Clinical Study

Oncology

Oncology 2015;89(suppl 2):42–46
DOI: 10.1159/000440630

Published online: November 19, 2015

Comparison of Daclatasvir and Asunaprevir for Chronic HCV 1b Infection with Telaprevir and Simeprevir plus Peginterferon and Ribavirin, with a Focus on the Prevention of Occurrence and Recurrence of Hepatocellular Carcinoma

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Key Words

Prevention · Hepatocellular carcinoma · Occurrence · Recurrence · Daclatasvir · Asunaprevir · Direct-acting antivirals · Interferon-free treatment

Abstract

Objectives: The efficacy of the all-oral administration of daclatasvir and asunaprevir for 24 weeks was compared with that of telaprevir for 12 weeks plus pegylated interferon and ribavirin (PEG-IFN/RBV) for 24 weeks, and that of simeprevir for 12 weeks plus PEG-IFN/RBV for 24 weeks, with a focus on the prevention of occurrence and recurrence of hepatocellular carcinoma (HCC). The levels of alanine aminotransferase (ALT) and α-fetoprotein (AFP) as suppressive markers of HCC were also measured. ***Methods:*** Patients received daclatasvir and asunaprevir (n = 17), simeprevir plus PEG-IFN/RBV (n = 15) and telaprevir plus PEG-IFN/RBV (n = 25). Sustained virological response (SVR) and the mean change in the level of serum ALT, AFP and platelet (PLT) count were compared among the three groups. ***Results:*** No difference in SVR was observed in patients given daclatasvir with asunaprevir (SVR4), telaprevir plus PEG-IFN/RBV or simeprevir plus PEG-IFN/RBV (SVR24). Also, no significant difference was observed in the mean change of serum ALT, AFP or PLT count among the three groups. ***Conclusion:*** The preventive effect of the IFN-free, all-oral regimen of daclatasvir and asunaprevir was observed with a focus on the occurrence and recurrence of HCC, as was IFN-based treatment with telaprevir or simeprevir plus PEG-IFN/RBV.

Introduction

The treatment of chronic hepatitis C virus (HCV) infection typically includes a regimen of interferon (IFN) and ribavirin (RBV), with or without direct-acting antivirals [1].

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Combined with pegylated interferon (PEG-IFN) and RBV, HCV protease inhibitors telaprevir, boceprevir or simeprevir achieve overall sustained virological response (SVR) rates ranging from 68 to 89% in treatment-naive patients with HCV genotype 1 infection [2–4].

In the past 2 decades, IFN treatment including PEG-IFN has been used to treat chronic hepatitis C (CHC), with the goal of altering the natural history of the disease; also, eradication of HCV with IFN treatment of CHC has been shown to prevent hepatocellular carcinoma (HCC) [5–9].

After IFN treatment, alanine aminotransferase (ALT) and α-fetoprotein (AFP) levels are significantly associated with hepatocarcinogenesis, and measuring their levels is useful in predicting the future HCC risk [10–12].

IFN-free treatment of CHC, such as with direct-acting antivirals, has improved remarkably in recent years, especially the all-oral 24-week regimen of daclatasvir (NS5A replication complex inhibitor) plus asunaprevir (NS3 protease inhibitor) approved in Japan in July 2014, for the first time worldwide.

With the 24-week regimen of daclatasvir plus asunaprevir, SVR24 has been achieved in 87.4% of patients ineligible for or intolerant to IFN-based treatment, and in 80.5% of patients previously nonresponsive to treatment [1]. Nonetheless, the prevention of HCC occurrence and recurrence with daclatasvir plus asunaprevir, an IFN-free treatment, remains to be clarified. If HCC recurrence is reduced, repeated curative treatments such as resection [13, 14], ablation [15] or transplantation [16–18] can be applicable.

Here, we compared the all-oral 24-week regimen of daclatasvir plus asunaprevir with that of telaprevir or simeprevir plus PEG-IFN and RBV for 12 and 24 weeks, respectively, to assess their efficacy in the prevention of occurrence and recurrence of HCC, by measuring the levels of ALT and AFP as HCC markers.

Patients and Methods

Patients

A total of 57 patients seen at Kobe Asahi Hospital and diagnosed with chronic HCV and high viral loads of genotype 1b were enrolled in the study: 17 patients (3 men, 14 women, 67.9 ± 11.4 years old) received daclatasvir and asunaprevir (group DA); 25 patients (15 men, 10 women, 56.2 ± 10.2 years old) received telaprevir plus PEG-IFN and RBV (PEG-IFN/RBV; group TL), and 15 patients (6 men, 9 women, 62.4 ± 12.4 years old) received simeprevir plus PEG-IFN/RBV (group SM). Patients demonstrating hemoglobin levels ≥11 g/dl (women) or ≥12 g/dl (men), a platelet (PLT) count ≥9×10^4/mm^3, HCV RNA ≥5.0 log IU/ml, a neutrophil count ≥1,500/mm^3 and thyroid-stimulating hormone levels within normal limits were included in the study; those demonstrating HIV or hepatitis B coinfection, creatinine clearance <50 ml/min, liver disease other than CHC, evidence of advanced liver disease such as liver cirrhosis (Child-Pugh B and C), preexisting psychiatric conditions or a history of severe psychiatric disorder were excluded. Informed written consent was obtained from each patient, and the study protocol conformed to the ethical guidelines approved by the Ethics Committee of Kobe Asahi Hospital.

Study Design

Patients in group DA received 60 mg of daclatasvir once/day and asunaprevir 200 mg twice/day for 24 weeks; those in group TL received 750 mg of telaprevir every 8 h postprandial for 12 weeks plus PEG-IFN/RBV for 24 weeks, and those in group SM received 100 mg simeprevir once/day for 12 weeks plus PEG-IFN/RBV for 24 weeks. Groups TL and SM received 1.5 μg of PEG-IFNα-2b/kg/body weight (BW) and 180 μg of PEG-IFNα-2a per week, respectively, and RBV 600 mg per day (for BW ≤60 kg), 800 mg per day (for BW >60 to ≤80 kg) or 1,000 mg per day (for BW >80 kg).

Laboratory Tests

HCV RNA was extracted from 140 μl serum with the use of a commercially available kit (QIAmp viral RNA kit; Qiagen, Tokyo, Japan). Genetic polymorphism rs8099917 around the IL28B gene was determined by real-time polymerase chain reaction with the TaqMan assay [19]. The IL28B major allele was defined as homozygous (TT) for the major sequence and the IL28B minor allele as homozygous (GG) or heterozygous (TG) for the minor sequence.

Efficacy Assessment

The primary endpoint was SVR24 defined as an undetectable HCV RNA level 24 weeks after the end of treatment in groups TL and SM. In group DA, the primary endpoint was SVR4 defined as an undetectable HCV RNA level 4 weeks after the end of treatment due to the short follow-up period after the approval of medical insurance coverage in Japan. In a previous study, SVR4 has been observed at almost the same rate as that of SVR24 [1]. Consequently, SVR4 of group DA was compared with SVR24 of groups TL and SM, and the mean change in the level of ALT, AFP and PLT count was assessed in patients who achieved SVR. The mean change in ALT was defined as (ALT at achieved SVR – baseline ALT)/baseline ALT. The mean change in the level of serum AFP and PLT count was similarly defined.

Statistical Analysis

The rate of SVR4 in group DA was compared with that of SVR24 in groups TL and SM by Fisher's exact test or the χ^2 test. The baseline data, including ALT, AFP and PLT count, were compared with data at achieved SVR by the Mann-Whitney U test in each group. To compare the mean change in the level of serum ALT, AFP and PLT count among the three groups, the Kruskal-Wallis test was used after the Steel-Dwass pairwise multiple comparison test.

Variables with a p value <0.05 were considered statistically significant. All statistical analyses were carried out with the use of Excel Statistics 2011 by SSRI.

Table 1. Patient baseline characteristics

	Group DA	Group TL	Group SM
Age, years	67.9 (45–86)[a]	56.2 (42–80)	62.4 (37–77)
Men/women	3/14[a]	15/10	6/9
ALT, IU/l	42.2 (8–223)	45.6 (17–104)	57.9 (14–199)
AFP, ng/ml	19.0 (2.3–81.8)	9.3 (1.8–48.2)	11.8 (2.9–34)
PLT, $\times 10^4/mm^3$	10.5 (4.5–16.9)[b]	16.3 (7.8–27.4)	16.9 (8.1–26.9)
HCV RNA, KIU/ml	6.0 (5.1–7.0)[c]	6.5 (4.9–7.7)	6.2 (4.3–7.4)
IL28B			
Major	7	14	8
Minor	10	11	7
Previous treatment for HCC	1	13	5
Response to prior HCV treatment			
Nonresponse	11	5	5
Relapse	3	7	5
IFN intolerant	2	0	0
Cirrhosis	10	not applicable	not applicable
Treatment of HCC-experienced	8	not applicable	not applicable

Data are given as either number of patients or the mean with ranges in parentheses. [a] $p = 0.01$, statistically significant difference versus group TL; [b] $p = 0.003$, 0.008, statistically significant difference versus groups TL and SM; [c] $p = 0.01$, statistically significant difference versus group TL.

Results

Baseline Characteristics

The patients in group DA were older than those in the other groups (DA 67.9 years, TL 56.2 years and SM 62.4 years; DA vs. TL, $p = 0.01$; DA vs. SM, $p = 0.14$). In group DA, 70.6% (12/17) of the patients were aged ≥65 years, 58.8% (10/17) had liver cirrhosis, and 47.1% (8/17) had undergone curative treatment for HCC. No significant difference was observed in ALT and AFP, but a significant difference was observed in PLT count. The PLT count in group DA was lower than that in groups TL and SM (DA $10.5 \times 10^4/mm^3$, TL $16.3 \times 10^4/mm^3$ and SM $16.9 \times 10^4/mm^3$; DA vs. TL, $p = 0.003$; DA vs. SM, $p = 0.008$). Pretreatment of the HCV RNA level in group TL was significantly higher than that in group DA (DA 6.0 KIU/ml and TL 6.5 KIU/ml; $p = 0.01$; table 1).

Efficacy

SVR4 was achieved in 88% (15/17) of the patients in group DA, and SVR24 in 76% (19/25) and 73% (11/15) in groups TL and SM, respectively. No significant difference in SVR was observed among the three groups, and none of the patients discontinued treatment prematurely attributed to adverse events.

Serum values of ALT, AFP and PLT count were measured at baseline and at achieved SVR. The serum ALT value at achieved SVR (DA 9.7 IU/l, TL 14.5 IU/l and SM 26.7 IU/l) was significantly lower than that at baseline (DA 45.4 IU/l, TL 47.7 IU/l and SM 66.0 IU/l) in all groups ($p < 0.05$). The serum AFP value was significantly lower at achieved SVR (DA 9.0 ng/ml and SM 5.8 ng/ml) compared with the baseline level (DA 20.9 ng/ml and SM 10.4 ng/ml; $p < 0.05$). On the other hand, the serum PLT count

Table 2. Comparison between baseline data and data at achieved SVR

	At baseline	At achieved SVR	p
Treatment group DA			
ALT, IU/l	45.4	9.7	0.0007
AFP, ng/ml	20.9	9.0	0.0007
PLT, $\times 10^4/mm^3$	10.9	11.6	0.0609
Treatment group TL			
ALT, IU/l	47.7	14.5	0.0001
AFP, ng/ml	10.0	4.0	0.1380
PLT, $\times 10^4/mm^3$	17.1	18.6	0.0077
Treatment group SM			
ALT, IU/l	66.0	26.7	0.0033
AFP, ng/ml	10.4	5.8	0.0033
PLT, $\times 10^4/mm^3$	18.8	19.5	1.0000

Data shown are mean values.

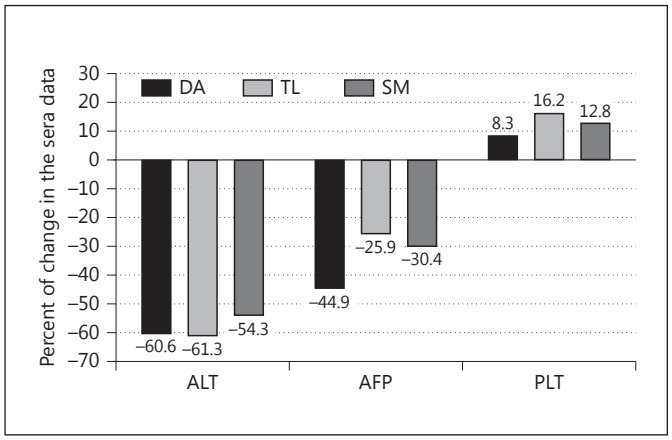

Fig. 1. Comparison of the mean change in ALT, AFP and PLT count at baseline and at achieved SVR among groups DA, TL and SM. The mean change in the ALT level was defined as (ALT at achieved SVR – baseline ALT)/baseline ALT. The mean change in the AFP level was defined as (AFP at achieved SVR – baseline AFP)/baseline AFP. The mean change in the PLT count level was defined as (PLT count at achieved SVR – baseline PLT count)/baseline PLT count. There was no significant difference in the mean change in the level of serum ALT, AFP and PLT count among the three groups.

at achieved SVR (TL 18.6 × 10^4/mm^3) was significantly higher than that at baseline (TL 17.1 × 10^4/mm^3; p = 0.0077; table 2).

In addition, the mean change in the level of serum ALT, AFP and PLT count was calculated as follows: values at achieved SVR – values at baseline/values at baseline, giving the following results for ALT: –60.6% in group DA, –61.3% in group TL and –54.3% in group SM; for AFP: –44.9% in group DA, –25.9% in group TL and –30.4% in group SM, and for PLT: 8.3% in group DA, 16.2% in group TL and 12.8% in group SM.

No significant difference was observed among the three groups (fig. 1).

Discussion

Approximately 2 million people in Japan – nearly 2% of the population – are chronically infected with HCV [20]. It is estimated that 15–30% of such patients will develop serious complications, including liver cirrhosis, end-stage liver disease and HCC [21]. Such patients in Japan differ from those in other countries in that they are predominately infected with genotype 1, are generally older, have more advanced liver disease and are more likely to have received previous treatment for HCV infection [22, 23]. These factors affect the response to treatment [24].

Prevention of HCC by eradication of HCV has a direct effect on the prognosis of these patients. Nonetheless, HCC sometimes develops even after eradication of the virus. According to multivariate analyses, old age, male gender, advanced fibrosis, severe steatosis, lower serum albumin levels, non-SVR and high ALT and AFP levels after IFN treatment have been identified as independent factors significantly associated with the development of HCC. Cutoff values of ALT and AFP for the prediction of HCC risk have been determined at 40 IU/l and 6.0 ng/ml, respectively, and negative predictive cutoff values as high as 0.960 for each value [10].

A decrease in these values after IFN treatment reduces the HCC risk even in patients without HCV eradication [10].

A population of elderly patients chronically infected with HCV and with more advanced liver disease, such as liver cirrhosis, is at an especially high risk of contracting HCC [25]. Also, patients who have undergone previous treatment for HCC are at a very high risk of disease recurrence [26].

Although IFN-based treatment such as telaprevir, boceprevir or simeprevir plus PEG-IFN and RBV is not indicated for patients with liver cirrhosis, IFN-free treatment such as daclatasvir plus asunaprevir is advocated.

The response rates with daclatasvir plus asunaprevir have been similar in patients with and without cirrhosis (90.9 and 84.0%, respectively) [1].

In our study, 70.6% of patients were aged ≥65 years, 58.8% had cirrhosis, and 47.1% had undergone previous curative treatment for HCC.

Irrespective of such a background, no difference in SVR was observed between treatment with daclatasvir plus asunaprevir (SVR4) and that with telaprevir or simeprevir plus PEG-IFN/RBV (SVR24).

Because of viral eradication, ALT and AFP levels decreased in all groups. Also, ALT levels in all groups met the cutoff value (40 IU/ml), according to the criteria of Asahina et al. [10] for ALT as a suppressive marker of HCC occurrence.

In our study, although the TL and SM groups met this cutoff level of AFP (6 ng/ml), the DA group did not.

In view of the relatively high AFP baseline level in the DA group (attributed to the enrollment of a relatively higher number of patients with liver cirrhosis and those who had undergone previous curative treatment for HCC) and the same mean change in the level of AFP as

that of the TL and SM groups, prevention of HCC in the DA group is thought to be identical to that in the TL and SM groups.

Taken together, the results suggest that the prevention of occurrence and recurrence of HCC observed in group DA, as well as in groups TL and SM, could be attributed to viral eradication.

Since PLT count is an essential factor in ablative treatment, such as radiofrequency ablation for HCC, elevation of the PLT count is crucial in patients with advanced stage of chronic HCV infection. In our study, based on the mean change among the three groups, elevation of the PLT count was observed in the treatment with daclatasvir plus asunaprevir and in the IFN-based treatment with telaprevir or simeprevir plus PEG-IFN/RBV attributed to viral eradication.

In the safety analyses, no serious adverse effects and no discontinuation of treatment were demonstrated in the DA group.

In conclusion, we believe it is now time for a shift in the paradigm of treatment for chronic HCV infection with IFN-free agents.

Acknowledgment

We thank Prof. Yasuhito Tanaka for the examination of the IL28B and Ms. Mika Matsui for the assistance in the preparation of the manuscript.

Disclosure Statement

The authors declare that they have no financial conflicts of interest.

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