1 Predictors of therapeutic efficacy of SMV-based combination therapy

### 3.1.1 IL28B

In the Japanese CONCERTO –1 trials using SMV-based combination therapy, subanalysis according to IL28B alleles (rs8099917 SNP) yielded an SVR24 rate of 94% (77/82) for the TT allele, and 78% (32/41) for the TG/GG alleles.[9] This represents a relatively high SVR rate for the TG or GG minor alleles achieved with SMV-based combination therapy, unlike Peg-IFN + RBV dual therapy, whose therapeutic efficacy is strongly affected by IL28B polymorphism (Fig. 4). A similar trend was seen in the CONCERTO-4 trial, with an SVR24 rate of 100% (16/16) for the TT allele, and 75% (6/8) for the TG/GG alleles, although subject numbers were small.[11]

In the overseas QUEST-1 and QUEST-2 trials using SMV-based combination therapy, SVR12 rates stratified

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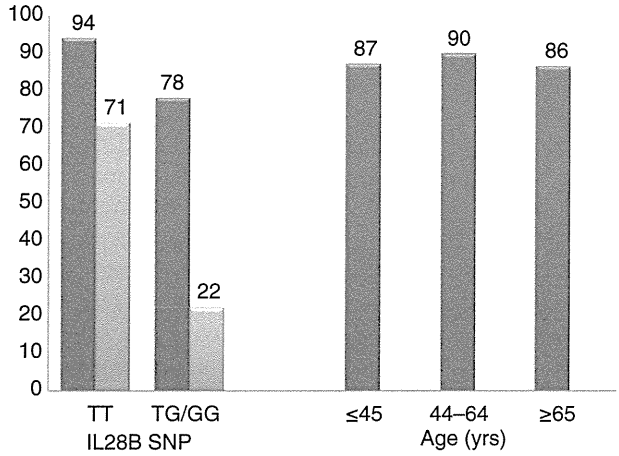


**Figure 4** Results in treatment-naïve patients using the SMV + Peg-IFNα-2a + RBV triple therapy regimen; influence of IL28B polymorphism and age (CONCERTO-1 trial[9]). ■, SMV + Peg-IFNα-2a + RBV; ■, Peg-IFNα-2a + RBV.

for IL28B alleles (rs12979860 SNP) were 97% (72/77) and 96% (72/77) respectively for the CC allele, 76% (114/150) and 80% (114/142) for the CT allele, and 65% (24/37) and 58% (23/40) for the TT allele, showing a similar trend to the Japanese studies (Table 3).

### 3.1.2 Age and fibrosis

SVR24 rates stratified for age in the CONCERTO-1 trial were 87% (20/23) for subjects ≤ 45, 90% (70/78) for those aged 44–64, and 86% (19/22) for those ≥65. No clear differences were seen in SVR rates according to age for those ≤70 years old (Fig. 4). As for fibrosis, QUEST-1 and QUEST-2 examined the relationship between hepatic fibrosis and SVR12 rates, finding SVR12 rates of 83% and 85% respectively for F0-2, 78% and 67% for F3, and 58% and 65% for F4 (Table 3). These results suggest a correlation between the degree of hepatic fibrosis and the efficacy of SMV-based combination therapy. However, the classification F4 is not included in Japanese clinical trials, and there have been no reports of therapeutic results stratified for the degree of hepatic fibrosis.

Taken together, the results of Japanese and overseas clinical trials showed no clear age-related differences in therapeutic effect of SMV + Peg-IFN + RBV triple therapy. Although IL28B SNPs and the degree of fibrosis may influence therapeutic efficacy, SVR rates of 60–80% were still achieved in patients with IL28B minor alleles and advanced fibrosis ≥ F3. Accordingly, at present we cannot say that age, IL28B SNPs or the degree of fibrosis exerts any great influence on the therapeutic efficacy of this treatment regimen.

*Recommendations*

- ***SMV + Peg-IFN + RBV triple therapy is at present the treatment of first choice in IFN-naïve patients.***
- ***IL28B polymorphism has little influence on the SVR rate in IFN-naïve patients undergoing SMV + Peg-IFN + RBV triple therapy, with relatively high SVR rates achieved even in patients with the TG/GG minor alleles.***
- ***In Japanese clinical trials conducted with subjects aged ≤ 70, no clear correlation could be identified between age and SVR rates.***
- ***Although Japanese data is lacking, the results of overseas clinical trials indicate that advanced hepatic fibrosis may influence SVR rates.***
- ***From the above, in general, if treatment is likely to be tolerated, SMV-based triple therapy is indicated in all patients who meet the criteria for antiviral therapy (ALT > 30 U/L or platelet count <150 000/μL), irrespective of IL28B SNP status.***
- ***In some patients, however, in whom adverse reactions are a concern, and the risk of carcinogenesis is***

**Table 3** Overseas results with SMV + Peg-IFN + RBV triple therapy; influence of IL28B polymorphism and age (SVR12, %) (QUEST-1,[12] QUEST-2[13] and PROMISE trials[14])

| | | IL28B SNP | | | Fibrosis (METAVIR) | | |
|---|---|---|---|---|---|---|---|
| | | CC | CT | TT | F0-2 | F3 | F4 |
| QUEST-1 | SMV+Peg-IFN+Rib | 97 | 76 | 65 | 83 | 78 | 58 |
| | Peg-IFN+Rib | 78 | 42 | 24 | | | |
| QUEST-2 | SMV+Peg-IFN+Rib | 96 | 80 | 58 | 85 | 67 | 65 |
| | Peg-IFN+Rib | 81 | 41 | 19 | | | |
| PROMISE | SMV+Peg-IFN+Rib | 89 | 78 | 65 | 82 | 73 | 74 |
| | Peg-IFN+Rib | 53 | 34 | 18 | | | |

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*considered low, it may be possible to await the introduction of the new agents with more favorable safety profiles.*

## 3.2 Selection of antiviral therapy in treatment-naïve patients (Fig. 5)

### 3.2.1 Elderly patients

In this patient group at high risk of hepatocellular carcinogenesis, the best possible antiviral therapy should be promptly commenced. However, the possibility of adverse reactions, and the possibility that viral eradication may not be achieved, should be thoroughly explained to the patient in advance. Although the introduction of TVR + Peg-IFN + RBV triple therapy improved SVR rates in comparison to Peg-IFN + RBV dual therapy,[1] postmarketing surveys revealed serious adverse reactions in approximately 40% of elderly patients. Accordingly, it is recommended that TVR therapy should be commenced at a reduced dosage of 1500 mg/day,[18] although great caution is still required in its use in this age group. On the other hand, clinical trials of SMV + Peg-IFN + RBV triple therapy for treatment-naïve patients have reported an SVR rate of 86% (19/22) in elderly patients aged ≥ 65 (and ≤70), indicating a therapeutic efficacy similar to that seen in non-elderly patients (Fig. 4). Furthermore, very little difference is seen between SMV-based triple therapy and Peg-IFN + RBV dual therapy in terms of safety. Accordingly, SMV + Peg-IFN + RBV triple therapy should be commenced as soon as possible if treatment is likely to be tolerated.

If antiviral therapy is not introduced due to concerns about tolerability, and ALT levels are abnormal, protective therapy (stronger neo-minophagen C; SNMC and/or ursodeoxycholic acid; UDCA) should be commenced.[1] Long-term low dose Peg-IFN (IFN) therapy is another option.[1]

*Recommendations*

- *Elderly patients are at high risk of hepatocellular carcinogenesis, and should commence antiviral therapy promptly.*
- *SMV + Peg-IFN + RBV triple therapy is the antiviral treatment of first choice in treatment-naïve elderly patients.*
- *If antiviral therapy is not introduced and ALT levels are abnormal, protective therapy (SNMC, UDCA) should be commenced. Long-term low dose Peg-IFN (IFN) therapy is another option.*

### 3.2.2 Non-elderly patients

Although the risk of hepatocellular carcinogenesis is relatively low in non-elderly patients, the introduction of antiviral therapy is inevitably necessary in cases of advanced hepatic fibrosis, as in elderly patients. In general, SMV + Peg-IFN + RBV triple therapy should be administered to patients with advanced fibrosis. Also consider IFNβ + RBV combination therapy in patients with depressive symptoms.[1] The risk of carcinogenesis is considered lower in patients with mild fibrosis, so it may be reasonable to await the advent of newer agents with fewer adverse reactions. Determination of IL28B SNP status may be of benefit when the decision whether to commence treatment is a difficult one. However, as mentioned above, clinical trials of SMV + Peg-IFN + RBV triple therapy in treatment-naïve subjects reported SVR rates of approximately 80% in patients

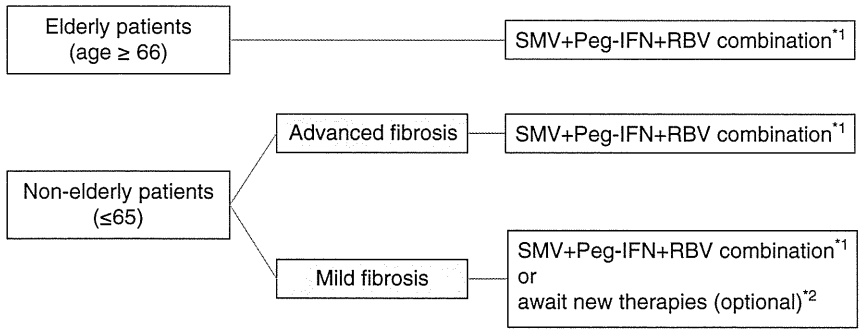


**Figure 5** Treatment flow chart for treatment-naïve patients. Use IL28B testing as a reference if available. Follow therapy protocol for treatment-naïve patients if previous therapy was Peg-IFN (IFN) monotherapy or details of previous therapy with Peg-IFN (IFN) and RBV are unknown. Consider IFNβ + RBV combination if depressive symptoms present. *1 TVR + Peg-IFN + RBV triple therapy is another option (TVR should be commenced at a reduced dosage of 1500 mg/day in the elderly). *2 Protective therapy or low dose Peg-IFN(IFN) therapy if abnormal ALT levels.

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with IL28B minor alleles (Fig. 4). SMV-based triple therapy should therefore be considered in all patients who meet the criteria for antiviral therapy (ALT > 30 U/L or platelet count < 150 000/μL)[1] if treatment is likely to be tolerated, irrespective of IL28B SNP status. If antiviral therapy is not introduced, and ALT levels are abnormal, protective therapy should be commenced.[1]

*Recommendations*

- *Although the risk of hepatocellular carcinogenesis is relatively low in non-elderly patients, the introduction of antiviral therapy is inevitably necessary in cases of advanced hepatic fibrosis, as in elderly patients. Waiting for advent of newer agents with fewer adverse reactions is an option in patients with mild fibrosis.*
- *In general, SMV + Peg-IFN + RBV triple therapy should be administered to treatment-naïve non-elderly patients with advanced fibrosis.*
- *Although treatment may be delayed in non-elderly patients with mild fibrosis, SMV-based triple therapy should be considered in all patients who meet the criteria for antiviral therapy (ALT > 30 U/L or platelet count < 150 000/μL) if treatment is likely to be tolerated. If antiviral therapy is not introduced, and ALT levels are abnormal, protective therapy should be commenced.*

## 4. PREVIOUSLY-TREATED CASES (RETREATMENT)

### 4.1 Predictors of therapeutic efficacy of SMV-based combination therapy

SEVERAL LINES OF clinical studies indicate that, in retreatment using SMV + Peg-IFN + RBV combination therapy, response to the previous treatment is the best indicator of the efficacy of retreatment when IFN/Peg-IFN + RBV combination therapy is ineffective.[10,11,17] In the overseas phase II trial (ASPIRE trial), administering SMV + Peg-IFN + RBV triple therapy to previously treated subjects, Peg-IFN + RBV combination therapy was administered for 48 weeks, in combination with SMV 100 mg or 150 mg/day for the first 12 or 24 weeks, or the entire 48 weeks. As described above, SVR rates for the different SMV dosages (100/150 mg/day) were 85%/85% in relapsers, 57%/75% in partial responders, and 46%/51% in null responders. No differences were seen in SVR rates according to dosage, whereas the response to previous therapy did influence SVR rates, with a greater therapeutic effect seen in partial responders than in null responders.[17] Similarly, in Japanese phase III trials (CONCERTO-2/3[10]) administering SMV + Peg-IFN + RBV triple therapy to previously treated subjects, SVR rates in relapsers and non-responders were 90% (44/49) and 51% (27/53), respectively (Fig. 3). In the CONCERTO-4[11] using Peg-IFNα-2b, the SVR rate was 97% (28/29) in relapsers, and 38% (10/26) in non-responders, a similar result to the CONCERTO-2/3[10] trials using Peg-IFNα-2a (Fig. 2).

Examination of the therapeutic efficacy of SMV-based combination therapy in relapsers, stratified for IL28B SNP status, revealed SVR24 rates of 91% (32/35) for the TT allele, and 86% (12/14) for the TG/GG alleles in the CONCERTO-3 trial (Fig. 6), and 96% (25/26) for the TT allele, and 100% (3/3) for the TG/GG alleles in the CONCERTO-4 trial. High SVR rates were achieved in relapsers in both studies, irrespective of IL28B SNP status. On the other hand, in the CONCERTO-2 trial,[10] conducted with non-responders, SVR24 rates stratified for IL28B SNP status were 50% (7/14) for the TT allele, and 42% (39/92) for the TG/GG alleles (Fig. 6), again showing no difference in SVR rates associated with IL28B polymorphism.

In the overseas PROMISE trial,[14] conducted with relapsers, SVR12 rates stratified for IL28B alleles (rs12979860 SNP) were 89% (55/62) for the CC allele, 78% (131/167) for the CT allele, and 65% (20/31) for the TT allele. Examination of the relationship between hepatic fibrosis and SVR12 rates yielded SVR12 rates of 82% for F0-2, 73% for F3, and 74% for F4 (Table 3). These results demonstrated that, unlike treatment-naïve cases, high SVR rates can be achieved irrespective of the

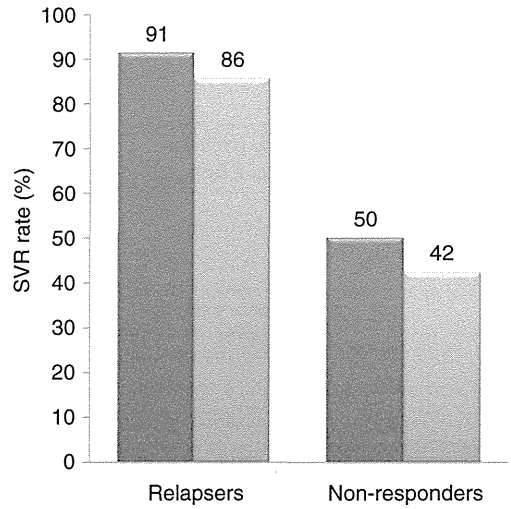


**Figure 6** Results of treatment using SMV + Peg-IFNα-2a + RBV triple therapy in relapsers and non-responders depending on IL28B status (CONCERTO-2/3 trial[10]). ■, TT; ■, TG/GG.

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degree of hepatic fibrosis in relapsers. However, the classification F4 is not included in Japanese clinical trials, and there have been no reports of therapeutic results stratified for the degree of hepatic fibrosis.

In this way, the response to previous therapy is at present the most important predictive factor for SVR rates achieved by SMV + Peg-IFN + RBV triple therapy.

There is presently no evidence available concerning the therapeutic efficacy of SMV + Peg-IFN + RBV triple therapy in non-responders to previous TVR + Peg-IFN + RBV triple therapy. However, retreatment with SMV-based therapy, with particular caution regarding adverse reactions, is an option in patients previously administered TVR-based therapy who were unable to tolerate adequate dosages of one or more agents due to adverse reactions.

When previously treated patients undergo retreatment with a combination including RBV, if RBV was not included in the previous IFN or Peg-IFN monotherapy regimen, the response to the earlier therapy is not a strong predictive factor for the efficacy of further treatment, so in general follow the treatment protocol for treatment-naïve patients. If the HCV RNA decrease at week 12 of the previous treatment is unknown, but it is clear that HCV RNA did not become negative, follow the retreatment protocol for null responders.

*Recommendations*

- *The response to previous therapy is the best indicator for the response to retreatment in patients who were non-responders to previous IFN/Peg-IFN + RBV combination therapy. The relationship between IL28B SNPs and therapeutic efficacy is unclear at present.*
- *Retreatment with RBV combination therapy in patients previously administered IFN or Peg-IFN monotherapy should in general follow the treatment protocol for treatment-naïve cases. If the HCV RNA decrease at week 12 of the previous treatment is unknown, but it is clear that HCV RNA did not become negative, follow the null response retreatment protocol.*
- *There is presently no evidence available concerning the therapeutic efficacy of SMV + Peg-IFN + RBV triple therapy in non-responders to previous TVR + Peg-IFN + RBV triple therapy.*

## 4.2 Selection of antiviral therapy in previously-treated patients (retreatment) (Fig. 7A, 7B)

### 4.2.1 Elderly patients

SMV + Peg-IFN + RBV triple therapy should be commenced promptly if treatment is likely to be tolerated. In particular, relapsers and partial responders are favorable indications. As for null responders, in the overseas clinical trial (ASPIRE), SVR rates of approximately 50% were achieved when SMV + Peg-IFN + RBV combination therapy administered to null responders to previous treatment. Introduction of this regimen is therefore recommended to null responders, although it may be an option to await the advent of newer agents with fewer adverse reactions if problems with tolerability are anticipated. TVR + Peg-IFN + RBV triple therapy is another option, although it is recommended that TVR therapy should be commenced at a reduced dosage of 1500 mg/day as in treatment-naïve cases, and great caution is still required in its use.

The risk of hepatocellular carcinogenesis is high in elderly patients, and when viral eradication cannot be achieved protective therapies (SNMC, UDCA) should be administered with the aims of biochemical improvement and inhibiting hepatocellular carcinogenesis.[1] Long-term low dose Peg-IFN (IFN) therapy is another option.[1]

*Recommendations*

- *In retreatment of elderly patients, if treatment is likely to be tolerated, SMV + Peg-IFN + RBV triple therapy should be administered to relapsers and partial responders.*
- *SVR rates of approximately 50% are achieved with SMV + Peg-IFN + RBV combination therapy in null responders to previous treatment, and introduction of this regimen is therefore recommended to null responders as well. If problems with tolerability are anticipated, it may be an option to await the advent of newer agents with fewer adverse reactions.*
- *When viral therapy is not administered, protective therapies should be administered to patients with abnormal ALT levels. Long-term low dose Peg-IFN (IFN) therapy is another option.*

### 4.2.2 Non-elderly patients

As with elderly patients, as a general rule non-elderly patients with advanced fibrosis and associated high risk of hepatocellular carcinogenesis should be administered SMV + Peg-IFN + RBV combination therapy. Even in patients with mild fibrosis and a lower risk of carcinogenesis, a high SVR rate of approximately 90% is achieved with SMV + Peg-IFN + RBV combination therapy in relapsers and partial responders. Therefore, if treatment is likely to be tolerated, SMV-based triple therapy should be administered to this patient group.

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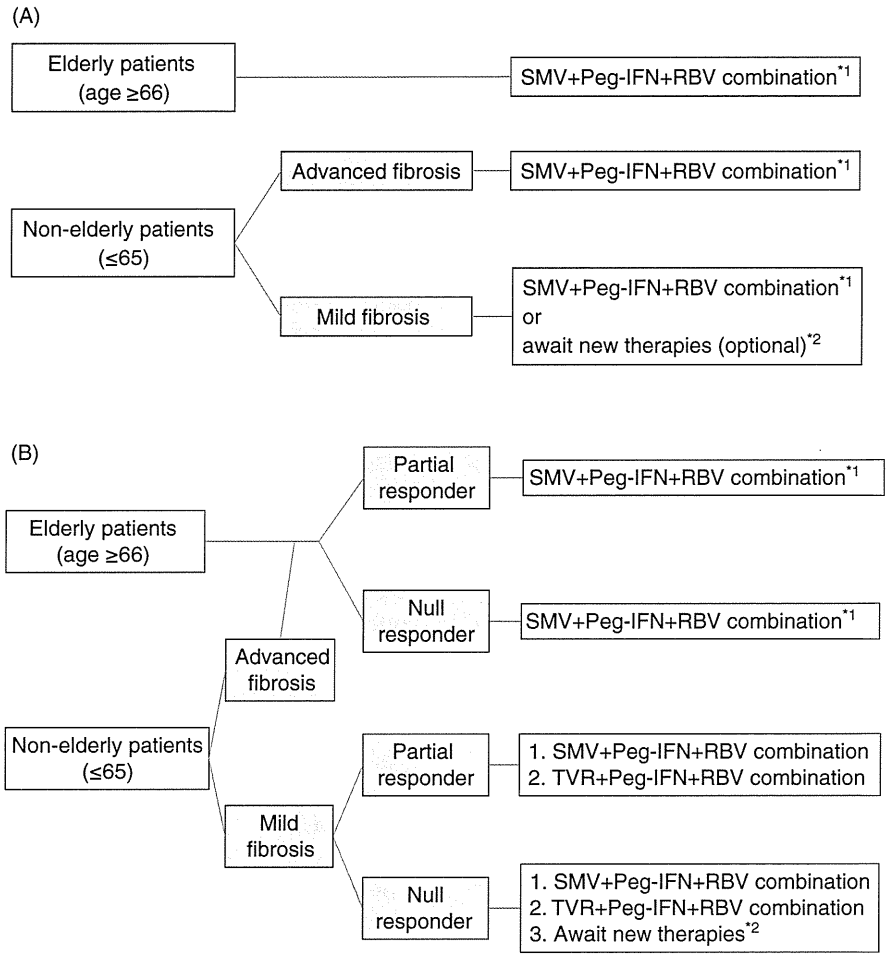


**Figure 7** Treatment flow chart for previously-treated patients (retreatment). A. Relapsers. B. Non-responders. "Previously-treated" refers to previous treatment with Peg-IFN(IFN)/RBV combination therapy. Consider IFNβ + RBV combination if depressive symptoms present. Follow the null response retreatment protocol in non-responders if the quantitative decrease in HCV RNA at week 12 of the previous treatment is unknown. *1 TVR + Peg-IFN + RBV triple therapy is another option (TVR should be commenced at a reduced dosage of 1500 mg/day in the elderly). *2 Protective therapy or low dose Peg-IFN/IFN therapy if abnormal ALT levels.

On the other hand, for non-elderly null responders with mild fibrosis, if adverse reactions are a concern, it may be reasonable to await the advent of newer agents with fewer adverse reactions. When there are no problems with tolerability, SMV + Peg-IFN + RBV combination therapy can be commenced in patients who meet the therapeutic indications for antiviral therapy (ALT > 30 U/L or platelet count < 150 000/μL).

TVR + Peg-IFN + RBV triple therapy is an alternative option in cases with mild fibrosis, where safety is relatively guaranteed.

*Recommendations*

- *In general, SMV + Peg-IFN + RBV triple therapy should be administered for retreatment of non-elderly patients with advanced fibrosis, as for elderly patients.*
- *Even in patients with mild fibrosis, a high SVR rate of approximately 90% is achieved with SMV + Peg-IFN + RBV combination therapy in relapsers and partial responders. If treatment is likely to be tolerated, SMV-based triple therapy should be therefore administered to this patient group.*
- *On the other hand, for non-elderly null responders with mild fibrosis, if adverse reactions are a concern, it may be reasonable to await the advent of newer agents with fewer adverse reactions. When there are no problems with tolerability, SMV + Peg-IFN + RBV combination therapy can be commenced in patients who meet the therapeutic indications for antiviral*

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*therapy (ALT > 30 U/L or platelet count < 150 000/μL).*

- *In non-responders (partial and null responders), TVR + Peg-IFN + RBV triple therapy is an alternative option in cases with mild fibrosis, if treatment is likely to be tolerated.*

## CONFLICTS OF INTEREST

THE MEMBERS OF Drafting Committee for Hepatitis Management Guidelines have received royalty from SRL, lecture fees from Ajinomoto Pharmaceuticals, MSD, Daiichi-Sankyo, Dainippon-Sumitomo Pharma, Mitsubishi Tanabe Pharma, Chugai Pharmaceutical, Bristol-Myers-Squibb, Janssen Pharmaceutical Companies, and research support from Eisai, MSD, Kan Research Institute, Chugai Pharmaceutical, Mitsubishi Tanabe Pharma, Dainippon-Sumitomo Pharma, Toray, Minophagen Pharmaceutical.

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***Special Report***

# JSH Guidelines for the Management of Hepatitis B Virus Infection

Drafting Committee for Hepatitis Management Guidelines and the Japan Society of Hepatology*,**

## PREFACE

THE JAPAN SOCIETY of Hepatology established the Drafting Committee for Hepatitis Management Guidelines in November 2011, and published the Guidelines for the Management of Hepatitis C in May 2012 (English version, Jan 2013). Thence the Committee decided our next task of high priority is to produce the practical guidelines for hepatitis B, also a significant burden to the health care system. Here the Committee has launched the Guidelines for the Management of Hepatitis B Virus Infection. As with hepatitis C virus, this is a field that changes rapidly with the accumulation of new evidence, accompanied by changes in the level of evidence, so we have elected not to show evidence levels. We plan to update these guidelines at appropriate intervals, as new evidence comes to hand.

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## 1. INTRODUCTION

### 1.1 Hepatitis B virus

IT IS ESTIMATED that there are 400 million patients of persistent hepatitis B virus (HBV) infection in the world.[1] In Japan, the HBV infection rate is around 1%. HBV infection at birth or during infancy leads to persistent infection in over 90% of cases. Approximately 90% of these undergo seroconversion from HBe antigen (HBeAg) positive at the initial stage to anti-HBe antibody positive and become inactive carriers, and in virtually all cases the condition effectively stabilizes. But in the remaining 10% the virus remains active, leading to chronic hepatitis, and in around 2% of cases annually, there is further progression to liver cirrhosis, with potential for hepatocellular carcinoma (HCC) and liver failure.[2–4]

Clinical research on HBV dates back to the discovery of the Australia antigen (later renamed HBs antigen; HBsAg) by Blumberg *et al.* in 1964. Prince *et al.* and Okouchi *et al.* subsequently reported a link between the Australia antigen and hepatitis. And there have been various other discoveries demonstrating that the existence of an asymptomatic carrier, who does not develop hepatitis following HBV infection and indicating HBV as a cause of chronic liver diseases. The base form of HBV, known as the Dane particle, was discovered in 1970, followed by the identification of HBeAg in 1972. In 1979, the whole HBV genome was successfully cloned from virus particles, enabling measurement of the virus gene (HBV DNA) for the first time.

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In Japan, screening for the HBsAg was introduced at blood centers in 1972. 1986 was the year of the introduction of an anti-HBV vaccine and immunoglobulin for newborns designed to prevent vertical (mother-to-child) infection. This was highly effective in arresting the development of new HBV carriers through vertical infection, causing a marked decline in HBsAg positive rates among juveniles. The incidence of acute hepatitis caused by HBV infection, however, has not declined, mainly as a result of horizontal transmission associated with sexual activity. In recent years, there has been an increase in infection rates for the HBV genotype A, which frequently causes persistent infection.[5]

## 1.2 Natural history of patients with persistent HBV infection

HBV in itself is considered to have little or no cytotoxicity. Hepatocellular damages are generally caused by cellular immunity associated with cytotoxic T cells, which represent the host's immune response attacking HBV infected cells. Other immunity-associated cells such as antigen-specific helper T cells, macrophages, natural killer cells and natural killer T cells also contribute to inflammation and illness. Patients suffering from persistent HBV infection generally are categorized into four phases defined by the host immune response and the replication of HBV DNA, as shown in Figure 1.

(1) Immune tolerance phase

In infants, when the host immune response is immature, HBV infection inevitably leads to persistent infection. This is followed by a state of immune tolerance, with high levels of HBeAg and HBV DNA replication activity. The host in this phase is termed as an asymptomatic carrier, with ALT levels within the normal range and negligible activity of hepatitis. Infectivity is high. In most cases, infection during infancy is followed by a prolonged immune tolerance period lasting from a few to more than 20 years.

(2) Immune clearance phase

By adulthood, the immune response to HBV becomes an active one, which develops active hepatitis in the immune clearance phase. During the process of HBeAg seroconversion, with disappearance of HBeAg and appearance of anti-HBe antibody, the replication of

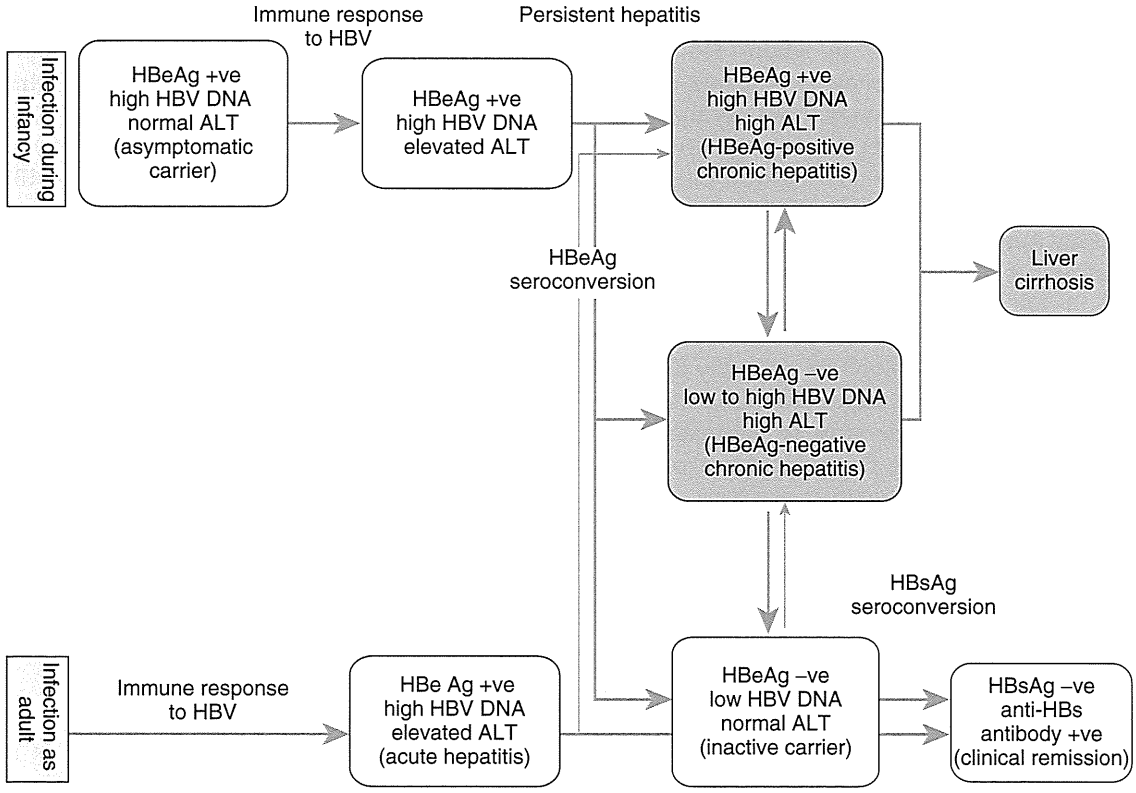


**Figure 1** Natural course of persistent HBV infection.

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HBV DNA is inhibited, thereby encouraging quiescence of hepatitis. However liver disease can progress in cases of persistent hepatitis that remain HBeAg positive for extended periods (HBeAg-positive hepatitis).

(3) Low replicative phase (inactive phase)

HBeAg seroconversion usually results in quiescence of hepatitis, with HBV DNA levels dropping below 4 log copies/mL (inactive carrier). In 10–20% of cases, however, HBeAg seroconversion is followed by increased HBV replication in the HBeAg negative state, causing the exacerbation of hepatitis (HBeAg-negative hepatitis). In a further 4–20% of cases, the HBeAg actually reappears and anti-HBe antibody disappears, a phenomenon known as reverse seroconversion.

(4) Remission phase

In some cases, HBeAg seroconversion causes appearance of anti-HBs antibody and disappearance of HBsAg. In the remission phase, improvement is seen in both blood tests and liver biopsy findings. The natural rate of disappearance of HBsAg in patients with persistent HBV infection is thought to be around 1%.

The natural course of persistent HBV infection can be therefore a progression from HBeAg-positive asymptomatic carrier, through HBeAg-positive (or negative) chronic hepatitis, to cirrhosis. HCC occurs at an annual rate of 5–8% in patients with cirrhosis. At the same time, however, in inactive carriers, in whom HBV DNA declines and serum ALT values are persistently normal following HBeAg seroconversion without any therapeutic intervention, there is a lower risk of progression and hepatocarcinogenesis with a good long-term prognosis. Thus it is important that treatment of patients with persistent HBV infection should be based on a thorough understanding of the natural course as described above.

Where infection occurs after the patient has reached adulthood, an immune reaction will normally develop against HBV during the early stages of infection. After a period of acute hepatitis, the virus is eliminated and quiescence occurs. With the rising incidence of HBV genotype A in recent years, however, we have seen an increasing number of adult infection cases progressing to chronic hepatitis.[5]

## 1.3 Treatment goals – what should we aim for?

The treatment goal of antiviral therapy for persistent HBV infection is to improve the life expectancy and quality of life (QOL) of the patient with HBV infection.

HBV infection is directly associated with the life expectancy in three ways, due to acute liver failure, chronic liver failure, and HCC. Of these three, acute liver failure usually presents the most difficult challenge in terms of prediction and prevention. Management usually centers on preventing HBV reactivation associated with immunosuppressant agents. Meanwhile, the risk factors for chronic liver failure and HCC associated with persistent HBV infection are known, and can be successfully eliminated via antiviral therapy in order to reduce the risk of disease. In other words, we can say that the treatment goal of antiviral therapy in patients with persistent HBV infection should be to inhibit activity of hepatitis and progression of hepatic fibrosis in order to prevent chronic liver failure and reduce the risk of HCC, thereby improving the life expectancy and QOL of the patient with HBV infection. HBsAg is considered the most effective surrogate marker for achieving this ultimate goal, and HBsAg elimination should be defined as the long-term goal of antiviral therapy in patients with persistent HBV infection (Table 1).

Antiviral therapy has three short term goals leading to the elimination of HBsAg: persistent normalization of ALT (≤30 U/L), HBeAg negative and anti-HBe antibody positive (HBeAg seroconversion in HBeAg-positive cases and maintain HBeAg negative status in HBeAg-negative cases), and suppression of HBV DNA replication.

Target serum HBV DNA levels differ between chronic hepatitis and cirrhosis, and also depending on the therapeutic agents. Nucleos(t)ide analogue (NA) therapy is highly effective at producing negative HBV DNA, and at maintaining a negative status through treatment. Thus the on-treatment goal should be to attain an HBV DNA negative status, as determined using high-sensitivity real-time PCR, for both chronic hepatitis and cirrhosis alike. For interferon (IFN) therapy, since HBeAg seroconversion and HBsAg reduction or elimination are expected outcomes following completion of therapy, there is no need for an on-treatment goal of reduced HBV DNA. It should be recommended to complete the full course of therapy over 24 to 48 weeks.

The off-treatment goal (i.e., after IFN therapy has concluded and NAs are no longer administered) is the absence of active hepatitis with no risk of further progression on no medication. Accordingly, the target at 24 to 48 weeks after the end of treatment is set as <4.0 log copies/mL for chronic hepatitis, and negative HBV DNA for cirrhosis.

*Recommendations*

- ***The treatment goal for antiviral therapy in patients with persistent HBV infection is to prevent liver failure and inhibit HCC by suppressing activity of hepatitis***

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**Table 1.** Treatment goals for antiviral therapy

| | Chronic hepatitis | Liver cirrhosis |
|---|---|---|
| **Long-term goal** | HBsAg elimination | HBsAg elimination |
| **Short-term goals** | | |
| ALT | Persistent normal[*1] | Persistent normal[*1] |
| HBeAg | Negative[*2] | Negative[*2] |
| HBV DNA[*3] | | |
| On-treatment (Ongoing NA therapy) | Negative | Negative |
| Off-treatment (IFN completed/NA therapy ceased[*4]) | < 4 log copies/ml | Negative[*5] |

Notes
[*1]. Normal range of ALT is defined as ≤30 U/L.
[*2]. Conversion to HBeAg-negative in HBeAg-positive cases, and maintain HBeAg-negative in HBeAg-negative cases.
[*3]. As measured using high-sensitivity PCR (real-time PCR).
[*4]. At 24–48 weeks following completion of antiviral therapy.
[*5]. NA therapy should not to be ceased in patients with cirrhosis.

*and progression of liver fibrosis, thereby improving the patient's life expectancy and overall QOL.*

- *HBsAg is considered the most effective surrogate marker for attaining this treatment goal. The long-term goal of antiviral therapy is to eliminate HBsAg.*
- *The three short-term goals of antiviral treatment prior to elimination of HBsAg are persistent normalization of ALT, HBeAg negative and positive anti-HBe antibody, and suppression of HBV DNA replication.*
- *The on-treatment goal is negative HBV DNA; this applies to both chronic hepatitis and cirrhosis.*
- *Since HBeAg seroconversion and reduction (or elimination) of HBsAg are expected outcomes following completion of therapy, on-treatment HBV DNA target levels are not applied, and it should be recommended to complete a full course of treatment of 24 to 48 weeks.*
- *The off-treatment goals (following IFN therapy and cessation of NAs) are <4.0 log copies/mL HBV DNA (chronic hepatitis), and negative HBV DNA (cirrhosis).*

## 1.4 Pharmacotherapy – which agents should we use?

Currently IFN and NAs are employed in antiviral therapy for persistent HBV infection. Table 2 lists the approval process of main antiviral therapy agents used in Japan by national medical insurance.

IFN therapy is intended to achieve lasting benefits from a limited treatment period. IFN therapy was first introduced to Japan in 1987. Initially, it was limited to a 28-day course of treatment, although this was extended to 6 months in 2002. In 2011, Peg-IFN (pegylated interferon) was approved for treatment of chronic hepatitis B in clinical settings. In addition to inhibiting the replication of HBV DNA, IFN has both antiviral and immunomodulatory effects. Therapeutic effects of IFN further improved with the advent of Peg-IFN.

IFN therapy offers some key advantages. Treatment is for a fixed period, and if an adequate therapeutic response is achieved, no further treatment is required. IFN therapy can therefore produce lasting therapeutic benefits in the drug-free state. Furthermore, overseas studies have reported that IFN therapy is also highly effective at eliminating HBsAg over the long term. However, disadvantages include the fact that only 20–30% of HBeAg positive cases and 20–40% of HBeAg negative cases respond well to Peg-IFN treatment; patients are required to attend hospital weekly; there are several possible adverse reactions associated with treatment; and finally, Peg-IFN treatment for cirrhosis is not currently approved by Japanese national medical insurance.

Meanwhile, NAs are a form of antiviral agent originally developed as a pharmacological therapy for

**Table 2** Approval process of antiviral therapy in Japan

| | |
|---|---|
| 1987 | Conventional interferon (28-day course, HBeAg positive only) |
| 2002 | Conventional interferon (six-month course, HBeAg positive only) |
| 2000 | Lamivudine |
| 2004 | Adefovir |
| 2006 | Entecavir |
| 2011 | Peg-IFN |

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**Table 3** Peg-IFN versus entecavir – key characteristics

| | Peg-IFN | Entecavir |
|---|---|---|
| Mechanism | Induces antiviral proteins, immunopotentiation | Directly inhibits virus replication |
| Route of administration | Subcutaneous injection | Oral |
| Therapy period | Limited to 24–48 weeks | Generally unrestricted (long-term) |
| Drug resistance | None | Around 1% after 3 years |
| Adverse effects | Frequent and varied | Rare |
| Teratogenicity/carcinogenicity | None | Teratogenic; possibly carcinogenic when administered for long periods |
| Use during pregnancy | Generally contraindicated during pregnancy* | Generally contraindicated during pregnancy |
| Decompensated liver cirrhosis | Contraindicated | Allowed |
| Therapeutic response rate | 20–30% in HBeAg positive, 20–40% in HBeAg negative (difficult to estimate) | Very high |
| Ongoing benefits post therapy | Very high where seroconversion occurs | Low |

*Guidelines for the treatment of chronic hepatitis B from the European Association for the Study of the Liver (EASL)[6] and the Asia-Pacific Association for the Study of the Liver (APASL)[7] prohibit administration of Peg-IFN to pregnant women.

human immunodeficiency virus (HIV). Once it was established that NAs also hinder the reverse transcription mechanism in HBV proliferation, the use of lamivudine, adefovir and entecavir for hepatitis B was approved over the period 2000 to 2006. NAs have a powerful inhibiting effect on HBV DNA proliferation, regardless of genotype, and act as antiviral agents and promote quiescence of hepatitis in nearly all patient types, including those of more advanced age with little prospect of spontaneous remission.

In particular entecavir, currently the first-choice drug, has a very low incidence of resistant mutations compared to lamivudine, and is highly effective at HBV DNA negative conversion and ALT normalization, irrespective of baseline factors. It has virtually no adverse reactions in the short term. On the other hand, it requires a lengthy administration period, due to the propensity for flare-up if treatment is withdrawn, increasing the likelihood of drug-resistant mutations and raising safety issues. Entecavir is also said to be less successful than IFN treatment in reducing the HBsAg load.

Thus, Peg-IFN and entecavir have quite different pharmacological properties and cannot be compared directly, as shown in Table 3. In both HBeAg positive[8–21] and negative cases,[15,22–26] Peg-IFN has been shown to be more effective in terms of the long term goal of HBsAg elimination, while entecavir is more effective in terms of the short-term goals of normalizing ALT and suppressing HBV DNA proliferation (see Tables 4,5). Peg-IFN

**Table 4** Peg-IFN versus entecavir – outcomes for HBeAg positive patients

| | Peg-IFN | Entecavir |
|---|---|---|
| Short term goals | | |
| HBV DNA negative | | |
| Short term | 14%[8] | 67~75%[14,15] |
| Long term | 13%[11–13] | 93~94%[15,16] |
| HBeAg seroconversion | | |
| Short term | 24~36%[8–10] | 16~21%[14,15] |
| Long term | 37~60%[11–13] | 34~44%[17–19] |
| ALT normalization | | |
| Short term | 37~52%[8–10] | 68~81%[14,15] |
| Long term | 47%[11–13] | 87~95%[15,20] |
| Long term goals | | |
| HBsAg elimination | | |
| Short term | 2.3~3.0%[8–10] | 1.7%[14] |
| Long term (overall) | 11%[11] | 0.6~5.1%[16,17,21] |
| Long term (responders*) | 30%[11] | |

**Peg-IFN** (Peg-IFNα-2a[8–10,12] and Peg-IFNα-2b[11,13]):
Short term: 24 weeks after ending treatment.[8–10]
Long term: Three years after ending treatment.[11]
*Responders: HBe negative at 26 weeks after the end of treatment (37% of total, though 21% received additional lamivudine treatment).
**Entecavir**
Short term: One year after starting treatment.[14]
Long term: Two years[20,21], three years,[17–19] four years,[15] and five years[16] after starting treatment.

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**Table 5** Peg-IFN versus entecavir – outcomes for HBeAg negative patients

| | Peg-IFN | Entecavir |
|---|---|---|
| Short term goals | | |
| HBV DNA negative | | |
| Short term | 19~20%[22] | 90~99%[15,25] |
| Long term | 18~21%[23,24] | 100%[15] |
| Reduced HBV DNA levels | | |
| Short term (<20,000 copies/mL) | 43~44%[22] | |
| Long term (<10,000 copies/mL) | 25~28%[23] | |
| ALT normalization | | |
| Short term | 59~60%[22] | 78~85%[15,25] |
| Long term | 31%[23] | 91%[15] |
| Long term goals | | |
| HBsAg elimination | | |
| Short term | 2.8~4.0%[22] | 0.3%[25] |
| Long term (overall) | 8.7~12%[23,24] | 0%[15] |
| Long term (responders*) | 44%[23] | |

**Peg-IFN** (Peg-IFNα-2a:[22–24])
Short term: 24 weeks after ending treatment.[22]
Long term: Three years[23] and five years[24] after ending treatment.
*Responders: HBV DNA negative three years after ending treatment (15% of total).
**Entecavir**
Short term: One year after starting treatment.[25]
Long term: Four years after starting treatment.[15]

and entecavir also differ in terms of predictive factors for therapeutic efficacy, as shown in Table 6. It is therefore important that treatment of HBV should be tailored to the individual patient, based on a thorough understanding of the natural course of the disease and of the key differences between Peg-IFN and entecavir.

*Recommendations*

- *Peg-IFN and entecavir are substantially different pharmacotherapeutic agents that do not bear direct comparison.*
- *HBV treatment regimens should be tailored to the individual patient, based on a thorough understanding of the natural course of the disease and of the key differences between Peg-IFN and entecavir.*

## 1.5 Indications for treatment – who should we treat?

Indications for antiviral therapies for persistent HBV infection are based on the need for treatment, related to a range of factors such as age, disease stage, degree of liver disease (inflammation and fibrosis), and risk of further progression to liver cirrhosis and/or HCC. The three key criteria that are currently used in determining whether to treat are histological progression, ALT levels and HBV DNA levels. In numerous reports on factors linked to antiviral therapeutic effects, ALT and HBV DNA levels have been shown to influence the progression of the disease, and are also noted as common factors associated with therapeutic effects for both IFN and NAs. Guidelines from the American Association for the Study of Liver Diseases (AASLD),[27] the European Association for the Study of the Liver (EASL),[6] the Asia Pacific Association for the Study of the Liver (APASL),[7] and the Japanese Ministry of Health, Labour and Welfare (MHLW) research group[28] all nominate these factors as patient selection criteria, as shown in Table 7. ALT and HBV DNA levels change over the natural course of the disease, and this must be taken into account when deciding when to initiate treatment.

Recently a link has been posited between HBsAg levels and carcinogenesis, with some reports claiming that patients with high HBsAg levels (even when the HBV

**Table 6** Peg-IFN versus entecavir – predictive factors for therapeutic efficacy

| | HBeAg positive | | HBeAg negative | |
|---|---|---|---|---|
| | Peg-IFN | Entecavir | Peg-IFN | Entecavir |
| Race | None | None | None | None |
| Age | Inconsistent | None | None or young | None |
| Gender | None or female | None | None or female | None |
| ALT | High | High | None or high | None or high |
| HBV DNA levels | Low | Low | None or low | Low |
| HBsAg levels | Low | | None | |
| Genotype | None or A (vs D) | None | None or B, C (vs D) | None |
| IL28B | Major | | | |

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**Table 7** Treatment target selection criteria in leading guidelines

| | AASLD (2009)[6] | EASL (2012)[7] | APASL (2008)[27] | MHLW (2013)[28] |
|---|---|---|---|---|
| HBeAg-positive chronic hepatitis | | | | |
| HBV DNA (log copies/mL) | ≥5 | ≥4 | ≥5 | ≥4 |
| ALT | 1) >2 × ULN<br>2) 1–2 × ULN<br>>40 years<br>Family history of HCC → liver biopsy | 1) >1 × ULN<br>2) <1 × ULN<br>→ liver biopsy | 1) >2 × ULN<br>2) ≤2 × ULN<br>>40 years<br>→ liver biopsy | ≥31 U/l |
| HBeAg-negative chronic hepatitis | | | | |
| HBV DNA (log copies/mL) | ≥4 | ≥4 | ≥4 | ≥4 |
| ALT | 1) >2 × ULN<br>2) 1–2 × ULN<br>>40 years<br>Family history of HCC<br>→ liver biopsy | 1) >1 × ULN<br>2) <1 × ULN<br>→ liver biopsy | 1) >2 × ULN<br>2) ≤2 × ULN<br>>40 years<br>→ liver biopsy | ≥31 U/L |
| Cirrhosis | | | | |
| HBV DNA (log copies/mL) | ≥4<br>(<4†) | detectable | ≥4 | ≥2.1 |
| ALT | >1 × ULN<br>(>2 × ULN†) | normal | normal | normal |

†If ALT >2 × ULN, treatment may be indicated even when HBV DNA is <4 log copies/mL.

DNA level is less than 4 log copies/mL following HBeAg seroconversion) have higher rates of further progression and cancinogenesis.[29] However there is still insufficient evidence on the link between HBsAg levels and long term outcomes, and further studies are required before HBsAg levels can be incorporated into the patient selection criteria.

*Recommendations*

- ***The three key criteria currently used to determine whether to treat persistent HBV infection are histological progression, ALT levels and HBV DNA levels.***
- ***The question of whether HBsAg levels should be added to these criteria requires further studies.***

### 1.5.1 Chronic hepatitis – who are not indicated for treatment?

Indications for treatment for chronic hepatitis include abnormal ALT levels, high HBV DNA levels, and presence of histological liver disease. Treatment is therefore not indicated when ALT levels are within the normal range and histological disease is mild or absent altogether – in other words, for HBeAg positive asymptomatic carriers during the immune tolerance phase and inactive carriers following HBeAg seroconversion. Note that in cases of HBeAg-positive chronic hepatitis with elevated ALT levels, there is a 7–16% probability (in annual terms) of the HBeAg seroconversion over the natural course of the disease.[4,30–32] Therefore, it may be advisable in such cases to wait a year before commencing treatment, in the anticipation of HBeAg seroconversion, where there is no evidence of advanced fibrosis and the patient is considered not at risk of fulminant hepatitis.

*Recommendations*

- ***Treatment is not indicated in HBeAg-positive asymptomatic carriers and HBeAg-negative inactive carriers.***
- ***In patients with HBeAg-positive chronic hepatitis with elevated ALT levels with no evidence of advanced fibrosis and not considered at risk of acute liver failure, it may be advisable to wait for 12 months before commencing treatment.***

### 1.5.2 Definition of inactive carriers

The diagnosis of inactive carrier status requires considerable caution.

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The first issue concerns the definition of the threshold for abnormal ALT levels. There is no broad consensus in the medical profession on what constitutes the upper limit of normal (ULN) for ALT levels. In nearly all clinical studies conducted in Japan and elsewhere, the normal value is defined as the standard or control value for the institution conducting the study. Some researchers have proposed an ULN of 30 U/L for males and 19 U/L for females,[33] although these figures have not been validated for hepatitis B. The threshold ALT value as treatment indication seems to be slowly lowered, encouraging more aggressive therapeutic intervention. In Japan, an MHLW research group has defined the indication for treatment at an ALT levels ≥31 U/L since 2008,[28] and thus the current Guidelines propose a normal ALT range for chronic hepatitis of ≤30 U/L, with ≥31 U/L defined as abnormal and therefore the trigger for treatment. When elevated ALT levels are associated with factors unrelated to HBV, such as fatty liver, or consumption of drugs and/or alcohol, antiviral therapy is not indicated.

Similarly, consensus is lacking on the definition of a normal HBV DNA level. As Table 7 shows, the latest AASLD, EASL and APASL guidelines employ differing treatment indications, although in all these guidelines levels have been progressively lowered in line with advances in treatment regimes. In cases of persistent HBV infection, studies have demonstrated that HCC occurs even in patients with normal ALT levels and cancer rates increase in line with the HBV DNA levels, with a statistically significant increase in the rate of carcinogenesis when the HBV DNA levels are over 4 log copies/mL.[34] Liver biopsies in HBeAg negative patients with ALT levels consistently lower than 40 U/L (measured at least three times in a year) indicate negligible active hepatitis and fibrosis when the HBV DNA levels is less than 4 log copies/mL, with a good long term prognosis.[35]

Therefore, in the current Guidelines, inactive carriers after HBeAg seroconversion in whom treatment is not indicated is defined as subjects in a drug free status (no antiviral therapy) satisfy all the following conditions in three or more blood tests taken over the course of at least one year:

1 Persistently negative HBeAg;
2 Persistently normal ALT levels (≤30 U/L); and
3 HBV DNA <4.0 log copies/mL.

Note that patients who satisfy the above conditions but exhibit fibrosis are considered to have a high risk of hepatocarcinogenesis. Therefore, if fibrosis is suspected on the basis of imaging studies or platelet counts, a liver biopsy should be conducted to assess the need for treatment.

In the current Guidelines, the abovementioned off-treatment goals for chronic hepatitis are consistent with the definition of an HBeAg negative inactive carrier, namely an HBV DNA level of less than 4.0 log copies/mL. Accordingly, when the off-treatment goal is achieved the patient becomes an HBeAg negative inactive carrier and treatment is no longer required.

*Recommendation*

- ***An HBeAg negative inactive carrier is defined as a patient who satisfies three key requirements in three or more blood tests taken over the course of a year or more: HBeAg negative, ALT ≤ 30 U/L, and HBV DNA < 4 log copies/mL.***

### 1.5.3 Indications for liver biopsy

A liver biopsy provides valuable information for determining whether antiviral therapy is indicated. In cases where ALT levels are normal or show a gradual or intermittent increase, a liver biopsy is optionally considered, irrespective of whether the treatment indication thresholds given below are met. Treatment is indicated when findings of liver biopsy demonstrate moderate or greater liver fibrosis (Metavir 2 or more) or active hepatitis. A liver biopsy is particularly important in patients ≥40 years with high HBV DNA levels,[2,36,37] or platelet counts <150 000 /μl, or a family history of HCC,[38,39] due to the increased risk of carcinogenesis. Since it is often difficult to distinguish whether fibrosis is advanced or not in HBeAg negative inactive carriers, a liver biopsy is required in order to ensure an accurate diagnosis. Conversely, a liver biopsy solely for the purpose of assessing treatment indication is not considered necessary for clinically demonstrable cases of cirrhosis or chronic hepatitis where the ALT levels is persistently greater than twice the upper limit of normal.

Hepatic fibrosis can be evaluated via noninvasive alternatives to biopsy, such as serum fibrosis markers, imaging studies including CT and ultrasound, and liver stiffness measurement.[40–44] Confirmation of hepatic fibrosis using any of these techniques is considered a treatment indication. Note that the use of serum fibrosis markers alone is not sufficiently accurate for assessment of the degree of fibrosis. There are several useful serum fibrosis markers, including platelet count, serum γ globulin levels, and serum α macroglobulin levels, but none of these should be used as the sole marker.[45]

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### 1.5.4 Chronic hepatitis – who are indicated for treatment?

Chronic hepatitis cases that qualify as neither asymptomatic carriers nor inactive carriers are indicated for antiviral therapy. As Table 8 shows, cases of chronic hepatitis with ALT of 31 U/l or more and HBV DNA levels of 4.0 log copies/mL or more should be indicated for treatment, irrespective of HBeAg status and age. Patients who meet the definition of an inactive carrier but exhibit positive HBV DNA and progression of fibrosis are considered to have a high risk of hepatocarcinogenesis and should be indicated for treatment.

*Recommendations*

- *Treatment is indicated in patients with chronic hepatitis with ALT levels ≥31 U/L and HBV DNA levels ≥4 log copies/mL, regardless of HBeAg status.*
- *Even in those cases not meeting the above criteria, if ALT levels rise slowly or intermittently, or the patient is aged ≥40 with a high HBV DNA levels, platelet count <150 000 /μl and/or family history of HCC, or if advanced fibrosis is suspected by imaging studies, the risk of hepatocarcinogenesis is high and liver biopsy (or noninvasive alternative) should be performed as an optional investigation to determine the extent of fibrosis.*

Table 8 Treatment indications for persistent HBV infection

| | ALT | HBV DNA levels |
|---|---|---|
| Chronic hepatitis†‡§ | ≥31 U/L | ≥4.0 log copies/mL |
| Cirrhosis | – | Detectable |

Notes
†The chronic hepatitis criteria apply to both HBeAg positive and negative patients.
‡Treatment is not indicated in asymptomatic and inactive carriers (defined as HBeAg negative, ALT ≤ 30 U/L, and HBV DNA < 4 log copies/mL measured at least three times over a period of one year or more). In patients with HBeAg positive hepatitis with rising ALT levels, no evidence of advanced fibrosis and not considered at risk of acute liver failure, it may be advisable to withhold treatment for a year while monitoring ALT, HBeAg and HBV DNA levels. Note that treatment is indicated in inactive carriers with both positive HBV DNA and advanced fibrosis.
§In cases where ALT is rising slowly or intermittently, or the patient is aged ≥40 with high HBV DNA levels, platelet count <150 000 /μl and/or family history of HCC, or if advanced fibrosis is suspected by imaging studies, liver biopsy (or noninvasive alternative) should be performed to determine the extent of fibrosis.

- *Even in patients meeting the definition of an inactive carrier, the combination of positive HBV DNA and advanced fibrosis suggests a high risk of hepatocarcinogenesis, and treatment is indicated.*

### 1.5.5 Liver cirrhosis

The criteria for treatment of chronic hepatitis – ALT and HBV DNA levels – are also considered in patients with cirrhosis. However, more aggressive therapeutic intervention is normally required and the treatment indications are different, since the risk of progression to hepatic failure and HCC is increased in cirrhotic patients. As Table 8 shows, treatment is indicated in cirrhosis patients with detectable HBV DNA irrespective of HBeAg status, ALT levels or HBV DNA levels, whereas if HBV DNA is below the detectable threshold antiviral treatment is not indicated.

*Recommendation*

- *Treatment is indicated in patients with liver cirrhosis with detectable HBV DNA, regardless of HBeAg status and ALT or HBV DNA levels.*

### 1.5.6 Follow-up taking into consideration risk of hepatocarcinogenesis

Certain patients on a monitoring regimen with no treatment may yet be at high risk of hepatocarcinogenesis and should be placed under HCC surveillance with regular imaging, particularly those with contributing factors such as age ≥40, male, alcohol consumption, high HBV load, family history of HCC, simultaneous infection with HCV/HDV/HIV, advanced liver fibrosis, low platelet count associated with advanced fibrosis, genotype C, and core promoter mutation. In patients with chronic hepatitis who become HBsAg negative and anti- HBs antibody positive, if cirrhosis was already present prior to elimination of HBsAg there is a high risk of hepatocarcinogenesis.[46–52] It is important to be aware of the ongoing risk of HCC even where cccDNA has been eliminated, due to HBV genome recombination.[53–55]

*Recommendations*

- *Patients under a monitoring regimen who are at a high risk of hepatocarcinogenesis should be placed under HCC surveillance with regular imaging.*
- *It is important to be aware of the risk of HCC in cases of chronic hepatitis in whom HBsAg has disappeared.*

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## 2. CLINICAL SIGNIFICANCE OF HBV MARKERS

HBV MARKERS ARE an indispensable tool for the evaluation of acute hepatitis, chronic hepatitis and cirrhosis caused by HBV. Of the many different HBV markers used in clinical settings, in this section we will discuss HBV genotype, HBV DNA, HBsAg and HB core related antigens (HBcrAg), which are central to predicting disease course and therapeutic effects.

### 2.1 HBV genotype

Generally speaking, DNA viruses have fewer genetic mutations than RNA viruses; yet HBV, a DNA virus, is characterized by a viral proliferation mechanism including reverse transcription, and high rates of mutation.[56] HBV genotypes are classifications used to denote differences in the nucleic acid sequence associated with these genetic mutations. At present, nine genotypes have been identified, from A through J (with genotype I being a subtype of C). Types A, B, C and D account for nearly all genotypes extant in Japan. HBV genotype detection techniques include RFLP (restriction fragment length polymorphism), EIA (enzyme immunoassay), and nucleic acid sequence phylogenetic analysis. Of these only EIA, the technique developed by Usuda *et al.*, is approved by Japanese national medical insurance. EIA uses a combination of monoclonal antibodies capable of recognizing genotype-specific amino acids in the PreS2 domain.[57] Many differences have been reported in the clinical picture of HBV genotypes, which are useful for predicting outcomes and therapeutic effects, as shown in Table 9.[58]

HBV genotype A has been linked to horizontal infection among young people in Japan, with a steady increase seen in the relative incidence of HBV genotype A, most notably in urban areas.[59] Recent studies have demonstrated a marked increase in infection rates for HBV genotype Ae, a genotype traditionally more prevalent in Western countries. This trend is particularly noticeable among young people in Japan, and has been attributed to sexual transmission and illicit drug usage. The normal pattern for a person who becomes infected with HBV during adulthood is a period of acute hepatitis after which the virus is eliminated, leading to quiescence of hepatitis. But with HBV genotype A, the virus tends to remain in the body after the acute phase, making the patient more likely to become a HBV carrier.[5] Nevertheless, outcomes are generally favorable for infections with HBV genotype A.

HBV genotype B is divided into two subtypes: HBV genotype Bj, found in Japan, and HBV genotype Ba, found in the rest of Asia. The Japanese strain (HBV genotype Bj) is distributed widely throughout Japan, from the Tohoku region and parts of Hokkaido in the north to Okinawa in the south. It generally causes very mild disease; most cases remain indefinitely as asymptomatic carriers with a negligible incidence of HCC. However, the Bj subtype has a mutation that can enter site 1896 in the pre-core region. Infection with the pre-core mutation strain causes the virus to proliferate rapidly through the body, potentially leading to fulminant hepatitis. Caution is requires, as HBV genotype Bj and the 1896 mutation have been identified as independent risk factors for fulminant hepatitis.[60] HBV genotype Ba is a recombinant gene arrangement resembling in part HBV genotype C from the core promoter through to the core. HBV genotype Ba reportedly has a relatively high HCC risk, though the characteristics differ significantly between subtypes.

**Table 9** Characteristics of HBV genotypes

| Genotype | Regional specificity | Clinical characteristics in Japan |
|---|---|---|
| A | Western strains (HBV/A2/Ae) | Often becomes chronic (5%–10%) |
| | Asian/African strains (HBV/A1/Aa) | Increasing prevalence, particularly in younger age groups |
| B | Asian strains (HBV/Ba) | Often becomes fulminant |
| | Japanese strains (HBV/B1/Bj) | 10%–20% of total |
| C | Southeast Asia (HBV/Cs) | High rate HCC |
| | East Asia (HBV/Ce) | Around 85% of total |
| D | Southern Europe, Egypt, India, etc. | Rare in Japan, resistant to treatment |
| E | Distributed through Western Africa | Extremely rare in Japan |
| F | Primarily central and southern America | Extremely rare in Japan |
| G | Reported in France, Germany, North America, etc. | Extremely rare in Japan |
| H | Primarily in central and southern America | Extremely rare in Japan |
| J | Borneo? | Extremely rare in Japan |

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HBV genotype C has a high HCC risk (higher even than HBV genotype Ba) and poor prognosis.[61] HBV genotype C is resistant to conventional IFN treatment.

HBV genotype D is normally found in Western countries. There are several localized pockets of infection and a number of subtypes in existence. The most common form is HBV genotype D1, which has been studied extensively and found to include a specific genetic mutation linked to disease phenotype.[62] Reports from Europe suggest that HBV genotype D is more resistant to IFN treatment than HBV genotype A, with a poor overall prognosis.[63]

*Recommendations*

- ***HBV genotype A has been linked to horizontal infection among young people in Japan, who often become carriers following the acute hepatitis phase.***
- ***Among HBV genotype B, subtype Bj is found only in Japan. Most cases remain asymptomatic carriers indefinitely, with negligible risk of HCC. However infection with pre-core mutations can lead to fulminant hepatitis.***
- ***HBV genotype C has a high HCC risk and is resistant to conventional IFN treatment. The prognosis is poor.***

## 2.2 HBV DNA quantification

HBV DNA quantification is for assessment of liver disease, evaluation of therapeutic effects, and diagnosis of breakthrough hepatitis via HBV mutation. It is also linked to prognosis, since high HBV DNA levels indicates a high risk of cancer.[34] Conventional techniques for measuring HBV DNA levels in the past included the Amplicor HBV Monitor test (Roche Diagnostics Systems, Branchburg, NJ, USA) and the HBV DNA TMA-HPA test (transcription-mediated amplification-hybridization protection assay, Chugai Diagnostics Science, Tokyo). Real-time detection PCR testing has become more popular in recent years, as it offers greater sensitivity and a wider measurement range. Real-time detection PCR installs primers and a probe on the well conserved S domain sequences on the HBV genome. The HBV probe is a short oligonucleotide for 5′-end fluorescence labeling and 3′-end quencher labeling. Real-time PCR HBV DNA quantification offers both high sensitivity and a broad dynamic range for detecting the quantity of PCR products based on PCR cycles once the fluorescence intensity reaches a given level. In addition to evaluation of antiviral therapeutic effects, improved sensitivity allows detection of viral breakthroughs, detection of HBV in HBeAg negative cases and latent HBV infections, as well as early prediction of exacerbation of hepatitis and HBV reactivation. Given that results correlate well with those of TMA methods, the real-time PCR method is now recommended for HBV DNA quantification in clinical settings.

Note the difference in units for HBV DNA levels. In the current Guidelines and in Japan in general, HBV DNA is expressed as copies/mL, but elsewhere the unit IU/mL is used (IU stands for international units). The AASLD, EASL and APASL guidelines all use IU/mL. Table 10 shows conversion rates between IU/mL and copies/mL. For example, the general treatment cutoff of 2000 IU/mL is equivalent to 4.07 log copies/mL (conversion rate 5.82) using the TaqMan method (Roche). Note that conversion rates may differ between real-time PCR methods; for example, the same treatment standard would be 3.83 log copies/mL (conversion rate 3.41) using the AccuGene method (Abbott). Further research is required into these discrepancies.

*Recommendation*

- ***Real-time PCR is recommended for HBV DNA quantification in the clinical setting.***

**Table 10** HBV DNA quantification using real-time PCR TaqMan versus AccuGene – measurement ranges and conversion rate

| Method | Sample | Measurement range | | | | Equivalent to 2,000 IU/mL |
|---|---|---|---|---|---|---|
| | | IU/mL | Conversion rate | copies/mL | log copies/mL | |
| TaqMan (Roche) | Serum/blood plasma | 20~1.7×10$^8$ | ⇒ (×5.82) | 116~ 9.9×10$^8$ | 2.1~9.0 | 4.07 log copies/mL |
| AccuGene (Abbott) | Serum/blood plasma | 10~1.0×10$^9$ | ⇒ (×3.41) | 34~ 3.4×10$^9$ | 1.53~9.5 | 3.83 log copies/mL |

Due to different conversion rates for TaqMan and AccuGene (IU to copies), reported values expressed as copies/mL cannot be compared directly (1:1).

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## 2.3 HBsAg quantification

HBsAg is an antigen within the HBV envelope that is present within the blood as the Dane particle as well as empty particles, small spherical particles and tubular particles, all of which are generated from covalently closed circular DNA (cccDNA) in the hepatocytes, as shown in Figure 2.

Qualitative reagents have traditionally been used for measuring HBsAg and for the diagnosis of hepatitis B. But recent years have seen the development of a number of new quantitative reagents with considerable potential for prognosis and evaluation of therapeutic effects.[64,65] Table 11 lists reagents used for measuring HBsAg.

Observations generated by qualitative reagents are expressed in terms of a cut-off index (COI), where a value of 1.0 or higher is deemed positive and higher measurements are semiquantitative, used for reference purposes. Common quantitative reagents include Architect (Abbott) and HISCL (Sysmex). Table 11 shows the threshold criteria and measurement ranges in IU/mL. Quantification covers a wide range through dilution. A newly developed quantitative reagent for HBsAg called Lumipulse HBsAg-HQ claims ten times the sensitivity of conventional reagents, and shows considerable potential for clinical settings.

HBsAg levels vary in accordance with factors such as age, HBV DNA levels and HBV genotype.[66] HBV DNA is considered unsuitable for evaluating therapeutic effects because the HBV DNA levels often falls below the limit of detection shortly after the commencement of antiviral treatment. Several reports therefore recommend monitoring the HBsAg levels over time instead. There have been overseas studies of HBeAg positive patients with chronic hepatitis B stating that the HBsAg levels at 24 weeks after commencing administration of Peg-IFN α-2a, either in isolation or in combination with lamivudine, can be used to predict HBeAg seroconversion, HBV DNA levels and HBsAg elimination rate at 24 weeks after the end of treatment.[67] Similarly, it has been reported that the HBsAg levels at 12 and 24 weeks in a 48 week Peg-IFN therapy regimen can be used to predict HBeAg seroconversion and HBV DNA negative status (sustained viral response or SVR) six months after the end of treatment, as shown in Figure 3.[68–71]

On the other hand, it has been reported that by monitoring the rate of decline in HBsAg levels during treatment of HBeAg negative chronic hepatitis B patients – specifically at 12, 24 and 48 weeks – it is possible to predict the HBV DNA levels one year after the end of treatment as well as disappearance of HBsAg five years later.[72,73]

Some researchers argue that HBsAg monitoring is necessary not only for predicting antiviral therapeutic effects, but throughout the natural course of HBV. A prospective study in Taiwan of the natural course of HBV infection in patients with no history of antiviral

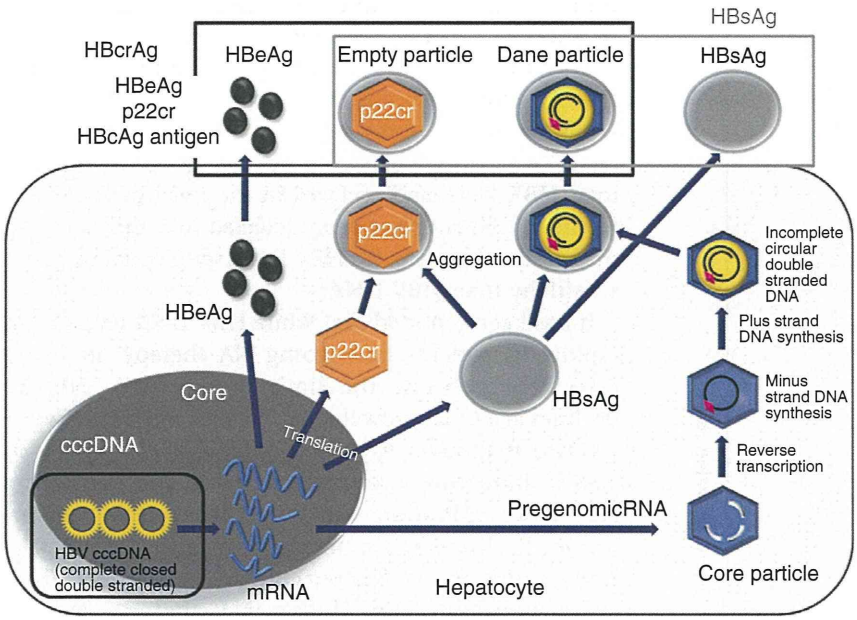


**Figure 2** HBV related markers.

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**Table 11** Reagents for HBsAg measurement

| Device Trade Name | | LUMIPULSE HBsAg | cobas ECLusys HBsAg II | ADVIA Centaur HBsAg | ARCHITECT HBsAg QT | HISCL HBsAg | LUMIPULSEHBsAg-HQ |
|---|---|---|---|---|---|---|---|
| Manufacturer | | Fujirebio | Roche Diagnostics | Siemens Healthcare Diagnostics | Abbott Japan | Sysmex | Fujirebio |
| Principle of operation | | CLEIA | ECLIA | CLIA | CLIA | CLEIA | CLEIA |
| Unit | | COI (qualitative) | COI (qualitative) | COI (qualitative) | IU/mL (quantitative) | IU/mL (quantitative) | IU/mL (quantitative) |
| Antibodies | Capture | Poly | Mono (two types) | Mono | Mono (two types) | Mono (various) | Mono (two types) |
| | Conjugate | Mono (two types) | Poly/mono | Mono | Poly | Mono (various) | Mono (two types) |
| Reaction time (min) | | 30 | 18 | 30 | 30 | 17 | 30 |
| Sample volume (μL) | | 100 | 50 | 100 | 75 | 20 | 100 |
| Positive criterion | | C.O.I ≥ 1.0 | C.O.I ≥ 1.0 | C.O.I ≥ 1.0 | ≥0.05 IU/mL | ≥0.03 IU/mL | ≥0.005 IU/mL |
| Measuring range† | | 0.1~2000 C.O.I. | 0.001~C.O.I. | 0.1~1000 Index | 0.05~250 IU/mL (manual/auto dilution) | 0.03~2500 IU/mL (auto dilution) | 0.005~150 IU/mL (auto dilution) |

†Theoretical value range.

therapy (see Fig. 4) found that the rate of HCC development increases with the baseline HBV DNA levels (>2000 IU/mL), while the actual incidence of HCC in HBeAg negative patients with a low virus load (below 2000 IU/mL) correlated with the HBsAg levels.[29]

Thus, patients with HBV-DNA <2000 IU/mL (=4 log copies/mL), but HBsAg ≥1000 IU/mL, are still at high risk of developing HCC. The risk is greater still if the HBsAg levels remain ≥1000 IU/mL for three years. A prospective study in Alaska reported the incidence of HCC at 0.0368/year following elimination of HBsAg. This is significantly lower in statistical terms than the reported 0.1957/year for patients with persistently positive HBsAg.[51] We may conclude that the elimination of HBsAg effectively reduces cccDNA in the liver, in turn inhibiting carcinogenesis.

Thus, monitoring of the HBV DNA levels during antiviral treatment of chronic HBV should be augmented by regular observation of HBsAg levels in line with a long term treatment goal of elimination of HBsAg.

*Recommendation*

- ***In antiviral treatment of chronic hepatitis B, both HBV DNA and HBsAg levels should be monitored in line with a long term treatment goal of eliminating HBsAg.***

## 2.4 HBcrAg

As Figure 2 shows, HBcrAg is the generic term for three types of antigen structural protein: HBcAg translated from pregenomic mRNA, HBeAg translated from precore mRNA and p22cr antigen. This provides a simple measurement framework, developed in Japan, that can be used to generate automated results in a relatively short time frame. In patients not on antiviral therapy, HBcrAg correlated positively with serum HBV DNA levels, in both HBeAg positive and negative patients alike.[74] A positive correlation was also observed between total HBV DNA and cccDNA in the liver, as shown in Figure 5.[75] HBcrAg has been detected in samples below the limit of detection for HBV DNA, with equal or better sensitivity than HBV DNA.

It has been reported that while HBV DNA levels drop rapidly in patients undergoing NA therapy, in many cases falling below the limit of detection, HBcrAg declines at a much slower rate.[76] The divergence between the two is thought to be attributable to the action of NAs in hindering reverse transcription and preventing HBV DNA replication, while the HBV cccDNA remaining in the liver tissue continues to discharge HBcrAg. And it turns out that HBcrAg correlates with the cccDNA levels in liver tissue during NA therapy, thereby

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