Long-term outcome

The end-point of antiviral therapy is to prevent liver cirrhosis and HCC. Meta-analysis of five studies including 935 patients revealed that IFN treatment significantly decreased the incidence of cirrhosis with the combined risk ratio of 0.65 (95% confidence interval [CI] = 0.47–0.91).[195] Meta-analysis of 11 studies including 2082 patients revealed that IFN treatment significantly decreased the incidence of HCC with the combined risk ratio of 0.59 (95% CI = 0.43–0.81).[195] These results suggest that IFN prevents progression of liver disease to liver cirrhosis or delays the development of HCC, as long as it is within 4–7 years of follow up which is the length of follow up in these studies. Sustained response to IFN therapy was associated with increased survival.[175,181,196,197] To further elucidate the impact of IFN on the natural course of chronic hepatitis B, studies with larger populations followed for longer periods may be needed.

Consensus statement 12

12-1 IFN therapy prevents progression to cirrhosis or the development of HCC. (Level 1a.)

12-2 IFN therapy is associated with improved survival. (Level 1b.)

Adverse effects

The most frequent adverse effects are flu-like symptoms, fatigue, myelosuppression and dermal reaction at the injection site. Others include alopecia, depression and thyroid dysfunction. Less frequent but severe adverse events include interstitial pneumonitis, exacerbation of underlying autoimmune disorders, cerebral vascular events and flare of hepatitis.

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医療安全対策

透析患者におけるB型肝炎ウイルスマーカー測定の意義

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key words：B型肝炎ウイルス，再活性化，HBV DNA，B型肝炎，病期

要　旨

透析患者は血液を介して感染するウイルスのハイリスクグループであり，B型肝炎ウイルス（HBV）もその1つである．透析施設におけるHBV感染の制御や，すでに透析を受けているHBVキャリアの診療にはウイルスマーカーの測定が欠かせない．近年，治療法の変化やマーカー測定法の進歩に伴い，ウイルスマーカーに対する考え方も変化している．このため，HBVマーカーの新しい理解は透析医にとっても重要な課題である．

はじめに

透析治療では，常に観血的処置を伴う医療行為を集団で行っており，透析患者は血液を介して感染する肝炎ウイルスのハイリスクグループである．さらに，透析患者では免疫能が低下しているため，感染の病態も健常者とは異なる可能性があり，診療にさいしては注意が必要である．

血液を介して感染するB型（HBV）およびC型肝炎ウイルスに対する感染対策は進歩し，最近では透析患者における感染の危険性は大きく低下した．しかし，透析患者がハイリスクグループであることには変わりなく，新規感染に対する対策は常に行う必要がある．また，透析患者では過去に感染したキャリアも多く，肝炎に対する対策も重要な課題である．

以前より透析施設では，患者および医療従事者に肝炎の集団発生がみられていたが，その大部分がHBV感染に伴うものである．また，透析患者でのHBV感染率は一般健常者に比較し高いことが知られている．さらに，透析患者の生命予後が大きく改善されると，ウイルス肝炎に伴う肝発癌の危険性も大きな問題となってきた．

肝炎ウイルス感染の監視やウイルス肝炎の診療には，関連したウイルスマーカーの測定が必須である．近年，治療法の変化やマーカー測定法の進歩に伴い，ウイルスマーカーに対する考え方も新しくなってきた．さらに，B型肝炎は複雑な病態を示すため多くのウイルスマーカーが使用されている[1]．これらのことから，HBVマーカーの理解は，非専門医には容易ではない領域と言える．

本稿では，透析医のために，透析患者の診療に必要なHBVマーカーの臨床的意義をできるだけわかりやすく解説する．

1　B型肝炎の病期と自然経過

HBVキャリアはその自然経過の中で，無症候性キャリア，慢性肝炎，肝発癌，急性増悪，再活性化などの多彩な病態を示す．これらの病態の変化はウイルス増殖と免疫応答の関係の変化に起因するものであり，B型肝炎の臨床ではこれらを十分理解する必要がある[2~4]．HBVキャリアの自然経過は，ALT値，HBe抗原，HBV DNA量，予測される免疫状態などから病期が分類されており，代表的なものを表1に示した[3]．

Clinical significance of hepatitis B viral markers in patients on hemodialysis
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表1 HBVキャリアの病期とウイルスマーカー

病期	肝炎	血中			肝臓	免疫状態
		DNA量	HBe抗原	HBs抗原	cccDNA	
免疫寛容期	−	8〜11	+	+	+	免疫寛容
慢性肝炎 eAg（+）	持続	6〜10	+	+	+	免疫排除
eAg（−）	変動	3〜8	−	+	+	
非活動性キャリア	−	<4	−	+	+	免疫監視
回復期	−	−	−	−	+	免疫監視

HBV DNA量：log copies/ml

1-1 免疫寛容期

免疫寛容期ではHBV増殖は活発であるがALT値は正常で，組織学的にも正常か軽度の炎症にとどまる．周産期にHBVに感染した場合，免疫寛容期は思春期〜若年成人まで続くことが多い．宿主の免疫はHBVを非自己とは認識せず，これを排除しようとしていないと考えられるので，この時期は免疫寛容期と呼ばれる．

1-2 免疫排除期

HBe抗原陽性の慢性肝炎では，HBV排除に働く宿主の免疫反応が起こり肝炎が惹起される．HBe抗原陽性の慢性肝炎が長期に続くと肝硬変へ進行するが，多くの患者ではHBe抗体へセロコンバージョンし非活動性キャリアとなる．

HBe抗原陰性になると総じて予後が良いと考えられていた．しかし，最近，逆に予後が悪い病態が報告され，重要な病期の一つとして分類されている．このHBe抗原陰性慢性肝炎は，HBe抗原が抗体へセロコンバージョンしてもHBV DNA量が十分低下せず慢性肝炎が持続する場合や，一旦非活動性キャリアとなった後に肝炎の再活性化が起こる場合がある[5]．特徴としては，HBV DNA量は中等度の範囲で変動し，間欠的に激しい肝炎を起こす傾向がある．また，この肝炎はHBe抗原非産生変異株により惹起され，肝硬変や肝癌へ進行しやすいことが報告されている．

1-3 免疫監視期

非活動性キャリア期ではHBVに対する宿主の免疫が優位になり，HBVの増殖は持続的に低下する．この結果，肝炎は沈静化し肝発癌率も低いので予後は良いと考えられている．しかし，自然経過または宿主の免疫抑制により，B型肝炎の再活性化がみられることがあるので経過観察は必要である．

非活動性キャリアを経過した後，一部ではHBs抗原が陰性化し，回復期となる．この時期は肝炎はなく肝発癌率も低いとされている．しかし，高齢者や肝硬変のHBs抗原消失例では肝発癌に対する注意が必要である．また，HBs抗原は陰性化しても肝細胞の核内にcccDNAの形でHBVが残存するので，HBVが完全に排除されたことにはならない[6,7]．

2 HBV感染の診断，HBs抗原とIgM-HBc抗体

HBVキャリアの診断にはHBs抗原の測定が最も優れている（表2）．HBs抗原はHBVの表面抗原であり，ビリオンの表面に存在する．しかし，これ以外にもHBs抗原粒子として血中に大量に分泌されるため，診断に用いられている．HBs抗原が陽性であるということは現在HBVに感染していることを示す．通常，HBVキャリアではHBc抗体も陽性である．

近年，HBs抗原の測定は非常に高感度となり，感度不足による偽陰性の危険性は大きく低下した．このため，キャリアと非キャリアの鑑別はHBs抗原の測定のみで十分とされている．ただし，HBs抗原検査試薬には一般測定用と精密測定用があり，前者は経済的であるが感度の点でやや劣るので，厳密にHBV感染を確認する場合には後者を用いる必要がある．

急性肝炎の診断にはHBs抗原に加えIgM-HBc抗体を同時に測定する必要がある．この理由の一つは，急性肝炎ではHBs抗原が早期に陰性化することがあり，HBs抗原だけの測定では診断ができない場合があるためである．このような場合でもIgM-HBc抗体は陽性（高力価）となるので，急性肝炎の診断が可能となる．第二の理由は，キャリアからの急性増悪との鑑別である．過去の感染状況が不明の場合，この急性増悪と急性肝炎を臨床的に鑑別することは困難であり，

表2　B型肝炎ウイルスマーカーの臨床的意義

マーカー	臨床的意義
HBs抗原	HBVに感染している（通常HBc抗体も陽性）
HBs抗体	HBVの感染既往（多くはHBc抗体も陽性） HBVワクチン接種後
HBc抗体	HBVの感染既往（多くはHBs抗体も陽性） HBVに感染している（HBs抗原も陽性）
IgM-HBc抗体	B型急性肝炎（高力価） B型慢性肝炎の急性増悪（低力価）
HBe抗原	HBVの増殖力が強い
HBe抗体	HBVの増殖力が弱い
HBV DNA	HBV量を反映
HBコア関連抗原	
核酸アナログ非使用時	HBV量を反映
核酸アナログ使用時	肝細胞中HBV cccDNA量を反映
HBV遺伝子型	感染経路や予後を推定
HBV遺伝子変異	病態や予後を推定

IgM-HBc抗体の測定が役立つ．すなわち，急性肝炎では抗体が高力価陽性（10.0 COI以上）となるのに対し，キャリアの急性増悪では陽性となっても低力価である．

3　HBVの活動性を示すマーカー

B型肝炎の診療では，HBVの活動性を測定するマーカーは欠くことができない．これは，キャリアの病期はHBVの活動性と肝炎の有無から判断されることや，抗ウイルス療法の効果判定にはこの測定が欠かせないからである．HBV活動性の指標としては，HBe抗原・抗体系が古くから用いられてきたが，最近はHBV DNA量がより重要視されるようになった．

3-1　HBe抗原・抗体

HBe抗原はHBV感染肝細胞から血中へ分泌されるたんぱく質で，ウイルス粒子とは別に存在する．HBVにとってのHBe抗原の役割は必ずしも明らかではないが，HBVの持続感染化と関連していると考えられている．

HBe抗原は臨床的にHBV増殖を反映するマーカーとして用いられており，陽性者ではHBVの増殖は盛んである（表2）．免疫寛容期では，基本的にHBe抗原陽性でウイルス量は多い．免疫排除期において，HBe抗原からHBe抗体にセロコンバージョンするとウイルス量は低下し肝炎が沈静化する．このため，HBe抗原のセロコンバージョンはB型肝炎の経過の中で大きな意味を持つ現象であり，重要な治療目標の一つである．しかし，HBe抗体陽性となってもウイルス量が十分低下しない症例や重症肝炎が惹起される症例もあり，セロコンバージョンだけでは不十分な場合もある．これがHBe抗原陰性の慢性肝炎であるが，HBe抗原陽性の慢性肝炎に比較し病変の進行が早いことがあり注意が必要な病態である．

3-2　血中HBV DNA量

血中HBV DNA量の測定は病態の把握や予後の予測に有用である．さらに，抗ウイルス療法の適応を決定したり治療効果を判定するのにも用いられる，最も重要なマーカーである．以前のHBV DNA量測定法は感度が低く，その有用性は限られていた．しかし，高感度で定量域の広い測定法の開発により，核酸アナログ治療にも対応する測定法となった．現在はTaqMan PCR法（2.1～9.0 log copy/ml）が，測定レンジがさらに広く感度も良いことから，臨床で広く使用されている．

HBV DNA量とその後の臨床経過には強い関連がある．すなわち，ウイルス量が多いほどその予後は悪く，肝硬変進展率や肝発癌率が高くなる[8,9]．逆に，HBV DNA量が4.0 log copy/ml未満になると肝炎は沈静化し肝発癌率も低下する．非専門医には定量値の意義を記憶することは苦痛と思われるので，図1にHBV

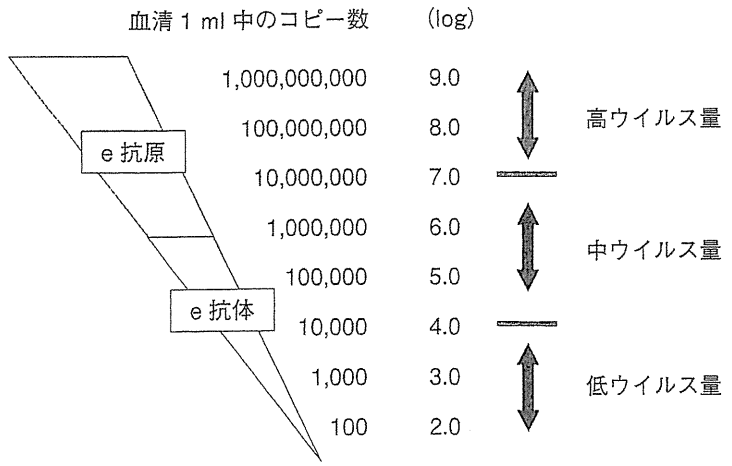

図 1　HBV DNA 量と HBe 抗原・抗体

DNA 量のイメージ図を示した．7.0 log copy/ml 以上は高ウイルス量で，抗ウイルス療法にも抵抗することが多い．4.0～7.0 log copy/ml は中ウイルス量であり，4.0 log copy/ml 未満が低ウイルス量となる．治療目標は低ウイルス量で安定させることである．市民講座などでは「イー，スー，チー」で覚えるように話している．

4　核酸アナログ薬治療と HBV マーカー

2000 年に核酸アナログ薬が導入され，B 型肝炎の治療は大きく進歩した．核酸アナログ薬は HBV に対して強い抗ウイルス効果を有し，免疫能が低下した透析患者でも HBV の増殖を強力に抑制する．核酸アナログ薬の治療効果は血中 HBV DNA 量を測定して判定する．すなわち，核酸アナログ薬投与開始後速やかに HBV DNA 量は低下し，多くの症例では陰性化する．また，耐性株出現時には最初に HBV DNA 量の増加がみられる．

核酸アナログ薬治療の問題点は，抗ウイルス効果が強力であっても最終的に HBV を完全に駆除することは困難であり，この結果として耐性株の出現や治療中止後の肝炎の再燃が起こることである．この問題を理解するために，HBV の複製過程と HBV cccDNA について，さらにこの cccDNA 量を反映するコア関連抗原量について説明する．

4-1　HBV の複製と肝細胞中 cccDNA

HBV の複製過程を図 2 に示した．HBV は肝細胞に感染後，不完全 2 重鎖の DNA 遺伝子が閉環し cccDNA (covalently closed circular DNA) となる．この cccDNA

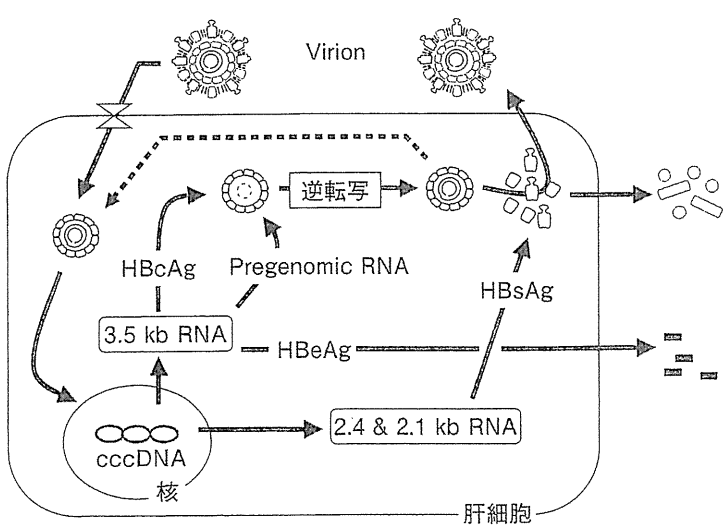

図 2　HBV 複製過程と逆転写

が核内に蓄積され，ここからpregenome RNAやmRNAが作られウイルスが複製される[10~12]．

HBV cccDNAはHBVの複製の起点であり，この存在が耐性株出現や治療中止後の肝炎の再燃と深くかかわっている．また，ミニ染色体とも言える安定した構造であり，長期に肝細胞中に残存することから，この存在がHBVの駆除を困難にしている．肝細胞中のcccDNA量を直接測定することは技術的に可能であるが，肝生検を要するため実際的ではない．このため，cccDNA量を反映する血清マーカーとしてHBコア関連抗原測定系が開発された．

4-2 血中HBコア関連抗原量

HBコア関連抗原測定系は，HBVのプレコア・コア遺伝子から転写・翻訳されるすべての抗原（c抗原，e抗原，等）をリニアエピトープとして同時に測定する方法である[13,14]．自然経過では，血中のコア関連抗原量とHBV DNA量は直線的に相関するので，ウイルス量の判定に使用可能である．これに対し，核酸アナログ投与下ではHBV DNA量と異なった動きを示す．すなわち，核酸アナログ投与開始後HBV DNA量は速やかに低下するのに対し，HBコア関連抗原量は緩徐に低下する．このHBコア関連抗原量の低下は肝細胞中のHBV cccDNA量の低下と相関し，核酸アナログ薬投与下において，HBコア関連抗原量はHBV cccDNA量と有意に相関する[15,16]．

HBVコア関連抗原量の特性を，HBV複製過程との関連で説明すると以下のようになる．HBVの複製で逆転写の過程が阻害されると血中へウイルス粒子が分泌されず，血中HBV DNA量は低下する．これに対し，HBコア関連抗原は，cccDNAから転写されるmRNAから直接翻訳されるので核酸アナログ薬の影響は受けにくい．この差が核酸アナログ薬投与下でのHBV DNA量とコア関連抗原量の推移の差に出ると考えられる．HBコア関連抗原量測定の有用性に関してはこれまで以下のものが報告されている[16~20]．HBコア関連抗原が低い症例では高い症例に比較して，①耐性株出現率が低い，②中止後の肝炎の再燃が弱い，③組織学的に進行しにくい，④肝発癌率が低いなどである．

5 その他のマーカー

5-1 HBs抗体

HBs抗原に対する抗体であり，中和抗体としてHBVに対する感染防御機能をもつ．HBs抗体が陽性であることは過去にHBV感染を受けたこと，またはHBワクチン接種を受けたことを示す（表2）．時にはHBIG投与後，輸血・血液製剤使用後などにもこの抗体が陽性となる．HBs抗体は定量的に測定することが可能であり，WHOの勧告ではHBs抗体価が10 mIU/ml未満になった時，追加のワクチン接種が推奨されている．

5-2 HBc抗体

これはHBc抗原に対する抗体であり，感染の比較的早期から血中に出現し，長年月持続する．HBV感染者を既往者も含めて最も広く拾い出す検査である（表2）．

既往感染者は低抗体価で，通常HBs抗体も同時に陽性である．HBVキャリアでは通常高抗体価であるが，肝炎を経験していない症例では低抗体価陽性または陰性である．従来より，HBc抗体を低抗体価と高抗体価に分けることによりHBV感染状態の把握を行ってきた．しかし，その後の研究や測定系の進歩により，この分類の意義は失われている．具体的には，HBV感染の判定にはHBs抗原の精密測定が，また急性肝炎かキャリアの急性増悪かの鑑別には後述のIgM-HBc抗体の測定が優れている．臨床的には，HBc抗体は定性レベルで陽性か陰性かの判定が重要である．すなわち，HBs抗原陰性でHBc抗体陽性の場合は，HBs抗体の有無にかかわらずHBVの既往感染であることを示す．

5-3 HBV遺伝子型

HBVの遺伝子型はA～Hの8型に分類されている．日本では遺伝子型BとCがほとんどで，前者は後者に比較し自然経過での予後は良く，抗ウイルス治療に対する反応性も良い．また，近年海外から持ち込まれた遺伝子型Aでは，成人の初感染でもキャリア化しやすいことが知られている．

5-4 プレコア変異，コアプロモーター変異

HBe抗原の合成が停止または減少するプレコアと，コアプロモーターの変異が測定可能である．これらの変異は，HBe抗原のセロコンバージョン予測や，急性増悪時の重症化予測などに有用である．

6 B型肝炎の再活性化

B型肝炎の再活性化は，HBVの増殖が十分抑制された状態から，なんらかの原因でHBVの増殖が再び活発になり肝炎が再燃することである[21~23]．原因の多くは強力な化学療法や免疫抑制療法によるものであるが，自然経過でも起こる．当然，腎移植でも再活性化は大きな問題であり，移植予定の患者はHBs抗原，HBs抗体，HBc抗体の測定を行いHBVの感染状況を確認する必要がある．さらに，HBs抗原陽性のキャリアが腎移植を受ける場合はHBVの再活性化は必須であり，核酸アナログ薬による予防を行う．

以前，HBV既往感染者（HBs抗原陰性でHBs抗体and/or HBc抗体陽性）ではHBVは完全に排除されたと考えられていたが，その後の研究で，ウイルス遺伝子がcccDNAの形で肝細胞核内に残存していることが明らかになった．通常，免疫監視によりHBVの増殖は起こらないが，免疫抑制下ではこのcccDNAを起点としてHBVの増殖が起こり，肝炎が再活性化する．この肝炎をde novo B型肝炎と呼んでいる．

腎移植では，ドナーがHBV既往感染の場合はde novo B型肝炎の危険性は低い．これに対し，レシピエントが既往感染の場合は再活性化に対する注意が必要である．この場合，核酸アナログ薬の予防投与は保険適用ではないので，現状では定期的な検査（HBV DNA，HBs抗原）でHBV再活性化の早期発見につとめることが推奨される．

医療の進歩に伴い化学療法や免疫抑制療法を行う機会が増え，さらに使用される薬物もより強力なものとなった．この結果，再活性化によるB型肝炎は増える傾向にある．再活性化による肝炎は劇症化率，死亡率は共に高く，重篤な病態を呈する．さらに，透析を含む多くの診療科が関係するため，近年注目されている病態である[24]．

おわりに

以上，B型肝炎ウイルスマーカーの意義を透析患者の診療を中心に述べた．ある意味で専門的な領域であり，透析医がすべてを理解する必要はない．しかし，透析患者でのHBV感染の危険性を考えると，基礎的な知識として知っておく意義は大きいと考える．

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Hepatology Research 2010; **40**: 1–7 doi: 10.1111/j.1872-034X.2009.00633.x

Review Article

Guidelines for the treatment of chronic hepatitis and cirrhosis due to hepatitis B virus infection for the fiscal year 2008 in Japan

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In the 2008 guidelines for the treatment of patients with cirrhosis, who are infected with hepatitis B virus (HBV), the main goal is to normalize levels of alanine and aspartate aminotransferases by eliminating HBV or reducing viral loads. In patients with compensated cirrhosis, the clearance of HBV from serum is aimed for by entecavir, as the main resort, for histological improvement toward the prevention of hepatocellular carcinoma (HCC). In patients with decompensated cirrhosis, by contrast, meticulous therapeutic strategies are adopted for the reversal to compensation, toward the eventual goal of decreasing the risk of HCC. For maintaining liver function and preventing HCC, branched chain amino acids and nutrient supplements are applied, in addition to conventional liver supportive therapies. For patients with chronic hepatitis B, separate guidelines are applied to those younger than 35 years and those aged 35 years or older. Even for patients with chronic hepatitis who are negative for hepatitis e antigen (HBeAg), but who harbor HBV DNA in titers of 7 log copies/mL or more, a "drug-free state" is aimed for by sequential treatment with interferon (IFN) plus entecavir as the first line. For patients with chronic hepatitis B aged 35 years or older, who are HBeAg-negative and carry HBV DNA in titers of less than 7 log copies/mL, long-term IFN for 24–48 weeks is adopted anew. To HBeAg-negative patients who have either or both platelet counts of less than $150 \times 10^3/mm^3$ and less than 7 log copies of HBV DNA, also, long-term IFN for 24–48 weeks is indicated.

Key words: chronic hepatitis, cirrhosis, hepatitis B virus, hepatocellular carcinoma, interferon, liver supportive therapies, nucleos(t)ide analogs

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Received 26 October 2009; revision 4 November 2009; accepted 11 November 2009.

INTRODUCTION

SINCE THE FISCAL year 2002, guidelines for the treatment of patients with viral hepatitis have been compiled annually by the Study Group for the Standardization of Treatment of Viral Hepatitis Including Cirrhosis, under the auspice of the Ministry of Health, Labor and Welfare of Japan, supported by enduring efforts of many specialists recruited from all over the nation. Guidelines have been improved every year with many supplementary issues, which had surfaced as our understanding of many facets of viral hepatitis deepened and treatment options widened increasingly with time. For the fiscal year 2008, guidelines have been worked out for a comprehensive standardization of the treatment of chronic hepatitis and cirrhosis due to hepatitis B virus (HBV) and hepatitis C virus (HCV) infections in Japan. These guidelines have been observed by more than 70% of practicing hepatologists treating patients with viral liver disease in Japan. It is hoped that these guidelines will continue being widely accepted and implemented to help as many patients as possible who are suffering from sequelae of persistent hepatitis virus infections.

Here, we relate excerpts of the 2008 guidelines for the treatment of patients with liver disease due to HBV, covering a wide range from those with chronic hepatitis to those with decompensated cirrhosis. The 2008 guidelines for the treatment of liver disease due to HCV are reported in an accompanying paper.

GUIDELINES FOR THE TREATMENT OF PATIENTS WITH CHRONIC HEPATITIS B

PATIENTS WITH CHRONIC hepatitis B can stabilize the activity of liver disease in their natural course, after they have seroconverted from hepatitis B e antigen (HBeAg) to the corresponding antibody (anti-HBe), accompanied by decrease in HBV DNA titers. For that reason, treatment guidelines were constructed separately for the patients younger than 35 years and those aged 35 years or older.

GUIDELINES FOR THE TREATMENT OF PATIENTS WITH CHRONIC HEPATITIS B YOUNGER THAN 35 YEARS

PATIENTS WITH CHRONIC hepatitis B younger than 35 years are treated in accordance with the guidelines summarized in Table 1. Criteria for the treatment eligibility are: (i) serum levels of alanine aminotransferase (ALT) of 31 IU/L or more; and (ii) HBV DNA titers of 5 log copies of more in HBeAg-positive patients and 4 log copies or more in HBeAg-negative patients. In the 2008 guidelines, the indication of treatment is extended to the patients with cirrhosis due to HBV who carry HBV DNA in titers of 3 log copies/mL or more.

In Japan, most HBeAg-positive patients with 7 log copies or more of HBV DNA have been infected with HBV of genotype C by perinatal infection at birth;

Table 1 Guidelines for the treatment of patients with chronic hepatitis B younger than 35 years

Eligibility criteria	ALT	≥31 IU/L
	HBV DNA	HBeAg-positive patients: ≥5 log copies/mL HBeAg-negative patients: ≥4 log copies/mL Patients with cirrhosis: ≥3 log copies/mL
HBV DNA	≥7 log copies/mL	<7 log copies/mL
HBeAg-positive	(1) Long-term IFN for 24–48 weeks (2) Entecavir	(1) Long-term IFN for 24–48 weeks (2) Entecavir
HBeAg-negative	(1) Sequential treatment† (entecavir plus IFN) (2) Entecavir	(1) Regular follow up (2) Long-term IFN for 24 weeks
	Start with entecavir in HBeAg-negative patients who have platelet counts $<15 \times 10^3/mm^3$ and in those with advanced liver disease of stage F2 or higher.	

†Sequential treatment: patients who have lost hepatitis B virus (HBV) DNA after treatment with nucleos(t)ide analogs receive combined interferon (IFN) for 4 weeks, and then IFN monotherapy is continued for 20 weeks, and lifted thereafter. ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen.

Table 2 Guidelines for the treatment of patients with chronic hepatitis B aged 35 years or older

Eligibility criteria	ALT	≥31 IU/L
	HBV DNA	HBeAg-positive patients: ≥5 log copies/mL HBeAg-negative patients: ≥4 log copies/mL Patients with cirrhosis: ≥3 log copies/mL
HBV DNA	≥7 log copies/mL	<7 log copies/mL
HBeAg-positive	(1) Entecavir (2) Sequential treatment† (entecavir plus IFN)	(1) Entecavir (2) Long-term IFN for 24–48 weeks
HBeAg-negative	Entecavir	(1) Entecavir (2) Long-term IFN for 24–48 weeks

†Sequential treatment: patients who have lost hepatitis B virus (HBV) DNA after treatment with nucleot(s)ide analog receive combined interferon (IFN) for 4 weeks, and then IFN monotherapy is continued for 20 weeks, and lifted thereafter. ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen.

accordingly, they would be resistant to interferon (IFN) therapy. Should they receive nucleos(t)ide analogs, however, the duration would become inevitably longer, because they start the treatment when younger than 35 years old. Hence, IFN for 24–48 weeks is the first choice in their treatment. The standard treatment of 3 months is favored, which can be extended to the maximum of 6 months. Non-pegylated (standard) IFN-α is recommended to them, because self-injection at home is approved for preparations of IFN-α; it helps improve their quality of life (QOL). There are many patients who are refractory to IFN and in whom improvement of ALT levels and/or decrease in HBV DNA titers are hardly achievable. Therefore, as another option, monotherapy with entecavir can be applied for the purpose of clearing HBeAg from serum and lowering HBV DNA titers. For HBeAg-positive patients with lower HBV DNA titers (<7 log copies/mL), also, long-term IFN is endorsed as a rule.

There are HBeAg-negative patients in whom ALT levels increase to 31 IU/mL or more repeatedly. In the 2008 guidelines, sequential treatment with IFN and entecavir is introduced as a new arm of therapeutic options for such patients.[1]

For HBeAg-negative patients with less than 7 copies/mL of HBV DNA, in general, regular follow up without therapeutic intervention is deemed to suffice for the majority. For those of them in whom ALT levels flare to 31 IU/mL or more time after time, long-term IFN for 24 weeks is indicated. Because liver disease progresses in many HBeAg-negative patients, for those with platelet counts of less than $150 \times 10^3/mm^3$ or in fibrosis stage F2 or higher, treatment with entecavir is indicated.

GUIDELINES FOR THE TREATMENT OF PATIENTS WITH CHRONIC HEPATITIS B AGED 35 YEARS OR OLDER

TABLE 2 SUMS up treatment modalities for patients with chronic hepatitis B who are aged 35 years or older. HBeAg-positive patients in this age range who carry HBV DNA in titers of 7 log copies/mL or more rarely, if ever, seroconvert to the loss of HBeAg by IFN-based therapies. Hence, entecavir is the first choice in their treatment.[2,3] Because HBV mutants resistant to entecavir can be elicited by it, sequential treatment with IFN plus entecavir is amended in the 2008 guidelines.[1] In view of low viral loads in patients who possess HBV DNA in titers of less than 7 log copies/mL, entecavir is selected as the first choice, followed by long-term IFN as the second choice of treatment in these patients. HBeAg-negative patients who have high viral loads (≥7 log copies/mL), on the other hand, can normalize ALT levels by monotherapy with entecavir. Therefore, entecavir becomes their first choice, and this is the case even in patients with HBV DNA titers less than 7 copies/mL.

GUIDELINES FOR THE TREATMENT WITH NUCLEOS(T)IDE ANALOGS OF PATIENTS WITH CHRONIC HEPATITIS B WHO ARE RECEIVING LAMIVUDINE

TABLE 3 DETAILS guidelines for the treatment with nucleos(t)ide analogs of patients with chronic hepatitis B who are receiving lamivudine. Because a number of drug-resistant HBV mutants emerge increasingly with time in patients on long-term treatment with lamivudine, the fundamental rule is to switch them to ente-

Table 3 Guidelines for the treatment with nucleos(t)ide analogs in patients with chronic hepatitis who are receiving lamivudine

Lamivudine	Less than 3 years		3 years or longer
HBV DNA			
<1.8 log copies/mL persistently	May be switched to entecavir 0.5 mg daily		Continued on lamivudine 100 mg daily
≥1.8 log copies/mL	VBT (−)	May be switched to entecavir 0.5 mg daily	
	VBT (+)	Adefovir 10 mg daily add-on lamivudine	Adefovir 10 mg daily add-on lamivudine

HBV, hepatitis B virus; VBT, virological breakthrough.

cavir. For this reason, patients are stratified by the duration of lamivudine treatment, less than 3 years and 3 years or more, as well as HBV DNA titers persistently below 1.8 log copies/mL and 1.8 log copies/mL or more, and separate treatment strategies have been worked out for the patients in each category. Because by far the majority of patients with a duration of lamivudine treatment of less than 3 years and HBV DNA titers of less than 1.8 copies/mL possess drug-resistant mutants in low frequencies, they are recommended to switch to entecavir 0.5 mg daily as soon as possible. Likewise, patients who have received lamivudine for 3 years or longer, but in whom drug-resistant mutants have never developed, are recommended to switch to entecavir 0.5 mg daily. By contrast, for patients in whom drug-resistant mutants have emerged already and who have undergone virological breakthroughs,[4] adefovir 10 mg daily add-on lamivudine is started for the purpose of stabilizing liver function.[5] In regard of the patients who have received lamivudine for 3 years or longer, those without drug-resistant mutants can stay on lamivudine 100 mg daily.

SUPPLEMENTS TO GUIDELINES FOR THE TREATMENT OF CHRONIC HEPATITIS B (PART I)

FOR THE FISCAL year 2008, the following three items have been added to previous guidelines for the treatment of chronic hepatitis B (Table 4).

1 In the treatment of patients with chronic hepatitis B, IFN is the first resort for those younger than 35 years, toward the eventual goal of gaining a "drug-free state". For the patients aged 35 years or older, persistently negative HBV DNA is the aim of nucleos(t)ide analogs, with the first choice being entecavir in their primary treatment. On the other hand, for patients with HBV mutants resistant to lamivudine and/or entecavir, combined treatment with adefovir and lamivudine is the principal rule (Table 3).[6–8]
2 Therapeutic responses to antiviral treatment are much different in patients with chronic hepatitis B who are infected with HBV of distinct genotypes. It is recommended therefore to determine HBV genotypes before making a decision on the treatment choice. In particular, the patients infected with HBV of genotype A or B respond to IFN in high rates, even if they are aged 35 years or older. For these reasons, IFN becomes the first choice in their antiviral treatment.
3 The duration of IFN treatment is 24 weeks basically. In the patients in whom the efficacy of IFN has been achieved with decrease in HBV DNA titers and normalization of ALT, the treatment duration is better extended to 48 weeks.

Table 4 Supplements to guidelines for the treatment of patients with chronic hepatitis B (part I)

1 Treatment of patients with chronic hepatitis B aims at a "drug-free state" by IFN-based therapies in those younger than 35 years, and at persistently negative HBV DNA in those aged 35 years or older, with entecavir as the first choice in the primary therapy. Lamivudine plus adefovir forms the basis for the treatment of HBV mutants resistant to lamivudine or entecavir.
2 In view of antiviral response much different in patients infected with HBV of distinct genotypes, it is desired to make treatment choices based on genotypes. In particular, because genotypes A and B respond to IFN with high efficacy, even in patients aged 35 years or older, IFN is recommended as the first treatment choice in these patients.
3 The duration of IFN is for 24 weeks basically, but extension to 48 weeks is recommended in patients who respond to IFN with decrease in HBV DNA titers and normalization of ALT levels.

ALT, alanine aminotransferase; HBV, hepatitis B virus; IFN, interferon.

Table 5 Supplements to guidelines for the treatment of patients with chronic hepatitis B (part II)

- Self-injection of IFN at home is recommended to patients, who are eligible to do it, for improving their quality of life.
- Treatment with nucleos(t)ide analogs should be continued in patients in whom cirrhosis or HCC has been cured.
- Antiviral treatment is considered in patients with ALT levels of ≥31 IU/L. To patients aged 35 years or older in whom viral replication persists, even to those with normal ALT levels, antiviral treatments are indicated. It is possible, however, to follow for outcomes in patients who are elderly or HBeAg-negative and in whom antiviral treatments are difficult, while they receive liver supportive therapy (e.g. SNMC, UDCA).
- In patients co-infected with HBV and HIV, entecavir cannot be used due to the possibility for emergence of HIV variants resistant to antiretroviral therapies.
- Immunosuppressive and anticancer drugs should be used with utmost caution, even in patients with low HBV DNA titers and normal ALT levels, because they can induce severe liver damage along with elevation in HBV DNA titers.

ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; IFN, interferon; SNMC, stronger neo-minophagen C; UDCA, ursodeoxycholic acid.

SUPPLEMENTS TO GUIDELINES FOR THE TREATMENT OF CHRONIC HEPATITIS B (PART II)

FURTHER, THE FOLLOWING five supplements have been added to the 2008 guidelines (Table 5).

To patients who are eligible, self-injection of IFN at home is recommended, taking into consideration their QOL. Because IFN-based therapies are not recommended for patients in whom HBV has been transmitted by perinatal infection, sequential treatment with IFN plus entecavir serves as another option in their antiviral treatment.

Treatment with nucleos(t)ide analogs should be extended to patients in whom cirrhosis or hepatocellular carcinoma (HCC) has been cured after successful therapies.

Antiviral treatment has to be considered in patients with ALT levels of 31 IU/L or more. Patients aged 35 years or older with normal ALT levels but in whom HBV replication persists, need to be considered for antiviral treatments. Elderly and HBeAg-negative patients, as well as those to whom the administration of antiviral drugs is difficult, can be followed regularly while they receive liver supportive therapy (e.g. stronger neo-minophagen C,[9] ursodeoxycholic acid [UDCA][10]).

Patients co-infected with HBV and HIV type 1 cannot receive entecavir due to the possibility of emergence of HIV mutants resistant to antiretroviral drugs.

Even in patients with low HBV DNA titers and normal ALT levels, HBV DNA loads can increase massively to induce severe liver damages in them, while they receive immunosuppressive or anticancer drugs. Hence, utmost caution should be exercised if they are to undergo antiviral treatments.

GUIDELINES FOR THE TREATMENT OF PATIENTS WITH CIRRHOSIS DUE TO HBV

TABLE 6 SUMMARIZES guidelines for the treatment of patients with type B cirrhosis. Patients with compensated or decompensated cirrhosis, who are infected with HBV, receive entecavir for persistent clearance of HBV DNA detectable by the real-time polymerase chain reaction and normalization of aspartate aminotransferase as well as ALT levels. Combined lamivudine plus adefovir therapy are indicated for patients in whom HBV mutants resistant to lamivudine or entecavir have developed. Guidelines for maintaining liver function, for preventing the development of HCC, include liver supportive therapy with glycyrrhizin and UDCA, either alone or in combination. For treatment toward sup-

Table 6 Guidelines for treatment of type B cirrhosis

Principles
- Compensated: termination of HBV infection by antiviral treatment with entecavir as the mainstay.
- Decompensated: reversal to compensation and prevention of HCC.

Methods
1. Eradication of HBV and normalization of ALT/AST (compensated and decompensated cirrhosis).
   a) Entecavir.
   b) Combined lamivudine and adefovir (for patients with HBV mutants resistant to lamivudine or entecavir).
2. Maintenance of liver function (improvement of ALT/AST and albumin) for preventing HCC.
   a) Liver supportive therapy such as SNMC or UDCA.
   b) Branched chain amino acids (Livact).
3. Supplementation with nutrients (for stabilizing liver function in decompensated cirrhosis).

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; SNMC, stronger neo-minophagen C; UDCA, ursodeoxycholic acid.