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## Retrospective Study

**Efficacy and safety of dual therapy with daclatasvir and asunaprevir in elderly patients**

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**Author contributions:** Tarao K designed the research; Tanaka K, Nozaki A, Ishii T, Komatsu H, Ikeda T, Komatsu T and Matsushima S followed up the HCV patients in field practice; Oshige K analyzed the data; Tarao K wrote the paper; all the descriptions of the paper were distributed to all authors and confirmed.

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## Abstract

### AIM

To survey the efficacy and safety of dual therapy with daclatasvir and asunaprevir in the elderly hepatitis C virus (HCV) patients multicentricity.

### METHODS

Interferon-ineligible/intolerant patients and non-responders to previous pegylated-interferon/ribavirin therapy with chronic HCV genotype 1b infection were enrolled. Child B, C cirrhotic patients were excluded.

Patients received oral direct acting antiviral treatment consisting of 60 mg daclatasvir once daily plus 200 mg asunaprevir twice daily for 24 wk. We divided the patients into two groups of 56 elderly patients ( $\geq 75$  years-old) and 141 non-elderly patients ( $< 75$  years old) and compared the efficacy and safety.

### RESULTS

Ninety-one point one percent of elderly patients and 90.1% of non-elderly patients achieved sustained virological response at 24 wk (SVR<sub>24</sub>). In the former, 1.8% experienced viral breakthrough, as compared with 3.5% in the latter (not significant). Adverse events occurred in 55.4% of the former and 56.0% of the latter. In the former, 7 cases (12.5%) were discontinued due to adverse events, and in the latter 9 cases were discontinued (6.4%, not significant).

### CONCLUSION

Dual therapy with daclatasvir and asunaprevir achieved the same high rates of SVR<sub>24</sub> in HCV elderly patients without more adverse events than in the non-elderly patients.

**Key words:** Asunaprevir; Chronic hepatitis; Daclatasvir; Dual oral therapy; Elderly patients; Hepatitis C virus infection; Hepatitis C virus; Liver cirrhosis

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**Core tip:** Recently, it was demonstrated that dual oral therapy with daclatasvir and asunaprevir without pegylated-interferon/ribavirin was well tolerated and achieved high sustained virological response rates in Japanese patients with chronic hepatitis C virus genotype 1b infection, including patients with liver cirrhosis (Child A stage). However, the efficacy and side effects of these drugs was previously studied in non-elderly patients (less than 70 years of age). Those in elderly patients, who are supposed to have higher incidence of hepatocellular carcinoma, have not been studied. We demonstrated that efficacy and side effects in elderly patients were nearly the same as in non-elderly patients.

Tarao K, Tanaka K, Nozaki A, Sato A, Ishii T, Komatsu H, Ikeda T, Komatsu T, Matsushima S, Oshige K. Efficacy and safety of dual therapy with daclatasvir and asunaprevir in elderly patients. *World J Hepatol* 2017; 9(11): 544-550 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v9/i11/544.htm> DOI: <http://dx.doi.org/10.4254/wjh.v9.i11.544>

### INTRODUCTION

Recently, it was demonstrated that dual oral therapy with daclatasvir and asunaprevir without pegylated-interferon/ribavirin (PegIFN $\alpha$ /RBV) was well tolerated and achieved high sustained virological response (SVR)

rates in difficult-to-treat Japanese patients with chronic hepatitis C virus (HCV) genotype 1b infection, including patients with liver cirrhosis (Child A stage)<sup>[1-4]</sup>.

It is generally accepted that the average age of the patients with HCV-associated liver disease in Japan is increasing, and indeed patients more than 60 years of age represent more than 70% of all patients<sup>[5]</sup>. Moreover, Kumada *et al*<sup>[6]</sup> recently analyzed the age distribution of 3388 persistent HCV-infected patients and found that the median age was 70 years, and 2249 (66.4%) were elderly patients of more than 65 years.

Also, recently, Asahina *et al*<sup>[7]</sup> demonstrated that the risk for hepatocellular carcinoma (HCC) after interferon treatment was age-dependent and increased predominantly when the age at primary liver biopsy was  $> 65$  years. They also demonstrated that progression of fibrosis over time was significantly accelerated in older patients. In addition, elderly patients with HCV-associated chronic hepatitis are thought to develop liver cirrhosis more rapidly, and HCC might develop more frequently as a result. An increase in the aged population is an impending problem, and we must eradicate the HCV infection as soon as possible in elderly patients.

We therefore retrospectively examined the efficacy and safety of dual therapy with the nonstructural protein 5A inhibitor, daclatasvir, and the nonstructural protein 3 protein inhibitor, asunaprevir, in elderly patients ( $\geq 75$  years of age) with hepatitis C chronic hepatitis or liver cirrhosis (Child A stage), who may have suffered from longer periods of HCV infection, in many large hospitals in Kanagawa Prefecture in Japan.

### MATERIALS AND METHODS

#### Study design

This study included two populations of patients with HCV genotype 1b infection: Null responders ( $< 2 \log_{10}$  decline in serum HCV RNA levels after 12 wk of prior PegIFN $\alpha$ /RBV), and PegIFN $\alpha$ /RBV ineligible/intolerant patients. The latter group was either patients who discontinued prior therapy with PegIFN $\alpha$ /RBV due to intolerance after  $< 12$  wk, or patients who were treatment-naïve but poor candidates for PegIFN $\alpha$ /RBV for medical reasons such as advanced age or complications of depression, anemia, myelosuppression, diabetes or cardiovascular or renal dysfunction. Of the cirrhotic patients, only those with Child-Pugh stage A were enrolled<sup>[8]</sup>, and patients with Child-Pugh stages B and C were omitted.

The patients were out-patients and visited the following hospitals in Kanagawa Prefecture of Japan between 1 September 2014 and 30 March 2015: Tarao's Gastroenterological Clinic, Yokohama City University Medical Center, Yokohama Seibu Hospital of St. Marianna University, Yokohama Municipal Citizens Hospital, Yokosuka General Hospital Uwamachi, and National Hospital Organization Yokohama Medical Center.

Elderly patients were defined as those equal to or over 75 years old. Enrolled patients were divided into

**Table 1** Background of elderly ( $\geq 75$  years old) and non-elderly ( $< 75$  years old) patients

Parameter	Elderly patients, <i>n</i> = 56	Non-elderly patients, <i>n</i> = 141	<i>P</i>
Cirrhosis/chronic hepatitis	30/26	44/97	0.003
Age in years	77.8 (75-83)	65.3 (34-74)	
Male/female	23/33 (41.1%/58.9%)	54/87 (38.3%/61.7%)	
HCV genotype 1b, %	100	100	
HCV RNA, mean log <sub>10</sub> IU/mL	5.85 ± 0.77	6.12 ± 0.70	
Pegylated-interferon/ribavirin non-responder, %	17.9	25.5	0.251

HCV: Hepatitis C virus.

two groups, elderly patients ( $\geq 75$  years old) and non-elderly patients ( $< 75$  years old), and efficacy and safety assessments were compared. The primary efficacy end-point was the proportion of patients with undetectable HCV RNA at 24 wk post-treatment (SVR<sub>24</sub>).

Written informed consent was obtained from all patients. The study was approved by institutional review boards in each hospital and conducted in compliance with the Declaration of Helsinki.

### Patients

Eligible patients were men and women, aged 34-83 years, with HCV genotype 1 infection with chronic hepatitis or compensated liver cirrhosis. Patients with cirrhosis were confined to Child-Pugh stage A<sup>[8]</sup>, and patients with stage B and C cirrhosis were excluded. Exclusionary laboratory findings included alanine aminotransferase (ALT)  $> 5 \times$  upper limit of normal (ULN), total bilirubin  $> 2$  mg/dL, albumin  $< 3.5$  g/dL, hemoglobin  $< 9.0$  g/dL, white blood cells  $< 1500$  mm<sup>3</sup>, platelets  $< 50000$ /mm<sup>3</sup>, and creatinine  $> 1.8 \times$  ULN. No patients had prior exposure to HCV direct-acting antivirals.

### Analysis of resistant-associated variants

At pre-treatment points and the resistant-associated variants (RAVs) in NS5A (Y93H) were investigated by PCR-invader assay. PCR-invader assays were conducted by BML Inc. (Saitama, Japan), and weakly positive and negative samples were defined as substitution-negative. In 132 out of 197 cases, the RAVs was examined and the results were as follows: Y93H  $\leq 1\%$  in 116 cases (87.9%), 2%-5% in 14 cases (10.6%), 23% in 1 case (7.6%), 64% in 1 case (7.6%).

### Study drug dosing

Patients received 24 wk of treatment with 60 mg daclatasvir once daily combined with 200 mg asunaprevir twice daily, and participated in 24 wk of post-treatment follow-up. HCV RNA, physical examinations, adverse events, laboratory parameters and concomitant medications were assessed at day 1 (baseline), treatment weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24, and post-treatment weeks 4, 8, 12 and 24.

### Statistical analysis

Pearson's  $\chi^2$  test and the Student's *t*-test were used for statistical analyses. Statistical significance was considered

to exist at  $P < 0.05$ .

## RESULTS

A total of 197 patients were enrolled in this retrospective study, and included 56 elderly patients and 141 non-elderly patients. Backgrounds of the patients are shown in Table 1. In the elderly patients, the number of cirrhotic patients (53.6%) was significantly larger, as compared with 31.2% in the non-elderly patients ( $P = 0.003$ ). The average age was 77.8 years in the elderly patients and 65.3 years in the non-elderly patients. The male/female ratio was nearly the same in the two groups ( $P = 0.719$ ). HCV genotype was 1b in all patients. HCV RNA (mean log<sub>10</sub> IU/mL) was 5.85 ± 0.77 in the former and 6.12 ± 0.70 in the latter ( $P = 0.016$ ). Percentages of the non-responder patients in the prior PegIFN $\alpha$ /RBV therapy group were 17.9% in the former and 25.5% in the latter ( $P = 0.251$ ).

### Virologic outcomes

Of the elderly patients, 51 (91.1%) achieved SVR<sub>24</sub>, while in the non-elderly patients, 127 (90.1%) achieved SVR<sub>24</sub>. The ratio of patients achieving SVR<sub>24</sub> was nearly the same in the two groups (Table 2). The ratio of patients who achieved SVR<sub>24</sub> in the group that discontinued due to side effects was 71.4% (5/7) for the elderly and 77.8% (7/9) for the non-elderly patients (Table 2).

### Viral breakthrough

Only one patient out of 56 (1.8%) experienced viral breakthrough in the elderly group, as compared with 5 out of 141 (3.5%) in the non-elderly group (not significant,  $P = 0.519$ ). Post-treatment relapse was seen in 2 (3.6%) of the elderly patients, as compared with 7 (5.0%) of the non-elderly patients (not significant,  $P = 0.675$ ) (Table 2).

### Safety

Adverse events and laboratory abnormalities in each group are shown in Table 3. There were no significant differences in each event between elderly and non-elderly groups. The total number of patients who showed adverse events in the elderly group was 31 out of 56 (55.4%), which was nearly the same in the non-elderly group (79 out of 141, 56.0%) (Table 4).

Table 5 shows the causes of discontinuation and

**Table 2** Virologic outcomes

Parameter	Elderly patients, <i>n</i> = 56	Non-elderly patients, <i>n</i> = 141	<i>P</i>
SVR <sub>24</sub>	51 (91.1)	127 (90.1)	
Viral breakthrough	1 (1.8)	5 (3.5)	0.519
Post-treatment relapse	2 (3.6)	7 (5.0)	0.675
Ratio of patients who achieved SVR <sub>24</sub> in the discontinued cases due to side effects	5/7 (71.4)	7/9 (77.8)	

Data are presented as *n* (%). SVR<sub>24</sub>: Sustained virological response at 24-wk.

**Table 3** Adverse events and laboratory abnormalities

Event	Elderly patients, <i>n</i> = 56	Non-elderly patients, <i>n</i> = 141
Nasopharyngitis	5 (8.9)	6 (4.3)
Headache	4 (7.1)	9 (6.4)
Diarrhea	3 (5.4)	5 (3.5)
Pyrexia	2 (3.6)	12 (8.5)
Malaise	7 (12.5)	8 (5.7)
Anorexia	6 (10.7)	8 (5.7)
AST elevation	15 (26.8)	55 (39.0)
ALT elevation	14 (25.0)	54 (38.3)
Hb decrease	8 (14.3)	11 (7.8)
Total bilirubin increase	2 (3.6)	11 (7.8)
Creatinine increase	8 (14.3)	13 (9.2)

Data are presented as *n* (%). ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; Hb: Hemoglobin.

**Table 4** Total number of adverse events in the elderly and non-elderly patients

	Elderly patients	Non-elderly patients
No. of total patients enrolled	56	141
No. of patients who experienced adverse events	31	79
Percentage of patients who experienced adverse events	55.4	56.0

the numbers of patients in whom the drugs were discontinued due to adverse effects in each group. The levels of elevation of ALT and total bilirubin at which the drug was discontinued were 200 INU (5-folds of normal) for ALT and 3.0 mg/dL for total bilirubin. In the elderly group, 7 out of 56 cases (12.5%) were discontinued, and in the non-elderly group, 9 out of 141 (6.4%). The ratio of discontinuation was greater for the elderly patients but the difference was not significant ( $P = 0.336$ ). The ratio of patients who achieved SVR<sub>24</sub> in the discontinued due to side effects subgroup was 71.4% (5/7) in the elderly and 77.8% (7/9) in the non-elderly patients (Table 2).

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Informed consent was obtained from all patients for being included in the study. The protocol was approved by the ethics committees/institutional review boards

**Table 5** Causes of discontinuation and numbers of patients in whom the study drugs were discontinued due to adverse events in the elderly and non-elderly groups

Elderly patients	Non-elderly patients
16 w Malaise, Anorexia <sup>1</sup>	18 w Elevation of ALT <sup>1</sup>
6 w Malaise, Anorexia <sup>1</sup>	6 w Elevation of ALT <sup>1</sup>
6 w Elevation of ALT <sup>1</sup>	2 w Pyrexia <sup>1</sup>
8 w Elevation of ALT <sup>1</sup>	3 w Pyrexia
3 w Pyrexia	13 w Sepsis due to hemolytic streptococcus <sup>1</sup>
4 w Cough	18 w Abdominal fullness <sup>1</sup>
18 w Development of HCC <sup>1</sup>	2 w Elongation of PT
	3 w Elevation of total bilirubin <sup>1</sup>
	18 w Development of HCC <sup>1</sup>
Total 7/56 (12.5%)	9/141 (6.4%)

<sup>1</sup>Patients achieved sustained virological response at 24-wk. Level of elevation of ALT and total bilirubin at which the drug was discontinued: 200 INU (5-folds of normal) for ALT and 3.0 mg/dL for total bilirubin. HCC: Hepatocellular carcinoma; ALT: Alanine aminotransferase.

of participating centers and conformed to Good Clinical Practice guidelines and Declaration of Helsinki principles. This article does not contain any studies with animal subjects.

## DISCUSSION

In recent years, patients presenting with HCV-associated chronic hepatitis or liver cirrhosis have been older, especially those patients with liver cirrhosis<sup>[5-7]</sup>. Among these patients, the occurrence of HCC is also increasing. It is generally well accepted that aging is a potent risk factor for HCC development in patients with HCV-associated liver disease<sup>[7-11]</sup>. Peg-IFN $\alpha$ /RBV therapy was shown to be effective in preventing the development of HCC in younger patients<sup>[12]</sup>; however, older patients are poor candidates for Peg-IFN $\alpha$ /RBV therapy.

More recently, oral dual therapy with daclatasvir/asunaprevir was demonstrated to be very effective in eradicating HCV infection. Overall, 76.7% of patients achieved SVR<sub>12</sub> and SVR<sub>24</sub> in an initial trial<sup>[2]</sup>.

In this study, we demonstrated that the proportion of patients with SVR at 24 wk post-treatment was almost the same among elderly patients ( $\geq 75$  years old), who were thought to have longer durations of HCV infection, as among younger patients ( $< 75$  years old, 91.1% vs 90.1%).

We also demonstrated that the degree of side effects

was nearly the same in the elderly and younger patients. Hitherto, no report has dealt with age differences in the efficacy and side effects of oral dual administration of daclatasvir/asunaprevir. The question remains: Is there any essential benefit in eradicating HCV in elderly patients ( $\geq 75$  years old) with HCV-associated liver disease by administering daclatasvir/asunaprevir?

There is much evidence that the eradication of HCV virus (*i.e.*, SVR) by IFN or Peg-IFN $\alpha$ /RBV treatment brings about a low incidence of HCC development<sup>[12-18]</sup>. Yet, there is no definite evidence that the eradication of HCV virus by dual therapy with daclatasvir/asunaprevir can bring about a low incidence of HCC in SVR patients. There is some potential, however, for these drugs to lower the risk of HCC development. First, there is some evidence of lowering serum alpha-fetoprotein (AFP) levels after eradicating HCV virus by the dual therapy, which is one of the potential risk factors for HCC development in HCV-associated liver diseases<sup>[19-24]</sup>. Oka *et al.*<sup>[25,26]</sup> actually demonstrated that the serum AFP level was a potential risk factor for HCC development in cirrhotic patients.

Karino *et al.*<sup>[20]</sup> compared the changes of serum AFP levels after treatment by Peg-IFN $\alpha$ /RBV and by daclatasvir/asunaprevir treatment; they were 13.7→4.9 ng/mL on average for Peg-IFN $\alpha$ /RBV and 15.2→4.8 ng/mL for daclatasvir/asunaprevir. Moreover, the proportions of patients who showed below 5 ng/mL after SVR were 56% in Peg-IFN $\alpha$ /RBV and 65% in daclatasvir/asunaprevir treatment, suggesting nearly the same effect on AFP levels with both treatments. More recently, Miyaki *et al.*<sup>[24]</sup> examined the changes in AFP levels before and after the dual therapy (median 27 mo after the completion of the therapy), and found a significant decrease in SVR patients (AFP levels decreased to within the normal limit in all patients by 18 mo after treatment).

Second is the potential of dual therapy with daclatasvir/asunaprevir to reduce liver fibrosis. Miyaki *et al.*<sup>[24]</sup> also observed the changes of liver fibrosis markers before and after the administration of the drugs and found a significant increase in platelet counts and a significant decrease in liver fibrosis markers such as hyaluronic acid, type IV collagen and M2BPGi (a liver fibrosis glycomarker) at 27 mo (median) after completion of the treatment. van der Meer *et al.*<sup>[27]</sup> also demonstrated a significant increase in the platelet counts associated with a decrease in spleen volume after the completion of IFN therapy.

There is some evidence that eradication of HCV-virus by IFN might bring about a decrease in the fibrosis staging score of HCV-associated chronic hepatitis. Shiratori *et al.*<sup>[28]</sup> demonstrated that the fibrosis score after IFN therapy had regressed in patients with a sustained response at a rate of -0.28 U/year in the histological examination of the biopsied specimens, suggesting that the staging of fibrosis might be reduced by one step in every 4 years by IFN in SVR patients. And, it is well known that the staging of fibrosis has a close association with the incidence of HCC development<sup>[29]</sup>. Omata<sup>[29]</sup> surveyed

the relationship between the degree of fibrosis and the incidence of HCC in HCV-associated chronic hepatitis and found that the incidence of HCC was 0.46%/year in patients with slight fibrosis (F1 stage), while in patients with moderate fibrosis (F3 stage) it was 3%/year, and in patients with severe fibrosis (F4 stage) it was 7%/year.

In support of this concept, van der Meer *et al.*<sup>[27]</sup> demonstrated an increase in platelet counts associated with a decrease in spleen volume in the IFN-treated SVR patients among HCV-associated patients with Ishak 4-6 fibrosis, and concluded that the portal hypertension was decreased in those patients.

Considering the above evidence, it is possible that the eradication of HCV virus by dual therapy with daclatasvir/asunaprevir might bring about reduction in fibrosis and a lower incidence of HCC development even in patients over 75 years old, who have an impending risk of HCC development.

However, long-term observations of SVR patients after therapy with daclatasvir/asunaprevir will be necessary to make any final conclusions about the effect on prevention of HCC development.

## COMMENTS

### Background

Recently, direct acting antivirals (DAAs), including dual therapy with daclatasvir/asunaprevir, have been widely used in the therapy of chronic hepatitis C virus (HCV) genotype 1b infection. Dual therapy with daclatasvir/asunaprevir was demonstrated to be highly effective without serious side-effects. However, those results were studied in the non-elderly (patients under 70 years old). The effectiveness and safety in the elderly patients (> 70 years old) should be studied.

### Research frontiers

Although, DAAs were widely used in the treatment of HCV-associated liver diseases, few prior reports surveyed the difference in the efficacy and side effects of dual oral therapy with daclatasvir/asunaprevir between elderly patients and non-elderly patients.

### Innovations and breakthroughs

In this study, the effectiveness and safety of the therapy with daclatasvir/asunaprevir were demonstrated in elderly patients as well as in non-elderly patients.

### Applications

In Japanese, recently the aged population is increasing rapidly among cases of HCV-associated liver disease, and these individuals are at high risk for developing hepatocellular carcinoma. Eradicating HCV in this population is important and many approaches have been proposed. Now, the authors can eradicate HCV by oral therapy with daclatasvir/asunaprevir effectively and safely.

### Peer-review

The manuscript is an interesting one, discussing a very important issue as regarding new DAAs with HCV treatment.

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