《トピックス》

# 4 データマイニングを用いた治療効果予測

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**ポイント**

- データマイニングとは，過去のデータを分析し，そのなかから有効な規則性を発見して重要な意思決定支援を促進する先進的情報解析システムである．
- 一般的には，金融ビジネス流通分野において広く導入されている手法で統計解析とは異なる．
- HCV1型症例のC型慢性肝炎に対するペグインターフェロンとリバビリン併用療法の治療効果予測にデータマイニング解析結果を紹介する．

**キーワード** データマイニング解析，C型慢性肝炎，ペグインターフェロンとリバビリン併用療法

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## ◉データマイニングとは？

マイニング（mining）の意味を辞書で調べてみると「採掘」と記載されている．データマイニング（datamining：Dm）とは，過去のデータを分析し，そのなかから有効な規則性を発見して重要な意思決定支援を促進する先進的情報解析システムで，金融ビジネス流通分野において広く導入されている手法である．従来の統計解析手法は限られたサンプル数を用いて仮説を検証する方法であり，網羅性，迅速性において難点があるも，Dmでは膨大なデータから網羅的に高速探索し精緻な解析が可能である[1,2]．

Dmの歴史は，1980年代末からIBMアルデマン基礎研究所のDr. ラティシュ・アグルワルが開発した相関関係分析アルゴリズムに始まり，データマイニングという造語も最初に彼が唱えたといわれている．1990年代後半にデータマイニング・ソフトウェアが流通し始めたころから，Dmは金融，流通業界に浸透し始め，本解析手法が，これらの領域での未来予測に有用であることが広く知られるようになった．

一方，医学領域では，2000年ごろまで，その有用性，存在自体ともに，ほとんど知られていなかったが，筆者らが，肝疾患領域でのDmの有用性を検討し，その結果を報告するようになってから，徐々にではあるが，認知されるようになった．

Dmを理解するうえで重要なポイントは，統計解析との違いを明確に理解することである．統計解析とDmの相違点を**表**に示す．統計解析は限られたサンプルのなかから仮説を検証する解析手法で解析前に前提となる仮説をあらかじめ設ける必要があるのに対し，Dmでは仮説を必要としない．Dmは膨大なデータから網羅的に高速探索し精緻に解析して仮説を発見するという仮説発見型の解析手法で，両者の根本的な概念はまったく異なる[1,2]．

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表　統計解析とデータマイニングの相違

| 統計解析：多変量解析 | データマイニング |
|---|---|
| 限られたサンプルから仮説を検証する. | 膨大なデータから網羅的に高速探索し，精緻に解析して仮説を発見する. |
| 仮説検証型 | 仮説発見型 |
| 近似的な定式化 | 厳密な定式化 |
| 特定の線形関数 | 任意の非線形関数 |
| $y=f(x)=a+bX$ | $y=f(x)=\sum_{i=1} wi^{*}\exp\{(x-c)^{**}2/2\sigma^{**}2\}$ |

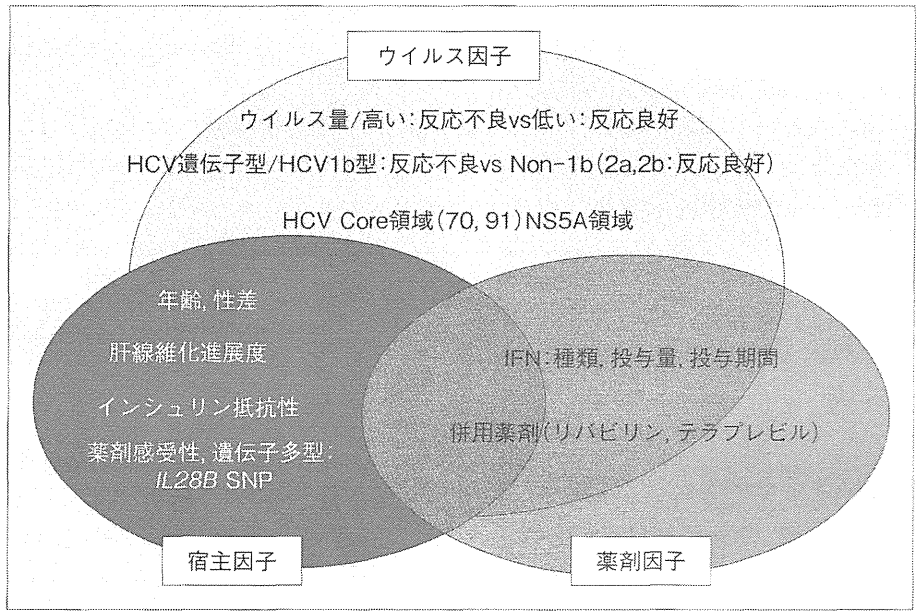


図 1　C 型肝炎の IFN 治療効果に影響を及ぼす因子

## ◉C 型慢性肝炎に対するインターフェロン，ペグインターフェロン/リバビリン併用療法の治療効果にかかわる因子

C 型慢性肝炎に対するインターフェロン（IFN），ペグインターフェロン（PegIFN）/リバビリン（RBV）併用療法の治療効果に影響を及ぼす因子としては，大きくは，ウイルス因子（ウイルスの型と量，遺伝子変異），薬剤因子（IFN の種類，投与量，投与期間，併用薬剤の有無など），宿主因子（患者の年齢，性，肝線維化進展度，インシュリン抵抗性，薬剤感受性の遺伝的要因，遺伝多型：SNP：*IL28B* 遺伝子多型など）の 3 因子に大別される（**図 1**）.

## ◉データマイニング（決定木法：SPRINT）で求めた PegIFN/RBV 併用療法の治療効果にかかわる因子

厚生労働科学研究費補助金（肝炎等克服緊急対策研究事業）データマイニング手法を用いた効果的な治療方法に関する研究班（主任研究者：八橋弘）では，2008 年から 2010 年までの研究期間内に C 型慢性肝炎に対する PegIFN/RBV 併用療法の治療成績に関する Dm 解析を行ってきたので，その成績を紹介する．2004 年 12 月から 2009

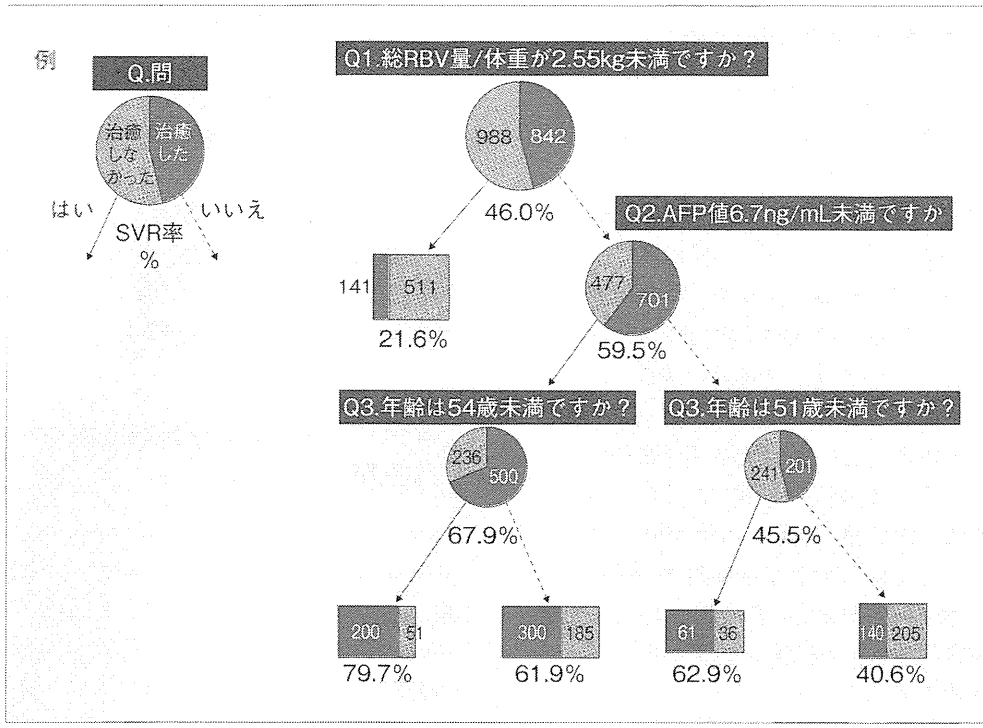


図 2 人工知能である Dm 解析によって作成された治療効果予測の道筋（アルゴリズム）とそれぞれの因子の条件（Q：問い）を満たした集団の SVR 率

年 3 月までの期間，国立病院機構および国際医療センターを合わせた 30 施設で，PegIFN/RBV 併用療法が導入された HCV1 型 C 型慢性肝炎症例（肝硬変例を含む）1,830 例が対象例である．

sustained viral responder（SVR）すなわち治癒に寄与する因子について，22 因子のなかから多変量解析を行ったところ，年齢（59 歳未満＞60 歳以上），性（男性＞女性），IFN 治療歴（初回治療例＞再治療例），総 RBV 量/体重（3.1 g/kg 以上＞-未満），HCVRNA 量（1,831KIU/mL 未満＞-以上），AST 値（48 IU/L 未満＞-以上），γ-GTP 値（39 IU/L 未満＞-以上），AFP 値（6 ng/mL 未満＞-以上），治療期間（331 日以上＞-未満），臨床診断（慢性肝炎＞肝硬変）の 10 因子が有意な因子として抽出された．しかし，これらの因子のなかで，どの因子がより重要なのかについては多変量解析では見出し難い．

一方，Dm（決定木法：解析関数として SPRINT 法を用いた）を用いて解析を行った結果が**図 2** である．決定木法では，より重要な因子は上位に位置し，それぞれの条件を Yes，No とアルゴリズムのようにして辿り着くことで，それらの条件を満たす集団の SVR 率が求められる．本対症例で Dm 解析を用いて治療効果にかかわる因子について重みづけを行ったところ①総 RBV 量/体重（2.55 g/kg 未満か以上か），②AFP 値（6.7 ng/mL 未満か以上か），③年齢（54 歳未満か以上か，51 歳未満か以上か）の順に因子が選択され，これらの因子が治療効果を規定する重要な因子として抽出された．

具体的に SVR 率を提示すると，1,830 例の全体の SVR 率は 46.0%（842/1,830），総 RBV 量/体重が 2.55 g/kg 未満の症例は 652 例で，そのうち 141 例（21.6%）が SVR となったが，総 RBV 量/体重が 2.55 g/kg 以上の症例は，1,178 例でそのうち 701 例（59.5%）が SVR となった．

## ◉Dm 解析で得られた因子をどのように考えるか

Dm 解析で得られた因子をどのように考えるか，3 因子について考察してみた．

まず総 RBV 量/体重とは，治療期間と強く相関する因子である．1 日の RBV 服用量には上限があることから十分な総 RBV 量/体重を確保するためには，十分な治療期間を確保することが必要である．また，治療途中で極端に RBV 投与量を減量した症例では，仮に治療中に血中 HCVRNA が陰性化しても治療終了後高率に再燃することが今までの報告から明らかとなっている．Dm 解析で総 RBV 量/体重の因子が第一に抽出された理由としては，十分な治療期間の確保，また治療後も血中 HCVRNA を再燃させないための十分な RBV 投与量の確保が必要であることを意味していると考えられる．

2 番目に重要な因子として選択された AFP は肝癌の診断時に用いるマーカーである．通常，肝癌診断時の AFP 値は 100～400 ng/mL の値を示す．しかし，AFP 値 10～20 ng/mL レベルでも，10 年後の C 型肝炎患者での肝癌発生リスクが上昇すること，またこのレベルの AFP 値と肝の線維化所見（F0～F4）とは有意な相関関係が認められることを我々は報告してきた[3]．本解析では AFP 値 6.7 ng/mL 未満か以上かで SVR 率 67.9%，と 45.5%の 2 つの群に分岐された．解析に用いた変数のなかには血小板数も含まれているが，多変量解析，Dm 解析ともに血小板数は抽出されず，血小板数よりも AFP 値のほうが PegIFN/RBV 治療効果の観点からの肝線維化進展度も反映して治療効果予測のうえで優れている可能性が示唆される．

3 番目に重要な因子として選択された年齢の因子については，高齢者が多い日本の C 型肝炎患者での PegIFN/RBV 治療効果に影響を及ぼす因子としてすでに多くの施設が認めている因子である．高齢者では，薬剤量として十分投与できないことが多く，また副作用中断率が高いことなども高齢者で SVR 率が低い理由と考えられる．

## ◉データマイニング解析結果の解釈と問題点

Dm 解析（決定木法）で示されたアルゴリズムを絶対視してはいけない．決定木を例えて言えば，登山における，山の頂上に到達するための道筋の一つを示したに過ぎない．他の優れた道が隠れている可能性を否定してはいけない．Dm の解析結果の評価には検証が必要であり，他の集団でも同じような解析結果が得られるか確認する必要がある．

### 文　献


1) 八橋　弘：インターフェロンの治療効果予測—SNP とデータマイニングを用いた解析．肝臓 46(10)：599-603, 2005
2) 八橋　弘，山内　勉，河村佳洋：データマイニング（Data mining）を用いた治療効果予測．肝胆膵 57(5)：851-859. 2008
3) Tateyama M, Yatsuhashi H, Taura N, et al.：Alpha-fetoprotein above normal levels as a risk factor for the development of hepatocellular carcinoma in patients infected with hepatitis C virus. J Gastroenterol 46(1)：92-100. 2011

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# Relationship between inosine triphosphate genotype and outcome of extended therapy in hepatitis C virus patients with a late viral response to pegylated-interferon and ribavirin

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## Abstract

**Background and Aim:** It is not yet clear which factors are associated with the outcome of 72-week treatment with pegylated-interferon and ribavirin (RBV) in patients with chronic hepatitis C virus (HCV) infection.

**Methods:** In 66 patients with HCV genotype 1 who had a late viral response (LVR) to 72-week treatment of pegylated-interferon and RBV, we examined the factors that determined the outcome, including single nucleotide polymorphisms of interleukin-28B and inosine triphosphatase (*ITPA*) genes.

**Results:** Thirty seven of 66 (56%) patients with LVR achieved a sustained viral response (SVR). The mean age of these 37 SVR patients was 55, compared with 61 in 29 relapsed patients ($P = 0.009$). Twenty six of 54 (48%) patients with the CC genotype and 11 of 12 (92%) with the CA/AA genotype of *ITPA* rs1127354 achieved SVR ($P = 0.006$). The SVR rates were 79%, 40%, 60%, and 33% in patients with undetectable HCV RNA on weeks 16, 20, 24, and 28 or later, respectively ($P = 0.014$). Finally, serum RBV concentration at week 44 of treatment was significantly higher in the SVR group (2651 ng/mL) than in the relapse group (1989 ng/mL, $P = 0.002$). In contrast, the rate of the interleukin-28B genotype was not different between the groups. Multiple regression analysis showed that age < 60 years, *ITPA* CA/AA genotype, and serum RBV concentration were significant independent predictive factors for SVR.

**Conclusions:** Our findings elucidated the association of four factors, including *ITPA* genotype, with the outcome of 72-week treatment in LVR patients.

## Introduction

Hepatitis C virus (HCV) infection continues to be a major cause of liver cirrhosis and hepatocellular carcinoma.[1] An estimated 120–130 million people worldwide are infected with HCV.[2] Sustained viral response (SVR), defined as undetectable serum HCV RNA levels 24 weeks after cessation of therapy, is the aim of treatment. Although the current treatment regimen of pegylated-interferon (PEG-IFN) combined with ribavirin (RBV) greatly improved SVR in patients with HCV genotypes 2 and 3, the outcomes in patients with HCV genotype 1 and high viral load (> $10^5$ IU/mL) remain unsatisfactory, and SVR is attained in approximately 50% of cases.[3–8]

For HCV genotype 1, patients with rapid viral response, defined as undetectable serum HCV on week 4, achieve high rates of SVR up to 91% with combination therapy. Patients with early viral

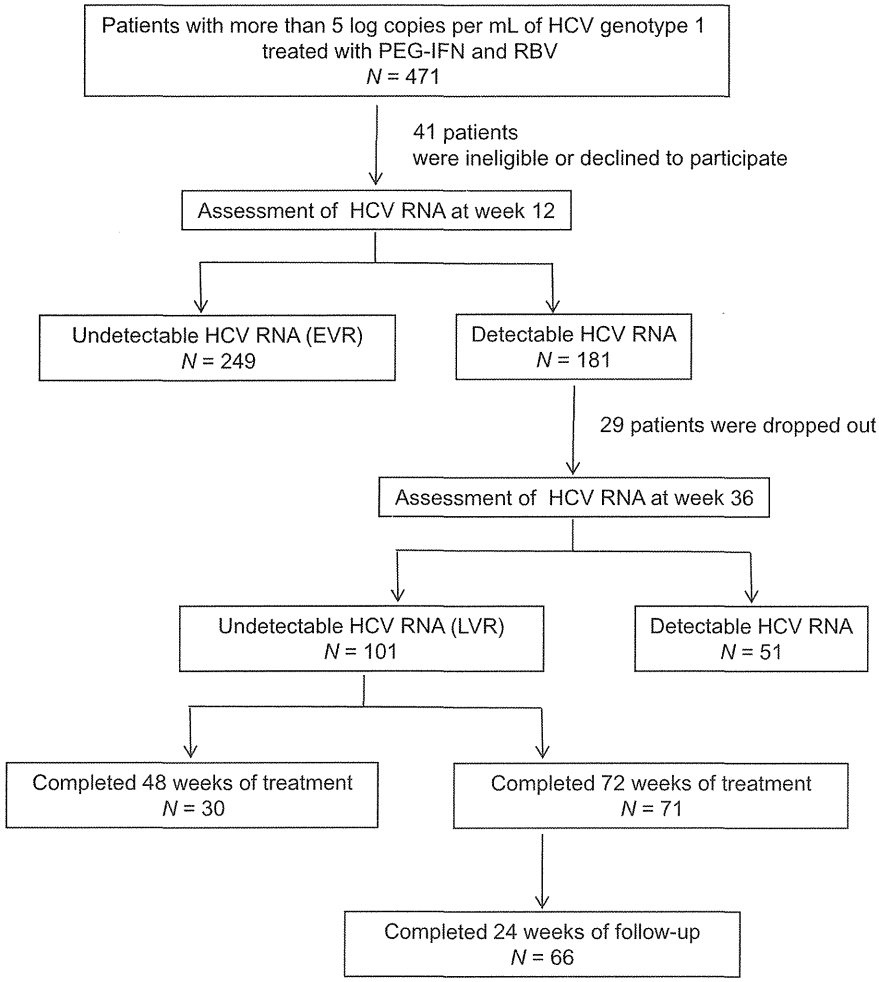


**Figure 1** Flow of participants throughout the study. EVR, early viral response; HCV, hepatitis C virus; LVR, late viral response; PEG-IFN, pegylated-interferon; RBV, ribavirin.

response, defined as undetectable serum HCV on week 12, achieved SVR rates of 65–81%. However, patients with a late viral response (LVR), who remained positive for HCV RNA on week 12 after the start of treatment but became negative for HCV RNA during weeks 13–36 of treatment, showed a lower SVR rate of 14–44%.[4,9–19] Although extending therapy to 72 weeks has been reported to decrease relapse in such patients,[12–17,20,21] it remains unclear which patient with LVR can benefit from extended treatment.

Inosine triphosphatase (*ITPA*) single nucleotide polymorphism (SNP) rs1127354, causing ITPase deficiency, was found to be associated with protection from RBV-induced anemia and to decrease the need for RBV dose reduction, but not to be associated with clinical outcome.[22–25] The present study was performed to identify that factors, including interleukin-28B (*IL28B*) and *ITPA* genotype, associated with the outcome of extended 72-week treatment in patients with HCV genotype 1 who had LVR to PEG-IFN and RBV.

## Methods

***Patients.*** A total of 471 patients were recruited at Osaka City University Hospital between December 2004 and June 2012. The flow of patients through the trial is presented in Figure 1. Sixty-six patients with HCV genotype 1 who were treated with PEG-IFN alpha 2a (Pegasys; Chugai Pharmaceutical Co., Ltd, Tokyo, Japan) or 2b (Pegintron; MSD, Osaka, Japan) and RBV (Rebetol, MSD) combination therapy were enrolled in this study. All patients had a viral load of $> 10^5$ IU/mL according to COBAS Amplicor HCV Monitor test, version 2.0 (Roche Diagnostics, Branchburg, NJ, USA), or a viral load of > 5 log copies/mL as determined by COBAS TaqMan HCV test (Roche Diagnostics). HCV RNA levels were investigated before and every 4 weeks after the start of treatment. All patients gave written informed consent to participate in this study, in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and according to the process approved by the ethical committee of Osaka City University, Graduate School of Medicine. Only the patients who completed 72-week combination therapy without discontinuation and in whom HCV RNA was detected on week 12 but not on weeks 13–36 were enrolled in this study.

Exclusion criteria included a history or evidence of a serious chronic or poorly controlled medical or psychiatric condition, infection with human immunodeficiency virus or hepatitis B virus, and receipt of systemic immunomodulatory or antineoplastic therapy within the previous 6 months. Pregnant or breastfeeding women and partners of pregnant women were also excluded.

The following factors were analyzed to determine whether they were related to the efficacy of combination therapy: patient age, gender, pretreatment biochemical parameters, such as neutrophil and platelet counts, hemoglobin concentration, levels of alanine transaminase, creatinine, HCV viral load, histopathological evaluation of hepatitis activity and hepatic fibrosis according to the METAVIR scoring system, total doses of PEG-IFN and RBV, and serum RBV concentration at week 44.

***Treatment protocol.*** The initial dose of PEG-IFN alpha 2a was 180 μg per week, and that of PEG-IFN alpha 2b was 1.5 μg per kg body weight per week. The initial dose of RBV was 400, 600, 800, or 1000 mg/day for patients weighing < 40 kg, 40–60 kg, 60–80 kg, or > 80 kg, respectively.

***RBV concentration.*** Serum RBV concentration was measured using an assay consisting of phenylboronic acid solid phase extraction, followed by HPLC at a commercial laboratory (SRL Inc., Osaka, Japan).[26] Briefly, the RBV concentrations in 200-μL samples were measured by validated HPLC with column switching. Serum samples deproteinized with perchloric acid were injected into the column, and RBV was detected by monitoring absorption of ultraviolet at 215 nm. The calibration curve was linear in the range of 50–20 000 ng/mL. A set of calibration standards at 0, 5, 10, 25, 50, 100, 250, 500, 1000, 2000, and 5000 mg/L RBV was prepared, extracted and analyzed with each series, together with internal quality controls at three levels.

***SNP genotyping.*** We examined genetic polymorphisms of the *IL28B* and *ITPA* genes in patients who consented to genome analysis. Whole blood was collected from all patients and centrifuged to separate the buffy coat. Genomic DNA was extracted from the buffy coat using a QIAamp DNA Blood Midi Kit (Qiagen Sciences Inc, Germantown, MD, USA). Genetic polymorphisms of *IL28B* rs8099917 and rs12979860 and *ITPA* rs1127354 were genotyped by TaqMan SNP Genotyping Assay on the 7500 Fast Real-Time PCR System (Applied Biosystems, Foster City, CA, USA). All samples were also genotyped by direct sequencing to confirm the genotype. Exon 2 of the *ITPA* gene and flanking intronic regions were amplified by polymerase chain reaction (PCR) using the following primers: forward, 5′-CTTTAGG AGATGGGCAGCAG-3′; reverse, 5′-CACAGAAAGTCAGGTC ACAGG-3′.[27] PCR was carried out in a total volume of 15 μL with 1× Premix Ex Tag (Applied Biosystems), 300 nM of each primer, and 100 ng of genomic DNA. The PCR profile consisted of 94°C for 10 min, followed by 35 cycles of 94°C for 30 s, 63°C for 30 s, and 72°C for 1 min, with a final extension at 72°C for 7 min. PCR products were sequenced bidirectionally using a BigDye Terminator v3.1 Cycle Sequencing Kit and ABI 3130XL Genetic Analyzer (Applied Biosystems). Genotyping analysis was permitted by the ethical committee of our university (approval number 1871).

***Statistical analysis.*** All data analyses were conducted using the JMP program, version 9.0 (SAS Institute, Cary, NC, USA). Individual characteristics between groups were evaluated by Wilcoxon's two-sample test for numerical variables, or Fisher's exact test for categorical variables. Variables exhibiting values of $P < 0.1$ on univariate analysis were subjected to stepwise multivariate logistic regression analysis. In the two-tailed test, $P < 0.05$ was taken to indicate statistical significance.

**Table 1** Characteristics of HCV genotype 1 patients with late virologic response†

| | Total ($n$ = 66) |
|---|---|
| Age (years) | 60 (21–77) |
| Gender (male/female) | 43/23 |
| HCV viral load (log copies/mL) | 6.5 (5.1–7.7) |
| Body mass index (kg/m$^2$) | 22.7 (16.5–28.0) |
| WBC (/μL) | 4600 (2000–8600) |
| Hb (g/dL) | 13.6 (10.9–17.3) |
| Platelet (× 10$^4$/μL) | 17.1 (8.5–45.0) |
| ALT (IU/L) | 54 (17–194) |
| Creatinine (mg/dL) | 0.66 (0.36–1.16) |
| *IL28B* rs8099917 (TT/TG+GG) | 45/21 |
| *IL28B* rs12979860 (CC/CT+TT) | 44/22 |
| *ITPA* rs1127354 (CC/CA+AA) | 54/12 |
| Liver biopsy | |
| Activity grading (0/1/2/3/ND) | 7/40/13/1/5 |
| Fibrosis staging (1/2/3/4/ND) | 38/15/8/0/5 |
| PEG-IFNα2a/PEG-IFNα2b | 12/54 |
| Week when HCV RNA was undetectable (16 weeks/20 weeks/24 weeks/28 weeks or delayed) | 24/20/10/12 |
| RBV concentration at week 44 (ng/mL) | 2467 (1006–4283) |
| Total dose of administered RBV (g/kg body weight) | 5.07 (1.56–7.21) |

†Continuous variables are medians (min-max).
ALT, alanine transaminase; Hb, hemoglobin; HCV, hepatitis C virus; *IL28B*, interleukin 28B gene; *ITPA*, inosine triphosphatase gene; ND, not done; PEG-IFN, pegylated-interferon; RBV, ribavirin; WBC, white blood cell.

## Results

***Patient profile and response rate.*** The characteristics of the overall 66 LVR patients, consisting of 43 men and 23 women, are shown in Table 1. The mean age of this cohort was 60 years. All of the patients who were infected with HCV genotype 1 with viral load > 5 log copies/mL, were treated with PEG-IFN/RBV for 72 weeks. HCV RNA was tested 24 weeks after completion of treatment when SVR and relapse were defined if HCV RNA was negative and positive, respectively. After 72 weeks of combination therapy, 37 (56%) patients achieved SVR, while the remaining 29 (44%) relapsed.

Direct sequencing and TaqMan SNP genotyping assay were used to genotype SNP *ITPA* rs1127354, and 100% of SNP results were concordant between both methods. Among the 66 LVR patients, 54 (82%) had the major CC genotype (wild-type), 10 (15%) were heterozygous for the CA genotype, and the remaining 2 (3%) had the minor AA genotype.

***Association between clinical factors and SVR rate.*** Among the 17 factors screened by univariate analysis, four factors were associated with treatment response, that is, patient

**Table 2** Comparison of the clinical characteristics of patients with SVR and those with relapse†

| | SVR ($n$ = 37) | Relapse ($n$ = 29) | $P$-value |
|---|---|---|---|
| Age (years) | 55 ± 7 | 61 ± 7 | 0.009* |
| Gender (male/female) | 24/13 | 19/10 | 0.956 |
| HCV viral load (log copies/mL) | 6.6 ± 0.4 | 6.4 ± 0.5 | 0.195 |
| Body mass index (kg/m$^2$) | 22.6 ± 2.9 | 22.1 ± 2.5 | 0.438 |
| WBC (/μL) | 4748 ± 1235 | 4693 ± 1281 | 0.861 |
| Hb (g/dL) | 13.9 ± 1.3 | 13.9 ± 1.6 | 0.892 |
| Platelets (× 10$^4$/μL) | 18.2 ± 7.8 | 16.6 ± 4 | 0.698 |
| ALT (IU/L) | 63.8 ± 40.6 | 62.6 ± 37.9 | 0.861 |
| Creatinine (mg/dL) | 0.71 ± 0.19 | 0.67 ± 0.12 | 0.473 |
| *IL28B* rs8099917 (TT/TG+GG) | 25/12 | 20/9 | 0.904 |
| *IL28B* rs12979860 (CC/CT+TT) | 24/13 | 20/9 | 0.930 |
| *ITPA* rs1127354 (CC/CA+AA) | 26/11 | 28/1 | 0.006* |
| Liver biopsy | | | |
| Activity grading (0/1/2/3/ND) | 3/24/6/1/3 | 4/16/7/0/2 | 0.563 |
| Fibrosis staging (1/2/3/4/ND) | 20/11/3/0/3 | 18/4/5/0/2 | 0.211 |
| PEG-IFNα2a/PEG-IFNα2b | 6/31 | 6/23 | 0.64 |
| Week when HCV RNA was undetectable (16 weeks/20 weeks/24 weeks/28 weeks or delayed) | 19/8/6/4 | 5/12/4/8 | 0.014* |
| RBV concentration at week 44 (ng/mL) | 2651 ± 675 | 1989 ± 525 | 0.002* |
| Total dose of RBV administered (g/kg body weight) | 5.08 ± 1.3 | 4.59 ± 1.11 | 0.059 |

*$P$ < 0.05.
†Continuous variables are medians (min-max).
ALT, alanine transaminase; Hb, hemoglobin; HCV, hepatitis C virus; *IL28B*, interleukin 28B gene; *ITPA*, inosine triphosphatase gene; ND, not done; PEG-IFN, pegylated interferon; RBV, ribavirin; WBC, white blood cell.

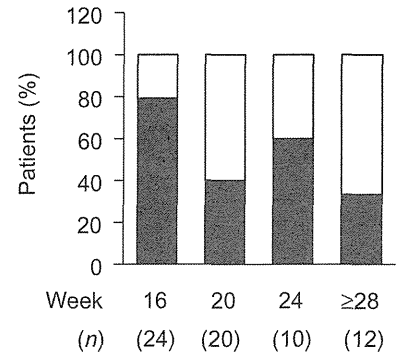


**Figure 2** Effects of combination therapy in patients with genotype 1 according to the time at which HCV was undetectable (week). Earlier HCV RNA disappearance was significantly associated with treatment outcome ($P$ = 0.014). SVR rates were 79% (19/24) in patients with undetectable HCV RNA at week 16, 40% (8/20) at week 20, 60% (6/10) at week 24, and 33% (4/12) at week 28 or delayed. HCV, hepatitis C virus; SVR, sustained viral response. (□) Relapse, (■) SVR.

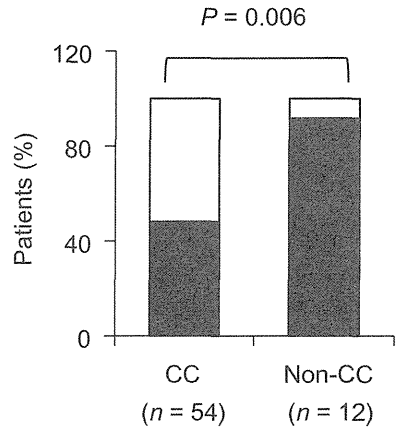


**Figure 3** Effects of combination therapy in patients with genotype 1 according to *ITPA* SNP rs1127354 genotype. SVR (black bar) was achieved in 48% (26/54) of patients with the rs1127354 CC genotype, and in 92% (11/12) of those with a non-CC genotype at rs1127354. Patients with the rs1127354 CA/AA genotype were significantly more likely to be associated with SVR ($P$ = 0.006). In the relapse group (white bar), the major CC allele occurred in 28/54 patients but the minor CC allele in only 1/12 patients. *ITPA*, inosine triphosphatase gene; SNP, single nucleotide polymorphism; SVR, sustained viral response. (□) Relapse, (■) SVR.

age, *ITPA* SNP rs1127354, time of undetectable HCV RNA, and RBV concentration (Table 2). The mean age of patients with SVR was significantly younger than that of patients with relapse (55 *vs* 61 years, respectively, $P$ = 0.009). Eleven of 37 (30%) patients with SVR and 1 of 29 (3%) patients with relapse had the CA/AA genotype of *ITPA*, indicating a significant association between the CA/AA genotype and SVR ($P$ = 0.006). In contrast, the proportion of the *IL28B* genotype was not different between patients with SVR and relapse. Earlier HCV RNA disappearance was significantly associated with treatment outcome ($P$ = 0.014); SVR rate was 79% (19/24) in patients with undetectable HCV RNA on week 16, 40% (8/20) on week 20, 60% (6/10) on week 24, and 33% (4/12) on or after week 28 (Fig. 2). Finally, when RBV concentration in the peripheral blood was examined on week 44 of treatment, it was significantly higher in the SVR group (2651 ng/mL) than the relapse group (1989 ng/mL, $P$ = 0.002).

***Association between SNP ITPA rs1127354 and clinical factors.*** Twenty six of 54 (48%) patients with the CC genotype and 11 of 12 (92%) with the CA/AA genotype achieved SVR (Fig. 3), indicating a significant association between the CA/AA genotype and SVR ($P$ = 0.006). The decline in hemoglobin concentration on week 12 from the baseline was 3.56 g/dL in patients with the CC genotype, compared with 2.16 g/dL in CA/AA patients ($P$ = 0.0004, Fig. 4a).

Evaluation of the association between SNP rs1127354 and RBV concentration or total dose of administered RBV showed no significance ($P$ = 0.27 and 0.65, respectively) (Fig. 4b,c).

***Independent predictive factors of combination therapy for SVR.*** Factors exhibiting values of $P$ < 0.1 on univariate analysis were age, *ITPA* genotype, week at which HCV

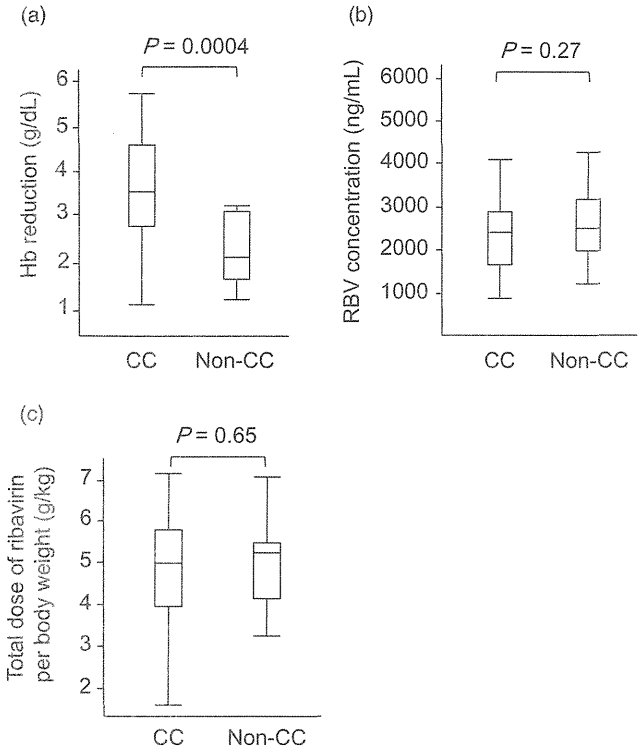


**Figure 4** Association between *ITPA* polymorphism and clinical factors: hemoglobin reduction at week 12 (a), ribavirin concentration at week 44 (b), and total dose of administered ribavirin (mg/kg of body weight (c). Hb reduction in wild-type (CC) was significantly higher than those with heterozygous (CA) or homozygous (AA) rs1127354 (3.56 *vs* 2.16 g/dL, respectively, $P = 0.0004$). There were no significant associations between *ITPA* SNP rs1127354 and ribavirin concentration and total ribavirin dose administered ($P = 0.27$ and 0.65, respectively). *ITPA*, inosine triphosphatase gene; SNP, single nucleotide polymorphism.

RNA was undetectable, RBV concentration, and total dose of RBV administered. These factors were categorized below: (i) younger or older than 60 years, (ii) CC or non-CC genotype of *ITPA* SNP rs1127354, (iii) HCV RNA undetectable at < 24 weeks or ≥ 24 weeks, (iv) RBV concentration < 2500 ng/mL or ≥ 2500 ng/mL, and (v) total RBV dose of < 4.9 g/kg or ≥ 4.9 g/kg. Multiple regression analysis indicated that age, *ITPA* rs1127354, and RBV concentration were significant independent predictive factors for SVR ($P = 0.002$, 0.006, and 0.045, respectively Table 3).

## Discussion

Previous studies have shown that extended 72-week combination therapy with PEG-IFN/RBV improves SVR rate,[14,15] while extended treatment is recommended only for HCV genotype 1 infection with LVR but not for general HCV patients.[13] However, Buti *et al.* showed that SVR rates were similar among LVR patients who received a standard dose of PEG-IFN alpha-2b and weight-based RBV for 48 or 72 weeks.[17] Although the overall SVR rate has been shown to improve in patients with LVR, it is necessary to determine which group of patients can benefit from extended therapy. The present study showed that age, timing of HCV RNA disappearance, serum RBV concentration, and *ITPA* SNP rs1127354 were related to the outcome of 72-week PEG-IFN/RBV therapy for patients with LVR.

**Table 3** Multiple regression analysis

| | Odds ratio (95% CI) | *P*-value |
|---|---|---|
| Age (≥ 60 years/< 60 years) | 9.7 (1.8–82.6) | 0.005* |
| *ITPA* rs1127354 (CA/AA *vs* CC) | 15.8 (1.7–415) | 0.012* |
| At week of undetectable HCV RNA (> 24 weeks/≤ 24 weeks) | 1.1 (0.2–6.4) | 0.897 |
| Ribavirin concentration on week 44 (≥ 2500 ng/mL/< 2500 ng/mL) | 12 (2.2–105.4) | 0.003* |
| Total dose of ribavirin administered (≥ 4.9 g/kg/< 4.9 g/kg) | 2 (0.4–9.7) | 0.361 |

*$P < 0.05$.
HCV, hepatitis C virus; *ITPA*, inosine triphosphatase gene.

However, *IL28B* SNPs were not associated with the outcome of 72-week treatment in patients with LVR. *IL28B* SNP was originally reported as a host marker to predict null responders to 48-week treatment.[28] The patients enrolled in our study were late viral responders, but not null responders. Including only patients with a specific on-treatment viral response may reduce the influence of *IL28B* SNP on the outcome. Our results are consistent with those of Mangia *et al.*,[29] showing that *IL28B* genotyping had limited clinical utility in the arrangement of response-guided therapy for patients with genotype 1.

In contrast, 11 (92%) of 12 patients with CA or AA at *ITPA* SNP rs1127354 achieved SVR among 66 patients with LVR. Polymorphic variation in the *ITPA* gene causing ITPase deficiency leads to an elevated concentration of inosine triphosphate (ITP) in erythrocytes. Similarly, RBV-induced anemia is triggered by the accumulation of RBV active forms of triphosphate (RBV-TP) in erythrocytes. ITP competes with RBV-TP, thus protecting cells from the lytic effects of RBV-TP. Patients with the rs1127354 CA/AA genotype have a lower risk for a hemoglobin decline of > 3 g/dL.[22,30] In fact, we found that hemoglobin was significantly lower in patients with the CC genotype than in those with the CA/AA genotype during the initial 12 weeks of treatment (Fig. 4a). It has been reported that a cumulative reduction in RBV is more frequent in patients with the CC genotype than in patients who are non-CC. Additionally, *ITPA* SNP rs1127354 is one of the predictive factors for SVR.[31] However, other studies have shown that *ITPA* SNP is associated with RBV-induced anemia but not with treatment outcome in patients who undergo standard therapy.[22–25] In the 165 patients who underwent 48 weeks of therapy in our hospital, *ITPA* genotype was not related to outcomes of patients who underwent standard therapy (data not shown). In the present study, LVR patients were the subjects. We speculate that LVR patients have different clinical backgrounds, including genotype, related to outcome of PEG-IFN and RBV combination therapy. In a subset of patients with the favorable TT genotype of *IL28B* SNP rs8099917, rs1127354 SNP of *ITPA* seemed to be associated with the outcome of combination therapy.[32] This is the first study to demonstrate an association between *ITPA* SNP and SVR rate in LVR patients who underwent extended treatment.

It is unclear why the *ITPA* genotype was associated with outcomes of LVR patients who underwent extended treatment. It has been reported that expression of several genes before combination therapy is related to *ITPA* genotype.[30] One of these might play an important role in the response to elongated therapy. In the present study, seven of 10 patients with *ITPA* non-CC type showed > 2500 ng/mL RBV at week 44. In contrast, 19 of 41 patients with the *ITPA* CC type had > 2500 ng/mL RBV at week 44. Many patients with *ITPA* non-CC type had > 2500 ng/mL RBV at week 44.

We did not detect associations between *ITPA* variants and RBV concentrations at week 44 (Fig. 4b). RBV concentration is affected by both the dose administered and its clearance; the latter is regulated by renal function.[33] Serum creatinine level was within the normal range in the patients included in the present study, indicating that their renal function is sufficient to receive RBV adjusted by body weight. The RBV dose administered is dependent on body weight and is correlated with RBV-related adverse events, particularly anemia. Recently, it was reported that both *SLC28A2* rs11854484 genotype and *ITPA* genotype were related to RBV-related anemia. However, the factor associated with RBV concentration at weeks 4 and 8 was the *SLC28A2* rs11854484 genotype, but not the *ITPA* genotype.[34] In patients with LVR, RBV concentration and *ITPA* genotype were independently associated with the outcome of extended treatment (Table 3).

Our data suggest that serum RBV concentration at week 44 was significantly higher in patients with SVR than in those with relapse ($P = 0.002$). On the other hand, total dosage of RBV was not related to the outcome of extended therapy. In previously published data regarding 48-week therapy, both the RBV dose administered and the RBV concentration in peripheral blood were associated with the outcome of combination therapy with PEG-IFN and RBV.[35,36] Furusyo *et al.* reported that in both groups with < 60% and ≥ 60% of RBV assigned total dosage, the mean RBV concentration at 48 weeks in patients with SVR was > 1500 ng/mL and was significantly higher than in those with relapse, suggesting that RBV concentration was unaffected by the assigned total dosage.[37] In the present study, no association between RBV concentration on week 44 and the total dose of RBV administered was identified (data not shown).

Many novel interferon-free antiviral regimens for HCV are now under clinical investigation. Some of these include RBV in combination with one or two direct-acting antiviral agents.[38,39] RBV will remain a key drug for treatment of chronic HCV infection in the forthcoming era of oral combination antiviral therapy. Further studies are required to evaluate the significance of *ITPA* SNP as predictors of not only RBV-induced anemia but also of treatment outcome.

In conclusion, age, RBV concentration, timing of HCV RNA disappearance, and *ITPA* SNP rs1127354 were associated with a higher SVR rate in LVR patients given 72-week treatment. These predictive factors may allow more efficient extended treatment with PEG-IFN and RBV for patients with LVR.

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## References

1 Shepard CW, Finelli L. Global epidemiology of hepatitis C virus infection. *Lancet Infect. Dis.* 2005; **5**: 558–67.
2 Global Burden of Hepatitis C Working Group. Global burden of disease (GBD) for hepatitis C. *J. Clin. Pharmacol.* 2004; **44**: 20–9.
3 Manns MP, McHutchison JG, Gordon SC *et al.* Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomized trial. *Lancet* 2001; **358**: 958–65.
4 Fried MW, Shiffman ML, Reddy KR *et al.* Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N. Engl. J. Med.* 2002; **347**: 975–82.
5 Hadziyannis S, Sette H Jr, Morgan TR *et al.* Peginterferon-alfa-2a plus ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann. Intern. Med.* 2004; **40**: 346–55.
6 Zeuzem S, Hultcrantz R, Bourliere M *et al.* Peginterferon alfa-2b plus ribavirin for treatment of chronic hepatitis C in previously untreated patients infected with HCV genotypes 2 or 3. *J. Hepatol.* 2004; **40**: 993–9.
7 Yamaguchi Y, Tamori A, Tanaka Y *et al.* Response-guided therapy for patients with chronic hepatitis who have high viral loads of hepatitis C virus genotype 2. *Hepatol. Res.* 2012; **42**: 549–57.
8 Zeuzem S. Heterogeneous virologic response rates to interferon-based therapy in patients with chronic hepatitis C: who responds less well? *Ann. Intern. Med.* 2004; **140**: 370–81.
9 Ferenci P, Fried MW, Shiffman ML *et al.* Predicting sustained virologic responses in chronic hepatitis C patients treated with peginterferon alfa-2a (40 KD)/ribavirin. *J. Hepatol.* 2005; **43**: 425–33.
10 Jensen DM, Morgan TR, Marcellin P *et al.* Early identification of HCV genotype 1 patients responding to 24 weeks peginterferon alpha-2a (40 kd)/ribavirin therapy. *Hepatology* 2006; **43**: 954–60.
11 Dienstag JL, McHutchison JG. American Gastroenterological Association medical position statement on the management of hepatitis C. *Gastroenterology* 2006; **130**: 225–30.
12 Ferenci P, Laferl H, Scherzer TM *et al.* Peginterferon alfa-2a/ribavirin for 48 or 72 weeks in hepatitis C genotypes 1 and 4 patients with slow virologic response. *Gastroenterology* 2010; **138**: 503–12.
13 Berg T, von Wagner M, Nasser S *et al.* Extended treatment duration for hepatitis C virus type 1: comparing 48 versus 72 weeks of peginterferon-alfa-2a plus ribavirin. *Gastroenterology* 2006; **130**: 1086–97.
14 Sanchez-Tapias JM, Diago M, Escartin P *et al.* Peginterferon-alfa2a plus ribavirin for 48 versus 72 weeks in patients with detectable hepatitis C virus RNA at week 4 of treatment. *Gastroenterology* 2006; **131**: 451–60.
15 Pearlman BL, Ehleben C, Saifee S. Treatment extension to 72 weeks of peginterferon and ribavirin in hepatitis C genotype 1-infected slow responders. *Hepatology* 2007; **46**: 1688–94.
16 Mangia A, Minerva N, Bacca D *et al.* Individualized treatment duration for hepatitis C genotype 1 patients: a randomized controlled trial. *Hepatology* 2008; **47**: 43–50.
17 Buti M, Lurie Y, Zakharova N *et al.* Randomized trial of peginterferon alfa-2b and ribavirin for 48 or 72 weeks in patients with HCV genotype 1 and slow virologic response. *Hepatology* 2010; **52**: 1201–7.
18 McHutchison JG, Lawitz EJ, Shiffman ML *et al.* Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. *N. Engl. J. Med.* 2009; **361**: 580–93.
19 Oze T, Hiramatsu N, Yakushijin T *et al.* Pegylated interferon alpha-2b (PEG-IFN **a**-2b) affects early virologic response

dose-dependently in patients with chronic hepatitis C genotype 1 during treatment with PEG-IFN **a**-2b plus ribavirin. *J. Viral Hepat.* 2009; **16**: 578–85.
20 Oze T, Hiramatsu N, Yakushijin T *et al.* The efficacy of extended treatment with pegylated interferon plus ribavirin in patients with HCV genotype 1 and slow virologic response in Japan. *J. Gastroenterol.* 2011; **46**: 944–52.
21 Di Martino V. Response-guided peg-interferon plus ribavirin treatment duration in chronic hepatitis C: meta-analyses of randomized, controlled trials and implications for the future. *Hepatology* 2011; **54**: 789–800.
22 Fellay J, Thompson AJ, Ge D *et al.* ITPA gene variants protect against anemia in patients treated for chronic hepatitis C. *Nature* 2010; **464**: 405–8.
23 Ochi H, Maekawa T, Abe H *et al.* ITPA polymorphism affects ribavirin-induced anemia and outcomes of therapy-A genome-wide study of Japanese HCV virus patients. *Gastroenterology* 2010; **139**: 1190–7.
24 Thompson AJ, Fellay J, Patel K *et al.* Variants in the ITPA gene protect against ribavirin-induced hemolytic anemia and decrease the need for ribavirin dose reduction. *Gastroenterology* 2010; **139**: 1181–9.
25 D'Avolio A, Ciancio A, Siccardi M *et al.* Inosine triphosphatase polymorphisms and ribavirin pharmacokinetics as determinants of ribavirin-associate anemia in patients receiving standard anti-HCV treatment. *Ther. Drug Monit.* 2012; **34**: 165–70.
26 Tsubota A, Horose Y, Izumi N *et al.* Pharmacokinetics of ribavirin in combined interferon-alpha 2b and ribavirin therapy for chronic hepatitis C virus infection. *Br. J. Clin. Pharmacol.* 2003; **55**: 360–7.
27 Bakker JA, Lindhout M, Habets DD, van den Wijngaard A, Paulussen AD, Bierau J. The effect of ITPA polymorphisms on the enzyme kinetic properties of human erythrocyte inosine triphosphatase toward its substrates ITP and 6-Thio-ITP. *Nucleosides Nucleotides Nucleic Acids* 2011; **30**: 839–49.
28 Tanaka Y, Nishida N, Sugiyama M *et al.* Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. *Nat. Genet.* 2009; **41**: 1105–9.
29 Mangia A, Thompson AJ, Santoro R *et al.* Limited use of interleukin 28B in the setting of response-guided treatment with detailed on-treatment virological monitoring. *Hepatology* 2011; **54**: 772–80.
30 Birerdinc A, Estep M, Afendy A *et al.* Gene expression profiles associated with anemia and ITPA genotypes in patients with chronic hepatitis C (CH-C). *J. Viral Hepat.* 2012; **19**: 414–22.
31 Azakami T, Hayes CN, Sezaki H *et al.* Common genetic polymorphism of ITPA gene affects ribavirin-induced anemia and effect of peg-interferon plus ribavirin therapy. *J. Med. Virol.* 2011; **83**: 1048–57.
32 Kurosaki M, Tanaka Y, Tanaka K *et al.* Relationship between polymorphisms of the inosine triphosphatase gene and anemia or outcome after treatment with pegylated interferon and ribavirin. *Antivir. Ther.* 2011; **16**: 685–94.
33 Morello J, Rodríguez-Novoa S, Jiménez-Nácher I, Soriano V. Usefulness of monitoring ribavirin plasma concentrations to improve treatment response in patients with chronic hepatitis C. *J. Antimicrob. Chemother.* 2008; **62**: 1174–80.
34 Rau M, Stickel F, Russmann S *et al.* Impact of genetic SLC28 transporter and ITPA variants on ribavirin serum level, hemoglobin drop and therapeutic response in patients with HCV infection. *J. Hepatol.* 2013; **58**: 669–75.
35 Ogawa E, Furusyo N, Kajiwara E *et al.* An inadequate dose of ribavirin is related to virological relapse by chronic hepatitis C patients treated with pegylated interferon alpha-2b and ribavirin. *J. Infect. Chemother.* 2012; **18**: 689–97.
36 Kurosaki M, Hiramatsu N, Sakamoto M *et al.* Age and total ribavirin dose are independent predictors of relapse after interferon therapy in chronic hepatitis C revealed by data mining analysis. *Antivir. Ther.* 2012; **17**: 35–43.
37 Furusyo N, Murata M, Ogawa E *et al.* Ribavirin concentration in the later stages of 48 week pegylated interferon-alpha2b plus ribavirin therapy for chronic hepatitis C is useful for predicting virological response. *J. Antimicrob. Chemother.* 2011; **66**: 1127–39.
38 Gane EJ, Stedman CA, Hyland RH *et al.* Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. *N. Engl. J. Med.* 2013; **368**: 34–44.
39 Poordad F, Lawitz E, Kowdley KV *et al.* Exploratory study of oral combination antiviral therapy for hepatitis C. *N. Engl. J. Med.* 2013; **368**: 45–53.

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LETTER TO THE EDITOR

# Treatment guidelines for HCV genotype 1: mono for low, triple for high, and dual for 'middle'?

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In the United States, dual therapy with pegylated interferon (Peg-IFN) and ribavirin had been the standard treatment for chronic hepatitis C virus genotype 1 (HCV-1) infection until recently, irrespective of viral load [1]. Since HCV NS3/4 serine protease inhibitors, such as telaprevir and boceprevir, became available, the standard treatment was replaced by triple therapy with a protease inhibitor, Peg-IFN, and ribavirin [2]. Guidelines proposed by the Japanese Study Group for the Standardization of Treatment of Viral Hepatitis [3] had recommended monotherapy with pegylated or non-pegylated IFN for treatment-naïve patients with low HCV-1 loads (<5 $\log_{10}$ IU/mL), and dual therapy with Peg-IFN and ribavirin for patients with high HCV-1 loads (≥5 $\log_{10}$ IU/mL) until the approval of telaprevir in 2011.

We read the JSH Guidelines for the Management of Hepatitis C Virus Infection in a recent issue of the *Journal of Gastroenterology* [4]. The Guidelines recommend monotherapy for treatment-naïve patients with low HCV-1 loads and triple therapy including telaprevir for patients with high HCV-1 loads. For example, the Guidelines recommend monotherapy if HCV RNA is 4.9 $\log_{10}$ IU/mL and triple therapy if HCV RNA is 5.0 $\log_{10}$ IU/mL. We wonder if there is a range of 'middle' viral loads for which dual therapy can be indicated. A phase III clinical trial in Japan showed that the rate of sustained virologic response (SVR) was higher with triple therapy than with dual therapy, but the difference did not reach statistical significance in the subgroup of patients with HCV RNA of 5.0–6.9 $\log_{10}$ IU/mL (74/100 vs. 26/45, $P = 0.056$) [5]. We retrospectively analyzed the relation between baseline HCV RNA loads and treatment outcomes in patients who received dual therapy in our hospital during several years before telaprevir was approved.

Between December 2004 and May 2011, 183 treatment-naïve patients (75 men/108 women; 57 ± 11 years old) with high HCV-1 loads started dual therapy with Peg-IFN-α2b and ribavirin. The median laboratory values (interquartile range) at baseline were as follows: aspartate aminotransferase 45 (36–66) IU/L, alanine aminotransferase 52 (37–81) IU/L and platelet count 171 (134–204) × $10^3$/mm$^3$. Of the 169 patients who underwent liver biopsy, the stage of fibrosis was F1 in 125 (74 %), F2 in 28 (17 %), F3 in 12 (7.1 %), and F4 in 4 (2.4 %). Of the 141 patients who consented to genome analysis, the *interleukin 28B* genotype at rs8099917 was TT in 104 (74 %) and TG/GG in 37 (26 %) [6]. The SVR rate was 79 % in the 19 patients with HCV RNA of 5.0–5.4 $\log_{10}$ IU/mL, 47 % in the 34 with 5.5–5.9 $\log_{10}$ IU/mL, 51 % in the 110 with 6.0–6.9 $\log_{10}$ IU/mL, and 50 % in the 20 with ≥7.0 $\log_{10}$ IU/mL; the rate was significantly higher in the 19 patients with HCV RNA 5.0–5.4 $\log_{10}$ IU/mL than in the remaining 164 patients with HCV RNA ≥5.5 $\log_{10}$ IU/mL ($P = 0.027$). One possible explanation why the rate of SVR did not decline with an increase in viral loads when HCV RNA exceeded 5.4 $\log_{10}$ IU/mL is that the duration of treatment was extended from 48 to 72 weeks if a patient had a late virologic response, in accordance with the concept of 'response-guided therapy.'

In summary, in patients with genotype 1 HCV RNA of 5.0–5.4 $\log_{10}$ IU/mL, the SVR rate was sufficiently high (about 80 %) in response to Peg-IFN and ribavirin. Dual

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therapy may thus be indicated for such patients with 'middle' HCV-1 loads, especially when telaprevir is poorly tolerated by elderly patients. However, the proportion of patients with HCV RNA in the 'middle' range was quite small (about 10 % of patients with high viral loads); therefore, the updated Guidelines in Japan for the treatment of HCV appear to be basically valid.

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## References

1. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology. 2009;49:1335–74.
2. Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology. 2011;54:1433–44.
3. Kumada H, Okanoue T, Onji M, et al. Guidelines for the treatment of chronic hepatitis and cirrhosis due to hepatitis C virus infection for the fiscal year 2008 in Japan. Hepatol Res. 2010;40:8–13.
4. Chayama K, Hayes CN, Ohishi W, Kawakami Y. Treatment of chronic hepatitis C virus infection in Japan: update on therapy and guidelines. J Gastroenterol. 2013;48:1–12.
5. Kumada H, Toyota J, Okanoue T, Chayama K, Tsubouchi H, Hayashi N. Telaprevir with peginterferon and ribavirin for treatment-naive patients chronically infected with HCV of genotype 1 in Japan. J Hepatol. 2012;56:78–84.
6. Tanaka Y, Nishida N, Sugiyama M, et al. Genome-wide association of *IL28B* with response to pegylated interferon-α and ribavirin therapy for chronic hepatitis C. Nat Genet. 2009;41:1105–9.