表4　Cox比例ハザードモデルによる肝硬変進展に影響する因子の解析(文献11より一部改変)

因子	30歳未満			30歳以上		
	リスク比	95% CI	P	リスク比	95% CI	P
男性/女性	0	—	0.972	0	0.000～3.993	0.969
HBe抗原						
陽性	1	0.028～6.469	0.538	1	0.185～3.250	0.727
陰性	2.36			1.29		
線維化						
Mild - Moderate	1	0.080～1.030	0.053	1	0.296～3.238	0.972
Severe	10.87			1.02		
Genotype						
B	1	0.019～2.883	0.258	1	0.033～0.916	0.039
C	4.24			5.75		

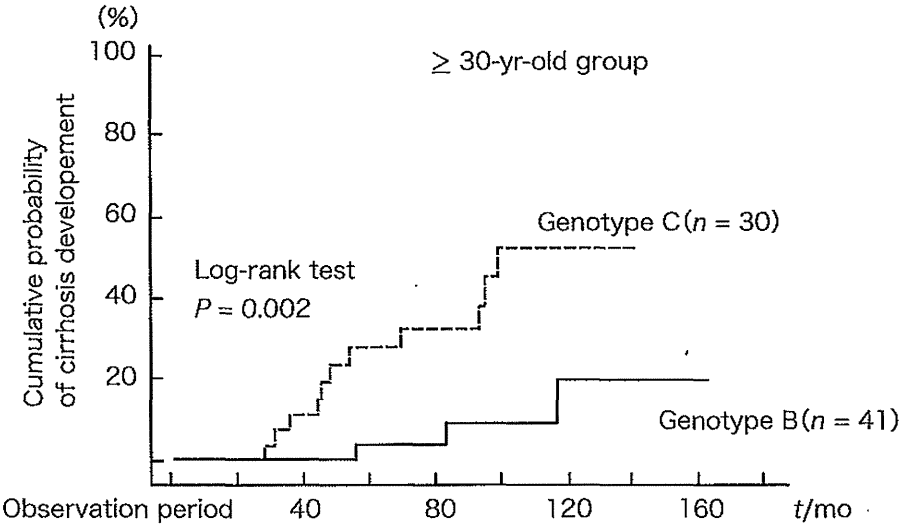

図2　30歳以上のHBV感染者における，genotypeによる肝硬変進展リスク(文献11より引用)

このうち15例においてHBs抗原消失前後で肝生検を施行したところ，血中のHBs抗原が陰性化しているにも関わらず，15例全例で肝組織中にHBV DNAが検出された．また肝組織中の壊死炎症反応は有意に改善されていたが($P < 0.0001$)，肝線維化は有意なレベルまで改善されておらず($P = 0.072$)，2例ではむしろ悪化していた．また観察期間中，肝発癌はHBs抗原消失49例中5例(10.2%)において認められ，肝硬変合併，周産期の感染，30年以上の長期間の感染歴，がリスク因子であったとされている．このことはHBs抗原消失後も肝線維化進展や肝発癌のリスクがあることを示すものであり，HBs抗原消失後のマネージメントに関する診療ガイドライン策定の必要性をうかがわせるものである．

HBV genotypeが肝硬変の進展にどのように影響するのか，genotype B感染が多い沖縄県からgenotype Cとの比較検討が報告されている[11]．それによると，B型慢性肝炎121例において，30歳未満では有意なLCへの進展予測因子は認めなかったが，30歳以上になるとgenotype Cであることが有意な予測因子となっていた(表4，図2)．特にHBe抗原陽性例では予後不良であることから，抗ウイルス治療の適応を考えるうえで示唆する所

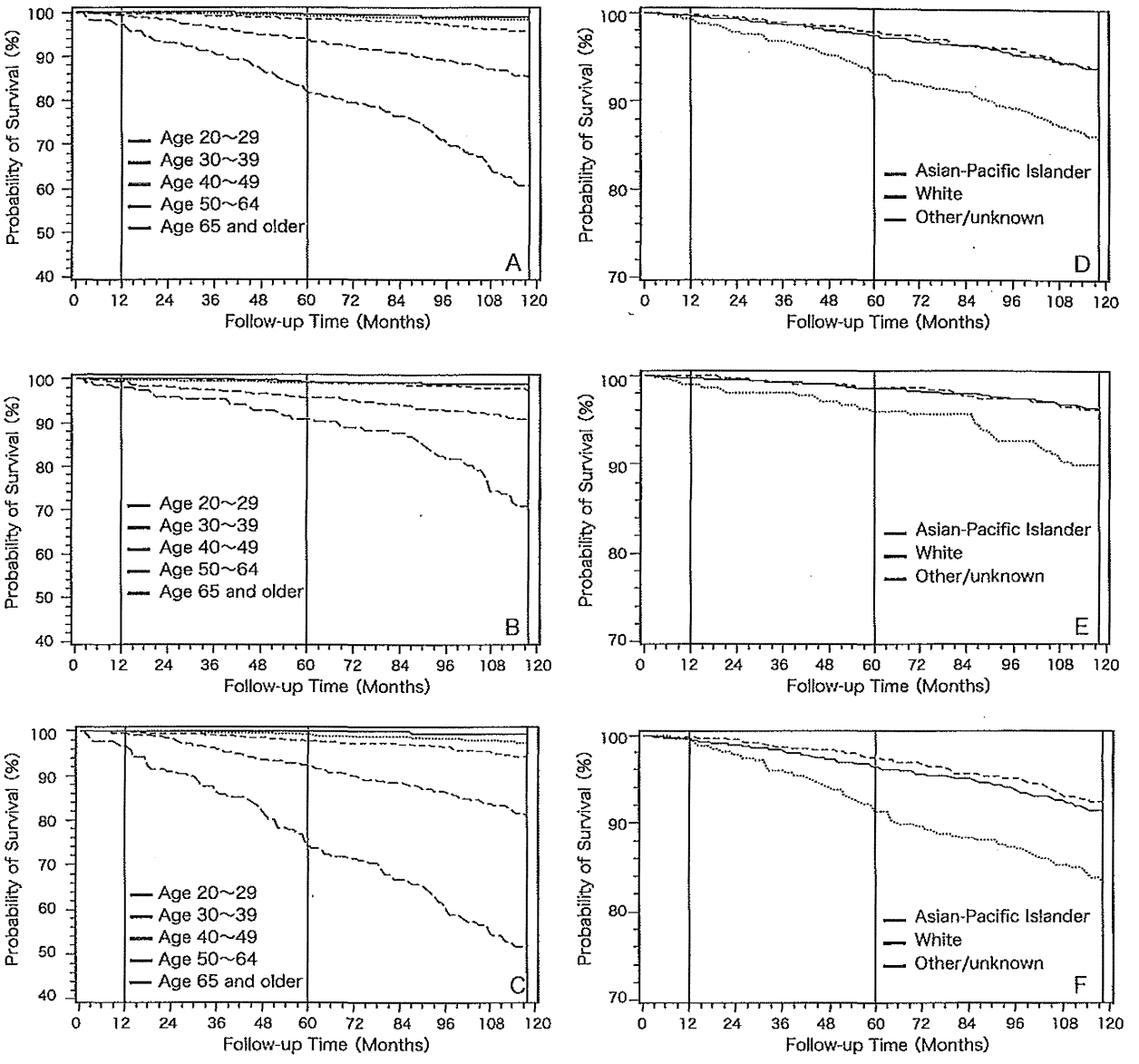

図3　性別・年齢別HBV関連生存率

死亡率は年齢に伴い増加し，特に女性に比し男性で死亡率が高い．またHBV関連死亡率はアジア太平洋家系のほうが白人よりも高い．（文献12より引用）

見と思われる．

3　米国におけるB型肝炎自然予後

欧米の論文では無治療の住民を対象としたB型肝炎予後に関する報告は少ないが，米国では，HBs抗原陽性であった一過性感染例を除く未治療の6,689人を対象にした10年間の追跡で，HBV関連死を含む総死因調査を行っている[12]．人種の内訳は，68.3％はアジア太平洋出身，11.8％は白人であった．10年間の総死亡率は男性(8.9％)が女性(4.1％)より高く，またHBV関連死も女性(1.2％)に比し男性(4.8％)で高率であった(図3)．死亡率は年齢とともに高くなり，40歳以上の総死亡のうち40％はHBV関連死であった．多変量解析ではHBV関連死に最も影響する因子は男女ともに年齢であった(表5)．米国においてもB型肝炎はHBV感染者の死因の40％を占めていることが明らかとなり，年齢とともにそのリスクが高くなることから，HBVキャリアの囲い込みを今後どうしていくのか注目される．

表5　HBV関連死予測因子（多変量解析）（文献12より一部改変）

予測因子	全体(6,657)			女性(3,237)			男性(3,420)		
	死亡数	HR (95% CI)	P	死亡数	HR (95% CI)	P	死亡数	HR (95% CI)	P
	37	0.3 (0.2～0.4)	<0.01	N/A			N/A		
女性									
初診年齢									
0～39歳	11	referent		2	referent		9	referent	
40～64歳	129	8.5 (4.6～15.8)	<0.01	24	11.4 (2.7～48.5)	<0.01	105	7.8 (3.9-15.5)	<0.01
65歳以上	48	36.7 (18.7～71.9)	<0.01	11	50 (10.7～233.7)	<0.01	37	34.4 (16.3-72.6)	<0.01
人種									
アジア太平洋	127	0.9 (0.6～1.4)	0.72	30	3.2 (0.8～13.5)	0.12	97	0.8 (0.5-1.2)	0.23
白人	36	referent		2	referent		34	referent	
その他	25	0.8 (0.5～1.3)	0.31	5	2.2 (0.4～11.1)	0.36	20	0.7 (0.4-1.2)	0.17

4　Community-based cohortからみたB型肝炎の長期予後の検討（上五島コホート）

本邦には，地域住民を対象としたB型肝炎コホート研究が現在も行われている地域がある．長崎県上五島は，長崎県の西方にある五島列島の北部に位置し，離島という閉鎖的な環境により住民の異動が比較的少なく最終転帰が把握しやすいこと，また人口がおよそ2.5万人と，コホート研究として比較的取り扱いやすい地域である．

上五島病院の白濱，国立長崎医療センター・臨床研究センターの山崎，八橋らは，1978年より上五島地区全住民を対象にHBs抗原スクリーニングを行っており，これまでにB型肝炎の長期予後に関するさまざまな検討を行っている．これらは本稿のテーマにふさわしい疫学研究と考えられるので，著者の許可をいただき，ここでその概要について，①肝硬変・肝癌罹患，②HBe抗体と肝機能からみた臨床的治癒率，③HBs抗原自然消失，そして④同地区一般住民と比較したHBV感染住民の生命予後，に関する研究成果を紹介させていただく（personal communication）[13]．

1．上五島の感染予防対策

上五島地区の平成10年～14年の肝癌標準化死亡比は男215，女149と極めて高く，HBs抗原は1978年から，HCV抗体は1990年からスクリーニングが開始された．

B型肝炎に対してはHBVキャリアの撲滅をめざし，1978年スクリーニングと同時に母児間感染ブロックも開始した．当初はHBVグロブリン，1980年からはHBVワクチンを導入した．その結果1980年代出生者のHBs抗原陽性率は0.5％と激減し，1990年以降の出生者からHBs抗原陽性者はいまだ確

認されず，ほぼ撲滅状態となった．

2. 肝硬変・肝癌罹患ハザード比

2008年までに延べ34,517名が受診し，HBs抗原陽性1,474名(4.3％；genotype C＝92％)のうち，解析可能であったHBs抗原陽性持続感染者1,045例を最終対象としている．平均観察期間は18.5年(最長で33.8年)，男性605例(58％)，年齢中央値44歳(0.6～95歳)であった．

一般住民をコントロールとしたB型関連肝疾患ハザード比をみると，HBe抗原陽性肝硬変(LC)：0.138（95％CI 0.089-0.215)，HBe抗原陰性LC：0.249（95％ CI 0.152-0.408)，HBe抗原陽性慢性肝炎(CH)：0.378（95％ CI 0.214-0.668)，HBe抗原陽性ASC:0.372（95％ CI 0.147-0.943)，HBe抗原陰性CH:0.393(95％ CI 0.213-0.726)，HBe抗原陰性ASC：0.827(95％ CI 0.669-1.021)であった．

3. HBe抗体と肝機能からみた臨床的治癒

HBe抗体陽転・肝機能正常に至る臨床的治癒率を検討したところ，観察開始時20歳未満群では年率4％であったが，35歳までに累積100％の治癒となった．またこれら臨床的治癒例におけるHBs抗原自然消失率は年率1％であった．一方，35歳時HBe抗原陽性群では臨床的治癒率は年率1％であり，また治癒に至ってもその半数が肝硬変に進展していた．このことから20歳未満HBe抗原陽性キャリアへの治療介入は不要であるものの，35歳以上でHBe抗原陽性例では積極的な治療介入の必要性が示唆される結果となった．

4. HBs抗原自然消失と肝発癌

一方，初診時HBe抗原陰性ASC群において，観察開始から20年ほど経過すると136例(22.6％)にHBs抗原消失を認め，この群におけるHBs抗原累積消失率は20年で27.2％であった．HBs抗原が自然消失した全175例における平均10年間の肝発癌は3例に認め，うち2例はHCV重感染例であり，HBV単独感染例は1例であった．

5. 一般住民と比較したHBVキャリアの生命予後

興味深いことに，HBe抗原陰性ASCの生存率は一般住民に比し観察開始から20年までは低いものの，それ以降はキャリアと一般住民の間で差がなかった．また肝疾患関連死の割合は一般住民群1.1％に対し，HBV持続感染群では33.8％と有意に高かった．

さらに，HBs抗原消失175例の累積生存率を算出し一般住民に対するハザード比を求めると，注目すべきことに死亡リスク比は同等であった．このことから，地域住民コホートからみると，B型肝炎は非活動期の無症候性キャリアに至っても一般住民より生命予後は不良だが，HBs抗原が消失した場合，一般住民の生命予後と同等にまで改善することがわかった．

このコホートは本邦におけるB型肝炎自然史を知り得る極めて貴重なものであり，B型肝炎の目指すべき治療目標はHBs抗原消失であることを示唆するものである．さらなる追跡結果の集積が日本の医療施策に反映されることを期待している．

5 C型肝炎多発地域におけるHBV，HCV感染状況

一方，本邦には地域住民のHCV抗体陽性率が10％を超える，いわゆるHCV感染高浸淫地域がいくつか知られている．このような地域でHBVとHCV感染状況を比較することは，双方の感染経路の違いを考えるうえで重要なことである．

新澤らは[14] 1991年～1993年の3年間に就学年齢以上の住民7,292人に対し行ったHCV

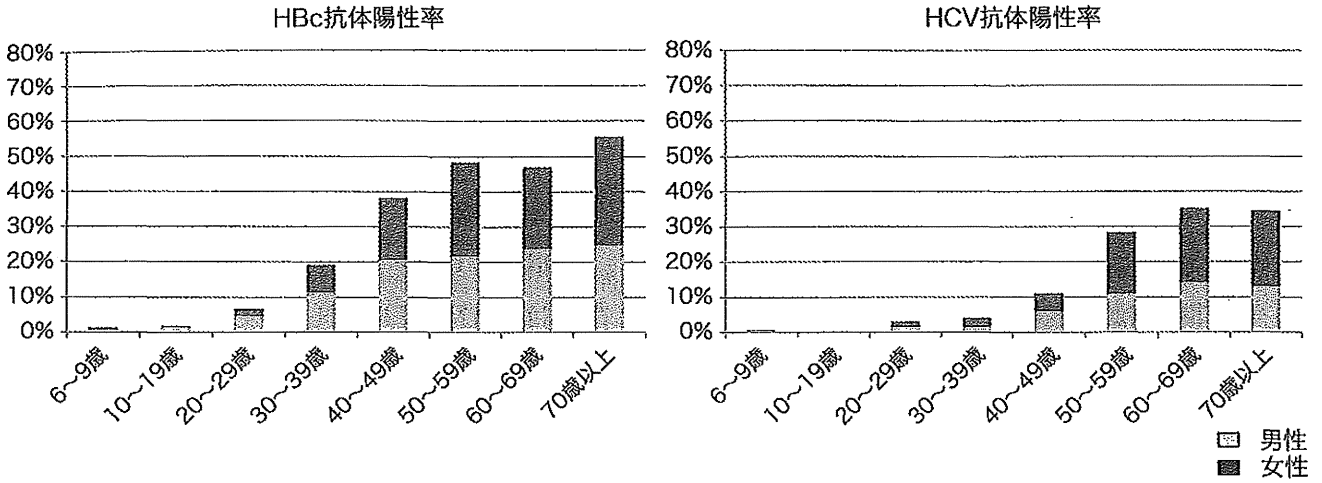

図4　性別・年齢階層別HBc抗体・HCV抗体陽性率(文献14より改変)

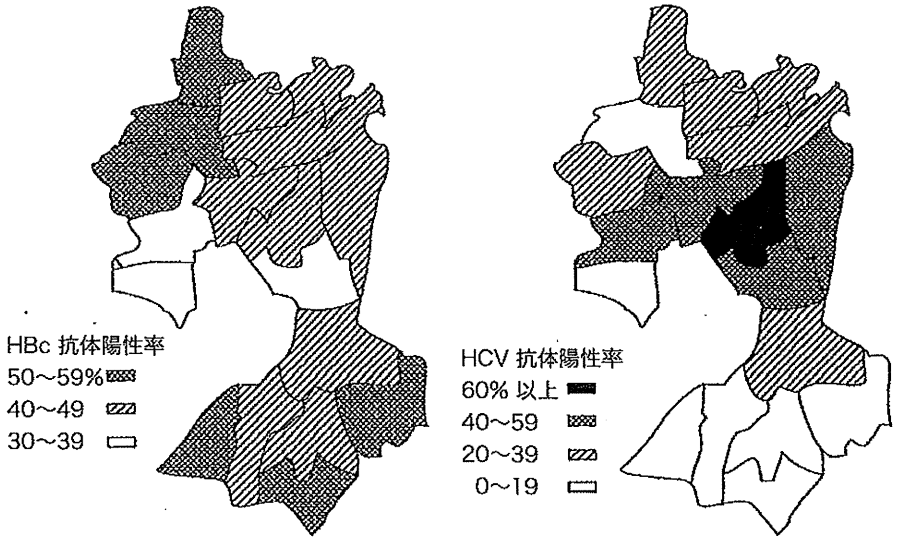

図5　地域別HBc抗体，HCV抗体陽性率(文献14より引用)

高浸淫地域における住民検診で，検診に応じた4,425人(受診率60.7％)を対象に，HBV，HCV感染状況を比較検討した．なお住民検診の性格上，現在あるいは過去のHBV感染を問わず，HBc抗体陽性者をHBV感染者としている．

性別・年齢階層別にHBs抗原，HBc抗体陽性率をみてみると，ともに男性で陽性率が高かったが，HCV抗体陽性率は女性で高かった．HBs抗原陽性率は6～9歳で0.4％，10～19歳で0.6％，20～29歳で0.5％，30～39歳で2.7％，40～49歳で2.9％，50～59歳で2.9％，60～69歳で2.8％，70歳以上で2.5％であった．すなわち20歳代までの若年では0.5％前後であったが，30歳代以上では2.5％以上の陽性率であった．またHBc抗体陽性率は20歳代まで緩やかに上昇し，30歳代からは急峻な上昇を示す一方，HCV抗体陽性率は30歳代まで段階的にわずかに上昇し，40歳代以降，急峻な上昇を示した(図4)．以上より，HBV感染者のピークはHCV感染者よりも10歳若年であり，男性に感染者が多いことが明らかとなった．

本地域集落別のHCV感染率(HCV抗体陽

性)とHBV感染率(HBc抗体陽性)を調べると(図5)，HCV抗体陽性率は同心円状に陽性率の推移を認め，明らかな集積性がみられたのに対し，HBc抗体陽性率はそのような集積性はみられなかった．この地域はHCV抗体陽性率が18.7%，HBc抗体陽性率は33.4%であるが，地域内陽性率の比較からは，HBVとHCV感染が共通の感染経路によるものではない可能性が示唆された．

6 おわりに

B型肝炎自然予後に関し，国内外の住民コホートから得られた知見の一部を紹介した．無治療キャリアからの肝発癌，HBs抗原自然消失，そして生命予後に与える影響など，その機序を含め今後明らかにしなければならない点は多いが，そのためにも自然史を理解するためのさらなるエビデンスの集積が欠かせないと思われる．ここで紹介した自然予後に関わる知見はいずれもウイルス側あるいは疾患因子であるが，今後住民コホートを用いたHBVキャリアのGWASあるいは次世代シークエンサーによる宿主因子解析が進められれば，患者コホートデータとあわせ，B型肝炎自然史に影響するkey molecule (s)がみいだされることが大いに期待される．

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Original Article

Characteristics and prediction of hepatitis B e-antigen negative hepatitis following seroconversion in patients with chronic hepatitis B

Susumu Morita,[1]* Akihiro Matsumoto,[1]* Takeji Umemura,[1] Soichiro Shibata,[1] Nozomi Kamijo,[1] Yuki Ichikawa,[1] Takefumi Kimura,[1] Satoru Joshita,[1] Michiharu Komatsu,[1] Kaname Yoshizawa[1,2] and Eiji Tanaka[1]

[1]*Department of Medicine, Shinshu University School of Medicine, Matsumoto, and* [2]*Department of Gastroenterology, National Hospital Organization Shinshu Ueda Medical Center, Ueda, Japan*

Aim: We analyzed the characteristics of alanine aminotransferase (ALT) abnormality after achieving hepatitis B e-antigen (HBeAg) seroconversion (SC) and other factors associated with the occurrence of HBeAg negative hepatitis.

Methods: We followed 36 patients with chronic hepatitis B from 3 years prior to at least 3 years after SC (mean, 11.6 years) and examined ALT, hepatitis B virus (HBV) DNA, HB surface antigen, HB core-related antigen (HBcrAg) levels and mutations related to HBeAg SC.

Results: ALT normalization (<31 IU/L for at least 1 year) was primarily observed until 2 years following SC, after which it became more infrequent. We next divided patients into abnormal (≥31 IU/L, $n = 20$) and normal (<31 IU/L, $n = 16$) groups based on integrated ALT level after the time point of 2 years from SC, and considered the former group as having HBeAg negative hepatitis in the present study. Although changes in median levels of ALT and HBcrAg differed significantly between the groups, multivariate analysis showed ALT normalization within 2 years after SC to be the only significant determining factor for this disease ($P = 0.001$). We then assessed the 19 patients whose ALT was normal at 2 years following SC, four of whom developed HBeAg negative hepatitis. Increased levels of HBV DNA ($P = 0.037$) and HBcrAg ($P = 0.033$) were significant factors of potential relevance.

Conclusion: ALT abnormality after 2 years of SC may be evaluated as HBeAg-negative hepatitis. ALT, HBV DNA and HBcrAg levels may be useful in predicting the outcome of patients who achieve HBeAg SC.

Key words: hepatitis B core-related antigen, hepatitis B virus, reactivation, seroconversion

INTRODUCTION

HEPATITIS B VIRUS (HBV) infection is a major health concern with an estimated 350–400 million carriers worldwide. Whereas acute infection in adults is generally self-limiting, that during early childhood develops into persistent infection in most individuals, which can lead to chronic hepatitis and eventually liver cirrhosis and hepatocellular carcinoma (HCC).[1–3] The natural history of chronic HBV infection can be classified into several phases based on levels of alanine aminotransferase (ALT) and HBV DNA, hepatitis B e-antigen (HBeAg) status and estimated immunological status.[4] In the immune tolerance phase, HBeAg is positive, ALT level is normal, histological evidence of hepatitis is absent or minimal, and HBV DNA level is elevated. The chronic hepatitis B phase is characterized by raised ALT and HBV DNA levels. In this phase, the host's immune system initiates a response that results in active hepatitis. In patients 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 (SC) of HBeAg to HBe antibodies and the fall of HBV DNA level result in the disappearance of disease activity despite persisting hepatitis B surface antigen (HBsAg) and low HBV DNA level. The SC of

Correspondence: Dr Takeji Umemura, Department of Medicine, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto 390-8621, Japan. Email: tumemura@shinshu-u.ac.jp
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*These authors contributed equally to this study.
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HBeAg marks the transition from the hepatitis phase to the inactive carrier phase, which is generally thought to be a benign course for the HBV carrier, although hepatitis can sometimes reactivate spontaneously.[5]

Patients experiencing HBV reactivation undergo another transition characterized by increases in HBV DNA and ALT levels and disease activity without the reappearance of HBeAg. This phase is referred to as HBeAg negative chronic hepatitis B. Occasional severe hepatitis B flare-ups with moderate HBV DNA level occur in this phase.[6,7] It is thought that HBeAg negative chronic hepatitis B is caused by mutant strains of HBV that are unable to produce HBeAg[6,8] and tends to develop into cirrhosis and HCC more frequently than does HBeAg positive chronic hepatitis B.[9–13] Therefore, it is important to identify patients who are likely to develop HBeAg negative hepatitis after HBeAg SC from those who can maintain an inactive carrier phase. In the present study, we evaluated 36 patients with HBeAg SC to examine the effects of host factors and viral factors, including serum quantitative HBsAg, hepatitis B core-related antigen (HBcrAg), HBV DNA, PC (A1896) mutation and BCP mutations (T1762 and A1764) before, during and after SC.

METHODS

Patients

A TOTAL OF 36 patients with sustained HBeAg SC (24 men and 12 women; median age, 38 years [range, 23–65]) were enrolled in this study after meeting the following criteria: (i) follow ups for at least 3 years before and after HBeAg SC; and (ii) serum samples at several time points before, during and after SC available for testing. HBeAg SC was defined as seroclearance of HBeAg with the appearance of anti-HBe that was not followed by HBeAg reversion or loss of anti-HBe. All patients were seen at Shinshu University Hospital from 1985 to 2009. The median follow-up period after SC was 11.6 years (range, 3.2–26.0). HBsAg was confirmed to be positive on two or more occasions at least 6 months apart in all patients. No patients had other liver diseases, such as alcoholic or non-alcoholic fatty liver disease, autoimmune liver disease or drug-induced liver injury. Patients who were complicated with HCC or who showed signs of hepatic failure were excluded from the study. HBV genotype was C in all patients, who were also negative for antibodies to hepatitis C virus and HIV. Nucleoside/nucleotide analog (NUC) therapy was introduced in 14 patients after HBeAg SC on physicians' decision, and then follow up was stopped. No patient was treated with interferon during the study period. ALT, albumin, bilirubin, platelet and other relevant biochemical tests were performed using standard methods.[14] The integration value of ALT after SC was calculated using the method described by Kumada *et al.*[15] (median determination frequency, 4.7/year per person [range, 1.6–13.9]) because a previous study showed integration values to be more meaningful than arithmetic mean values in long-term follow-up cohorts.[16] As guidelines released by the Ministry of Health, Labor and Welfare of Japan advise consideration of antiviral therapy for patients with ALT levels of 31 IU/L or more,[17] an ALT integration value of less than 31 IU/L was defined as normal in this report. Serum samples were stored at −20°C until tested. Liver biopsies were performed by percutaneous sampling of the right lobe with a 14-G needle in eight patients with HBeAg negative hepatitis, as reported previously.[14] All biopsies were 1.5 cm or more in length. Liver histological findings were scored by the histology activity index of Knodell *et al.*[18] The protocol of this study was approved by the ethics committee of our university and was in accordance with the Declaration of Helsinki of 1975. Informed consent was obtained from each patient.

Hepatitis B viral markers

Serological markers for HBV, including HBsAg, HBeAg and anti-HBe, were tested using commercially available enzyme immunoassay kits (Abbott Japan, Tokyo, Japan).[19] Quantitative measurement of HBsAg was done using a chemiluminescence enzyme immunoassay (CLEIA)-based HISCL HBsAg assay manufactured by Sysmex (Kobe, Japan).[20] The assay had a quantitative range of −1.5 to 3.3 log IU/mL. Serum HBcrAg level was measured using a CLEIA HBcrAg assay kit with a fully automated Lumipulse System analyzer (Fujirebio, Tokyo, Japan) as described previously.[21] We expressed HBcrAg level in terms of log U/mL, with a quantitative range set at 3.0–6.8 log U/mL. End titers of HBsAg and HBcrAg were determined by diluting samples with normal human serum when initial results exceeded the upper limit of the assay range. HBV DNA level was measured using an Amplicor monitor assay with a dynamic range of 2.6–7.6 log copies/mL.[22] Six major genotypes (A–F) of HBV were determined using the method reported by Mizokami *et al.*,[23] in which the surface gene sequence amplified by polymerase chain reaction was analyzed by restriction fragment length polymorphism.

The PC and BCP mutations of HBV were assessed as previously described. Briefly, the stop codon mutation in the PC region (A1896) was detected with an enzyme-linked mini-sequence assay kit (Smitest; Roche Diagnostics, Tokyo, Japan) with a sensitivity of 1000 copies/mL. The results were expressed as the percent mutation rate as defined by Aritomi *et al.*[24] The PC mutation was judged to exist when the mutation rate exceeded 50% in the present study because the mutation rate would increase to 100% once surpassing this value.[25] The BCP double mutation was detected using an HBV core promoter detection kit (Smitest; Genome Science Laboratories) with a detection limit of 1000 copies/mL.[24] The BCP mutation was judged to exist for all classifications of mutant in the present study.

Statistical analysis

Clinical factors were compared between patients with and without HBeAg negative hepatitis after SC using the χ^2-test and Fisher's exact test, and group medians were compared using the Mann–Whitney *U*-test. Receiver-operator curves (ROC) with Youden's index were used to decide each cut-off point for predicting HBeAg negative hepatitis after SC. Differences between the analyzed groups were assessed using Kaplan–Meier analysis and the log-rank test. Sex, age at SC, HBcrAg level, ALT level, HBV DNA level, HBsAg level, PC mutation and BCP mutation were all suspected to be associated with ALT elevation after SC. Factors attaining a *P*-value of less than 20% in univariate analysis were used in multivariate analysis that employed a stepwise Cox proportional hazard model. These included level of serum albumin and platelet count at SC, levels of ALT at 0, 1, 2 and 3 years after SC, and levels of HBcrAg at 1, 2 and 3 years after SC. All tests were performed using the IBM SPSS Statistics Desktop for Japan ver. 19.0 (IBM Japan, Tokyo, Japan). *P*-values less than 0.05 were considered to be statistically significant.

RESULTS

Baseline characteristics of patients

ALL 36 PATIENTS enrolled showed abnormal levels of ALT before SC, with the majority showing normalization around the time of SC. We defined ALT normalization as a decrease in ALT level to less than 31 IU/L for at least 1 year. The change in ratio of patients not achieving normalization over time revealed two distinct phases (Fig. 1): the first was a fast decline phase from 2 years before SC to 2 years afterwards, and the second was a slow decline phase from 2 years after SC to the end of follow up. Normalization of ALT during the fast phase was presumed to be associated with HBeAg SC, which was seen in 53% (19/36) of total patients. Based on this, we analyzed the risk factors associated with ALT abnormality after the time point of 2 years from SC by calculating integrated ALT levels (Fig. 2). We defined patients whose integrated ALT level exceeded 30 IU/L as having HBeAg negative hepatitis in the present study. Serum HBV DNA of over 4.0 log copies/mL was observed in all patients with HBeAg negative hepatitis.

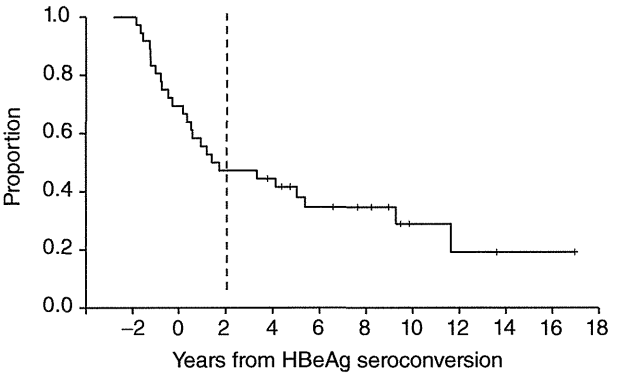

Figure 1 Changes in the proportion of patients with alanine aminotransferase (ALT) abnormality. ALT normalization was defined as ALT level decreasing to lower than 31 IU/L and maintained for at least 1 year. These data reveal two distinct time frames: a fast decline phase around the seroconversion (SC) period until 2 years afterwards, and a slow decline phase from 2 years after SC to the end of follow up. The vertical broken line at 2 years after SC indicates the borderline between the two phases. HBeAg, hepatitis B e-antigen.

Of the 36 patients enrolled, 20 (56%) developed HBeAg negative hepatitis and 16 (44%) did not. ALT normalization within 2 years after SC was significantly less frequent in patients with HBeAg negative hepatitis (Table 1). Median age, sex distribution and follow-up period did not differ between the two groups. Median albumin level tended to be lower in patients with HBeAg negative hepatitis, but only modestly. Eight of 20 HBeAg negative hepatitis patients underwent liver biopsy after SC. All had necroinflammatory activity. Initiation of NUC therapy was more common in the HBeAg negative hepatitis group.

Clinical and virological profiles

Changes in median levels of ALT, HBV DNA, HBsAg and HBcrAg during the course of SC have been compared between patients with and without HBeAg negative

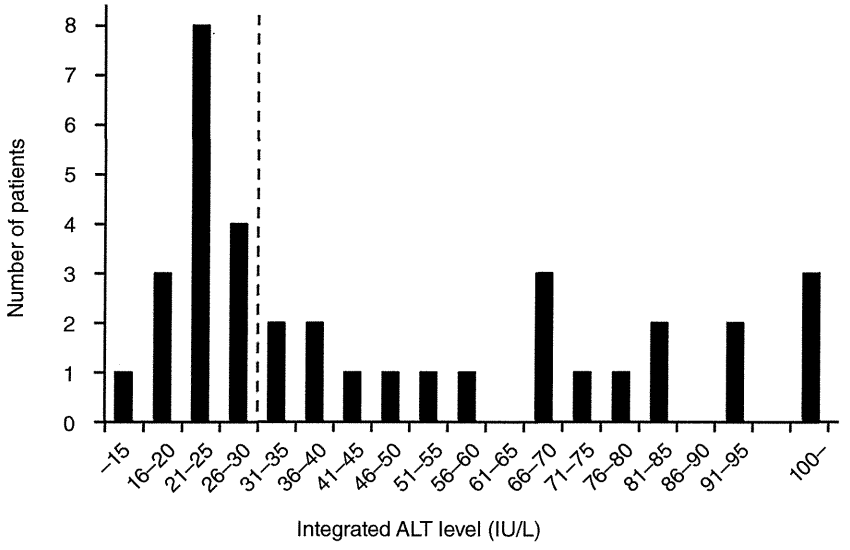

Figure 2 Distribution of integrated alanine aminotransferase (ALT) level from the time point of 2 years after seroconversion (SC) to the end of follow up.

hepatitis in Figure 3. We observed that median ALT level decreased around the time of SC in patients without HBeAg negative hepatitis, but did not in the other group. Overall, median ALT differed significantly between the two groups at the time of SC (43.0 vs 21.5 IU/L; $P = 0.009$) and at 1 (67.0 vs 15.0 IU/L; $P = 0.001$), 2 (52.0 vs 14.5 IU/L; $P < 0.001$) and 3 years (41.5 vs 15.0 IU/L; $P < 0.001$) afterwards (Fig. 3a). Median HBV DNA level decreased similarly in both groups around the time of SC (Fig. 3b). Median HBsAg level was unchanged or minimally decreased in both groups around the time of SC, but was significantly lower in patients with HBeAg negative hepatitis at 1 (3.9 vs 3.2 log IU/mL; $P = 0.025$) and 2 years (3.9 vs 3.2 log IU/mL; $P = 0.045$) before SC and at 2 years (3.7 vs 3.0 log IU/mL; $P = 0.023$) after SC (Fig. 3c). Median HBcrAg level decreased in both groups around the time of SC, but this decline was more gradual in patients with HBeAg negative hepatitis, becoming significantly higher at 1 (5.2 vs 3.9 log U/mL; $P = 0.011$), 2 (4.6 vs 3.5 log

Table 1 Comparison of host and viral factors between patients with and without HBeAg negative hepatitis among total patients

Clinical characteristics	HBeAg negative hepatitis		*P*
	Present ($n = 20$)	Absent ($n = 16$)	
Age at SC (years)†	40 (23–64)	38 (24–65)	0.504
Sex (male : female)	15:5	9:7	0.298
Follow-up period (years)†	10.6 (3.8–26.0)	12.4 (3.2–23.1)	0.610
Laboratory data at SC			
Albumin (g/dL)†	4.1 (3.6–4.6)	4.3 (3.7–4.8)	0.030
Bilirubin (mg/dL)†	1.0 (0.4–2.6)	0.8 (0.5–1.3)	0.319
Platelets (/μL)†	13.9 (8.5–24.3)	18.1 (9.6–22.9)	0.187
ALT normalization within 2 years after SC‡	4 (20)	15 (94)	<0.001
Events during follow-up period			
Initiation of NUC therapy‡	12 (60)	2 (13)	0.006
Development of HCC‡	2 (10)	1 (6)	1.000

†Data are expressed as median (range).
‡Data are expressed as number of patients (%).
ALT, alanine aminotransferase; HBeAg, hepatitis B e-antigen; HCC, hepatocellular carcinoma; NUC, nucleoside/nucleotide analog; SC, seroconversion.

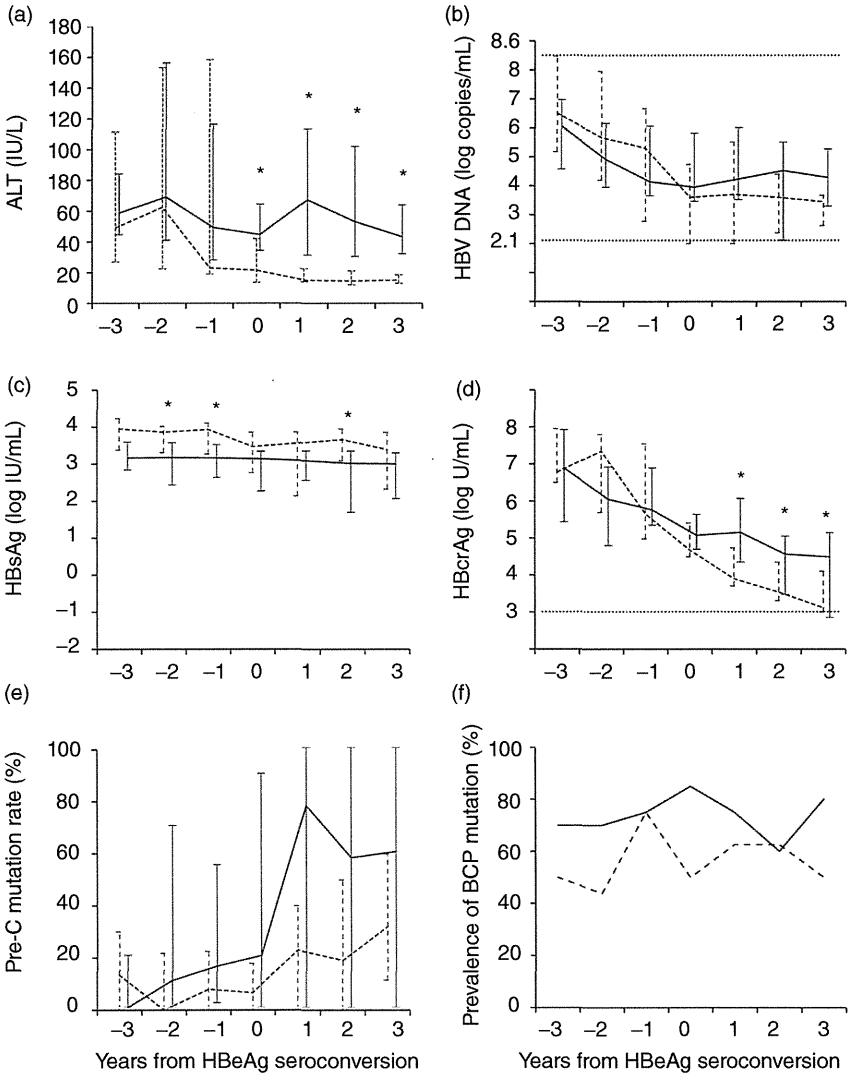

Figure 3 Changes in median levels of serum alanine aminotransferase (ALT) (a), hepatitis B virus (HBV) DNA (b), hepatitis B surface antigen (HBsAg) (c), hepatitis B core-related antigen (HBcrAg) (d) and PC mutation rate (e) are compared between patients with and without the occurrence of hepatitis B e-antigen (HBeAg) negative hepatitis. A similar comparison is made for prevalence of patients with BCP mutations (f). Solid lines indicate patients with HBeAg negative hepatitis ($n = 20$) and broken lines indicate those without ($n = 16$). Data are shown as median values with 25% and 75% ranges at each point for (a–e). Horizontal broken lines in (b) and (d) indicate the upper and lower detection limits of the corresponding markers. *$P < 0.05$.

U/mL; $P = 0.041$) and 3 years (4.6 vs 3.1 log U/mL; $P = 0.016$) after SC (Fig. 3d). PC mutation rate increased similarly in both groups during the course of SC (Fig. 3e), and the prevalence of BCP mutation positive patients remained comparatively high in both groups throughout the study period (Fig. 3f).

All factors that were associated with the occurrence of HBeAg negative hepatitis were evaluated for independence by multivariate analysis. We found that only abnormal level of ALT (≥31 IU/L) at 2 years after SC (odds ratio, 42.0; 95% confidence interval, 4.3–405.4; $P = 0.001$) was an independent predictive factor. Therefore, we examined for factors associated with the occurrence of HBeAg negative hepatitis in the 19 patients whose ALT level had normalized by 2 years after SC. Four (21%) of these patients developed HBeAg negative hepatitis and the remaining 15 (79%) did not. We found no significant differences between the two groups with regard to age at SC, sex or laboratory data (Table 2). We next analyzed HBV DNA, HBsAg and HBcrAg levels at 2 years after SC to see if these factors could discriminate between patients with and without the development of HBeAg negative hepatitis. Cut-off values for each factor were determined by ROC analysis. As shown in Figure 4, serum levels of HBV DNA (7% vs 60%; $P = 0.037$) and HBcrAg (0% vs 44%; $P = 0.033$) were significant factors indicating susceptibility, but HBsAg was not.

Table 2 Comparison of host and viral factors between patients with and without HBeAg negative hepatitis in 19 patients whose ALT levels were normal at 2 years after SC

Clinical characteristics	HBeAg negative hepatitis		*P*
	Present ($n = 4$)	Absent ($n = 15$)	
Age at SC (years)†	41 (30–43)	37 (23–65)	0.549
Sex (male : female)	2:2	8:7	1.000
Follow-up period (years)†	9.1 (8.3–14.1)	12.2 (3.2–23.1)	0.610
Laboratory data at SC			
Albumin (g/dL)†	4.3 (3.8–4.3)	4.3 (3.7–4.7)	0.364
Bilirubin (mg/dL)†	1.0 (1.0–1.3)	0.8 (0.5–1.3)	0.083
Platelets (/μL)†	14.9 (13.3–16.4)	16.9 (9.6–22.5)	0.667
Events during follow-up period			
Initiation of NUC therapy‡	3 (75)	2 (13)	0.037
Development of HCC‡	1 (25)	1 (7)	0.386

†Data are expressed as median (range).
‡Data are expressed as number of patients (%).
ALT, alanine aminotransferase; HBeAg, hepatitis B e-antigen; HCC, hepatocellular carcinoma; NUC, nucleoside/nucleotide analog; SC, seroconversion.

DISCUSSION

ALTHOUGH ACTIVE HEPATITIS usually subsides following HBeAg SC, it recurs in a considerable proportion of patients several years afterwards. Hsu *et al.*[5] followed 283 patients with HBeAg SC for a median follow-up period of 8.6 years and observed that ALT elevation of over twice the upper limit of normal occurred in 94 patients (33%). Of these, 68 (72%) were considered to have HBeAg negative hepatitis B because HBV DNA was detectable without the reappearance of HBeAg at the time of ALT elevation. HBeAg negative hepatitis is a major health concern because its occurrence is closely associated with progression to cirrhosis and development of HCC,[9–12] and thus prediction of its onset is important. Hsu *et al.*[5] found that patients with more frequent acute exacerbations of hepatitis before HBeAg SC and those with cirrhosis at the time of HBeAg SC had a higher risk of developing HBeAg negative hepatitis. Although significant, these factors were insufficient to accurately predict the occurrence of the disease.[26–30] Therefore, we analyzed several additional factors, including HBV DNA, HBsAg and HBcrAg levels, as well as viral mutations that halt HBeAg production.

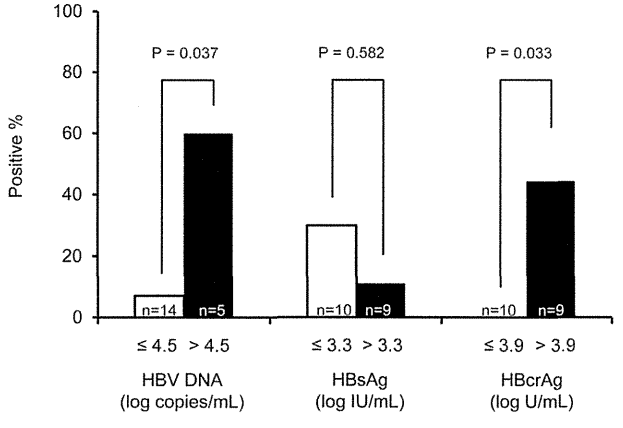

Figure 4 Occurrence of hepatitis B e-antigen (HBeAg) negative hepatitis is compared among patients using higher and lower levels of corresponding markers at 2 years after seroconversion (SC). The cut-off value for each marker was determined by receiver-operator curve analysis. HBcrAg, hepatitis B core-related antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

In the present study, we found that the majority of patients with HBeAg SC achieved normalization of ALT within 2 years following SC, after which such normalization became relatively rare. Abnormal ALT was determined using the distribution of integrated ALT level from 2 years after SC to the end of follow up, which clearly showed the existence of two groups. We defined patients with an abnormal integrated level of ALT as having HBeAg negative hepatitis because this abnormality tended to persist and was preceded by HBV DNA elevation. Our result also conferred the important realization that ALT abnormality within 2 years after SC may not necessarily indicate the occurrence of HBeAg negative hepatitis, which has a poor prognosis. NUC

therapy was not available for patients with chronic hepatitis B in Japan when our subjects began follow up. Hence, the natural history of SC has been evaluated in this cohort. Follow up stopped in this study when NUC therapy was commenced. Currently, we perform NUC therapy on patients with HBe negative hepatitis based on age and ALT activity, as advised by the Ministry of Health, Labor and Welfare.[17]

Many host and viral factors were also analyzed to predict the occurrence of HBeAg negative hepatitis in the current study. Host factors, including age and sex, did not differ between the groups with and without HBeAg negative hepatitis, but changes in median ALT level around SC clearly differed between the two groups. Specifically, ALT level did not decrease even after SC in patients with HBeAg negative hepatitis, while it normalized during the SC period in those without. Viral factors were analyzed at several time points around SC. Among them, median HBcrAg level clearly differed between the groups; HBcrAg showed a steep decrease around the SC period in patients without HBeAg negative hepatitis, while it exhibited a significantly slower decline in those with. Similarly to earlier reports, median levels of HBV DNA and HBsAg showed some differences between the two groups, but these were not remarkable when analyzed chronologically. Negative results were also seen in the analyses of PC and BCP mutations. Multivariate analysis showed that abnormal ALT level at 2 years after SC was the only significant factor to predict the occurrence of HBeAg negative hepatitis among the factors analyzed. Because patients with normal ALT had maintained that level for at least 1 year, this result may indicate that continuous normalization of ALT is rare in patients with HBeAg negative hepatitis after SC and that ALT abnormality is associated with higher levels of HBcrAg and HBV DNA.

Because ALT level was closely related to the occurrence of HBeAg negative hepatitis, we next analyzed for predictive factors in patients whose ALT level was normal (<31 IU/L) at 2 years after SC. We observed that increased HBV DNA and HBcrAg levels at 2 years after SC were significant factors for predicting the occurrence of HBeAg negative hepatitis, but that HBsAg level was not. Single or combined monitoring use of HBV DNA and HBcrAg levels may therefore be useful to predict the recurrence of hepatitis in patients whose ALT level normalizes following HBeAg SC. However, further studies are required to verify this in the clinical setting.

Whereas HBsAg is a serum marker commonly used for the diagnosis of HBV infection, HBcrAg assays measure serum levels of HBc, HBe and the 22-kDa precore antigens simultaneously using monoclonal antibodies that recognize the common epitopes of these three denatured antigens.[31] Because the latter assay measures all antigens transcribed from the precore/core gene, it is regarded as core-related.[21] It has been suggested that viral antigen levels, including those of HBsAg and HBcrAg, are differently associated with HBV activity from HBV DNA and ALT levels, and thus are useful for predicting the future activity of hepatitis B. For example, HBcrAg level was seen to predict hepatitis relapse after discontinuation of NUC therapy,[32,33] and HBsAg level has been reportedly associated with the response to pegylated interferon therapy differently from HBV DNA.[34,35] Both antigen levels are believed to be related to intracellular levels of HBV cccDNA. However, it is possible that levels of HBsAg and HBcrAg have different roles in monitoring viral activity because the transcription of these two antigens is regulated by alternative enhancer–promoter systems in the HBV genome.[1] The serum level of HBcrAg was more useful than that of HBsAg to predict the occurrence of HBeAg negative hepatitis in the present study. This difference may be attributed to the fact that the production of all antigens that constitute HBcrAg is regulated by the same system as that of HBeAg, while the production of HBsAg is not.

Lastly, it is reasonable to presume that the PC and BCP mutations which halt HBeAg production are associated with integrated values of ALT elevation because the disease is essentially caused by HBV containing these mutations.[8,10] However, the prevalence of either mutation did not differ between the groups at any time point during the study. Our results showed that almost all patients had PC and/or BCP mutations, especially after SC, and implied that the existence of these mutations alone was not sufficient for developing ALT elevation. HBV genotype is also closely associated with HBeAg SC,[36] but we could not include genotype as a factor because our entire cohort was genotype C.

A recent review by Papatheodoridis *et al.*[37] showed that histologically significant liver disease is rare in HBeAg negative patients with persistently normal ALT based on stringent criteria and serum HBV DNA of 20 000 IU/mL or less. They suggest that such individuals can be considered as true inactive HBV carriers, who require continued follow up rather than liver biopsy or immediate therapy. On the contrary, liver biopsy samples obtained from eight of our patients with HBeAg negative hepatitis having elevated ALT levels after SC revealed necroinflammatory activity. Hence, it remains controversial if histological findings are important for diagnosis of HBeAg negative hepatitis.

This study has the main limitations of a retrospective design and a small cohort size. However, our findings from careful extended follow up indicate that ALT abnormality after 2 years from SC can be considered to be HBeAg negative hepatitis, and that HBcrAg and HBV DNA levels may be useful for predicting the long-term outcome of patients who achieve HBeAg SC and ALT normalization.

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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.

*Drafting Committee for Hepatitis Management Guidelines (in alphabetical order): Yasuhiro Asahina, Department of Gastroenterology and Hepatology, Department for Hepatitis Control, Tokyo Medical and Dental University; Norio Hayashi, Kansai Rosai Hospital; Naoki Hiramatsu, Department of Gastroenterology and Hepatology, Osaka University Graduate School of Medicine; Namiki Izumi, Division of Gastroenterology and Hepatology, Musashino Red Cross Hospital; ‡Kazuhiko Koike, Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo; Hiromitsu Kumada, Department of Hepatology, Toranomon Hospital; Masayuki Kurosaki, Division of Gastroenterology and Hepatology, Musashino Red Cross Hospital; Makoto Oketani, Digestive and Lifestyle-related Diseases, Kagoshima University Graduate School of Medical and Dental Sciences; Fumitaka Suzuki, Department of Hepatology, Toranomon Hospital; †Hajime Takikawa, Department of Medicine, Teikyo University School of Medicine; Atsushi Tanaka, Department of Medicine, Teikyo University School of Medicine; Eiji Tanaka, Department of Medicine, Shinshu University School of Medicine; Yasuhito Tanaka, Department of Clinical Molecular Informative Medicine, Nagoya City University Medical School Graduate School of Sciences; Hirohito Tsubouchi, Kagoshima City Hospital; Hiroshi Yotsuyanagi, Department of Internal Medicine, Graduate School of Medicine, The University of Tokyo (†Chairman, ‡Special Committee Member).

**Correspondence: Atsushi Tanaka, Department of Medicine, Teikyo University School of Medicine, 2-11-1, Kaga, Itabashi-ku, Tokyo 173-8605, Japan. Email: a-tanaka@med.teikyo-u.ac.jp*

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.

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

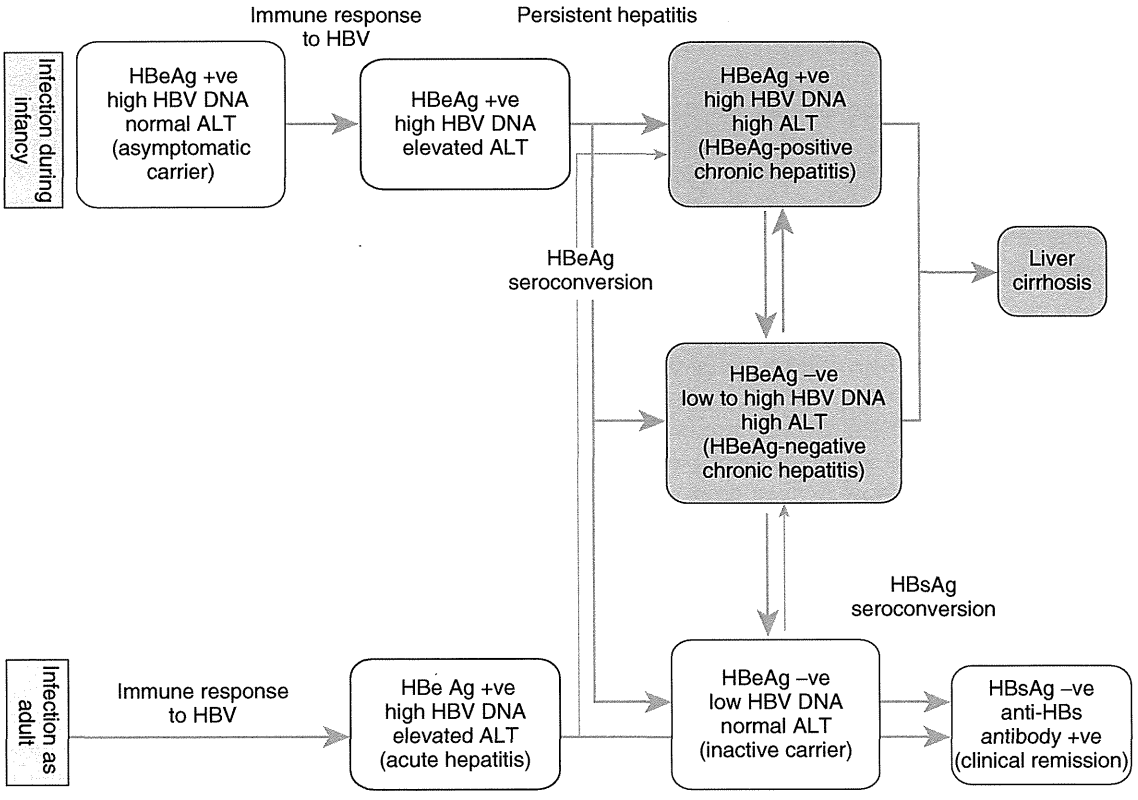

Figure 1 Natural course of persistent HBV infection.

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***

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

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.