索引用語：C型慢性肝炎，リバビリン併用療法，
NS3-4Aプロテアーゼ阻害剤

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英文要旨

The efficacy of virological response in treatment-naïve patients with chronic hepatitis C treated by NS3-4A protease inhibitor (telaprevir), pegylated interferon and ribavirin for 12 weeks

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We investigated the efficacy of the triple treatment with telaprevir, pegylated interferon (PEG-IFN) and ribavirin for 12 weeks in treatment-naïve patients infected with hepatitis C virus (HCV) genotype 1b and high baseline viral loads. All of 10 cases became HCV-RNA negative during treatment. SVR rate attained to a high rate, 70% (7/10). Especially, SVR rate of females over 50 years old attained 100% (3/3). HCV RNA was lost from serum rapidly in patients infected with HCV-1b in high viral loads, and SVR rate of the triple treatment for 12weeks was high. Our results suggested that triple treatment with telaprevir, PEG-IFN and ribavirin could improve the efficacy in treatment-naïve patients.

Key words: chronic hepatitis C,
interferon plus ribavirin
combination therapy,
NS3-4A protease inhibitor

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＜短　報＞

核酸アナログ未使用のB型慢性肝炎症例へのエンテカビル治療中にrtA181T変異ウイルスが増殖した1症例

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緒言：核酸アナログ未使用のB型慢性肝炎患者へのエンテカビル治療中に，既報のエンテカビル耐性ウイルスが出現していないにもかかわらず，viral reboundを生じた症例を経験したため，報告する．

症例：51歳女性．1978年にB型慢性肝炎と診断され，2008年6月よりエンテカビル（0.5 mg/日）治療を開始した．治療開始時HBV-DNA 7.2 log copies/ml，HBeAg陽性，genotype Cであった．2009年2月HBV-DNA 2.5 log copies/mlまで下がるも，その後2009年4月HBV-DNA 6.0 log copies/ml，8月8.2 log copies/mlとviral reboundが出現し，トランスアミナーゼの上昇も認めた（Fig. 1）．

治療開始時および治療中のHBV-DNA polymerase RT領域のアミノ酸配列の比較検討：患者血清から抽出されたHBV-DNAはPCR法にて増幅したのち，direct sequence法にて塩基配列を決定した．クローニング解析もあわせて行った．ダイレクトシークエンスでは核酸アナログ未使用であるにもかかわらず，エンテカビル開始時にrtA181T変異のわずかな混在を認め，クローニング解析では8.5%（3/35クローン）にrtA181T変異を確認した．また治療開始後15カ月ではダイレクトシークエンスにてrtA181T変異の混在の割合が増加しており，クローニング解析にてrtA181T変異は39.5%（17/43クローン）に増加していた．尚，エンテカビル開始時および治療中にrtA181以外の既報のエンテカビル耐性に関与するアミノ酸（rtL180，T184，S202，M204，M250）に変異は認められなかった（Fig. 1）．

考察：今回我々は，エンテカビル投与にてrtA181T変異が増殖した症例を経験した．本症例はエンテカビル投与中にviral reboundを生じ，その際既報のエンテカビル耐性ウイルスは出現せず，治療開始時よりわずかに認められていたrtA181T変異ウイルスが増殖していた．クローニング解析にてrtA181T変異ウイルスは治療開始時8.5%から治療開始15カ月後に39.5%に増加し，他に有意なアミノ酸変異を認めないことから，rtA181T変異がエンテカビル耐性に関与している可能性が考えられた．しかし本症例で出現したrtA181T変異ウイルスのエンテカビル耐性への関与を証明するためには，今後本症例の血清を使用したin vitroの実験にて評価する必要があると考える．また本症例ではviral reboundと同時にトランスアミナーゼ上昇も認めたが，軽度上昇にとどまっているため，現在もエンテカビル治療を継続し厳重にフォローしている．

本症例は，核酸アナログ未使用のB型慢性肝炎症例であったにもかかわらず，エンテカビル治療開始前よりrtA181T変異が存在していた．核酸アナログ未使用症例にラミブジン耐性に関与するrtL180M，rtM204V変異が存在するという報告はあるが，本症例のようにrtA181T変異が核酸アナログ使用前に存在したという報告は過去になく，初めての報告である．

rtA181T変異は以前よりアデホビル耐性に関与するアミノ酸変異として知られていたが，最近ではラミブジンとアデホビルの交差耐性のある変異であることがわかっている[1]．このためrtA181T変異に対してエンテカビルの効果が期待されている．しかし海外からは，ラミブジン耐性ウイルスに対するアデホビル単独治療

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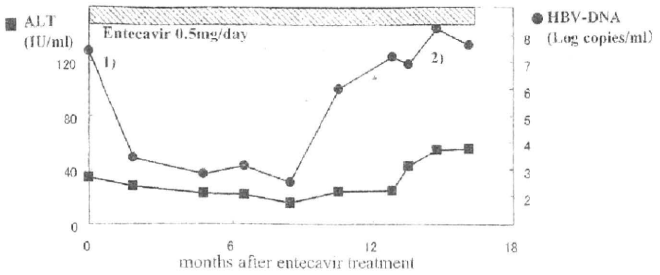

	rtI81	rt184	rt202	rt204	rt250	No. of clones (Relative rate (%) of clones)
Amino acid(AB033550)	MGVGLSPFLLAQFTSAI		AFSYMDDL		NFMG	
1) At the beginning of ETV						
a) wild						32 (91.5%)
b) mutant	----------T------					3 (8.5%)
2) 15 months after ETV						
a) wild						26 (60.5%)
b) mutant	----------T------					17 (39.5%)

Fig. 1　Clinical course and clonal analysis of samples from patient with viral rebound during entecavir therapy

中に耐性ウイルス(rtA181T/VまたはN236T変異ウイルス)が出現した症例は，ラミブジン耐性ウイルスのみの症例に比べ，エンテカビル治療におけるウイルス抑制効果が低いという報告があり[2]，また本症例のようにエンテカビル治療にてrtA181T変異ウイルスが増加する症例も存在することから，今後rtA181T変異ウイルスに対する治療として，エンテカビル以外の核酸アナログ（テノフォビル，その他新規薬剤等）の有効性も検討していく必要があると考えられる．

索引用語：エンテカビル，耐性ウイルス，rtA181T

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英文要旨

Increase of rtA181T mutant strains during entecavir therapy for a patient with chronic hepatitis B virus infection

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A 51-year-old Japanese woman with chronic hepatitis B who had never treated with nucleotide analogues was admitted to our hospital and treated with entecavir. In this patient, entecavir successfully reduced the HBV level, but viral and biochemical breakthrough was observed at 10 months after the beginning of therapy. The HBV viral load reached up to 8.2 log copies/ml, but direct sequence analysis showed no LAM and ETV resistant-related mutation (rtT184, S202, M204, M250). Comparison by clonal analysis of samples obtained before and after the viral breakthrough showed the increase of the rtA181T mutant strains (8.5% versus 39.5%). It was considered that the rtA181T mutant

strain in this case might be related to entecavir resistance.

Key words: entecavir, drug-resistant mutant, rtA181T

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＜速　報＞

IL28B と HCV Core aa70 置換との関連

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はじめに：C型慢性肝炎の治療法であるPEG-IFN/Rivabirin併用療法のHCV genotype 1bで高ウイルス量症例では，その排除率が50%台である．この難治症例の治療効果予測因子としてHepatitis C virus NS5A領域のInterferon sensitivity-determining regionやCore領域の70番目，91番目のアミノ酸置換が有用であることは周知のごとくであったが，近年アメリカ・日本から宿主側因子として*IL28B*のSNPsがPEG-IFN/Rivabirin併用療法の治療効果予測として有用であると報告[1~5]されている．今回我々は，C型慢性肝疾患患者のHCV Core aa70と*IL28B*を測定し性差との関連性を検討した．

対象と方法：1997年から2005年までに虎の門病院倫理委員会及びヒトゲノム委員会で承認された同意書を得た患者291人のchromosome 19上の*IL28B*近傍の2つのSNPs（rs8099917（T/G），rs12979860（C/T））とHCV Core領域aa70を測定したHCV genotype 1bとした．内訳は，男性177人（年齢：21-82（中央値56歳），女性114人（年齢：37-82（中央値61）歳）であった．

*IL28B*のSNPs（rs8099917，rs12979860）のタイピングはInvador assay，Taqman assayまたはdirect sequencing法にて決定した．rs8099917は290例，rs12979860は289例のタイピング可能であった．HCV Core領域aa70の測定は，PCR-direct sequence法にて測定した．性別とSNPの遺伝子型を検討した．

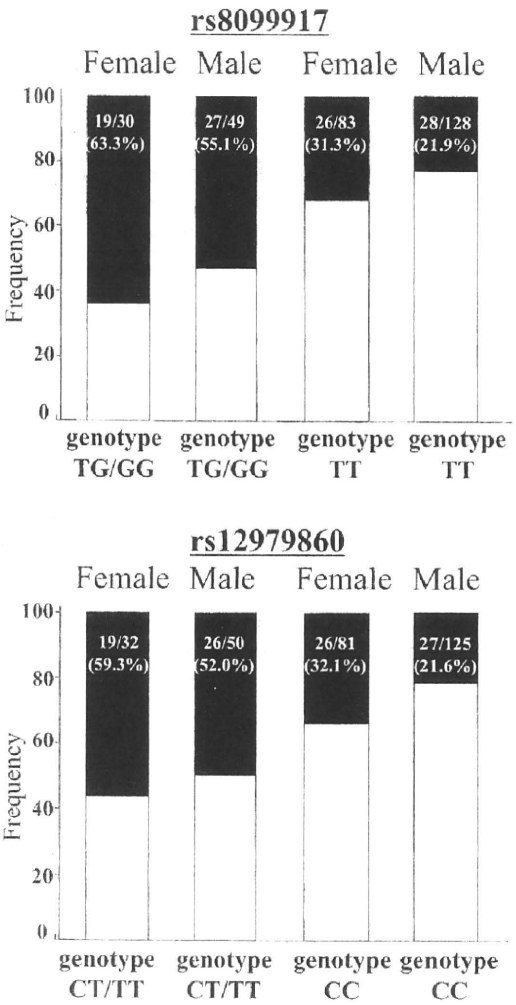

Fig. 1　Relationship between *IL28B* SNPs and amino acid substitution in hepatitis C virus core region in patients with chronic hepatitis C. Black bars represent aa70 mutant (Gln) while white bars represent aa70 wild (Arg)

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結果：Core aa70 置換からみた *IL28B* の SNP と性差の頻度

rs8099917 に関しては，Core aa70 の Mutant(Gln)がもっとも高頻度にみられたのは genotype TG/GG の女性で 19/30 例(63.3%)，次いで男性の genotype TG/GG で 27/49 例（55.1%），女性の genotype TT で 26/83 例(31.3%)であり，最も低率であったのが男性の genotype TT で 28/128 例（21.9%）であった（Fig. 1）．

rs12979860 においても同様の傾向を認め，女性の genotype CT/TT で 19/32 例（59.3%），男性の genotype CT/TT で 26/50 例(52.0%)であり，女性の genotype CC で 26/81 例(32.1%)，男性の genotype CC で 27/125 例（21.6%）であった（Fig. 1）．

考案：近年，*IL28B* 領域の SNPs が C 型肝炎ウイルスの自然排除[1]および慢性肝炎の PEG-IFN/Ribavirin 併用療法の治療効果と関連があることが報告された[1~3]．我々は，ウイルス側の予測因子である Core aa70 置換について性差を加味して SNP の遺伝子型別にその頻度を解析したところ 2 つの SNP で女性のマイナーアレルホモ接合体及びヘテロ接合体群において Core aa70 (Gln) Mutant の頻度がいずれも 50% 台であった．このことは，高齢の女性は PEG-IFN/Ribavirin 併用療法の治療効果が低い傾向を示すことなんらかの関連が推測され，女性において Core aa70 は，経過観察中にメジャークローンとマイナークローンが入れ代わる可能性が示唆された．今後，治療効果予測として宿主側因子の一つである *IL28B* の SNPs と Core aa70 置換の組み合わせにより，より有効な治療効果予測が可能になると思われた．

索引用語：C 型慢性肝疾患，*IL28B*，コア領域

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英文要旨

Relationship between SNPs in the *IL28B* region and amino acid substitutions in HCV core region in Japanese patients with chronic hepatitis C

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IL28 locus polymorphisms have been reported to affect PEG-IFN plus ribavirin combination therapy for patients with genotype 1b hepatitis C virus (HCV) infection. We examined a relationship between *IL28B* SNPs (rs8099917 and rs12979860) and amino acid substitutions in core region of HCV in patients with genotype 1b chronic hepatitis C. In each SNP, frequency of core aa 70 mutation was higher rate in female patients carrying minor allele than in male or female patients carrying no minor allele. Measurement of *IL28B* and Core aa70 before treatment is useful in PEG-IFN plus ribavirin therapy.

Key words: *IL28B*, HCV, core region

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分担研究報告書

c

C型慢性肝炎症例に対する再治療を含めた response guided therapyの有用性に関する臨床研究

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研究要旨：C型慢性肝炎に対する標準治療は、ペグインターフェロン・リバビリン併用療法である。難治例であるセロ１型高ウイルス量（5 log copies/ml以上）の症例では48週の併用治療において約40%が完全にHCVを排除(SVR)でき、またセロ２型では24週の併用治療にて80%の症例が治癒すると報告されている。より効率的な治療法として併用療法中のHCV陰性化時期を参考に治療期間を調整することが、推奨されている。そこで本臨床試験では、セロ１型高ウイルス量群の再治療症例について初回併用療法における抗ウイルス効果を参考に治療効果を評価した。その結果、前治療にて12週までにHCVが陰性化していた再燃症例では再治療にて67%の症例がSVRとなった。一方、前治療に一度もHCVが陰性化しなかった症例では、1例のみしかSVRとならなかった。HCVまたセロ２型症例について、治療開始４週目にウイルス陰性化した（RVR）症例を16週へ治療期間を短縮したが、全例SVRとなった。一方、非RVR症例を48週へ延長投与したが、24週間の標準治療と比較してSVR率の改善は得られなかった。

A．研究目的

現在のC型慢性肝炎に対する標準治療は、ペグインターフェロン・リバビリン併用療法である。難治例であるセロ１型高ウイルス量症例では48週の併用治療において約40%が完全にHCVを排除でき、またセロ２型では24週の併用治療にて80%の症例が治癒すると報告されている。より効率的な治療法として併用療法中のHCV陰性化時期を参考に治療期間を調整することが、推奨されている。そこで本臨床試験では、セロ１型高ウイルス量群の再治療症例について初回併用療法における抗ウイルス効果を参考に治療効果を評価した。またセロ２型症例については、治療開始４週目におけるウイルス陰性化の有無にて治療期間を短縮あるいは延長することによってより効率的な抗ウイルス効果を得ることが可能か否かを検討した。

B．研究方法

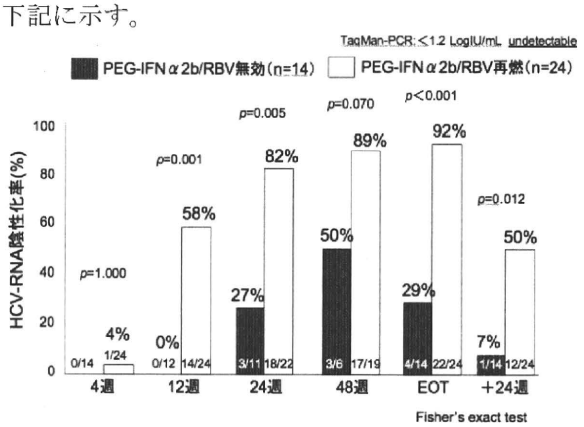
本臨床研究はふたつのデザインにて当院および関連施設にて実施した。

研究1.セロ１型高ウイルス量（5 log copies/ml以上）症例にて初回ペグインターフェロンα2b・リバビリン併用療法48週間にて治癒しなかった38例に対してペグインターフェロンα2a・リバビリン併用療法を実施した。治療期間は、48週以上として担当医の判断に委ねた。初回治療効果の内訳は、一度もHCV RNAが陰性化しなかた無効例14例と再燃例24例である。

研究2.セロ2型症例に対して治療開始４週目のHCV RNAの陰性化をリアルタイムPCR法にて判定し、陰性化したRVR症例を16週間の短縮治療とし、陰性化しなかった非RVR症例を48週間の延長治療とした。治療期間の調整に同意を得られなかった症例を24週間治療とした。

C．研究結果

研究1 再治療による抗ウイルス効果は、治療開始12週にてHCV RNA陰性化率64%,治療終了時陰性化率68%でありSVRは13例(34%)であった。SVRに寄与する因子を単変量解析すると初回治療時の抗ウイルス効果が再燃であることペグインターフェロンの投与率が多いことが有意であった。また治療前血小板数が多いこともSVRに関与する傾向があった。一方、年齢、性別、治療前HCV RNA量およびリバビリンの投与率等には有意差がなかった。そこで初回治療効果別の再治療時HCV RNA陰性化の推移を下記に示す。



上記をまとめると前治療にて12週までにHCVが陰性化した再燃症例では再治療にて67%の症例がSVRとなった。一方、前治療に一度もHCVが陰性化しなかった症例では、1例のみしかSVRとならなかった。

研究2 セロ2型102症例中、RVR症例は38例であった。この内短縮治療に同意した12例では16週間のペグインターフェロンα2b・リバビリン併用療法を実施した。12例全例がSVRとなった。一方、26例は24週間治療を行い25例がSVRとなった。次に、

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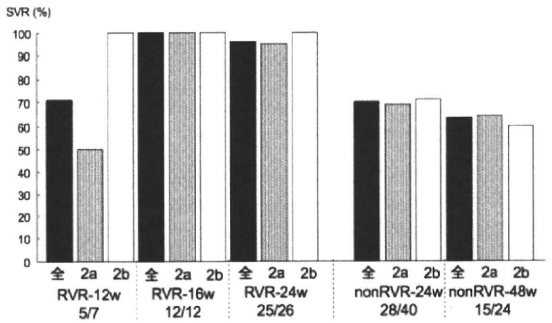
分担研究報告書

非RVR例64例では、40例が24週間治療を行い28例(70%)がSVRとなった。48週間へ延長した24例では、15例(62.5%)がSVRとなった。セロ2型症例をgenotype 2aと2bに分けた成績を下記に示す。



D．考察

我が国のC型慢性肝炎患者に対する抗ウイルス治療のガイドラインでは、セロ1型症例に対して治療中のHCV RNA陰性化時期に応じて治療期間を48週間から72週間へ延長することが推奨されている。このresponse guided therapyはセロ2型症例にも応用可能と考えられる。すなわち欧米での臨床試験では、治療効果良好なRVR症例に対する治療期間短縮に関して検討されている。今回、我々はより検査感度が良好なリアルタイムPCR法にてHCV RNA陰性化時期を判定することによりRVR症例での治療短縮にてSVR率の低下を認めなかった。一方、非RVR例では治療期間を延長してもSVR率は改善しなかった。今後セロ2型症例の中の難治例に対する治療法も検討すべきであると考えられた。前治療にて12週までにHCVが陰性化した再燃症例において再治療により高率にSVRとなっており、再治療を実施するに際しては前治療の抗ウイルス効果を評価する必要がある。

E．結論

セロ2型においてもペグインターフェロン・リバビリン併用療法中のHCV RNAの陰性化時期によって治療期間を調整することは、効率的な手法と考えられた。また再治療の選択は、前治療での治療効果を評価して決定すべきであると考えられた。

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H．知的財産権の出願・登録状況（予定を含む。）

特になし。

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Hepatology Research

Hepatology Research 2010; 40: 347–368 doi: 10.1111/j.1872-034X.2010.00642.x

Special Report

Management of hepatitis C; Report of the Consensus Meeting at the 45th Annual Meeting of the Japan Society of Hepatology (2009)

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The consensus meeting for the diagnosis, management and treatment for hepatitis C was held in 45th annual meeting for the Japan Society of Hepatology (JSH) in June 2009 where the recommendations and informative statements were discussed including organizers and presenters. The Several important informative statements and recommendations have been shown. This was the fourth JSH consensus meeting of hepatitis C, however, the recommendations have not been published in English previously. Thus, this is the first report of JSH consensus of hepatitis C. The rate of development of hepatocellular carcinoma (HCC) in HCV-infected patients in Japan is higher than in the USA, because the average age of the HCV-infected patients is greater and there are more patients with severe fibrosis of the liver than in the USA. In Japan, more than 60% of HCV-infected patients are genotype 1b infection, and they show lower response to perinterferon and ribavirin combination treatment. To improve the response rate is also an important issue in our country. To establish the original recommendations and informative statements to prevent the development of HCC is a very important issue in Japan.

Key words: chronic hepatitis C, peginterferon, ribavirin, fibrosis of the liver, hepatocellular carcinoma, HCV mutation

INTRODUCTION

HEPATITIS C VIRUS (HCV) infection is a major public health problem and a leading course of death from liver disease in Japan. Two million people are infected, and more than 30 000 patients die from hepatocellular carcinoma (HCC) and/or liver cirrhosis every year. HCC is the fourth leading cause of death from malignant neoplastic disease, and prevention of the development of HCC is an urgent issue in Japan. The purpose of this consensus is to provide clinicians with consensus-based approaches to diagnosis and treatment of HCV infection.

The consensus meeting for the diagnosis, management and treatment for hepatitis C 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 and compared with AASLD practice guidelines which has been published in *Hepatology*.[1] This was the fourth JSH consensus meeting of hepatitis C, however, the recommendations have not been published in English previously. This is the first report of the JSH consensus of hepatitis C. Established information regarding the pathogenesis and contributing factors for disease

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Table 1 Grading system for recommendations

	Description
Classification	
Class I	Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation procedure or treatment is beneficial, useful and effective
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a diagnostic evaluation, procedure or treatment
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy
Class IIb	Usefulness/efficacy is less well established by evidence/opinion
Class III	Conditions for which there is no evidence and/or general agreement that a diagnostic evaluation, procedure/ treatment is not useful/effective and in some cases may be harmful
Level of evidence	
Level A	Data derived from multiple randomized clinical trials or meta-analysis
Level B	Data derived from a single randomized trial, or non-randomized studies
Level C	Only consensus opinion of experts, case studies or standard of care

progression which were agreed by the organizers and presenters are shown as informative statements, and clinically useful consensuses are shown as "Recommendations". The rate of development of HCC in HCV-infected patients in Japan is higher than that in the USA, because the average age of the patient is greater and there are more patients with severe fibrosis of the liver than in the USA. To establish original recommendations and informative statements to prevent the development of HCC is a very important issue in our country. The quality of recommendations or informative statements is required to show a "class" (reflecting benefit vs risk) and "level" (assessing strength or certainty) of evidence according to AASLD practice guidelines (Table 1).[1,2]

PATHOGENESIS OF HEPATITIS C

HEPATITIS C VIRUS infection causes acute and chronic hepatitis (CH), cirrhosis and HCC. The severity and rate of progression of the disease are highly variable and may reflect both host and viral factors, but the mechanisms of pathogenesis are incompletely understood. Thus, understanding the mechanisms of HCV pathogenesis is an important goal of HCV research.

Entry pathway of HCV

For the virus, the first step in propagation is enter into hepatocytes. A decade ago, the HCV envelop protein E2 was shown to bind human CD81, a tetraspanin expressed on various cell types including hepatocytes and B lymphocytes.[3] Next, two other essential proteins, scavenger receptor class B type I (SR-B1)[4] and claudin-1 (CLDN1),[5] and potentially additional accessory factors such as glycosaminoglycans and low-density protein receptors[6] were identified as receptors involved in HCV entry. Finally, the crucial factor was identified as the tight junction protein occludin (OCLN).[7] Interestingly, both CLDN1 and OCLN are components of tight junctions which are structures forming firm seals between adjacent cells. The initial adhesion of HCV to hepatocytes may be mediated by accessory factors and/or direct interaction with SR-B1 and CD81 proteins. On transfer to a tight junction complex, HCV may interact directly with CLDN1 and/or OCLN, allowing viral uptake into the cell.

Hepatitis C virus infects only humans and chimpanzees. Once these HCV entry factors were identified, the next concern was to determine which factors dictate species-specific tropism. CD81 proteins from other mammals, such as the mouse, are used inefficiently by HCV.[8] Although HCV does not discriminate between human and mouse SR-B1 and CLDN1, mouse OCLN like CD81 cannot substitute for the related human protein in aiding viral entry. These findings indicate that CD81 and OCLN represent minimal human-specific entry factors.

Informative statement: CLDN1 and OCLN in addition to CD81 and SR-B1 are required for entering of HCV into hepatocytes, and especially CD81 and OCLN represent minimal human-specific entry factors. (Grade A.)

Evasion of intracellular host defense by HCV

One of the mechanisms by which HCV infection is likely to lead to be persistent is evasion of intracellular host defense through a complex combination of processes that include interference of interferon (IFN) signaling, modulation of its effectors and continual viral genetic variation. The HCV genome contains pathogen-associated molecular pattern (PAMP) signatures which

are recognized by the retinoic-inducible gene I (*RIG-I*) and specific Toll-like receptors when introduced into naïve cells.[9–11] Viral signaling through *RIG-I* and its adaptor protein, IFN promoter-stimulator 1 (IPS-1), activates IFN regulatory factor-3 (IRF-3) and the host IFN- / response that limits virus infection.[12,13] HCV NS3/4A protease cleaves IPS-1, releasing IPS-1 from the mitochondrial membrane.[14] Cleavage results in subcellular redistribution of IPS-1 and loss of interaction with *RIG-I*, thereby preventing downstream activation of IRF-3 and induction of IFN .[15]

Secreted IFN engages the local tissue through the autocrine and paracrine processes of binding the IFN- / receptors. This results in activation of the Jak-signal transducer and activator of transcription (STAT) pathway, in which the receptor-associated Jak and Tyk1 protein kinases catalyze the phosphorylation of STAT proteins. The resulting IFN-stimulated gene factor-3 (ISGF3) transcription factor complex localizes in the cell nucleus, where it binds to the IFN-stimulated response element (ISRE) within the promoter/enhancer region of IFN-stimulated genes (ISG). Jak-STAT signaling leads to a second wave of transcriptional activity stimulating ISG expression in the infected cells. Expression of the HCV core protein has been associated with increased expression levels of suppressor of cytokine signaling (SOCS)-3.[16] The SOCS proteins are known for their role as negative regulators and inhibitors of Jak-STAT signaling, where they mediate a classic negative feedback loop on IFN- / receptor signaling events.[17] The HCV NS5A protein has been shown to induce interleukin (IL)-8 production leading to partial inhibition of the IFN-induced antiviral response, probably through the alteration of ISG expression.[18] The HCV NS5A and E2 proteins also bind double-strand RNA-activated protein kinase (PKR) and inhibit its catalytic activity,[19,20] which allows HCV to evade in part the translational-suppressive actions of IFN. Thus, HCV evasion of the host response includes various strategies directed by viral proteins to control IFN signaling, ISG expression or function.

Informative statement: HCV evades intracellular host defenses through a complex combination of processes that include IFN signaling, modulation of its effectors and continual viral genetic variation. These mechanisms include cleavage of IPS-1 by the NS3/4A protease, inhibition of Jak-STAT signaling by HCV-induced SOCS3, inhibition of the IFN-induced antiviral response by NS5A-induced IL-8, and/or inhibition of catalytic activity of PKR by the NS5A and E2 proteins. (Grade A.)

Oxidative stress induced by HCV

Oxidative stress is well known to be present in CH-C to a greater degree than in other inflammatory liver diseases. Although the mechanisms underlying oxidative stress induced by HCV have not been elucidated fully, there are several lines of evidence suggesting that HCV directly generates reactive oxygen species (ROS) *in vitro* and *in vivo*. Hepatic ROS production is significantly higher in HCV core transgenic mice than in normal control mice in the absence of hepatic inflammation.[21] HCV core protein also produces ROS in human hepatoma Huh-7 cells and HeLa cells.[22] Analysis of the interaction of HCV core protein with mitochondria in transgenic mice and direct interaction of recombinant core protein and isolated mitochondria indicated oxidation of the mitochondrial glutathione pool and an increase in ROS production by the mitochondrial electron transport complex I, suggesting that direct interaction of core protein with mitochondria is an important cause of the oxidative stress seen in CH-C.[23]

Informative statement: Mitochondrial dysfunction induced by HCV leads to ROS generation that causes the oxidative stress seen in CH-C. (Grade A.)

Metabolic disorders caused by HCV

Epidemiological studies have suggested a link between type 2 diabetes and chronic HCV infection, which implies HCV-induced insulin resistance. A high level of tumor necrosis factor (TNF)- and disturbance of tyrosine phosphorylation of the insulin receptor substrate (IRS)1 by TNF- has been demonstrated in HCV core transgenic mice.[24] Another possible mechanism is that HCV core-induced SOCS3 promotes proteosomal degradation of IRS1 and IRS2 through ubiquitination.[25] Hepatic steatosis is one of the histopathological features in CH-C. HCV core protein inhibits microsomal triglyceride transfer protein activity and secretion of very low density lipoprotein.[26] HCV core protein also upregulates the sterol regulatory element binding protein (SREBP)1c promoter activity through the enhanced binding of the LXR /RXR to LXR-response element,[27] which leads to an increase in transcription of genes involved in hepatic fatty acid synthesis. Hepatic iron accumulation is also a histopathological feature of CH-C, even though its levels are not extremely high. HCV-induced ROS downregulates the transcriptional activity of hepcidin, a negative regulator in iron homeostasis, in transgenic mice expressing the HCV polyprotein[28] and in HCV replicon cells[29] (Fig. 1).

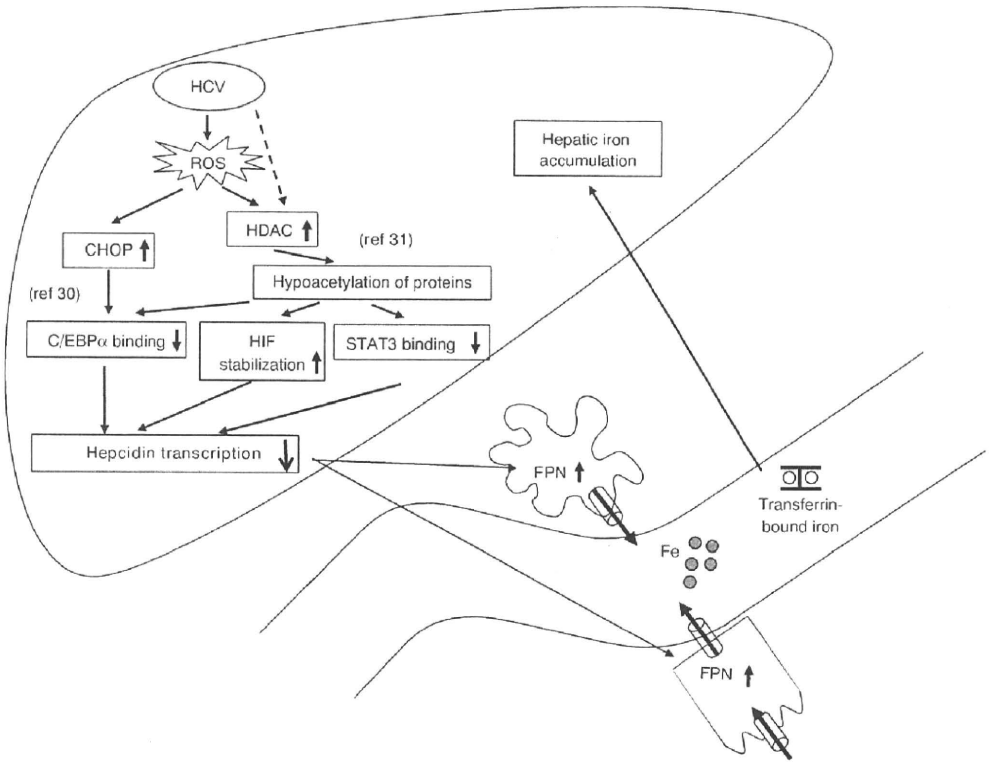

Figure 1 Schematic diagram depicting the mechanisms underlying the hepatic iron accumulation induced by HCV. HCV-induced ROS reduces hepcidin transcription through the inhibited binding of CHOP and/or STAt3 to the hepcidin promoter, and/or stabilization of HIF that is negative hepcidin regulator. C/EBP, CCAAT/enhancer-binding protein; CHOP, C/EBP homology protein; FPN, ferroportin; HCV, hepatitis C virus; HDAC, histone deacetylase; HIF, hypoxia inducible factor; ROS, reactive oxygen species; STAT, signal transducer and activation of transcription.

Metabolic disorders caused by HCV such as insulin resistance, hepatic steatosis and iron accumulation are clinically important in terms of amplification of oxidative stress and involvement in hepatocarcinogenesis in CH-C.[30–33] In addition, these metabolic disorders are related to the response to antiviral therapy. Insulin resistance[34] and hepatic steatosis[35] seem to be negatively correlated with response to antiviral therapy in CH-C.

Informative statement: HCV induces insulin resistance, hepatic steatosis, and/or hepatic iron accumulation, which is associated with hepatocarcinogenesis in CH-C. (Grade A.)

Recommendation 1: Insulin resistance and hepatic steatosis seem to be negatively correlated with response to antiviral therapy in CH-C, whereas it remains controversial whether hepatic iron accumulation is related to a poor response to therapy. (Level 2a, Grade C.)

Liver biopsy for evaluating pathogenesis of hepatitis C

Assessment of the extent of liver fibrosis is still of great importance in terms of predicting the response to antiviral therapy and hepatocarcinogenesis in CH-C. It is also apparent that as many as a quarter of CH-C patients with persistently normal aminotransferase values have significant fibrosis.[36] The recently developed transient elastography that uses ultrasound and low-frequency elastic waves to measure liver elasticity has

Table 2 Definitions of virological responses to interferon therapy

RVR (rapid virological response)	Undetectable HCV RNA at week 4
cEVR (complete early virological response)	Undetectable HCV RNA at week 12
pEVR (partial early virological response)	Two log drop of HCV RNA without undetectable level at week 12
LVR (late virological response)	Undetectable HCV RNA between week 13 and 24 week
NVR (null virological response)	Positive HCV RNA during treatment
Relapse	Undetectable HCV RNA at end of treatment followed by detectable level after treatment
SVR (sustained virological response)	Undetectable HCV RNA at 24 weeks after treatment

improved the ability to define the extent of fibrosis without a liver biopsy, particularly when combined with other non-invasive markers,[37] but it is not yet ready to replace liver biopsy. Among the pathological features, steatosis and excess hepatocellular iron that affect disease progression and possibly impede treatment response are difficult to diagnose without liver biopsy. Thus, a liver biopsy should be considered if it is desirable to determine the stage of fibrosis or presence of steatosis or excess hepatocellular iron for prognostic purposes or making a decision regarding treatment.

Recommendation 2: A liver biopsy should be considered if it is desirable to determine the stage of fibrosis or presence of steatosis or excess hepatocellular iron for prognostic purposes or making a decision regarding treatment. (Level 1, Grade C.)

VIRAL LOAD, GENOTYPE, VIRAL MUTATIONS

DEFINITIONS OF VIROLOGICAL responses to IFN therapy are summarized in Table 2.

HCV RNA assay and genotype

In clinical practice, the usual approach is to test initially for antibodies to HCV (anti-HCV), then to use HCV RNA to document viremia. The quantity of HCV RNA is useful to know before providing and monitoring HCV treatment. For HCV RNA determination, quantitative tests based on target amplification (reverse transcriptase polymerase chain reaction [RT-PCR]) and signal amplification (branched DNA [bDNA]) techniques with differing sensitivity and linear measuring ranges are commercially available. The COBAS Amplicor HCV Monitor Test v2.0 (Roche Molecular Systems, Branchburg, NJ, USA), however, requires sample dilutions for accurate quantification of high-titer specimens. In addition, the assay displays relatively low sensitivities of approximately 600 IU/mL. Recently, the COBAS AmpliPrep/COBAS TaqMan HCV test (Roche Molecular Systems) and AccuGene m-HCV (Abbott Molecular, Des Plaines, IL, USA) have become available. These meet the requirements for highly sensitive detection and reliable quantification of HCV in clinical samples.

There are six major HCV genotypes. Genotype specificity predicts the likelihood of treatment response and determines the duration of treatment. Therefore, HCV genotype should be determined in all HCV-infected persons prior to treatment in order to determine the duration of therapy and likelihood of response.[38]

Many reports showed that sustained virological response (SVR) rates in IFN monotherapy and IFN plus ribavirin (RBV) combination therapy were higher in patients who had lower pretreatment RNA levels and genotype 2 infections.[39–41]

Recommendation 3: HCV RNA level and genotype should be determined in all HCV-infected persons prior to treatment in order to predict the efficacy of response of therapy. SVR rate in IFN therapy are higher in patients who had lower pretreatment RNA levels and genotype 2 HCV infections in IFN therapy. (Level 1, Grade A.)

HCV mutation

IFN sensitivity determining region (ISDR)

Enomoto *et al.* were able to demonstrate a strong correlation between the number of mutations within the carboxy terminal region of the NS5A gene, the ISDR spanning codons 2209–2248, and response to IFN therapy.[42] Thus, no patient infected with HCV with a wild-type ISDR sequence (identical to the prototype Japanese HCV strain [HCV-J]) responded to IFN therapy whereas all patients infected with the "mutant type", defined by four or more amino acid substitutions in this region, showed an SVR.[43] These initial findings have been confirmed by other Japanese studies but controversial data were reported from other parts of the world, particularly from Europe and the

USA. This may indicate that geographical factors account for different sensitivities of HCV genotype 1b infection to antiviral therapy. Pascu *et al.* reported that the distribution of wild-, intermediate- and mutant-type ISDR sequences differed significantly between Japanese (n = 655) (44.1%, 37.6% and 18.3%, respectively) and European patients (n = 525) (24.8%, 63.4% and 11.8%, respectively; P = 0.001). However, there was a significant positive correlation between the number of ISDR mutations and SVR rate, irrespective of geographical region.[44]

Moreover, Shirakawa *et al.* reported that a logistic regression model that includes the sequence of ISDR of HCV, and other factors (T-helper cell [Th]1/Th2 ratio, bodyweight and neutrophil count) can be useful for accurately predicting accurately the SVR rate before pegylated (PEG)-IFN and RBV combination therapy.[45]

Recommendation 4: The ISDR should be evaluated before IFN treatment in order to predict the response to treatment. (Level 2b, Grade B.)

IFN/RBV resistance-determining region (IRRDR)

El-Shamy *et al.* have reported recently that a high degree of sequence variation in the V3 and the pre-V3 regions (amino acid [aa]2334-2355) of NS5A, which they refer to collectively as the IRRDR (aa2334-2379), was closely correlated with virological response in HCV-1b-infected patients treated with PEG-IFN and RBV.[46] A high degree (>6 aa substitutions) of sequence variation in the IRRDR should be a useful marker for predicting SVR, whereas a less diverse (<5) IRRDR sequence predicts non-SVR.

Amino acid substitutions in the HCV core region

Akuta *et al.* identified pretreatment substitutions of aa70 and aa91 in the core region as independent and significant pretreatment factors associated with virological non-response, based on 48-week combination therapy of IFN plus RBV.[47] Moreover, they identified aa70 and aa91 substitutions in the core region as predictors of response to PEG-IFN-RBV therapy in Japanese patients infected with HCV genotype 1b[48] (Table 3). Donlin *et al.* reported sequencing the complete pretreatment genotype 1 HCV open reading frame using samples from 94 participants in the Virahep-C study to assess the effects of viral diversity on response to therapy.[49] Genotype 1b sequences from patients with more than 3.5 log declines in viral RNA levels by day 28 (marked responders) were more variable than those from patients with declines of less than 1.4 log (poor responders) in core and NS3. Moreover, arginine (R) at aa70 in the core region was related to a marked response.

Recently evaluations were made of the impact of aa substitutions in HCV core region on hepatocarcinogenesis. Akuta *et al.* reported that cumulative hepatocarcinogenesis rates in double wild-type (arginine at aa70/leucine at aa91) of the HCV core region were significantly lower than those in the non-double wild type in CH-C patients.[50] Moreover, another report showed that a logistic regression model developed

Table 3 Factors associated with sustained virological response to 48-week pegylated interferon plus ribavirin combination therapy in patients infected with hepatitis C virus genotype 1b, identified by multivariate analysis (n = 114) 52)

Factor	Category	Risk ratio (95% confidence interval)	P
Amino acid substitution in core region	1: double wild	1	
	2: non-double wild	0.102 (0.022–0.474)	0.004
Low-density lipoprotein cholesterol (mg/dL)	1: <86	1	
	2: ≥86	12.87 (2.177–76.09)	0.005
Sex	1: male	1	
	2: female	0.091 (0.017–0.486)	0.005
ICG R15 (%)	1: <10	1	
	2: ≥10	0.107 (0.017–0.678)	0.018
-Glutamyltransferase	1: <109	1	
	2: ≥109	0.096 (0.0011–0.819)	0.032
Ribavirin dose (mg/kg)	1: <11.0	1	
	2: ≥11.0	5.173 (1.152–23.22)	0.032

through analysis of full-length core gene sequences identified seven polymorphisms significantly associated with increased HCC risk (36G/C [aaK12N], 209A [aaR70Q], 271U/C [aaL91M], 309A/C, 435A/C, 481A and 546A/C).[51] HCV core gene sequence data might provide useful information about HCC risk.

Recommendation 5: Amino acid substitutions in the HCV core region (aa70 and aa91) should be determined before IFN treatment in order to predict the response to treatment. (Level 2b, Grade B.)

NS3 protein secondary structure

Recently, Ogata *et al.* reported that HCV-1b strains can be classified into different groups based on the secondary structure of an amino-terminal portion of the NS3 protein and that specific strains are more prevalent among patients with HCC.[52] Moreover, the cumulative incidence of HCC was highest among patients infected with specific group HCV-1b, in whom the risk of HCC significantly increased compared with that among patients infected with another group (hazard ratio = 4.95 [95% confidence interval = 1.43–17.11]) after adjustment for age and histological stage.[53]

Informative statement: NS3 protein secondary structure may be related to hepatocarcinogenesis. (Grade B.)

NATURAL HISTORY OF CH-C

Progression to cirrhosis and HCC

PREVIOUS PUBLICATIONS REPORTED that approximately 60–80% of patients with acute hepatitis C develop chronic infection in the natural course.[54–57] Because it is difficult to ascertain precisely when the HCV infection occurred except for patients who had blood transfusions, and because chronic infection progresses slowly and asymptomatically, the natural entity of the disease has not been elucidated fully. Seeff *et al.* compared the long-term prognosis of HCV antibody-positive and -negative young men and reported that liver disease-related death was very rare in HCV antibody-positive patients.[58,59] Kenny-Walsh studied the liver histology of 363 young women 17 years after HCV infection and showed that 83% had no or mild hepatic fibrosis whilst 2% had liver cirrhosis.[60] These results demonstrate that progression to serious liver disease is a rare event two decades after infection of young people with HCV.

On the other hand, in blood transfusion-associated CH-C patients the mean interval to liver cirrhosis is estimated to be approximately 20–30 years and that to HCC approximately 30–40 years.[61,62] Because HCC is the most serious complication of HCV-infected people, it is desirable to predict the overall incidence of HCC in each patient. Up to now, many investigators have reported a close relationship between the stage of hepatic fibrosis and incidence of HCC. According to reports from Japan, the annual incidence of new HCC in liver cirrhosis is estimated to be approximately 5–8%.[63–65]

Informative statement: The natural history of CH-C is highly variable. HCV infection does not have much impact on the overall mortality of all the infected people, whereas progression to liver cirrhosis is observed 20–30 years and to HCC 30–40 years after infection. In Japan, the annual incidence of HCC in liver cirrhosis is estimated to be 5–8%. (Level 2b, Grade B.)

Recommendation 6: Treatment of HCV-infected people should be determined in consideration of the higher annual incidence of HCC in patients with liver cirrhosis in Japan as compared to Western countries. (Level 2b/3, Grade B.)

Progression of fibrosis

The rate of progression of fibrosis varies among patients with CH-C. Poynard *et al.*[66] calculated the average progression rate of hepatic fibrosis in CH-C to be 0.133 fibrosis units/year. In Japan, Shiratori *et al.*[67] reported this to be 0.10 fibrosis units/year. In HCV carriers with persistently normal aminotransferase levels (PNALT), progression of hepatic fibrosis is slower. Persico *et al.*[68] reported that median histological scores did not differ after 5 years of follow up in PNALT and Okanoue *et al.*[69] calculated the average progression rate of hepatic fibrosis in PNALT to be 0.05 fibrosis units/year.

Informative statement: On average, progression of hepatic fibrosis in CH-C is 0.10–0.13 fibrosis score units/year. The hepatic stage/grade score of HCV carriers with PNALT *are generally low and the progression of hepatic fibrosis is slow. Excessive alcohol intake, insulin resistance and hepatic steatosis are the major factors which induce the progression of hepatic fibrosis. (Level 2b, Grade B.)*

Alanine aminotransferase (ALT) levels

Alanine aminotransferase is an easy tool to evaluate hepatocellular damage in liver diseases. In the past, a higher incidence of HCC was reported in liver cirrhotic patients with elevated ALT levels. "The normal range of serum ALT level varies according to the institutions or hospitals, but it is likely to be located between 30 IU/L

and 40 IU/L. Recently, Kumada *et al.*[31,32] demonstrated that the cumulative incidence of hepatocarcinogenesis increased in parallel with the increase in ALT average integration value in CH-C even in patients with normal ALT levels. In a community-based study, an elevated ALT level (>35 IU/l) was shown to be a significant risk factor of HCC development.[33]

Recommendation 7: To prevent the occurrence of HCC, levels of serum ALT should be controlled at below 30 IU/l. (Level 3, Grade A.)

IFN administration

More than two decades have passed since IFN began to be used to treat CH-C patients. Nowadays, more than 70% of HCV-infected people can be cured by the combination therapy of PEG-IFN plus RBV. However, even in patients who were cured of HCV infection and attained an SVR, the occurrence of HCC may be reported long after completion of IFN therapy. The risk factor of HCC occurrence after IFN therapy is a combination of advanced hepatic fibrosis score before therapy, older age and male sex.[34–36] Bruno *et al.*[35] reported that annual incidence of HCC occurrence in liver cirrhosis after attaining SVR was 0.66%, which was one-third of the incidence of HCC in liver cirrhosis without a virological response (non-SVR).

Recommendation 8: Surveillance is required for the occurrence of HCC in patients with CH-C and liver cirrhosis. Even if IFN-based therapy is successful in attaining SVR, screening for the detection of HCC by computed tomography (CT), magnetic resonance imaging or ultrasonography and measurement of the serum tumor markers should be carried out routinely, especially for patients with advanced hepatic fibrosis, older age and male sex, because they are at high risk for the occurrence of HCC. (Level 2b, Grade A.)

Indication of IFN therapy for CH-C

Interferon-based therapy is used to treat chronic HCV-infected patients worldwide and PEG-IFN plus RBV is the first choice indication for CH-C patients. Because IFN and RBV have a variety of adverse effects including depression and thyroid dysfunction, "who and how" to treat should be determined with caution. The AALSD practice guideline advocates that treatment decision should be individualized based on the severity of liver disease, the potential for serious side-effects, the likelihood of treatment response, the presence of comorbid condition and the patient's readiness for treatment.[1]

Recommendation 9: Treatment decision of IFN therapy for CH-C should be individualized based on the body/mental condition, probability of successful therapy and prolonged survival, and likelihood of provoking serious adverse effects. Scores of hepatic stage/grade should be considered as well. For aged patients, in whom HCV infection is regarded as the major determinant of survival, IFN-based therapy should be considered with caution. (Level 3, Grade A.)

PEG-IFN AND RBV COMBINATION THERAPY

Factors associated with virological response to PEG-IFN and RBV combination therapy

TREATMENT WITH PEG-IFN- -2A or -2b together with RBV has been evaluated in two nationwide phase III registration trials in Japan.[37,38] In one trial, which determined efficacy of PEG-IFN -2b and RBV,[37] the SVR rate to 48-week combination therapy was 48% (121/254) in patients with HCV genotype 1b and a high viral load (≥100 KIU/mL). Another trial using PEG-IFN--2a and RBV demonstrated an SVR rate to 48-week combination therapy of 59% (57/96) in patients with HCV genotype 1b and a high viral load (≥100 KIU/mL).[80] Based on these results, the currently recommended standard therapy for the patients with CH-C in Japan is the combination of a PEG-IFN together with RBV, except for the treatment naïve patients with a low viral load for whom a PEG-IFN monotherapy is recommended.

These clinical trials identified the following factors that are associated with non-SVR in patients with HCV genotype 1b and a high viral load: (i) older patients; (ii) non-responders to previous IFN therapy; (iii) advanced fibrosis; (iv) female sex; and (v) poor adherence below 80%. In marked contrast to the data from Europe and the USA, the SVR rate in Japanese female patients is lower than that in the male patients. Several community-based retrospective studies in Japan also demonstrated that female patients, especially older female patients, are more difficult to treat compared with other patients.[81–87] Other factors associated with virological response reported from Japan include the low-density lipoprotein cholesterol level,[83] -fetoprotein (AFP) level,[83] whole-body insulin sensitivity index,[84] single nucleotide polymorphisms of MAP-KAPK3,[85] *RIG-I*/IPS-1 ratio,[86] Th1/Th2 ratio[45] and PKR response.[87] Association between viral mutations and treatment response is discussed in depth above.

Recommendation 10: Predictors associated with a non-SVR to PEG-IFN and RBV include: (i) age older than 60 years, particularly older women; (ii) advanced fibro-

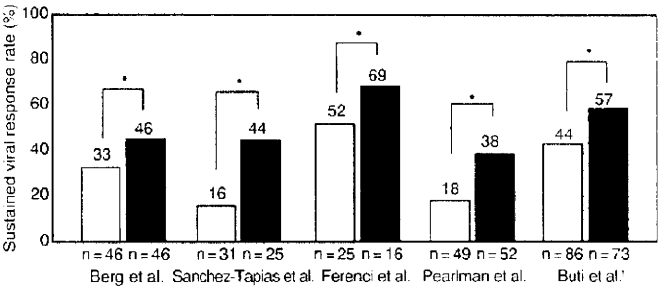

Figure 2 Comparison of sustained virological response rate between 48-week (open column) and 72-week (closed column) treatment with pegylated interferon and ribavirin in patients with partial early virological responder, which is defined as ≥2 log reduction in hepatitis C virus (HCV) RNA level compared to baseline HCV RNA level but detectable HCV RNA at treatment week 12. *Statistical significance between two treatment groups. †Comparison in patients with ≥80% adherence is shown.

sis; (iii) non-responder to previous IFN therapy; and (iv) poor adherence below 80%. (Level 2a, Grade B.)

Response-guided therapy for patients with HCV genotype 1

Measuring the rate of viral clearance from serum is helpful in predicting the likelihood of a response to PEG-IFN and RBV, and useful for determining the optimal duration of therapy. In two nationwide registration trials conducted in Japan,[77,78] the SVR rate was high, from 76–100% in patients whose HCV RNA was cleared rapidly from serum by week 4, and 71–73% in patients who achieved undetectable HCV RNA from week 5 to week 12. In contrast, the SVR rate in patients with late clearance of HCV RNA from week 13 to week 24 was low at 29–36%. No patients without clearance of HCV RNA by week 24 achieved SVR. It should be noted that time point of HCV clearance was determined by measurement of serum HCV RNA utilizing the Ampricor HCV method in these trials.

Recommendation 11: Measuring the time of viral clearance from serum is helpful in predicting the likelihood of a response to PEG-IFN and RBV. Measurement of HCV RNA is recommended at weeks 4, 12 and 24. (Level 1, Grade A.)

As mentioned above, patients whose HCV RNA measured by Amplicor HCV had not cleared by week 24 were unable to achieve SVR with 48-week standard PEG-IFN and RBV therapy. However, in a retrospective study conducted in 52 patients without HCV RNA clearance from serum by week 24, the rate of ALT normalization 6 months after the completion of therapy (so-called biochemical response) was 56% (5/9) and 62% (8/13) of patients achieved ALT normalization up to 2 years after the completion of therapy (sustained biochemical response).[86] Therefore, the proposal that recommends a continuation of PEG-IFN and RBV therapy for 48 weeks in biochemical responders at week 24 even without HCV clearance has been accepted widely in Japan. This proposal is in marked contrast to the AASLD practice guideline,[3] in which treatment discontinuation is strongly recommended in patients whose HCV RNA remains positive at week 24.

Recommendation 12: It is impossible to achieve SVR in patients without HCV RNA clearance by week 24 measured by Amplicor HCV. (Level 1, Grade A.) However, it is recommended to continue the therapy for 48 weeks even in patients without HCV RNA clearance by week 24 if ALT normalizes at week 24, because a sustained biochemical response can be obtained in these patients. (Level 4, Grade C.)

The strategy of extending therapy in patients with delayed virological responses, defined as clearance of HCV RNA between weeks 12 and 24, was evaluated in five studies.[80–84] These results cannot be compared directly with each other because of the heterogeneous study populations, differences in the baseline characteristics and the different regimens utilized amongst them. Nevertheless, the results showed a trend toward a higher SVR rate by extending therapy from 48 to 72 weeks in patients with delayed virological response (Fig. 2).[80–84]

In Japan, a randomized controlled trial was conducted in 113 patients with HCV genotype 1b and a high viral load, comparing a 48-week treatment group and extended treatment group where patients were treated for an additional 44 weeks after clearance of

HCV RNA from serum. In this trial, the SVR rate was 36% in the 48-week treatment group and 53% in the extended treatment group, and the SVR rate was significantly higher in patients in the extended treatment group who became HCV RNA-negative during the period week 16–24 (9% vs 78%, $P = 0.005$).[91] In addition, in a case–control study matched for age, sex and the timing of HCV RNA clearance from serum, the SVR rate was high at 62% in the 72-week treatment group ($n = 65$) compared to 33% in the 48-week treatment group ($n = 130$), and the extended treatment was particularly effective in patients with HCV core mutations at aa70 and aa91 as well as patients a with wild type of ISDR sequence.[3] Accordingly, 72-week extended treatment is recommended for patients who are slow to clear of HCV RNA between weeks 12 and 24.

Currently, HCV RNA clearance from serum is determined by real-time PCR detection, although most of former studies utilized the Amplicor HCV method for this purpose. Because real-time PCR is highly sensitive, it should be reevaluated in terms of who gains benefit from extended therapy. Currently, there is no sufficient evidence to determine this. Nevertheless, substantial number of community-based Japanese study using real-time PCR detection suggested that SVR could be obtained by 72-week treatment if HCV RNA became undetectable by week 36. Accordingly, when determining the timing of HCV RNA clearance using real-time PCR detection, 72-week treatment could be recommended for patients who achieve HCV RNA clearance between weeks 12 and 36.

Recommendation 13: 72-week extended therapy should be considered for patients with HCV genotype 1 who have delayed HCV RNA clearance from serum between weeks 12 and 24. (Level 2a, Grade B.)

Recommendation 14: When using a real-time detection PCR method for measurement of HCV RNA, SVR can be obtained by 72-week extended treatment in patients who have achieved HCV RNA clearance by week 36. (Level 2b, Grade C.)

Response-guided therapy for patients with HCV genotype 2

Six trials have evaluated a shortening of the duration of therapy from 24 weeks to 12–16 weeks for patients with chronic HCV genotype 2 and 3.[84,85,99] Although the data from some of these trials suggest that patients with genotype 2 and 3 infection who achieve viral clearance from serum by week 4 can shorten their treatment duration to 12–16 week,[80,92,99] the benefit of a shortening the duration of therapy remains controversial.[99] In a recent study by Mangia *et al.*, the factors associated with relapse after shorter duration of therapy are identified as age over 45 years, pre-treatment platelet count of less than 140 10^9/L, and body mass index over 30 kg/m^2,[100] suggesting shortening the duration of therapy can be considered only in particular patients without predictors associated with relapse. Because most Japanese patients have risk factors for relapse such as older age and advanced fibrosis, shortening the duration of the therapy is not generally recommended for Japanese patients with genotype 2, even if they achieve viral clearance by week 4.

PEG-IFN and RBV combination therapy in patients with compensated cirrhosis

In the early Western registration trials, patients with HCV-related compensated cirrhosis did achieve SVR but at lower rates than did those without cirrhosis.[101–103] Subsequently, there was one treatment study that focused exclusively on patients with compensated cirrhosis.[104] In this study, 124 patients with compensated cirrhosis were assigned randomly to an RBV 1000/1200-mg (standard dose) group and 600/800-mg (low dose) group to determine the efficacy of PEG-IFN and RBV combination therapy. The SVR was achieved in 52% of patients who received the standard RBV dose and in 38% of those treated with the low dose. Serious adverse events developed in 14% and 18% of recipients of the standard and low RBV doses, respectively, while dose reduction was necessary in 78% and 57% of the two groups, respectively. HCV genotype 2/3 and platelet count over 150 10^9/L were identified as factors contributing to SVR. Thus, patients with HCV-related compensated cirrhosis can be treated successfully with PEG-IFN and RBV but careful observation is needed because of an anticipated higher rate of adverse effects. Although PEG-IFN and RBV for patients with compensated cirrhosis has not been approved yet in Japan, the following recommendation is reasonable.

Recommendation 15: Patients with HCV-related compensated cirrhosis can be treated successfully with PEG-IFN and RBV but careful observation is needed because of an anticipated higher rate of adverse effects. (Level 3, Grade B.)

Retreatment with PEG-IFN and RBV combination therapy for patients who failed to respond to previous IFN treatment

Seven randomized controlled trials have been reported so far that examine the efficacy of PEG-IFN and RBV