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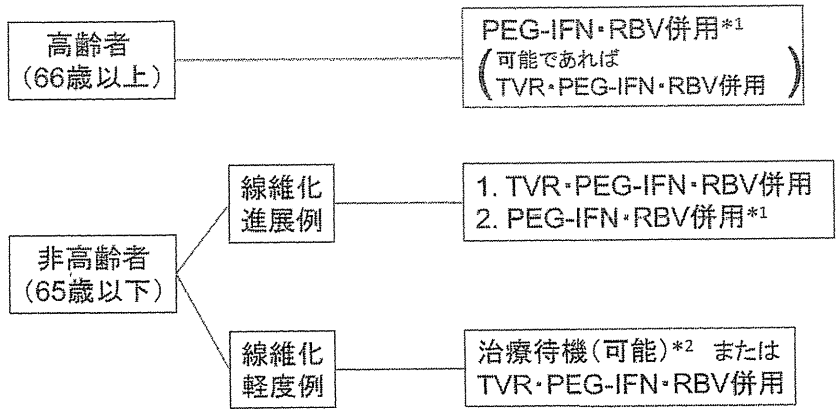
資料1　治療フローチャート

C型慢性肝炎ゲノタイプ1型・高ウイルス量症例 治療の原則（初回治療）

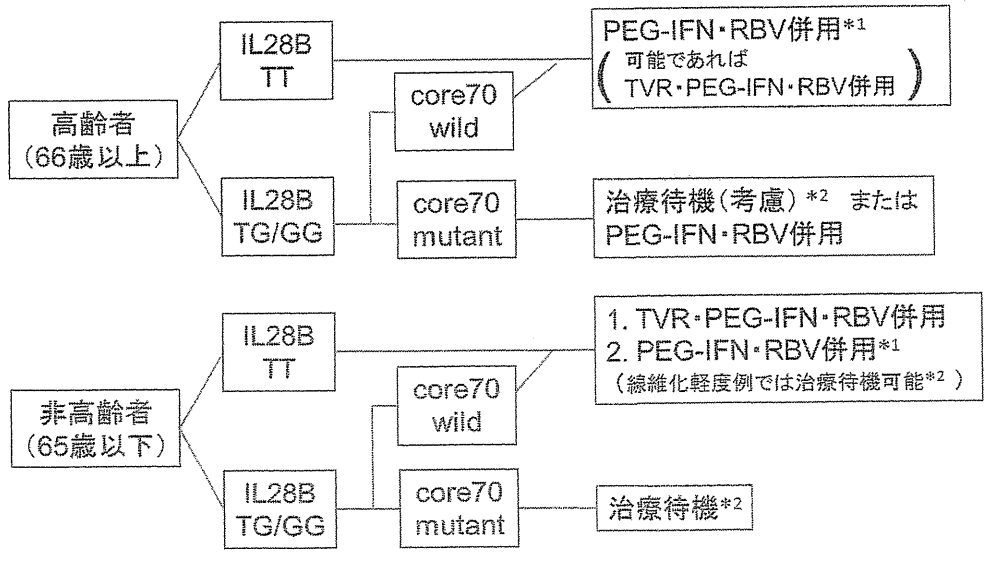
＜IL28B SNP/core70番アミノ酸変異が測定できない場合＞



*1 うつ症状合併ではIFN-β・RBV併用も考慮に入れる
*2 ALT値異常例では肝庇護療法またはPEG-IFN・IFN少量長期

C型慢性肝炎ゲノタイプ1型・高ウイルス量症例 治療の原則（初回治療）

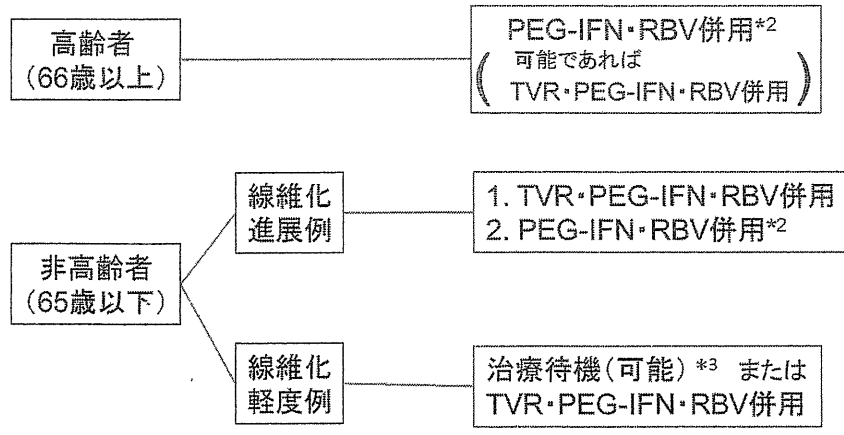
＜IL28B SNP/core70番アミノ酸変異が測定できる場合＞



*1 うつ症状合併ではIFN-β・RBV併用も考慮に入れる
*2 ALT値異常例では肝庇護療法またはPEG-IFN・IFN少量長期

C型慢性肝炎ゲノタイプ1型・高ウイルス量症例 治療の原則（既治療）

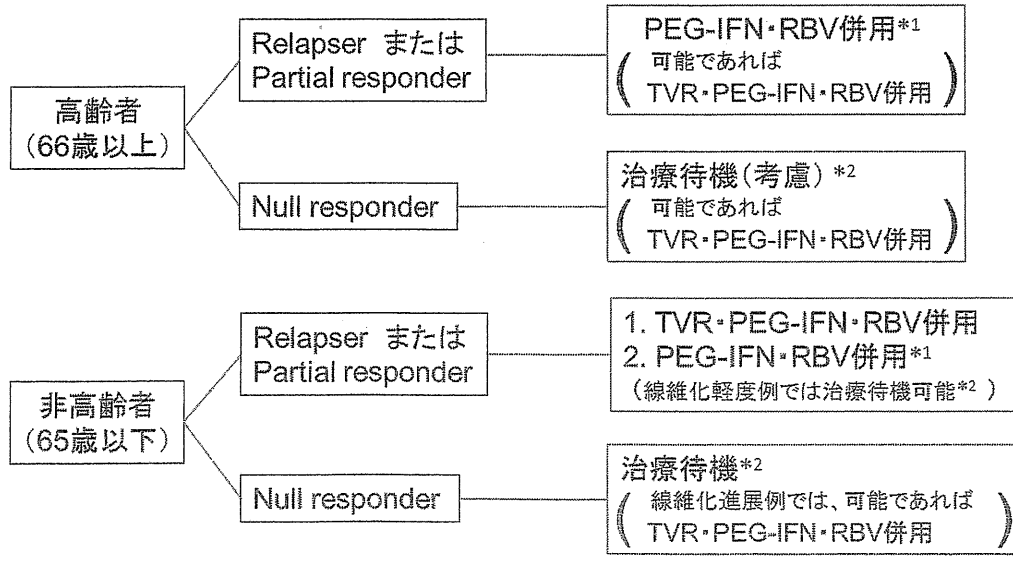
＜前治療歴が不明の場合 *1＞



*1 IL28B SNP/core70番アミノ酸変異が測定可能な場合は初回治療の方針に準じる
*2 うつ症状合併ではIFN-β・RBV併用も考慮に入れる
*3 ALT値異常例では肝庇護療法またはPEG-IFN・IFN少量長期

C型慢性肝炎ゲノタイプ1型・高ウイルス量症例 治療の原則（既治療）

＜前治療歴が判明している場合＞



*1 うつ症状合併ではIFN-β・RBV併用も考慮に入れる
*2 ALT値異常例では肝庇護療法またはPEG-IFN・IFN少量長期

資料2 治療中止基準

(1) Peg-IFN+リバビリン併用療法の治療中止基準

HCV RNA 量低下が治療開始 8 週で 1 log 未満、あるいは 12 週で 2 log 未満の症例では、治療を終了することを検討すべきであり、12 週で 2 log 以上の HCV RNA 量低下を認めた場合も、36 週までに HCV RNA の陰性化がない場合には治療を中止する。

ただし、肝細胞癌発生リスクが高く、治療開始後 36 週の時点で AST/ALT が正常化した症例では、治療中止基準を満たした場合でも生化学的改善効果を目指して、治療を中止せず 48 週までの継続治療を考慮する。

(2) テラプレビル+Peg-IFN+リバビリン併用療法の治療中止基準

治療開始 4 週で HCV RNA 量が 3 logcopy/ml 以下にならない症例、12 週時に HCV RNA が陰性化しない症例、ならびに治療中に HCV RNA 量が 2 logcopy/ml 以上上昇する症例では、治療を中止すべきである。

(3) 生化学的改善を目指した Peg-IFN (IFN)少量投与の治療中止基準：

治療開始 6 か月以内に ALT 値改善(40 IU/L 以下)あるいは AFP 値改善(10 ng/ml 以下)を認めない場合は治療を中止する。

資料3 ウイルス学的反応の定義

ウイルス学的反応	定義
Rapid virological response (RVR)	治療開始後4週で血中HCV RNA感度以下
extended RVR	治療開始後4週・12週のいずれにおいても血中HCV RNA感度以下
Early virological response (EVR)	cEVRあるいはpEVR
Complete EVR(cEVR)	治療開始後12週で血中HCV RNA感度以下
Partial EVR(pEVR)	治療開始後12週で血中HCV RNAが陽性だが2 log以上低下
End-of-treatment response (ETR)	治療終了時血中HCV RNA感度以下
Sustained virological response (SVR)	治療終了後24週で血中HCV RNA感度以下
Breakthrough	治療中にいったん感度以下となった血中HCV RNAが治療中に再出現
Relapse	治療中にいったん感度以下となった血中HCV RNAが治療終了後に再出現
Non-responder	治療中にHCV-RNAが感度以下にならず
Null responder	治療開始後12週で血中HCV RNAの減少が2 log未満
Partial responder	治療開始後12週で血中HCV RNAが2 log以上減少、しかし治療開始後24週で血中HCV RNAが感度以下にならない

注：AASLDから2009年に発表された「C型肝炎ガイドライン」[116]では、「治療開始後24週で血中HCV RNAが感度以下にならない」「治療開始後24週で血中HCV RNAの減少が2 log未満」「治療開始後24週で血中HCV RNAが2 log以上減少、しかし感度以下にならない」を、それぞれnonresponder、null responder、partial responderと定義していた。しかし、テラプレビルとボセプレビルの登場を期してアップデートされた2011版[101]では、nonresponderというカテゴリーは採用されず、null responder、partial responderが「治療開始後12週で血中HCV RNAの減少が2 log未満」「治療開始後12週で血中HCV RNAが2 log以上減少、しかし治療開始後24週で血中HCV RNAが感度以下にならない」と再定義されている。

本ガイドラインでは2011年版のAASLDに準じてnull/partial responderを定義し、さらにnull/partial responderを包括した“無効”として”Non-responder”を定義する。

資料4　HCVについての外注検査

IL28B SNP、HCV コア領域・NS5A 領域のアミノ酸変異は保険適用外であるものの、外注検査で測定可能である。各施設の検査会社担当者に直接照会されたい。

（1）IL28B SNP 測定

ある検査会社では、専用容器（EDTA-2Na 加）、検体量 5.0 ml、報告日数 12～16 日としている。なお、価格については各施設の検査会社担当者に直接照会されたい。

なお、IL28B 測定はヒトゲノムを検体としており、医療領域では「医療・介護関係事業者における個人情報の適切な取り扱いのためのガイドライン（厚生労働省）」、および「遺伝学的検査に関するガイドライン」（遺伝医学関連 10 学会）、「ファーマコゲノミクス検査の運用指針」（日本臨床検査医学会など）を、また研究領域では「ヒトゲノム・遺伝子解析研究に関する倫理指針」（文部科学省・厚生労働省・経済産業省）を遵守する必要がある。したがって、個人の遺伝情報の保護に十分留意しつつ、IL28B SNP 検査について患者に対して文書による説明を十分に行い、同意を得なければならない。検査会社によっては説明文書・同意書を用意しているところもあるので、参考にされたい。また、施設内に倫理委員会が設置されていれば、IL28B SNP 測定についてあらかじめ倫理委員会に申請し、承認を得るべきである。

（2）HCV コア領域・NS5A 領域のアミノ酸変異測定

ある検査会社によればそれぞれ以下のとおりである。

HCV コア領域 70 番・91 番アミノ酸変異：専用容器、検体量 5.0 ml、報告日数 10～14 日。

HCV NS5A 領域アミノ酸変異（ISDR）：専用容器、検体量 5.0 ml、報告日数 10～14 日。

なお、価格については各施設の検査会社担当者に直接照会されたい。

参考資料　平成 23 年度厚生労働省科学研究費肝炎等克服緊急対策研究事業（肝炎分野）ウイルス肝炎における最新の治療法の標準化を目指す研究班による平成 24 年 B 型 C 型慢性肝炎・肝硬変治療ガイドライン

（http://www.jsh.or.jp/medical/date/H24_guideline.pdf）

Treatment Guidelines of Hepatitis C

The Committee for Hepatitis Clinical Guidelines, Japan Society of Hepatology

Key words: hepatitis C　guidelines　telaprevir　interferon　ribavirin

Kanzo 2012; 53: 355—395

The Committee for Hepatitis Clinical Guidelines, JSH

Yasuhiro Asahina[1)], Namiki Izumi[2)], Makoto Oketani[3)], Hiromitsu Kumada[4)], Kazuhiko Koike[5)], Fumitaka Suzuki[4)], Hajime Takikawa[6)※], Atsushi Tanaka[6)*], Hirohito Tsubouchi[3)], Norio Hayashi[7)], Naoki Hiramatsu[8)], Hiroshi Yotsuyanagi[9)]（In order of the Japanese syllabary）

1）Department of Gastroenterology and Hepatology, Department for Hepatitis Control, Tokyo Medical and Dental University, Tokyo, Japan
2）Division of Gastroenterology and Hepatology, Musashino Red Cross Hospital, Tokyo, Japan
3）Digestive and Lifestyle Disease, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan
4）Department of Hepatology, Toranomon Hospital, Tokyo, Japan
5）Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan (Director General of JSH)
6）Department of Medicine, Teikyo University School of Medicine, Tokyo, Japan
7）Kansai Rosai Hospital, Amagasaki, Japan
8）Department of Gastroenterology and Hepatology, Osaka University Graduate School of Medicine, Osaka, Japan.
9）Department of Internal Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

*Corresponding author: a-tanaka@med.teikyo-u.ac.jp
※Chair, The Committee for Hepatitis Clinical Guidelines

Hepatology Research

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Short Communication

Prediction of a favorable clinical course in hepatitis C virus carriers with persistently normal serum alanine aminotransferase levels: A long-term follow-up study

Takeshi Nishimura,[1] Kanji Yamaguchi,[1] Hideki Fujii,[1] Yorihisa Okada,[1] Chihiro Yokomizo,[1] Toshihisa Niimi,[1] Yoshio Sumida,[1] Kohichiroh Yasui,[1] Hironori Mitsuyoshi,[1] Masahito Minami,[1] Atsushi Umemura,[1] Toshihide Shima,[2] Takeshi Okanoue[2] and Yoshito Itoh[1]

[1]*Molecular Gastroenterology and Hepatology, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, Kyoto, and* [2]*Hepatology Center, Saiseikai Suita Hospital, Osaka, Japan*

Aim: This study examined serum alanine aminotransferase (ALT) levels at first visit and their relationship with long-term normal serum ALT levels in hepatitis C virus (HCV) carriers with persistently normal ALT (PNALT).

Methods: HCV carriers with PNALT were identified as those patients with positivity of serum HCV RNA, ALT levels of 30 IU/L or less over a 12-month period on at least three different occasions, platelet count of more than 15×10^4 μl/mL and body mass index of 30 kg/m^2 or less. Outcome was retrospectively studied in 49 HCV carriers with PNALT, who were followed up for more than 10 years.

Results: During the mean follow-up period of 14.7 ± 2.5 years, ALT levels of 30 IU/L or less were preserved in only eight patients (8/49; 16.3%). Among the 17 patients with initial ALT levels of 19 IU/L or less, nine patients remained with ALT levels of 30 IU/L or less after 10 years (9/17; 52.9%). The probability of ALT levels in PNALT being maintained at 30 IU/L or less was significantly higher ($P = 0.001$) in these patients than in those with initial ALT levels of 20 IU/L or more ($n = 32$). Abnormal ALT levels were more common in female PNALT patients aged 45–55 years, which is usually the time of menopause onset.

Conclusion: Because antiviral therapy in the treatment of chronic hepatitis C is rapidly advancing, waiting for more effective and safer treatments may be an option. The results of this study provide an important insight into this issue.

Key words: alanine aminotransferase threshold, hepatitis C virus carriers with persistently normal alanine aminotransferase, long-term follow up

INTRODUCTION

HEPATITIS C VIRUS (HCV) infection is a major public health concern worldwide. Antiviral therapy to eradicate HCV has progressed.[1,2] Currently, peginterferon (PEG IFN) and ribavirin (RBV) combination therapy is widely used to treat chronic hepatitis C, and triple therapy with a protease inhibitor, telaprevir, is also available.[3–5] However, some physicians are reluctant to treat patients using IFN-based therapy because of the development of new therapies, some of which may be more effective and safer.[6]

Compared with fibrosis progression in patients with elevated transaminase levels, HCV carriers with persistently normal alanine aminotransferase (PNALT) and mild liver fibrosis are unlikely to develop severe fibrosis,[7–10] whereas only some reports presented dissimilar results.[11,12] A report at the consensus meeting of the Japan Society of Hepatology held in 2009 concluded that the progression of hepatic fibrosis in HCV carriers with PNALT is generally slow.[2]

Sustained viral response (SVR) rates of HCV carriers with PNALT are similar to those of patients with elevated transaminase levels.[13,14] The decision to utilize IFN-based therapies should be determined not by ALT

Correspondence: Dr Yoshito Itoh, Molecular Gastroenterology and Hepatology, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, Kawaramachi-Hirokouji, Kamigyou-ku, Kyoto 602-8566, Japan. Email: yitoh@koto.kpu-m.ac.jp
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values but by the patient's physical condition, probability of successful therapy or prolonged survival, and likelihood of serious adverse effects.[1,2]

Prediction of ALT abnormality in patients with PNALT may be helpful in determining treatment timing, namely, immediately or 2–3 years later, taking into account the probability of hepatocellular carcinoma (HCC) occurrence.[15] The present retrospective study addressed this issue by evaluating outcome in HCV carriers with PNALT who were followed up for more than 10 years.

METHODS

Patients and follow-up study

WE HAVE REPORTED a follow-up study (>5 years) of 69 patients among the 129 HCV carriers with PNALT.[10] In the present study, 49 HCV carriers with PNALT, in whom follow up was possible every 3–6 months, in principle, at our outpatient clinic for more than 10 years, were retrospectively studied. All 49 patients belonged to the previous study[10] and 16 patients who showed ALT levels of 30 IU/L or more before 10 years follow up were treated with PEG IFN-α-2b and RBV (Shering-Plough, Kenilworth, NJ, USA). Other patients with ALT levels of 30 IU/L or more were followed or treated with ursodeoxycholic acid. The other 80 patients in the previous study[10] were excluded from this study because they were lost to follow up before 10 years or received IFN-based therapy while the ALT levels were 30 IU/L or less. The end-points of follow up in this study are ALT elevation of 30 IU/L or more or last visit to our hospital (≥10 years from the first visit).

Hepatitis C virus carriers with PNALT were identified as those patients with positivity of serum HCV RNA, serum ALT levels of 30 IU/L or less over a 12-month period on at least three different occasions, platelet counts of more than 15×10^4 μl/mL, body mass index (BMI) of 30 kg/m^2 or less, and no evidence of oral contraceptive, co-infection with HIV or known liver disease other than hepatitis C.

Liver biopsy was performed using a Menghini needle guided by ultrasound. Liver biopsy specimens were fixed in 10% formalin and stained with hematoxylin–eosin and Masson-trichrome. Histopathological diagnosis was based on the scoring of the New Inuyama Classification.[16] Evaluation was performed by two expert hepatologists who were blinded to the clinical data of the patients.

This study was a retrospective sub-analysis of the study entitled "Analysis of the pathophysiology of HCV carriers with persistent normal ALT levels", which was approved by the ethics committee of the university and conformed to the provisions of the Declaration of Helsinki.

Statistical analysis

All data analyses were performed using SPSS statistical software (ver. 17.0; SPSS, Chicago, IL, USA). Individual characteristics were presented as means ± standard deviations and compared by Mann–Whitney *U*-test or Pearson's χ^2-test. Receiver–operator curve (ROC) analysis was performed, followed by proper categorization of the data. Probability of PNALT maintenance was determined using the Kaplan–Meier method and analyzed using the log–rank test. $P < 0.05$ was considered statistically significant.

RESULTS

Clinical characteristics of PNALT

CLINICAL CHARACTERISTICS OF the HCV carriers with PNALT are summarized in Table 1. We inves-

Table 1 Clinical characteristics of the 49 HCV carriers with PNALT at first visit

Follow-up period (years)	14.7 ± 2.5
Age (years)	
Male ($n = 4$)	34.8 ± 5.9
Female ($n = 45$)	48.0 ± 11.2
ALT (IU/L)	
Male ($n = 4$)	16.8 ± 4.7
Female ($n = 45$)	21.9 ± 5.3
PLT ($\times 10^4$/μL)	
Male ($n = 4$)	20.3 ± 4.7
Female ($n = 45$)	21.5 ± 4.7
BMI (kg/m^2)	
Male ($n = 4$)	20.3 ± 1.5
Female ($n = 45$)	21.3 ± 2.5
Genotype (G1/G2/ND)	25/16/8
Liver histology	
Male (F0/F1/F2/F3/F4)	3/1/0/0/0
(A0/A1/A/2/A3)	1/3/0/0
Female (F0/F1/F2/F3/F4)	11/32/2/0/0
(A0/A1/A2/A3)	2/39/4/0

Data are presented as means ± standard deviations.
Liver histology was classified based on New Inuyama Classification.[16]
ALT, alanine aminotransferase; BMI, body mass index; G1, genotype 1; G2, genotype 2; HCV, hepatitis C virus; ND, not determined; PLT, platelets; PNALT, persistently normal alanine aminotransferase.

tigated whether or not the patients who maintained normal ALT levels (≤30 IU/L) for 10 years or more ($n = 8$) are significantly different from those who did not ($n = 41$) in clinical characteristics. We revealed no significant differences in age ($P = 0.109$), platelet count ($P = 0.371$), BMI ($P = 0.989$), hemoglobin concentration ($P = 0.549$), HCV load ($P = 0.712$), HCV genotype (1 or 2; $P = 0.495$), serum ferritin ($P = 0.710$), hepatic fibrosis score (F0/1,2) ($P = 0.588$), hepatic activity score (A0/1,2) ($P = 0.421$) or iron deposition (positive or negative; $P = 0.251$, $n = 20$). Only the initial ALT levels were significantly lower in patients who maintained normal ALT levels (≤30 IU/L) for 10 years or more ($P = 0.003$).

Initial ALT values and clinical outcome of patients with PNALT

To estimate a cut-off initial ALT level predicting the maintenance of ALT of 30 IU/L or less, the ROC analysis was performed (Fig. 1). The result revealed that 19.5 IU/L was an optimal ALT level predicting the maintenance of ALT of 30 IU/L or less, because it achieved the highest sensitivity (0.756%) and specificity (0.875%), yielding an area under the curve of 0.83 and *P*-value of 0.003.

Among the 17 patients with initial ALT levels of 19 IU/L or less, nine patients remained at ALT levels of 30 IU/L or less after 10 years (52.9%) (Fig. 2). The probability of ALT levels being maintained at 30 IU/L or less was significantly higher ($P = 0.001$) in these patients than in those with initial ALT levels of 20 IU/L or more ($n = 32$).

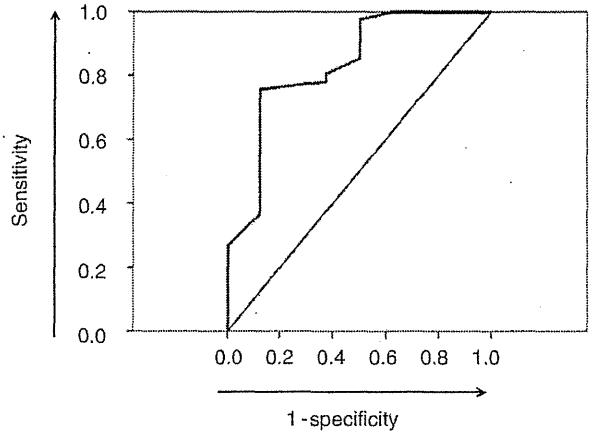

Figure 1 Receiver–operator curve analysis of the relationship between initial alanine aminotransferase (ALT) values and maintenance of normal ALT.

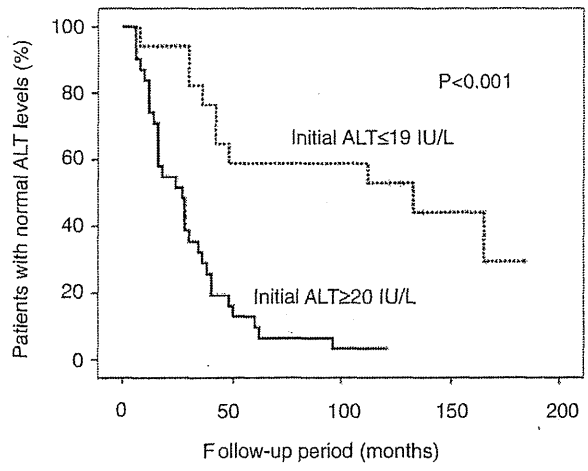

Figure 2 Maintenance of normal alanine aminotransferase (ALT) values (≤30 IU/L) during the follow up. Seventeen patients had initial ALT levels of ≤19 IU/L and 32 of ≥20 IU/L.

Relationship between menopause and ALT elevation

The ages of female PNALT patients at which abnormal ALT first occurred are presented in Figure 3(a). Abnormal ALT levels were most frequently recorded in female patients aged 45–55 years, which is usually the time of menopause onset. We sent a questionnaire to 45 female patients to investigate the relationship between ALT elevation and menopause, but only 16 patients responded. Of the respondents, age of menopause onset varied between 48 and 56 years, except for one patient who underwent hysterectomy at 37 years old and experienced menopause before consulting our hospital. ALT levels were found to be elevated within 3 years of their awareness of menopause in 10 patients (Fig. 3b), but before 3 years of menopause in three patients (Fig. 3c). The remaining three patients experienced menopause before consultation to our outpatient clinic (data not shown).

DISCUSSION

THE COURSE OF illness in HCV carriers with PNALT is not well known. The general consensus in Japan is that most HCV carriers with PNALT exhibit mild liver damage and/or fibrosis.[10] During the follow-up period of 10 years, interestingly, ALT levels remained stable at 30 IU/L or less in 52.9% (9/17) of patients with initial ALT levels of 19 IU/L or less. The probability of PNALT being maintained was significantly higher in patients

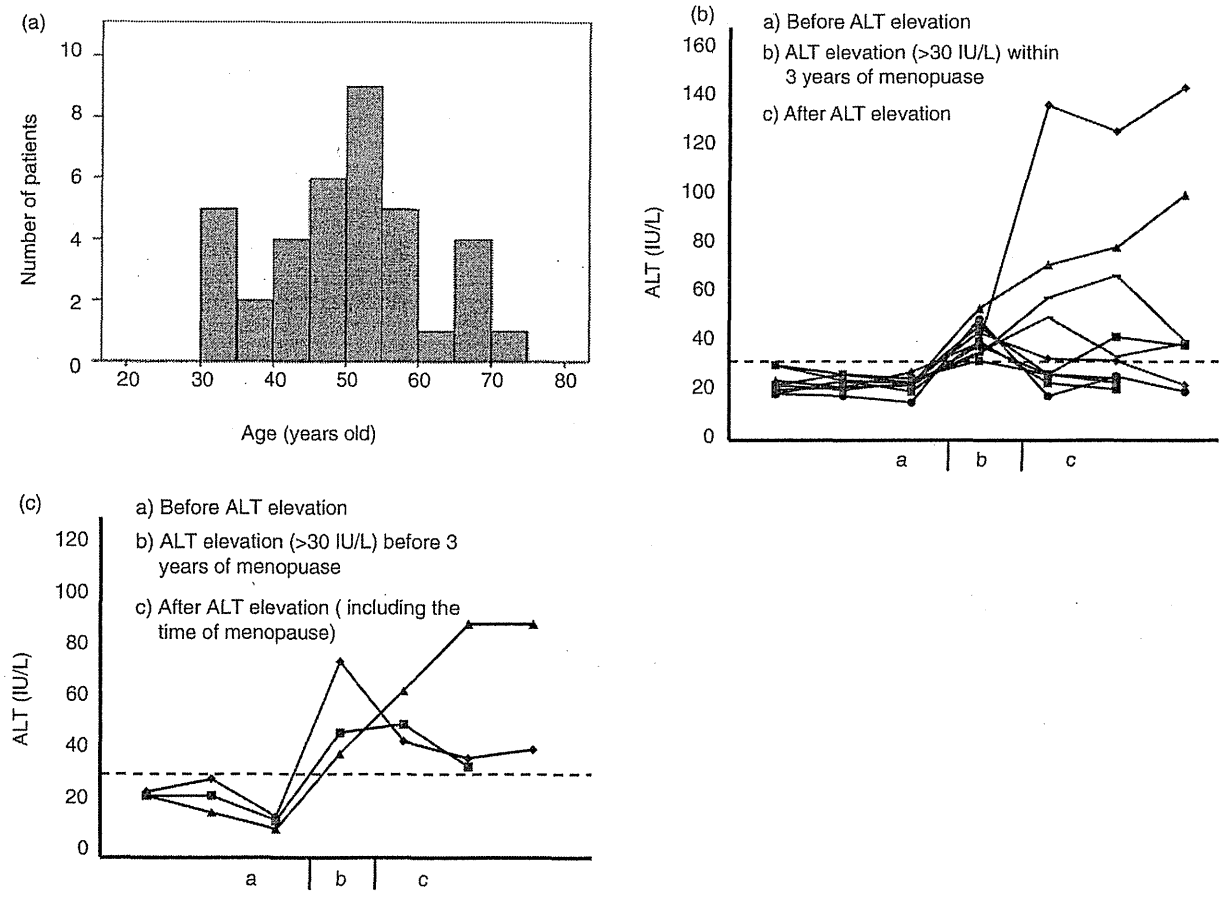

Figure 3 (a) Age of female persistently normal alanine aminotransferase (PNALT) patients at which abnormal ALT first occurred ($n = 37$). (b) PNALT with first ALT levels of >30 IU/L within 3 years of menopause. (c) PNALT with first ALT levels of >30 IU/L before 3 years of menopause.

with initial ALT levels of 19 IU/L or less than in those with initial ALT levels of 20 IU/L or more (Fig. 2, $P < 0.001$). Although the progression of hepatic fibrosis could not be evaluated by repeated liver biopsy during the observation period, this result suggests a benign course in a subgroup of HCV carriers with PNALT, whose ALT levels were 19 IU/L or less at the first visit.

Interestingly, a report from a hyperendemic area in Japan revealed that a basal ALT level of 20 IU/L or more was an important predictive factor of ALT flare-up in HCV carriers with PNALT.[17] This result accords with the favorable ALT levels documented in our study (Fig. 2). Furthermore, 19 IU/L is the updated upper limit of the healthy range for serum ALT level in female patients with chronic HCV infection or non-alcoholic fatty liver disease, as advocated by Prati *et al.*[18]

Concerning the possibility of HCC, one Japanese report demonstrated that HCV carriers with PNALT and ALT levels of more than 20 IU/L were, to some extent, at risk of both hepatocarcinogenesis and ALT elevation.[19] These results reinforce the finding in this study that patients with initial ALT levels of 20 IU/L or more and 30 IU/L or less were at a high risk for ALT elevation during the follow-up period (Fig. 2).

The relationship between menopause and the first abnormal ALT level in female patients was also examined. As shown in Figure 3(a), first abnormal ALT levels in female PNALT patients were frequently observed at 45–55 years of age, which is usually the time of menopause onset.

Although only 16 patients responded to the questionnaire, ALT levels were found to be elevated within

3 years of their awareness of menopause in 10 patients. This finding is interesting because previous studies have reported an association between menopause and progression of hepatic fibrosis[20,21] or resistance to antiviral therapy.[22] Recently, production of the HCV particle has been reported to be inhibited by 17-β-estradiol *in vitro*.[23] Further study in this field will clarify this issue.

Although the mechanism of abnormal ALT is uncertain, we speculate that one of the plausible causes of abnormal ALT levels might be enhanced immunological response against HCV. Recently, Itose *et al.*[24] demonstrated that the frequency of regulatory T cells is higher in PNALT patients and that depletion of $CD25^+$ cells enhanced HCV-specific T-cell response. So, we speculate that some immunological activation may underlie the cause of ALT elevation. Increased BMI during the observation may be another cause of abnormal ALT, although we do not have precise data on that point.

In conclusion, because antiviral therapy for chronic hepatitis C is making rapid and encouraging progress, waiting for more effective and safer treatments may be an option. The results of this study provide an important insight into this issue.

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Original Article

Treatment extension may benefit female genotype 1 chronic hepatitis C patients with complete early virological response to peginterferon-alpha-2b and ribavirin combination therapy

Takeshi Nishimura,[1] Kanji Yamaguchi,[1] Hiroaki Hashimoto,[3] Toshihisa Niimi,[1] Chihiro Yokomizo,[1] Hideki Fujii,[2] Masahito Minami,[1] Masafumi Sakamoto,[2] Naoki Ohnish,[2] Yasuyuki Nagao,[4] Mika Okita,[4] Atsushi Umemura,[3] Toshihide Shima,[3] Takeshi Okanoue[3] and Yoshito Itoh[1]

[1]*Molecular Gastroenterology and Hepatology, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, and* [2]*Department of Internal Medicine, Aiseikai Yamashina Hospital, Kyoto, and* [3]*Hepatology Center, Saiseikai Suita Hospital, and* [4]*Department of Gastroenterology, Matsushita Memorial Hospital, Osaka, Japan*

Aim: Little is known about the appropriate use of peginterferon-α-2b (PEG IFN-α-2b) or ribavirin (RBV) in genotype 1 chronic hepatitis C (CH-C) patients with complete early virological response (cEVR). Female patients, especially the older, are known to experience inferior treatment outcomes.

Method: A total of 150 CH-C patients with cEVR treated for 48 weeks ($n = 104$) or 52–64 weeks ($n = 46$) with PEG IFN-α-2b and RBV combination therapy were retrospectively analyzed to evaluate the benefits of extended treatment.

Results: In the 48-week group, patients without a sustained virological response (SVR) were more often female ($P = 0.004$) and had received a significantly lower total RBV dose ($P = 0.003$) than those with SVR. The SVR rate in these female patients was similar to males with hepatitis C virus (HCV) RNA negativity at treatment week 8 ($P = 0.413$); however, it was lower than that in males with HCV RNA negativity at treatment week 12 ($P = 0.005$). In the 52–64-week group, although the total RBV dose (mg/kg) after treatment week 48 was less in females than in males ($P = 0.027$), the SVR rate in females was equivalent to that in males ($P = 0.604$).

Conclusion: Genotype 1 CH-C patients treated with PEG IFN-α-2b and RBV combination therapy without SVR were more often female and had received a lower total RBV dose than males. The smaller SVR rate in female patients with cEVR compared to males may be overcome by extending treatment even if the RBV dose is lowered due to anemia.

Key words: chronic hepatitis C, complete early virological response, female, genotype 1, ribavirin

INTRODUCTION

HEPATITIS C VIRUS (HCV) infection is a major public health concern in Japan. It is estimated that 2 million people in Japan are infected with HCV and the annual number of deaths of HCV infected patients from hepatocellular carcinoma or hepatic failure is greater than 30 000.[1] To date, tremendous efforts have been made to cure HCV infection with antiviral therapy using interferons (IFN).

Peginterferon (PEG IFN) and ribavirin (RBV) combination therapy has been the most commonly used treatment for chronic hepatitis C (CH-C) worldwide, including in Japan.[1,2] In genotype 1 CH-C patients treated with PEG IFN and RBV according to the standard regimen of 48 weeks and attaining an undetectable serum HCV RNA by treatment week 12 (achieving a complete early virological response [cEVR]), approximately 71–73% are expected to have a sustained viral

Correspondence: Dr Yoshito Itoh, Molecular Gastroenterology and Hepatology, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, Kawaramachi-Hirokouji, Kamigyou-ku, Kyoto 602-8566, Japan. Email: yitoh@koto.kpu-m.ac.jp
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response (SVR).[1] However, optimal use of PEG IFN and RBV for cEVR patients has not been studied in detail.

Recent studies in Japan have reported that older female patients were difficult to treat with PEG IFN and RBV combination therapy for CH-C.[3–5] To address this problem, a protease inhibitor, telaprevir, is now administrated in combination with PEG IFN-α-2b and RBV in Japan. This triple therapy is the first-choice treatment for genotype 1 CH-C in Japan as well as in the USA;[6,7] however, several issues have been raised concerning severe adverse effects.

Many female patients with low baseline hemoglobin concentrations are not suitable for the triple therapy, and therefore must rely on PEG IFN and RBV combination therapy to avoid severe anemia. The triple therapy is sometimes accompanied by severe skin rash ranked as grade 3 or abrupt anemia at an earlier time point in the therapy, which leads to its discontinuation. Therefore, the optimal use of RBV remains the mainstay of treatment techniques, even in the era of triple therapy.

In the present study, we retrospectively analyzed 150 genotype 1 CH-C patients with cEVR treated with PEG IFN and RBV combination therapy (104 patients treated for 48 weeks and 46 patients treated for 52–64 weeks). We distinguished between SVR and non-SVR in 48-week-treated patients based upon items in their clinical backgrounds which differed significantly. We then examined whether or not extending therapy (52–64 weeks) for cEVR patients was worthwhile.

METHODS

Patients

THIS STUDY WAS a retrospective subanalysis of the study titled "Establishment of a protocol of PEG IFN and RBV combination therapy for chronic hepatitis C to improve therapeutic outcome" conducted at 15 multicenter hospitals in the Kinki area of Japan (Kyoto, Osaka, Nara, Shiga Prefecture). The study protocol was approved by the ethics committee of each institution in 2005 and it conformed to the provisions of the Declaration of Helsinki. Patients with decompensated liver disease, co-infection with hepatitis B virus (HBV) or HIV, autoimmune hepatitis, primary biliary cirrhosis, hemochromatosis or Wilson's disease were excluded. Patients with uncontrollable hypertension or diabetes mellitus and those with a history of alcohol abuse were also excluded.

Of the 466 Japanese patients with genotype 1 CH-C with high viral loads (≥100 KIU/mL according to the Amplicor GT HCV monitor version 2.0 high range; Roche Diagnostics, Tokyo, Japan) who were treated with PEG IFN and RBV combination therapy, 150 cEVR patients aged 25–74 years were analyzed (Table 1). All patients were evaluated by HCV RNA qualitative polymerase chain reaction (PCR) assay at treatment weeks 4, 8 and 12. The definition of cEVR was HCV RNA positivity at treatment week 4, and HCV RNA negativity at treatment week 12 based on the HCV RNA qualitative PCR assay. SVR was defined as HCV RNA negativity at 24 weeks after the cessation of combination therapy. Those who failed to attain SVR were categorized as non-SVR patients.

Among the 150 patients, 114 underwent a liver biopsy prior to treatment, which was performed using a Sonopsy cl needle (Hakko Co. Ltd., Tokyo, Japan) guided by ultrasound. The specimens were fixed in 10% formalin and stained with hematoxylin–eosin, and Masson-trichrome. Histopathological diagnosis was based on the New Inuyama Classification.[8] The fibrosis scores were as follows: F0, no fibrosis; F1, portal fibrous widening; F2, portal fibrous widening with bridging fibrosis; and F3, bridging fibrosis plus lobular distortion. Inflammation scores were as follows: A0, none to minimal; A1, mild; A2, moderate; and A3, severe cases.

Study design

All patients received weekly injections of PEG IFN-α-2b (PEG-INTRON; Schering-Plough, Kenilworth, NJ, USA) of 1.5 μg/kg bodyweight and p.o. administration of RBV (Rebetol; Schering-Plough) of 600–1000 mg/day. The amount of RBV was adjusted based on bodyweight (600 mg for <60 kg, 800 mg for ≥60 but <80 kg, and 1000 mg for ≥80 kg). Patients with a lower hemoglobin concentration, neutrophil count or platelet count began the therapy with reduced doses of RBV or PEG IFN based upon the information in the package inserts of the therapeutic agents. Those patients who fell into the stop criteria during the therapy were excluded from the study. The dose of PEG IFN-α-2b was decreased by 50% when the platelet count was less than $8 \times 10^4/mm^3$ or the neutrophil count was less than $750/mm^3$. The dose of RBV was lowered by 200 mg/day when the hemoglobin concentration was less than 10 g/dL. The original dose regimen was reinstated when the adverse effects subsided.

Statistical analysis

All data analysis was conducted using SPSS statistical software ver. 17.0 (SPSS, Chicago, IL, USA). Individual

Table 1 Clinical background of the patients ($n = 150$)

Treatment period	48 weeks ($n = 104$)	52–64 weeks ($n = 46$)	P-value
Male/female	65/39	29/17	0.949
Age (years)	53 (25–71)	55 (27–74)	0.612
BMI (kg/m^2)	22.8 (16.0–31.2)	23.0 (17.7–37.4)	0.767
HCV RNA (log IU/mL)	6.2 (5.2–6.7)	6.3 (5.2–6.7)	0.774
Hb (g/dL)	14.5 (10.7–17.6)	14.4 (11.5–18.1)	0.930
PLT ($\times 10^{-4}$/μL)	17.8 (9.9–39.9)	16.2 (8.9–45.5)	0.355
Neu (/μL)	2617 (778–6222)	2467 (1319–7772)	0.897
ALT (IU/L)	61 (15–740)	68 (22–285)	0.988
HCV RNA negativity (8w/12w)	20/84	0/46	–
Total PEG IFN (μg/kg)	67.9 (22.0–94.2)	79.5 (35.9–96.0)	<0.001
Total RBV (mg/kg)	3423 (1100–5050)	4359 (1725–5016)	<0.001
Activity score 0,1/2,3	37/37	17/23	0.444
Fibrosis score 0,1/2,3	45/29	17/23	0.061

Liver biopsy was performed in 74 patients treated for 48 weeks.
ALT, alanine aminotransferase; BMI, body mass index; Hb, hemoglobin; HCV, hepatitis C virus; Neu, neutrophil count; PEG IFN, peginterferon; PLT, platelet count; RBV, ribavirin; w, weeks.

characteristics between groups were evaluated using the Mann–Whitney U-test, Fisher's exact test or χ^2-test. Variables exhibiting statistical significance were subjected to multivariate logistic regression analysis with a forward stepwise method. $P < 0.05$ was considered statistically significant.

RESULTS

Clinical backgrounds of the patients with cEVR following PEG IFN-α-2b and RBV combination therapy categorized by treatment period or therapeutic outcome

CLINICAL BACKGROUNDS OF 48-week-treated and 52–64-week-treated patients are presented and compared in Figure 1. The backgrounds of the two groups were similar but for the total PEG IFN and RBV dose. Interestingly, the fibrosis score in 52–64-week-treated patients tended to be higher ($P = 0.061$) than that in 48-week-treated patients. Clinical backgrounds were also compared between SVR and non-SVR patients in the 48-week-treated group (Table 2). Patients with cEVR who failed to achieve SVR were more often female ($P = 0.004$), and had lower platelet counts ($P = 0.044$) compared to those with SVR. Patients without SVR were maintained on lower total RBV doses ($P = 0.003$). The total PEG IFN dose did not differ between SVR and non-SVR patients ($P = 0.431$). Multivariate regression analysis revealed that RBV dose was the only factor independently associated with SVR ($P = 0.017$; Table 3).

Although total RBV dose (mg/kg) was the independent factor associated with SVR, the optimal dose can be determined only after completion of the therapy; therefore, we examined the difference in SVR rate between female and male cEVR patients (Fig. 1). As expected, the SVR rate in females was 64.1% (25/39), which was significantly ($P = 0.004$) lower than that in males (87.7%; 57/65).

Differences in clinical backgrounds between SVR and non-SVR patients were also examined in cEVR patients

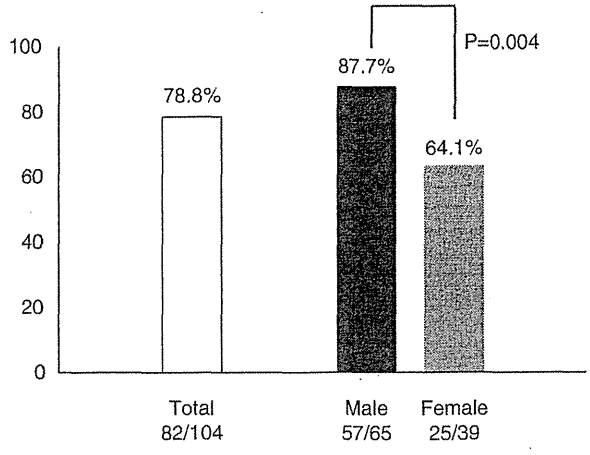

Figure 1 SVR rate of cEVR patients treated for 48 weeks. The SVR rate of cEVR patients in the 48-week-treated group is presented as total or as male or female. cEVR, complete early virological response; SVR, sustained virological response. (■) Male; (▩) female.

Table 2 Clinical backgrounds of SVR and non-SVR cEVR patients (48 weeks of treatment, $n = 104$)

	SVR ($n = 82$)	Non-SVR ($n = 22$)	*P*-value
Male/female	57/25	8/14	0.004
Age (years)	53 (25–71)	56.5 (37–69)	0.279
BMI (kg/m^2)	22.9 (16–31.2)	21.9 (18.7–27.0)	0.192
HCV RNA (log IU/mL)	6.2 (5.2–6.7)	6.3 (5.3–6.7)	0.147
Hb (g/dL)	14.6 (10.7–17.6)	13.8 (11.9–16.7)	0.105
PLT ($\times 10^{-4}$/μL)	18.3 (9.9–39.9)	16.7 (10.0–26.5)	0.044
Neu (/μL)	2617 (1033–6222)	2638 (778–3652)	0.803
ALT (IU/L)	61 (15–740)	54.5 (19–144)	0.494
HCV RNA negativity (8w/12w)	17/65	3/19	0.340
Total PEG IFN (μg/kg)	68.4 (22.0–94.2)	65.5 (27.9–82.8)	0.431
Total RBV (mg/kg)	3422 (1100–5050)	2817 (2021–3926)	0.003

ALT, alanine aminotransferase; BMI, body mass index; cEVR, complete early virological response; Hb, hemoglobin; HCV RNA, hepatitis C virus RNA; Neu, neutrophil count; PEG IFN, peginterferon; PLT, platelet count; RBV, ribavirin; SVR, sustained virological response; w, weeks.

treated for 52–64 weeks; however, no significant differences were noted, possibly because of the small number of patients (Table 4).

Effect of treatment extension on the SVR rate of cEVR patients

We analyzed the SVR rate according to the timing of HCV RNA negativity in the serum in the 48-week-treated group (Fig. 2). While the SVR rate in females was comparable to that in males with initial HCV RNA negativity at treatment week 8 (78.8% vs 90.9%, $P = 0.413$), it was significantly lower than that in males with initial HCV RNA negativity at treatment week 12 (60.0% vs 87.0%, $P = 0.005$).

In cEVR patients who were initially serum HCV RNA negative at treatment week 12 and were treated for

Table 3 Multivariate logistic regression analysis of factors associated with SVR in cEVR patients (48 weeks of treatment, $n = 104$)

	Odds ratio	95% CI	*P*-value
Total RBV dose (mg/kg)	1.0008	1.0001–1.0015	0.017

CI, confidence interval; RBV, ribavirin.

Table 4 Clinical backgrounds of SVR and non-SVR cEVR patients (52–64 weeks of treatment, $n = 46$)

	SVR ($n = 37$)	Non-SVR ($n = 9$)	*P*-value
Male/female	24/13	5/4	0.604
Age (years)	55 (35–74)	55 (27–68)	0.533
BMI (kg/m^2)	22.5 (17.7–35.6)	25.3 (18.5–37.4)	0.136
HCV RNA (log IU/mL)	6.2 (5.2–6.7)	6.4 (5.6–6.7)	0.144
Hb (g/dL)	14.6 (11.5–18.1)	13.4 (12.3–16.4)	0.076
PLT ($\times 10^{-4}$/μL)	16.5 (8.9–45.5)	14.9 (10.9–23.7)	0.382
Neu (/μL)	2518 (1318–7772)	2070 (1579–3358)	0.089
ALT (IU/L)	74 (22–285)	53 (24–201)	0.261
HCV RNA negativity (8w/12w)	0/37	0/9	–
Total PEG IFN (μg/kg)	81.8 (35.9–96.0)	78.9 (38.7–84.0)	0.325
Total RBV (mg/kg)	4400 (1725–5016)	4004 (2619–4940)	0.160

ALT, alanine aminotransferase; BMI, body mass index; cEVR, complete early virological response; Hb, hemoglobin; HCV RNA, hepatitis C virus RNA; Neu, neutrophil count; PEG IFN, peginterferon; PLT, platelet count; RBV, ribavirin; SVR, sustained virological response; w, weeks.

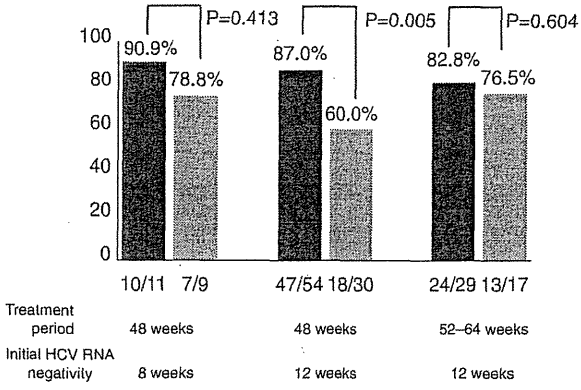

Figure 2 SVR rate of cEVR in male and female patients classified by the time of HCV RNA negativity in 48-week-treated or 52–64-week-treated groups. cEVR, complete early virological response; HCV RNA, hepatitis C virus RNA; SVR, sustained virological response. (■) Male; (▩) female.

52–64 weeks, the SVR rate in females was 76.5%, which was not significantly ($P = 0.604$) different from that in males (82.8%) (Fig. 2).

Comparison of clinical backgrounds between male and female cEVR patients with HCV RNA negativity at treatment week 12

We compared clinical backgrounds between males and females in 48-week-treated (Table 5) and 52–64-week-treated (Table 6) groups. In both groups, hemoglobin concentration was significantly higher in males. Whereas the SVR rate in females was similar to that in males in the 52–64-week-treated group (76.5% vs 82.8%, $P = 0.604$, Fig. 2), the total RBV dose beyond treatment week 48 was significantly lower in females than in males ($P = 0.027$, Table 6).

We also compared the SVR rate of female cEVR patients with initial HCV RNA negativity at treatment week 12 in 48-week-treated and 52–64-week-treated groups; however, no statistical significance was observed ($P = 0.252$, data not shown). The rate of advanced hepatic fibrosis (F2 and F3) tended to be higher in the 52–64-week-treated group compared to those in the 48-week-treated group ($P = 0.086$, Table 7).

DISCUSSION

IN THE PRESENT study, we retrospectively analyzed 150 genotype 1 CH-C patients demonstrating cEVR with PEG IFN and RBV combination therapy. In the group treated for 48 weeks, patients without SVR were more often female ($P = 0.004$), had lower platelet counts ($P = 0.044$) and received lower total RBV doses ($P = 0.003$). These findings are in accordance with a consensus report from Japan demonstrating that sex, severity of liver fibrosis and adherence to drug treatment are important predictors of the outcome with PEG IFN and RBV combination therapy.[1]

Ribavirin is an antiviral drug effective for HCV when used in combination with IFN-α/β or PEG IFN-α. Several publications have reported that short-term or cumulative RBV exposure is closely associated with EVR or SVR,[9–12] and a recent report presented evidence that RBV can promote IFN signaling in patients with CH-C *in vivo*.[13] In clinical practice, Hiramatsu *et al.* demonstrated that RBV dose reduction is associated with relapse of hepatitis in patients with cEVR.[14]

Table 5 Comparison of clinical backgrounds between male and female cEVR patients with HCV RNA negativity at week 12 (48 weeks of treatment, $n = 84$)

	Male ($n = 54$)	Female ($n = 30$)	*P*-value
Age (years)	56 (25–70)	54 (30–71)	0.926
BMI (kg/m^2)	22.7 (16.0–30.5)	22.7 (18.7–29.6)	0.259
HCV RNA (Log IU/mL)	6.2 (5.1–6.7)	6.2 (5.2–6.7)	0.411
Hb (g/dL)	15.1 (11.3–16.9)	13.5 (10.7–15.2)	<0.001
PLT (×10^4/μL)	16.8 (10.0–36.6)	18.7 (9.9–39.9)	0.373
Neu (/μL)	2601 (1033–5017)	2435 (1033–4344)	0.173
ALT (IU/L)	64 (21–740)	53 (15–126)	0.040
Total PEG IFN (μg/kg)	66.7 (22.0–94.2)	68.6 (44.2–82.8)	0.115
Total RBV (mg/kg)	3460 (1444–5050)	3.427 (1357–4454)	0.575

ALT, alanine aminotransferase; BMI, body mass index; cEVR, complete early virological response; Hb, hemoglobin; HCV RNA, hepatitis C virus RNA; Neu, neutrophil count; PEG IFN, peginterferon; PLT, platelet count; RBV, ribavirin; SVR, sustained virological response; w, weeks.