Hepatology Research

Hepatology Research 2012; 42: 333–339 doi: 10.1111/j.1872-034X.2011.00937.x

Review Article

Risk of hepatitis B reactivation in patients treated with tumor necrosis factor-α inhibitors

Eiji Tanaka[1] and Yukitomo Urata[2]

[1]Department of Medicine, Shinshu University School of Medicine, Matsumoto, and [2]Department of Rheumatology, Seihoku Chuo Hospital, Gosyogawara, Japan

The use of tumor necrosis factor-α (TNF-α) inhibitors has been increasing especially in patients with rheumatoid arthritis (RA). As TNF-α inhibitors are strongly immunosuppressive, the occurrence of hepatitis B virus (HBV) reactivation has recently been observed. Reports suggest a higher risk of complicating HBV reactivation in carriers who are treated with TNF-α inhibitors. Therefore, HBV carriers are recommended to undergo prophylactic administration of nucleos(t)ide analogs (NAs). Our literary analysis uncovered several characteristics of de novo hepatitis B due to TNF-α inhibitors. First, the time between the start of TNF-α inhibitors and the occurrence of de novo hepatitis was longer than one year. Second, patients were usually treated with additional non-biologic agents, which also had immunosuppressive effects. Third, the disease could be fatal. Fourth, several types of TNF-α inhibitors exhibited a risk of developing de novo hepatitis. Although the incidence of de novo hepatitis B varied among reports (0–5%/year), it is suggested that patients with prior HBV infection are at risk of developing de novo hepatitis due to TNF-α inhibitors. Many reports maintain that regular measurement of HBV DNA is effective in preventing de novo hepatitis. Prophylactic administration of NAs is also considered useful to avoid de novo hepatitis, although the issue of cost-effectiveness needs to be addressed. Lastly, whereas maintenance of circulating anti-HBs titer using HB vaccines may be effective in responders to prevent de novo hepatitis, further studies are required to clarify the utility of HB vaccination.

Key words: hepatitis B, nucleos(t)ide analog, de novo hepatitis B, reactivation, rheumatoid arthritis, tumor necrosis factor-α inhibitor

INTRODUCTION

APPROXIMATELY 3 BILLION people have been exposed to the hepatitis B virus (HBV), and there are an estimated 350 million chronic carriers worldwide.[1,2] HBV infection is usually detected by the presence of hepatitis B surface antigen (HBsAg) in the serum, and clearance of HBsAg is generally considered as an indication of hepatitis B resolution. However, recent studies have shown that HBV replication persists at low levels in the liver and peripheral blood mononuclear cells for decades, even in HBsAg-negative patients with resolved HBV infection.[3–5] In such patients, HBV replication is suppressed by immune responses to HBV, for instance specific cytotoxic T lymphocyte-mediated responses.[3]

Hepatitis B virus reactivation in patients with resolved HBV infection has been reported in increasing numbers as the number of patients undergoing strong immunosuppressive therapy grows worldwide for malignant neoplasms, autoimmune disorders, and following transplantation for prevention of rejection. In patients like these with resolved HBV infection, reactivation of hepatitis B is recognized as de novo hepatitis B, which can lead to fulminant hepatic failure and often death.[6,7] Thus, de novo hepatitis B is becoming a well-recognized severe complication of immunosuppressive therapy that should be prevented.[6,8]

The risk of developing de novo hepatitis B varies among immunosuppressive therapies; it is as high as 14–20% in patients who receive hematopoietic stem cell transplantation and as low as 1–3% in those who undergo conventional chemotherapies.[9–13] The introduction of rituximab, a genetically engineered chimeric anti-CD20 monoclonal antibody,[14,15] in the treatment of

Correspondence to: Professor Eiji Tanaka, Department of Medicine, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto, Nagano 390-8621, Japan. Email: etanaka@shinshu-u.ac.jp
Received 22 September 2011; revision 22 October 2011; accepted 25 October 2011.

CD20+ B-cell non-Hodgkin's lymphoma increased the risk of de novo hepatitis B. Hui *et al.*[16] analyzed the occurrence of de novo hepatitis B in patients who were treated for lymphoma and reported that its risk was significantly higher in patients who received rituximab and steroids (12%) than in other patients (1%). Similarly, Yeo *et al.*[17] reported that the risk of de novo hepatitis B was significantly higher in patients who were treated with chemotherapy including rituximab (24%) than in those treated with chemotherapy only (0%). Because the introduction of rituximab increased the risk of de novo hepatitis B considerably in lymphoma patients, the need to examine the occurrence of HBV reactivation has emerged when a new agent that suppresses host immune responses is introduced.

Tumor necrosis factor-α is a crucial pro-inflammatory and immunoregulatory cytokine in the pathogenesis of various inflammatory and autoimmune conditions. Inhibitors of TNF-α have recently been introduced in treatments for various kinds of autoimmune and inflammatory disorders, including rheumatoid arthritis (RA), ankylosing spondylitis, psoriatic arthritis, and Crohn's disease. TNF-α inhibitors have revolutionized the therapeutic approaches and treatment paradigms for these patients. However, their optimal use requires consideration of possible adverse effects; increased risks of tuberculosis and other infections are a major concern in TNF-α treatment.[18] Complicating tuberculosis is considered to be caused by reactivation of latent tuberculosis.[19] A similar reactivation of HBV has also been reported, which leads to de novo hepatitis B and possibly fulminant hepatic failure and death. In the present review article, we summarize reports regarding reactivation of hepatitis B due to TNF-α inhibitors to clarify its characteristics and occurrence (Table 1).

Table 1 Summary of references regarding reactivation hepatitis due to tumor necrosis factor-α inhibitors

Category/Reference	Publication type
Case report and review in HBV carriers	
25. Ostuni P, *et al.* Ann Rheum Dis. 2003	Case report
26. Carroll MB, *et al.* Clin Rheumatol. 2010	Review
27. Kuroda T, *et al.* Rheumatol Int. 2010	Case report & review
28. Verhelst X, *et al.* Eur J Gastroenterol Hepatol. 2010	Case report & review
29. Pyrpasopoulou A, *et al.* Rheumatol Int. 2011	Case report
30. Esteve M, *et al.* Gut. 2004	Case report
31. Ojiro K, *et al.* J Gastroenterol. 2008	Case report
34. Wendling D, *et al.* Joint Bone Spine. 2009	Case report
Risk and prevention in HBV carriers	
32. Zingarelli S, *et al.* Reumatismo. 2008	Original
33. Kalyoncu U, *et al.* Rheumatol Int. 2009	Original
35. Vassilopoulos D, *et al.* Ann Rheum Dis. 2010	Original
36. Lan JL, *et al.* Ann Rheum Dis. 2011	Original
37. Calabrese LH, *et al.* Ann Rheum Dis. 2006	Review
Case report of de novo hepatitis B	
40. Madonia S, *et al.* Inflamm Bowel Dis. 2007	Case report
41. Matsumoto T, *et al.* Liver Int. 2010	Case report
42. Montiel PM, *et al.* Liver Int. 2008	Case report
43. Zingarelli S, *et al.* J Rheumatol. 2009	Case report
Risk of de novo hepatitis B	
18. Takeuchi T, *et al.* Ann Rheum Dis. 2008	Original
44. Charpin C, *et al.* Arthritis Res Ther. 2009	Original
45. Caporali R, *et al.* Arthritis Care Res (Hoboken). 2010	Original
46. Tamori A, *et al.* J Gastroenterol. 2011	Original
47. Mori S. Mod Rheumatol. 2011	Original
48. Kim YJ, *et al.* J Rheumatol. 2010	Original
49. Urata Y, *et al.* Mod Rheumatol. 2011	Original

REACTIVATION OF HEPATITIS IN HBV CARRIERS

THE MAJORITY OF patients with a confirmed diagnosis of RA use disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, but the rate of biologic agent use is rising rapidly.[20,21] Since both methotrexate[22–24] and biologic agents carry the danger of HBV reactivation, the advent of new biologic agents, such as TNF-α inhibitors, has increased this risk. Patients with RA who developed reactivation of hepatitis B due to TNF-α inhibitors were first reported in 2003.[25–29] Because these cases had been HBV carriers prior to starting TNF-α inhibitors, the authors recommended preliminary serological tests for HBV infection.

Caroll *et al.* conducted a systemic literature review on HBV reactivation in carriers who were treated with TNF-α inhibitors for RA and reported that reactivation was seen in six (17%) of 35 patients.[26] They concluded that clinicians prescribing TNF-α inhibitors to HBsAg-positive patients should consider prophylactic antiviral therapy and close monitoring for any clinical or sero-

logical evidence of hepatitis. Reactivation of hepatitis B was also reported in patients with Crohn's disease who were treated with TNF-α inhibitors,[30,31] and thus reactivation became considered to be drug dependent and not disease dependent.

Prophylaxis using nucleos(t)ide analogs (NAs) has been reported to be effective in preventing the occurrence of hepatitis reactivation in HBV carriers.[32–36] Vassilopoulos *et al.*[35] administered lamivudine in 14 HBV carriers with RA who were treated with TNF-α inhibitors and showed that reactivation of hepatitis B did not occur in any patient except one. The appearance of lamivudine resistance was considered to be the cause of reactivation in this exceptional patient, and so the authors concluded that TNF-α inhibitors represented a safe option for patients with chronic HBV infection when combined with NAs. Zingarelli *et al.*[32] reported 20 patients with RA who were treated with DMARDs and/or TNF-α inhibitors. Prophylaxis and therapy with lamivudine were performed in patients with a high risk of HBV reactivation, and no cases of viral reactivation were observed. Thus, it is likely that prophylaxis using NAs may prevent the occurrence of hepatitis reactivation in HBV carriers who are treated with TNF-α inhibitors. Indeed, Calabrese *et al.*[37] recommended that all HBsAg-positive patients be started on prophylactic anti-viral drugs before receiving immunosuppressive therapy. However, long-term follow-up studies in large groups of patients are required to ensure the safety of prophylaxis with NAs.

Descriptions of HBV reactivation due to TNF-α inhibitors in the guidelines of rheumatologist associations several years ago tended to be brief and passive. It was described that TNF-α inhibitor therapy should be avoided in patients with hepatitis B infection until more definitive data were available in the 2005 guidelines of The British Society for Rheumatology.[38] In the 2007 Japanese guidelines,[39] it was advised that TNF-α inhibitors should be avoided in patients with HBV infection. However, if the potential benefits of treatment with TNF-α inhibitors exceeded the risk of reactivation, such therapy could be pursued provided that patients were pre-treated with lamivudine.

RISK OF DE NOVO HEPATITIS B

ALTHOUGH IT HAS become clear that HBsAg-positive patients are prone to developing HBV reactivation during TNF-α inhibitor therapy, little is known about the occurrence of de novo hepatitis B. Several cases of de novo hepatitis B due to TNF-α inhibitors have been reported recently.[40–43] Mondonia *et al.*[40] reported a 41-year-old woman with Crohn's disease who developed de novo hepatitis B after having been treated with prednisolone for 13 years and infliximab for 3 years. The hepatitis subsided with lamivudine administration. Montiel *et al.*[42] described a 73-year-old man with ankylosing spondylitis who developed de novo hepatitis 15 months after starting etanercept. The patient had also undergone treatment with prednisolone for 23 years. Although etanercept was discontinued when the hepatitis occurred, it could be re-started with concurrent lamivudine administration. Matsumoto *et al.*[41] reported a 71-year-old woman with RA who developed de novo hepatitis 22 months after starting treatment with infliximab, methotrexate, and prednisolone. Although entecavir was given when hepatitis occurred, the patient died of hepatic failure. Such case reports reveal several characteristics of de novo hepatitis B due to TNF-α inhibitors. First, the duration between the start of the drugs and the occurrence of de novo hepatitis was at least one year. Second, patients were treated not only with TNF-α inhibitors, but also with DMARDs and prednisolone, which themselves had immunosuppressive effects. Third, there was a risk of death from de novo hepatitis. Fourth, several kinds of TNF-α inhibitors appeared able to cause de novo hepatitis.

The incidence of HBV reactivation from occult HBV infection and ensuing de novo hepatitis B due to TNF-α inhibitor therapy in patients with RA has been reported by several groups. Charpin *et al.*[44] followed 21 patients with RA who were HBsAg-negative and hepatitis B core antibody (HBcAb)-positive before starting TNF-α inhibitors, and found that no patient developed HBV reactivation during a mean follow-up period of 27.2 months. They concluded that TNF-α inhibitor therapy was likely safe in patients with a past hepatitis B serological pattern. However, they also suggested that such patients required HBV virological follow-up, especially those with a low HBs antibody (HBsAb) titer at baseline because HBsAb decreased significantly during therapy. Caporali *et al.*[45] followed 67 patients with RA who also had HBV markers of past HBV infection, and found no elevations of HBV DNA in sera or appearances of HBsAg during a mean follow-up period of 42.5 months. Of the 67 patients, 23 were treated with infliximab, 23 with etanercept, and 19 with adalimumab. Almost all patients underwent methotrexate (51 patients) and/or prednisolone (43 patients) administration in addition to TNF-α inhibitors. Tamori *et al.*[46] followed 50 patients with RA who were positive for HBcAb for a mean period of 23 months. All patients were treated with immunosuppressive agents such as

methotrexate, prednisolone, and/or TNF-α inhibitors for more than one year. HBV reactivation was observed in two of five patients with HBsAg, compared with only in one of the remaining 45 patients without it. Therefore, HBV reactivation leading to de novo hepatitis B was observed in 2% (1%/year) of patients. It should be noted that the lone HBsAg-negative reactivation patient had been treated with methotrexate but not with TNF-α inhibitors. Mori[47] performed a cross-sectional analysis of 239 patients with RA who were treated with biological and/or non-biological agents, among whom 60 were found to have HBV markers indicating earlier HBV infection. Of these, two were signal-positive for serum HBV DNA but without ALT elevation or HBsAg positivity: one patient was treated with tacrolimus, prednisolone, and methotrexate, and the other was treated with adalimumab, prednisolone, and methotrexate. Whereas HBV DNA level in the former patient increased and HBsAg and HBeAg became weakly positive after 10 weeks, the latter patient became HBV DNA-negative without additional anti-viral therapy. The authors also concluded that biological and non-biological agents are relatively safe in RA patients with past HBV infection. Thus, these studies suggested that the occurrence of de novo hepatitis B was rare in RA patients who were treated with TNF-α inhibitors in addition to DMARDs over the medium term. A large-scale post-marketing surveillance study was carried out in Japan to determine the safety profile of infliximab in patients with RA.[18] All patients with RA who were treated with infliximab were prospectively monitored for any adverse events for a period of 6 months after the initiation of infliximab. No cases of de novo hepatitis B were found. Although the follow-up period was short, the number of patients enrolled was over 5000. This report indicated that de novo hepatitis B due to TNF-α inhibitors would be very rare over the short-term as well.

In contrast to the abovementioned reports, several studies have suggested a relatively high incidence of de novo hepatitis B due to TNF-α inhibitor therapy. Kim *et al.*[48] followed 266 patients with RA who were treated with TNF-α inhibitors and analyzed the occurrence of clinically significant (over two times higher than normal range) and persistent (two or more incidences) alanine aminotransferase (ALT) elevation in relation to HBV markers. Elevation of ALT was significantly more frequent in patients with HBcAb (HBsAg negative) than in those without (16% vs. 6%, $P = 0.009$). In multiple logistic regression analysis controlling for various potential confounding factors, such as methotrexate, nonsteroidal anti-inflammatory drugs, and type of TNF-α inhibitor, only potential occult HBV infection was identified as a significant risk factor for ALT elevation, suggesting a close association between HBcAb-positivity and ALT elevation during TNF-α inhibitor therapy in RA patients. However, it cannot be confirmed whether ALT elevations in that study were indeed caused by reactivation of occult HBV because HBV DNA was not measured along with ALT. Urata *et al.*[49] prospectively followed 135 patients with RA who had HBV markers suggesting past HBV infection for 12 months. The cohort was treated with biological and/or non-biological anti-rheumatic agents and followed for a total mean period of approximately 20 months, including the period before follow-up. Serum HBV DNA was measured every 3 months during the study period, and revealed that HBV reactivation occurred in seven patients (5%/year). HBV reactivation was significantly associated with use of TNF-α inhibitors with a hazard ratio of 10.9 ($P = 0.008$). This study suggested that careful monitoring of HBV DNA level is required in RA patients with resolved hepatitis B when receiving anti-rheumatic agents, especially biologic ones.

In Japan, HBV reactivation rates tend to differ regionally. A study from Aomori prefecture[49] in the northern part of Japan reported a relatively higher rate of de novo hepatitis stemming from TNF-α inhibitors than studies from Osaka[46] and Kumamoto[47] prefectures in the central and southern parts of Japan, respectively. It is speculated that these differences are attributed to variations in HBV genotype distribution; whereas genotype B is predominant in the former area, genotype C is more frequent in the latter areas.[50] Further studies are required to address this phenomenon.

In light of the above findings, it is evident that RA patients with past HBV infection who are treated with anti-rheumatic agents are at risk of developing HBV reactivation and ensuing de novo hepatitis B, especially those being treated with anti-rheumatic agents, such as TNF-α inhibitors, for an extended time. Spontaneous remission of HBV reactivation was observed in one of the two patients reported by Mori[47] and two of the seven patients reported by Urata *et al.*,[49] and so it should be noted that HBV reactivation does not necessarily result in the occurrence of de novo hepatitis B.

PROPHYLACTIC MEASURES FOR DE NOVO HEPATITIS B

THREE MEASURES ARE generally used to prevent de novo hepatitis B due to immunosuppressive therapy.[7] The first measure is to regularly check for

serum HBV DNA during immunosuppressive therapy and administer NAs should it be detected. The second measure is to administer NAs from the onset of immunosuppressive therapy. The third measure is to maintain circulating HBsAb titer using HB vaccines and/or HB immunoglobulins. Reports have suggested that regular evaluation of HBV DNA is effective in avoiding de novo hepatitis in patients treated with TNF-α inhibitors because HBV reactivation could be controlled by NAs when found at an early stage.[46,49] It is still unclear how often and for how long patients should be tested to detect HBV viremia. Prophylactic administration of NAs is also an option to preempt de novo hepatitis B due to TNF-α inhibitors because NAs are normally used to prevent reactivation in carrier patients. However, the issue of cost-efficiency versus relatively low incidence of de novo hepatitis B needs to be reconciled. Lastly, maintenance of circulating HBsAb titer using HB vaccines may be effective in responders since several studies[44,46] have shown that HBsAb titer decreases during TNF-α inhibitor therapy. As with HBV DNA monitoring and prophylactic NA administration, further studies are required to clarify the extent of HB vaccination effectiveness in preventing de novo hepatitis B due to TNF-α inhibitors.

ACKNOWLEDGEMENTS

THIS REVIEW ARTICLE was supported in part by a Grant-in-Aid from the Ministry of Health, Labour, and Welfare of Japan.

We thank Mr. Trevor Ralph for his English editorial assistance.

REFERENCES

1 Ganem D, Prince AM. Hepatitis B virus infection – natural history and clinical consequences. *N Engl J Med* 2004; **350**: 1118–29.
2 Lee WM. Hepatitis B virus infection. *N Engl J Med* 1997; **337**: 1733–45.
3 Rehermann B, Ferrari C, Pasquinelli C, Chisari FV. The hepatitis B virus persists for decades after patients' recovery from acute viral hepatitis despite active maintenance of a cytotoxic T-lymphocyte response. *Nat Med* 1996; **2**: 1104–8.
4 Yotsuyanagi H, Yasuda K, Iino S *et al.* Persistent viremia after recovery from self-limited acute hepatitis B. *Hepatology* 1998; **27**: 1377–82.
5 Yuki N, Nagaoka T, Yamashiro M *et al.* Long-term histologic and virologic outcomes of acute self-limited hepatitis B. *Hepatology* 2003; **37**: 1172–9.
6 Umemura T, Tanaka E, Kiyosawa K, Kumada H. Mortality secondary to fulminant hepatic failure in patients with prior resolution of hepatitis B virus infection in Japan. *Clin Infect Dis* 2008; **47**: e52–6.
7 Tanaka E, Umemura T. History and prevention of de novo hepatitis B virus-related hepatitis in Japan and the World. *Clin J Gastroenterol* 2008; **1**: 83–6.
8 Yeo W, Johnson PJ. Diagnosis, prevention and management of hepatitis B virus reactivation during anticancer therapy. *Hepatology* 2006; **43**: 209–20.
9 Lok AS, Liang RH, Chiu EK, Wong KL, Chan TK, Todd D. Reactivation of hepatitis B virus replication in patients receiving cytotoxic therapy. Report of a prospective study. *Gastroenterology* 1991; **100**: 182–8.
10 Chen PM, Fan S, Liu CJ *et al.* Changing of hepatitis B virus markers in patients with bone marrow transplantation. *Transplantation* 1990; **49**: 708–13.
11 Dhedin N, Douvin C, Kuentz M *et al.* Reverse seroconversion of hepatitis B after allogeneic bone marrow transplantation: a retrospective study of 37 patients with pretransplant anti-HBs and anti-HBc. *Transplantation* 1998; **66**: 616–9.
12 Knoll A, Boehm S, Hahn J, Holler E, Jilg W. Reactivation of resolved hepatitis B virus infection after allogeneic haematopoietic stem cell transplantation. *Bone Marrow Transplant* 2004; **33**: 925–9.
13 Onozawa M, Hashino S, Izumiyama K *et al.* Progressive disappearance of anti-hepatitis B surface antigen antibody and reverse seroconversion after allogeneic hematopoietic stem cell transplantation in patients with previous hepatitis B virus infection. *Transplantation* 2005; **79**: 616–9.
14 Czuczman MS, Grillo-Lopez AJ, White CA *et al.* Treatment of patients with low-grade B-cell lymphoma with the combination of chimeric anti-CD20 monoclonal antibody and CHOP chemotherapy. *J Clin Oncol* 1999; **17**: 268–76.
15 Coiffier B, Lepage E, Briere J *et al.* CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med* 2002; **346**: 235–42.
16 Hui CK, Cheung WW, Zhang HY *et al.* Kinetics and risk of de novo hepatitis B infection in HBsAg-negative patients undergoing cytotoxic chemotherapy. *Gastroenterology* 2006; **131**: 59–68.
17 Yeo W, Chan TC, Leung NW *et al.* Hepatitis B virus reactivation in lymphoma patients with prior resolved hepatitis B undergoing anticancer therapy with or without rituximab. *J Clin Oncol* 2009; **27**: 605–11.
18 Takeuchi T, Tatsuki Y, Nogami Y *et al.* Postmarketing surveillance of the safety profile of infliximab in 5000 Japanese patients with rheumatoid arthritis. *Ann Rheum Dis* 2008; **67**: 189–94.
19 Keane J, Gershon S, Wise RP *et al.* Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med* 2001; **345**: 1098–104.

20 Pressman Lovinger S. Use of biologics for rheumatoid arthritis tempered by concerns over safety, cost. *JAMA* 2003; **289**: 3229–30.
21 Scott DL, Kingsley GH. Tumor necrosis factor inhibitors for rheumatoid arthritis. *N Engl J Med* 2006; **355**: 704–12.
22 Hagiyama H, Kubota T, Komano Y, Kurosaki M, Watanabe M, Miyasaka N. Fulminant hepatitis in an asymptomatic chronic carrier of hepatitis B virus mutant after withdrawal of low-dose methotrexate therapy for rheumatoid arthritis. *Clin Exp Rheumatol* 2004; **22**: 375–6.
23 Ito S, Nakazono K, Murasawa A *et al.* Development of fulminant hepatitis B (precore variant mutant type) after the discontinuation of low-dose methotrexate therapy in a rheumatoid arthritis patient. *Arthritis Rheum* 2001; **44**: 339–42.
24 Gwak GY, Koh KC, Kim HY. Fatal hepatic failure associated with hepatitis B virus reactivation in a hepatitis B surface antigen-negative patient with rheumatoid arthritis receiving low dose methotrexate. *Clin Exp Rheumatol* 2007; **25**: 888–9.
25 Ostuni P, Botsios C, Punzi L, Sfriso P, Todesco S. Hepatitis B reactivation in a chronic hepatitis B surface antigen carrier with rheumatoid arthritis treated with infliximab and low dose methotrexate. *Ann Rheum Dis* 2003; **62**: 686–7.
26 Carroll MB, Forgione MA. Use of tumor necrosis factor alpha inhibitors in hepatitis B surface antigen-positive patients: a literature review and potential mechanisms of action. *Clin Rheumatol* 2010; **29**: 1021–9.
27 Kuroda T, Wada Y, Kobayashi D *et al.* Effect of etanercept and entecavil in a patient with rheumatoid arthritis who is a hepatitis B carrier: a review of the literature. *Rheumatol Int* 2010; DOI: 10.1007/s00296-009-1344-2.
28 Verhelst X, Orlent H, Colle I, Geerts A, De Vos M, Van Vlierberghe H. Subfulminant hepatitis B during treatment with adalimumab in a patient with rheumatoid arthritis and chronic hepatitis B. *Eur J Gastroenterol Hepatol* 2010; **22**: 494–9.
29 Pyrpasopoulou A, Douma S, Vassiliadis T, Chatzimichailidou S, Triantafyllou A, Aslanidis S. Reactivation of chronic hepatitis B virus infection following rituximab administration for rheumatoid arthritis. *Rheumatol Int* 2011; **31**: 403–4.
30 Esteve M, Saro C, Gonzalez-Huix F, Suarez F, Forne M, Viver JM. Chronic hepatitis B reactivation following infliximab therapy in Crohn's disease patients: need for primary prophylaxis. *Gut* 2004; **53**: 1363–5.
31 Ojiro K, Naganuma M, Ebinuma H *et al.* Reactivation of hepatitis B in a patient with Crohn's disease treated using infliximab. *J Gastroenterol* 2008; **43**: 397–401.
32 Zingarelli S, Airo P, Frassi M, Bazzani C, Scarsi M, Puoti M. Prophylaxis and therapy of HBV infection in 20 patients treated with disease modifying antirheumatic drugs or with biological agents for rheumatic diseases. *Reumatismo* 2008; **60**: 22–7.
33 Kalyoncu U, Yonem O, Calguneri M *et al.* Prophylactic use of lamivudine with chronic immunosuppressive therapy for rheumatologic disorders. *Rheumatol Int* 2009; **29**: 777–80.
34 Wendling D, Di Martino V, Prati C, Toussirot E, Herbein G. Spondyloarthropathy and chronic B hepatitis. Effect of anti-TNF therapy. *Joint Bone Spine* 2009; **76**: 308–11.
35 Vassilopoulos D, Apostolopoulou A, Hadziyannis E *et al.* Long-term safety of anti-TNF treatment in patients with rheumatic diseases and chronic or resolved hepatitis B virus infection. *Ann Rheum Dis* 2010; **69**: 1352–5.
36 Lan JL, Chen YM, Hsieh TY *et al.* Kinetics of viral loads and risk of hepatitis B virus reactivation in hepatitis B core antibody-positive rheumatoid arthritis patients undergoing anti-tumour necrosis factor alpha therapy. *Ann Rheum Dis* 2011; **70**: 1719–25.
37 Calabrese LH, Zein NN, Vassilopoulos D. Hepatitis B virus (HBV) reactivation with immunosuppressive therapy in rheumatic diseases: assessment and preventive strategies. *Ann Rheum Dis* 2006; **65**: 983–9.
38 Ledingham J, Deighton C. Update on the British Society for Rheumatology guidelines for prescribing TNFalpha blockers in adults with rheumatoid arthritis (update of previous guidelines of April 2001). *Rheumatology (Oxford)* 2005; **44**: 157–63.
39 Koike R, Takeuchi T, Eguchi K, Miyasaka N. Update on the Japanese guidelines for the use of infliximab and etanercept in rheumatoid arthritis. *Mod Rheumatol* 2007; **17**: 451–8.
40 Madonia S, Orlando A, Scimeca D, Olivo M, Rossi F, Cottone M. Occult hepatitis B and infliximab-induced HBV reactivation. *Inflamm Bowel Dis* 2007; **13**: 508–9.
41 Matsumoto T, Marusawa H, Dogaki M, Suginoshita Y, Inokuma T. Adalimumab-induced lethal hepatitis B virus reactivation in an HBsAg-negative patient with clinically resolved hepatitis B virus infection. *Liver Int* 2010; **30**: 1241–2.
42 Montiel PM, Solis JA, Chirinos JA, a Casis B, Sanchez F, Rodriguez S. Hepatitis B virus reactivation during therapy with etanercept in an HBsAg-negative and anti-HBs-positive patient. *Liver Int* 2008; **28**: 718–20.
43 Zingarelli S, Frassi M, Bazzani C, Scarsi M, Puoti M, Airo P. Use of tumor necrosis factor-alpha-blocking agents in hepatitis B virus-positive patients: reports of 3 cases and review of the literature. *J Rheumatol* 2009; **36**: 1188–94.
44 Charpin C, Guis S, Colson P *et al.* Safety of TNF-blocking agents in rheumatic patients with serology suggesting past hepatitis B state: results from a cohort of 21 patients. *Arthritis Res Ther* 2009; **11**: R179.
45 Caporali R, Bobbio-Pallavicini F, Atzeni F *et al.* Safety of tumor necrosis factor alpha blockers in hepatitis B virus occult carriers (hepatitis B surface antigen negative/anti-hepatitis B core antigen positive) with rheumatic diseases. *Arthritis Care Res (Hoboken)* 2010; **62**: 749–54.

46 Tamori A, Koike T, Goto H *et al.* Prospective study of reactivation of hepatitis B virus in patients with rheumatoid arthritis who received immunosuppressive therapy: evaluation of both HBsAg-positive and HBsAg-negative cohorts. *J Gastroenterol* 2011; **46**: 556–64.
47 Mori S. Past hepatitis B virus infection in rheumatoid arthritis patients receiving biological and/or nonbiological disease-modifying antirheumatic drugs. *Mod Rheumatol* 2011; DOI: 10.1007/s10165-011-0458-z.
48 Kim YJ, Bae SC, Sung YK *et al.* Possible reactivation of potential hepatitis B virus occult infection by tumor necrosis factor-alpha blocker in the treatment of rheumatic diseases. *J Rheumatol* 2010; **37**: 346–50.
49 Urata Y, Uesato R, Tanaka D *et al.* Prevalence of reactivation of hepatitis B virus replication in rheumatoid arthritis patients. *Mod Rheumatol* 2011; **21**: 16–23.
50 Orito E, Ichida T, Sakugawa H *et al.* Geographic distribution of hepatitis B virus (HBV) genotype in patients with chronic HBV infection in Japan. *Hepatology* 2001; **34**: 590–4.

Hepatology Research

Hepatology Research 2011; 41: 1–21 doi: 10.1111/j.1872-034X.2010.00739.x

Review Article

Management of hepatitis B: Consensus of the Japan Society of Hepatology 2009

Osamu Yokosuka,[1] Masayuki Kurosaki,[2] Fumio Imazeki,[1] Yasuji Arase,[3] Yasuhito Tanaka,[4] Kazuaki Chayama,[5] Eiji Tanaka,[6] Hiromitsu Kumada,[3] Namiki Izumi,[2] Masashi Mizokami[7] and Masatoshi Kudo[8]

[1]*Department of Medicine and Clinical Oncology, Postgraduate School of Medicine, Chiba University, Chiba,* [2]*Division of Gastroenterology and Hepatology, Musashino Red Cross Hospital, Tokyo,* [3]*Department of Hepatology, Toranomon Hospital, Kawasaki,* [4]*Department of Virology and Liver Unit, Nagoya City University Graduate School of Medical Sciences, Nagoya,* [5]*Department of Medicine and Molecular Science, Hiroshima University, Hiroshima,* [6]*Department of Medicine, Shinshu University School of Medicine, Matsumoto,* [7]*Research Center for Hepatitis and Immunology, International Medical Center of Japan Kounodai Hospital, Ichikawa, and* [8]*Department of Gastroenterology and Hepatology, Kinki University School of Medicine, Osaka, Japan*

Recently, much progress has been made in the field of hepatitis B, such as natural history of the disease in relation to the amount of hepatitis B virus (HBV) DNA, genotypes of HBV influencing the natural course and treatment effects, mutations of HBV influencing the severity of the disease and development of hepatocellular carcinoma, and antiviral treatment such as nucleos(t)ide analogues and pegylated interferon. To make the consensus for the diagnosis, management and treatment of hepatitis B, a meeting was held during 45th annual meeting of Japan Society of Hepatology (JSH) in June 2009. In the meeting, recommendations and informative statements were discussed on the following subjects: (i) natural history of HBV infection; (ii) clinical implication of HBV genotypes; (iii) HBV mutations and their potential impact on pathogenesis of HBV infection; (iv) indications for antiviral treatment of chronic hepatitis B; (v) nucleos(t)ide analogues for chronic hepatitis B; and (vi) interferon therapy for chronic hepatitis B. The presenters reviewed the data on these subjects and proposed the consensus statements and recommendations. These statements were discussed among the organizers and presenters, and were approved by the participants of the meeting. In the current report, the relevant data were reviewed and the 12 consensus statements and nine recommendations on chronic hepatitis B were described.

Key words: genotype, hepatitis B virus, interferon, mutation, natural history, nucleotide analogue

Hepatitis B virus (HBV) is one of the most distributed viruses which infect humankind. More than 3 billion people, one half of the world's population, have been exposed to HBV during their life.[1] Acute infection in adults is self-limited in general whereas infection during early childhood will develop into persistent chronic infection in most individuals.[2] More than 400 million people worldwide are chronically infected with HBV and are at risk of developing life-threatening complications including liver cirrhosis and hepatocellular carcinoma (HCC).[1] HBV is a major public health problem worldwide especially in East Asia and Africa. In Japan, approximately 1.5 million people are infected with HBV and it is one of the major causes of HCC and chronic hepatic failure. Other complications of HBV infection include fulminant hepatitis and acute liver failure.

The consensus meeting for diagnosis, management and treatment for hepatitis B was held during the 45th annual meeting of the Japan Society of Hepatology (JSH) in June 2009 (Congress President: M Kudo), where the recommendations and informative statements were discussed. Although the JSH consensus meeting of hepatitis B had been held four times so far, recommendations were hitherto published only in Japanese and this is the first report in English. Established

Correspondence: Professor Osamu Yokosuka, Department of Medicine and Clinical Oncology, Postgraduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba 260-8670, Japan. Email: yokosukao@faculty.chiba-u.jp
Received 6 April 2010; revision 25 August 2010; accepted 20 September 2010.

information for pathogenesis and contributing factors for disease progression which was agreed by the organizers and presenters are shown as "consensus statements", and clinically useful consensus are shown as "recommendations". The quality of recommendations or informative statements are required to show a "level" (assessing strength or certainty) of evidence and "grading" of recommendations or assessment according to a standard reporting system of clinical guidelines.[3]

NATURAL HISTORY OF HBV INFECTION

AN EVALUATION OF studies on the natural history of HBV infection was done using the scoring system proposed by MacMahon *et al.*[4] in the present analysis because scoring systems for treatment studies cannot always be applied directly to those using natural history. The proposed scoring system consists of levels 1 (1a, 1b), 2 (2a, 2b, 2c), and 3. Level 1a is defined as a population-based longitudinal cohort study with a hepatitis B surface antigen (HBsAg) negative comparison group. Level 1b is identical to level 1a, but with no comparison group. Level 2a is defined as a clinic-based longitudinal cohort study, level 2b is a population-based or clinic-based cohort nested case–control study, and level 2c is a cross-sectional clinic-based study. Level 3 is defined as an observation study case series.

The natural history of chronic HBV infection can be classified into several phases based on levels of alanine aminotransferase (ALT), hepatitis B e-antigen (HBeAg) status, amounts of HBV DNA, and estimated immunological states.[4–9] A representative classification of these phases is shown in Table 1. In the immune tolerance phase, HBeAg is positive, serum levels of ALT are normal, histological activities of hepatitis are absent or minimal, and levels of HBV DNA are elevated. The immune tolerance phase is thought to occur most frequently in individuals who are infected through perinatal transmission, and this phase usually lasts until adolescence or young adulthood.[10–12]

The chronic hepatitis B phase is characterized by elevated ALT and HBV DNA levels. In this phase, the host's immune system recognizes HBV as being foreign and initiates an immune response that results in hepatitis. In cases who are HBeAg positive, active hepatitis can be prolonged and may result in cirrhosis. However, chronic hepatitis B eventually transitions into an inactive phase with a loss of HBeAg positivity in the majority of patients. Seroconversion to anti-HBe and the fall of serum HBV DNA to low levels result in the disappearance of disease activity, despite persisting HBsAg and low levels of HBV DNA.[13–16] Seroconversion rates range 7–16% per year according to reports with higher evidence levels (levels 1b, 2a).[16–19] Factors associated with seroconversion are age (level 1b),[20] ALT levels (level 1b), occurrence of acute exacerbation of hepatitis (level 1b),[19,21] and genotype (level 2c).[22,23]

The seroconversion of HBeAg results in the transition from hepatitis phase to inactive carrier phase, which is generally thought to be a benign course for HBV carrier, but sometimes hepatitis can be reactivated spontaneously.[24] Patients experiencing reactivation undergo another transition, with increases in HBV DNA and ALT levels and disease activity without reappearance of HBeAg.[24] This phase is referred to as HBeAg negative chronic hepatitis B. Occasional severe hepatitis B flare-ups with middle range HBV DNA levels (3–8 log copies/mL) occur in this phase.[8,25] HBeAg negative chronic hepatitis B is caused by mutant strains of HBV unable to produce HBeAg,[25,26] and tends to develop into cirrhosis and complicate HCC more than HBeAg positive chronic hepatitis B.[27–30]

Table 1 Phases in the natural history of HBV carriers (modified from [4])

Phase	Hepatitis	Blood			Liver
		DNA	HBeAg	HBsAg	cccDNA
Immune tolerance	–	8–11	+	+	+
HBeAg positive Chronic hepatitis	Usually Persistent	6–10	+	+	+
HBeAg negative Chronic hepatitis	Often Fluctuating	3–8	–	+	+
Inactive carrier	–	<4	–	+	+
Recovery	–	–	–	–	+

HBV DNA: log copies/mL. cccDNA, covalently close circular DNA; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

Many factors that are associated with the development of HCC have been reported so far. Higher age (level 1a), male sex (level 1a), presence of cirrhosis (level 2a) and familial cluster of carriers (level 2c) are reported as host factors.[31,32] Viral factors include high viral load (level 1b),[33–36] existence of pre-core and core promoter mutations (level 2a), genotype C and high ALT levels (level 1b). High viral load should be considered as a factor in patients over 35–40 years of age. Co-infection with hepatitis C virus, hepatitis D virus or HIV (level 2a), drinking habit (level 2c) and exposure to aflatoxin (level 2c) are reported as social and environmental factors.[37–39] Other lifestyle-related factors, such as smoking habit, obesity and complications from diabetes mellitus, have been documented as well.

Consensus 1
In patients with chronic hepatitis B, seroconversion of HBeAg usually results in the transition from hepatitis phase to inactive carrier phase, which generally has low HBV replication and normal ALT levels. However, reactivation of chronic hepatitis can spontaneously occur without the reappearance of HBeAg. At this point, active hepatitis continues and the risk of complicating cirrhosis and HCC is high in patients with HBeAg negative chronic hepatitis B. (Level 1b.)

In the inactive carrier phase, HBV replication is continuously suppressed as a result of predominantly host immunological pressure against HBV. Patients in the inactive carrier phase generally have a benign course because active hepatitis subsides and the risk of HCC decreases.[19,20,24,40] However, regular follow up is required because reactivation of HBV sometimes occurs spontaneously or as a result of immunosuppressive therapy.[19,24]

Hepatitis B surface antigen is known to fall to undetectable levels in some inactive carriers. This HBsAg negative phase, referred to as the recovery phase, has no hepatitis and a low risk of HCC. Still, caregivers must be aware that patients who are old or cirrhotic have a relatively higher risk of HCC.[41,42] Disappearance of HBsAg in the recovery phase does not indicate complete eradication of HBV because the HBV genome remains as covalently close circular DNA (cccDNA) in the nucleus of hepatocytes.

Consensus 2
2-1 HBV can not be completely eradicated using any currently existing treatment measures. (Level 2a.)
2-2 Patients in the inactive carrier or recovery phase have a benign clinical course. However, regular follow up of such patients is required because reactivation of hepatitis B and ensuing HCC can occur. (Level 1b, 2a.)

Clinicians have to consider two types of hepatitis B reactivation: one during the inactive carrier phase and the other in the recovery phase.[4] Both types of reactivation have been attributed with increasing incidence to strong immunosuppressive therapies. De novo hepatitis B, a reactivation of hepatitis B in the recovery phase, tends to develop into fulminant hepatitis, which has a very high mortality rate.[43–46] Thus, establishment of effective measures to prevent reactivation of hepatitis B is necessary.

Consensus 3
3-1 Reactivation of hepatitis B can occur during the inactive carrier or recovery phases and stems mainly from strong immunosuppressive treatment courses. (Level 2a.)
3-2 Recent advances in medical care have increased the use of immunosuppressive agents and thus the incidence of hepatitis B reactivation. (Level 2a.)
3-3 Reactivation of hepatitis B tends to develop into fulminant hepatitis. (Level 2a.)

Recommendation 1
In addition to the loss or seroconversion of HBeAg, a substantial decrease in HBV viral load and subsequent disappearance of hepatitis are the primary targets in the treatment of patients with chronic hepatitis B. (Level 1b.)

Recommendation 2
The main goals of HBV carrier treatment are patients in the inactive carrier and recovery phases. However, caregivers should be aware that reactivation of hepatitis B and complication of HCC can occur even in these benign phases. (Level 1b.)

Recommendation 3
Reactivation of hepatitis B due to immunosuppressive therapy tends to develop into severe hepatitis, thus requiring the establishment of effective preventative measures. (Level 2a.)

CLINICAL IMPLICATION OF HBV GENOTYPES

DISTINCT CLINICAL AND/OR virological characteristics of the HBV infection have been reported in different geographical parts of the world and are increasingly associated with host factors, environmental factors and the genetic diversity of the infecting virus.[47] HBV is classified into at least eight genotypes (A–H) based on an intergroup divergence of 8% or more in the complete nucleotide sequence and a number of subgenotypes (Aa/A1, Ae/A2, Bj/B1, Ba/B2, Cs/C1, Ce/C2, D1, D2, and so forth) that are currently known to have distinctive association with ethnic and/or geographical distribution.[48]

Association between HBV genotype and clinical manifestation

Acute hepatitis

The universal vaccination program against HBV has significantly reduced the number of new infection cases in most countries with levels of endemicity estimated from intermediate to high.[49] However, efficiency of universal vaccination in countries with a low level of endemicity still remains controversial. Japan is one of the countries with a low level of endemicity and mainly vertical (mother to baby) transmission route.[50] In Japan, HBV vaccination in combination with HBV immunoglobulin treatment is the only recommended measure for infants born to HBsAg positive mothers. Studies in Japan indicated genotype C (subgenotype Ce/C2) to be the major type in the country and genotype B (subgenotype Bj/B1) is the second distributed. Surveillance studies have shown a recent trend toward increase in number of acute hepatitis B infection among young adults mainly through sexual contacts.[51,52] Although most cases are associated with genotype C infection, there is a continuous trend toward increase in prevalence of genotype A among acute hepatitis cases.[51,53–56] Patients infected with genotype C have been known to be rarely associated with development of chronic persistence after acute infection in immune competent adults in Japan (1%) in contrast to the higher rates of those infected with genotype A (6–23%).[53,54] A recent multicenter study in Japan indicated a trend among chronic hepatitis B patients toward increase in prevalence of genotype A (from 1.7% in 2002 to 3.5% in 2006), whereas other genotypes remained stable at their prevalence during the same period.[57] The shift in genotype prevalence with the increase of genotype A among chronically infected carriers can be explained by higher risk of genotype A to develop persistence. This is consistent with higher rates of chronic persistence after acute infection in adults in European countries where genotype A is prevalent (10%).[48,58] This is also consistent with results of *in vitro* and *in vivo* comparisons of different genotype strains showing different dynamics of replication: slow for genotype A and rapid by genotype C.[59,60] The surveillance study indicated that all patients treated with lamivudine (LVD) recovered from acute hepatitis, whereas none of the three patients who developed a chronic outcome had received antiviral treatment during their acute phase of infection, indicating that LVD might be able to prevent the chronic outcome.[54] Cumulatively, these data indicate the clinical importance of routine genotyping for acute hepatitis B patients.

Fulminant hepatitis

One of the most serious complications of acute HBV infection is fulminant hepatitis. In Japan, the annual number of fulminant hepatitis reported was approximately 400 cases, with approximately half of these caused by HBV infection. Despite its rather low incidence, fulminant hepatitis is a national problem because the mortality rate is extremely high.[61] It is important to understand factors predisposing for development of fulminant hepatitis. Viral factors associated with the development of fulminant hepatitis are mutations in the core promoter (T1762/A1764)[62] and the pre-core region (A1896).[54,63,64] However, these findings were not consistent with studies in Europe and the USA.[65–67] A large-scale cross-sectional study in Japan revealed association between genotype B (subgenotype Bj/B1) infection and development of fulminant hepatitis; on the other hand, no cases of fulminant hepatitis were registered among those infected with genotype A (subgenotype Ae/A2).[54] Differences in genotypes circulating in Asia and Europe/USA may indicate that distinct viral factors are playing roles in manifestation of infection by different genotype.

Chronic hepatitis

Chronic HBV infection is the most common cause of HCC in Asia.[68] Efficient surveillance and early diagnosis of development of this life complication requires risk stratification of chronic hepatitis B patients. Older age, male sex and liver cirrhosis are well recognized factors associated with increased risk of HCC.[69,70] In addition, recent large-scale population-based and clinical case–control studies carried out in Asia, have shown that infecting virus factors associated with a high risk of HCC, include HBV DNA levels,[71,72] HBV basal core promoter mutations,[35] genotype C (vs B),[22,36,73,74] and sub-

genotype Ce/C2.[71,75] There are data indicating that genotype C infection associated with a higher viral load than genotype B.[76] Association of genotype F with HCC was found to be higher than that of genotype C in Alaskan natives.[77,78] Unfortunately, there are few prospective studies examining other HBV genotypes for association with adverse outcomes. Genotype A (subgenotype Aa/A1) was found in association with development of HCC in young adults in South Africa.[79,80] However, very high rates of detection of subgenotype Aa/A1 among asymptomatic carriers suggest contribution of environmental factors (aflatoxin contained in food) for the development of HCC. In comparison with Aa/A1, HCC associated with Ae/A2 is found primarily in older individuals. In addition, the rate of complications, including HCC, for those infected with subgenotype Ae/A2 appears to be less than that found in those infected with genotype D, C or F1.[77,81] A prospective study in Spain showed that genotype A (presumably Ae/A2) infection was associated with a significantly higher cumulative rate of sustained biochemical remission, HBV DNA and HBsAg clearance in patients with chronic HBV infection than genotype D infection.[81]

Consensus 4

4-1 Recently, there is an increase of HBV genotype A proportion among acute hepatitis B infection cases in Japan. (Level 3.)

4-2 HBV genotype A acute infection has a tendency to evolve in chronic hepatitis compared to genotype B/C. (Level 3.)

4-3 Antiviral therapy of acute infection might be efficient in prevention of chronic carrier stage. (Level 3.)

4-4 Genotype C compared with genotype B is associated with higher risk of outcome in HCC in chronic carriers. (Level 2a, grade B.)

4-5 Genotype A compared with genotype D and F in chronic carriers is associated with better prognosis in terms of spontaneous ALT normalization and DNA clearance. (Level 2a, grade B.)

HBV MUTATIONS AND THEIR POTENTIAL IMPACT ON PATHOGENESIS OF HBV INFECTION

THE HBV GENOME consists of double-stranded DNA, 3200 bp in length. HBV replicates through reverse transcription of a RNA intermediate, the pregenome RNA, different from all known mammalian DNA viruses. HBV infection is characterized by high levels of virus production, however, the HBV reverse transcriptase is an error-prone enzyme lacking proof-reading capacity, resulting in a large number of nucleotide substitutions during replication. The misincorporation rate has been estimated to be of the order of 10^{10} incorrect nucleotide incorporations per day. As a result, HBV has a quasispecies distribution in infected patients.

Naturally occurring mutations identified in the HBV genome are more prevalent in patients with chronic hepatitis than in HBeAg positive asymptomatic carriers. Among them, several specific mutations have been shown to be associated with the pathogenesis of HBV infection.

HBeAg seroconversion

A HBV strain harboring stop codon mutation in the precore region was first reported in anti-HBe positive patients with chronic hepatitis.[25] The precore region located upstream of the core region is involved in the production and secretion of HBeAg protein. HBeAg is secreted into blood after removal of N-terminal 19 amino acids (a.a.) and C-terminal 34 a.a. from HBeAg precursor protein composed of precore and core regions. Nucleotide substitution of G to A at nt 1896 confers stop codon (TAG) mutation from tryptophan (TGG) at codon 28 in the precore region, resulting in a failure to produce HBeAg protein.[82–84] Although controversial, 10 genotypes have been identified tentatively so far[85] and genotypes affect the occurrence of stop codon mutation in the precore region. The stop codon mutation in the precore region (G1896A) is rarely encountered in HBV genomes of genotype A, some of genotype C and F, because they possess C at position 1858 that makes a pair with G at position 1896 in the stem-loop structure of the *cis*-encapsidation signal.[86]

The HBV core promoter regions located upstream of core region are involved in the transcription of precore mRNA and pregenomic RNA. Nucleotide substitution of A to T at nt 1762 combined with substitution of G to A at nt 1764 in the core promoter region give rise to a reduced transcription of precore mRNA and increased level of viral DNA, resulting in a decreased production of HBeAg protein and enhanced viral replication.[87–89]

Consensus 5

Nucleotide substitution G1896A confers stop codon mutation in the precore region. Nucleotide substitution A1762T combined with substitution G1764A in

the core promoter region give rise to a reduced transcription of precore mRNA. These nucleotide changes in combination with a reduction of HBeAg caused by suppressed replication of HBV are closely associated with HBeAg seroconversion. (Level 2b, grade B.)

Association between HBV mutations and clinical manifestation

Fulminant hepatitis

Precore and core promoter mutations are very frequent in patients with fulminant hepatitis from Asia[62,63,90] and the Middle East.[64] However, these mutations were not detected in those from Western countries.[65,67,91,92] This difference could be attributable to the difference of genotype prevalence, frequent genotype Ae and rare Bj in Western countries.[86] The patients infected with the former genotype rarely have precore mutant virus, while the latter frequently have the mutant virus. Stop codon mutation in the precore region is inhibited in genotype A because of C at position 1858 that makes a pair with G at position 1896 in the stem-loop structure of the *cis*-encapsidation signal.[93]

Ozasa *et al.* analyzed the difference of host and viral factors between 40 patients with fulminant hepatitis B and 256 with acute self-limited hepatitis B in a multicenter cross-sectional study,[54] and showed that precore stop codon mutation of G1896A and genotype Bj are associated with fulminant hepatitis in Japan. They also reported the marked enhancement of viral replication by introducing either G1896A or A1762T/G1764A mutation into the Bj clone in *in vitro* transfection study. Because this type of HBV mutant is found not only in patients with fulminant hepatitis but also in asymptomatic HBV carriers,[94] the interaction between the virus and the host's immune response might influence the outcome of HBV infection.

In addition to the mutants mentioned above, pre-S2 defective virus or HBV defective in secretion because of surface gene mutations are reported in patients with fulminant hepatitis. These mutant viruses showed a characteristic feature of virus retention in hepatocytes and misassembly with high replication capacity.[95–97]

HCC development

Evidence has been accumulating over the past decade that the risk of developing cirrhosis and HCC is influenced by the patient's viral status, such as genotype, viral load and genomic mutations. Naturally occurring mutations have been identified in the structural and non-structural genes as well as the regulatory elements of the virus, and these mutations are more prevalent in patients with chronic hepatitis than in HBeAg positive asymptomatic carriers.[98]

A double mutation, A1762T/G1764A in the basal core promoter region has been found in patients with advanced liver disease and HCC. Several case–control studies,[30,35,99–102] retrospective cohort studies[103,104] and one prospective cohort study[105] confirmed this finding, while some conflicting results were also reported in the case–control studies[106,107] and one prospective study.[108]

The role of deletions in the pre-S region of the HBV genome has been shown to be associated with the development of progressive liver diseases including HCC. Several case–control studies confirmed this finding.[27,107–110] A further mapping study of the pre-S region showed that all the deletion regions encompassed T- and B-cell epitopes and most of them lost one or more functional sites including the polymerized human serum albumin-binding site.[109] Deletion of these functional sites may cause intracellular retention of HBV envelope proteins and viral particles and contribute to more progressive liver damage and HCC development.

In addition to these common mutations, several other mutations, C1653T in the enhancer II region, T1753C/A/G in the core promoter region, and G1317A/T1341C/A/G in enhancer I region, have been reported to be associated with the development of HCC in some case–control studies.[30,107,111]

Consensus 6
There is some evidence that emergence of HBV genomic mutations arising during the course of chronic infection influence the outcome of chronic liver disease. Among them, core promoter mutations A1762T/G1764A might have a potential for developing progressive liver disease and HCC. (Level 2a, grade B.)

HBsAg escape mutant

The HBsAg mutant was first described in a child born to a HBsAg positive mother who developed acute hepatitis B in spite of vaccination and passive immunization against HBV.[112] This viral strain contained a substitution of glycine to arginine at position 145 (sG145R) and was able to escape the immune surveillance, resulting in an infection despite the presence of anti-HBs antibodies, vaccine escape mutant. Similar mutants have been detected all over the world.[113–115]

Patients after liver transplantation for HBV-related chronic liver disease who had received anti-HBs antibodies to prevent re-infection of the graft showed an "immune escape mutant".[116–118] Furthermore, "diagnosis escape mutants" have also been described because HBsAg detection assays are based on anti-HBs antibodies.[119] The emergence of these variants may contribute to occult HBsAg negative HBV infection.[120]

The HBV genome is organized in such a way that the envelope gene is overlapped by the polymerase gene; therefore, HBV with changes in the polymerase gene associated with resistance to the nucleos(t)ide analog which are described in detail in section 5 may have consequent changes in the envelope gene. A triple mutant causing LVD resistance (rtV173L + rtL180M + rtM204V), which have an enhanced replication capacity compared with rtL180M + rtM204V alone, causes two amino acid changes in the overlapping surface gene (sE164D + sI195M). This mutant reduces anti-HBs binding to levels seen only with the vaccine escape mutant sG145R.[121] Some patients treated with LVD showed seroclearance of HBsAg with detectable circulating HBV DNA. An sP120A mutation was associated with HBsAg seroconversion in these patients and this mutation produces a reduced anti-HBs binding which causes the failure to detect HBsAg.[122]

Consensus 7
Amino acid substitutions, deletions or insertions across the "a" determinant of HBsAg, such as a substitution sG145R, give rise to vaccine and immunoglobulin escape mutant. (Level 4, grade C.)

INDICATIONS FOR ANTIVIRAL TREATMENT OF CHRONIC HEPATITIS B

ONCE THE LIVER is persistently infected with HBV, it is difficult to eradicate the virus. It is reported that the natural clearance rate of HBsAg in asymptomatic HBsAg carriers is approximately 1–2% per year.[123] Therefore, the first goal in treating chronic hepatitis B is to prevent patients from progression to cirrhosis and occurrence of HCC.

When the initiation of antiviral therapy for chronic hepatitis B is considered, it is very important to estimate the fibrosis stage of each patient. If possible, a liver biopsy should be performed in order to obtain sufficient information to determine the extent of hepatic fibrosis. When the fibrosis stage of patients with chronic hepatitis B is moderate to severe, or when the patients have cirrhotic liver, the administration of antiviral therapy should be considered. When inflammatory activity is high and the fibrosis seems to be progressive, the introduction of antiviral therapy should also be considered.

In order to prevent the occurrence of hepatic fibrosis and HCC, virological factors as well as biochemical factors are important. A long-term follow-up study of untreated HBsAg positive individuals in Taiwan in which the cumulative incidence of HCC and cirrhosis were studied for 13 years revealed that high baseline HBV DNA was associated with increased risk of HCC and cirrhosis. Incidence rate of HCC in patients whose viral load of HBV DNA was less than 300 copies/mL was 1.3%, whereas in patients whose viral load was more than 1 000 000 copies/mL the incidence rate was 14.9%.[33] Moreover, incidence of cirrhosis in patients whose viral load was less than 300 copies/mL was 4.5%, whereas it was 36.2% in patients whose viral load was more than 1 000 000 copies/mL.[124] Therefore, the introduction of antiviral therapy should be considered based on biochemical and virological findings.

As mentioned above, although high viral load of HBV DNA is one of the strong risk factors in predicting poor prognosis of HBV carriers, low HBV DNA level does not rule out risk in Asian patients. Among HBeAg positive patients, HBV DNA levels of less than 10^5 copies/mL predicted better histological outcome; however, 14.3% of patients still had established fibrosis.[125] The liver biopsy is also very useful for such cases.

Recommendation 4
- 4-1 Introduction of antiviral therapy should be considered on the biochemical and virological findings. (Level 2a, grade B.)
- 4-2 Antiviral therapy should be considered for patients with low virus load but progressed hepatic fibrosis. (Level 2a, grade B.)
- 4-3 Liver biopsy finding (if available) should be useful to determine the introduction of antiviral therapy. (Level 2a, grade B.)

On the other hand, when patients with HBV have obscure or mild fibrosis, a close observation without any medication could be considered for them. Once antiviral therapy with a nucleos(t)ide analogue is started, it is very difficult to stop. Therefore, for patients who are in an inactive carrier state and whose fibrosis stage is relatively mild, a coarse observation without any treatment could be a useful choice to treat the patients.

Young patients with chronic hepatitis B, especially those who are HBeAg positive, often face the flare-up of hepatitis. Because such patients are likely to achieve spontaneous HBe seroconversion and go into an inactive carrier state, unnecessary antiviral therapy should be avoided for them. A coarse observation without any medications should be considered for young patients or those with mild fibrosis.

Recommendation 5
Indication of antiviral therapy for chronic hepatitis B: Observation without therapy should be considered for young patients or those with mild fibrosis. (Level 3, grade B.)

NUCLEOS(T)IDE ANALOGUES FOR CHRONIC HEPATITIS B

AS STATED ABOVE, the goal of antiviral therapy in patients with chronic hepatitis B is to prevent cirrhosis and HCC. Maintaining persistent suppression of HBV replication reduces the development of cirrhosis and HCC. In the last decade, there has been a major advance in the treatment of chronic hepatitis B with nucleos(t)ide analogues such as LVD, adefovir (ADV), entecavir (ETV), telbivudine and tenofovir.[126–132] In treatment by nucleos(t)ide analogues for chronic hepatitis B in Japan, LVD, ADV and ETV are mainly used at present. Nucleos(t)ide analogues are potent inhibitors of the polymerase/reverse transcriptase and are easy to administrate p.o. to chronic hepatitis B patients because of low adverse effects and strong efficacy to suppress HBV replication. Thus, nucleotide analogue therapy could rescue liner decompensation, reduce fibrosis progression and prevent the development of HCC.[133–136] On the other hand, there are major disadvantages including requirement of prolonged or even indefinite therapy for most patients and the high incidence of antiviral resistance. Disadvantages of nucleos(t)ide analogues include the development of antiviral resistance.[137–140] Drug-resistant viruses emerge during the treatment and could be associated with flare-up of hepatitis. Due to no proof of reading activity of HBV polymerase, the spontaneous substitution rate of HBV genome is high in the natural course of the disease. Through the selection of pre-existing resistant variants and gradual accumulation of new a.a. substitutions, the mutations exhibiting the best replication capacity in the presence of the drug are selected under the circumstance of antiviral pressure. The level of intrinsic resistance and the replicative fitness determine the mutant spread and hence the annual incidence of drug resistance.

LVD

Lamivudine was the first nucleoside analogue licensed for the treatment of chronic HBV infection in Japan in 1999. LVD was given at a dose of 100 mg daily and has excellent safety and tolerability.[141–143]

Liaw *et al.* reported that continuous treatment with LVD delays the clinical progression of chronic hepatitis B with advanced fibrosis or cirrhosis by significantly reducing the incidence of hepatic decompensation and risk of HCC (level 1b).[134] Matsumoto *et al.* also showed that LVD therapy effectively reduces the incidence of HCC in Japanese patients with chronic hepatitis B.[144] Thus, it is generally considered that control of viral load using nucleos(t)ide analogues is effective to prevent complicating HCC in patients with active chronic hepatitis B.

Consensus 8
The control of viral load using nucleos(t)ide analogues reduces the risk of complicating HCC in patients with chronic hepatitis B. (Level 1b, grade B.)

Lamivudine resistance is characterized by the mutation of the highly conserved tyrosine, methionine, aspartate, aspartate (YMDD) nucleotide-binding motif in the catalytic domain of the enzyme. YMDD to YIDD (rtM204I) or YVDD (rtM204V) mutations are associated with LVD resistance.[142,145,146] These resistant mutants appear to replicate less efficiently than the wild-type virus *in vitro*, however, additional mutations such as rtV173L and rtL180M can restore partially the replication capacity *in vitro*.[147,148] LVD resistance occurred in approximately 20% of patients after 1 year, which increased to approximately 70% after 5 years (Fig. 1).

A meta-analysis, which included Asian patients and North American/European patients, indicated that HBV subtype ayw (genotype D) appears to respond significantly better to LVD treatment than does HBV subtype adw (genotype A). Insufficient suppression of the adw subtype during the early phase of treatment may lead to the high incidence of LVD resistance in HBV subtype adw.[149] In a study comparing the virological outcome among infections with HBV genotypes A, B and C, patients infected with genotype A had the lowest rate of HBV DNA clearance than those with genotype B or C, and had the highest incidence of resistant mutations.[150]

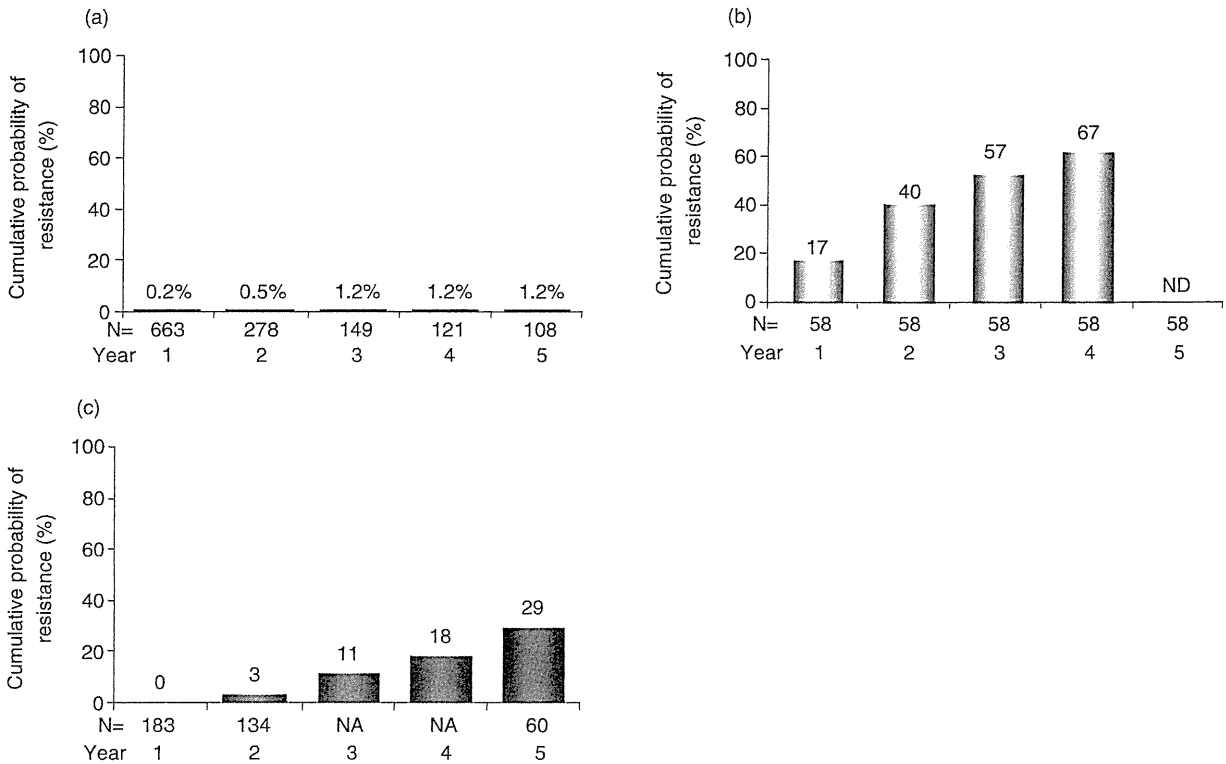

Figure 1 Cumulative probability of resistance after the initiation of entecavir (ETV), lamivudine (LVD) and adefovir (ADV) for patients with hepatitis B e-antigen. (a) Cumulative probability of resistance after the initiation of ETV.[159] (b) Cumulative probability of resistance after the initiation of LVD.[138] (c) Cumulative probability of resistance after the initiation of ADV.[153]

Lamivudine or hepatitis B immunoglobulin (HBIg) treatment induced vaccine/HBIg-escape mutations sP120T and sG145R in combination with LVD-resistance mutations. These mutations are associated with rtT128N and rtW153Q in the polymerase protein and have been found to partially restore the *in vitro* replicative capacity of LVD-resistant HBV.[121]

Another LVD resistant mutation, rtA181T, concomitantly generates a stop codon in the surface antigen (sW172stop), resulting in impaired secretion of HBsAg.[151] Neither the adefovir associated resistance mutation rtN236T nor the tenofovir associated resistance mutation rtA194T causes changes in the envelop protein.

ADV

Adefovir dipivoxil is a prodrug of ADV and has structural similarity to the natural substrate, dATP. Several studies have also been conducted using ADV.[128,152–154] In HBeAg positive patients, treatment with ADV for 1 year resulted in HBeAg seroconversion in 12%, serum HBV DNA in less than 10^3 copies/mL in 21% and normalization of ALT in approximately 48% of patients.[127] The rate of HBeAg seroconversion increased to 29% after 2 years and 43% after 3 years of treatment. In HBeAg negative patients, serum HBV DNA of less than 10^3 copies/mL and normalization of ALT were observed in 51% and 72%, respectively, after 1 year of ADV.[154] After 5 years of therapy, the serum HBV DNA were less than 10^3 copies/mL in 67% of patients, and ALT level normalized in 69%. The reported incidence of ADV resistance is 0% after 1 year, 3% after 2 years and 29% after 5 years of antiviral therapy (Fig. 1).[154] The primary mutations associated with ADV resistance are rtN236T and rtI233V in the D domain and rtA181V in the B domain of HBV polymerase. In comparison with more than 100-fold decrease in sensitivity to LVD associated with the two primary mutations, the rtN236T mutation confers only a 5–10-fold decrease in sensitivity to ADV *in vitro*,[155] which may explain the delayed emergence of this mutant.

In LVD-resistant patients treated with ADV monotherapy, the rate of antiviral resistance was 6–18% after

1 year and 21–38% after 2 years.[156,157] Switching therapy from LVD to ADV may enhance the acquisition of another mutation and induce replication of HBV DNA.[158–160] On the other hand, combination therapy of LVD and ADV effectively suppressed viral replication and maintained high efficacy in LVD-resistant patients with chronic HBV infection.

ETV

Entecavir is a guanine analogue and Chang *et al.* have reported that ETV is effective in reducing the serum level of HBV DNA compared with LVD in HBeAg positive patients (Table 2).[159] The cumulative proportion of patients with undetectable HBV DNA (<300 copies/mL) increased to 81% after 1 year of therapy and 93% after 5 years of therapy.[160] After 1 year of treatment with ETV, the serum ALT level was normalized in approximately 70% of patients, and increased to 90% of patients after 5 years. Lai *et al.* have reported that ETV is more efficacious in HBeAg negative patients compared with LVD (Table 2).[161] ETV is the most potent of the currently available anti-HBV drugs because it affects multiple functions of the polymerase, including priming, reverse transcription and DNA elongation.[162]

Entecavir was licensed for the treatment of chronic hepatitis B in Japan in 2006. In nucleos(t)ide-naive patients, ETV is given at dose of 0.5 mg/day.

The rate of ETV resistance was extremely low in nucleoside-naive patients.[160,163,164] The incidence of ETV resistance in nucleos(t)ide analogue-naive patients was reported to be 1.2% at 3 years (Fig. 1).[160,163,164] HBeAg loss was observed in 8% of these patients. The response to ETV was lower in LVD-resistant patients than in nucleos(t)ide analogue-naive patients. In LVD-resistant patients, 20% of patients had undetectable HBV DNA levels after 48 weeks of ETV therapy, and the resistance rate to ETV was 26% at 3 years. Patients with HBeAg at the initiation of ETV had a resistance rate to ETV of 36% at 3 years. On the other hand, patients without HBeAg at the initiation of ETV did not have resistance to ETV at 3 years (Fig. 2).[160,165] In LVD-resistant patients, the risk of the development of resistance to ETV is much higher than those without LVD resistance.[160,165]

The resistance to ETV is principally associated with the mutations rtM250V, rtI169T or rtS202I in addition to the primary LVD resistance mutations rtM204V + rtL180M. The need for multiple mutations to induce ETV resistance suggests a higher genetic barrier to resistance and explains the low rate of resistance to ETV in nucleos(t)ide analogue-naive patients.

Table 2 Efficacy of nucleoside analogues for chronic hepatitis B

	Subject: HBeAg positive patients[159]						
	n	Change of HBV DNA (log copies/mL)		Negativity of HBV DNA of <300 copies/mL		Normalization of ALT	SC
ETV 0.5 mg	354	−6.9	$P < 0.001$	67%	$P < 0.001$	68%	$P < 0.05$	21%	$P = 0.33$
LVD 100 mg	355	−5.4		36%		60%		18%	
	Subject: HBeAg negative patients[161]						
	n	Change of HBV DNA (log copies/mL)		Negativity of HBV DNA of <300 copies/mL		Normalization of ALT	
ETV 0.5 mg	325	−5.0	$P < 0.001$	90%	$P = 0.001$	78%	$P < 0.05$		
LVD 100 mg	323	−4.5		72%		71%			

ALT, alanine aminotransferase; ETV, entecavir; HBeAg, hepatitis B e-antigen; HBV, hepatitis B virus; LVD, lamivudine; SC, seroconversion; VR, virological response.

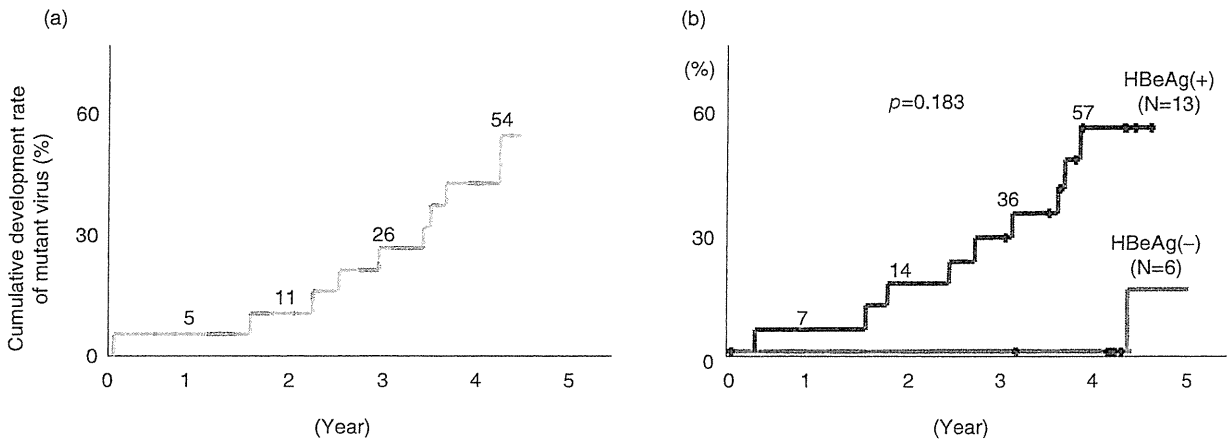

Figure 2 Cumulative development rate of mutant virus after the initiation of entecavir monotherapy in hepatitis B patients with resistance after the administration of lamivudine monotherapy.[164] (a) Cumulative development rate of mutant virus in all patients. (b) Cumulative development rate of mutant virus based on the difference of hepatitis B patients with positive hepatitis B e-antigen (HBeAg) and hepatitis B patients with negative HBeAg.

Consensus 9
Drug-resistant virus with specific mutations in the polymerase/reverse transcriptase gene emerges during nucleos(t)ide analogue therapy in chronic hepatitis B patients. The rtM204V/I and rtL180M mutations are associated with LVD resistance, the rtN236T and rtI233V or rtA181V with ADV resistance, and the rtM250V or rtT184G or rtS202I combined with rtM204V + rtL180M with ETV resistance. (Level 4, grade C.)

Recommendation 6
When patients with chronic hepatitis B are treated with nucleos(t)ide analogues, ETV should be given as the first-line drug because of its high efficacy and low emergence of viral resistant mutant. (Level 1b, grade A.)

Recommendation 7
The combination therapy of LVD and ADV is an effective treatment for LVD-resistant patients. (Level 1b, grade B.)

INTERFERON THERAPY FOR CHRONIC HEPATITIS B

INTERFERON (IFN) WAS the first antiviral treatment approved for chronic HBV infection. IFN-α and -β have a predominantly antiviral effect but also have an immunomodulatory effect and antiproliferative effect which is in contrast to direct antiviral agents such as nucleos(t)ide analogues. The duration of treatment is defined (usually 24–48 weeks) in IFN therapy. This finite duration of therapy is an advantage over direct antiviral agents which are usually given indefinitely. The long-term outcome of therapy is more precisely described in IFN compared to LVD due to its longer history of clinical usage.

Selection of patients

Factors associated with favorable response to IFN therapy are vigorously studied (Table 3). For HBeAg positive patients, high pretreatment ALT levels,[166] high grade of necroinflammation on liver histology and low serum HBV DNA level have consistently been shown to be predictive of favorable response.[167] Other predictive factors include female sex,[166] younger age,[168,169] and HBV genotype A versus D or B versus C.[169,170] Patients fulfilling these predictors are the best candidates for IFN treatment. For HBeAg negative patients, there is no consistent predictor of response. Adverse events such as severe infection or exacerbations of liver disease were common when IFN was given for decompensated cirrhosis. Thus, patients with decompensated cirrhosis should not be treated with IFN due to a risk of precipitating hepatic failure and fatal complications.[171,172]

Table 3 Predictive factors for response to interferon therapy

Predictive factors	HBeAg positive	HBeAg negative
Race	No correlation	No correlation
Age	No correlation or Younger	No correlation or Younger
Sex	No correlation or Female	No correlation or Female
ALT	Higher level	No correlation or Higher level
Activity	Higher grade	No correlation
Fibrosis	Conflicting	No correlation
HBV DNA titer	Lower titer	No correlation or lower titer
Genotype	A > D, B > C	A > D, B > C
Precore	Conflicting	No correlation
Core promoter	mutant	

ALT, alanine aminotransferase; HBeAg, hepatitis B e-antigen; HBV, hepatitis B virus.

Recommendation 8
Younger age, high ALT levels, low HBV load, genotype A or B and high inflammatory activity in liver biopsy are predictive of good response to IFN. IFN therapy should be considered in patients fulfilling these predictors. (Level 2a, 2b, grade B.)

Recommendation 9
Interferon should be avoided for patients with decompensated cirrhosis. (Level 4, grade D.)

Standard IFN therapy in HBeAg positive chronic hepatitis B

A meta-analysis of 16 randomized controlled studies have shown that treatment with IFN-α for 16–24 weeks versus an untreated control is associated with higher rate of HBeAg loss (33% vs 12%), HBeAg seroconversion (difference of 18%), undetectable HBV DNA by hybridization or branched chain assay (37% vs 17%), HBsAg loss (7.8% vs 1.8%) and ALT normalization (difference of 23%) (Table 4).[173] A controlled trial has shown that extending therapy for up to 32 weeks in patients who remained HBeAg positive at the end of 16 weeks of therapy improved the rate of HBeAg seroconversion.[174] The durability of HBeAg seroconversion is more than 80%, and even delayed seroconversion could occur in 10–15% of patients 1–2 years after completion of therapy.[175–177] The loss of HBsAg is reported to occur in 12–65% of patients who cleared HBeAg.[175,178] However, this is a rare event in Asian patients.[176,177]

Consensus statement 10
10-1 In HBeAg positive patients, treatment with IFN versus untreated control is associated with higher rate of HBeAg loss, HBeAg seroconversion, undetectable HBV DNA, HBsAg loss and ALT normalization. Extension of therapy improves the rate of HBeAg seroconversion. (Level 1a,1b.)
10-2 Durability of HBeAg seroconversion is more than 80%. The loss of HBsAg is rare in Asian patients. (Level 1b.)

Standard IFN therapy in HBeAg negative chronic hepatitis B

Although the rate of response at the end of therapy is 60–90%, the durability of long-term response is less

Table 4 Standard interferon therapy for HBeAg positive chronic hepatitis B. Meta-analysis of 16 randomized controlled trials

	Interferon		Control	*P*-value
Loss of HBV DNA	37%		17%	0.0001
Loss of HBeAg	33%		12%	0.0001
Loss of HBsAg	7.8%		1.8%	0.001
Seroconversion		Difference of 18%		0.002
ALT normalization		Difference of 23%		0.0001

ALT, alanine aminotransferase; HBeAg, hepatitis B e-antigen; HBV, hepatitis B virus.

than 50%.[179,180] Longer duration of therapy is associated with improved durability of response: 10–15% with 4–6 months of therapy, 22–30% with 6–12 months of therapy and 30% with 24 months of therapy.[181–184]

Consensus statement 11

11-1 Durability of response is less than 50% in HBeAg negative patients. (Level 1b.)

11-2 Longer duration of therapy (>48 weeks) is associated with improved durability of response. (Level 2b.)

Pegylated IFN (PEG IFN)

Twenty four weeks of PEG IFN-α-2a monotherapy had higher rate of combined response (loss of HBeAg, suppression of HBV DNA <500 000 copies/mL and ALT normalization) compared to standard IFN-α-2a.[185] Another study with 24 weeks of PEG IFN-α-2b monotherapy also showed a higher rate of HBeAg loss and HBV DNA suppression compared to standard IFN-α-2b.[169]

Controlled studies comparing the 48 weeks of PEG IFN-α-2a and LVD in HBeAg positive and negative patients revealed that PEG IFN had a higher rate of sustained response.[170,171] Seroconversion of HBeAg (32% vs 19%), ALT normalization (41% vs 28% in HBeAg positives and 59% vs 44% in HBeAg negatives), HBV DNA suppression (HBV DNA <10 000 copies/mL, 32% vs 22% in HBeAg positives; HBV DNA <20 000 copies/mL, 43% vs 29% in HBeAg negatives) and negative HBV DNA (14% vs 5% in HBeAg positives and 19% vs 7% in HBeAg negatives) were more frequent in PEG IFN treated patients.

Differences were reported in outcome of the antiviral treatment of patients infected with different genotypes; genotype B is associated with a higher rate of antiviral response to IFN treatment than HBV genotype C among Asian patients with HBeAg positive chronic hepatitis B.[169,186,187] In multicenter trials comparing combination therapy of PEG IFN-α-2b and LVD versus PEG IFN-α-2b alone, it was shown that treatment with PEG IFN-α-2b is the best therapy to achieve HBsAg clearance in patients with genotype A compared with D.[188,189]

Combination or sequential therapy

Combination of two antiviral agents with different mechanisms of action seems a logical approach to improve efficacy. In fact, simultaneous combination of LVD and PEG IFN has a higher rate of HBV suppression, ALT normalization and less frequent emergence of LVD-resistant mutant virus compared to LVD alone. However, there is no difference in treatment response between the simultaneous combination of LVD and IFN or PEG IFN compared to IFN or PEG IFN alone (Table 5).[132,133,170]

There are several clinical trials of sequential therapy with LVD followed by IFN.[190–194] Common to all studies is that the sequential therapy had no advantage over IFN alone. Some studies have shown the suggestive evidence that sequential therapy had a higher rate of HBV suppression, ALT normalization and less frequent emergence of LVD-resistant mutant virus compared to LVD alone (Table 5).[190–194] However, because the study protocols and their results are variable, a conclusive result could not be drawn.

Table 5 Sequential therapy of lamivudine and interferon

		BR	SC	VR	LVD-R
Manesis *et al.* 2006	Sequential	39%	NA	28%	
($n = 36$)[190]	IFN	22%	NA	19%	
Shi *et al.* 2006	Sequential	53%	NA	14%	0%
($n = 162$)[191]	LVD	36%	NA	18%	23%
Yurdaydin *et al.* 2005	Sequential	51%	NA	54%	24%
($n = 78$)[193]	LVD	41%	NA	59%	53%
Sarin *et al.* 2005	Sequential	40%	40%	40%	15%
($n = 75$)[194]	LVD	14%	11%	16%	8%
Schalm *et al.* 2000	Sequential	50%	36%	55%	0%
($n = 226$)[192]	IFN	50%	22%	49%	0%
	LVD	63%	19%	63%	31%

BR, biochemical response; IFN, interferon; LVD, lamivudine; LVD-R, lamivudine resistant mutation; NA, not applicable because hepatitis B e-antigen patients are studied; SC, seroconversion; VR, virological response.