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Original article

Telaprevir is effective given every 12 h at 750 mg with pegylated interferon-α2b and ribavirin to Japanese patients with HCV-1b IL28B rs8099917 TT

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Background: The aim of this study is to explore the efficacy, safety and pharmacokinetics of 750 mg telaprevir (TVR) given at 8 or 12 h intervals during triple therapy with pegylated interferon-α2b (PEG-IFN) and ribavirin (RBV) for patients with chronic HCV infection.

Methods: A total of 52 patients with high viral loads of HCV genotype 1b who were expected to respond well to therapy (rs8099917 TT genotype or relapse to previous therapy) were randomly assigned to two groups who were given 750 mg TVR at either 8 h (q8h) or 12 h (q12h) intervals in combination with PEG-IFN and RBV for 12 weeks, followed by 12 additional weeks of treatment with PEG-IFN and RBV alone. The primary end point of the study was undetectable HCV RNA at 12 weeks after the end of treatment (sustained virological response [SVR_{12}]).

Results: SVR_{12} rates were 92.3% (24/26) for both q8h and q12h. The changes in mean $\log_{10}$ HCV RNA levels and viral response were also similar in q8h compared to q12h, whereas pharmacokinetic properties such as maximum plasma concentration, area under the concentration-time curve at 24 h and trough plasma concentration of TVR were slightly higher in q8h than in q12h ($P>0.2$). The frequency of TVR discontinuation due to anaemia or renal damage was significantly higher in q12h than in q8h (6/26 [23%] versus 0/20 [0%], respectively; $P=0.02$).

Conclusions: TVR given at 12 h intervals should be considered for patients with lower body weight, especially patients with prior relapse and with IL28B polymorphisms at rs8099917 TT (interferon-λ 4 ss469415590 polymorphism TT/TT) genotype in patients with genotype 1b HCV infection.

Introduction

There are estimated to be 170 million HCV carriers worldwide [1,2]. Approximately 30% of carriers develop serious liver diseases, such as decompensated cirrhosis and hepatocellular carcinoma [3,4]. Eradication of the virus is necessary to prevent the development of severe liver damage in these patients.

Telaprevir (TVR), an HCV NS3/4A serine protease inhibitor, has recently been approved in the US, Canada, the European Union and Japan for treatment of patients with chronic HCV genotype 1 infection. In Phase III studies, sustained virological response (SVR) rates increased significantly in both treatment-naive as well as previously treated patients when TVR was administered in combination with pegylated interferon (PEG-IFN) and ribavirin (RBV) compared to PEG-IFN and RBV alone [5–7]. High SVR rates were also observed in Phase III studies in Japan [8,9]; however, side effects of triple therapy in the Japanese studies were so severe that many patients were forced to discontinue therapy due to adverse events, such as anaemia and fatigue [5–9]. Anaemia, in particular, is commonly associated with triple therapy. The frequency of anaemia ranged from 15% to 19% [5,6] in patients treated with PEG-IFN and RBV alone, whereas in patients treated with triple

therapy, the frequency of anaemia increased to between 30% and 37% [5,6]. In addition, RBV dose-reduction rates and discontinuation rates of TVR treatment due to severe adverse events are higher in Japan than in the US and European Union [5–9]. The higher discontinuation rate may result from taking the same standard prescription dosage of TVR despite the lighter body weight of Japanese patients compared with patients in other countries. Japanese patients also tend to be relatively older, and may therefore be at greater risk of severe side effects due to poorer drug metabolism rates. The aim of this study is thus to compare effects and safety of triple therapy with TVR administered at 12 h intervals compared with the standard 8 h interval regimen. We also studied pharmacokinetics of TVR in both groups of patients to see how the reduction of TVR affects the concentration of TVR.

Methods

Patients

We enrolled patients at Hiroshima University Hospital (Hiroshima, Japan), Toranomon Hospital (Tokyo, Japan) and Sapporo Kosei General Hospital (Hokkaido, Japan). Patients were enrolled from August 2012, and the last patient completed follow-up in May 2013. Criteria for inclusion were age between 20 and 70 years, chronic infection with HCV genotype 1b, and plasma HCV RNA level ≥100,000 IU/ml. We selected patients who were expected to respond well to triple therapy based on one of the following criteria: patients with the treatment-favourable rs8099917 TT genotype in the IFN-λ 3 (IL28B) locus or patients who experienced relapse during prior treatment with PEG-IFN and RBV combination therapy. In order to avoid poor response to reduction of TVR, we excluded patients who were expected to have poor response to the therapy, including prior non-responders to PEG-IFN and RBV therapy (that is, patients who failed to become negative for HCV RNA) and patients with rs8099917 T/G or G/G genotypes. Exclusion criteria also included liver disease due to other causes, decompensated cirrhosis, presence of liver cancer, HBV or HIV infection, renal insufficiency, history of heart disease or cerebral infarction, and pregnancy or current breastfeeding. IL28B rs8099917, IFN-λ 4 (IFNL4) ss469415590 and inosine triphosphate pyrophosphatase (ITPA) polymorphism (rs1127354) were genotyped using the Invader assay (Third Wave Technologies, Madison, WI, USA), TaqMan assay (Life Technologies, Carlsbad, CA, USA) or by direct sequencing, as described elsewhere [10–12]. Amino acid substitutions in the HCV core were determined using direct sequencing of PCR products after extraction and reverse transcription of HCV RNA. Core amino acid substitutions at positions 70 and 91 (core 70 and core 91, respectively) were determined as reported by Akuta *et al.* [13,14]. The demographic and baseline characteristics of patients are shown in Table 1. Median body weight was 62.3 kg and 25 (48%) patients had body weight <60 kg. IFNL4 ss469415590 and IL28B rs8099917 genotypes were completely linked, except in one patient (Additional file 1).

Study design and randomization

This was an exploratory prospective multicenter randomized study. Experimental procedures were approved by the institutional review boards at participating hospitals, and informed consent was obtained from all participants. Sample size was not based on hypothesis testing other than the precision estimate of SVR. If we assume that 80%, 85% and 90% of subjects will have undetectable HCV RNA 12 weeks after the end of therapy (SVR_{12}), then 25 subjects per arm would yield two-sided 95% confidence intervals of 64.3% to 95.7%, 71.0% to 99.0% and 78.0% to 100%, respectively. The study was conducted in accordance with the Declaration of Helsinki, and the trial was registered with UMIN Clinical Trials (UMIN000006758). Randomization was stratified according to the combination of prior treatment experience and amino acid substitution at HCV core amino acid 70 (treatment-naive and wild type, naive and mutant, transient response and wild type, transient response and mutant, non-response and wild type, or non-response and mutant), age (<60 or ≥60 years), gender (male or female) and baseline haemoglobin level (<13 or ≥13 g/dl). As shown in Table 1, the demographic and baseline characteristics were well balanced in the two groups of patients.

Mythos (Osaka, Japan), a third party institute that was not involved in the conduct of the study, randomly allocated the two groups of patients to different doses of TVR by means of computer-generated randomization codes.

Study procedures

TVR was administrated at a randomized dose of 750 mg after meals at 8 h (q8h) or 12 h (q12h) intervals. PEG-IFN-α2b (PegIntron; MSD, Tokyo, Japan) was administered subcutaneously at a dose of 1.5 μg/kg of body weight once weekly, and oral RBV (Rebetol; MSD) was administered at a total dose of 600 to 1,200 mg/day based on body weight. Patients received 12 weeks of treatment with TVR plus PEG-IFN/RBV followed by PEG-IFN/RBV alone for an additional 12 weeks. Follow-up observation was performed for 12 weeks (Additional file 2). RBV dosage was reduced or discontinued as required, based on reduction of haemoglobin levels or the development of adverse events. When haemoglobin decreased

Table 1. Baseline characteristics of patients

Characteristic	TVR 750 mg q8h (*n*=26)	TVR 750 mg q12h (*n*=26)	*P*-value
Gender	–	–	0.77
Male	17	18	–
Female	9	8	–
Age, years	61 (24–68)	61 (37–70)	0.99
Body weight, kg	61.4 (39–82)	63.3 (40–81)	0.76
Body mass index, kg/m^2	23.5 (16.8–32.0)	22.5 (17.8–27.7)	0.61
White blood cell count, cells/mm^3	4,890 (3,500–8,920)	4,995 (2,970–11,830)	0.67
Haemoglobin, g/dl	14.2 (12.2–16.5)	15.2 (11.4–17.4)	0.17
Platelet count, $\times 10^4$ cells/μl	15.9 (5.7–25.3)	16.9 (5.2–25.6)	0.74
ALT, IU/l	36 (16–292)	40 (14–117)	0.62
γ-GTP, IU/l	26 (13–125)	20 (10–192)	0.25
eGFR, ml/min	80 (62–105)	80 (60–120)	0.61
HCV RNA, log IU/ml	6.8 (5.3–7.4)	6.9 (5.2–7.8)	0.26
Previous IFN therapy	–	–	0.42
Treatment-naive	14	11	–
Relapse	9	11	–
Non-response	3	4	–
rs8099917	–	–	0.32
TT	25	26	–
TG	1	0	–
ss469415590	–	–	0.49
TT/TT	24	26	–
TT/ΔG	2	0	–
rs1127354	–	–	0.39
CC	18	20	–
Non-CC	8	5	–
ND	0	1	–
HCV core 70	–	–	0.67
Wild type	17	20	–
Mutant	6	4	–
ND	3	2	–

Data are median (range) or *n*. ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; IFN, interferon; ND, not done; q8h, every 8 h; q12h, every 12 h; TVR, telaprevir; γ-GTP, γ-glutamyl transpeptidase.

<10 g/dl, the daily dose of RBV was reduced from 600 to 400 mg, from 800 to 600 mg and from 1,000 to 600 mg, depending on the initial dose of each patient. RBV was withdrawn when haemoglobin decreased <8.5 g/dl. Decrease of TVR dose was not permitted, but administration was stopped if necessary due to the development of adverse events.

Efficacy assessments

Serum HCV RNA levels were measured using COBAS TaqMan HCV RNA 2.0 assay (Roche Diagnostics, Tokyo, Japan), with a lower limit of quantification of 25 IU/ml and a lower limit of detection of 10 IU/ml. The lower limit of detection was used in the determination of undetectable HCV RNA at week 4. HCV RNA levels were measured on day 1 and at the following times: weeks 2, 4, 8, 12, 16, 20, 24 and every 4 weeks until 12 weeks after the end of treatment.

End points

The primary end point was the proportion of patients who had undetectable plasma HCV RNA 12 weeks after the end of treatment (SVR_{12}). The secondary end point was the rate of discontinuation of the therapy due to adverse events.

Pharmacokinetic assessments

Blood samples were collected immediately prior to administering the first morning dose, and at week 2 at 1, 2.5, 4, 6, 8 and 12 h after the first dose to determine the concentration of TVR (750 mg q8h or 750 mg q12h) in the plasma. Plasma concentrations of TVR were determined using a HPLC apparatus fitted with a mass spectrometer. Area under the concentration-time curve (AUC) at 24 h ($AUC_{24\ h}$) was calculated by multiplying $AUC_{8\ h}$ by 3 or $AUC_{8\ h}$ by 2. The maximum plasma concentration (C_{max}) and trough plasma concentration (C_{trough}) were

directly determined from the observed values at week 2. RBV concentration was measured prior to the morning dose at week 2.

Safety assessments

Safety assessments including physical examinations, clinical laboratory tests and evaluation of adverse events were performed at each hospital visit during and after treatment at least every 4 weeks until 12 weeks after cessation of the therapy.

Statistical analyses

Analysis was performed on the intention-to-treat population, defined as all randomly assigned patients who received one dose of the study medication. Categorical variables between groups were compared using Fisher's exact test and continuous variables using the Mann-Whitney test. All analyses were performed using R version 2.15.3.

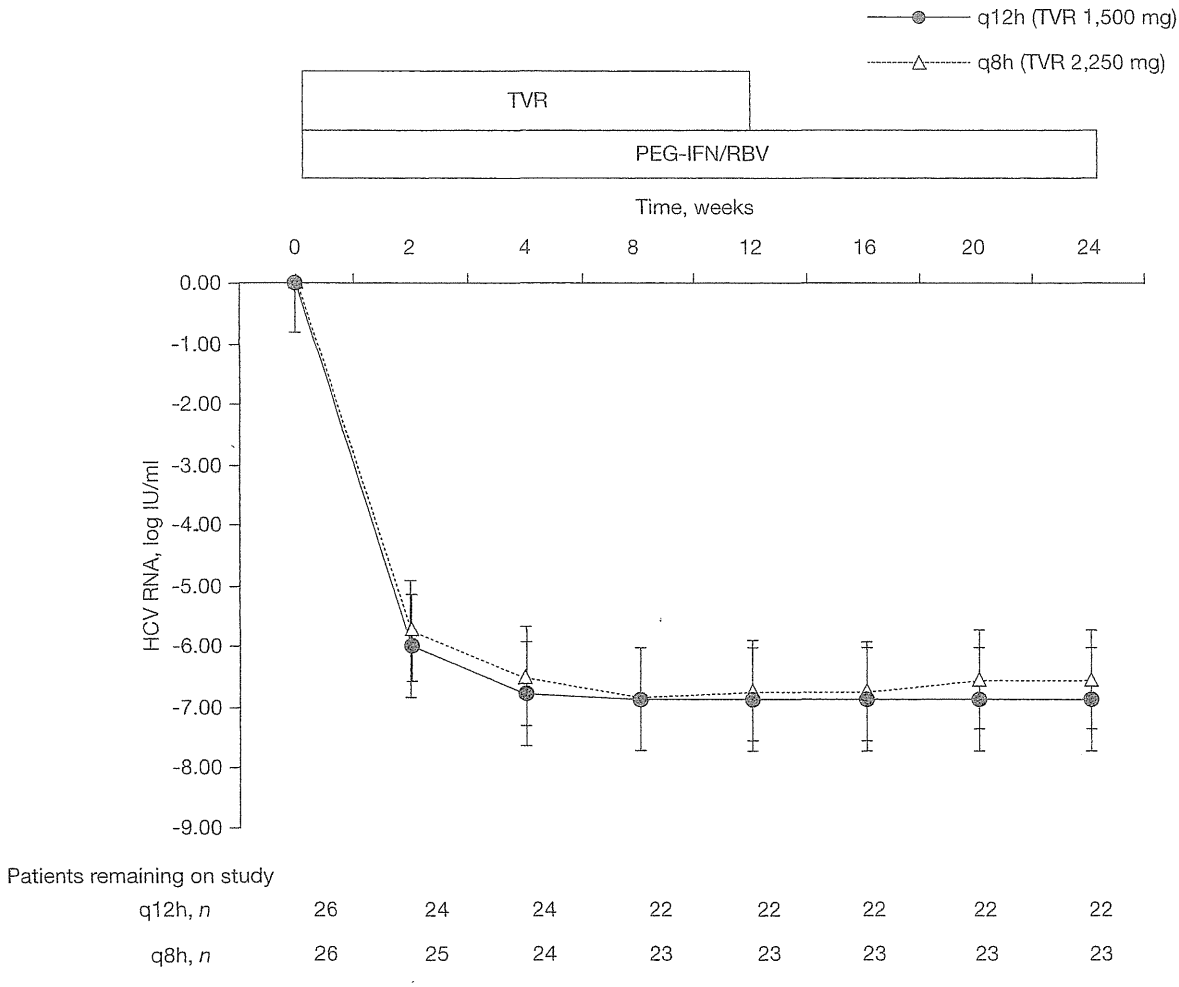
Results

Efficacy

SVR_{12} rates were 92.3% (24/26) for both q8h and q12h (Additonal file 2). The percentage of patients with undetectable HCV RNA at weeks 2, 4, 12, 24 and at 12 weeks after the end of treatment (SVR_{12}) was not statistically different between the two groups of patients (Additional file 2). Similar decreases in mean $\log_{10}$ HCV RNA levels were observed in both groups of patients (Figure 1). The SVR_{12} rate did not differ when the patients were divided by response to previous therapy, age, gender and platelet count (Additional file 1). These results show that the antiviral effect of triple therapy was nearly equivalent between the two patient groups.

Four patients did not achieve SVR_{12}. The characteristics of these four patients were as follows: median 64 years (range 62–65), male/female gender n=3/1, median viral

Figure 1. Decrease of HCV RNA during therapy



Data are shown as mean (SD). PEG-IFN, pegylated interferon; RBV, ribavirin; q8h, every 8 h; q12h, every 12 h; TVR, telaprevir.

load 6.9 log IU/ml (range 5.8–7.2) and median platelet count 17×10^4 cells/μl (range 12–22).

Pharmacokinetics

Mean pharmacokinetic parameters of TVR are shown in Table 2. C_{trough} was slightly lower in the q12h group than in the q8h group. $AUC_{24\ h}$ was also slightly higher in the q8h group than in the q12h group. However, these differences were not statistically significant. C_{max} was similar in both groups of patients.

The mean (SD) of RBV concentration (C_{trough}) at week 2 in the q8h and q12h groups was 1,706 (221) and 1,562 (222) ng/ml, respectively. Although the concentration was slightly higher in the q8h group than in the q12h group, the difference was not statistically significant (P=0.515).

Safety

There were no deaths or serious adverse effects. Adverse events with a frequency of >5% in total patients are listed in Table 3. The overall safety profile was similar in both groups of patients except for the frequency of renal damage. The ratios of discontinuation of all treatment due to adverse events were 12% (3/26) in the q8h group and 15% (4/26) in the q12h group (Additional file 1). Discontinuation of TVR occurred in 42.3% (11/26) of patients in the q8h group and 21.4% (6/28) of patients in the q12h group. Frequency of TVR discontinuation due to anaemia or renal damage was significantly higher in q12h than in q8h (6/26 [23%] versus 0/20 [0%], respectively; P=0.02; Additional file 1).

For anaemia, decreases of mean haemoglobin levels were similar during the initial 6 weeks. Although mean haemoglobin levels continued to decrease in the q8h group, haemoglobin levels stopped decreasing in the q12h group after week 6 (Figure 2). Low haemoglobin (<8.5 g/dl) occurred in 8 (30.8%) patients in the q8h group and 6 (23.1%) patients in the q12h group. The genotype of the ITPA single nucleotide polymorphism (SNP) had no significant effect on the frequency of anaemia. In terms of renal damage, during the 12 weeks of the triple therapy, estimated glomerular filtration rate decreased significantly more in the q8h group than in the q12h group (Figure 3).

Adherence to PEG-IFN and RBV treatment was higher in the q12h group, although the difference was not statistically significant (Additional file 1).

Table 2. Pharmacokinetic parameters of telaprevir at week 2

Pharmacokinetic parameter	TVR 750 mg q8h (n=10)	TVR 750 mg q12h (n=10)	P-value
C_{trough}, μg/ml	2.80 (1.33)	2.00 (0.59)	0.243
1 h, μg/ml	2.93 (1.35)	3.07 (0.81)	0.661
2.5 h, μg/ml	3.60 (1.66)	3.24 (1.22)	0.842
4 h, μg/ml	3.42 (1.40)	3.03 (1.02)	0.661
6 h, μg/ml	3.02 (1.41)	2.51 (0.97)	0.549
8 h, μg/ml	2.48 (1.37)	1.98 (0.77)	0.549
12 h, μg/ml	3.42 (1.47)	1.36 (0.70)	<0.001
C_{max}, μg/ml	3.90 (1.50)	3.74 (0.99)	0.720
$AUC_{24\ h}$, μg•h/ml[a]	74.91 (32.91)	57.16 (18.12)	0.243

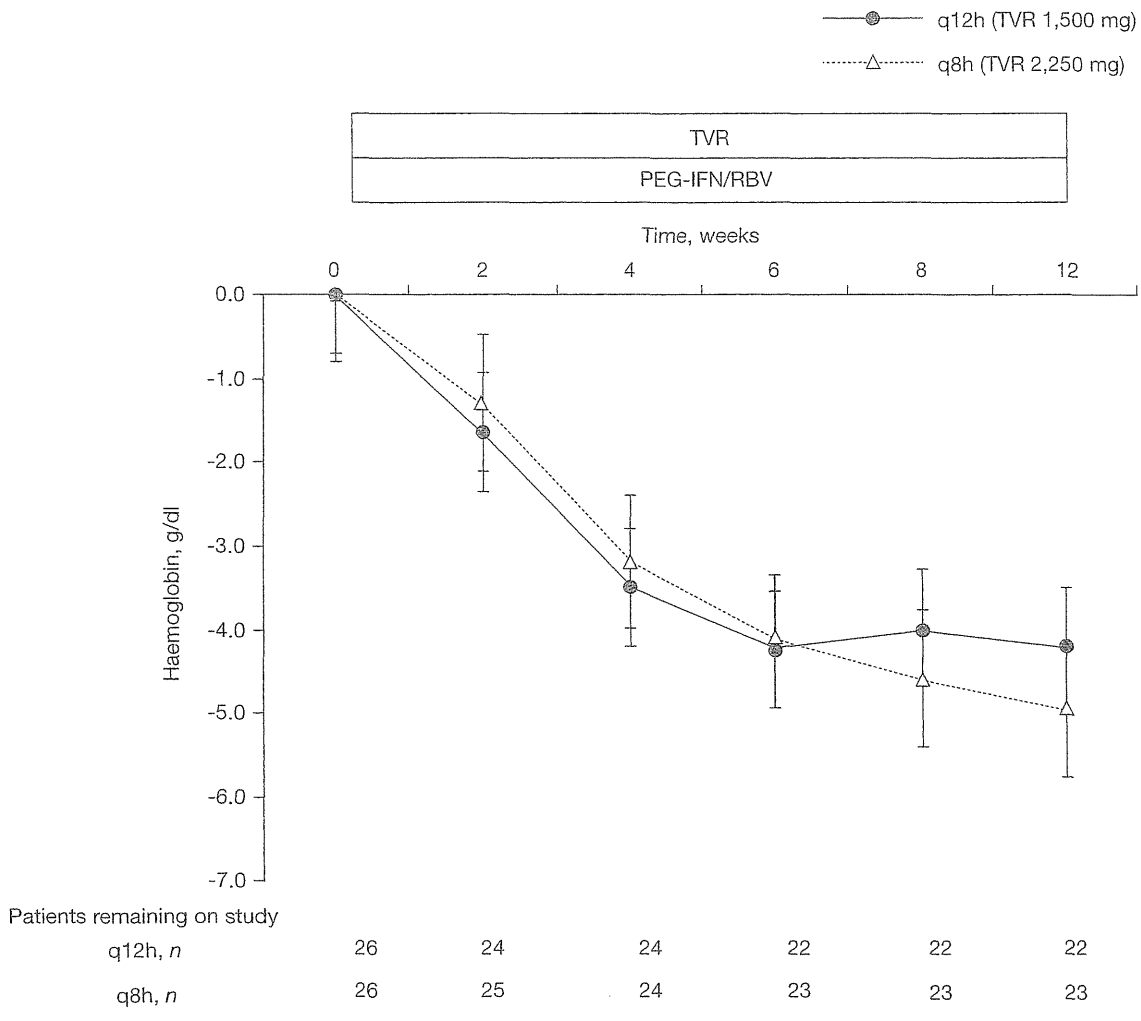
All values are expressed as mean (SD). [a]Area under the curve (AUC) at 24 h ($AUC_{24\ h}$) was calculated by multiplying $AUC_{0\ h}$ by 3 or $AUC_{12\ h}$ by 2. C_{max}, maximum plasma concentration; C_{trough}, trough plasma concentration; q8h, every 8 h; q12h, every 12 h; TVR, telaprevir.

Table 3. Adverse events occurring in >5% of participants

Adverse event	TVR 750 mg q8h (n=26)	TVR 750 mg q12h (n=26)	P-value	All (n=52)
White blood cell count decreased	26 (100)	26 (100)	1.00	52 (100)
Platelet count decreased	26 (100)	26 (100)	1.00	52 (100)
Anaemia	26 (100)	26 (100)	1.00	52 (100)
Blood creatinine increased (eGFR decreased)	21 (80.8)	12 (46.2)	0.02	33 (63.5)
Skin rash	11 (42.3)	13 (50)	0.59	24 (46.2)
Blood uric acid increased	10 (38.5)	6 (23.1)	0.37	16 (30.1)
Anorexia	4 (15.4)	2 (7.7)	0.67	6 (11.5)
General fatigue	3 (11.5)	1 (3.8)	0.61	4 (7.7)

Data are n (%). eGFR, estimated glomerular filtration rate; q8h, every 8 h; q12h, every 12 h; TVR, telaprevir.

Figure 2. Time course of haemoglobin levels during the triple therapy

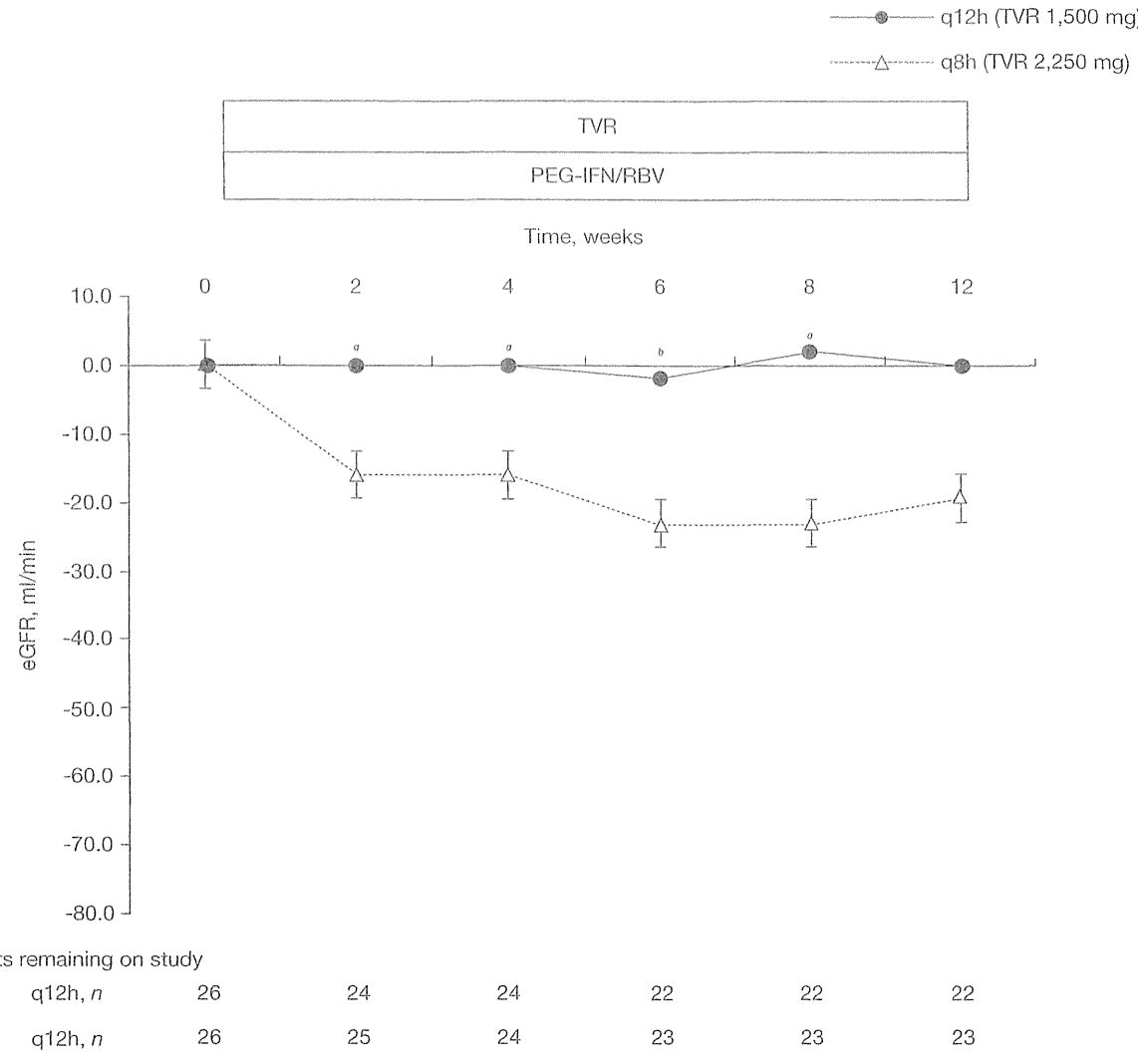


Change from baseline haemoglobin concentrations are noted as mean (SD). PEG-IFN, pegylated interferon; q8h, every 8 h; q12h, every 12 h; RBV, ribavirin; TVR, telaprevir.

Discussion

With the introduction of TVR, the eradication rate of HCV has improved significantly [5–7]. However, severe adverse effects associated with TVR have also been reported, some or which occur more frequently in Japanese patients [8,9]. The dose of TVR for use in triple therapy was determined based on a dose-finding study conducted in the US and Europe [15], which found that the q8h dosage regimen achieved the greatest reduction of HCV RNA. However, body weights of Japanese patients who were treated with TVR, PEG-IFN-α2b and RBV [9] were 61–63 kg compared to 79–91 kg among American and European patients who were treated with boceprevir, PEG-IFN-α2b and RBV combination therapy [16]. As the dose of TVR is the same among countries where triple therapy is approved, we considered the possibility that the dose of TVR might be too high for smaller Japanese patients and could be reduced. Suzuki *et al.* [17] previously reported that the antiviral effect of triple therapy was similar when patients were given TVR at 1,500 mg/day (q8h at 500 mg) compared with those given at 2,250 mg/day (q8h at 750 mg) in the Japanese patients, suggesting that reduction of TVR might be possible. However, the treatment period of their study was only 12 weeks, and the study was a non-randomized controlled study with a small number of patients. Therefore, we conducted a randomized controlled trial to confirm that the dose reduction is as effective as the approved regimen. Therefore, we also attempted to test if TVR is as effective when administered at 12 h intervals instead of 8 h intervals, based on a pharmacokinetics study in which Marcellin *et al.* [18] found no difference in viral response and safety profiles

Figure 3. Time course of eGFR levels from baseline during triple therapy



Statistically significant differences between patients treated with 1,500 mg versus 2,250 mg telprevir (TVR): $^{a}P<0.01$, $^{b}P<0.05$. eGFR, estimated glomerular filtration rate; PEG-IFN, pegylated interferon; q8h, every 8 h; q12h, every 12 h; RBV, ribavirin.

between patients treated with the triple therapy with TVR 2,250 mg (q12h) and TVR 2,250 mg (q8h). Furthermore, Buti *et al.* [19] reported that the effectiveness and safety were similar between patients treated with triple therapy with 2,250 mg TVR (q12h) and 2,250 mg TVR (q8h) in the OPTIMIZE trial (Phase IIIb).

We showed in this study that the effect of TVR given q12h at 750 mg with PEG-IFN-α2b and RBV is the same as TVR given q8h among Japanese chronic hepatitis C patients. However, four patients failed to achieve SVR_{12}, and all treatment was discontinued within 4 weeks in these patients. Safety profiles were similar except for differences in the frequency of anaemia and renal damage. Haemoglobin levels continued to decline only in patients who received the larger 2,250 mg dose, whereas haemoglobin levels plateaued by week 6 in patients who received the 1,500 mg dose. We also found that the 1,500 mg dosage was also accompanied with a lower frequency of renal damage (Figure 3). Incidence of TVR discontinuation was significantly less frequent in patients treated with the 1,500 mg regimen. These results suggest that reduction of TVR to 1,500 mg and administration of the drug q12h is as effective as the approved 2,250 mg dose and is less likely to result in premature termination of TVR therapy (Additional file 1).

We assessed the effect of reduced TVR only in patients who relapsed under previous PEG-IFN/RBV therapy or had the IL28B SNP rs8099917 TT genotype that is associated with a good response to IFN therapy. Patients who had relapsed during previous

PEG-IFN/RBV therapy have been reported to respond well to triple therapy [9]. The majority of patients with the rs8099917 TT genotype have also been reported to successfully eradicate the virus with triple therapy [20,21]. The effect of TVR reduction on patients who are expected to be difficult to treat should be further explored in a different trial.

Until recently it was unknown why SNPs near the IL28B locus, such as rs8099917 and rs12979860, are associated with the outcome of IFN therapy. However, the recent characterization of IFNL4 and its association with polymorphism ss469415590 (TT or ΔG) has shed light on this issue [22]. Genotype ss469415590 TT, which fails to express functional IFNL4, is associated with both eradication of HCV by PEG-IFN plus RBV combination therapy as well as spontaneous clearance of the virus [22]. As this polymorphism is in strong linkage disequilibrium with rs8099917 and rs12979860 in Asian populations [22], it is assumed that in the majority of patients the IL28B and IFNL4 ss469415590 genotypes are in complete linkage disequilibrium, and in fact, there was only one patient who had a discrepancy between ss469415590 and rs8099917 genotypes (Additional file 1). Taken together, patients with ss469415590 genotype TT/TT are expected to be successfully treated with the 1,500 mg regimen.

Our results were obtained from Japanese patients with body weights between 61 and 63 kg in each group of patients (Table 1). Results obtained here should be confirmed in patients with a larger body weight. Alternatively, administration of TVR based on body weight should be considered in order to maintain high eradication rates while reducing the risk of adverse effects. However, it should be noted that the limitations of the study are the relatively small patient numbers and enrolling two main groups including prior relapsers and treatment-naive patients with favourable INFL4 genotypes. A more comprehensive study is essential in the future.

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Disclosure statement

The authors declare no competing interests.

Additional files

Additional file 1: Supplementary tables illustrating a comparison between IFNL3 (rs8099917) and IFNL4 (ss469415590) genotypes; SVR_{12} rates stratified by response to previous therapy, age, gender and platelet count; adverse events leading to discontinuation of all treatment or TVR only; and the rate of treatment completion without reduction or discontinuation can be found at http://www.intmedpress.com/uploads/documents/3050_Kawakami_Additional_File_1.pdf

Additional file 2: Supplementary figures displaying the study design; enrolment and outcomes; and the cumulative rate of undetectable HCV RNA in serum during treatment can be found at http://www.intmedpress.com/uploads/documents/3050_Kawakami_Additional_File_2.pdf

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Estimating the Long-Term Clinical and Economic Outcomes of Daclatasvir Plus Asunaprevir in Difficult-to-Treat Japanese Patients Chronically Infected with Hepatitis C Genotype 1b

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ABSTRACT

Objectives: Japan has one of the highest endemic rates of hepatitis C virus (HCV) infection. Treatments in Japan are currently limited to interferon-alfa–based regimens, which are associated with tolerability and efficacy issues. A novel regimen combining two oral HCV therapies, daclatasvir and asunaprevir (DCV + ASV), has shown favorable results in Japanese patients with chronic genotype 1b HCV infection. Comparisons of clinical and economic outcomes associated with DCV + ASV treatment and current standards of care were investigated. **Methods:** The MOdelling the NAtural histoRy and Cost-effectiveness of Hepatitis cost-effectiveness model projected outcomes in 1000 patients aged 70 years with either chronic hepatitis C or compensated cirrhosis over a lifetime simulation. Japanese-specific disease transition rates were used, and discounting was applied annually at a rate of 2%. Efficacy data for DCV + ASV and telaprevir triple therapy (telaprevir + pegylated interferon-alfa + ribavirin [TVR + pegIFN-α/RBV]) were obtained from a Japanese subgroup analysis found within a global meta-analysis: sustained virological response rates of 74%, 85%, and 87% were reported for null responders (NRs), partial responders (PRs), and interferon-alfa–ineligible/intolerant patients, respectively, treated with DCV + ASV, and rates of 42% and 59% were reported for NRs and PRs, respectively, treated with TVR + pegIFN-α/RBV. **Results:** Initiating DCV + ASV treatment in patients in the chronic hepatitis C disease stage resulted in quality-adjusted life-year gains of 0.96 and 0.77 over TVR + pegIFN-α/RBV for NRs and PRs, respectively, and a gain of 2.61 in interferon-alfa–ineligible/intolerant patients over no treatment. Similarly, quality-adjusted life-year gains of 1.11, 0.90, and 3.05 were observed when initiating treatment in patients in the compensated cirrhosis stage. Cumulative lifetime events of decompensated cirrhosis, hepatocellular carcinoma, and liver-related mortality were reduced by up to 66, 115, and 128, respectively, with DCV + ASV treatment. **Conclusions:** There is a lack of successful therapies for patients with HCV who have previously failed to achieve sustained virological response or are ineligible for interferon-alfa–based therapies. Results demonstrate that the provision of an alternative, interferon-alfa–free regimen, such as DCV + ASV, offers significant value in terms of avoiding life-threatening liver complications and increasing patients' quality of life.

Keywords: asunaprevir, clinical effectiveness, daclatasvir, hepatitis C.

Introduction

The global burden of the hepatitis C virus (HCV) is significant, with an estimated 3% of the world's population chronically infected [1]. Japan has one of the highest endemic rates of HCV infection; approximately 2 million people are infected, predominately with genotype 1b, resulting in more than 30,000 liver-related deaths each year [2–4]. An interferon-alfa–based treatment regimen is the mainstay of therapy for HCV-infected individuals [5], with the aim of eradicating the infection and thereby preventing disease progression. The recognized clinical end point for HCV eradication is sustained virological response (SVR), and recent advances have given rise to SVR rates of the order of 70% in treatment-naive patients, using a triple therapy regimen consisting of pegylated interferon-alfa, ribavirin, and a protease inhibitor (e.g., telaprevir or boceprevir [6,7]). Interferon-alfa–based regimens, however, are associated with tolerability issues; adverse events commonly observed include anemia, pyrexia, rash, renal toxicity, and gastrointestinal-related disorders [8,9], and there remains a proportion of patients who do not achieve SVR, particularly if they are previous nonresponders. For those patients intolerant of or ineligible for interferon-alfa–based

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therapy, there is currently no approved treatment option and they remain at risk of developing life-threatening complications including decompensated cirrhosis (DC) and hepatocellular carcinoma (HCC).

An interferon-alfa–free, all-oral regimen comprising daclatasvir and asunaprevir has been investigated for the treatment of patients with HCV genotype 1b infection [10]. Both daclatasvir and asunaprevir have demonstrated robust antiviral activity, with no clinically meaningful pharmacokinetic interactions when coadministered [11]. This regimen presents a significant step forward in the treatment of HCV infection for both untreated patients and those intolerant of or ineligible for interferon-alfa–based regimens. Daclatasvir is a first-in-class NS5A replication complex inhibitor with potent pan-genotypic antiviral activity in vitro (HCV genotypes 1–6) [12], and asunaprevir is a selective NS3 protease inhibitor with antiviral activity against HCV genotypes 1, 4, 5, and 6 in vitro [13].

This study aimed to model the lifetime clinical and economic outcomes associated with the use of daclatasvir combined with asunaprevir (DCV + ASV) for the treatment of patients with chronic HCV genotype 1b infection, specifically in a Japanese setting, who are either intolerant of or ineligible for interferon-alfa–based therapies, and those who did not respond to previous interferon-alfa–based treatment. Comparisons against current treatment options were made: telaprevir combined with pegylated interferon-alfa and ribavirin (TVR + pegIFN-α/RBV), pegylated interferon-alfa and ribavirin (pegIFN-α/RBV), and no treatment. Because of the relative lack of data associated with DCV + ASV treatment, sensitivity analyses were performed using efficacy rates derived from a global meta-analysis, with the intention of gaining a broader perspective of how DCV + ASV might perform in the clinical setting.

Methods

Model

The objective of this study was to compare the long-term clinical and economic outcomes of DCV + ASV with the current standard of care for chronic HCV genotype 1b infection in Japan. A modeling analysis was performed to predict the lifetime clinical and economic outcomes associated with DCV + ASV treatment using a previously published and validated computer cohort simulation model [14]. The model used (the MOdelling the NAtural histoRy and Cost-effectiveness of Hepatitis [MONARCH] model) is a cohort-based Markov lifetime simulation created in Microsoft Excel and designed to model the natural history of HCV and its complications [14–16]. The model runs in annual cycles over a variable time horizon, up to patient lifetime (80 years from start). Cohorts of 1000 patients are defined and enter the model at either the chronic hepatitis C (CHC) or the compensated cirrhosis (CC) disease stage. From here, those with CHC can progress to CC and all patients can progress to DC, HCC, death, or a state of SVR. The MONARCH model flow diagram is presented in Figure. 1. The model outputs total costs, incidence of clinical events, quality-adjusted life-years (QALYs), and life expectancy. Costs, QALYs, and life-years were all discounted at a rate of 2%, in line with current Japanese guidelines.

Disease transition rates are applied annually to the prevalent population in each health state to model the natural history of HCV. Patients who achieve SVR from the state of CHC remain in the state of SVR for the duration of the simulation, whereas those who achieve SVR from the state of CC may relapse and progress to HCC. In those subjects failing to respond to treatment, CHC progression continues from whichever disease stage they were in at initiation of antiviral therapy. All transition rates are drawn from recently published literature specific to the Japanese setting.

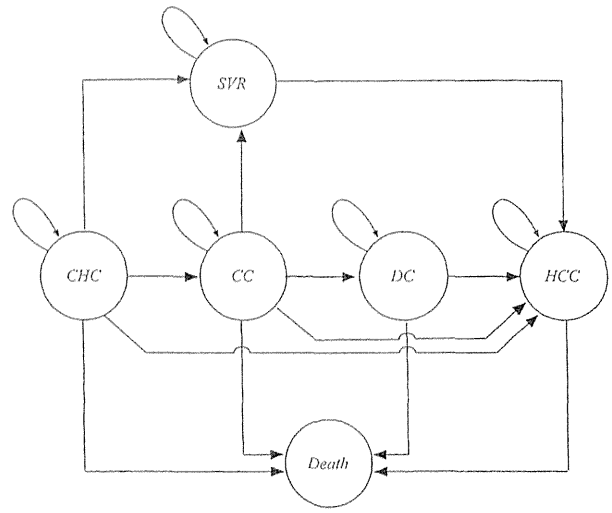

Fig. 1 – Flow diagram of the MONARCH model. CC, compensated cirrhosis; CHC, chronic hepatitis C; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; MONARCH, MOdelling the NAtural histoRy and Cost-effectiveness of Hepatitis; SVR, sustained virological response.

All-cause mortality is incorporated into the model via the use of Japanese-specific abridged life tables and affects patients in the CHC, CC, and SVR Markov states. The transition rates used in the model are presented in Table 1.

Health states within the model are subject to specific cost and utility values, applied annually. Health state utility values were obtained from the literature. To estimate health state costs, 10 Japanese hepatologists were surveyed between March 2013 and May 2013. Information regarding the treatment of CHC and CC in clinical practice was collected, including the treatments used, clinical tests, frequency of examinations, and adverse events. This information was then pooled and translated into costs; unit prices for disease management, clinical tests performed, and treatments prescribed were derived from the medical service fee or National Health Insurance price list. All costs and health utility

Table 1 – Disease transition rates.

Transition (genotype 1b)	Mean (SE)	Source
CHC to CC	0.065 (0.011)	Nakamura et al. [23]
CHC to HCC	0.016 (0.004)	Nakamura et al. [23]
CC to DC	0.021 (0.006)	Imazeki et al. [24]
CC to HCC	0.043 (0.008)	Hayashida et al. [25]
DC to HCC	0.083 (0.022)	Nakamura et al. [23]
DC to death	0.153 (0.017)	Nakamura et al. [23]
HCC to death	0.200 (0.012)	Nakamura et al. [23]
CC SVR to HCC	0.018 (0.011)	Arase et al. [26]

CC, compensated cirrhosis; CHC, chronic hepatitis C; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; SE, standard error.

values are therefore specific to Japan and are illustrated in Table 2.

Therapy-specific efficacy data are applied to the cohort to determine the distribution of patients among CHC, CC, and SVR health states after treatment initiation. Each therapy uses a course of antiviral treatment. The duration of antiviral consumption differs depending on the drugs used and affects the adverse-event profile associated with each treatment. Efficacy data sources for this study are described below. It is assumed that all patients complete treatment.

The costs associated with adverse events are modeled as a per-event cost. Each patient who suffers an adverse event is assumed to incur a cost that relates to the duration of his or her respective treatment. Only rash and anemia are modeled; it is assumed that all other adverse events would either not incur an additional cost or would occur too infrequently to affect the results substantially. The weekly costs of rash and anemia used (¥2,634.08 and ¥2,135.63, respectively) were derived from the hepatologist survey and National Health Insurance costs, assuming an average duration of 24 weeks, the same duration as therapy with pegIFN-α/RBV.

Analysis Plan

Using Japanese-specific disease progression rates, the natural history of HCV infection in cohorts of 1000 patients aged 70 years was modeled; 50% of the cohort members were female. Patients were simulated until death, and the predicted clinical outcomes and costs were recorded. Results for DCV + ASV were compared with simulations of treatment with TVR + pegIFN-α/RBV, pegIFN-α/RBV, and no treatment to quantify the potential benefit of DCV + ASV antiviral therapy. The base-case analysis incorporated the following:

1. Previous interferon-alfa–based therapy null responders
   a. DCV + ASV versus TVR + pegIFN-α/RBV
   b. DCV + ASV versus pegIFN-α/RBV
   c. DCV + ASV versus no treatment
2. Previous interferon-alfa–based therapy partial responders
   a. DCV + ASV versus TVR + pegIFN-α/RBV
   b. DCV + ASV versus pegIFN-α/RBV
   c. DCV + ASV versus no treatment
3. Pegylated interferon-alfa–intolerant/ineligible patients
   a. DCV + ASV versus no treatment

Null response was defined as a decrease in HCV RNA by at least 2 log by week 12 but detectable HCV RNA during the therapy period. Partial response was defined as a reduction of 2 log or more from baseline in HCV RNA but never achieving undetectable HCV RNA after at least 12 weeks. Pegylated interferon-alfa–intolerant/ineligible patients include those who previously discontinued interferon-alfa–based therapy because of an adverse reaction or have a contraindication, and are therefore naive to interferon-alfa–based therapy.

A sensitivity analysis using results from a global meta-analysis was undertaken to provide insight into the potential variation in treatment effects.

Data Sources and Assumptions

Base-case analysis

For the base-case analysis, Japanese-specific results were taken from a previously undertaken global meta-analysis, in which a subgroup analysis of Japan-only studies was incorporated [17,18]. A recent phase 3 clinical trial for DCV + ASV undertaken in Japanese patients with chronic HCV genotype 1b infection (AI447026, NCT01497834) was incorporated within the meta-analysis. Results from this trial were incorporated in the base-case analysis to provide an insight into the clinical effectiveness of DCV + ASV in an interferon-alfa–ineligible and intolerant cohort, which was not part of the meta-analysis. Treatment-related effects are reported in Table 3.

DCV + ASV phase 3 clinical trial

AI447026 included two parallel populations: prior nonresponder (null and partial responders; n = 87) and interferon-alfa–intolerant/ineligible (n = 135) [10]. All subjects were administered 60 mg of daclatasvir once daily and 100 mg of asunaprevir twice daily for 24 weeks and followed for 24 weeks after the last dose of study drug. The primary efficacy end point was the proportion of subjects with SVR_{24}, defined as HCV RNA below the lower limit of quantitation (<15 IU/mL) target detected or not detected at follow-up week 24 for each population. Safety was assessed as a secondary end point.

Meta-analysis and Japanese-specific subgroup analysis

The meta-analysis was performed to determine the relative efficacy and safety of different HCV treatment regimens used worldwide [17,18]. Trials investigating the treatment of adults with CHC, regardless of HCV genotype, who were either naive to treatment or had been previously treated with an interferon-alfa–based therapy, were included. Relevant articles published in the year 2000 or later were identified through searches of the PubMed

Table 2 – Health state costs and utilities.

Health state	Mean cost (¥) (SE)	Source	Mean utility (SE)	Source
SVR CHC (first year only)	57,186 (8,515)	Japanese hepatologist survey	0.960 (0.082)	Ishida et al. [27]
SVR CC (first year only)	124,439 (33,346)	Japanese hepatologist survey	0.960 (0.082)	Ishida et al. [27]
CHC monitoring*	119,227 (8,851)	Japanese hepatologist survey	0.920 (0.078)	Ishida et al. [27]
CHC care†	97,610 (21,817)	Japanese hepatologist survey		
CC monitoring*	170,657 (17,308)	Japanese hepatologist survey	0.860 (0.037)	Okida [28]
CC care†	177,705 (46,894)	Japanese hepatologist survey		
DC	1,568,874 (597,016)	Japanese hepatologist survey	0.670 (0.057)	Okida [28]
HCC	2,086,385 (793,949)	Nakamura et al. [23]	0.380 (0.032)	Ishida et al. [3]
Death	0	Assumed	0.000 (0.000)	Assumed

CC, compensated cirrhosis; CHC, chronic hepatitis C; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; SE, standard error; SVR, sustained virological response.

* CHC/CC monitoring refers to costs including inpatient/outpatient care and tests required.

† CHC/CC care refers to costs including hepatoprotective medication, nutritional therapy, and other medication required.

Table 3 – Base-case treatment-related outcomes: Mean (SE).

Regimen	Duration (wk)	Population	Japanese-specific subgroup of global meta-analysis			Source
			SVR_{24}	Rash incidence	Anemia incidence	
DCV + ASV	24	Treatment-intolerant/ ineligible*	0.874 (0.029)	0.046 (0.022)	0.011 (0.011)	026 phase 3 clinical trial data [10] Broglio et al. [17,18]
		Previous null responder	0.740 (0.097)	0.050 (0.046)	0.020 (0.036)	Broglio et al. [17,18]
		Previous partial responder	0.850 (0.071)	0.050 (0.046)	0.020 (0.036)	Broglio et al. [17,18]
TVR + pegIFN-α/RBV	12†	Previous null responder	0.420 (0.074)	0.280 (0.084)	0.580 (0.148)	Broglio et al. [17,18]
		Previous partial responder	0.590 (0.082)	0.280 (0.084)	0.580 (0.148)	Broglio et al. [17,18]
PegIFN-α/RBV	48	Previous null responder	0.080 (0.026)	0.160 (0.066)	0.380 (0.143)	Broglio et al. [17,18]
		Previous partial responder	0.140 (0.048)	0.160 (0.066)	0.380 (0.143)	Broglio et al. [17,18]

DCV + ASV, daclatasvir + asunaprevir; pegIFN-α/RBV, pegylated interferon-alfa + ribavirin; SE, standard error; SVR, sustained virological response; TVR + pegIFN-α/RBV, telaprevir + pegylated interferon-alfa + ribavirin.

* Adverse-event data were taken directly from the data tables provided within the meta-analysis relating to the DCV + ASV trial, and SVR rates were taken directly from the trial itself.

† Combined with 24 wk of pegIFN-α/RBV.

database. Randomized clinical trials of pegIFN-α/RBV and either single-arm or randomized clinical trials of TVR + pegIFN-α/RBV were included. The primary efficacy outcome measure was SVR 24 weeks following the completion of treatment (SVR_{24}). A total of 58 studies were included in the meta-analysis; among these, five were conducted in Japan and included in the Japanese-specific subgroup analysis.

The meta-analysis was performed with a Bayesian hierarchical model. The foundational treatment was set as pegIFN-α/RBV and, for each end point, the response rate of pegIFN-α/RBV was allowed to vary from study to study; however, the odds ratio between each pair of treatments was assumed to be constant across studies, conditional on covariates and treatment arms. Each study was assumed to be sampled from a larger population of studies. The log odds of response for pegIFN-α/RBV in study s was modeled as follows:

$$\alpha_s = \log\left(\frac{P_{o,s}}{1-P_{o,s}}\right)$$

where $P_{t,s}$ is the probability of response for treatment t in study s.

Study-level effects are modeled with a distribution of $\alpha_s \sim N(\mu_\alpha, \tau_\alpha^2)$ using the following weak hyper priors:

$\mu_\alpha \sim N(0,10^2)$ and τ_α^2 = Inverse Gamma(0.5,0.001)

The data are allowed to shape the amount of variability across studies and, because of the hyper priors carrying little prior information, the amount of heterogeneity between studies is also largely determined by the data. The log-odds of response to a treatment is as follows:

$$\log(\square)\left(\frac{P_{t,s}}{1-P_{t,s}}\right) = \alpha_s + \theta_t + \beta Z$$

for $t = 0, 1, \ldots, 4$

The θ's represent treatment effects. For pegIFN-α/RBV, the treatment effect is assumed to be 0, allowing α_s to be identified as the pegIFN-α/RBV log-odds for study s, while the treatment effects for TVR + pegIFN-α/RBV and DCV + ASV are modeled independently with "flat" prior distributions $N(0,10^2)$.

The following covariates (denoted by Z) were incorporated in the analysis of SVR_{24} rates:

- Treatment history (whether patients are treatment-naive, prior null or partial responders, or have had a relapse or breakthrough response to previous pegIFN-α/RBV treatment);
- HIV coinfection;
- HCV genotype (1a, 1b, 2 or 3 [grouped], 4);
- Country (Japan or outside Japan); and
- Interaction term between previously treated with pegIFN-α/RBV and the relevant therapy.
- The following covariates were incorporated in the analysis of adverse events:
- Treatment history (treatment-naive or previously treated);
- HIV coinfection; and
- HCV genotype (1 vs. not).

The β's represent covariate effects and are modeled independently with "flat" prior distributions $N(0,10^2)$. Posterior distributions for the terms in the model were computed and, on the basis of these, posterior mean odds ratios for response with DCV + ASV therapy versus other therapies were calculated.

The Japanese-specific subgroup meta-analysis for SVR_{24} modeled the effects of the covariates using all studies (58 studies globally) and all populations, as in the global meta-analysis, but the estimates of the efficacy of the therapies in Japanese patients uses only the Japanese trials (five trials conducted in Japan). This modeling creates common effects of the covariates, but completely separate effects for a treatment arm, depending on country (Japan vs. outside Japan). Of the five studies conducted in Japan, safety/tolerability end points were available from the extracted populations or treatment arms for only three of these studies. Because of sparse data, formal modeling of the safety and tolerability end points for the Japan subgroup was not performed; thus, although adverse-event rates applied in the model are therapy-specific, they remain constant across analyses.

Sensitivity analysis

Because data regarding the effectiveness of DCV + ASV are relatively few, sensitivity analyses were undertaken around the base case to provide some insight into the potential effect on outcomes with varying efficacy. Patients with chronic HCV infection were modeled. Results from the full data set of the

Table 4 – Results of base-case analysis for patients with chronic HCV (N = 1,000).

Outcome	DCV + ASV			TVR + pegIFN-α/RBV		PegIFN-α/RBV		No treatment		
	Null responder	Partial responder	Ineligible/ intolerant	Null responder	Partial responder	Null responder	Partial responder	Null responder	Partial responder	Ineligible/ intolerant
Number achieving SVR	740	850	874	420	590	80	140	0		
Per-patient QALYs	13.03	13.35	13.43	12.07	12.58	11.05	11.23	10.82		
Per-patient life-years	13.99	14.16	14.20	13.49	13.76	12.96	13.06	12.84		
Additional per-patient cost of complication management compared with DCV + ASV	NA	NA	NA	1,975,431	1,613,146	4,040,136	4,342,040	4,463,999	5,128,189	5,273,817
Total observed clinical events										
CC	147	85	71	328	232	520	486	565		
DC	24	14	12	53	38	85	79	92		
HCC	93	54	45	208	147	330	308	359		
LM	104	60	50	232	164	368	344	400		
Numbers needed to treat to avoid one event when using DCV + ASV										
CC	NA	NA	NA	6	7	3	2	2	2	2
DC	NA	NA	NA	34	42	16	15	15	13	12
HCC	NA	NA	NA	9	11	4	4	4	3	3
LM	NA	NA	NA	8	10	4	4	3	3	3

CC, compensated cirrhosis; DC, decompensated cirrhosis; DCV + ASV, daclatasvir + asunaprevir; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LM, liver-related mortality; NA, not applicable; pegIFN-α/RBV, pegylated interferon-alfa + ribavirin; SVR, sustained virological response; TVR + pegIFN-α/RBV, telaprevir + pegylated interferon-alfa + ribavirin; QALY, quality-adjusted life-year.

Notes: Costs and QALYs are presented on a per-patient level. Comparisons of cost differences and numbers needed to treat are made against appropriate comparators, for example, DCV + ASV: Null responders are compared only with other null responder cohorts (or the no treatment cohort).

Table 5 – Results of base-case analysis for patients with compensated cirrhosis (N = 1,000).

Outcome	DCV + ASV			TVR + pegIFN-α/RBV		PegIFN-α/RBV		No treatment		
	Null responder	Partial responder	Ineligible/ intolerant	Null responder	Partial responder	Null responder	Partial responder	Null responder	Partial responder	Ineligible/ intolerant
Number achieving SVR	740	850	874	420	590	80	140	0		
Per-patient QALYs	11.21	11.59	11.68	10.10	10.69	8.91	9.12	8.63		
Per-patient life-years	12.75	12.96	13.01	12.11	12.45	11.43	11.55	11.27		
Additional per-patient cost of complication management compared with DCV + ASV	NA	NA	NA	1,949,966	1,592,455	3,987,613	4,285,538	4,405,110	5,060,546	5,204,264
Total observed clinical events										
DC	54	31	26	120	85	190	178	207		
HCC	322	296	290	396	357	476	462	494		
LM	345	305	296	461	399	584	562	613		
Numbers needed to treat to avoid one event when using DCV + ASV										
DC	NA	NA	NA	15	19	7	7	7	6	6
HCC	NA	NA	NA	13	16	6	3	6	2	5
LM	NA	NA	NA	9	11	4	2	4	2	3

DC, decompensated cirrhosis; DCV + ASV, daclatasvir + asunaprevir; HCC, hepatocellular carcinoma; LM, liver-related mortality; NA, not applicable; pegIFN-α/RBV, pegylated interferon-alfa + ribavirin; SVR, sustained virological response; TVR + pegIFN-α/RBV, telaprevir + pegylated interferon-alfa + ribavirin; QALY, quality-adjusted life-year.

Notes: Costs and QALYs are presented on a per-patient level. Comparisons of cost differences and numbers needed to treat are made against appropriate comparators, for example, DCV + ASV: Null responders are compared only with other null responder cohorts (or the no treatment cohort).

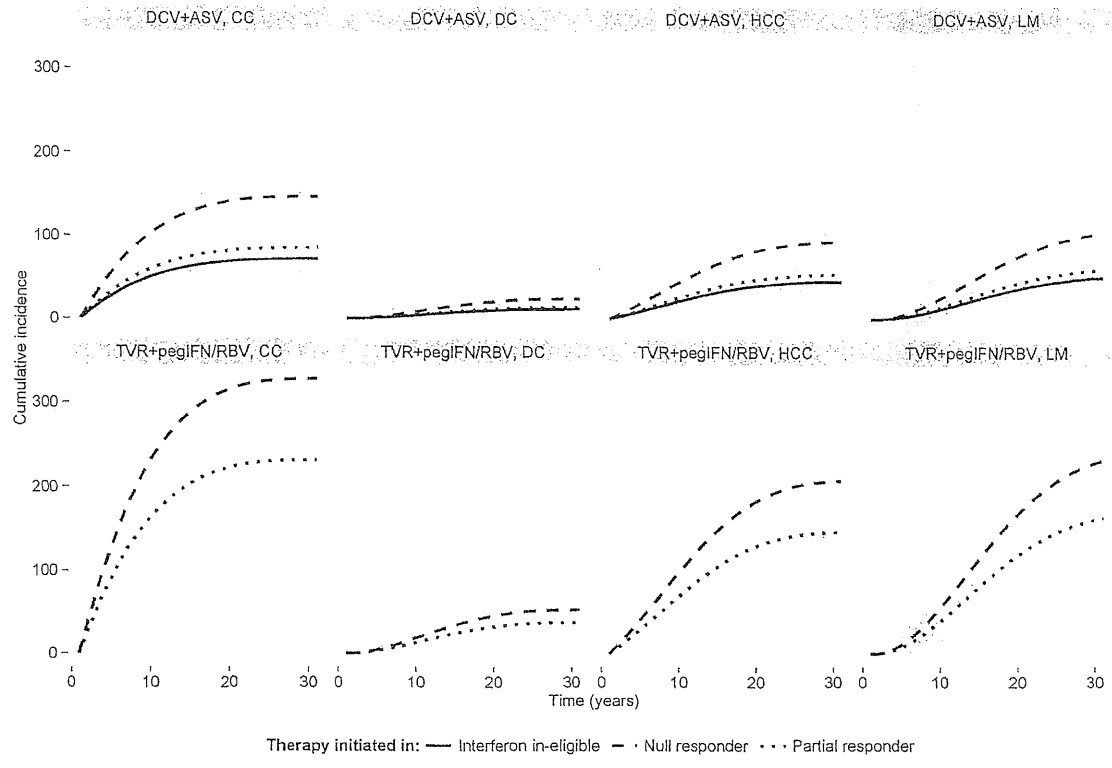

Fig. 2 – Estimated cumulative incidence of end-stage liver disease complications (base-case analysis). CC, compensated cirrhosis; DC, decompensated cirrhosis; DCV + ASV, daclatasvir + asunaprevir; HCC, hepatocellular carcinoma; LM, liver-related mortality; TVR + pegIFN-α/RBV, telaprevir + pegylated interferon-alfa + ribavirin.

global meta-analysis were used to provide additional insight into the effects of treatment among null and partial responders.

Efficacy (SVR_{24}) and safety (rate of anemia and rash) data used in both the base-case and sensitivity analysis are included in Table 4.

Model assumptions

1. If a patient achieves SVR from chronic HCV, he or she remains in a state of SVR and cannot progress to end-stage liver disease complications.
2. Liver transplant is not considered as a treatment option/disease state because of it not being possible or appropriate for most patients in Japan [3].
3. No patients discontinue therapy.
4. No therapy-related QALY decrements are applied to patients when receiving treatment because of a lack of consistent information.
5. Efficacy rates remain constant across CHC and CC disease stages.
6. Therapy costs are not modeled because of the costs of daclatasvir and asunaprevir not being published.

Results

Base Case

The base-case analysis suggested that DCV + ASV is superior to TVR + pegIFN-α/RBV, pegIFN-α/RBV, and no treatment in terms of clinical outcomes, reductions in cost, and total health benefit for patients receiving treatment from both the CHC and CC disease states (Tables 4 and 5). Treatment with DCV + ASV in patients with CHC who previously had a null response was associated with an increased number of QALYs per patient: 13.03, compared with 12.07, 11.05, and 10.82 when treated with TVR + pegIFN-α/RBV, pegIFN-α/RBV, and no treatment, respectively. Among previous partial responders and interferon-alfa–ineligible/intolerant patients, total per-patient QALYs of 13.35 and 13.43 were observed when treated with DCV + ASV, compared with 12.58, 11.23, and 10.82 among partial responders when using TVR + pegIFN-α/RBV, pegIFN-α/RBV, and no treatment regimens, respectively, and 10.82 among interferon-alfa–ineligible/intolerant patients who receive no treatment. Furthermore, treating patients with CC resulted in increased relative per-patient QALY gains when initiating therapy with DCV + ASV therapy, yielding increases of up to 1.11, 2.47, and 3.05 when compared with TVR + pegIFN-α/RBV, pegIFN-α/RBV, and no treatment, respectively.

Because of the higher efficacy seen with DCV + ASV, the lifetime risk of CC, DC, HCC, and liver-related mortality was greatly reduced in this treatment arm. Null responders incurred a reduced relative risk of 55.17% and 18.84% to 55.17% when treated with DCV + ASV from the CHC and CC disease stage, respectively, compared with TVR + pegIFN-α/RBV, while relative risk reductions of 63.41% and 17.01% to 63.41%, respectively, were observed in the partial responder cohort when compared with no treatment. The greatest reduction was observed among ineligible/intolerant patients. These relative risk reductions resulted in a significantly lower cost of end-stage liver disease complication management: up to ¥1,975,431 less in null responders and ¥1,613,146 less in partial responders compared with TVR + pegIFN-α/RBV and ¥5,273,817 less in interferon-alfa–ineligible/

Table 6 – Sensitivity analysis of patients with chronic HCV (N = 1,000).

Population	Results of global meta-analysis: Mean (SE)				Analysis					
	SVR_{24}	Rash incidence	Anemia incidence	Source	Per-patient QALYs	Additional per-patient cost of complication management compared with DCV + ASV	Total events			
							CC	DC	HCC	Liver mortality
DCV + ASV: Previous null responder	0.670 (0.120)	0.080 (0.066)	0.010 (0.013)	Broglio et al. [17,18]	12.82	NA	186	30	118	132
DCV + ASV: Previous partial responder	0.790 (0.092)	0.080 (0.066)	0.010 (0.013)	Broglio et al. [17,18]	13.17	NA	119	19	75	84
TVR + pegIFN-α/RBV: Previous null responder	0.390 (0.074)	0.350 (0.071)	0.310 (0.099)	Broglio et al. [17,18]	11.98	1,723,110	345	56	219	244
TVR + pegIFN-α/RBV: Previous partial responder	0.550 (0.066)	0.350 (0.071)	0.310 (0.099)	Broglio et al. [17,18]	12.46	1,481,587	254	41	161	180
PegIFN-α/RBV: Previous null responder	0.050 (0.013)	0.200 (0.054)	0.160 (0.066)	Broglio et al. [17,18]	10.96	3,779,734	537	87	341	380
PegIFN-α/RBV: Previous partial responder	0.090 (0.026)	0.200 (0.054)	0.160 (0.066)	Broglio et al. [17,18]	11.08	4,262,781	514	84	326	364

CC, compensated cirrhosis; DC, decompensated cirrhosis; DCV + ASV, daclatasvir + asunaprevir; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; NA, not applicable; pegIFN-α/RBV, pegylated interferon-alfa + ribavirin; SE, standard error; SVR, sustained virological response; TVR + pegIFN-α/RBV, telaprevir + pegylated interferon-alfa + ribavirin.

intolerant patients compared with no treatment. Figure. 2 presents a graphical interpretation of the cumulative incidence of end-stage liver events of the lifetime of a cohort of patients treated in the CHC stage of HCV and further demonstrates the significance of the observed event reductions associated with DCV + ASV.

Sensitivity Analysis

When using data from the global meta-analysis, similar results to the base-case analysis were observed (Table 6). DCV + ASV was still associated with fewer end-stage liver complications compared with all alternative therapies. The relative risk reductions of end-stage liver complications were 45.90% for null responders and 53.33% for partial responders treated in the CHC disease stage, when compared with treatment with TVR + pegIFN-α/RBV. Furthermore, treatment with DCV + ASV was associated with QALY gains of between 0.71 and 0.84 over treatment with TVR + pegIFN-α/RBV and gains of between 1.86 and 2.09 over pegIFN-α/RBV. Complication cost reductions of between ¥1,481,587 and ¥4,262,781 were observed when using DCV + ASV therapy. Overall, the sensitivity analysis reported results consistent with those of the base-case analysis.

Discussion

In modeling lifetime events associated with the use of different treatment strategies in hard-to-treat patients specific to the Japanese setting, results suggested that DCV + ASV is superior to TVR + pegIFN-α/RBV, pegIFN-α/RBV, and no treatment in terms of clinical outcomes, reductions in complication management costs, and total health benefit. This is reflected in increased QALY gains and reductions in end-stage liver disease complication incidence rates for DCV + ASV over treatment regimens reflective of the current standard of care. A conclusion of the global meta-analysis was that there is a 98.1% probability that DCV + ASV is superior to TVR + pegIFN-α/RBV among previously treated patients [17,18]; therefore, the validity of the results obtained within this analysis further support the previously demonstrated claims of clinical superiority. Furthermore, it is likely that the benefit of treatment with DCV + ASV has been underestimated because of conservative estimates of SVR used in this study. A recent phase 3 trial in Japanese patients reported SVR rates of 90.9% and 91.9% in cirrhotic and elderly patients (≥65 years), respectively [10].

There are difficulties in comparing outcome data across treatment regimens because of the lack of head-to-head trials performed in hepatitis C research. In the absence of direct comparisons, mixed-treatment and indirect comparative data can provide a useful perspective, but have inherent limitations. Because studies incorporated into the Japanese subgroup of the meta-analyses were limited and it was uncertain how well this would relate to real-world observations in clinical practice, comparisons of the outcomes observed in the broader, global meta-analysis were carried out. When using the global meta-analysis data, the sensitivity analysis produced similar results to those seen in the base case; similarly, when using individual trial data for DCV + ASV and TVR + pegIFN-α/RBV interferon-alfa–ineligible and intolerant patients, DCV + ASV was favorable in terms of complication event rates, QALYs, and complication cost outcomes.

SVR is a clinically meaningful end point in the treatment of HCV, and a high rate of SVR observed in clinical trials of DCV + ASV translates into a reduction in life-threatening complication rates compared with standard of care in difficult-to-treat patients. For patients treated in the CC stage, the observed incidence of HCC and resultantly liver mortality are elevated over those treated in CHC. This is due to these patients being in a more severe disease state on initiating treatment, and only these patients may still progress to HCC and liver mortality following SVR; those in CHC state do not. Lower estimates of transition to HCC in patients who have achieved SVR from the CC stage have been reported consistently [19–22]; however, in this analysis, a rate more reflective of real-world disease progression in Japan was adopted.

Tolerability, with regard to rates of rash and anemia, two significant adverse events observed with current treatment regimens, is greatly improved when using DCV + ASV. Tolerability has an inherent effect on uptake and adherence, as well as on the quality of life in those undergoing treatment. These factors have the potential to significantly affect economic analyses and, subsequently, influence public health decisions. Furthermore, higher rates of SVR within a population could have an effect on disease transmission, an important consideration in a country with one of the highest endemic rates of infection.

Treatment options available to Japanese patients are currently limited to interferon-alfa–based regimens. Where a patient is unable to receive or has previously not responded to interferon-alfa–based therapy, they do not currently have an alternative for treatment; in these patients, progression to life-threatening complications of HCV infection is likely. Conditional on the modeling assumptions applied, this study shows that the provision of an alternative, interferon-alfa–free regimen, such as DCV + ASV, could offer valuable benefit in terms of avoiding life-threatening liver complications and increasing patients' quality of life.

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