after living-donor liver transplantation. Transplantation 2008;85:855–62.
[4] Sugawara Y, Makuuchi M, Matsui Y, Kishi Y, Akamatsu N, Kaneko J, et al. Preemptive therapy for hepatitis C virus after living-donor liver transplantation. Transplantation 2004;78: 1308–11.
[5] Sugawara Y, Makuuchi M. Living donor liver transplantation to patients with hepatitis C virus cirrhosis. World J Gastroenterol 2006;12:4461–5.
[6] Roche B, Sebagh M, Canfora ML, Antonini T, Roque-Afonso AM, Delvart V, et al. Hepatitis C virus therapy in liver transplant recipients: response predictors, effect on fibrosis progression, and importance of the initial stage of fibrosis. Liver Transpl 2008;14:1766–77.
[7] Lodato F, Berardi S, Gramenzi A, Mazzella G, Lenzi M, Morelli MC, et al. Clinical trial: peg-interferon alfa-2b and ribavirin for the treatment of genotype-1 hepatitis C recurrence after liver transplantation. Aliment Pharmacol Ther 2008;28:450–7.
[8] Dinges S, Morard I, Heim M, Dufour JF, Mullhaupt B, Giostra E, et al. Pegylated interferon-alpha2a/ribavirin treatment of recurrent hepatitis C after liver transplantation. Transpl Infect Dis 2009;11:33–9.
[9] Saab S, Oh MK, Ibrahim AB, Durazo F, Han S, Yersiz H, et al. Anemia in liver transplant recipients undergoing antiviral treatment for recurrent hepatitis C. Liver Transpl 2007;13:1032–8.
[10] Sugawara Y, Makuuchi M. Living donor liver transplantation for patients with hepatitis C virus cirrhosis: Tokyo experience. Clin Gastroenterol Hepatol 2005;3(10 Suppl 2):S122–4.
[11] Berg T, von Wagner M, Nasser S, Sarrazin C, Heintges T, Gerlach T, 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.
[12] 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.
[13] Tamura S, Sugawara Y, Yamashiki N, Kaneko J, Kokudo N, Makuuchi M. Pre-emptive antiviral therapy in living donor liver transplantation for hepatitis C: observation based on a single-center experience. Transpl Int 2009;23:580–8.
[14] Ueda Y, Takada Y, Marusawa H, Egawa H, Uemoto S, Chiba T. Individualized extension of pegylated interferon plus ribavirin therapy for recurrent hepatitis C genotype 1b after living-donor liver transplantation. Transplantation 2010 (In press).
[15] Enomoto N, Sakuma I, Asahina Y, Kurosaki M, Murakami T, Yamamoto C, et al. Mutations in the nonstructural protein 5A gene and response to interferon in patients with chronic hepatitis C virus 1b infection. N Engl J Med 1996;334:77–81.
[16] Akuta N, Suzuki F, Sezaki H, Suzuki Y, Hosaka T, Someya T, et al. Predictive factors of virological non-response to interferon-ribavirin combination therapy for patients infected with hepatitis C virus of genotype 1b and high viral load. J Med Virol 2006;78:83–90.
[17] Akuta N, Suzuki F, Kawamura Y, Yatsuji H, Sezaki H, Suzuki Y, et al. Predictive factors of early and sustained responses to peginterferon plus ribavirin combination therapy in Japanese patients infected with hepatitis C virus genotype 1b: amino acid substitutions in the core region and low-density lipoprotein cholesterol levels. J Hepatol 2007;46:403–10.
[18] Akuta N, Suzuki F, Sezaki H, Suzuki Y, Hosaka T, Someya T, et al. Association of amino acid substitution pattern in core protein of hepatitis C virus genotype 1b high viral load and non-virological response to interferon-ribavirin combination therapy. Intervirology 2005;48:372–80.
[19] Berenguer M, Palau A, Fernandez A, Benlloch S, Aguilera V, Prieto M, et al. Efficacy, predictors of response, and potential risks associated with antiviral therapy in liver transplant recipients with recurrent hepatitis C. Liver Transpl 2006;12:1067–76.
[20] Hanouneh IA, Miller C, Aucejo F, Lopez R, Quinn MK, Zein NN. Recurrent hepatitis C after liver transplantation: on-treatment prediction of response to peginterferon/ribavirin therapy. Liver Transpl 2008;14:53–8.
[21] Akuta N, Suzuki F, Kawamura Y, Yatsuji H, Sezaki H, Suzuki Y, et al. Predictors of viral kinetics to peginterferon plus ribavirin combination therapy in Japanese patients infected with hepatitis C virus genotype 1b. J Med Virol 2007;79:1686–95.
[22] Kato N, Hijikata M, Ootsuyama Y, Nakagawa M, Ohkoshi S, Sugimura T, et al. Molecular cloning of the human hepatitis C virus genome from Japanese patients with non-A, non-B hepatitis. Proc Natl Acad Sci USA 1990;87:9524–8.
[23] Ferenci P, Fried MW, Shiffman ML, Smith CI, Marinos G, Goncales FL Jr, et al. Predicting sustained virological responses in chronic hepatitis C patients treated with peginterferon alfa-2a (40 KD)/ribavirin. J Hepatol 2005;43: 425–33.
[24] Zeuzem S, Buti M, Ferenci P, Sperl J, Horsmans Y, Cianciara J, et al. Efficacy of 24 weeks treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C infected with genotype 1 and low pretreatment viremia. J Hepatol 2006;44:97–103.
[25] Drusano GL, Preston SL. A 48-week duration of therapy with pegylated interferon alpha 2b plus ribavirin may be too short to maximize long-term response among patients infected with genotype-1 hepatitis C virus. J Infect Dis 2004;189:964–70.
[26] Akuta N, Suzuki F, Hirakawa M, Kawamura Y, Yatsuji H, Sezaki H, et al. A matched case-controlled study of 48 and 72 weeks of peginterferon plus ribavirin combination therapy in patients infected with HCV genotype 1b in Japan: amino acid substitutions in HCV core region as predictor of sustained virological response. J Med Virol 2009;81:452–8.
[27] Fukuhara T, Taketomi A, Okano S, Ikegami T, Soejima Y, Shirabe K, et al. Mutations in hepatitis C virus genotype 1b and the sensitivity of interferon-ribavirin therapy after liver transplantation. J Hepatol 2010;52:672–80.
[28] Kamal SM, Fouly AE, Kamel RR, Hockenjos B, Al Tawil A, Khalifa KE, et al. Peginterferon alfa-2b therapy in acute hepatitis C: impact of onset of therapy on sustained virologic response. Gastroenterology 2006;130:632–8.
[29] Ogata K, Ide T, Kumashiro R, Kumada H, Yotsuyanagi H, Okita K, et al. Timing of interferon therapy and sources of infection in patients with acute hepatitis C. Hepatol Res 2006;34:35–40.
[30] Delwaide J, Bourgeois N, Gerard C, De Maeght S, Mokaddem F, Wain E, et al. Treatment of acute hepatitis C with interferon alpha-2b: early initiation of treatment is the most effective predictive factor of sustained viral response. Aliment Pharmacol Ther 2004;20:15–22.
[31] Jaeckel E, Cornberg M, Wedemeyer H, Santantonio T, Mayer J, Zankel M, et al. Treatment of acute hepatitis C with interferon alfa-2b. N Engl J Med 2001;345:1452–7.

Hepatol Int (2010) 4:594–600
DOI 10.1007/s12072-010-9185-3

ORIGINAL ARTICLE

Evaluation of long-term entecavir treatment in stable chronic hepatitis B patients switched from lamivudine therapy

Tatsuya Ide · Michio Sata · Kazuaki Chayama · Michiko Shindo · Joji Toyota · Satoshi Mochida · Eiichi Tomita · Hiromitsu Kumada · Gotaro Yamada · Hiroshi Yatsuhashi · Norio Hayashi · Hiroki Ishikawa · Taku Seriu · Masao Omata

Received: 30 October 2009 / Accepted: 25 June 2010 / Published online: 8 July 2010

Abstract
Purpose Current Japanese guidelines recommend that patients should be switched from lamivudine to entecavir when they meet certain criteria. This analysis examines the efficacy and safety of long-term entecavir therapy in patients who were switched to entecavir after 24 weeks' lamivudine therapy in Japanese studies ETV-047 and ETV-060.
Methods The Phase II Japanese study ETV-047 assessed the efficacy of different entecavir doses when compared with lamivudine. A total of 33 Japanese patients who received lamivudine 100 mg daily in ETV-047 entered the open-label rollover study ETV-060 and subsequently received treatment with entecavir 0.5 mg daily. Hepatitis B virus (HBV) DNA suppression, alanine aminotransferase (ALT) normalization, hepatitis B e antigen (HBeAg) seroconversion, and resistance were evaluated among patients with available samples for up to 96 weeks. Safety was assessed throughout the treatment period.
Results After 96 weeks of entecavir therapy in ETV-060, 90% of patients achieved HBV DNA <400 copies/mL as compared to 21% of patients who completed 24 weeks of lamivudine therapy in ETV-047. Increasing proportions of patients achieved ALT normalization and HBeAg seroconversion following long-term entecavir treatment. No patients experienced virologic breakthrough, and substitutions associated with entecavir resistance were not

T. Ide (✉) · M. Sata
Division of Gastroenterology, Department of Medicine,
Kurume University School of Medicine, Fukuoka, Japan
e-mail: ide@med.kurume-u.ac.jp

K. Chayama
Department of Medicine and Molecular Science,
Graduate School of Biomedical Sciences,
Hiroshima University, Hiroshima, Japan

M. Shindo
Division of Liver Disease, Department of Internal Medicine,
Akashi Municipal Hospital, Akashi, Hyogo, Japan

J. Toyota
Department of Gastroenterology,
Sapporo Kosei General Hospital, Hokkaido, Japan

S. Mochida
Department of Gastroenterology and Hepatology,
Saitama Medical University, Saitama, Japan

E. Tomita
Department of Gastroenterology,
Gifu Municipal Hospital, Gifu, Japan

H. Kumada
Department of Hepatology, Toranomon Hospital, Tokyo, Japan

G. Yamada
Department of Internal Medicine, Center for Liver Diseases,
Kawasaki Medical School, Kawasaki Hospital, Okayama, Japan

H. Yatsuhashi
Clinical Research Center, National Hospital Organization
Nagasaki Medical Center, Nagasaki, Japan

N. Hayashi
Department of Gastroenterology and Hepatology,
Osaka University Graduate School of Medicine, Osaka, Japan

H. Ishikawa · T. Seriu
Research and Development, Bristol-Myers K.K, Tokyo, Japan

M. Omata
Department of Gastroenterology, Graduate School of Medicine,
University of Tokyo, Tokyo, Japan

observed in patients with detectable HBV DNA. Entecavir was well tolerated during long-term treatment.

Conclusions Switching lamivudine-treated patients with chronic hepatitis B to entecavir results in increased virologic suppression with no evidence of resistance through 2 years of entecavir therapy. These findings support recommendations in the current Japanese treatment guidelines that stable lamivudine patients should be switched to entecavir.

Keywords Japanese · Chronic hepatitis B · Entecavir · Lamivudine · Switch

Introduction

Chronic hepatitis B virus (HBV) infection affects more than 350 million people worldwide, and is a leading cause of liver-related mortality [1]. Although Japan has one of the lowest prevalence rates for chronic hepatitis B (CHB) (0.8%) among Asian countries, it is still estimated that over 1 million people are chronically infected with HBV [2]. These individuals are at an increased risk of developing cirrhosis, liver failure or hepatocellular carcinoma (HCC) [3].

Lamivudine was the first nucleoside analog introduced for the treatment of CHB. In clinical trials, it demonstrated superior efficacy to placebo for HBV DNA suppression, alanine aminotransferase (ALT) normalization and hepatitis B e antigen (HBeAg) seroconversion [4, 5]. However, a major limitation of lamivudine therapy is the development of resistance, which occurs in up to 70% of patients through 4 years of therapy [6]. Entecavir is a potent inhibitor of HBV replication [7]. In global Phase III studies, entecavir demonstrated superior histologic, virologic and biochemical responses when compared with lamivudine in nucleoside-naïve patients and lamivudine-refractory patients at 48 weeks [8–10]. In the Japanese Phase II study ETV-047, treatment with entecavir resulted in a superior reduction in HBV DNA as compared to lamivudine [11]. In contrast to lamivudine, entecavir has been shown to have a high genetic barrier to resistance; the cumulative probability of resistance through 5 years of treatment has been reported to be 1.2% [12]. The genetic barrier is lower in patients who are infected with lamivudine-resistant HBV and consequently higher resistance rates are observed in this population with long-term treatment [12].

Current Japanese treatment guidelines recommend that all treatment-naïve CHB patients with ALT levels $\geq$31 IU/L should be treated, dependent on their viral load. The thresholds for treatment are HBV DNA $\geq$5 $\log_{10}$ copies/mL in HBeAg-positive patients, $\geq$4 $\log_{10}$ copies/mL in HBeAg-negative patients, and $\geq$3 $\log_{10}$ copies/mL in cirrhotic patients [13]. Lamivudine, adefovir, and entecavir are currently approved for the treatment of CHB in Japan. Entecavir 0.5 mg once daily is the first choice therapy for treatment-naïve HBeAg-positive and negative patients aged 35 years or older. In treatment-naïve patients <35 years, the guidelines recommend treating first with interferon for HBeAg-positive patients, and treating HBeAg-negative patients with HBV DNA $\geq$7 $\log_{10}$ copies/mL with entecavir until undetectable HBV DNA is achieved, followed by a combination of entecavir and interferon for 4 weeks, and finally interferon monotherapy for 20 weeks. HBeAg-negative patients with HBV DNA <7 $\log_{10}$ copies/mL should be monitored or can receive interferon therapy. For patients who are lamivudine experienced, but not necessarily resistant, the guidelines also recommend that patients can be switched to entecavir 0.5 mg daily if they have received lamivudine therapy, and have HBV DNA <2.1 $\log_{10}$ copies/mL. Patients with HBV DNA $\geq$2.1 $\log_{10}$ copies/mL can also be switched to entecavir 0.5 mg once daily if they do not have viral breakthrough. Limited data on the efficacy of entecavir in this patient population are available; however, the design of the Japanese study ETV-047 and the rollover study ETV-060 presents an opportunity to assess the efficacy of this treatment option. This report examines the long-term efficacy, safety and resistance of entecavir 0.5 mg daily among patients who were directly switched from lamivudine following 24 weeks' treatment in ETV-047.

Materials and methods

Study population

Study ETV-047 was a Phase II, randomized, double-blind study conducted to evaluate the dose–response relationship of entecavir and compare the antiviral activity and safety of entecavir to lamivudine in Japanese patients with CHB. In ETV-047, 137 patients were randomized to receive one of three entecavir doses [0.01 mg (n = 35), 0.1 mg (n = 34) or 0.5 mg (n = 34), once daily] or lamivudine [100 mg (n = 34), once daily] for 24 weeks. The study design and complete inclusion criteria have been described previously [11]. Briefly, eligible patients had HBeAg-positive or -negative CHB with compensated liver disease, HBV DNA $\geq$7.6 $\log_{10}$ copies/mL by PCR assay, <12 weeks' prior therapy with anti-HBV nucleoside analogs and ALT levels 1.25–10 × upper limit of normal (ULN). After completion of treatment in ETV-047, all patients were eligible to enroll immediately in the rollover study ETV-060, with no gap in dosing.

The rollover study ETV-060 was designed to provide open-label entecavir for patients who had completed therapy in the Japanese Phase II program. Patients who completed 24 weeks of treatment in ETV-047 enrolled in ETV-060 and received 0.5 mg entecavir once daily. After 96 weeks of treatment in study ETV-060, patients could complete the study and were eligible to receive commercially available entecavir, which was approved by Japanese health authorities while study ETV-060 was ongoing.

The current analysis describes results for a subset of 33 patients who received lamivudine for 24 weeks in ETV-047 and entecavir 0.5 mg once daily for up to 96 weeks in ETV-060.

Efficacy analyses

Efficacy assessments evaluated the proportions of patients who had available samples (non-completer = missing) every 24 weeks through 120 weeks' treatment. Efficacy end points assessed included HBV DNA <400 copies/mL by PCR assay, ALT normalization ($\leq 1.0 \times$ ULN), HBeAg seroconversion among patients who were HBeAg-positive at baseline, and hepatitis B surface antigen (HBsAg) loss. Serum HBV DNA was determined by Roche Amplicor® PCR assay (Roche Diagnostics K.K., Tokyo, Japan; limit of quantification = 400 copies/mL) in a central laboratory. Clinical laboratory tests, PCR assays for HBV DNA, and serologic tests for HBV were performed at SRL, Inc. (Tokyo, Japan), the central clinical laboratory designated by the trial sponsor. On-treatment testing for resistance was carried out using a direct-sequencing PCR method.

Safety analyses

Safety analyses include the incidence of adverse events, serious adverse events, laboratory abnormalities, and discontinuations due to adverse events on-treatment throughout treatment in study ETV-060. On-treatment ALT flares were defined as ALT $>2 \times$ baseline and $>10 \times$ ULN.

Resistance analysis

Resistance testing was performed using a direct-sequencing PCR method. Paired samples from all patients with HBV DNA $\geq$400 copies/mL were analyzed for substitutions associated with entecavir or lamivudine resistance at week 96 (72 weeks of entecavir therapy) or week 120 (96 weeks of entecavir therapy). Patients who discontinued therapy prior to week 120 had their last on-treatment sample analyzed. All patients with virologic breakthrough (≥ 1 $\log_{10}$ increase from nadir on two consecutive measurements) were also tested for resistance.

Results

Study population

Of the 34 patients in ETV-047 who received treatment with lamivudine 100 mg once daily for 24 weeks, 33 entered ETV-060 and received treatment with entecavir 0.5 mg once daily. Two patients discontinued treatment during ETV-060: one due to an adverse event (depression) and the other due to insufficient effect. In addition, one patient completed treatment at week 76 (52 weeks of entecavir therapy) after meeting the criteria for protocol-defined complete response (undetectable HBV DNA by PCR assay, undetectable HBeAg and normal serum ALT).

Baseline demographic and disease characteristics for the switch cohort are presented in Table 1. The majority of patients (82%) in the cohort were male with a mean age of 43 years. The mean duration of entecavir therapy was 105.9 weeks (range 25–141 weeks). Baseline mean HBV DNA and ALT levels were 7.9 $\log_{10}$ copies/mL and 184 IU/L, respectively. Ninety-one percent of patients were HBeAg-positive and 88% had HBV genotype C infection.

Virologic end points

After completion of 24 weeks of lamivudine treatment in ETV-047, 21% (7/33) of patients in the switch cohort had achieved HBV DNA <400 copies/mL (Fig. 1). Following the switch to entecavir, the proportion of patients achieving HBV DNA <400 copies/mL increased to 82% (27/33) by week 48 (24 weeks of entecavir therapy). Viral suppression

Table 1 Baseline (pretreatment) demographics and disease characteristics: switch cohort

Characteristic	ETV-047/-60 lamivudine to entecavir switch cohort ($n = 33$)
Age, mean (years)	42.7
Male, *n* (%)	27 (82)
Ethnicity Japanese, *n* (%)	33 (100)
Entecavir treatment periods, mean (range) (weeks)	105.9 (25–141)
HbeAg-positive, *n* (%)	30 (91)
HBV DNA by PCR, mean $\log_{10}$ copies/mL (SD)	7.9 (0.80)
ALT (IU/L), mean (SD)	184.8 (132.9)
HBV genotype, *n* (%)	
A	2 (6)
B	2 (6)
C	29 (88)
Others	0

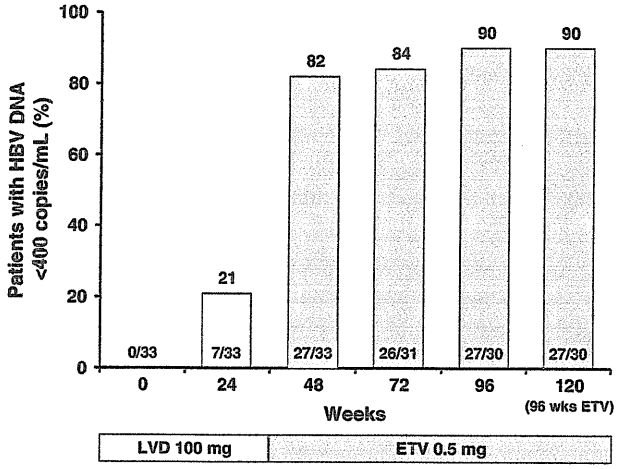

Fig. 1 Proportion of patients with HBV DNA <400 copies/mL through 120 weeks of therapy (ETV-047 to ETV-060). *Denominators* represent patients with available samples. *ETV* entecavir, *HBV* hepatitis B virus, *LVD* lamivudine

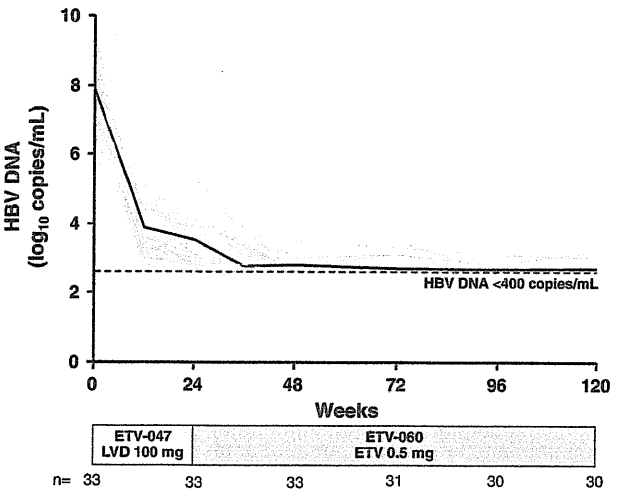

Fig. 2 HBV DNA suppression through week 120 (96 weeks of entecavir therapy). Individual patient HBV DNA profiles are plotted in *gray*. Mean HBV DNA levels are represented by the *solid black line*. *ETV* entecavir, *HBV* hepatitis B virus, *LVD* lamivudine

was maintained with longer entecavir treatment, with 84% (26/31) and 90% (27/30) achieving HBV DNA <400 copies/mL at weeks 72 and 120, respectively (48 and 96 weeks of entecavir therapy). Mean HBV DNA levels decreased from a baseline of 7.90 to 3.52 $\log_{10}$ copies/mL after 24 weeks of lamivudine therapy in ETV-047, and reached 2.69 $\log_{10}$ copies/mL after 96 weeks of entecavir therapy in ETV-060 (week 120; Fig. 2). No viral breakthrough was observed during entecavir therapy.

Biochemical end points

ALT normalization ($\leq$1.0 × ULN) was demonstrated in 76% (25/33) of patients after 24 weeks of lamivudine therapy in

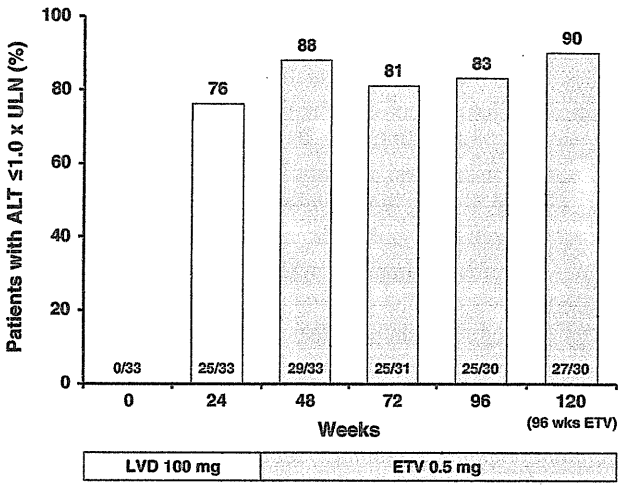

Fig. 3 Proportion of patients with ALT normalization ($\leq$1.0 × ULN) through 120 weeks of therapy (ETV-047 to ETV-060). *Denominators* represent patients with available samples. *ALT* alanine aminotransferase, *ETV* entecavir; *LVD* lamivudine, *ULN* upper limit of normal

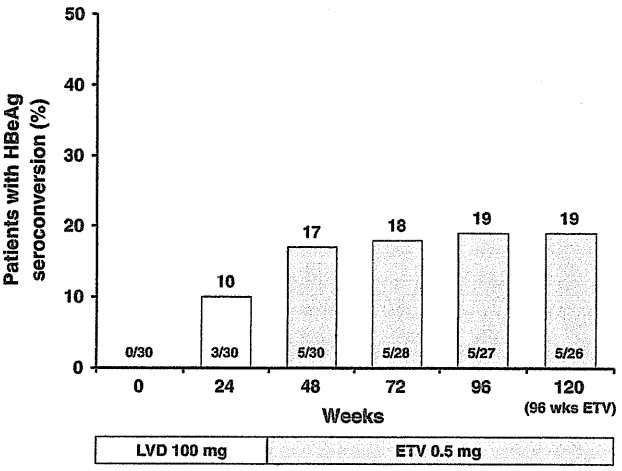

Fig. 4 Proportion of patients with HBeAg seroconversion through 120 weeks of therapy (ETV-047 to ETV-060). *Denominators* represent patients with available samples among the 30 patients HBeAg-positive at baseline. *ETV* entecavir, *HBeAg* hepatitis B e antigen, *LVD* lamivudine

ETV-047 (Fig. 3). Following treatment with entecavir in ETV-060, ALT normalization was maintained in 90% (27/30) of patients achieving this end point by week 120. Minor fluctuations in the proportion of patients achieving ALT normalization were attributed to patients discontinuing entecavir therapy during the course of study ETV-060.

Serologic end points

HBeAg seroconversion was assessed among the 30 patients in the switch cohort who were HBeAg-positive at baseline in ETV-047 (Table 1; Fig. 4). Three patients (10%)

achieved HBeAg seroconversion during the initial 24-week lamivudine treatment period in ETV-047 (Fig. 4). Following switch to entecavir in ETV-060, two additional patients developed HBeAg seroconversion by week 120 (96 weeks of entecavir therapy). None of the patients in the switch cohort experienced HBsAg loss during treatment in ETV-047 or ETV-060.

Resistance

Four of the 33 patients who received entecavir therapy in ETV-060 had HBV DNA ≥400 copies/mL either at treatment discontinuation or at week 120. One patient discontinued therapy at week 68 (44 weeks of entecavir therapy) due to insufficient effect. HBV DNA prior to treatment discontinuation was 3.1 $\log_{10}$ copies/mL, however, resistance testing revealed no substitutions associated with entecavir resistance. The remaining three patients had HBV DNA ≥400 copies/mL at weeks 96 and 120; however, only two patients had samples available for testing. Neither patient's samples had substitutions associated with entecavir or lamivudine resistance either at weeks 96 or 120.

Safety

Entecavir was well tolerated during long-term treatment and the safety profile of patients in the switch cohort was consistent with that previously reported for patients who received continuous entecavir therapy in studies ETV-047 and ETV-060 (Table 2). Serious adverse events (Meniere's disease, subcutaneous abscess and ALT flare) were reported in three patients (9.1%). The most frequently reported adverse events during treatment in ETV-060, occurring in ≥10% of patients, were nasopharyngitis (76%), diarrhea (21%), back pain (18%), influenza (18%), and allergic rhinitis (15%). One patient discontinued entecavir therapy due to depression, which the investigator considered was possibly related to entecavir therapy. An ALT flare (ALT >2 × baseline and >10 × ULN) occurred in one patient at week 18, and was judged a serious adverse event by the investigator, but was not associated with a change in HBV DNA. No deaths were reported during the study.

Table 2 Summary of safety in ETV-060: switch cohort

On-treatment in ETV-060	Patients, *n* (%)
Any adverse events	33 (100)
Clinical adverse events	33 (100)
Laboratory adverse events	33 (100)
Grade 3/4 clinical adverse event	1 (3)
Grade 3/4 laboratory adverse event	5 (15)
Clinical serious adverse event[a]	3 (9)
Discontinuations due to adverse events	1 (3)
Deaths	0
ALT flares[b]	1 (3)

[a] Including ALT flares

[b] ALT >2 × baseline and >10 × ULN

Discussion

Profound long-term suppression of HBV DNA is required for patients to meet the goals of CHB therapy, which are to prevent cirrhosis, hepatic failure, HCC and liver-related death [14–16]. A major concern with long-term therapy is the increasing risk of selecting resistance mutations, especially for therapies with a low-genetic barrier to resistance, such as lamivudine. The current analysis presents results for a cohort of Japanese patients who were switched directly from lamivudine to long-term entecavir therapy. The results show that this switch cohort achieved additional HBV DNA suppression after the switch to entecavir. The proportion of patients with HBV DNA <400 copies/mL increased from 21% after 24 weeks of lamivudine treatment to 82% following an additional 24 weeks of entecavir treatment. Mean HBV DNA decreased from 3.52 $\log_{10}$ copies/mL at week 24 to 2.80 $\log_{10}$ copies/mL at week 48. Rates of HBV DNA suppression were maintained in this cohort, with 90% of patients achieving HBV DNA <400 copies/mL through 96 weeks of entecavir therapy (week 120). These results are comparable to those achieved by the cohort of patients who received entecavir 0.5 mg once daily in the Japanese Phase II studies and the rollover study ETV-060 [17]. At baseline in ETV-060, 56% of this cohort had achieved HBV DNA <400 copies/mL, increasing to 83% through 96 weeks of entecavir therapy. Among patients with abnormal ALT levels at ETV-060 baseline, 88% of patients in the entecavir 0.5 mg cohort achieved normalized ALT levels at week 96 as compared to 90% of patients in the switch cohort. Rates of HBeAg seroconversion at week 96 in ETV-060 were also similar (20 vs. 19%, respectively). These rates of viral suppression also show comparison favorably to those reported for the global nucleoside-naïve cohorts treated for a similar period of time [18, 19]. The potent antiviral activity of entecavir and its high genetic barrier to resistance is expected to minimize the potential for resistance in the switch cohort, allowing long-term therapy for patients. Liver biopsies were not obtained from patients in the switch cohort; however, the histologic benefits of long-term entecavir therapy have been recently reported for a cohort of naïve Japanese patients in the ETV-060 rollover study [20]. Following treatment with entecavir 0.5 mg daily for 3 years, all patients experienced histologic improvement and 57% experienced improvement in fibrosis score. In

addition, the results from a separate global study have confirmed the histologic benefits of long-term entecavir treatment [21].

Previous Japanese (ETV-052/-060) and global (ETV-026) studies have examined the efficacy of entecavir in lamivudine-refractory patients. In these studies, entecavir demonstrated efficacy, with 54% of Japanese patients achieving HBV DNA <400 copies/mL through 3 years' treatment [10, 22]. However, as a result of the lower genetic barrier in these patients, a major drawback of entecavir therapy in this population is the development of resistance. The cumulative probabilities of genotypic entecavir resistance among lamivudine-refractory patients were 33% through 3 years' treatment in Japanese patients and 51% through 5 years' treatment among patients in the global cohort [12, 22]. In the current study, no entecavir- or lamivudine-associated resistance substitutions were detected after 96 weeks of entecavir treatment. However, in contrast to the previous studies where the majority of patients had high baseline HBV DNA and documented lamivudine resistance [10, 23], patients in the switch cohort received entecavir after achieving variable degrees of HBV DNA suppression with 24 weeks of lamivudine therapy. Therefore, the fact that no resistance has been observed in this cohort to date is not unexpected. This observation is consistent with an analysis of lamivudine-refractory patients enrolled in the worldwide lamivudine-refractory study ETV-026. Patients with baseline HBV DNA <7 $\log_{10}$ copies/mL had a higher probability of achieving HBV DNA <300 copies/mL as compared to those who had baseline HBV DNA ≥ 7 $\log_{10}$ copies/mL (73 vs. 16%) [24]. Furthermore, among the 42 entecavir-treated patients in ETV-026 who achieved HBV DNA <300 copies/mL through 96 weeks of therapy, only one patient subsequently developed entecavir resistance.

Current recommendations on the treatment of patients with documented lamivudine resistance suggest that patients should receive a second drug without cross resistance. The combination of lamivudine and adefovir has been shown to be superior to adefovir monotherapy for the treatment of lamivudine resistance, especially in preventing the selection of adefovir resistance [25–27]. Although only short-term clinical data are available for tenofovir, rates of viral suppression among lamivudine-experienced or -resistant patients who received tenofovir monotherapy do not differ significantly from those of treatment-naïve patients [28, 29]. Small studies have also shown pegylated interferon alpha-2a to be a safe and beneficial treatment option for lamivudine-experienced patients [30]. However, the treatment options for Japanese lamivudine-resistant patients are more limited, since neither tenofovir nor pegylated interferon alpha-2a are currently approved in Japan.

The Japanese guidelines recommend that patients with detectable YMDD mutations should receive treatment with a combination of lamivudine and adefovir [13]. However, the guidelines also allow patients who have received <3 years of lamivudine therapy, have HBV DNA <400 copies/mL, and no breakthrough hepatitis or YMDD mutations to switch directly to entecavir. The results presented in this analysis suggest that the strategy of switching to entecavir is an effective one that may avoid the additional cost and potential toxicity of combination treatment with lamivudine and adefovir. Among patients in the switch cohort, 96 weeks of entecavir treatment was well tolerated and the safety profile was comparable with previous experience in Japanese patients. One patient experienced an ALT flare (ALT $>2 \times$ baseline and $>10 \times$ ULN) 18 weeks after initiating entecavir, which was not associated with a change in HBV DNA. This low rate of ALT flares is consistent with previous findings and demonstrates that lamivudine-treated patients can be switched safely to entecavir with a minimal risk of such flares [10, 22].

In summary, the data from the switch cohort presented in this analysis demonstrate that CHB patients can be switched from lamivudine to long-term entecavir. The treatment with entecavir resulted in increased rates of virologic suppression with no evidence of resistance through 2 years of therapy. These findings support recommendations in the current Japanese treatment guidelines that patients on stable lamivudine therapy with no YMDD mutations should be switched to entecavir.

Acknowledgments Taku Seriu and Hiroki Ishikawa are employees of Bristol-Myers Squibb. Masao Omata serves as an advisor for Bristol-Myers Squibb. In addition to the authors, other study investigators included Kazuyuki Suzuki, Yoshiyuki Ueno, Osamu Yokosuka, Hidetsugu Saito, Naohiko Masaki, Yoshiyuki Arakawa, Yasunobu Matsuda, Shunichi Okada, Eiji Tanaka, Yoshiaki Katano, Etsuro Orito, Shinichi Kakumu, Noboru Hirashima, Takashi Kumada, Takeshi Okanoue, Kazuhiro Katayama, Michio Kato, Harumasa Yoshihara, Taizo Hijioka, Kosaku Sakaguchi, Keisuke Hino, Norio Horiike, Shotaro Sakisaka, Ryukichi Kumashiro, Keisuke Hamasaki, Masataka Seike, Yutaka Sasaki, Katsuhiro Hayashi, Teruaki Kawanishi, Mitsuhiko Kawaguchi and Keiji Kita. The study coordinating committee included Yasushi Shiratori and Hirohito Tsubouchi and the study efficacy and safety committee included Chifumi Sato, Kendo Kiyosawa and Kyuichi Tanikawa. Financial support for this research was provided by Bristol-Myers Squibb.

References

1. Lavanchy D. Worldwide epidemiology of HBV infection, disease burden, and vaccine prevention. J Clin Virol 2005;34(Suppl 1):S1–S3
2. Merican I, Guan R, Amarapuka D, Alexander MJ, Chutaputti A, Chien RN, et al. Chronic hepatitis B virus infection in Asian countries. J Gastroenterol Hepatol 2000;15:1356–1361
3. Fattovich G, Bortolotti F, Donato F. Natural history of chronic hepatitis B: special emphasis on disease progression and prognostic factors. J Hepatol 2008;48:335–352

4. Lai CL, Chien RN, Leung NW, Chang TT, Guan R, Tai DI, et al. A one-year trial of lamivudine for chronic hepatitis B. Asia Hepatitis Lamivudine Study Group. N Engl J Med 1998;339:61–68
5. Dienstag JL, Schiff ER, Wright TL, Perrillo RP, Hann HW, Goodman Z, et al. Lamivudine as initial treatment for chronic hepatitis B in the United States. N Engl J Med 1999;341:1256–1263
6. Lok AS, Lai CL, Leung N, Yao GB, Cui ZY, Schiff ER, et al. Long-term safety of lamivudine treatment in patients with chronic hepatitis B. Gastroenterology 2003;125:1714–1722
7. Innaimo SF, Seifer M, Bisacchi GS, Standring DN, Zahler R, Colonno RJ. Identification of BMS-200475 as a potent and selective inhibitor of hepatitis B virus. Antimicrob Agents Chemother 1997;41:1444–1448
8. Chang TT, Gish RG, de Man R, Gadano A, Sollano J, Chao YC, et al. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. N Engl J Med 2006;354:1001–1010
9. Lai CL, Shouval D, Lok AS, Chang TT, Cheinquer H, Goodman Z, et al. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. N Engl J Med 2006;354:1011–1020
10. Sherman M, Yurdaydin C, Sollano J, Silva M, Liaw YF, Cianciara J, et al. Entecavir for treatment of lamivudine-refractory, HBeAg-positive chronic hepatitis B. Gastroenterology 2006;130:2039–2049
11. Shindo M, Chayama K, Kumada H, Yokosuka O, Sata M, Hayashi N, et al. Investigation of the antiviral activity, dose-response relationship and safety of entecavir following 24-week oral dosing in nucleoside-naive adult patients with chronic hepatitis B: a randomized double-blind Phase II clinical trial in Japanese patients. Hepatol Int 2009;3:445–452
12. Tenney DJ, Rose RE, Baldick CJ, Pokornowski KA, Eggers BJ, Fang J, et al. Long-term monitoring shows hepatitis B virus resistance to entecavir in nucleoside-naive patients is rare through 5 years of therapy. Hepatology 2009;49:1503–1514
13. Kumada H. Report of the research for therapy standardization of viral hepatitis including liver cirrhosis. The Research on Hepatitis, Health and Labor Science Research Grants: revised edition; 2010
14. Lok AS, McMahon BJ. Chronic hepatitis B. Hepatology 2007;45:507–539
15. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of chronic hepatitis B. J Hepatol 2009;50:227–242
16. Liaw YF, Leung N, Kao JH, Piratvisuth T, Gane E, Han KH, et al. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2008 update. Hepatol Int 2009;2:263–283
17. Yokosuka O, Takaguchi K, Fujioka S, Shindo M, Chayama K, Kobashi H, et al. Long-term use of entecavir in nucleoside-naïve Japanese patients with chronic hepatitis B infection. J Hepatol 2010 (in press)
18. Han SH, Chang TT, Chao YC, Yoon S, Gish RG, Cheinquer H, et al. Five years of continuous entecavir for nucleoside-naive HBeAg(+) chronic hepatitis B: results from study ETV-901. Hepatology 2008;48(Suppl 1):705A–706A
19. Shouval D, Lai CL, Chang TT, Gadano A, Wu SS, Halota W, et al. Three years of entecavir re-treatment of HBeAg(-) entecavir patients who previously discontinued entecavir therapy: results from study ETV-901. Hepatology 2008;48(Suppl 1):722A–723A
20. Yokosuka O, Kumada H, Toyota J, Takaguchi K, Kobashi H, Shindo M, et al. Three-year assessment of entecavir resistance in nucleoside-naïve and lamivudine-refractory Japanese patients with chronic hepatitis B. Hepatol Int 2008;2:A161
21. Liaw YF, Chang TT, Wu SS, Schiff ER, Han KH, Lai CL, et al. Long-term entecavir therapy results in reversal of fibrosis/cirrhosis and continued histologic improvement in patients with HBeAg(+) and (−) chronic hepatitis B: results from studies ETV-022, -027 and -901. Hepatology 2008;48(Suppl 1):706A
22. Izumi N, Kumada H, Toyota J, Yokosuka O, Kobashi H, Shindo M, et al. Efficacy and safety of 3 years treatment with entecavir in lamivudine-refractory Japanese chronic hepatitis B patients. Hepatol Int 2008;2:A186
23. Suzuki F, Toyoda J, Katano Y, Sata M, Moriyama M, Imazeki F, et al. Efficacy and safety of entecavir in lamivudine-refractory patients with chronic hepatitis B: randomized controlled trial in Japanese patients. J Gastroenterol Hepatol 2008;23:1320–1326
24. Sherman M, Yurdaydin C, Simsek H, Silva M, Liaw YF, Rustgi VK, et al. Entecavir therapy for lamivudine-refractory chronic hepatitis B: improved virologic, biochemical, and serology outcomes through 96 weeks. Hepatology 2008;48:99–108
25. Peters MG, Hann HH, Martin P, Heathcote EJ, Buggisch P, Rubin R, et al. Adefovir dipivoxil alone or in combination with lamivudine in patients with lamivudine-resistant chronic hepatitis B. Gastroenterology 2004;126:91–101
26. Rapti I, Dimou E, Mitsoula P, Hadziyannis SJ. Adding-on versus switching-to adefovir therapy in lamivudine-resistant HBeAg-negative chronic hepatitis B. Hepatology 2007;45:307–313
27. Lampertico P, Marzano A, Levrero M, Santantonio T, Di M, V, Brunetto M, et al. Adefovir and lamivudine combination therapy is superior to adefovir monotherapy for lamivudine-resistant patients with HBeAg-negative chronic hepatitis B. J Hepatol 2008;46 Suppl 1:S191
28. Marcellin P, Heathcote EJ, Buti M, Gane E, de Man RA, Krastev Z, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. N Engl J Med 2008;359:2442–2455
29. van Bommel F, de Man RA, Wedemeyer H, Deterding K, Petersen J, Buggisch P, et al. Long-term efficacy of tenofovir monotherapy for hepatitis B virus-monoinfected patients after failure of nucleoside/nucleotide analogues. Hepatology 2010;51:73–80
30. Leemans WF, Flink HJ, Janssen HL, Niesters HG, Schalm SW, de Man RA. The effect of pegylated interferon-alpha on the treatment of lamivudine resistant chronic HBeAg positive hepatitis B virus infection. J Hepatol 2006;44:507–511

Hepatology Research 2010; 40: 557–565 doi: 10.1111/j.1872-034X.2010.00666.x

Original Article

Peginterferon-alpha-2b plus ribavirin therapy in patients with chronic hepatitis C as assessed by a multi-institutional questionnaire in Japan

Tatsuya Ide,[1] Michio Sata,[1] Shotaro Sakisaka,[2] Makoto Nakamuta,[3] Shigetoshi Fujiyama,[4] Toshihiko Mizuta,[5] Kenji Tahara,[6] Kunio Fujisaki,[7] Yasuji Komorizono,[8] Hiroshi Watanabe,[9] Yasuyo Morita[10] and Hirohito Tsubouchi[11]

[1]*Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine,* [2]*Department of Gastroenterology and Medicine, Fukuoka University School of Medicine,* [3]*Department of Gastroenterology, Kyushu Medical Center National Hospital Organization,* [9]*Division of Hepatology, Fukuoka Red Cross Hospital,* [10]*Nagata Hospital, Fukuoka,* [4]*Department of Gastroenterology and Hepatology, NTT West Kyusyu Hospital, Kumamoto,* [5]*Department of Internal Medicine, Saga Medical School, Saga,* [6]*Kagoshima Kouseiren Hospital,* [7]*Kirishima Medical Center,* [8]*Nanpuh Hospital, Kagoshima, and* [11]*Department of Digestive and Life-style Related Disease, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan*

Background and aim: There has so far been no questionnaire report on patients who were treated with peginterferon plus ribavirin (PEG IFN+RBV) therapy. The purpose of this study was to investigate the problems of this therapy by a questionnaire survey.

Patients and methods: A survey of 681 patients with chronic hepatitis C who received treatment with PEG IFN+RBV was conducted in the Kyushu region of Japan. Using an original questionnaire, the survey was conducted prior to the treatment, during the third month of treatment, at the completion of treatment or the discontinuation of treatment, and at 6 months after the completion of treatment.

Results: It was indicated that the patients had a high level of comprehension and understanding of chronic hepatitis C and PEG IFN+RBV treatment. However, the results also indicated that patients had a high level of anxiety. Side effects were adequately dealt with by physicians. However, dermatological symptoms were not adequately explained to the patients, although they were the second most severe side-effect. It was also revealed that side-effects were most distressing during the first and second months after the start of treatment.

Conclusion: The questionnaire survey provided new information that has never been reported. It is believed that understanding this information is important for future treatment.

Key words: hepatitis C virus, peginterferon, questionnaire, ribavirin

INTRODUCTION

INTERFERON THERAPY FOR chronic hepatitis C has greatly advanced in recent years, and combination therapy using peginterferon and ribavirin (PEG-IFN+RBV) has become a standard treatment method.[1–6] In Japan, PEG-IFN+RBV was approved in December 2004. However, there are many problems, such as side-effects, costs of treatment, and duration of the treatment. It is not known whether these problems are adequately being explained and managed by health care providers.

In order to clarify this issue, it is believed that information from patients is important, and understanding these problems will be beneficial for future treatment. Although there have been reports on patients with hepatitis C and their quality of life (QOL) while undergoing IFN treatment,[7–13] there have been no reports in which information regarding the side-effects and state of mind of patients that have been collected from the patients. Therefore, we conducted a questionnaire survey of patients who have been treated with PEG-IFN+RBV.

Correspondence: Dr Tatsuya Ide, Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine, 67, Asahi-machi, Kurume-shi, Fukuoka-ken 830-0011, Japan. Email: ide@med.kurume-u.ac.jp
Received 16 December 2009; revision 16 February 2010; accepted 22 February 2010.

PATIENTS AND METHODS

THIS STUDY WAS carried out from January 2005 to June 2008. Six-hundred eighty-one patients with a compensated chronic HCV genotype 1 infection who started PEG-IFN+RBV treatment at 63 hospitals in the Kyushu region were included. The eligible patients tested positive for HCV-RNA by a quantitative reverse-transcription polymerase chain reaction (PCR; Amplicor Monitor HCV vs. 2.0 using the 10-fold dilution method; Roche Diagnostics, Tokyo, Japan; lower limit of detection 5 KIU/mL) with a concentration >100 KIU/mL. Patients with an HCV genotype other than 1 infection, hepatitis B surface antigen, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, or decompensated cirrhosis were excluded. Patients with platelet counts of $8 \times 10^4/mm^3$ or less, leukocyte counts of $2500/mm^3$ or less, or hemoglobin levels of 12 g/dL or less were also excluded from the study. An HCV subtype was classified by either the method of Okamoto *et al.*[14] or that of Tanaka *et al.*[15] Genotypes 1a and 1b corresponded to serological group 1 according to the classification of Simmonds *et al.*[16] Chronic hepatitis was diagnosed based on the histological scoring system of Desmet *et al.*[17]

All patients received both 1.5 μg/kg/week s.c peginterferon α-2b (Pegintron; Schering-Plough, Kenilworth, NJ, USA) and oral ribavirin (Rebetol; Schering-Plough) at 600 mg/day (body weight <60 kg), 800 mg/day (body weight between 60 kg and 80 kg), or 1000 mg/day (body weight >80 kg) according to the manufacturer's drug information for ribavirin. All patients were monitored every 4 weeks. Serum HCV RNA was determined using the standardized automated qualitative PCR (Cobas Amplicor Hepatitis C Virus Test, version 2.0; Roche Diagnostics, Tokyo, Japan; detection limit: 50 IU/mL). Dose modification followed standard procedures in principle. Therefore, according to the intensity of the an adverse event or when laboratory results showed hemoglobin of <10 g/dL in subjects with no cardiac disease, the dose of ribavirin was decreased by 200 mg/day. When the neutrophil count was $<750/mm^3$ or the platelet count was $<80\,000/mm^3$, the dose of peginterferon was reduced by 50%. When the hemoglobin was <8.5 g/dL, the neutrophil count was $<500/mm^3$ or the platelet count was $<50\,000/mm^3$, then both drugs were discontinued. After the end of the treatment, the patients were followed-up for a further additional 24 weeks. The sustained viral response (SVR) was defined as undetectable serum HCV-RNA levels by qualitative PCR at the end of the 24-week post-treatment follow-up period. The others were classified as non-SVR.

All patients provided written informed consent and the study protocol was approved by the ethics committee of all participating hospitals.

Questionnaire

The questionnaires were distributed by the physicians in charge after informed consent was obtained, and were completed anonymously. As for the method of collection, the questionnaires were mailed to the office (Department of Digestive and Life-style Related Disease, Kagoshima University) by the patients due to the concern that it might be difficult for them to respond truthfully if their physicians were to collected the questionnaires directly from the patients. The survey was conducted four times in total: prior to the treatment, during the course of treatment (in the third month), at the end of treatment or at the discontinuation of treatment, and at 6 months after the completion of treatment. The details of the questionnaire are shown in Table 1. There were a total of 89 questions in 24 categories.

RESULTS

THE FOLLOWING NUMBER of questionnaires was collected: prior to the treatment: 681 cases; during the course of treatment: 458 cases; at the discontinuation of treatment: 59 cases; at the completion of treatment: 245 cases; and at 6 months after the completion of treatment: 188 cases. The characteristics of 437 patients were collected at baseline (Table 2). Excerpts from the questionnaire will be shown herein as it is not possible to refer to the results of all of the questions.

Questionnaire before therapy (681 patients)

In response to the question of whether they knew that chronic hepatitis C is a disease that can potentially progress to cirrhosis, 672 cases (98.7%) responded Yes and seven cases (1.3%) responded No (two were left blank). In response to the question of whether they knew that chronic hepatitis C is a disease that progresses to hepatocellular carcinoma, 672 cases (98.7%) responded Yes and 9 cases (1.3%) responded No. The reasons why they consulted the hepatologists were: Referral from a family doctor (437 cases, 64.2%); Referral from a friend (84, 12.3%); By coincidence (32, 4.7%); Newspapers and Internet (13, 1.9%); and None of the above/blank (115, 16.9%). The levels of satisfaction or anxiety regarding the treatment method and

Table 1 Details of questionnaire (Number of sections: 24)

Prior to the treatment (6 sections, 33 questions)
[Section 1] Treatment history (1 question)
[Section 2] Knowledge/understanding of chronic hepatitis (5 questions)
[Section 3] Explanations regarding treatment from physician (14 questions)
[Section 4] Level of expectation for treatment (4 questions)
[Section 5] Implementation of tests prior to the start of treatment (3 questions)
[Section 6] Survey of patient's attitudes (6 questions)
During the course of treatment (7 sections, 23 questions)
[Section 1] Practice regarding patient follow-up during the treatment (9 questions)
[Section 2] Implementation of tests during administration (2 questions)
[Section 3] Patient's perceptions of treatment (2 questions)
[Section 4] Care during treatment (2 questions)
[Section 5] Impact of lifestyle habits on treatment (4 questions)
[Section 6] Level of understanding of explanations from physician (2 questions)
[Section 7] Patient factors (2 questions)
At Discontinuation/Completion (7 sections, 23 questions)
[Section 1] Course of treatment (1 questions)
[Section 2] Practice regarding patient follow-up during the treatment (6 questions)
[Section 2] Implementation of tests during administration (4 questions)
[Section 4] Care during treatment (2 questions)
[Section 5] Impact of lifestyle habits on treatment (4 questions)
[Section 6] Level of understanding of explanations from physician (2 questions)
[Section 7] Patient factors (4 questions)
At 6 months after the end of treatment (4 sections, 10 questions)
[Section 1] Level of satisfaction with treatment (2 questions)
[Section 2] Explanations from physician regarding treatment effects (3 questions)
[Section 3] Impressions of the treatment (3 questions)
[Section 4] Patient's plans to visit medical institution (2 questions)

side-effects are shown in Figure 1. The patients were satisfied with the explanations regarding the treatment but were also feeling anxious. The causes of anxiety (multiple answers were allowed) were: Worried about side-effects (258 cases); Presence/absence of treatment efficacy (173); The duration of treatment is long (150); and Cost of treatment is high (109).

Table 2 Characteristics of patients at baseline

Age (years)	56.3 ± 10.2	(n = 473)
Sex (M : F)	232:241	
Body mass index (kg/m^2)	23.1 ± 2.9	(n = 451)
ALT (IU/L)	74.7 ± 60.1	(n = 471)
Platelet count (×10^4/mm^3)	15.6 ± 5.0	(n = 472)
Hemoglobin (g/dL)	14.0 ± 1.4	(n = 473)
Grade of activity		
0–1	126	
2–3	218	
Fibrosis stage		
0–2	273	
3–4	71	
HCV RNA level (KIU/mL)	1932 ± 1400	(n = 469)

Continuous variables are presented as mean ± SDs.

Questionnaire at three months into therapy

In response to the question asking to what extent they were satisfied with the course of treatment, Extremely satisfied and Very satisfied comprised 203 cases (44.3%) and 103 cases (22.5%), respectively, followed by Satisfied (136 cases, 29.7%) and Completely dissatisfied/Not satisfied (14, 3.1%) (two were left blank). In response to the question of whether the grade of side-effects was stronger in the explanations provided by their physicians or in their actual experience, the responses were: Same as explained (216 cases, 47.2%), Much stronger or Slightly stronger than what was explained (116, 25.3%), and Much lighter or Slightly lighter than what was explained (100, 21.8%) (26 were left blank). In addition, we investigated the grade of side-effect based on the interferon therapy history. Of 42 patients who had experienced interferon therapy, 10 cases (23.8%) responded Lighter than what was explained, 18 cases (42.9%) responded Same as explained, and 14 (33.3%) responded Stronger than what was explained. On the other hand, of 101 patients who had no experience of interferon therapy, 24 cases (23.8%) responded Lighter than what was explained, 50 (49.5%) responded Same as explained, and 27 (26.7%) responded Stronger than what was explained. There was no significant difference in grade of side-effects between those who had experienced and who had not experienced interferon treatment. Furthermore, we investigated the grade of side-effect based on sex and age. Of 56 female patients 60 years or more, 13 cases (23.2%) responded Lighter than what was explained, 31 cases (55.4%) responded Same as explained, and 12 (21.4%) responded Stronger than what was explained. Other results are given below as follows: sex, age, total number, number (%)

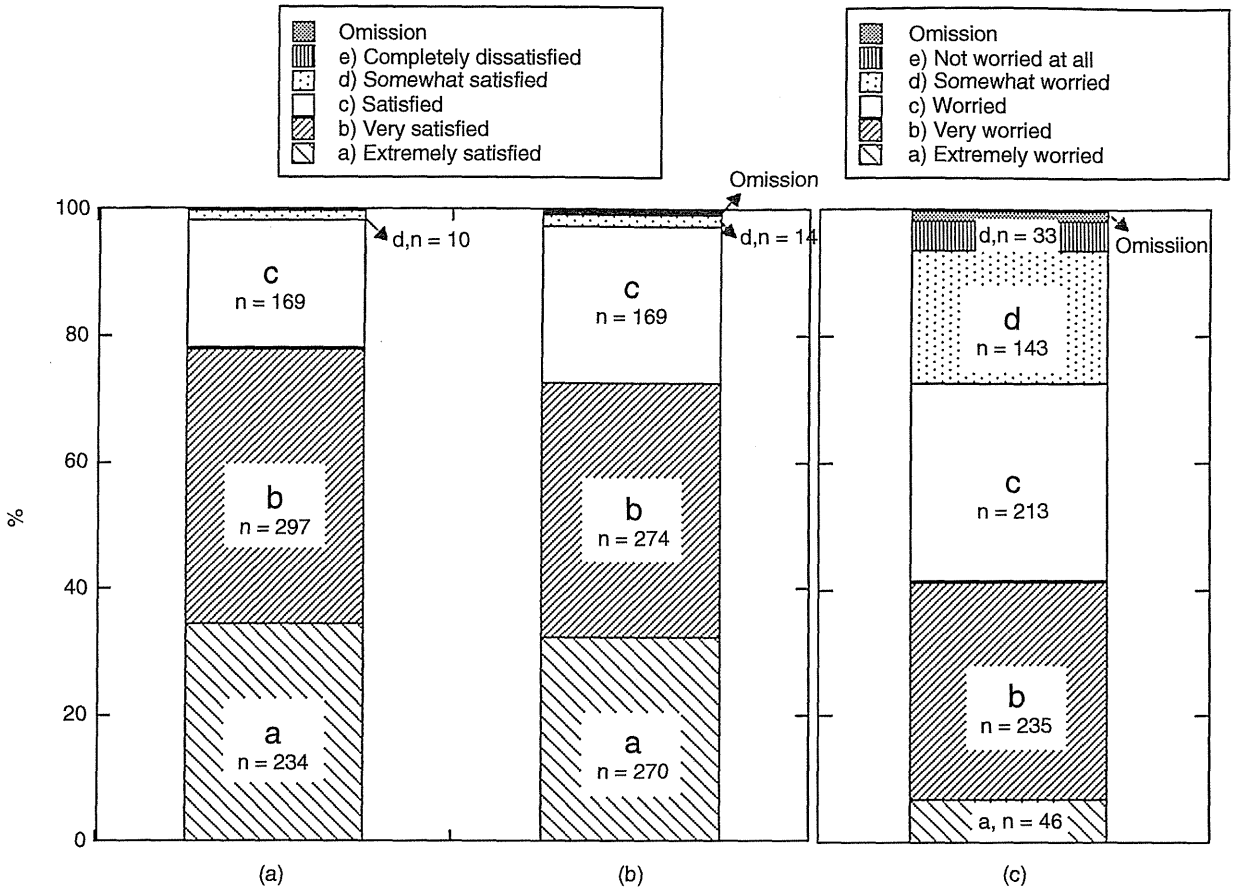

Figure 1 (a) To what extent are you satisfied with the explanations regarding the treatment method? (b) To what extent are you satisfied with the explanations regarding the side-effects? a. Extremely satisfied, b. Very satisfied, c. Satisfied, d. Somewhat satisfied, e. Completely dissatisfied C. To what extent are you worried about the therapy? a. Not worried at all, b. Somewhat worried, c. Worried, d. Very worried, e. Extremely worried.

responded Lighter than what was explained, number (%) responded Same as explained, number (%) responded Stronger than what was explained. Female, less than 60 years, 63, 15 (23.8%), 27 (42.9%), 21 (33.3%). Male, 60 years or more, 45, 8 (17.8%), 25 (55.6%), 12 (26.7%). Male, less than 60 years, 72,18 (25.0%), 36 (50.0%), 18 (25.0%). There were no significant differences between high age and low age, female and male.

In response to the question asking to what extent they were satisfied with the way their physicians dealt with the side-effects, Extremely satisfied and Very satisfied comprised 66 cases (14.4%) and 179 cases (39.1%), respectively, followed by satisfied (173 cases, 37.8%), and Slightly or Completely dissatisfied (31, 6.8%) (9 were left blank). In response to the question asking what they were most concerned about during the course of treatment (multiple answers were allowed), the responses were: Treatment efficacy (337 cases, 73.6%), Side effects (295, 64.4%), Costs of treatment (177, 38.6%), and Duration of treatment (144, 31.4%).

The most severe side-effects are shown in Figure 2. The most common side-effect was general malaise, and dermatological symptoms ranked second. In addition, wishes to discontinue the treatment and the reasons thereof are shown in Figure 3.

Questionnaire at either the end of therapy or at the discontinuation of therapy

Among the 59 cases of discontinuation, 34 cases were discontinued due to side-effects, 23 cases were discontinued because no disappearance of the hepatitis C virus in the sera was observed, and 2 cases were for other reasons. Among the 34 cases of discontinuation due to

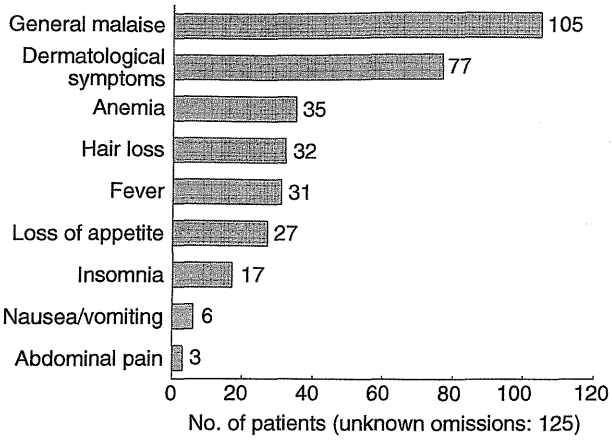

Figure 2 What was the most severe side-effect you experienced?

side-effects, five cases (14.7%) responded that they were not satisfied with the way their physicians dealt with the side-effects. In response to the question of whether the grade of side-effects was stronger in the explanations provided by their physicians or in their actual experience, in the completed treatment group, 55 cases (22.4%) responded Lighter than what was explained, 110 cases (44.9%) responded Same as explained, and 74 cases (30.2%) responded Stronger than what was explained (six were left blank). On the other hand, among the cases of discontinuation due to side-effects, there were 0 cases of Lighter than what was explained, 11 cases (32.4%) of Same as what was explained, and 22 cases (64.7%) of Stronger than what was explained (one case was left blank).

The number of cases that developed side-effects is shown in Figure 4. Among the side-effects for which no explanation was provided by the physicians, dermatological symptoms were the most common.

Questionnaire after 6 months of therapy

Regarding satisfaction with the treatment efficacy, the responses were: Extremely dissatisfied and Slightly dissatisfied (47 cases, 25.0%), followed by Satisfied (31, 16.5%) and Very satisfied or Extremely satisfied (110, 58.5%), indicating a high level of satisfaction. In response to the question asking whether they would recommend this treatment to other patients, the responses were: Definitely not or Probably not together accounted for 23 cases (12.2%), followed by Not sure (54 cases, 28.7%), and Probably and Definitely (111, 59.0%). As reasons for the recommendations, 99/111 cases (89.1%) responded that they achieved SVR. The reasons for not recommending the treatment were: Expected efficacy was not achieved (10/23 cases, 43.5%) and Side effects were severe (6/23, 26.1%).

The periods during which the patients experienced the most distressing side-effects are shown in Figure 5. The largest numbers were observed during the first and second months.

As the most distressing side-effect was general malaise and the period of that was during the first and second months, the association between general malaise and hemoglobin levels was investigated. The hemoglobin levels decreased by approximately 3 g/dL during the second month and then became flat. However, the decrease in hemoglobin levels was almost the same between patients whose most distressing side-effects

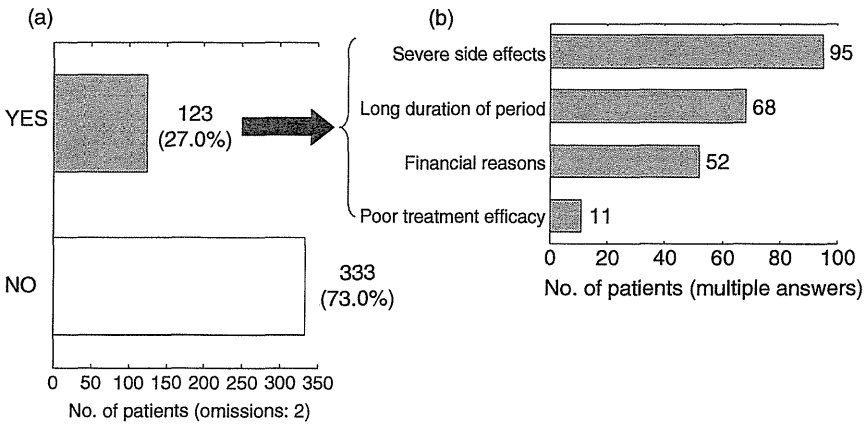

Figure 3 (a) Have you ever thought about discontinuing the treatment? (b) What was the reason why you intended to discontinue the treatment?

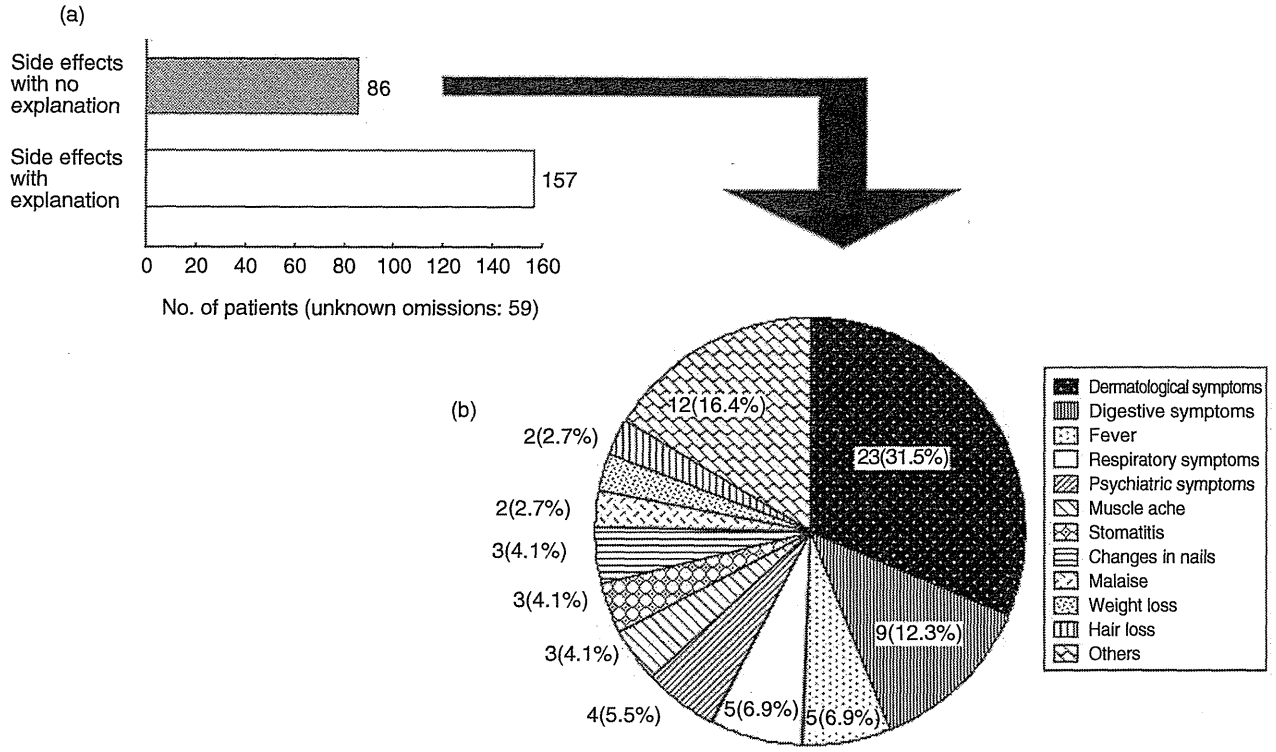

Figure 4 (a) Have you experienced side-effects that were not included in the explanations of your physician? (b) What kind of side-effects did you experience with no explanation?

were general malaise and patients for whom that was not the case (Fig. 6).

Efficacy of PEG•RBV therapy

Treatment efficacy was assessed among 439 patients who received follow-up for 24 weeks after completion of the therapy. Undetectable HCV RNA were observed in 235/411 cases (57.2%) by the 12th week after the start of treatment. At the end of treatment, of the 439 cases, 314 cases (71.5%) had undetectable HCV RNA. In the final results, SVR was observed in 206 cases (46.9%), and non-SVR was observed in 233 (53.1%).

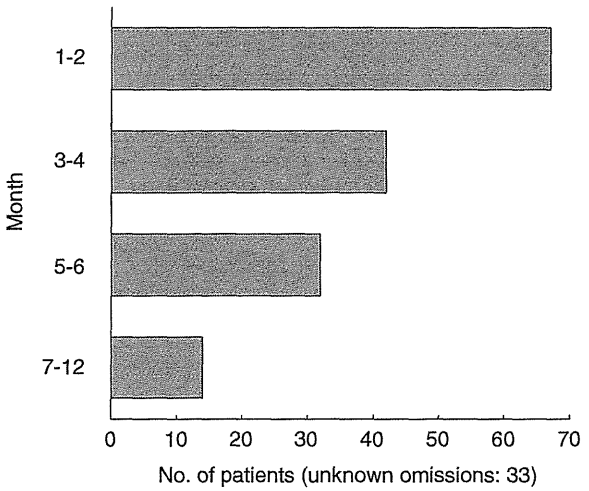

Figure 5 When did you experience the most distressing side-effects?

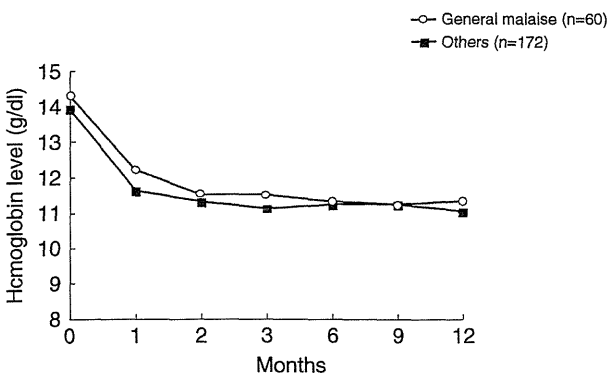

Figure 6 Changes of hemoglobin levels in patients whose most distressing side-effects were general malaise and patients for whom that was not the case.

DISCUSSION

AS NO REPORTS on questionnaire surveys similar to the one we conducted at this time were found, it is believed that this study is valuable.

Important information was obtained from the questionnaire survey. First, prior to the treatment, most of the patients understood the pathology and natural history of chronic hepatitis C, as well as the treatment method and its side-effects. However, it was revealed that they had a high level of anxiety.

Both the explanations regarding the course of treatment and the way in which health care providers managed the side-effects were adequate. It is believed that this is because patients were being seen by hepatologists mostly at hospitals where the survey was conducted.

This survey also revealed that dermatological symptoms were the second most severe side-effect. According to the data from a Phase 3 clinical trial in Japan, flu-like symptoms (96.7%) have been the most commonly observed side-effects, followed by loss of appetite (83.9%), hair loss (68.5%), and insomnia (66.9%). In addition, dermatological symptoms were injection site erythema (41.7%) and pruritus (61.0%). In this survey, however, nearly twice as many patients found dermatological symptoms to be severe, compared to anemia, hair loss, fever, loss of appetite, and insomnia. In addition, dermatological symptoms were the most commonly observed side-effects among the side-effects that were not explained by the physician. Based on these results, it is inferred that no adequate explanations are being provided prior to treatment and, moreover, management of the dermatological symptoms is not adequate.

Regarding the cases of discontinuation due to side-effects, only 14.7% of the patients were not satisfied with the way the side-effects were dealt with by their physicians, and it is believed that the physicians dealt with the side-effects relatively properly. While patients who discontinued the treatment due to side-effects felt that the side-effects were stronger than what was explained to them by the physicians, this perception was less common in the cases of completed treatment, and it is therefore suggested that it is not a lack of explanation by the physicians Of the patients, 27.0% wished to discontinue treatment, and side-effects were the most common reason; it is therefore important to manage side-effects. Regarding treatment efficacy, the SVR rate was 46.9%, which was equivalent to the 47.6% (121/254) from the Phase 3 trial that was carried out in Japan.

The level of satisfaction with treatment efficacy was 58.5%, and the level of satisfaction was higher in the cases in which SVR was achieved. The most distressing period was during the first and second months of treatment. It appears that this is because during this period, fever and malaise occur due to interferon, and anemia develops due to ribavirin, but after 3 months the patients subsequently were accustomed to these side-effects. It is believed that by letting the patients know in advance that the side-effects of the first and second months will not last until the end of the therapy, they can endure these side-effects.

In this survey, it was not possible to obtain responses from all of the cases. The reasons for this are: patients responded to the questionnaire on a voluntary basis; mere lack of explanation by the physicians; and the patients forgot to submit the questionnaire. In summary, explanations regarding dermatological symptoms were not adequately provided to the patients and, moreover, these symptoms were the second most severe side-effect. Also, it was revealed that the period when the side-effects were most distressing was during the first and second months after the start of treatment. Based on these results, it is necessary to provide explanations to the patients in order to alleviate their anxiety, etc.

ACKNOWLEDGEMENT

IN ADDITION TO the authors, the following members of the Kyusyu Hepatitis C Study Group participated in this study:

Shiro Murashima (Kurume University Medical Center, Fukuoka), Department of Gastroenterology, Sasebo kyosai Hospital, Nagasaki. Eiji Kajiwara (Department of Gastroenterology, Nippon Steel Yawata Memorial Hospital, Fukuoka), Hideto Chikazawa (Saiseikai Kumamoto Hospital, Kumamoto), Toshihiro Maruyama (Department of Medicine, Kitakyushu Municipal Medical Center, Fukuoka), Kazunori Noguchi (Omuta City General Hospital, Fukuoka), Akihiro Iwamitsu (Miyazaki Medical Center Hospital, Miyazaki), Kunihide Ishii (Asakura Medical Association Hospital, Fukuoka), Nobuyoshi Tajiri (Social Insurance Tagawa Hospital, Fukuoka), Yutaka Sasaki (Department of Gastroenterology and Hepatology Graduate School of Medical Sciences Kumamoto University, Kumamoto), Kazuhiro Sugi (National Hospital Organization Kumamoto Medical Center Department of Gastroenterology and Hepatology, Kumamoto), Hirofumi Fukushima (Department of Internal Medicine, Saiseikai

Futsukaichi Hospital, Fukuoka), Tomoko Mitsuyasu (Department of Gastroenterology Fukuoka University Chikushi Hospital, Fukuoka), Yasunori Ichiki (Department of Hepato-Biliary-Pancreatic Medicine, Oita Red Cross Hospital, Oita), Hideki Kitada, Yoshi Takekuma (Japanese Red Cross Kumamoto Hopital, Kumamoto), Kazuhiro Takahashi (Department of Medicine, Hamanomachi Hospital, Fukuoka), Hideyuki Nomura (The Center for Liver Diseases, Shin-Kokura Hospital, Fukuoka), Seiji Kawazoe (Saga Prefectual hospital KOSEIKAN, Saga), Masato Sasaki (Kumamoto Rousai Hospital, Kumamoto), Masataka Seike (Department of Internal Medicine I, Faculty of Medicine, Oita University, Oita), Yoshihiro Shuto (Oita cardiovascular hospital, Oita), Kazuo Kuroki (Kushima Municipal Hospital, Miyazaki), Kenji Nagata (Faculty of Medicine, University of Miyazaki, Miyazaki), Yoichi Yano (Saga Social Insurance hospital, Saga), Syuichi Hirono (Hirono Naika Clinic, Miyazaki), Takeaki Sato (Center for Liver Diseases, National Hospital Organization Kokura Medical Center, Fukuoka), Tetsu Mori (Mori Naika Clinic, Oita), Keiji Sakamoto (Department of Internal Medicine, Yamaga Hospital, Oita), Shuho Shigenobu (Saiseikai Sendai Hospital, Kagoshima), Tatsuji Maeshiro (First Department of Internal Medicine, Faculty of Medicine, University of the Ryukyus, Okinawa), Teruo Matsumoto (Department of Liver, Hakujuji Hospital, Fukuoka), Norito Matsukuma (Kurume Daiichi Social Insurance Hospital, Fukuoka), Kenichi Sakurai, Ikuo Matsushita (Kumamoto Central Hospital, Kumamoto), Takuya Tsutsumi (Nagasaki Municipal Hospital, Nagasaki), Hiroshi Yatsuhashi (Clinical Research Center, National Nagasaki Medical Center, Nagasaki), Yasufumi Oda (ODA Hospital Saga), Sadataka Inuzuka (Inuzuka Hospital, Saga), Jun Hayashi(Department of General Medicine, Kyushu University Hospital, Fukuoka), Noboru Kinoshita (Saesbo chuou Hospital, Nagasaki), Genryu Hirano (Department of Gastroenterology, Fukuoka City Medical Association Hospital, Fukuoka), Naofumi Ono (Eguchi Hospital, Saga), Kazuhiko Nakao (Departmennt of Gastroenterology and Hepatology Graduate School of Biomedical Sciences Nagasaki University, Nagasaki), Satoe Shigematsu (Yanagawa Hospital, Fukuoka), Takeshi Hori (Kagoshima City Hospital, Kagoshima), Yuichi Tanabe (Department of Internal Medicine, Fukuoka City Hospital, Fukuoka), Junya Shimono (Department of Medicine, Yahata Saiseikai Hospital, Fukuoka), Ei Sasaki (Tobata Kyoritsu Hospital, Fukuoka), Takeo City Hospital, Osami Inoue (Japan Labour and Welfaer Organization Nagasaki Labour Welfare Hospital, Nagasaki), Ikuo Kikuchi (Miyazaki Prefectural Miyazaki Hospital, Miyazaki), Katsuhiro Hayashi (Johnan Hospital, Miyazaki).

REFERENCES

1 National Institutes of Health. National Institutes of Health Consensus Development Conference Statement: management of hepatitis C: 2002. *Hepatology* 2002; **36**: S3–20.
2 Alberti A, Benvegnú L. Management of hepatitis C. *J Hepatol* 2003; **38**: S104–18.
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 randomised trial. *Lancet* 2001; **358**: 958–65.
4 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.
5 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**: 993–99.
6 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.
7 Taliani G, Rucci P, Biliotti E. Therapy expectations and physical comorbidity affect quality of life in chronic hepatitis C virus infection. *J Viral Hepat* 2007; **14**: 875–82.
8 Kallman J, Margaret O'Neil M, Larive B. Fatigue and health-related quality of life (HRQL) in chronic hepatitis C virus infection. *Dig Dis Sci* 2007; **52**: 2531–9.
9 Svirtlih N, Pavic S, Terzic D. Reduced quality of life in patients with chronic viral liver disease as assessed by SF12 questionnaire. *J Gastrointestin Liver Dis* 2008; **17**: 405–9.
10 McHutchison JG, Ware JE Jr Bayliss MS *et al.* Hepatitis Interventional Therapy Group. The effects of Interferon alpha-2b in combination with ribavirin on health related qualityof life and work productivity. *J Hepatol* 2001; **34**: 140–7.
11 Bernstein D, Kleinman L, Barker CM, Revicki DA, Green J. Relationship of health-related quality of life to treatment adherence and sustained response in chronic hepatitis C patients. *Hepatology* 2002; **35**: 704–8.
12 Hassanein T, Cooksley G, Sulkowski M *et al.* The impact of peginterferon alfa-2a plus ribavirin combination therapy onhealth-related quality of life in chronic hepatitis C. *J Hepatol* 2004; **40**: 675–81.
13 Arora S, O'Brien C, Zeuzem S *et al.* Treatment of chronic hepatitis C patients with persistently normal alanine aminotransferase levels with the combination of peginterferon alpha-2a (40 kDa) plus ribavirin: impact on health-related quality of life. *J Gastroenterol Hepatol* 2006; **21**: 406–12.

14 Okamoto H, Sugiyama Y, Okada S *et al.* Typing hepatitis C virus by polymerase chain reaction with type-specific primers: application to clinical surveys and tracing infectious sources. *J Gen Virol* 1992; **73**: 673–79.
15 Tanaka T, Tsukiyama-Kohara K, Yamaguchi K *et al.* Significance of specific antibody assay for genotyping of hepatitis C virus. *Hepatology* 1994; **19**: 1347–53.
16 Simmonds P, Alberti A, Alter HJ *et al.* A proposed system for the nomenclature of hepatitis C viral genotypes. *Hepatology* 1994; **19**: 1321–4.
17 Desmet VJ, Gerber M, Hoofnagle JH, Manna M, Scheuer PJ. Classification of chronic hepatitis: diagnosis, grading and staging. *Hepatology* 1994; **19**: 1513–20.

World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v16.i35.4400

World J Gastroenterol 2010 September 21; 16(35): 4400-4409
ISSN 1007-9327 (print)

ORIGINAL ARTICLE

Pegylated interferon α-2b plus ribavirin for older patients with chronic hepatitis C

Mosaburo Kainuma, Norihiro Furusyo, Eiji Kajiwara, Kazuhiro Takahashi, Hideyuki Nomura, Yuichi Tanabe, Takeaki Satoh, Toshihiro Maruyama, Makoto Nakamuta, Kazuhiro Kotoh, Koichi Azuma, Junya Shimono, Shinji Shimoda, Jun Hayashi, The Kyushu University Liver Disease Study Group

Mosaburo Kainuma, Norihiro Furusyo, Jun Hayashi, Department of General Internal Medicine, Kyushu University Hospital, Maidashi, Higashi-Ku, Fukuoka 812-8582, Japan
Eiji Kajiwara, Department of Internal Medicine, Nippon Steel Yawata Memorial Hospital, Harunomachi, Yahatahigashi-ku, Kitakyushu 805-0050, Japan
Kazuhiro Takahashi, Department of Medicine, Hamanomachi Hospital, Maiduru Chuo-ku, Fukuoka 810-8539, Japan
Hideyuki Nomura, The Center for Liver Disease, Shin-Kokura Hospital, Kanada, Kokurakita-ku, Kitakyushu, Fukuoka 803-8505, Japan
Yuichi Tanabe, Department of Medicine, Fukuoka City Hospital, Yoshiduka-honmachi, Hakata-ku, Fukuoka 812-0046, Japan
Takeaki Satoh, Center for Liver Disease, National Hospital Organization Kokura Medical Center, Harugaoka, Kokuraminami-ku, Kitakyushu 802-0803, Japan
Toshihiro Maruyama, Department of Medicine, Kitakyushu Municipal Medical Center, Bashaku, Kokurakita-ku Kitakyushu 802-0077, Japan
Makoto Nakamuta, Department of Gastroenterology, Kyushu Medical Center, National Hospital Organization, Jigyohama, Chuou-ku, Fukuoka 810-8563, Japan
Kazuhiro Kotoh, Department of Medicine and Bioregulatory Science, Graduate School of Medical Science, Kyushu University, Maidashi, Higashi-Ku, Fukuoka 812-8582, Japan
Koichi Azuma, Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Maidashi, Higashi-Ku, Fukuoka 812-8582, Japan
Junya Shimono, Saiseikai Yahata General Hospital, Harunomachi, Yahatahigashi-ku, Kitakyushu, Fukuoka 805-0050, Japan
Shinji Shimoda, Department of Medicine and Biosystemic Science, Graduate School of Medical Science, Kyushu University, Higashi-Ku, Fukuoka 812-8582, Japan
The Kyushu University Liver Disease Study Group, Kyushu University, Maidashi, Higashi-Ku, Fukuoka 812-8582, Japan
Author contributions: Kajiwara E, Takahashi K, Nomura H, Tanabe Y, Satoh T, Maruyama T, Nakamuta M, Kotoh K, Azuma K, Shimono J, Shimoda S and The Kyushu University Liver Disease Study Group carried out the field research for the study; Kainuma M analyzed the data and wrote the paper; Furusyo N and Hayashi J were instrumental in developing and coordinating the research project and reviewed the manuscript.

Correspondence to: Jun Hayashi, MD, PhD, Professor, Department of General Internal Medicine, Kyushu University Hospital, Maidashi, Higashi-Ku, Fukuoka 812-8582, Japan. hayashij@gim.med.kyushu-u.ac.jp
Telephone: +81-92-6425909 Fax: +81-92-6425916
Received: February 18, 2010 Revised: April 19, 2010
Accepted: April 26, 2010
Published online: September 21, 2010

Abstract

AIM: To analyze the efficacy and safety of a combination therapy of pegylated interferon (PEG-IFN) α-2b plus ribavirin (RBV) in older Japanese patients (65 years or older) infected with hepatitis C virus (HCV).

METHODS: This multicenter study included 938 patients with HCV genotype 1 who received 1.5 μg/kg per week PEG-IFN α-2b plus RBV 600-1000 mg/d for 48 wk and 313 HCV genotype 2 patients who received this treatment for 24 wk.

RESULTS: At 24 wk after the end of combination therapy, the overall sustained virological response (SVR) for genotypes 1 and 2 were 40.7% and 79.6%, respectively. The SVR rate decreased significantly with age in each genotype, and was markedly reduced in genotype 1 ($P < 0.001$). Moreover, the SVR was significantly higher in patients with genotype 1 who were less than 65 years (47.3% of 685) than in those 65 years or older (22.9% of 253) ($P < 0.001$) and was higher in patients with genotype 2 who were less than 65 years (82.9% of 252) than in those 65 years or older (65.6% of 61) ($P = 0.004$). When patients received a dosage at least 80% or more of the target dosage of PEG-IFN α-2b and 60% or more of the target dosage of RBV, the SVR rate significantly increased to 66.5% in patients less than 65 years and to 45.2% in those 65 years or older ($P <$

0.001). Adverse effects resulted in treatment discontinuation more often in patients with genotype 1 (14.4%) than in patients with genotype 2 (7.3%), especially by patients 65 years or older (24.1%).

CONCLUSION: PEG-IFN α-2b plus RBV treatment was effective in chronic hepatitis C patients 65 years or older who completed treatment with at least the minimum acceptable treatment dosage.

Key words: Hepatitis C virus; Gerontology; Pegylated interferon; Ribavirin

Peer reviewer: Emanuel K Manesis, MD, Professor of Medicine, Athens University School of Medicine, Liver Unit, Euroclinic, 19 Mavromateon Street, Athens 10 34, Greece

Kainuma M, Furusyo N, Kajiwara E, Takahashi K, Nomura H, Tanabe Y, Satoh T, Maruyama T, Nakamuta M, Kotoh K, Azuma K, Shimono J, Shimoda S, Hayashi J, The Kyushu University Liver Disease Study Group. Pegylated interferon α-2b plus ribavirin for older patients with chronic hepatitis C. *World J Gastroenterol* 2010: 16(35): 4400-4409 Available from: URL: http://www.wjgnet.com/1007-9327/full/v16/i35/4400.htm DOI: http://dx.doi.org/10.3748/wjg.v16.i35.4400

INTRODUCTION

Hepatitis C virus (HCV) infection is a major cause of chronic liver disease, affecting 170 million individuals worldwide[1]. It is well known that patients with chronic hepatitis C eventually develop hepatocellular carcinoma (HCC)[2]. Previous studies have made clear that interferon (IFN) treatment is effective for eliminating HCV[3,4] and that it significantly reduces the progression of liver fibrosis and the risk of HCC[5,6]. Antiviral treatment for chronic hepatitis C has greatly improved, and the combination treatment of pegylated (PEG)-IFN α-2b plus ribavirin (RBV) has been approved and recommended in Japan since 2004, as the first choice for chronic hepatitis C. This combination treatment attained a sustained virological response (SVR) rate of 50%-60% for genotype 1 in the United States and Europe[7]. However, SVR was relatively low (42.4%) in Japan[8], where chronic hepatitis C patients are older, indicating that older patients did not respond well to IFN treatment[9]. Moreover, the combination treatment was associated with more adverse effects than IFN monotherapy[7,10]. Older patients who have decreased cardiovascular, pulmonary and renal function have a higher incidence of adverse effects than younger patients. The rate of discontinuation due to adverse effects was reported to be significantly higher in patients aged 65 years or more than in those less than 65 years[11]. Older patients with HCV infection are at risk for progressive liver disease. It was reported that clearance of HCV after IFN therapy significantly reduces the incidence of HCC and death in older chronic hepatitis C patients[6,12]. Ikeda *et al*[13] demonstrated that IFN treatment is needed for 65-70-year-old patients with chronic hepatitis C to prevent the occurrence of HCC. We also consider older patients to be acceptable candidates for antiviral treatment to prevent the development of HCC, and previously reported that monotherapy with natural IFN α was not effective in older patients[9]. Therefore, in an attempt to ameliorate these problems, we decided to treat older patients with a combination of PEG-IFN plus RBV therapy.

Little data concerning the response and safety of this combination treatment in a large number of older patients with chronic HCV infection has been published. A multicenter study of the efficacy and safety of antiviral treatments for Japanese patients with chronic liver disease, the Kyushu University Liver Disease Study (KULDS), was launched in 2003[8,14]. The present prospective study was carried out to analyze the efficacy and safety of the combination treatment of PEG-IFN α-2b plus RBV in older patients.

MATERIALS AND METHODS

Patients

Treatment of chronic hepatitis C with a combination of PEG-IFN α-2b plus RBV was accepted by the Japanese Ministry of Health in October, 2004. We used this combination treatment from December 2004 to July 2008, and enrolled chronic hepatitis C patients with exclusion criteria which included: (1) clinical or biochemical evidence of hepatic decompensation, advanced cirrhosis identified by bleeding, high-risk esophageal varices, history of gastrointestinal bleeding, ascites, encephalopathy, or HCC; (2) hemoglobin level < 11.5 g/L, white blood cell count < 3×10^9/L, and platelet count < 50×10^9/L; (3) concomitant liver disease other than hepatitis C (hepatitis B surface antigen positive or HIV positive); (4) excessive active alcohol consumption > 60 g/d or drug abuse; (5) severe psychiatric disease; or (6) antiviral or corticosteroid treatment within 12 mo prior to enrollment. Patients who fulfilled the above criteria were recruited at Kyushu University Hospital and 32 affiliated hospitals in the northern Kyushu area of Japan. We have treated 2270 Japanese patients aged 18 years or older with PEG-IFN α-2b plus RBV. All patients who were positive for both antibody to HCV and HCV RNA for over 6 mo were enrolled in KULDS. Three months before the start of treatment and every 3 mo during the treatment period, each patient was tested for α-fetoprotein (AFP) and had an abdominal ultrasonographic examination. If an abnormal AFP level of 40 ng/mL and/or focal lesions on ultrasonographic examination were found at any testing, further testing for HCC was carried out, which included dynamic computed tomography, and angiography. Patients confirmed to have HCC within 3 mo after starting treatment were excluded from this study (n = 14). Of 2270 patients, 1021 were currently under combination treatment or we were not yet able to judge the effect of the combination treatment. This left the data of 1251 patients (938 with genotype 1 and 313 with genotype 2) available for analysis.

Table 1 Characteristics of 938 chronic hepatitis C genotype 1 patients treated with a combination of pegylated interferon plus ribavirin according to age (mean ± SD)

	Group A (age < 65 yr) (n = 685)	Group B (age ≥ 65 yr) (n = 253)	P-value
Age (yr)	53.1 ± 8.9	68.6 ± 3.1	< 0.001
Male/female	374/311	122/131	0.090
Body mass index (kg/m^2)	23.7 ± 3.3	22.8 ± 2.7	< 0.001
Prior IFN monotherapy, n (%)	163 (23.8)	76 (30.0)	0.052
Prior combined IFN plus RBV treatment, n (%)	51 (7.4)	20 (7.9)	< 0.001
Alanine aminotransferase (IU/L)	80.2 ± 62.0	67.9 ± 46.6	0.004
γ-glutamyltranspeptidase (IU/L)	60.2 ± 56.6	57.1 ± 49.2	0.708
Albumin (g/dL)	4.1 ± 0.4	4.0 ± 0.4	< 0.001
White blood cell count (/mm^3)	5200.0 ± 1476.7	4756.3 ± 1458.9	< 0.001
Hemoglobin (g/dL)	14.1 ± 1.4	13. 5 ± 1.4	< 0.001
Platelet count (10^9/L)	16.6 ± 5.3	15.0 ± 5.2	< 0.001
Creatinine (mg/dL)	0.7 ± 0.6	0.8 ± 1.4	0.107
Creatinine clearance (mL/min)	105.5 ± 28.7	75.8 ± 17.5	< 0.001
Serum HCV-RNA level (kIU/mL)	1776.1 ± 1500.0	1986.9 ± 1604.5	0.125
Histological fibrosis			0.008
F0/F1/F2/F3/F4	36/155/121/61/30	9/46/49/31/17	

IFN: Interferon; RBV: Ribavirin; HCV: Hepatitis C virus.

Table 2 Characteristics of 313 chronic hepatitis C genotype 2 patients treated with a combination of pegylated interferon plus ribavirin according to age (mean ± SD)

	Group C (age < 65 yr) (n = 252)	Group D (age ≥ 65 yr) (n = 61)	P-value
Age (yr)	47.7 ± 10.4	69.2 ± 3.4	< 0.001
Male/female	124/128	28/33	0.671
Body mass index (kg/m^2)	23.1 ± 3.5	22.8 ± 2.9	0.577
Prior IFN monotherapy, n (%)	47 (18.7)	16 (26.2)	< 0.001
Prior combined IFN plus RBV treatment, n (%)	5 (2.0)	4 (6.6)	0.056
Alanine aminotransferase (IU/L)	79.9 ± 78.7	68.9 ± 52.9	0.821
γ-glutamyltranspeptidase (IU/L)	55.8 ± 64.7	44.3 ± 34.7	0.937
Albumin (g/dL)	4.2 ± 0.4	3.9 ± 0.5	< 0.001
White blood cell count (/mm^3)	5276.3 ± 1636.3	4958.0 ± 1495.6	0.005
Hemoglobin (g/dL)	14.1 ± 1.4	13.4 ± 1.3	< 0.001
Platelet count (10^9/L)	18.9 ± 6.3	15.6 ± 4.7	< 0.001
Creatinine (mg/dL)	0.8 ± 1.5	0.7 ± 0.2	0.581
Creatinine clearance (mL/min)	112.1 ± 31.4	74.6 ± 17.2	< 0.001
Serum HCV-RNA level (kIU/mL)	1588.3 ± 1628.7	1195.4 ± 1645.5	0.036
Histological fibrosis			< 0.001
F0/F1/F2/F3/F4	30/77/39/10/10	1/21/9/2/12	

IFN: Interferon; RBV: Ribavirin; HCV: Hepatitis C virus.

Informed consent was obtained from all patients before enrollment in this study. The study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki and the International Conference on Harmonization of guidelines for good clinical practice.

Table 1 (genotype 1) and Table 2 (genotype 2) show the baseline characteristics of the enrolled patients, who were further classified into four groups according to age and genotype status: group A, genotype 1 aged less than 65 years (n = 685); group B, genotype 1 aged 65 years or older (n = 253); group C, genotype 2 aged less than 65 years (n = 252); and group D, genotype 2 aged 65 or older (n = 61). In group B, body mass index, prior combined IFN plus RBV treatment, alanine aminotransferase, albumin, white blood cell count, hemoglobin, platelet count, and creatinine clearance calculated using the Modification of Diet in Renal Disease equation[15] were significantly lower than in group A (P < 0.010). In group D, albumin, hemoglobin, platelet count, creatinine clearance and serum HCV RNA level were significantly lower than in group C (P < 0.010). The percentage of patients with platelet counts below 10 × 10^{10}/L was significantly higher in group B (36 of 253, 14.2%) than in group A (56 of 685, 8.2%) (P = 0.006), however, there was no significant difference between group C (16 of 252, 6.3%) and group D (7 of 61, 11.5%).

Liver histology

Liver biopsy was performed in 555 patients (59.2%) with genotype 1 and 209 patients (66.8%) with genotype 2. The other patients refused liver biopsy. Fibrosis was staged on a 0-4 scale as follows: F0 = no fibrosis, F1 = portal fibrosis without septa, F2 = portal fibrosis with few septa, F3 = numerous septa without cirrhosis, F4 = cirrhosis. Liver fibrosis was more advanced in group B than in group A