strain in this case might be related to entecavir resistance.

Key words: entecavir, drug-resistant mutant, rtA181T

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1) Department of Hepatology, Toranomon Hospital
2) Department of Research Institute for Hepatology, Toranomon Branch Hospital, Kawasaki
*Corresponding author: h-ooga@mx1.harmonix.ne.jp

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＜速　報＞

IL28B と HCV Core aa70 置換との関連

小林万利子[1)*]　鈴木　文孝[2)]　芥田　憲夫[2)]　鈴木　義之[2)]　瀬崎ひとみ[2)]
八辻　寛美[2)]　保坂　哲也[2)]　小林　正宏[2)]　川村　裕介[2)]　平川　美晴[2)]
荒瀬　康司[2)]　池田　健次[2)]　峰田　理恵[1)]　岩崎　里美[1)]　綿引　祥予[1)]
中村　祐輔[3)]　茶山　一彰[4)]　熊田　博光[2)]

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．

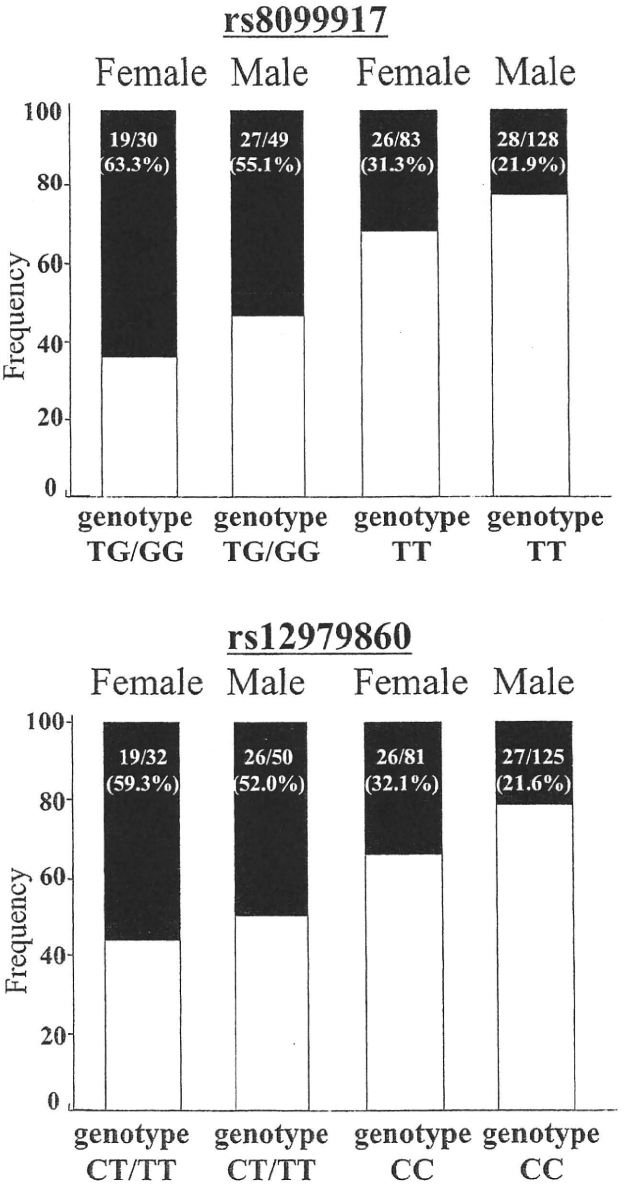

Fig. 1　Relationship between *IL28B* SNPs and amino acid substitution in hepatitis C virus core region in patients with chronic hepatitis C. Black bars represent aa70 mutant (Gln) while white bars represent aa70 wild (Arg)

1）虎の門病院肝臓研究室
2）虎の門病院肝臓センター
3）理化学研究所ゲノム医科学研究センター
4）広島大学大学院医歯薬学総合研究科分子病態制御内科学
*Corresponding author: vj7m-kbys@asahi-net.or.jp

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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[4]および慢性肝炎の PEG-IFN/Rivabirin 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/Rivabirin 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

Mariko Kobayashi[1)*], Fumitaka Suzuki[2)], Norio Akuta[2)], Yoshiyuki Suzuki[2)], Hitomi Sezaki[2)], Hiromi Yatsuji[2)], Tetsuya Hosaka[2)], Masahiro Kobayashi[2)], Yusuke Kawamura[2)], Miharu Hirakawa[2)], Yasuji Arase[2)], Kenji Ikeda[2)], Rie Mineta[1)], Satomi Iwasaki[1)], Sachiyo Watahiki[1)], Yusuke Nakamura[3)], Kazuaki Chayama[4)], Hiromitsu Kumada[2)]

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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1) Department of Research Institute for Hepatology, Toranomon Hospital, Kawasaki, Japan
2) Department of Hepatology, Toranomon Hospital, Tokyo, Japan
3) Laboratory for Molecular Medicine, Human Genome Center, The Institute of Medical Science, University of Tokyo, Tokyo, Japan
4) Department of Medicine and Molecular Science, Division of Frontier Medical Science, Programs for Biomedical Research, Graduate School of Biomedical Science, Hiroshima University, Hiroshima, Japan
*Corresponding author: vj7m-kbys@asahi-net.or.jp

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今月のテーマ●B型慢性肝炎に対する最新の治療

ラミブジンとアデホビル併用不応例に対するアデホビルとエンテカビル併用療法

小関　至　木村睦海　荒川智宏
中島知明　桑田靖昭　赤池　淳
大村卓味　佐藤隆啓　狩野吉康
豊田成司[1)]

要旨：ラミブジン（LAM）とアデホビル（ADV）併用療法を12カ月以上行い，HBV DNAが3log copies/ml以上を示したB型慢性肝疾患18例を対象とし，48週以上ADVとエンテカビル（ETV）の併用療法を行いウイルス動態についての検討を行った．LAM耐性例，ADV耐性例，ETV耐性例，多剤耐性例はそれぞれ100%，27.8%，33.3%，55.6%であった．平均HBV DNAはベースラインで4.1log copies/mlより48週の時点で2.9log copies/mlと低下した．ETV耐性を有する症例でHBV DNA減衰量は低下した．本併用療法による副作用は出現せず，48週の経過で新たに獲得したアナログ耐性は認めなかった．テノホビル（TDF）が使用できない本邦の現状ではLAMとADV併用不応例に対して，ADVとETV併用療法は試みるべき治療と思われた．

索引用語：ラミブジン，アデホビル，エンテカビル，B型肝炎ウイルス，耐性変異

はじめに

B型肝炎ウイルスによる持続感染の患者は世界で約3億5千万人いるといわれており[1)]，このウイルスによる持続感染はしばしば肝硬変，肝不全を惹起し，肝細胞癌の発生の原因となる[2)]．インターフェロン（interferon；IFN）製剤はB型肝炎ウイルスの増殖を抑制し，肝炎の鎮静に有効であるが，その効果は限定的であり，ペグインターフェロン（pegylated IFN；PEG-IFN）は30～40%の患者でsustained responseを達成するとされている[3)4)]が，本邦では現在治験中である．核酸アナログ製剤はB型肝炎ウイルスのDNAポリメラーゼを抑制してDNA合成を阻害し，ウイルス増殖を抑える薬剤であり，血液生化学検査値，肝組織所見の改善を促す[5)6)]．長期の核酸アナログ投与は肝硬変の進展や肝細胞癌の発生を抑制し，長期予後を改善する可能性が指摘されている[7)]．一方で長期に及ぶ核酸アナログ投与は薬剤に対する変異株の発生を促し，しばしば，ウイルス学的ブレイクスルーを引きおこす[8)]．実際に長期のラミブジン（lamivudine；LAM）投与は高率にLAM耐性ウイルスの出現を促した[8)9)]．近年登場した新規の核酸アナログ製剤であるエンテカビル（entecavir；ETV）はLAMと比較して耐性ウイルス

1）札幌厚生病院第3消化器科

Efficacy of entecavir and adefovir combination therapy in patients with chronic hepatitis B refractory to lamivudine and adefovir combination therapy

Itaru OZEKI, Mutsuumi KIMURA, Tomohiro ARAKAWA, Tomoaki NAKAJIMA, Yasuaki KUWATA, Jun AKAIKE, Takumi OHMURA, Takahiro SATO, Yoshiyasu KARINO and Joji TOYOTA[1)]
1）Department of Hepatology, Sapporo Kosei General Hospital
Corresponding author：小関　至（i.ozeki@ja-hokkaidoukouseiren.or.jp）

Table 1. 背景因子

性別		男性：13　女性：5
年齢（歳）	Mean＋/－SD	59.6＋/－9.0
肝硬変（あり）	(No. [%])	10 (55.6)
肝癌既往（あり）	(No. [%])	5 (27.8)
LAM＋ADV 治療期間（月）	Mean＋/－SD	29.1＋/－13.1
HBV genotype		Bj：1　C：17
HBV DNA (log_{10} copies/m*l*)	Mean＋/－SD	4.10＋/－1.18
HBeAg（＋）	(No. [%])	13 (72.2)
ALT (IU/L)	Mean＋/－SD	35.9＋/－17.7
LAM 耐性	(No. [%])	18 (100)
ADV 耐性	(No. [%])	5 (27.8)
ETV 耐性	(No. [%])	6 (33.3)
多剤耐性	(No. [%])	10 (55.6)

の出現が少なく，抗ウイルス作用が強いことがいくつかの臨床試験で明らかとされた[10)~12)]．本邦においてもETVは2007年の承認後LAMに代わり第一選択の核酸アナログ製剤となった．しかし，既に世界中で多くのLAM耐性患者を認めており，これらの症例に対して2009年の米国肝臓病学会（American Association for the Study of Liver Disease；AASLD）はアデホビル（adefovir dipivoxil；ADV），あるいはテノホビル(tenofovir disoproxil fumarate；TDF）のLAMとの併用投与，あるいはemtricitabine（FTC）とTDFの併用投与への切り替えを推奨した[13)]．同様にヨーロッパ肝臓病学会（European Association for the Study of the Liver；EASL）からはTDFの併用[14)]が，本邦からはADVの併用が推奨された[15)]．LAM耐性例に対するLAMとADV併用療法（以下LAM/ADV療法）による抗ウイルス効果の発現は緩徐であり，大多数のLAM耐性患者に有効であるが，少数例でHBV DNAの低下量が不十分であることが報告されている[16)17)]．今回われわれはLAM/ADV療法不応例に対するADVとETV療法（ADV/ETV療法）48週の成績を検討したので報告する．

I　対象と方法

LAM/ADV療法を少なくとも1年以上行い，HBV DNAが3log copies/m*l*（以下log）以上を示した18例を対象とした．自己免疫性肝炎，アルコール性肝障害，うっ血性肝障害の合併例，C型肝炎ウイルスあるいはヒト免疫不全ウイルスの併発例，黄疸・腹水・脳症・消化管出血をともなう患者は除外した．18例中6例はLAM耐性に対するETV投与の既往を有した．2名の患者がADV投与中に血清クレアチニン上昇をきたしたため，ADVは隔日投与が行われていた．

HBV DNAはTaqMan PCR法(Roche Diagnostics, Tokyo, Japan)，耐性ウイルスの検討はINNO-LiPA HBV DR version 2, version 3(Innogenetics Gent, Belgium）を用いた[18)]．

2群の検定にはStudent's t test, Mann-Whitney U test, chi-squared test, Fisher's exact testを用い，$p<0.05$を有意とした．

II　結　果

18例の背景因子をTable 1に示す．5例で肝癌の既往を認め，1例はADV/ETV療法中に肝癌を発症したが，肝部分切除あるいは経皮的ラジオ波焼灼療法で根治的な治療を受けた．10例は代償性肝硬変の状態で，遺伝子型では1例がBj型，17例がC型を示し，HBe抗原陽性は13例（72.2%）であった．LAM耐性は18例全例（100%），ADV耐性は5例（27.8%），ETV耐性

Table 2. ベースライン，48週の時点における HBV DNA，HBe抗原，ALT値の推移と INNO-LiPA 法によるベースラインのアナログ耐性

Case	HBV DNA (log copies/ml)			HBeAg (S/CO)		ALT (IU/L)		Resistance Mutation		
	0W	48W	0W-48W	0W	48W	0W	48W	LAM	ADV	ETV
1	7.6	3.1	4.5	1.7	3.4	74	39	+	+	
2	5.03	3.69	1.34	44	18	32	28	+		
3	3.09	1.8	1.29	—	—	31	16	+		+
4	4.12	2.51	1.61	245	106	27	20	+		+
5	4.9	4.6	0.3	528	359	49	36	+		+
6	3	1.8	1.2	3.7	—	27	28	+	+	
7	5.2	3.53	1.67	—	—	39	47	+		
8	3.87	2.93	0.94	1043	927	15	15	+		
9	4.93	3.91	1.02	87	39	28	25	+		+
10	5.24	4.17	1.07	161	121	48	43	+		
11	4.76	2.64	2.12	1.9	1.3	40	36	+		
12	3.46	3.36	0.1	—	—	37	30	+		
13	3	1.8	1.2	7.5	4.8	10	11	+	+	
14	3.61	2.51	1.1	3.9	3	28	25	+		
15	3.07	1.8	1.27	5.7	5.1	21	22	+		
16	3.96	3.11	0.85	164	94	73	138	+		+
17	3.17	1.8	1.37	—	—	28	42	+	+	
18	3.59	2.89	0.7	—	—	14	16	+	+	+

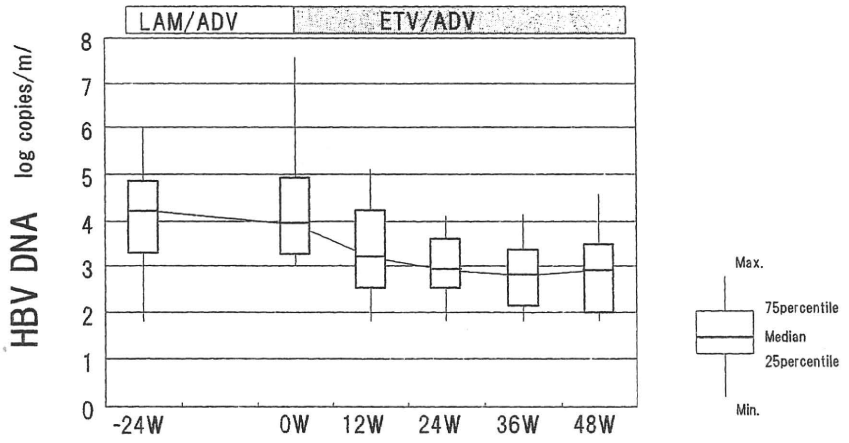

Figure 1. LAM/ADV療法・ADV/ETV療法による HBV DNA の推移：HBV DNA はベースライン 4.1log copies/ml から48週2.9log copies/ml と，48週で1.2log copies/ml 低下した．

は6例（33.3%），10例（55.6%）は3剤耐性を認めた（Table 2）．

平均 HBV DNA は ADV/ETV 療法にてベースライン 4.1log，12週 3.3log，24週 3.0log，36週 2.8log，48週 2.9log と緩徐に低下した（Figure 1）．18例中5例が48週の治療中に 2.1log 未満を呈した．18例中13例は48週で1log以上の HBV DNA 量の低下を示したが，残る5例の低下量は1log未満であった．HBe抗原陽性例・陰性例で治療48週の HBV DNA 低下量に差を認めなかった．アナログ耐性別の治療48週での HBV DNA の減衰量は LAM 耐性で 1.2log，LAM 耐性＋

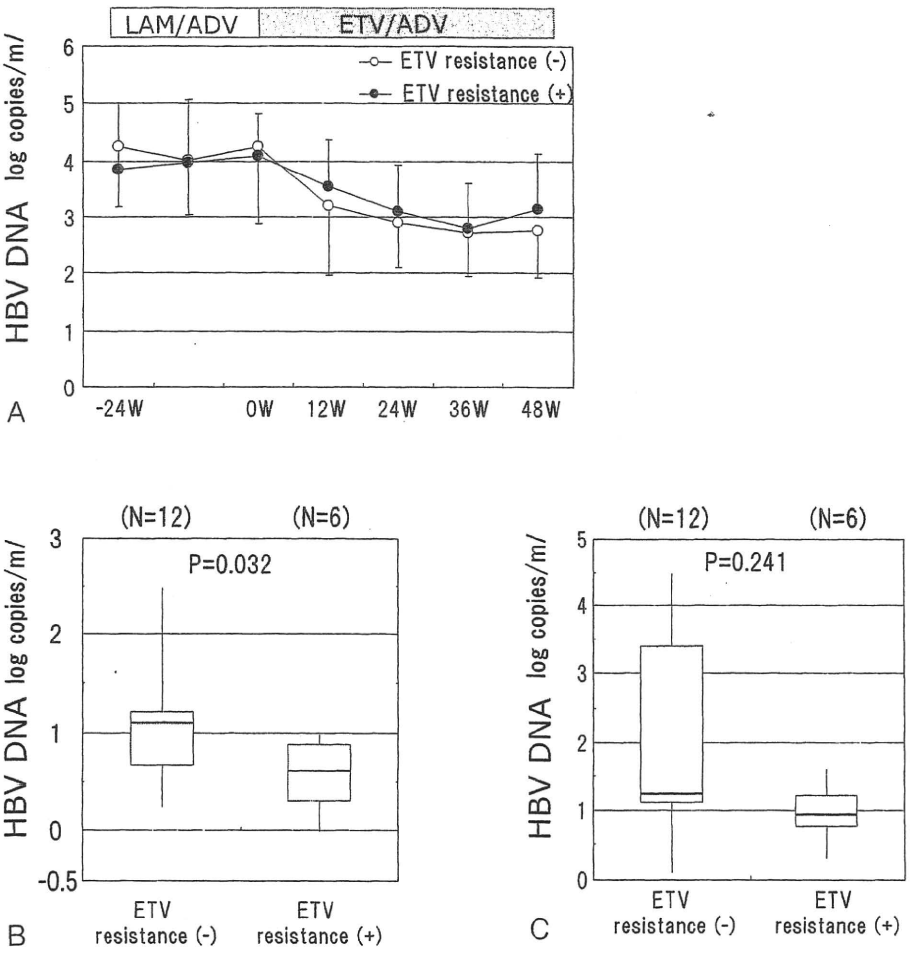

Figure 2. ETV 耐性の有無による LAM/ADV 療法・ADV/ETV 療法による HBV DNA の推移 **A**) HBV DNA の推移. **B**) ADV/ETV 療法ベースライン・12 週後の HBV DNA の減衰量の比較. **C**) ADV/ETV 療法ベースライン・48 週後の HBV DNA の減衰量の比較. ETV 耐性を有する症例で HBV DNA 低下量が乏しい傾向（12週 $p=0.032$, 48週 $p=0.241$）を示した.

ADV 耐性で 2.1log, LAM 耐性＋ETV 耐性で 1.0 log, 3 剤耐性で 0.7log であった. ETV 耐性を有する 6 例と有さない 12 例の投与 12 週, 48 週の HBV DNA 減衰量を比較すると, ETV 耐性を有する例で減衰量が低下した（ETV 耐性なし vs ETV 耐性あり 12 週 1.1log vs 0.6log, $p=0.032$, 48 週 1.5log vs 1.0log, $p=0.241$）(Figure 2).

ベースラインで HBe 抗原陽性を示した 13 例中 1 例が治療 8 週の時点で陰性となり, 1 例を除くと HBe 抗原量が低下した. ALT についてはベースライン, 治療後で有意な変化を認めなかった (Table 2).

INNO-LiPA 法による耐性部位の検出では, 治療 48 週において, 新たな耐性の出現を認めなかった. 一部の症例でコドン 181 の A/V が A, コドン 236 の T が N に変化するなどの耐性クローンの消失が認められた. ウイルス量の低下にともない 1 例で INNO-LiPA 法による検出が不能となった (Table 3).

本研究中に有害事象の出現による中止例は認めなかった. 2 例が LAM/ADV 療法の時点で腎障害のため既に ADV が隔日投与となっていたが, この 2 例を含めて ADV/ETV 療法に移行後の腎障害の増悪例は認めなかった.

Table 3. ETV/ADV 療法ベースライン，48 週における耐性部位の検出

A) Baseline											
Case	Codon	80	173	180	204	181	233	236	184	202	250	194
	1	L	V	L	I	A	I	T	T	S	M	A
	2	L	V	L/M	I	A	I	N	T	S	M	A
	3	L	V	L/M	V	A	I	N	T/SCGA	S	M/V	A
	4	L/I	V	L/M	V/I	A	I	N	T	S	M/L	A
	5	L	V	L/M	V	A	I	N	T/ILFM	S/G	M	A
	6	L	V	L	M/I	A/T	I	N	T	S	M	A
	7	I	V	L/M	V/I	A	I	N	T	S	M	A
	8	L/I	V	L/M	M/I	A	I	N	T	S	M	A
	9	L	V	L/M	V	A	I	N	T	S/G	M	A
	10	L	V	L/M	M/V/I	A	I	N	T	S	M	A
	11	L	V	M	V	A	I	N	T	S	M	A
	12	L	V	L/M	M/V/I	A	I	N	T	S	M	A
	13	L	V/L	L/M	M/V/I	A/T	I	N	T	S	M	A
	14	L	V/L	L/M	V/I	A	I	N	T	S	M	A
	15	L/I	V	L/M	M/V/I	A	I	N	T	S	M	A
	16	L	V	L/M	M/V/I	A	I	N	T/ILFM	S/G	M	A
	17	L/I	V	L/M	M/I	A/V	I	N	T	S	M	A
	18	L	V	L/M	V	A	V	N	T/SCGA	S	M	A
B) Week 48												
Case	Codon	80	173	180	204	181	233	236	184	202	250	194
	1	L	V	L	*	A	I	N	T	S	M	A
	2	L	V	L/M	*	A	I	N	T	S	M	A
	3	L	V	M	V	A	I	N	GA/IL	S	M/I	A
	4	L/I	V	L/M	I	A	I	N	T	S	M/L	A
	5	L	V	M	V	A	I	N	T/ILFM	S/G	M	A
	6	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	7	I	V	L/M	I	A	I	N	T	S	M	A
	8	L/I	V	L/M	I	A	I	N	T	S	M	A
	9	L	V	M	V	A	I	N	T	G	M	A
	10	L	V	L/M	V	A	I	N	T	S	M	A
	11	L	V	M	V	A	*	N	T	S	M	A
	12	L	V	M	V	A	I	N	T	S	M	A
	13	L	L	M	V	A/T	I	N	T	S	M	A
	14	L	L	L/M	V	A	I	N	*	S	M	A
	15	L/I	V	L/M	V/I	A	I	N	T	S	M	A
	16	L	V	M	V	A	I	N	T/ILFM	S/G	M	A
	17	I	V	L	I	A	I	N	T	S	M	A
	18	L	V	M	V	A	V	N	SCGA	S	M	A

A：alanine，C：cysteine，G：glysine，F：phenylalanine，I：isoleucine，L：leucine，M：methionine，N：asparagine，S：serine，T：threonine，V：valine.
ND：not detected. *：impossible to judge.

III 考 察

B型慢性肝疾患に対する核酸アナログ療法の最も重要な問題は耐性ウイルスの出現である．ETV やTDFの登場により耐性ウイルスの出現率は低下した[19]が，既にLAM耐性を獲得してしまった多くの患者が全世界中に存在している[9]．日本肝

臓病学会ではLAM耐性例に対してはADVを併用するよう推奨している[15]．このLAM/ADV療法は多くの患者に有効であるが，一部の患者ではHBV DNAの低下量が不十分であり，HBV DNAの陰性化が得られない[16][17]．また，LAM耐性例ではLAM/ADV療法中にADV耐性が出現することが報告[20][21]されており，HBV DNAが陰性化しない，いわゆる不応例においては，新規の治療法が望まれてきた．以前われわれはLAM耐性例に対するLAM/ADV療法中にADV耐性を獲得した1例を経験したが，この症例はウイルス学的ブレイクスルーを発症し，軽度であるが肝炎の増悪をきたした．LAMを中止し，ADVは継続したままでETVを追加したところ，良好な抗ウイルス効果が得られ，ALT値も正常化した（Table 2, case 1）．この症例の経験を踏まえて，LAM/ADV療法不応例に対するADV/ETV療法の臨床研究を行った．ETVはLAM耐性とADV耐性例に[22][23]，ADVはLAM耐性とETV耐性例に対して抗ウイルス効果を発揮する[24]ことが示されており，LAM/ADV療法不応例に対するADV/ETV療法はTDFが承認されていない本邦の現状を考慮すると，また，交叉耐性を考えても理にかなった治療法と考えられる．

ADV不応例に対するETV療法の報告は近年散見されるが，いずれも症例数が少なく，短期間の成績が示されるにすぎない．40例のADV不応例（14例でADV耐性あり）に対してETVを投与した報告では，HBV DNA陰性化率が10%と低率で，6例（15%）にETV耐性の出現を認めた[25]．一方でHBe抗原陽性ADV不応14例（3例でADV耐性あり）に対するETV投与では，HBV DNA陰性化率は低いものの，15カ月の経過でHBV DNAはLAM投与歴なしで3.4log，LAM投与歴のあるもので3.9log低下し，この報告ではETV耐性の出現は認めなかった[26]．LAMとADVの2剤耐性を有する50例に対するETV投与では48週の経過でHBV DNA陰性化率は10%，HBV DNA量はベースライン6.90logより2.96logと低下した．ETV耐性はわずか1例(2%)で出現した[27]．ADV投与歴を有する症例に対するETV投与ではLAM投与歴を有する24例（9例がADV耐性あり）でHBV DNA陰性化率は42%であり，17%の症例でETV耐性が出現した[28]．報告によりウイルス陰性化率やHBV DNA低下量に差があるのは，症例数が少ないことや，人種や遺伝子型などの対象症例が異なること，過去に受けた核酸アナログの治療内容や期間に差があるためと思われる．

今回われわれが行ったLAM/ADV不応例に対するADV/ETV療法48週では平均でHBV DNAは1.2log低下した．低下量は少ないが，18例中5例が48週の治療中に2.1log未満を呈した．先に記したが，ADV不応例に対するETV単独療法によりETV耐性出現が報告されている[25][27][28]が，ADV/ETV療法では，更なる耐性の出現は認めなかった．ADVの併用投与がETV耐性を抑制した可能性が示唆された．

ADV/ETV療法中，脱落例・中止例は認めなかった．ADVによる腎障害の報告が散見される[29][30]が，ETVも腎排泄型のため注意が必要である．血清クレアチニンによる腎機能のモニターを定期的に行い，必要に応じて投与量の調節を行うことが重要である．

おわりに

LAM/ADV療法不応例に対するADV/ETV療法の成績を示した．経過観察期間が短く，少数例の検討ではあるが，HBV DNAは低下し，新たなアナログ耐性の出現は認めなかった．今後，観察期間を延長し，ADV/ETV療法の効果と安全性を検証する必要があると思われた．

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Research Article

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Indications and limitations for aged patients with chronic hepatitis C in pegylated interferon alfa-2b plus ribavirin combination therapy

Tsugiko Oze[1], Naoki Hiramatsu[1,*], Takayuki Yakushijin[1], Kiyoshi Mochizuki[1], Masahide Oshita[2], Hideki Hagiwara[3], Eiji Mita[4], Toshifumi Ito[5], Hiroyuki Fukui[6], Yoshiaki Inui[7], Taizo Hijioka[8], Masami Inada[9], Kazuhiro Kaytayama[10], Shinji Tamura[11], Harumasa Yoshihara[12], Atsuo Inoue[13], Yasuharu Imai[14], Michio Kato[15], Takuya Miyagi[1], Yuichi Yoshida[1], Tomohide Tatsumi[1], Shinichi Kiso[1], Tatsuya Kanto[1], Akinori Kasahara[1], Tetsuo Takehara[1], Norio Hayashi[1]

[1]*Department of Gastroenterology and Hepatology, Osaka University Graduate School of Medicine, Suita, Japan;* [2]*Osaka Police Hospital, Osaka, Japan;* [3]*Kansai Rousai Hospital, Amagasaki, Japan;* [4]*National Hospital Organization Osaka National Hospital, Osaka, Japan;* [5]*Osaka Koseinenkin Hospital, Osaka, Japan;* [6]*Yao Municipal Hospital, Yao, Japan;* [7]*Hyogo Prefectural Nishinomiya Hospital, Nishinomiya, Japan;* [8]*National Hospital Organization Osaka Minami Medical Center, Kawachinagano, Japan;* [9]*Toyonaka Municipal Hospital, Toyonaka, Japan;* [10]*Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan;* [11]*Minoh City Hospital, Minoh, Japan;* [12]*Osaka Rosai Hospital, Sakai, Japan;* [13]*Osaka General Medical Center, Osaka, Japan;* [14]*Ikeda Municipal Hospital, Ikeda, Japan;* [15]*National Hospital Organization Minami Wakayama Medical Center, Tanabe, Japan*

Background & Aims: This study investigated the efficacy and adverse effects of pegylated interferon (Peg-IFN) plus ribavirin therapy in aged patients with chronic hepatitis C (CH-C).

Methods: A total of 1040 naïve patients with CH-C (genotype 1, $n = 759$; genotype 2, $n = 281$), of whom 240 (23%) over 65 years old (y.o.), were treated with Peg-IFN alfa-2b plus ribavirin and assessed after being classified into five categories, according to age.

Results: The discontinuance rate was higher for patients over 70 y.o. (36%), the most common reason being anemia. In the presence of genotype 1, the SVR rate was similar (42–46%) among patients under 65 y.o. and declined (26–29%) among patients over 65 y.o. For patients over 65 y.o., being male (Odds ratio, OR, 3.5, $p = 0.035$) and EVR (OR, 83.3, $p < 0.001$) were significant factors for SVR, in multivariate analysis. The Peg-IFN dose was related to EVR, and when EVR was attained, 76–86% of patients over 65 y.o. achieved SVR. SVR was not achieved (0/35, 0/38, respectively) if a 1-log decrease and a 2-log decrease were not attained at week 4 and week 8, respectively. In the presence of genotype 2, the SVR rate was similar (70–71%) among patients under 70 y.o. and declined among patients over 70 y.o. (43%).

Conclusions: Aged patients up to 65 y.o. with genotype 1 and 70 y.o. with genotype 2 can be candidates for Peg-IFN plus ribavirin therapy. The response-guided therapy can be applied for aged patients with genotype 1.

Keywords: Pegylated interferon plus ribavirin therapy; Chronic hepatitis C; Aged patients.

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* Corresponding author. Address: Department of Gastroenterology and Hepatology, Osaka University Graduate School of Medicine, 2-2, Yamadaoka, Suita City, Osaka 565-0871, Japan. Tel.: +81 6 6879 3621; fax: +81 6 6879 3629.

E-mail address: hiramatsu@gh.med.osaka-u.ac.jp (N. Hiramatsu).

Abbreviations: HCV, hepatitis C virus; CH-C, chronic hepatitis C; HCC, hepatocellular carcinoma; Peg-IFN, pegylated interferon; SVR, sustained virologic response; RVR, rapid virologic response; EVR, early virologic response; LVR, late virologic response; NR, non-response; WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; Plt, platelet; G-CSF, granulocyte–macrophage colony stimulating factor.

Introduction

Pegylated interferon (Peg-IFN) plus ribavirin combination therapy has led to a marked progress in the treatment of chronic hepatitis C (CH-C) [1–4]. However, in aged patients, problems remain with respect to its anti-viral effect and tolerability [5–9]. Recently, the addition of a protease inhibitor to Peg-IFN plus ribavirin combination therapy has been reported, on the one hand, to improve the anti-viral effect, and, on the other hand, to increase side effects, especially severe anemia [10–11].

Therefore, this new therapy does not solve the problems encountered when treating aged patients.

With aging, the progression of liver fibrosis and the occurrence of hepatocellular carcinoma (HCC) have been shown to be accelerated, especially in patients over 60 y.o. [12–14]. In general, the anti-viral therapy can lead to an improvement in liver fibrosis and thus diminish the risk of HCC and ameliorate the prognosis in patients with CH-C [15–21]. Among aged patients, those results are mainly achievable upon eradication of the hepatitis C virus (HCV) [18,21]. Accordingly, the first goal of treatment of aged patients with a high-risk of HCC should be HCV elimination.

Thus, a treatment strategy, aiming at the improvement of the anti-viral efficacy in aged patients, should be established based on detailed large-scale studies.

Some points need to be further elucidated when using the Peg-IFN plus ribavirin combination therapy for the treatment of aged patients with CH-C: (i) the characteristics before treatment

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that would lead to the successful elimination of HCV, (ii) the prediction factors of treatment efficacy after the initiation of the therapy, and (iii) the utility of a response-guided therapy established in the treatment.

In the present study, using a large cohort, we aimed at clarifying these points taking into account the patients' age.

Patients and methods

Patients

This study was a retrospective, multicenter trial conducted by the Osaka University Hospital and other institutions participating in the Osaka Liver Forum. A total of 1040 naïve patients with CH-C were enrolled between December 2004 and June 2007. All patients were Japanese, infected with a viral load of more than 10^5 IU/ml, and treated with a combination of Peg-IFN alfa-2b plus ribavirin. Patients were excluded from the study if they had decompensated cirrhosis or other forms of liver disease (alcohol liver disease, autoimmune hepatitis), co-infection with hepatitis B or anti-human immunodeficiency virus. This study was conducted according to the ethical guidelines of the 1975 Declaration of Helsinki and informed consent was obtained from each patient.

Treatment

All patients received Peg-IFN alfa-2b (PEGINTRON; Schering-Plough, Kenilworth, NJ, USA) plus ribavirin (REBETOL; Schering-Plough). Treatment duration was 48 weeks for patients with genotype 1 and 24 weeks for those with genotype 2. As a starting dose, Peg-IFN alfa-2b was given once weekly, at a dosage of 1.5 μg/kg, and ribavirin was given at a total dose of 600–1000 mg/day based on body weight (body weight <60 kg, 600 mg; 60–80 kg, 800 mg; >80 kg, 1000 mg), according to a standard treatment protocol for Japanese patients.

Dose reduction and discontinuance

Dose modification followed, as a rule, the manufacturer's drug information on the intensity of the hematologic adverse effects. The Peg-IFN alfa-2b dose was reduced to 50% of the assigned dose when the white blood cell (WBC) count was below 1500/mm^3, the neutrophil count below 750/mm^3 or the platelet (Plt) count below 8×10^4/mm^3, and was discontinued when the WBC count was below 1000/mm^3, the neutrophil count below 500/mm^3 or the Plt count below 5×10^4/mm^3. Ribavirin was also reduced from 1000 to 600 mg, 800 to 600 mg, or 600 to 400 mg when the hemoglobin (Hb) was below 10 g/dl, and was discontinued when the Hb was below 8.5 g/dl. Peg-IFN alfa-2b and ribavirin had to be both discontinued if there was a need to discontinue either of them. No ferric medicine or hematopoietic growth factors, such as epoetin alpha, or granulocyte-macrophage colony stimulating factor (G-CSF), were administered.

Virologic assessment and definition of virologic response

Serum HCV RNA level was quantified using the COBAS AMPLICOR HCV MONITOR test, version 2.0 (detection range 6–5000 KIU/ml; Roche Diagnostics, Branchburg, NJ) and qualitatively analyzed using the COBAS AMPLICOR HCV test, version 2.0 (lower limit of detection 50 IU/ml; Roche Diagnostics). The rapid virologic response (RVR) was defined as undetectable serum HCV RNA at week 4; the early virologic response (EVR) as undetectable serum HCV RNA at week 12; and the late virologic response (LVR) as detectable serum HCV RNA at week 12 and undetectable serum HCV RNA at week 24. Moreover, the sustained virologic response (SVR) was defined as undetectable serum HCV RNA, 24 weeks after treatment.

According to the protocol, genotype 1 patients, with less than a 2-log decrease in HCV RNA level at week 12 compared to the baseline, or with detectable serum HCV RNA at week 24, had to stop the treatment and were regarded as non-response (NR). Treatment discontinuance was evaluated except for those patients who had discontinued the treatment at up to 24 weeks, due to absence of response. Anti-viral efficacy was evaluated, for all study patients, using the intention-to-treat analysis (ITT analysis) and the per protocol analysis (PP analysis) for patients without treatment discontinuation due to side effects, and was assessed considering the definition of EVR or LVR for genotype 1, and RVR or non-RVR for genotype 2, as previously reported [1].

Assessment of drug exposure

The amounts of Peg-IFN alfa-2b and ribavirin, taken by each patient during the full treatment period, were evaluated by reviewing the medical records. The mean doses of Peg-IFN alfa-2b and ribavirin were calculated individually as averages, on the basis of the body weight at baseline: Peg-IFN alfa-2b expressed as μg/kg/week, ribavirin expressed as mg/kg/day.

Statistical analysis

Patients' baseline data are expressed as means ± SD or median values. To analyze the difference between baseline data, ANOVA or Mantel–Haenszel Chi-square test were performed. Factors associated with the viral response were assessed by univariate analysis using the Mann–Whitney *U* test or Chi-square test and multivariate analysis using logistic regression analysis. A two-tailed *p* value <0.05 was considered significant. The analysis was conducted with SPSS version 15.0J (SPSS Inc., Chicago, IL).

Results

Patient's profile

Baseline characteristics of the patients categorized by age are shown in Table 1.

Genotype 1 patients ($n = 759$) were distributed into five categories: 266 patients were under 55 y.o. (group 1A), 159 were 55–59 y.o. (group 1B), 149 were 60–64 y.o. (group 1C), 134 were 65–69 y.o. (group 1D), and 51 were 70 y.o. or older (group 1E). With advancing age, the male-to-female ratio and peripheral blood cell count (WBC, neutrophil count, Red blood cell (RBC), Hb, Plt) decreased significantly. Patients with a progression of liver fibrosis (METAVIR fibrosis score 3 or 4) significantly increased with age (Table 1A).

Genotype 2 patients ($n = 281$) were also distributed into five categories: 145 patients were under 55 y.o. (group 2A), 43 were 55–59 y.o. (group 2B), 38 were 60–64 y.o. (group 2C), 41 were 65–69 y.o. (group 2D), and 14 were 70 y.o. or older (group 2E). As observed in genotype 1 patients, the peripheral blood cell count decreased and the ratio of advanced fibrosis (score 3–4) increased significantly with age (Table 1B). For both genotypes, the initial doses of Peg-IFN in patients over 70 y.o. were lower than in those under 70 y.o., this was not the case for the ribavirin doses.

Dose reduction and discontinuance for adverse event

The overall discontinuance rate of treatment was 15% (140/919); 18% (112/639) for genotype 1 and 10% (28/280) for genotype 2, respectively. Table 2 shows the reason for and the rate of treatment discontinuance according to age. The discontinuance rate increased with age, being 10% (36/363) for patients under 55 y.o., 15% (27/182) for patients with 55–59 y.o., 17% (28/169) for patients with 60–64 y.o., 19% (28/147) for patients with 65–70 y.o., and significantly higher, 36%, (21/58) for patients over 70 y.o. The discontinuance of treatment due to hemolytic anemia was significantly higher for patients over 70 y.o. as compared to those under 70 y.o. (<70 y.o., 1% (9/861) vs. ⩾70 y.o., 16% (9/58), $p < 0.0001$).

The rate without dose reduction of both drugs decreased with age (<55 y.o., 41% (171/411); 55–59 y.o., 20% (40/202); 60–64 y.o., 26% (48/187); 65–69 y.o., 23% (41/175); ⩾70 y.o., 18% (12/65)). In the presence of genotype 1, the mean dose of Peg-IFN

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Table 1. Baseline characteristics of patients.

Patients with genotype 1							
Factor		<55 y.o.	55 - 59 y.o.	60 - 64 y.o.	65 - 69 y.o.	≥70 y.o.	*p* value
Number		266	159	149	134	51	
Age (y.o.)		44.4 ± 8.1	56.9 ± 1.4	62.0 ± 1.4	66.8 ± 1.4	71.4 ± 1.7	<0.001
Sex: male / female		160 / 106	64 / 95	57 / 92	54 / 80	23 / 28	<0.001
Body weight (kg)		64.6 ± 11.7	58.3 ± 9.4	58.1 ± 9.6	56.3 ± 9.3	56.3 ± 9.2	<0.001
White blood cells (/mm³)		5608 ± 1668	4901 ± 1664	4888 ± 1488	5113 ± 1426	4883 ± 1511	<0.001
Neutrophils (/mm³)		2923 ± 1214	2425 ± 1031	2559 ± 1155	2535 ± 1017	2599 ± 1149	<0.001
Red blood cells (×10⁴/mm³)		454 ± 47	432 ± 38	427 ± 40	424 ± 37	424 ± 46	<0.001
Hemoglobin (g/dl)		14.4 ± 1.5	13.8 ± 1.2	13.7 ± 1.3	13.6 ± 1.2	13.7 ± 1.4	<0.001
Platelets (×10⁴/mm³)		18.6 ± 6.2	16.3 ± 5.7	15.4 ± 5.3	15.1 ± 5.0	14.4 ± 4.2	<0.001
AST (IU/l)		62 ± 50	62 ± 45	64 ± 46	72 ± 45	64 ± 40	0.295
ALT (IU/l)		79 ± 68	76 ± 64	73 ± 63	77 ± 58	65 ± 41	0.657
Serum HCV RNA (KIU/ml)*		1800	1600	1700	1700	1700	0.691
Histology (METAVIR)‡:	Fibrosis, 0 - 2 / 3 - 4	177 / 19	99 / 20	90 / 19	76 / 28	21 / 9	0.001
	Activity, 0 - 1 / 2 - 3	117 / 79	63 / 56	59 / 50	47 / 57	13 / 16	0.146
Peg-IFN dose (μg/kg/week)¶		1.47 ± 0.14	1.47 ± 0.16	1.46 ± 0.18	1.44 ± 0.18	1.36 ± 0.24	<0.001
Ribavirin dose (mg/kg/day)¶		11.5 ± 1.1	11.5 ± 1.4	11.5 ± 1.4	11.5 ± 1.7	11.2 ± 2.2	0.65

Patients with genotype 2							
Factor		<55 y.o.	55 - 59 y.o.	60 - 64 y.o.	65 - 69 y.o.	≥70 y.o.	*p* value
Number		145	43	38	41	14	
Age (y.o.)		40.9 ± 8.9	56.7 ± 1.3	62.3 ± 1.4	66.7 ± 1.5	71.8 ± 1.8	<0.001
Sex: male / female		78 / 67	17 / 26	17 / 21	18 / 23	6 / 8	0.441
Body weight (kg)		63.4 ± 12.0	59.5 ± 11.5	58.6 ± 11.7	58.5 ± 9.8	55.9 ± 6.8	0.783
White blood cells (/mm³)		6011 ± 1965	4874 ± 1346	4982 ± 1210	5079 ± 1877	4414 ± 871	<0.001
Neutrophils (/mm³)		3214 ± 1511	2468 ± 971	2576 ± 950	2492 ± 1119	2521 ± 683	0.001
Red blood cells (×10⁴/mm³)		454 ± 48	430 ± 42	432 ± 50	430 ± 43	408 ± 48	<0.001
Hemoglobin (g/dl)		14.3 ± 1.6	13.5 ± 1.3	13.9 ± 1.4	13.9 ± 1.3	13.3 ± 1.2	0.001
Platelets (×10⁴/mm³)		21.3 ± 5.4	18.3 ± 6.1	17.0 ± 5.2	15.8 ± 5.4	13.9 ± 4.7	<0.001
AST (IU/l)		53 ± 59	57 ± 45	55 ± 38	83 ± 48	68 ± 29	0.029
ALT (IU/l)		65 ± 59	73 ± 70	68 ± 62	105 ± 62	78 ± 43	0.008
Serum HCV RNA (KIU/ml)*		1700	1100	900	1100	500	0.008
Histology (METAVIR)‡:	Fibrosis, 0 - 2 / 3 - 4	102 / 0	25 / 3	29 / 2	21 / 9	7 / 1	<0.001
	Activity, 0 - 1 / 2 - 3	68 / 34	18 / 10	18 / 13	9 / 21	5 / 3	0.01
Peg-IFN dose (μg/kg/week)¶		1.48 ± 0.16	1.48 ± 0.14	1.45 ± 0.18	1.46 ± 0.15	1.28 ± 0.26	0.001
Ribavirin dose (mg/kg/day)¶		11.5 ± 1.1	11.4 ± 1.2	11.5 ± 1.4	11.3 ± 1.6	11.0 ± 1.4	0.55

*, Data shown are median values.
†, 201 Missing.
‡, 82 Missing.
¶, Initial doses.

during the whole treatment period was lower (1.1 ± 0.3 μg/kg/week) for patients over 70 y.o. than for those under 70 y.o. (1.3 ± 0.3 μg/kg/week) and that of ribavirin decreased with age (<55 y.o., 10.3 ± 1.9 mg/kg/day; 55–59 y.o., 9.8 ± 1.9 mg/kg/day; 60–64 y.o., 9.3 ± 2.3 mg/kg/day; 65–69 y.o., 9.2 ± 2.3 mg/kg/day; ⩾70 y.o., 8.5 ± 2.5 mg/kg/day). The same tendency was observed with genotype 2.

Sustained virologic response

In genotype 1 patients, the overall SVR rate was 40% (305/759), being 46% (123/266) for group 1A, 44% (70/159) for group 1B, 42% (62/149) for group 1C, 26% (35/134) for group 1D, and 29% (15/51) for group 1E, following ITT analysis. The same tendency was observed using the PP analysis ($n = 647$). The SVR rates for patients over 65 y.o. were significantly lower than those for patients under 65 y.o. (ITT analysis: ⩾65 y.o., 27% vs. <65 y.o., 44%, $p < 0.0001$; PP analysis: ⩾65 y.o., 31% vs. <65 y.o., 50%, $p < 0.0001$) (Fig. 1A). Among genotype 1 patients over 65 y.o., the SVR rate was significantly lower for female patients than for male patients (ITT analysis: male, 40% (31/77) vs. female, 18% (19/108), $p < 0.001$; PP analysis: male, 49% (27/55) vs. female, 20% (18/90), $p < 0.001$).

Moreover, for genotype 2 patients, the overall SVR rate was 78% (220/281), being 88% (128/145) for group 2A, 70% (30/43) for group 2B, 71% (27/38) for group 2C, 71% (29/41) for group 2D, and 43% (6/14) for group 2E, following ITT analysis. The same tendency was observed with the PP analysis ($n = 253$). The SVR rates for patients over 70 y.o. were significantly lower than those for patients under 70 y.o. (ITT analysis: ⩾70 y.o., 43% vs. <70 y.o., 80%, $p < 0.0001$; PP analysis: ⩾70 y.o., 56% vs. <70 y.o., 85%, $p < 0.05$) (Fig. 1B). Among patients over 70 y.o. with genotype 2, the difference according to gender was not clear because of the small sample.

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Table 2. Reasons for treatment discontinuation.

Factor	<55 y.o. (n = 363)	55 - 59 y.o. (n = 182)	60 - 64 y.o. (n = 169)	65 - 69 y.o. (n = 147)	≥70 y.o. (n = 58)	Total (n = 919)
Neutropenia	2	3	0	0	0	5
Thrombopenia	1	0	1	1	0	3
Anemia	0	4	3	2	9	18
Fatigue	1	1	3	3	1	9
Gastrointestinal disorder	2	1	0	0	1	4
Cough, Dyspnea	1	0	3	0	0	4
Vertigo	1	0	0	0	3	4
Psychosis (depression)	7 (3)	7 (3)	4 (4)	3 (3)	2 (2)	23
Rash	5	2	5	7	1	20
Thyroid dysfunction	2	0	2	0	0	4
Fundal hemorrhage	0	2	0	2	0	4
Drug-induced hepatitis	3	1	0	0	0	4
Interstitial pneumonia	0	1	0	1	1	3
Cerebral hemorrhage, infarction	2	0	0	1	0	3
Others	9	5	7	8	3	32
Total	36 (10%)	27 (15%)	28 (17%)	28 (19%)	21 (36%)	140 (15%)

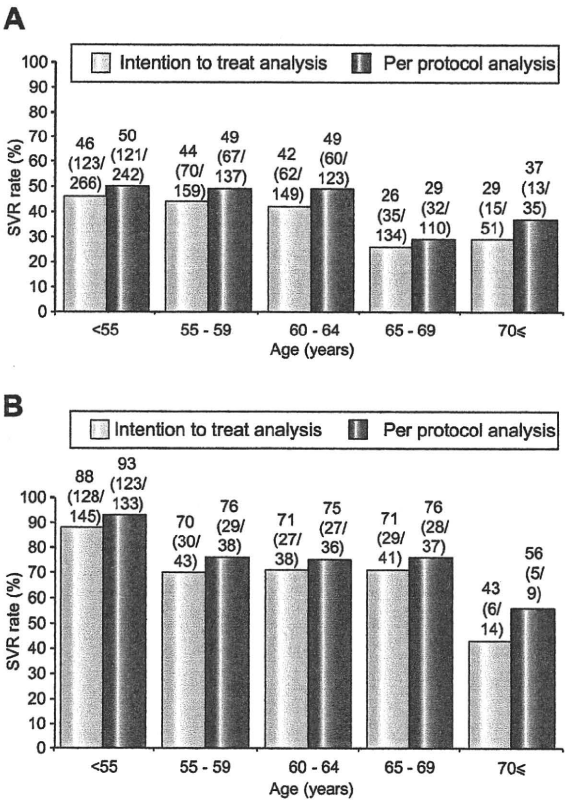

Fig. 1. SVR rate according to age. (A) Genotype 1. (B) Genotype 2.

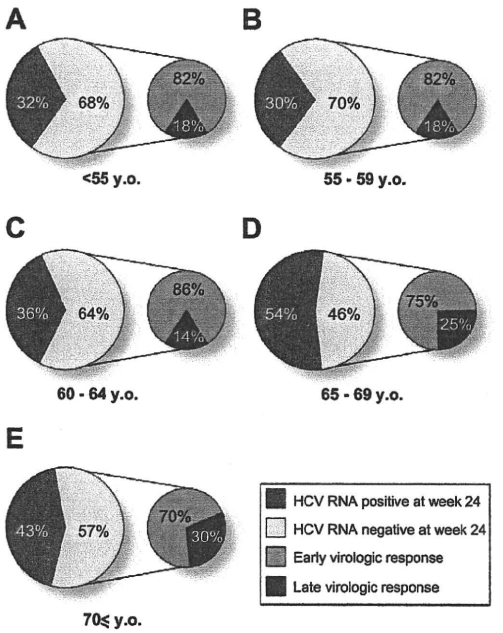

Fig. 2. Antiviral effect during treatment according to age. (A) <55 y.o. (B) 55–59 y.o. (C) 60–64 y.o. (D) 65–69 y.o. (E) ⩾70 y.o.

Timing of HCV RNA negativation for genotype 1, according to age

Treatment responses distributing EVR, LVR, and NR according to age are shown in Fig. 2. The rates of NR were similar in patient groups under 65 y.o. (30–36%), but increased in almost half of the patients over 65 y.o. (p <0.0001). Moreover, among the virologic responders, the proportion of LVR tended to increase in patients over 65 y.o. (25–30%) compared to patients under 65 y.o. (14–18%) (p = 0.06).

SVR rate according to the timing of HCV RNA negativation

SVR rates according to EVR or LVR in genotype 1, and RVR or non-RVR in genotype 2 are summarized in Table 3. Genotype 1 patients with EVR achieved high SVR rates regardless of age; in particular, if EVR had been attained, 76% of patients with 65–69

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Table 3. SVR rate according to genotype and viral response in patients responding to PEG-IFN plus ribavirin combination therapy.

Factor	<55 y.o.	55 - 59 y.o.	60 - 64 y.o.	65 - 69 y.o.	≥70 y.o.
Genotype 1					
with EVR, % (n)	85 (114/134)	79 (62/79)	81 (55/68)	76 (29/38)	86 (12/14)
with LVR, % (n)	23 (7/30)	29 (5/17)	46 (5/11)	23 (3/13)	17 (1/6)
Genotype2					
with RVR, % (n)	93 (57/61)	82 (14/17)	85 (17/20)	92 (11/12)	100 (4/4)
without RVR*, % (n)	96 (22/23)	60 (6/10)	57 (4/7)	50 (4/8)	0 (0/3)

RVR, rapid virologic response.
EVR, early virologic response.
LVR, late virologic response.
*, Serum HCV RNA was detectable at week 4, but undetectable at week 24.

Table 4. Multivariate analysis for the factors associated with SVR among all patients.

Factor	Category	Odds ratio	95% CI	*p*
Age (y.o.)	<65 / ≥65	0.485	0.295 - 0.799	0.005
Sex	male / female	0.524	0.353 - 0.777	0.001
Platelets ($\times 10^4$/mm^3)	<12 / ≥12	1.780	1.039 - 3.049	0.040
Serum HCV RNA (KIU/ml)	<2000 / ≥2000	0.599	0.401 - 0.896	0.010
Histology (METAVIR): Fibrosis	0 - 2 / 3 - 4	0.599	0.333 - 1.076	0.090

y.o. and 86% of patients over 70 y.o. achieved SVR, and these SVR rates compared favorably with those of younger patients. On the other hand, the SVR rates for patients with LVR ranged from 17% to 46%, which were lower than those for EVR patients in each age group, and no significant differences of SVR rates were found among LVR patients by age.

With genotype 2, patients with RVR achieved high SVR rates ranging from 82% to 100% regardless of age. Even for patients without RVR, 96% of those under 55 y.o. attained SVR, a rate that was significantly higher than that for patients over 55 y.o. (50%, 14/28) (p <0.001).

Factors associated with SVR for genotype 1

The factors associated with SVR were assessed for the variables shown in Table 1. The factors selected as significant by the univariate analysis: age, gender, WBC, neutrophils, RBC, Hb, Plt, aspartate aminotransferase, serum HCV RNA level, the degree of liver fibrosis, and the initial dose of Peg-IFN, were evaluated by multivariate logistic regression analysis. The factor of age over 65 y.o. was the independent factor for SVR (p = 0.005), apart from the gender (p = 0.001), Plt value (p <0.05), and serum HCV RNA level (p = 0.01) (Table 4).

Factors associated with EVR and SVR for patients over 65 y.o. with genotype 1

The results of univariate analysis for EVR among patients over 65 y.o. are shown in Table 5A. Gender, Plt value, and mean dose of Peg-IFN during the first 12 weeks were factors significantly associated with EVR. In multivariate analysis, the mean dose of Peg-IFN during the first 12 weeks was the independent factor for EVR (p = 0.03), apart from gender (p = 0.002) (Table 5B). The EVR rates were 41% (41/101) in patients who received ⩾1.2 μg/kg/week on average during the first 12 weeks, and declined to 36% (8/22) in patients given 0.9–1.2 μg/kg/week of Peg-IFN, and to 14% (3/22) in patients administered with <0.9 μg/kg/week of Peg-IFN.

The baseline and on-treatment factors, which are correlated with the SVR among the patients over 65 y.o., were assessed by univariate and multivariate analyses. Univariate analysis showed that factors significantly associated with SVR were gender and virologic response (Table 6A), and they were also selected as significant independent factors in multivariate analysis (p = 0.035, p <0.001) (Table 6B).

Negative prediction of SVR for patients over 65 y.o. with genotype 1

We tried positive and negative predictions of SVR for aged patients, focusing on the decrease of HCV RNA at treatment week 4 and 8. The SVR rate was 47% (29/62) for patients with more than a 1-log decrease in HCV RNA level at week 4, while no patients with less than a 1-log decrease at week 4 attained SVR (0/35) (p <0.0001). Similarly, 55% (35/64) of patients with more than a 2-log decrease at week 8 attained SVR, whereas no patients with less than a 2-log decrease at week 8 attained SVR (0/38) (p <0.0001).

Discussion

Peg-IFN plus ribavirin combination therapy can improve anti-viral efficacy and is presently recommended as first-line therapy [1–4]. However, with respect to aged patients with CH-C, there have been only a few small-scale cohort studies which reported poor anti-viral effect and poor tolerability in comparison with non-aged patients [5–9]. The problem in the treatment of aged patients with CH-C is most serious in Japan, because HCV carriers in Japan are 10–20 years older than those in the United States and European countries [22]. Therefore, in the present study, we examined the efficacy and prevalence of side effects with a focus on patient's age using a large-scale cohort.

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Table 5. Factors associated with EVR among patients over 65 y.o.

Univariate analysis				
Factor		EVR	Non-EVR	*p* value
Number		52	93	
Age (y.o.)		67.9 ± 2.3	67.8 ± 2.5	0.66
Sex: male / female		28 / 24	27 / 66	0.003
White blood cells (/mm³)		5063 ± 1474	5001 ± 1422	0.76
Neutrophils (/mm³)		2566 ±1110	2551 ± 1071	0.87
Red blood cells (×10⁴/mm³)		426 ± 36	421 ± 38	0.64
Hemoglobin (g/dl)		13.7 ± 1.2	13.5 ± 1.2	0.21
Platelets (×10⁴/mm³)		16.5 ± 5.5	14.0 ± 4.6	0.009
AST (IU/L)		70 ± 51	70 ± 40	0.49
ALT (IU/L)		76 ± 58	70 ± 41	0.80
Serum HCV RNA (KIU/ml)*		1700	1900	0.62
Histology (METAVIR)†:	Fibrosis, 0 - 2 / 3 - 4	25 / 10	47 / 20	0.54
	Activity, 0 - 1 / 2 - 3	16 / 19	29 / 37	0.52
Peg-IFN dose (μg/kg/week)‡		1.35 ± 0.24	1.25 ± 0.31	0.03
Ribavirin dose (mg/kg/day)‡		10.0 ± 2.2	9.6 ± 2.3	0.40

Multivariate analysis				
Factor	Category	Odds ratio	95% CI	*p* value
Sex	male / female	0.309	0.149 - 0.644	0.002
Platelets (×10⁴/mm³)	<12 / ≥12	-	-	N.S
Peg-IFN dose (μg/kg/week)‡	<1.2 / ≥1.2	2.481	1.079 - 5.705	0.03

*, Data shown are median values.
†, 43 Missing.
‡, Mean doses during 0 to 12 weeks.
N.S., not statistically significant.

Table 6. Factors associated with SVR among patients over 65 y.o.

Univariate analysis				
Factor		SVR	Non-SVR	*p* value
Number		45	100	
Age (y.o.)		68.0 ± 2.4	67.7 ± 2.5	0.45
Sex: male / female		27 / 18	28 / 72	<0.001
White blood cells (/mm³)		5006 ± 1516	5030 ± 1409	0.81
Neutrophils (/mm³)		2575 ±1130	2548 ± 1063	0.96
Red blood cells (×10⁴/mm³)		427 ± 40	421 ± 36	0.53
Hemoglobin (g/dl)		13.8 ± 1.3	13.5 ± 1.2	0.14
Platelets (×10⁴/mm³)		16.1 ± 5.6	14.3 ± 4.7	0.09
AST (IU/L)		71 ± 54	69 ± 40	0.47
ALT (IU/L)		76 ± 56	70± 43	0.77
Serum HCV RNA (KIU/ml)*		1700	2000	0.51
Histology (METAVIR)†:	Fibrosis, 0 - 2 / 3 - 4	21 / 8	51 / 22	1.00
	Activity, 0 - 1 / 2 - 3	14 / 15	31 / 41	0.66
Peg-IFN dose (μg/kg/week)‡		1.27 ± 0.28	1.23 ± 0.33	0.31
Ribavirin dose (mg/kg/day)‡		8.8 ± 2.1	9.1 ± 2.5	0.38
Virologic response: EVR / non-EVR		41 / 4	11 / 89	<0.001

Multivariate analysis				
Factor	Category	Odds ratio	95% CI	*p* value
Sex	male / female	0.283	0.088 - 0.914	0.035
Virologic response	EVR / non-EVR	0.012	0.004 - 0.043	<0.001

*, Data shown are median values.
†, 43 Missing.
‡, Mean doses during treatment.

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With respect to the side effects and discontinuance rate of treatment in aged patients with CH-C, treated with Peg-IFN plus ribavirin combination therapy, Reddy et al. reported that there was no difference related to the incidence and reason for side effects between non-aged and aged patients [6]. Another paper reported that the incidence of side effects was more frequent in aged patients [5]. In our study, not only the continuance rate without reduction of both drug decreased with age, but also the discontinuance rate of treatment increased with age, with a third of the patients over 70 y.o. discontinuing the treatment. The discrepancy, existing between our results and those reported in the former study cited above, is due to the difference in the number of aged patients enrolled; Reddy' s study analyzed a small cohort including only a few cases of patients over 65 y.o. and classified all those over 50 y.o. as aged patients.

Discontinuance of treatment due to progression of anemia was significantly higher in patients over 70 y.o., accounting for 43% (9/21) of the discontinuance in this group. Although the ratio of advanced fibrosis (score 3–4) increased with age, the high discontinuance rate due to anemia among patients over 70 y.o. was similar regardless of the progression of fibrosis (F0-2: <70 y.o., 1% (6/559) vs. ⩾70 y.o., 21% (6/28), p <0.0001; F3-4: <70 y.o., 0% (0/83) vs. ⩾70 y.o., 22% (2/9), p <0.0001). It is possible that poor hematopoietic function and renal function led to the progression of anemia in aged patients. For patients who develop severe anemia, using epoetin alpha or taribavirin, which are ribavirin prodrugs, has been shown to result in a lower incidence of anemia, although no significant increase of SVR has been reported so far, even with the addition of taribavirin to Peg-IFN [23–24].

With genotype 1 patients, the SVR rates were almost equal up to 65 y.o. (49–50%), but decreased to 31% (45/145) among the patients that were over 65 y.o., and even for those who completed the entire treatment schedule in this study. Since the degree of liver fibrosis and drug exposure have been shown to be associated with anti-viral efficacy, the progression of liver fibrosis or decrease of drug exposure with age could account for the reduction of SVR rate among the aged patients. However, the stratified analysis, according to the progression of liver fibrosis and drug exposure, revealed that older patients still yielded low a SVR rate (F0-2, Peg-IFN during the first 12 weeks ⩾1.2 μg/kg/week:<65 y.o., 55% (143/261) vs. ⩾65 y.o., 33% (15/46), p <0.0001; F0-2, Peg-IFN during the first 12 weeks <1.2 μg/kg/week:<65 y.o., 43% (26/60) vs. ⩾65 y.o., 23% (6/26), p = 0.07), which means that older patients would be difficult to treat. From our results showing a low SVR rate and a high discontinuance rate for patients over 65 y.o., the genotype 1 patients under 65 y.o were those who benefited the most from Peg-IFN plus ribavirin combination therapy. The high prevalence of treatment failure (non-SVR) among the aged patients seems to be due to the high populations of NR and LVR (Fig. 2). A high population of LVR is considered to lead to a higher transient response rate among aged patients, since those over 65 y.o. with LVR showed a much higher relapse rate (79%, 15/19) than those with EVR (21%, 11/52) (p <0.0001), as can be seen from Table 3.

In this study, multivariate analysis for SVR, in patients over 65 y.o., showed that the factors associated with SVR were EVR and gender. This indicates that better SVR can be expected even with older patients if EVR is attained and response-guided therapy guidelines can be useful for aged patients. A low SVR rate among aged female patients was as previously reported [7], although the mechanism remains unclear. This finding suggests that female patients should be treated before 65 y.o.

The next question is how aged patients should be treated in order to attain EVR. We have examined the impact of drug exposure on treatment efficacy [25–26] and reported that Peg-IFN is dose-dependently correlated with EVR [25]. In this study, the dose-dependent efficacy of Peg-IFN for EVR was also revealed in aged patients over 65 y.o., with less than 0.9 μg/kg/week of Peg-IFN leading to a low EVR rate for aged patients. If patients are difficult to treat with more than 1.2 μg/kg/week of Peg-IFN, using as much Peg-IFN as possible is desirable, in order to attain higher EVR rates. Accordingly, a reduction of Peg-IFN to 80% may need to be considered, although the manufacturer's drug information recommends reducing the dose of Peg-IFN to 50% of the assigned one. Since reduction of Peg-IFN has been reported to not affect the SVR rate after HCV RNA disappearance [26], using G-CSF for aged patients who develop severe neutropenia can be beneficial, especially in the first 12 weeks.

We also examined the negative prediction of SVR, i.e. an HCV RNA decrease at an earlier point of treatment than the usual prediction at treatment week 12 of a 2-log decrease, among aged patients with CH-C treated by Peg-IFN plus ribavirin combination therapy. We found that none of the patients without a 1-log decrease at week 4 or a 2-log decrease at week 8 could attain SVR, even if the complete treatment duration was given, the negative predictive value (NPV) for SVR equaled 100%. This earlier prediction is applied just as well to aged patients as to non-aged patients in order to avoid additional adverse effects. Recently, a genetic polymorphism near the *IL28B* gene has been reported to be associated with non-response to Peg-IFN plus ribavirin combination therapy [27–29], which is beneficial to patients. Nevertheless, even in the presence of this genetic polymorphism, NPV for SVR remains at 57–87%; 100% accuracy is not guaranteed. Thus, in addition to the pretreatment prediction, an earlier negative prediction for SVR during treatment is also considered to be useful.

We have shown in this study that, in the presence of genotype 2, HCV was easily eliminated even among aged patients; the SVR rates were over 75% for patients who had completed the treatment, and these rates were similar up to 70 y.o. The SVR rate of genotype 2 patients over 70 y.o. was 43%, however, the age limitation of the treatment among patients over 70 y.o. remains unclear, because of the small number of patients enrolled in this study. We have reported that the reduction of treatment drugs had little effect on anti-viral efficacy for patients with genotype 2, meaning that SVR can be attained even with aged patients who are usually given lower drug doses than non-aged patients [30]. Patients under 70 y.o. with genotype 2 should, at least, benefit from this therapy. The SVR rate was maintained among genotype 2 patients being 65–69 y.o., compared to genotype 1 patients. The higher efficacy with shorter treatment duration in genotype 2 aged patients can account for it.

In conclusion, the strategy of a response-guided therapy and an earlier negative prediction for SVR may be beneficial for aged patients, especially those with genotype 1. At present, aged patients up to 65–70 y.o. with CH-C can be candidates for Peg-IFN plus ribavirin combination therapy, if its efficacy and adverse effects are fully taken into account. At the same time, there is an urgent need to establish new treatment procedures, such as combination therapy with protease inhibitor plus polymerase inhibitor without Peg-IFN or ribavirin, for non-responders or patients

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with poor tolerability for Peg-IFN plus ribavirin combination therapy among aged patients.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this paper.

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Amino Acid Substitution in the Core Protein has no Impact on Relapse in Hepatitis C Genotype 1 Patients Treated With Peginterferon and Ribavirin

Yuko Inoue,[1] Naoki Hiramatsu,[1]* Tsugiko Oze,[1] Takayuki Yakushijin,[1] Kiyoshi Mochizuki,[1] Kazuto Fukuda,[2] Eiji Mita,[3] Yoshimichi Haruna,[4] Atsuo Inoue,[4] Yasuharu Imai,[2] Atsushi Hosui,[1] Takuya Miyagi,[1] Yuichi Yoshida,[1] Tomohide Tatsumi,[1] Shinichi Kiso,[1] Tatsuya Kanto,[1] Akinori Kasahara,[1] Tetsuo Takehara,[1] and Norio Hayashi[5]

[1]*Department of Gastroenterology and Hepatology, Osaka University Graduate School of Medicine, Suita, Japan*
[2]*Ikeda Municipal Hospital, Ikeda, Japan*
[3]*National Hospital Organization Osaka National Hospital, Osaka, Japan*
[4]*Osaka General Medical Center, Osaka, Japan*
[5]*Kansai Rousai Hospital, Amagasaki, Japan*

Previous reports demonstrated that amino acid (aa) substitutions in the hepatitis C virus (HCV) core protein are predictors of non-virological responses to pegylated interferon (Peg-IFN) and ribavirin combination therapy. The aim of this study was to investigate the impact of core aa substitutions on viral kinetics during the treatment and relapse after the treatment. The 187 patients with HCV genotype 1 enrolled in this study were categorized into four groups according to core aa substitution patterns: double-wild group (n = 92), Arg70/Leu91; 70-mutant group (n = 42), Gln70/Leu91; 91-mutant group (n = 31), Arg70/Met91; and double-mutant group (n = 22), Gln70/Met91. The relationship between the core aa substitutions and the virological response was examined. Multivariate logistic regression analyses showed that substitution at aa 70 was significantly associated with a poor virological response during the first 12 weeks (decline of <1 log from baseline at week 4, <2 log at week 12), and substitution at aa 91 was significantly associated with detectable HCV RNA at week 24. With respect to relapse, only the ribavirin exposure (odds ratio (OR), 0.77; 95% confidence interval (CI), 0.60–0.98) and HCV RNA disappearance between weeks 13 and 24 (OR, 23.69; 95% CI, 5.44–103.08) were associated independently with relapse, with no correlation being found with the core aa substitutions and relapse. In conclusion, the results showed that core aa substitutions can be strong predictive factors at pretreatment of the non-response, but not for relapse, for virological responders with HCV RNA disappearance during treatment. *J.*

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KEY WORDS: amino acid substitution; core protein; hepatitis C virus; peginterferon and ribavirin combination therapy; relapse

INTRODUCTION

The current standard of care for chronic hepatitis C patients is combination therapy using pegylated interferon (Peg-IFN) and ribavirin [Anonymous, 2002; Strader et al., 2004; Dienstag and McHutchison, 2006]. However, the treatment outcome in response to this combination therapy among patients infected with hepatitis C virus (HCV) genotype 1 is still unsatisfactory and the chance of sustained virological response ranges from 42% to 52% [Manns et al., 2001; Fried et al., 2002; Hadziyannis et al., 2004]. Therefore, tailoring treatment regimens for individual patients has become an important issue.

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*Correspondence to: Naoki Hiramatsu, MD, PhD, Department of Gastroenterology and Hepatology, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan. E-mail: hiramatsu@gh.med.osaka-u.ac.jp

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