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Hepatitis C Treatment in Elderly Patients

Takashi Honda, Masatoshi Ishigami,
Kazuhiko Hayashi, Teiji Kuzuya, Yoji Ishizu,
Yoshiki Hirooka and Hidemi Goto

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Abstract

The patients with chronic hepatitis C (CHC) are getting older and the demands for treatment to those patients are increasing due to the high risk of development of hepatocellular carcinoma. Elderly patients were previously defined as 60 years and over, however definition of the elderly patients shifted to be older year to year. Interferon (IFN) and ribavirin combination therapy was significantly improved efficacy of treatment, however ribavirin induces anemia, resulted in lower efficacy due to reduction of ribavirin for the elderly patients. And efficacy of over 60 years old was comparable to the patients under 60 years. In the CHC patients with genotype 1, the efficacy of elderly patient was significantly lower than that of younger patients, especially in female. Direct-acting antivirals (DAAs) therapy makes treatment efficacy improved to over 90% and side effect of treatment was dramatically reduced compared to IFN-based therapy. The efficacy of dual oral therapy by using asunaprevir (ASV) and daclatasvir (DCA) for elderly patients with hepatitis C virus (HCV) genotype 1b has not been fully clarified. In this article we would like to show the efficacy of elderly patients with CHC, especially patients infected with genotype 1b, from the era of IFN monotherapy to the era of new DAAs.

Keywords: hepatitis C virus, peginterferon, ribavirin, direct-acting antivirals, elderly patient

1. Introduction

The first in the world, the demand for treatment to the elderly patients with chronic hepatitis C (CHC) has increased in Japan. The prevalence of anti-hepatitis C virus (HCV) shows the peak is in the older generation and the rate of anti-HCV increases with the increase in age in Japan. In other country, the peak of prevalence differs from country to country. These differences

Figure 1. Patient age distribution by decade.

come from one of the reasons when the war was held in each country. During the war, HCV infection spread among drug users, blood donors and the wounded. Thereafter medical treatment with intravenous injection using contaminated needles and syringes during that time easily transmitted HCV. Therefore in Japan the peak of prevalence of anti-HCV was shifted to the older comparing to other country [1]. Previously, we compared SVR rate of ribavirin plus interferon (IFN)- α 2b in CHC patients aged ≥ 60 years with patients aged < 60 years [2]. Our study showed age distribution of the CHC patients treated by IFN- α plus ribavirin was peaked around 50 generation in 2002 (**Figure 1**). At that time we defined over 60 years as elderly patients.

2. Ribavirin and IFN-based treatment

The sustained virological response (SVR) rates of treatment in the patients with genotype 1 and a high viral load aged 60 years and older was below 10% by IFN monotherapy. However, SVR rate of IFN and ribavirin combination therapy was significantly improved by over 20%. And efficacy of over 60 years old was comparable to the patients under 60 years (**Figure 2**) [2]. In this study adding of ribavirin increased SVR rate, but ribavirin induces anemia, resulted in lower SVR rate due to reduction of ribavirin in the elderly patients. During combination of IFN- α 2b plus ribavirin therapy, over 50 generation and 60 generation had high dose reduction and cessation of treatment (**Figure 3**) [2].

Figure 2. Virologic response to combination therapy and interferon monotherapy. * Indicate significant differences vs the respective IFN monotherapy (* $P < 0.05$).

Figure 3. Ribavirin dose reduction and discontinuation rates according to age of patients.

3. Ribavirin and PegIFN-based treatment

Peginterferon (PegIFN) plus ribavirin therapy improved the SVR rate of HCV treatment. We conducted the study of efficacy of PegIFN- α 2b plus ribavirin and the number of the CHC patients in that study was 591. The distribution of elderly patients was around 20% in 2007. At that time elderly patients were defined as aged 65 years or older [3]. In the CHC patients with genotype 1, the SVR rate of elderly patient was significantly lower than that of younger patients, especially in female (Figure 4) [3]. On the other hand, patients with genotype 2 had comparable SVR rate of elderly patients to the younger patients (Figure 5) [3].

Figure 4. A virological response to combination therapy according to the age and gender of patients with genotype 1.

Figure 5. A virological response to combination therapy according to the age and gender of patients with genotype 2.

4. DAA-based treatment

Emergence of direct-acting antiviral's (DAA's) therapy makes SVR rate improved to over 90% and side effect of treatment was dramatically reduced compared to IFN-based therapy. Ribavirin free regimen also has benefit for the elderly patients due to avoidance of ribavirin-induced anemia. Akuta et al. reported that high SVR rate was achieved by daclatasvir (NS5A replication complex inhibitor) (DCA) and asunaprevir (NS3 protease inhibitor) (ASV) even in the elderly patients infected with HCV genotype 1b aged 70 and older [4]. They showed predictive factors associated with SVR12 in elderly patients was NS5A-Y93H mutation under 20%, non-treated by triple therapy with simeprevir, lower level of viremia under 6 logIU/mL, hemoglobin under 13.0 g/dL.

We also conducted the study of efficacy of DAA's therapy for the genotype 1-infected patients with CHC. Here we show the results of the patients with DCA and ASV therapy, 287 patients were analyzed and the patient's background shows that patients were getting older and we defined elderly patients as aged 70 older. The study protocol was approved by the ethics committee of our hospital and affiliated hospital. The inclusion criteria included positive anti-HCV and positive HCV RNA and having findings of active hepatitis. Exclusion criteria included positive for serum hepatitis B surface antigen, alcohol abuse, autoimmune hepatitis, primary biliary cirrhosis, coexisting serious psychiatric or medical illness.

Elderly patients account for 57.8% (166/287) of total treated patients (**Table 1**). Baseline ALT, γ -glutamyl transpeptidase (GGT) hemoglobin and eGFR in elderly patients were significantly lower than that of younger patients. Renal function in elderly patients was worse comparing

	Total patients (n = 287)	Patients aged <70 years (n = 121)	Patients aged ≥70 years (n = 166)	P value
Sex ratio (male/female)	123/164	55/66	68/98	0.448
Age (years)	72.0 (65.0–77.0)	63.0 (58.0–66.0)	76.0 (73.0–79.0)	<0.001
AST (IU/L)	46.0 (35.0–68.0)	48.0 (35.0–75.0)	44.0 (34.0–60.3)	0.124
ALT (IU/L)	39.0 (27.0–63.0)	48.0 (30.5–74.0)	37.0 (23.8–52.3)	<0.001
GGT (IU/L)	32.0 (22.0–53.0)	35.0 (22.0–69.0)	29.5 (21.0–46.0)	0.021
Hemoglobin (g/dL)	13.2 (12.0–14.2)	13.5 (12.3–14.4)	13.0 (11.8–14.0)	0.010
Platelets ($\times 10^4/\mu\text{L}$)	12.8 (8.8–17.1)	13.6 (9.2–18.1)	12.4 (8.5–16.8)	0.302
eGFR	71.7 (60.2–84.5)	80.6 (67.8–91.3)	68.2 (56.6–77.0)	<0.001
HCV RNA (KIU/mL)	6.1 (5.6–6.5)	6.1 (5.7–6.5)	6.1 (5.6–6.5)	0.556
Previous therapy (naive/ ineligible/intolerant/NVR/ relapse)	146/5/26/75/25	54/3/14/31/14	92/2/12/44/11	0.276
NS5A Y93H, n (%)	9 (3.1)	6 (5.0)	3 (1.8)	0.122
NS5A L31M, n (%)	4 (1.4)	3 (2.5)	1 (0.6)	0.230

ALT, alanine aminotransferase; GGT, γ -glutamyl transpeptidase; eGFR, estimated glomerular filtration rate; HCV RNA, hepatitis C virus RNA; KIU, kilo international units; NVR, null virological response.

Table 1. Baseline clinical characteristics of patients treated with DAA's therapy.

to the younger patients as expected. There was no patient with dose reduction due to renal insufficiency. The results of DAA's therapy showed that the SVR24 rate in elderly patients was high even in younger patients (92.2 vs. 85.1%). The factors associated with an SVR24 in DAA's therapy were determined by multivariate analysis. Gender [P = 0.014, odds ratio 0.301 (0.115–0.785)], GGT [P = 0.032, odds ratio 0.992 (0.985–0.999)] and absence of NS5A Y93H [P < 0.001, odds ratio 16.50 (3.801–71.66)] were significantly associated with an SVR24 while patient age did not affect SVR24. In elderly patients, the factors associated with an SVR24 in DAA's therapy were determined by multivariate analysis. Gender [P = 0.025, odds ratio 0.071(0.007–0.716)], GGT [P = 0.006, odds ratio 0.982 (0.970–0.995)] and absence of NS5A Y93H [P = 0.018, odds ratio 58.47 (2.024–1689.3)] were significantly associated with an SVR24.

5. Prevention of HCC

Aging is one of the factors associated with development of HCC in the CHC patients [5]. IFN therapy was reported to have reduction in development of HCC among virological or biochemical responders [6, 7]. We previously researched how benefit of reduction of HCC after eradication of HCV by PegIFN plus ribavirin. As shown in the **Figure 6** cumulative incidence of HCC in the elderly patients was higher than that in the younger patients [8]. However, if the elderly patients achieved a SVR, patients have marked reduction of cumulative incidence of HCC [8]. From the multivariate analysis in all patients age, advanced fibrosis, treatment efficacy and gender was associated with development of HCC. In elderly patients, GGT and treatment efficacy were factors associated with development of HCC. Receiver operating characteristic

Figure 6. Cumulative incidence of HCC after peginterferon alfa-2b and ribavirin in patients who achieved SVR (solid line) or did not achieve SVR(dashed line) in younger patients < 65 years old (A) and older patients ≥ 65years old (B).

Figure 7. Cumulative incidence of HCC after peginterferon alfa-2b and ribavirin in older patients who achieved SVR (solid line) or did not achieve SVR(dashed line), among those with GGT < 44 IU/L (A) and GGT $\geq$ 44 IU/L (B). HCC, hepatocellular carcinoma; GGT, gamma-glutamyltranspeptidase; SVR,sustained virological response.

(ROC) curve indicated the cut off vale was 44 IU/L to predict for HCC. Among elderly patients with GGT < 44 IU/L, the cumulative incidence of HCC in patients with non-SVR was higher than patients with SVR, but this difference was not significant (**Figure 7A**). However, in elderly patients with SVR and GGT $\geq$ 44 IU/L, there was a marked reduction in the development of HCC compared with the elderly patients with SVR and GGT $\geq$ 44 IU/L (elderly patients with GGT < 44 IU/L, $P = 0.265$; elderly patients with GGT $\geq$ 44 IU/L, $P = 0.020$, log-rank test) (**Figure 7B**).

6. Discussion

Elderly patients with CHC are getting older and definition of elderly patients shifted from 60 to 70 years in our study during 13 years. In these days, the change of physical function according to age is seen 10 years older than that was seen in 10–20 years ago. Therefore, The Japan Geriatrics Society proposed elderly patients are defines as 75 years and over due to these rejuvenation phenomenon and the extension of the average life expectancy in 2017. If this phenomenon would be seen in all over the world, it will be globally accepted in the future.

DCV/ASV therapy for Japanese elderly patients with CHC had high SVR rate and is comparable to younger patients [4]. Our result indicated there is a possible to be higher SVR rate in elderly patients treated by DCV/ASV therapy than that in younger patients. For another type of DAA's therapy Ledipasvir/Sofosbuvir (LDV/SOF) therapy for the older CHC patients with genotype 1 from the Phase III had high SVR rate as well as younger patients [9]. They

defined patients aged 65 years or older as elderly patients and those are still small population of CHC patients in the United States (12%). In other study CHC patients aged ≥ 65 years who were treated with different combinations of DAAs had high efficacy and took significantly more concomitant medications [10]. Therefore, they indicated assessment of concomitant medications and drug-drug interactions would be needed before DAAs therapy especially for the elderly patients. As well as PegIFN plus ribavirin therapy, DAA's therapy including ribavirin regimen needs close monitoring of anemia in the elderly patients. Elderly patients with GGT > 44 IU/L and advanced fibrosis have high risk of development of HCC when we treated older CHC patients by PegIFN plus ribavirin. These patients would be high priority to be treated with DAA, because patients who achieved SVR had a marked reduction in the development of HCC compared with elderly patients who did not achieve SVR. Compared to the RBV and IFN or PegIFN-based treatment, DAA-based treatment improved efficacy of treatment even in non-elderly patients. Therefore, indication for the elderly patients will expand. However, due to the high costs of current DAA's therapy at the moment, it is better to evaluate life expectancy. Higher age, HCV-related liver disease (advanced fibrosis, HCC) and other concomitant disease affect life expectancy. Elderly patients took many other medications, therefore evaluation of drug-drug interaction between DAA and other medication is necessary. If HCV-related liver diseases are likely to affect survival and quality of life (QOL) and there are no economic restrictions in country where patients will be treated, the patients are better to be treated. If HCV-related liver diseases are not likely to affect survival and QOL or there are economic restrictions in that country, the patients should be closely monitored and be regularly reevaluated. Therefore, physician needs more knowledge of interaction of other diseases and to have a long-term of view on the CHC patients.

Author details

Takashi Honda, Masatoshi Ishigami*, Kazuhiko Hayashi, Teiji Kuzuya, Yoji Ishizu, Yoshiki Hirooka and Hidemi Goto

*Address all correspondence to: masaishi@med.nagoya-u.ac.jp

Department of Gastroenterology and Hepatology, Nagoya University Graduate School of Medicine, Nagoya, Japan

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