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MINIREVIEWS

Role of *IL28B* genotype in older hepatitis C virus-infected patients

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Abstract

The average age of hepatitis C virus (HCV)-infected individuals is becoming increasingly higher in Japan and steps should be taken to treat older individuals infected with HCV. Until an interferon-free regimen becomes available, peginterferon plus ribavirin will play a critical role in the treatment. The perception that older HCV-infected patients may be at higher risk than younger patients for adverse events from peginterferon plus ribavirin treatment but may obtain less clinical benefit from it may be based on the underrepresentation of older patients in clinical trials. A recent genome-wide association study revealed that interleukin-28B (*IL28B*) genotype closely correlates with the treatment response against HCV. The relationship of IL28B genotype with the treatment response in older HCV-infected patients is also unknown. In this review, we focused on the treatment response in older patients infected with HCV and the effects of IL28B genotype. *IL28B* major genotype is a useful predictor of sustained virological response in the interferon-including treatment of older patients infected with HCV. It also seems useful for avoiding adverse events, although the mechanisms of the effects of IL28B genotype on the treatment outcome are still poorly understood and are currently under investigation. Further studies will be needed.

Key words: Hepatitis C virus; Interferon lambda 3; Interleukin-28B; Older patients; Telaprevir

Core tip: The exact mechanisms of the effects of interleukin-28B (*IL28B*) genotype on the treatment response in chronic hepatitis C patients are unclear. However, IL28B genotype is useful for the continued successful treatment of older patients infected with hepatitis C virus (HCV) and avoiding adverse events. Until the eventual availability of interferon-free regimens, it is important to determine *IL28B* genotype before treating HCV-infected individuals, especially in the screening of older patients.

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INTRODUCTION

Hepatitis C virus (HCV) infection is a cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma in the United States, Western countries and Japan[1-4]. Most cases of hepatocellular carcinoma are associated with chronic hepatitis B virus or HCV infections[5]. HCV variants are classified into at least 6 genotypes (representing the 6 genetic groups defined by phylogenetic analysis). It is well known that the treatment response differs among the different HCV genotypes[6]. Approximately 50% and

Table 1 Association between sustained virological response rates, age and gender in chronic hepatitis C patients treated with standard of care

Ref.	G	Number of patients	Naive	Age (yr, mean ± SD)/ gender (male)	Formula	SVR rates
McHutchison *et al*[17]	1	1016	Yes	47.5 ± 8.1/59.7%	Low-dose PegIFN alpha-2b plus RBV	38.00%
	1	1019	Yes	47.5 ± 7.8/60.2%	Standard-dose PegIFN alpha-2b plus RBV	39.80%
	1	1035	Yes	47.6 ± 8.2/59.2%	PegIFN alpha-2a plus RBV	40.90%
Jeffers *et al*[18]	1	78 (Black)	Yes	46.3 ± 0.7/72%	PegIFN alpha-2a plus RBV	26.00%
	1	28 (White)	Yes	44.7 ± 1.4/61%	PegIFN alpha-2a plus RBV	39.00%
Bruno *et al*[19]	1	163	Yes	49.9 ± 11.1/62%	PegIFN alpha-2b plus RBV	41.10%
	1	148	Yes	49.5 ± 11.1/62%	IFN alpha-2b plus RBV	29.30%
Conjeevaram *et al*[20]	1	196 (African-Americans)	Yes	49.0 ± (45.0, 52.5)/64.8%	PegIFN alpha-2a plus RBV	28.00%
	1	205 (Caucasian-Americans)	Yes	48.0 ± (43.0, 52.0)/65.8%	PegIFN alpha-2a plus RBV	52.00%
Miyauchi *et al*[21]	1	383	-	55.0 ± 10.9/62%	PegIFN alpha-2b plus RBV	61.80%
Kanda *et al*[22]	1	127	Yes	56.1 ± 10.7/48.8%	PegIFN alpha-2a plus RBV	56.60%
	1	69	No	59.0 ± 10.1/49.2%	PegIFN alpha-2a plus RBV	39.10%

G: Genotype; IFN: Interferon; SVR: Sustained virological response; RBV: Ribavirin.

80% achieve a sustained virological response, defined as undetectable HCV RNA at week 24 after stopping the treatment, following the current standard of care combination therapy with peginterferon plus ribavirin for 48 wk in HCV genotype 1 and 24 wk in HCV genotype 2[6].

In Japan, hepatocellular carcinoma is one of the major malignancies and patients with liver cirrhosis are encouraged to undergo examinations using a combination of real-time ultrasonography and alpha-fetoprotein measurement at regular intervals for an early detection of hepatocellular carcinoma[7]. The prognosis of elderly hepatocellular carcinoma patients was found to be similar to that for younger cases[8]. In Japan, as many people live to an advanced age, there are also many elderly hepatocellular carcinoma patients. Therefore, we need to treat elderly patients infected with HCV in order to decrease the mortality and incidence of HCV-related liver diseases[9,10].

The recent recognition that host genetic polymorphisms near interleukin-28B (IL28B) (*IL28B* genotype), such as a single nucleotide polymorphism (SNP) (rs8099917 or rs12979860), predict the treatment-induced and spontaneous HCV eradications remains an important discovery[11-15]. IL28B encodes interferon lambda 3 (IFNL3), a cytokine distantly related to type I interferons and IL10[16]. IL28B, interleukin-28A and interleukin-29 are three closely related cytokine genes that form a cytokine gene cluster on chromosome 19q13. This review focuses on HCV and host factor IL28B genotype in the treatment response of elderly patients with chronic hepatitis C and describes our experiences in treating such patients with chronic hepatitis C.

MOST HCV-INFECTED PATIENTS IN JAPAN ARE OLDER

Treatment response to standard of care in HCV genotype 1-infected patients is shown in Table 1[17-22]. The reported patients from the United States and European countries were, on average, younger than those from Japan[8,21-23]. This suggests that there might be different time spread and roots of transmission of HCV among these countries. In the United States, HCV genotype 1a-infected individuals appeared around 1960, at least 30 years later than the widespread introduction of HCV genotype 1b in the Japanese population[24]. The spread of HCV genotype 1b in Japan then started to decrease around 1995, whereas HCV genotype 1a in the United States is still growing exponentially[24]. Japan has high mortality rates from hepatocellular carcinoma, counting about 30000 deaths annually[25]. According to hepatitis virus carrier rates among first-time blood donors, the peak frequency of antibody to HCV was demonstrated by the 1931-1935 birth cohort, who are 78-82 years old in 2013[8]. So, to prevent death from hepatocellular carcinoma in Japan, we should treat relatively older patients infected with HCV. We and others previously reported that standard of care was also effective in chronic hepatitis C patients aged > 65 years[21,26].

SUSTAINED VIROLOGICAL RESPONSE RATES FOLLOWING STANDARD OF CARE IN OLDER HCV-INFECTED PATIENTS

First, we retrospectively analyzed 196 chronic hepatitis C patients aged ⩾ 65 years and treated with standard of care in our and affiliated hospitals[21,22,27,28] (Table 2). This work was carried out in accordance with the Declaration of Helsinki of the World Medical Association. The study protocol was approved by the Ethics Committee of Chiba University School of Medicine.

In the 196 patients treated with standard of care, sustained virological response was achieved in 46.9% (92/196). Sustained virological response was achieved in 43.9% (72/164) of HCV genotype 1 compared with 62.5% (20/32) of HCV genotype 2 patients (P = 0.082).

Table 2 Clinical characteristics of hepatitis C patients aged ≥ 65 years and treated with standard of care

	Total (n = 196)	Male (n = 104)	Female (n = 92)	P value[1]
Age (yr)	67.8 ± 2.5	68.1 ± 2.6	67.4 ± 2.4	
Gender (male/female)	104/92	104/0	0/92	
HCV viral load (high/low/unknown)	185/7/4	6/2/1996	1/2/1989	0.169
HCV genotypes 1/2	164/32	Nov-93	71/21	0.033
Treatment-naïve (yes/no/unknown)	108/87/1	55/48/1	52/39/1	0.704
ALT (IU/L)	61.3 ± 50.7	70.1 ± 57.1	51.4 ± 40.3	0.010
White blood cells (/μL)	4940 ± 1490	5160 ± 1670	4690 ± 1210	0.027
Neutrophils (/μL)	2660 ± 1080	2790 ± 1270	2530 ± 830	0.096
Hemoglobin (g/dL)	13.7 ± 1.5	14.1 ± 1.6	13.2 ± 1.3	0.000
Platelets (× 10^4/μL)	15.1 ± 4.7	15.0 ± 4.8	15.4 ± 4.6	0.553
Peg-IFN α - 2a / Peg-IFN α - 2b	86/110	41/63	45/47	0.233

Values are expressed as mean ± SD. [1]P value, comparison between male and female groups. HCV: Hepatitis C virus; ALT: Alanine aminotransferase; Peg-IFN: Peginterferon.

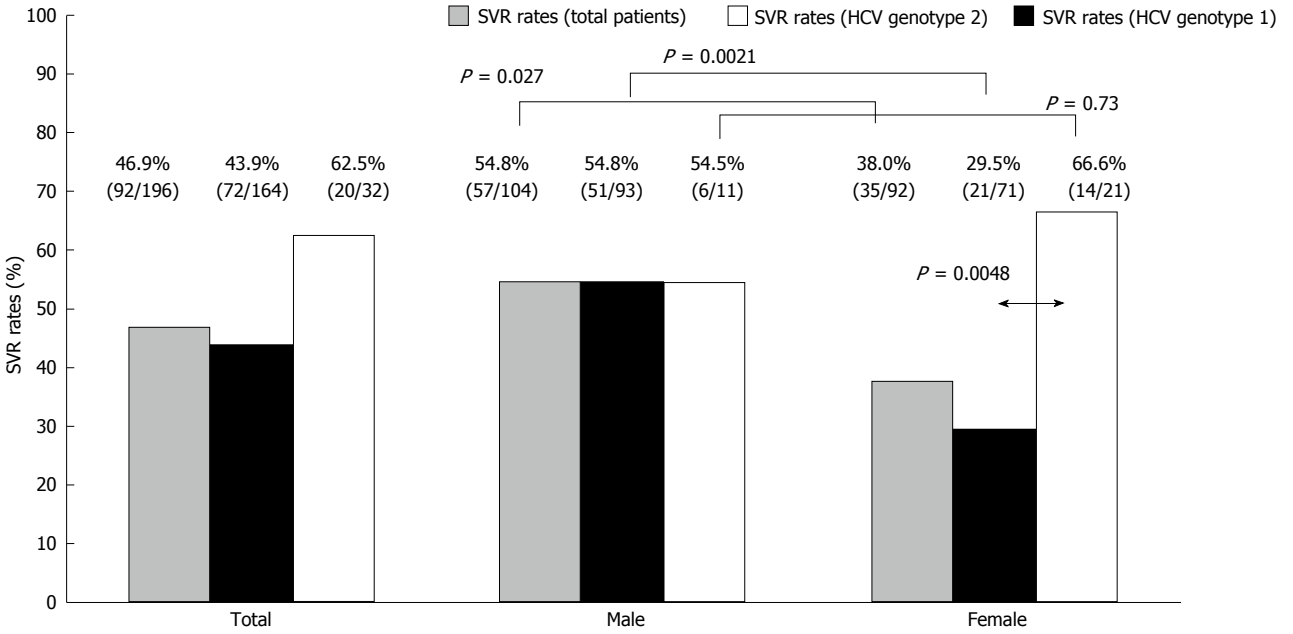

Figure 1 Sustained virological response rates in hepatitis virus genotypes 1/2 patients aged ≥ 65 years and treated with standard of care. Hepatitis C virus variants are classified into at least 6 genotypes (representing the 6 genetic groups defined by phylogenetic analysis). It is well known that the treatment response differs among the different hepatitis C virus genotypes[6]. SVR: Sustained virological response; HCV: Hepatitis C virus.

In 110 patients treated with peginterferon alpha-2b plus ribavirin, sustained virological response was achieved in 49.4% (44/89) of HCV genotype 1 compared with 66.6% (14/21) of HCV genotype 2 patients. In 86 patients treated with peginterferon alpha-2a plus ribavirin, sustained virological response was achieved in 37.3% (28/75) of HCV genotype 1 compared with 54.5% (6/11) of HCV genotype 2 patients. There were no differences in efficacies or adverse events between the two peginterferons.

In male and female patients aged ≥ 65 years and treated with standard of care, sustained virological response was achieved in 54.8% and 38.0%, respectively (Figure 1). Our results also supported previous studies[8,26]. Gender differences were more remarkable in HCV genotype 1 than in HCV genotype 2 patients (P = 0.0021). In older female patients, the treatment response in HCV genotype 2 was better than that of the others (Figure 1).

ADVERSE EVENTS FOLLOWING STANDARD OF CARE IN OLDER HCV-INFECTED PATIENTS

Interferon plus ribavirin combination therapy for chronic hepatitis C produces a number of well-described side-effects that are dominated by fatigue, influenza-like symptoms, hematological abnormalities and neuropsychiatric symptoms[29,30]. We defined "severe adverse event" if treatment had to be stopped. In chronic hepatitis C patients aged ≥ 65 years, we identified severe adverse events in 14.7% (29/196) (Table 3). In male and female patients, severe adverse events occurred in 14.4% (15/104) and 15.2% (14/92), respectively. Fried *et al*[31] reported that severe adverse events were observed in 7% when the mean age of patients treated with standard of care was 42.8 ±

Table 3 Severe adverse events in hepatitis C patients aged ≥ 65 years and treated with standard of care *n* (%)

Severe adverse events	No. of patient discontinuities
Occurrence of malignancies (Hepatocellular carcinoma)	5 (13.5)
Severe fatigue	5 (13.5)
Severe pulmonary symptoms (bloody phlegm, cough, or interstitial pneumonitis)	5 (13.5)
Severe anemia	5 (13.5)
Psychiatric disorders	3 (8.1)
Severe skin lesion	3 (8.1)
Neurological disorders	3 (8.1)
Severe thrombocytopenia or neutropenia	3 (8.1)
Severe denutrition	2 (5.4)
Upper gastrointestinal bleeding	1 (2.7)
Severe infection (tuberculosis)	1 (2.7)
Unknown	1 (2.7)

10.1 years. McHutchison *et al*[17] reported that severe adverse events were observed in 9.6%-13% when the mean age of patients treated with standard of care was 47 years. So, our results suggested that older HCV-infected patients treated with standard of care might be more susceptible to severe adverse events. Among them, occurrence of hepatocellular carcinoma, severe fatigue, severe pulmonary symptoms and severe anemia were observed in 13.5% each, although we did not use growth factors such as erythropoietin[32-34] in Japan. It should be emphasized that clinicians regularly check for the possible development of hepatocellular carcinoma even in chronic hepatitis C patients under treatment[10].

IL28B GENOTYPE AND TREATMENT RESPONSE TO STANDARD OF CARE

There have been several reports showing a close association between IL28B genotype and treatment response to standard of care[11-14,35-42]. Although the mechanisms for this association are still uncertain, several studies have indicated an association between plasma interferon-gamma-inducible protein-10 (IP-10) levels and *IL28B* genotypes[41], as well as between the expression of hepatic interferon-stimulated genes and *IL28B* genotypes[38]. We also reported that hepatic signal transducer and activator of transcription 1 -nuclear translocation and *IL28B* genotype could predict treatment outcomes in HCV genotype 1-infected patients[36]. A (TA) dinucleotide repeat, rs72258881, located in the promoter region, and the transcriptional activity of the promoter increasing gradually in a $(TA)_n$ length-dependent manner, was discovered[43]. A dinucleotide variant, ss469415590 (-G), is a flame-shift variant that creates a novel gene, designated as IFNL4, encoding the interferon-λ4 protein (IFNL4), which is moderately similar to IFNL3[44]. This novel TT/-G polymorphism in the CpG region upstream of IL28B is a better predictor of HCV clearance than rs12979860. Induction of IL28B and interferon-gamma-inducible protein-10 (IP-10) mRNA of peripheral blood mononuclear cells (PBMCs) relies on TT/-G polymorphism[45]. Further studies will be needed to clarify the significance of IL28B-related SNPs. In any case, IL28B genotypes (rs8099917 and rs12979860) are predictive factors of sustained virological response in standard of care for HCV[46,47]. Ge *et al*[11] reported that the major genotype in rs12979860 leads to 80% sustained virological response with standard of care, but a minor genotype in rs12979860 leads to only 30% sustained virological response. It was reported that the major genotype in rs8099917 leads to 75.3% sustained virological response, but a minor genotype in rs8099917 leads to only 24.7% sustained virological response in HCV genotype 1 patients, and also that major and minor genotypes at rs8099917, respectively, lead to 83.0% and 17.0% sustained virological response in HCV genotype 2 patients[47].

SUSTAINED VIROLOGICAL RESPONSE RATES BY STANDARD OF CARE AND IL28B GENOTYPE IN OLDER HCV-INFECTED PATIENTS

We retrospectively analyzed 41 chronic hepatitis C patients aged ≥ 65 years and treated with standard of care in our hospital (Table 4). This work was carried out in accordance with the Declaration of Helsinki of the World Medical Association. The study protocol was approved by the Ethics Committee of Chiba University School of Medicine. Our results showed that IL28B rs8099917 genotype is predictive of early virological response, which is undetectable HCV RNA at week 12 after the commencement of therapy, in standard of care for HCV-infected older patients. As early virological response is a predictive value for sustained virological response in standard of care treatment, IL28B genotyping could give us useful information for the prediction of sustained virological response with this treatment.

ROLES OF *IL28B* GENOTYPE IN TRIPLE THERAPY WITH PEGINTERFERON, RIBAVIRIN AND TELAPREVIR

In 2011, telaprevir and boceprevir were approved as direct-acting antivirals against HCV in Japan as well as in the United States and European countries[48]. Triple therapy with peginterferon, ribavirin, plus telaprevir or boceprevir improved sustained virological response rates greatly, up to 70%-80%, in treatment-naïve individuals and previous treatment relapsers[39,49-55], but these triple therapies also brought severe adverse events to the patients[56]. In Japan, only the telaprevir-including regimen was available in clinical practice at this time. We frequently observed dermatological side-effects[57], drug-drug interactions[58], anemia[59] and renal impairment[60] in chronic hepatitis C patients under triple therapy with telaprevir. Akuta *et al*[61] reported that *IL28B* genotype could predict the response

Table 4 Association between *IL28B* rs8099917 and treatment response in hepatitis C patients aged ≥ 65 years and treated with standard of care

	Total (n = 41)	*IL28B* TT (n = 31)	*IL28B* TG (n = 10)	[1]*P* values
Age (yr)	67.7 ± 2.6	68.0 ± 2.9	67.0 ± 1.3	0.141
Gender (male/female)	28/13	22/9	4/6	0.796
HCV viral load, (high/low)	41/0	31/0	10/0	NA
HCV genotype (G1/G2)	41/0	25/6	8/2	0.678
Treatment-naïve (yes/no)	29/12	24/7	5/5	0.208
ALT (IU/L)	56.5 ± 40.2	54.9 ± 41.2	61.1 ± 38.9	0.677
γ-GTP (IU/L)	36.4 ± 33.3	33.1 ± 33.1	46.6 ± 33.4	0.269
White blood cells (/μL)	4840 ± 1300	4730 ± 1160	5190 ± 1690	0.337
Hemoglobin (g/dL)	13.5 ± 1.3	13.6 ± 1.1	13.3 ± 1.8	0.528
Platelets (x104/μL)	14.9 ± 5.4	14.4 ± 5.1	16.5 ± 6.2	0.289
IL28B rs8099917 (TT/TG)	31/10	31/0	0/10	NA
EVR rates	34.1% (14/41)	45.1% (14/31)	0% (0/10)	0.025
SVR rates	43.9% (18/41)	48.3% (15/31)	30.0% (3/10)	0.514

Values are expressed as mean ± SD. [1]*P* value, comparison between IL28B TT and IL28B TG groups. HCV: Hepatitis C virus; ALT: Alanine aminotransferase; γ-GTP: γ-glutamyl transpeptidase; EVR: Early virological response; SVR: Sustained virological response; NA: Not available.

to peginterferon/ribavirin/telaprevir therapy. The efficacy of triple therapy was high in patients with IL28B rs8099917 genotype TT who accomplished sustained virological response (83.8%), but was low in patients with IL28B rs8099917 genotype TG or GG who accomplished sustained virological response (27.6%). The efficacy of triple therapy was also high in patients with IL28B rs12979860 genotype CC who accomplished sustained virological response (83.8%), but was low in patients with IL28B rs12979860 genotype CT or TT who accomplished sustained virological response (32.3%)[61], although it was reported that IL28B genotype had a limited impact on sustained virological response rates with telaprevir-based therapy in treatment-experienced patients[62].

ROLES OF IL28B GENOTYPE IN OLDER PATIENTS TREATED WITH PEGINTERFERON/RIBAVIRIN/TELAPREVIR

In our experience, we safely treated a 74 year old female, a previous treatment-relapser who had IL28B rs8099917 TT, with peginterferon/ribavirin/telaprevir and obtained a successful result. Although her dose of telaprevir was 1500 mg/d[63], she did not discontinue the treatment, had no adverse events and finally achieved sustained virological response. Because most Asian individuals are of relatively smaller physical stature compared to American or European individuals, it was reported that 24 wk triple therapy with telaprevir at 1500 mg/d seemed safe and efficacious for elderly patients infected with HCV genotype 1b[63]. In addition, *IL28B* genotyping seems to be one of the useful screening methods for older patients awaiting treatment with peginterferon/ribavirin/telaprevir[64]. Furusyo *et al*[64] reported that sustained virological response rates for patients aged > 60 with IL28B rs8099917 TT genotype (89.4%) was significantly higher than for those with IL28B TG/GG genotype (41.2%), and that multivariate analysis extracted IL28BTT and rapid virological response, which was defined as undetectable HCV RNA at week 4 after the commencement of therapy, as independent factors associated with sustained virological response. They observed severe anemia more frequently in patients aged > 60 years than in patients aged ≤ 60 years[64].

CONCLUSION

In summary, *IL28B* major genotype is a useful predictor of sustained virological response in the interferon-including treatment of older patients infected with HCV. In addition, it seems to play a useful role for avoiding adverse events. The mechanisms of the effects of IL28B genotype on the treatment outcome are now under investigation and further studies will be needed. Until the appearance of interferon-free regimens, it is important to determine *IL28B* genotype before treating HCV-infected individuals and this is especially true in the screening of older patients.

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