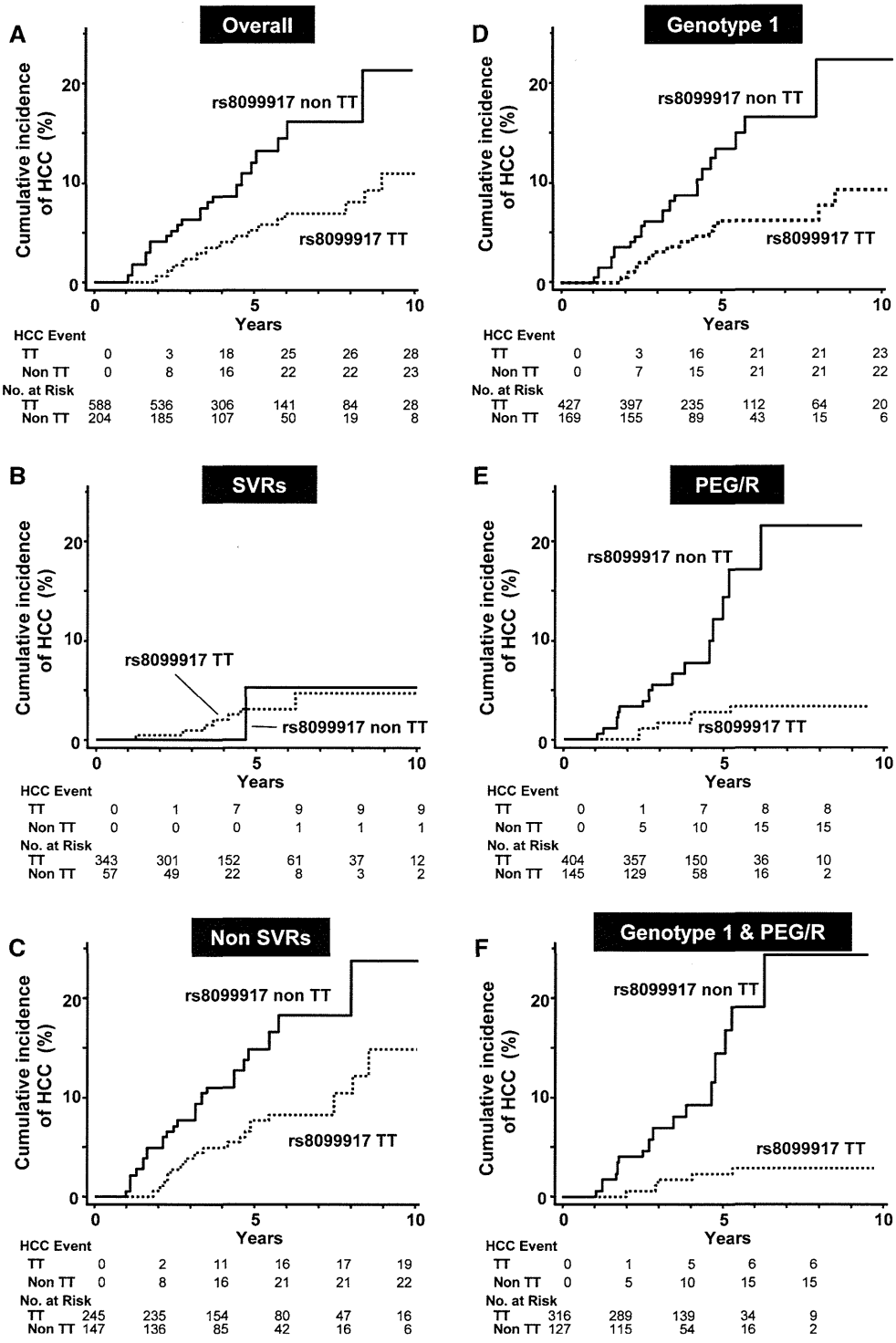

Fig. 1 Cumulative incidence of HCC according to genetic variation near *IL28B*. **a** Data for the entire patient group. Logrank test: $p = 0.002$. **b** Data for SVRs. Logrank test: $p = 0.775$. **c** Data for nonSVRs. Logrank test: $p = 0.016$. **d** Data for patients with HCV genotype 1. Logrank test: $p = 0.001$. **e** Data for patients who were treated with PEG-IFNα/RBV combination therapy. Logrank test: $p < 0.001$. **f** Data for patients with HCV genotype 1 who were treated with PEG-IFNα/RBV combination therapy. Logrank test: $p < 0.001$

significantly higher in nonTT patients than in TT patients (17.9, and 22.7 vs. 2.6, and 3.6 % at 5, and 9 years, respectively; logrank test, $p < 0.001$) (Fig. 1e). Particularly, in patients infected with HCV genotype 1 who were treated with PEG-IFNα/RBV ($n = 443$), the cumulative incidence of HCC was significantly higher in nonTT patients than in TT patients (19.5, and 24.5 vs. 2.2, and 3.2 % at 5, and 9 years, respectively; logrank test, $p < 0.001$) (Fig. 1f). Among patients infected with HCV genotype non-1 or those treated with other than PEG-IFNα/RBV therapy, no significant difference was found in the cumulative HCC incidence between TT and nonTT patients.

Influence of the SNPs near *IL28B* on progression of fibrosis over time

Among the 294 patients with evidence of a single blood transfusion, the annual FPR was similar between TT and nonTT patients ($p = 0.758$, Fig. 2). No difference was found in age at blood transfusion (26.0 [SD, 9.7] years old vs. 26.5 [SD, 9.6] years old, $p = 0.658$) and duration of HCV infection (34.7 [10.0] years vs. 36.1 [9.9] years, $p = 0.291$) between TT and nonTT patients.

Mean ALT and AFP levels after IFN therapy according to the SNPs near *IL28B*

Because we recently reported that post-IFN treatment ALT and AFP levels are significantly associated with hepatocarcinogenesis [8], the influence of ALT and AFP levels after IFN treatment was determined in TT and nonTT patients to address possible reasons associated with higher HCC development observed in nonSVRs with rs8099917 nonTT. Overall, mean serum ALT and AFP levels were reduced after IFN therapy. However, the reduction observed in mean ALT and AFP levels after IFN therapy was less in nonTT patients than in TT patients among nonSVRs (Fig. 3). The cutoff values of ALT and AFP after IFN treatment for predicting patients without HCC developments were determined as ALT <40 IU/L and AFP <6.0 ng/mL by the receiver–operator characteristics curves analysis in the original cohort [8]. The cumulative incidence of HCC development in nonSVRs was less in patients whose post-IFN ALT or AFP levels were below these cutoff values (Fig. 4a, b). Even in patients whose ALT ≥40 IU/L or AFP ≥6.0 ng/mL before IFN therapy, patients with a reduction of ALT <40 IU/L or AFP <6.0 ng/mL after IFN therapy showed significantly lower cumulative development of HCC than those without reduction in both TT and nonTT subgroups (Fig. 4c–f). However, the proportion of patients with reduction of ALT <40 IU/L or AFP <6.0 ng/mL after IFN therapy in nonSVRs was significantly smaller in nonTT patients than TT patients (Fig. 5).

As reported in the recent study [8], the persistence of post-IFN treatment ALT or AFP levels to more than the cutoff values after IFN therapy was associated with a significantly higher incidence of HCC in both SVRs and nonSVRs (Supplementary Figure). In contrast, even in nonSVRs with an equal or higher pre-IFN treatment ALT or AFP level than the cutoff values, the cumulative incidence of HCC was significantly suppressed in patients whose post-IFN treatment ALT or AFP level was reduced to less than the cutoff values (Supplementary Figure).

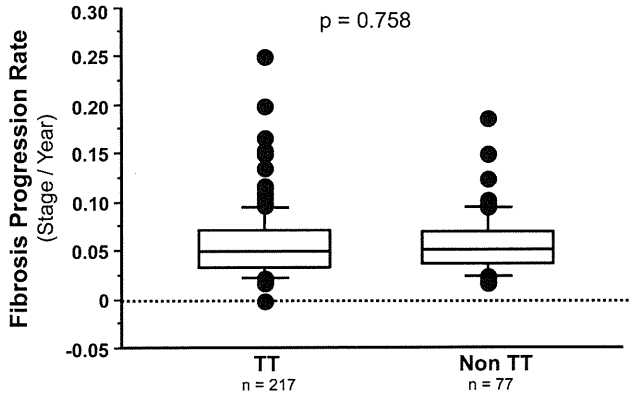

Fig. 2 Changes in fibrosis staging over time. Analysis in patients who showed evidence of a single blood transfusion as a known time of HCV infection ($n = 292$)

Influence of the SNPs near *IL28B* on HCC risk

Univariate analysis demonstrated that nonTT was one of the factors that increased the risk ratio for HCC development (Table 2). In the multivariate Cox model, age, sex, stage of fibrosis, pre-IFN treatment AFP level, post-IFN treatment ALT and AFP levels were independently associated with HCC risk among covariates including age, sex, stage of fibrosis, pre- and post-IFN treatment ALT and AFP levels, virological response and the SNPs near *IL28B* (Table 3). In patients infected with HCV genotype 1 who were treated with PEG-IFNα/RBV combination therapy, the SNPs near *IL28B* as well as age, sex, post-IFN treatment ALT level and pre-IFN treatment AFP level were identified as independent factors associated with the development of HCC among covariates including age, sex, stage of liver fibrosis, pre- and post-IFN treatment ALT and AFP levels, and virological response (Table 4). Although pre-IFN treatment AFP levels were significantly higher in patients with nonTT (Table 1; Fig. 3), our results for the multivariate analysis in this subgroup suggests that higher HCC incidence in nonTT patients is not fully explained by higher pre-IFN treatment AFP levels.

Discussion

By analyzing a large-scale, long-term cohort, we demonstrated that rs8099917 nonTT is significantly associated with HCC development particularly in patients infected with HCV genotype 1 who were treated with PEG-IFNα/RBV combination therapy. The possible relationship between the SNPs near *IL28B* and the risk of HCC development is controversial [11–13] mainly because of the lack of a longitudinal cohort study such as ours. Another possible reason for this controversy is the influence of antiviral therapy because the SNPs near *IL28B* are

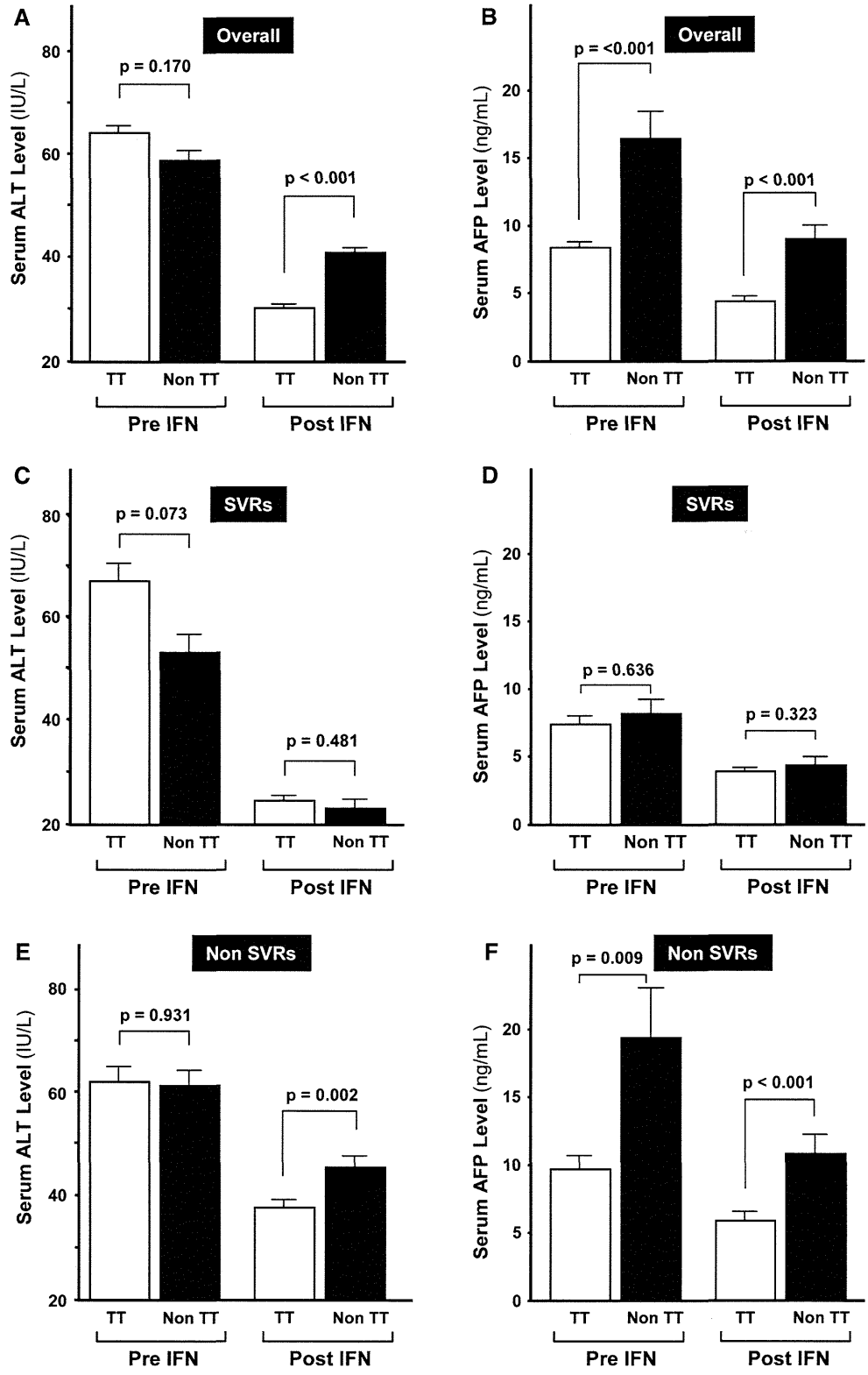

Fig. 3 Mean integration ALT and AFP values before and after interferon therapy in rs8099917 TT and nonTT patients. *Error bars* indicate the standard error. *p* values were determined by unpaired Student's *t* test

strongly associated with the antiviral response. Recent cross-sectional studies in patients without IFN treatment could not ascertain the relationship between the SNPs near *IL28B* and HCV-related HCC [12, 13]. From this viewpoint, our cohort is unique in that it includes only IFN-treated patients. In the Kaplan–Meier analyses, significantly higher incidence of HCC in nonTT was observed in patients infected with HCV genotype 1 and/or those treated with PEG-IFNα/RBV combination therapy, whereas it was not in patients infected with HCV genotype non-1 and

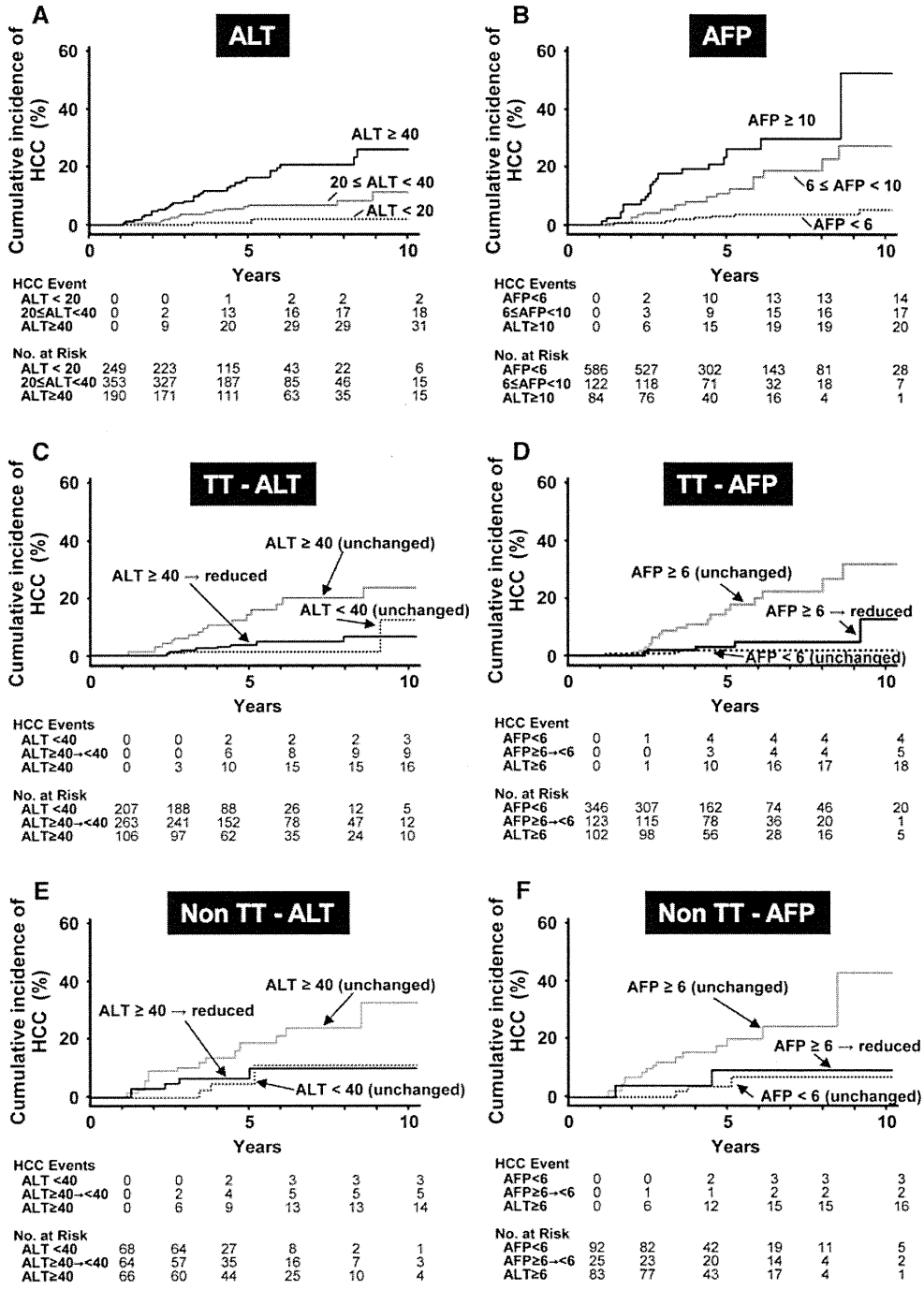

Fig. 4 Cumulative incidence of HCC stratified by mean integration values of post-IFN ALT and AFP levels. **a** Stratified by post-IFN treatment levels of ALT in all patients. Logrank test: $p < 0.001$. **b** Stratified by post-IFN treatment levels of AFP in all patients. Logrank test: $p < 0.001$. **c** According to changes in mean ALT levels before and after interferon therapy in patients with rs8099917 TT. Logrank test: $p < 0.001$. **d** According to changes in mean AFP levels before and after interferon therapy in patients with rs8099917 TT. Logrank test: $p < 0.001$. **e** According to changes in mean ALT levels before and after interferon therapy in patients with rs8099917 nonTT. Logrank test: $p = 0.040$. **f** According to changes in mean AFP levels before and after interferon therapy in patients with rs8099917 nonTT. Logrank test: $p < 0.001$

those treated other than PEG-IFNα/RBV. Moreover, our multivariate analyses demonstrated that an independent association between rs8099917 nonTT and HCC development was only found in patients infected with HCV genotype 1 who were treated with PEG-IFNα/RBV combination therapy. Because the SNPs near *IL28B* affects antiviral response particularly in patients infected with HCV genotype 1 and/or those treated with PEG-IFNα/RBV therapy, impact of the SNPs near *IL28B* on HCC risk may be indirect and is largely influenced by treatment effect.

Because a significantly higher incidence of HCC in nonTT patients was observed even in nonSVRs, higher HCC risk related to nonTT was not fully explained by the poor virological response rates observed in nonTT patients. Although we have reported that higher post-IFN treatment ALT and AFP levels were significantly associated with the risk of HCC [8], the relationship between *IL28B* SNPs and post-IFN treatment ALT and AFP levels has not yet been elucidated. Hence, to further address the higher HCC risk in nonTT patients, we directed our study at post-IFN

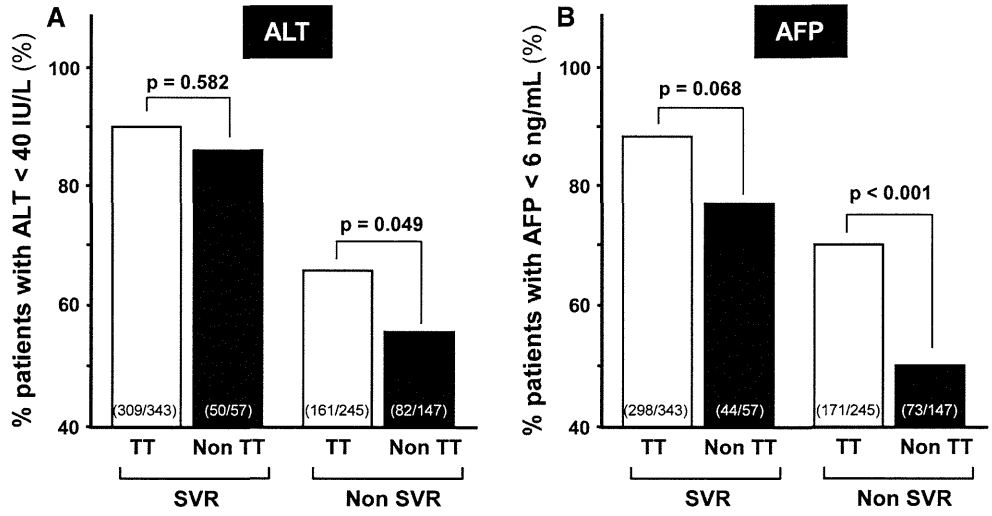

Fig. 5 Proportion of patients with reduction of ALT <40 IU/L or AFP <6.0 ng/mL after IFN therapy. **a** Percentage of patients with ALT <40 IU/L after IFN. **b** Percentage of patients with AFP <6 ng/mL after IFN

Table 2 Univariate analysis for the factors associated with hepatocellular carcinoma

Risk factor	Hazard ratio (95 % CI)	*p* value
IL28B genotype		
rs8099917 TT	1	
rs8099917 nonTT	2.36 (1.37–4.06)	0.002
Age (by every 10 year)	2.22 (1.51–3.28)	<0.001
Sex		
Female	1	
Male	2.17 (1.25–3.75)	0.006
Fibrosis stage		
F1/F2	1	
F3/F4	4.86 (2.82–8.37)	<0.001
γ-GTP (by every 40 IU/L)	1.27 (1.13–1.43)	<0.001
Core 70 mutation		
Wild	1	
Mutant	2.52 (0.94–6.78)	0.066
ISDR		
More than 1 mutation	1	
Wild or 1 mutation	1.08 (0.56–2.06)	0.826
IFN regimen		
IFN mono	1	
IFN + RBV	0.78 (0.31–1.98)	0.602
PEG-IFN mono	0.66 (0.27–1.61)	0.359
PEG-IFN + RBV	0.53 (0.25–1.12)	0.098
Pre-treatment ALT (by every 40 IU/L)	1.13 (1.00–1.22)	0.049
Post-treatment ALT (by every 40 IU/L)	3.02 (2.21–3.96)	<0.001
Pre-treatment AFP (by every 10 ng/mL)	1.09 (1.05–1.13)	<0.001
Post-treatment AFP (by every 10 ng/mL)	1.17 (1.09–1.26)	<0.001
Virological response		
SVR	1	
Non-SVR	3.07 (1.58–5.99)	0.001

Hazard ratios for the development of hepatocellular carcinoma were calculated by the Cox proportional hazards regression analysis

Table 3 Multivariate analysis for the factors associated with hepatocellular carcinoma in all patients

Risk factor	Hazard ratio (95 % CI)	*p* value
IL28B genotype		
rs8099917 TT	1	
rs8099917 nonTT	1.29 (0.72–2.33)	0.395
Age (by every 10 year)	2.59 (1.72–3.87)	<0.001
Sex		
Female	1	
Male	3.30 (1.80–6.06)	<0.001
Fibrosis stage		
F1/F2	1	
F3/F4	2.40 (1.36–4.24)	0.003
Pre-treatment ALT (by every 40 IU/L)	1.04 (0.89–1.17)	0.783
Post-treatment ALT (by every 40 IU/L)	2.58 (1.74–3.81)	<0.001
Pre-treatment AFP (by every 10 ng/mL)	1.38 (1.13–1.68)	0.002
Post-treatment AFP (by every 10 ng/mL)	1.61 (1.04–2.39)	0.028
Virological response		
SVR	1	
Non-SVR	1.64 (0.80–3.39)	0.177

Hazard ratios for the development of hepatocellular carcinoma were calculated by the Cox proportional hazards analysis

treatment ALT and AFP levels, which are considered to be possible biomarkers for the future development of HCC [8, 14]. These further analyses showed notable findings, which demonstrated that a decrease in ALT and AFP levels after IFN therapy is less in nonTT patients among nonSVRs, and

Table 4 Multivariate analysis for the factors associated with hepatocellular carcinoma in patients infected with HCV genotype 1 who were treated with PEG-IFNα/RBV combination therapy

Risk factor	Hazard ratio (95 % CI)	*p* value
IL28B genotype		
rs8099917 TT	1	
rs8099917 nonTT	4.50 (1.61–12.6)	0.004
Age (by every 10 year)	3.19 (1.72–5.99)	<0.001
Sex		
Female	1	
Male	6.17 (2.07–18.5)	0.001
Fibrosis stage		
F1/F2	1	
F3/F4	2.44 (0.86–6.97)	0.093
Pre-treatment ALT (by every 40 IU/L)	0.92 (0.59–1.49)	0.769
Post-treatment ALT (by every 40 IU/L)	2.38 (1.08–5.18)	0.034
Pre-treatment AFP (by every 10 ng/mL)	1.07 (1.01–1.13)	0.025
Post-treatment AFP (by every 10 ng/mL)	1.09 (0.94–1.27)	0.225
Virological response		
SVR	1	
Non-SVR	1.86 (0.46–7.41)	0.382

Hazard ratios for the development of hepatocellular carcinoma were calculated by the Cox proportional hazards analysis

that the proportions of patients with reductions of ALT <40 IU/L or AFP <6.0 ng/mL after IFN therapy in nonSVRs are significantly smaller in nonTT patients (Fig. 5). Although the essential mechanisms responsible for the relationship between elevated levels of ALT or AFP and HCC development are not known, these results suggest that a higher incidence of HCC observed in nonTT patients partly results from the limited suppressive effect of IFN on ALT and AFP levels, and might be reduced even in nonTT patients, whose ALT and/or AFP levels decrease after IFN-based antiviral treatment.

NonTT patients in our study exhibited a significant association with higher γ-glutamyl transpeptidase levels, increased frequency of hepatic steatosis, and increased frequency of the HCV core 70QH mutation; all these factors are associated with HCC development [2]. Therefore, HCC risk found in nonTT patients may also result from those factors coexisting with the *IL28B* minor allele.

Our results demonstrated that the SNPs near *IL28B* appeared to be independent of liver fibrosis. Recently, an association between the *IL28B* major allele and higher cirrhosis prevalence was reported in human immunodeficiency virus–HCV coinfected patients [15]. However, the limitations of this study were that it was a cross-sectional study involving only human immunodeficiency virus coinfected patients; moreover, hepatic elastography was used for determining liver fibrosis. Conversely, Marabita et al. [16] estimated the fibrosis progression rate in 247 patients with a known date of infection, and demonstrated that the *IL28B* genotype has no effect on the risk of developing advanced fibrosis. A recent study on the Swiss and the French cohorts showed a significant relationship between nonTT and a slow FPR; however, this relationship was found only in genotype non1-infected patients, and not in genotype 1-infected patients [17]. Our analysis of the FPR in HCV genotype 1b-dominant patient group demonstrated that the liver FPR did not differ between TT and nonTT patients. Taken together, the SNPs near *IL28B* do not appear to be closely associated with liver fibrogenesis in HCV genotype 1 monoinfected patients.

This study had a few limitations. The first was the heterogeneity of our cohort, which included various treatment regimens with different treatment responses. However, we obtained results in a more uniform subgroup of HCV genotype 1 patients treated with PEG-IFNα/RBV. The second limitation was the ethnic homogeneity of the Japanese population, who had a low minor allele frequency. A recent cross-sectional study in the Swiss cohort demonstrated a poor association between polymorphisms near *IL28B* and HCC occurrence [17]. Although many patients were included in that Swiss study, the number of patients with HCC development was few (3 %), which was inadequate to detect a significant effect of the polymorphism. Because the overall HCC risk varies among population groups (i.e. Japanese > European), longer-term longitudinal studies in larger cohorts with various population subgroups are required to verify the generality of our results. The third limitation involved the subanalyses of the original cohort. However, as shown in the Supplementary Table 1, SVR rates were equivalent between the original and the subcohort, although slight differences were found in proportion of gender, age and ALT levels. Moreover, characteristics of the patients with HCV genotype 1 who were treated with PEG-IFNα/RBV were identical between the original and the subcohort (Supplementary Table 2). Therefore, selection bias was unlikely to have affected our results, particularly in patients with HCV genotype 1 who were treated with PEG-IFNα/RBV, in whom SNPs near *IL28B* were identified as an independent factor associated with HCC development. The fourth limitation was that the effect of liver-supporting therapy such as ursodeoxycholic acid and glycyrrhizin was unclear in the present study, which may reduce ALT level and HCC risk in nonSVRs. However, it is likely that liver-supporting therapy was evenly indicated for both rs8099917 TT and nonTT patients, because we usually excluded the SNPs near *IL28B* from consideration when making decisions on therapeutic

indications of liver-supporting therapy. Moreover, suppressive effect on HCC development by liver-supporting therapy is presumably weak. Therefore, the effect of liver-supporting therapy was unlikely to have affected our results.

In conclusion, rs8099917 nonTT is a risk factor for HCC, in particular in patients infected with HCV genotype 1 who were treated with PEG-IFNα/RBV combination therapy. The effect of the SNPs near *IL28B* on HCC risk may be indirect, and higher HCC development observed in nonTT is presumably because of two reasons: (1) poor IFN efficacy in reducing ALT and/or AFP levels in patients with nonTT, (2) coexisting unfavorable risk factors for HCC. Not only HCV eradication but also suppression of ALT and/or AFP levels after IFN therapy may reduce the risk of hepatocarcinogenesis in nonTT patients.

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References

1. Kiyosawa K, Sodeyama T, Tanaka E, Gibo Y, Yoshizawa K, Nakano Y, et al. Interrelationship of blood transfusion, non-A, non-B hepatitis and hepatocellular carcinoma: analysis by detection of antibody to hepatitis C virus. Hepatology. 1990;12:671–5.
2. Asahina Y, Tsuchiya K, Tamaki T, Hirayama I, Tanaka T, Sato M, et al. Effect of aging on risk for hepatocellular carcinoma in chronic hepatitis C virus infection. Hepatology. 2010;52:518–27.
3. Yoshida H, Shiratori Y, Moriyama M, Arakawa Y, Ide T, Sata M, et al. IFN therapy reduces the risk for hepatocellular carcinoma: national surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. Ann Intern Med. 1999;131:174–81.
4. Bruno S, Stroffolini T, Colombo M, Bollani S, Benvegnù L, Mazzella G, et al. SVR to IFN-alpha is associated with improved outcome in HCV-related cirrhosis: a retrospective study. Hepatology. 2007;45:579–87.
5. Tanaka Y, Nishida N, Sugiyama M, Kurosaki M, Matsuura K, Sakamoto N, et al. Genome-wide association of IL28B with response to pegylated IFN-alpha and ribavirin therapy for chronic hepatitis C. Nat Genet. 2009;10:1105–9.
6. Suppiah V, Moldovan M, Ahlenstiel G, Berg T, Weltman M, Abate ML, et al. IL28B is associated with response to chronic hepatitis C IFN-alpha and ribavirin therapy. Nat Genet. 2009;10:1100–4.
7. Ge D, Fellay J, Thompson AJ, Simon JS, Shianna KV, Urban TJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature. 2009;461:399–401.
8. Asahina Y, Tsuchiya K, Nishimura T, Muraoka M, Suzuki Y, Tamaki N, et al. α-fetoprotein levels after interferon therapy and risk of hepatocarcinogenesis in chronic hepatitis C. Hepatology. 2013. doi:10.1002/hep.26442.
9. Asahina Y, Tsuchiya K, Muraoka M, Tanaka K, Suzuki Y, Tamaki N, et al. Association of gene expression involving innate immunity and genetic variation in interleukin 28B with antiviral response. Hepatology. 2012;55:20–9.
10. Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Scheuer PJ. Classification of chronic hepatitis: diagnosis, grading and staging. Hepatology. 1994;19:1513–20.
11. Eurich D, Boas-Knoop S, Bahra M, Neuhaus R, Somasundaram R, Neuhaus P, et al. Role of IL28B polymorphism in the development of hepatitis C virus-induced hepatocellular carcinoma, graft fibrosis, and posttransplant antiviral therapy. Transplantation. 2012;93:644–9.
12. Agúndez JA, García-Martin E, Maestro ML, Cuenca F, Martínez C, Ortega L, et al. Relation of IL28B gene polymorphism with biochemical and histological features in hepatitis C virus-induced liver disease. PLoS ONE. 2012;7:e37998.
13. Joshita S, Umemura T, Katsuyama Y, Ichikawa Y, Kimura T, Morita S, et al. Association of IL28B gene polymorphism with development of hepatocellular carcinoma in Japanese patients with chronic hepatitis C virus infection. Hum Immunol. 2012;73:298–300.
14. Osaki Y, Ueda Y, Marusawa H, Nakajima J, Kimura T, Kita R, et al. Decrease in alpha-fetoprotein levels predicts reduced incidence of hepatocellular carcinoma in patients with hepatitis C virus infection receiving interferon therapy: a single center study. J Gastroenterol. 2012;47:444–51.
15. Barreiro P, Pineda JA, Rallon N, Naggie S, Martín-Carbonero L, Neukam K, et al. Influence of interleukin-28B single-nucleotide polymorphisms on progression to liver cirrhosis in human immunodeficiency virus-hepatitis C virus-coinfected patients receiving antiretroviral therapy. J Infect Dis. 2011;203:1629–35.
16. Marabita F, Aghemo A, Nicola SD, Rumi MG, Cheroni C, Scavelli R, et al. Genetic variation in the interleukin-28B gene is not associated with fibrosis progression in patients with chronic hepatitis C and known date of infection. Hepatology. 2011;54:1127–34.
17. Bochud PY, Bibert S, Kutalik Z, Patin E, Guergnon J, Nalpas B, et al. IL28B alleles associated with poor HCV clearance protect against inflammation and fibrosis in patients infected with non-1 HCV genotypes. Hepatology. 2012;55:384–94.

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Special Report

Guidelines for the Management of Hepatitis C Virus Infection

First edition, May 2012, The Japan Society of Hepatology

Editors of the Drafting Committee for Hepatitis Management Guidelines: The Japan Society of Hepatology*,**

1. INTRODUCTION

THE JAPAN SOCIETY of Hepatology (JSH) has, until now, produced "A Management Guide for Chronic Hepatitis and Liver Cirrhosis", "A Management Guide for NASH and NAFLD", and "A Treatment Manual for Hepatocellular Carcinoma". The only official guidelines produced by the Society have been the "Clinical Practice Guidelines for Hepatocellular Carcinoma Based on Scientific Evidence", however, and we had not yet developed guidelines for hepatitis.

As a scientific body that promotes hepatology research, we considered it necessary to publish our official position on the diagnosis and treatment of hepatitis. The regular JSH board meeting on 19 October 2011 approved the establishment of the Drafting Committee for Hepatitis Management Guidelines.

The Committee decided that our first priority was the production of guidelines for the management of hepatitis C, most urgently needed by Society members, so we began with the production of these "Guidelines for the Management of Hepatitis C Virus Infection (First Edition)". We hope and anticipate that these guidelines will be used throughout Japan in the management of hepatitis C.

This is a field that changes rapidly with the accumulation of new evidence, accompanied by changes in the level of evidence, so we have elected not to show evidence levels. We plan to revise these guidelines at appropriate intervals, as new evidence comes to hand.

May 2012

Kazuhiko Koike
Director General, The Japan Society of Hepatology
Hajime Takikawa
Chairman, Drafting Committee for Hepatitis Management Guidelines

2. GENERAL STRATEGY AGAINTS HEPATITIS C VIRUS INFECTION

FOLLOWING THE IDENTIFICATION of the hepatitis C virus (HCV) by Choo *et al.* in the USA in 1989,[1] it became clear that over 90% of patients previously diagnosed with non-A non-B hepatitis, and over 50% of those diagnosed with alcoholic hepatitis, in fact suffered from liver disease caused by HCV. Currently, there are an estimated 170 million carriers worldwide, and 1.5–2 million in Japan. Even in healthy adults, once an HCV infection occurs, only approximately 30% resolve completely in the acute phase. HCV

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infection is prolonged in approximately 70% of cases, causing chronic hepatitis. Once an HCV infection has become chronic, spontaneous elimination of the virus is rare (0.2% annual rate), and persistent inflammation can induce fibrosis, progressing to cirrhosis or hepatocellular carcinoma (HCC).[2] Interferon (IFN) therapy commenced in 1986, when Hoofnagle *et al.* administered human recombinant IFN-α to patients with non-A non-B hepatitis, confirming normalization of transaminase levels.[3] IFN therapy has been used in the general clinical setting in Western countries since 1991, and in Japan since 1992. Since that time, with the development of the polymerase chain reaction (PCR) method, a revolutionary new technology for viral detection, quiescence of hepatitis has been confirmed in patients in whom HCV RNA was eradicated by IFN therapy;[4] furthermore, inhibition of progression of liver disease and hepatocellular carcinogenesis has been demonstrated in these patients.[5–8]

The aim of treatment of chronic hepatitis C is to improve the long-term prognosis of chronic liver disease (CLD) associated with persistent HCV infection; in other words, to prevent mortality associated with HCC and CLD. Sustained virological response (SVR) rates have improved with the standard therapy combining pegylated interferon (Peg-IFN) and ribavirin. SVR rates are no better than 40–50% in patients with genotype 1 infection who have high viral loads, however, so HCV cannot be eliminated in around half of these patients. In recent years, a number of new antiviral agents have been developed with the aims of increased therapeutic efficacy and decreased adverse reactions. In November 2011, the first generation protease inhibitor telaprevir became available for clinical use in patients with HCV genotype 1 infection and high viral loads. Triple therapy with telaprevir, Peg-IFN-α-2b and ribavirin has shown an increased antiviral effect, improving initial SVR rates to around 70% in treatment-naive cases, but adverse reactions are also increased, including severe anemia and serious skin rashes.[9–13] In Japan, trials are underway with triple therapy comprising a second generation protease inhibitor (TMC435,[14] MK7009[15] or BI-201335), Peg-IFN and ribavirin, as well as IFN-free oral antiviral therapy comprising a protease inhibitor and an NS5A inhibitor.[16] Much is anticipated from the next generation direct antiviral agents (DAA), reported to have considerably fewer adverse reactions, and even greater antiviral effects, with SVR rates exceeding 80% in treatment-naive cases.

Therapeutic guidelines for chronic hepatitis C should be formulated with the above-mentioned background in mind, with careful consideration of the appropriateness of the presently available antiviral therapies for each individual patient.

Indications for antiviral therapy for HCV infection

In general, in patients with chronic hepatitis C, liver disease progresses gradually in association with elevation of alanine aminotransferase (ALT) levels, and the risk of developing cancer increases with the progression of fibrosis.[8] Conversely, cancers are rarely seen arising from a normal liver with no inflammation or fibrosis. Accordingly, in general, antiviral therapy is indicated in all chronic hepatitis C patients with elevated ALT levels (ALT >30 IU/L), indicating hepatic inflammation, or a decreased platelet count (platelet count <150 000/μL), reflecting the degree of liver fibrosis. The indication for antiviral therapy should be individualized for patients with ALT ≤30 IU/L and a platelet count ≥150 000/μL, considering the risk of developing HCC is low.

Early viral eradication is required in the group at high risk of developing cancer. In patients with HCV infection, three factors have been identified as independent risk factors for hepatocellular carcinogenesis: (i) advanced age; (ii) advanced fibrosis; and (iii) male sex.[5–7] Accordingly, the risk of developing cancer is particularly high in patients with multiple risk factors, and early introduction of antiviral therapy should be considered in this group.

Basic guidelines for treatment of chronic hepatitis C

In developing these guidelines, we formulated separate treatment plans according to the risk of developing cancer in different subgroups of patients with chronic hepatitis C, for elderly and non-elderly patients, and those with advanced fibrosis and mild fibrosis. Analyses of hepatocellular carcinogenesis in older patients with chronic hepatitis C show that the risk of cancer increases with increasing age, although the definition of "older age" varies, considered by some to be greater than 55, 60 or 65 years. In these guidelines, we have defined "elderly" as ≥66 years old, based on Japanese clinical trials of telaprevir conducted with subjects aged ≤65 years,[11] and the increased risk of HCC over the age of 65 years.[17] Furthermore, although we have defined "advanced fibrosis" as a METAVIR score ≥F2, or platelet count of <150 000/μL, it should be kept in mind that the risk of cancer is particularly high in the

patient group with a METAVIR score ≥F3, or platelet count of <120 000/μL.

For the group at high risk of developing HCC (elderly and advanced fibrosis), antiviral therapy should be commenced as soon as possible with due consideration to tolerability. Early commencement of antiviral therapy is also desirable in the medium-risk group (elderly or advanced fibrosis). However, some in the particularly high-risk group, elderly and/or with advanced fibrosis, are non-responders, so in order to avoid adverse reactions and the development of drug-resistant mutations, the treatment discontinuation criteria should be kept in mind during antiviral therapy. On the other hand, in the low-risk group comprising non-elderly patients without advanced fibrosis, early introduction of antiviral therapy is not always necessary. In some patients, it may be possible to await the introduction of the new generation antiviral agents, so the present indication for antiviral therapy should be decided after consideration of anticipated therapeutic effect, adverse reactions and the risk of HCC.

In any patient group, in case it is difficult with any presently available antiviral regimens to ensure viral eradication, and ALT levels are elevated (≥30 IU/L), patients should be administered long-term low-dose Peg-IFN or supportive therapy, for example, stronger neo-minophagen C (SNMC), ursodeoxycholic acid (UDCA). If an adequate therapeutic effect is not achieved, and iron overload is suspected, then the addition of, or changeover to, therapeutic phlebotomy should be considered. The aim of these therapies is to keep the ALT level ≤30 IU/L, maintaining it as low as possible. Strict control of the ALT level is particularly necessary in the group at high risk of developing HCC. Low-dose Peg-IFN therapy should be discontinued if no improvement is seen within 6 months in the ALT level (to ≤40 IU/L) or the α-fetoprotein (AFP) level (to ≤10 ng/mL).[18,19]

Recommendations:

1 *In general, antiviral therapy is indicated in all chronic hepatitis C patients with elevated ALT levels (>30 IU/L) or a decreased platelet count (<150 000/μL).*
2 *The indication for antiviral therapy should be individualized for patients with ALT levels ≤30 IU/L and a platelet count ≥150 000/μL, considering the risk of developing HCC is low.*
3 *For the group at high risk of developing HCC (elderly and advanced fibrosis), antiviral therapy should be commenced as soon as possible with due consideration to tolerability.*
4 *Following commencement of antiviral therapy in patients either elderly or with advanced fibrosis, in order to avoid adverse reactions and the development of drug-resistant mutations, the treatment discontinuation criteria, used for the early detection of non-responders, should be kept in mind during antiviral therapy.*
5 *In the low-risk group (non-elderly, non-advanced fibrosis), the present indication for antiviral therapy should be decided after consideration of anticipated therapeutic effect, adverse reactions and the risk of HCC.*
6 *If viral eradication is not achieved, long-term low-dose Peg-IFN or supportive therapy (SNMC or UDCA) should be administered with the aim of preventing progression of liver disease and preventing hepatocellular carcinogenesis. If an adequate therapeutic effect is not achieved, and iron overload is suspected, then the addition of, or changeover to, therapeutic phlebotomy should be considered.*
7 *Low-dose Peg-IFN therapy should be discontinued if no improvement is seen within 6 months in the ALT level (to ≤40 IU/L) or the AFP level (to ≤10 ng/mL).*

3. INTERFERON THERAPY

3.1 Interferon

THE α- AND β-types of IFN have been approved for use in the treatment of chronic hepatitis C. IFN-α preparations come in non-pegylated and pegylated forms, depending on whether polyethylene glycol (PEG) has been attached. The former comes in the form of natural human IFN-α and recombinant IFN-α-2b, and the latter as Peg-IFN-α-2a and Peg-IFN-α-2b. IFN-β preparations comprise natural non-pegylated-IFN-β.

IFN-α

Standard non-pegylated-IFN-α is unstable, with a plasma half-life of 3–8 h, and becomes undetectable after 24 h.[20] Administration at least three times per week is therefore required when treating chronic hepatitis C. Adverse reactions, including fever, chills and headache, are common with non-pegylated-IFN due to repeated rises and falls in the plasma levels. Of the non-pegylated IFNs, natural human IFN-α is approved for self-injection, and patients only need to attend hospital once every 2 weeks. Furthermore, patients can self-inject at night before retiring, better taking advantage of diurnal variations in plasma cortisol levels, and minimizing fever and other adverse reactions.[21–23]

Peg-IFN-α

PEG is a water-soluble neutral molecule with no toxicity of itself. The number of ethylene oxide subunits determines the molecular weight. The aims of pegylating IFN are twofold: (i) to alter its *in vivo* pharmacodynamic properties; and (ii) protect the IFN molecule from recognition and elimination by the host immune defenses. Peg-IFN-α used in the treatment of chronic hepatitis C comes in the form of Peg-IFN-α-2a, with a 40-kD PEG branch chain covalently attached to IFN-α-2a, and Peg-IFN-α-2b, with a 12-kD PEG branch chain attached via a urethane bond to IFN-α-2b. They reach a maximum concentration (Cmax) at 72–96 and 15–44 h after administration, respectively, and after a single dose maintain plasma levels within the therapeutic range for approximately 168 and 80 h, respectively.[24] As the molecular weight of PEG attached to IFN in this way increases, the intracorporeal retention time also increases, although the pharmacological effect decreases in inverse proportion. The IFN activity of Peg-IFN-α-2a is 7% that of non-pegylated-IFN-α-2a, whereas the IFN activity of Peg-IFN-α-2b is 28% that of non-pegylated-IFN-α-2b, with the latter more active. Accordingly, the actual antiviral effect is determined in a complex fashion by the balance between intracorporeal retention time and IFN activity, as well as the patient's body type and weight. Peg-IFN-α-2a is approved as monotherapy and in combination with ribavirin for national medical insurance coverage, whereas Peg-IFN-α-2b is approved in combination with ribavirin with or without telaprevir.

The two forms of Peg-IFN-α have different standard doses. The standard dosage regimen for Peg-IFN-α-2a is fixed at 180 μg/week, and the dose of Peg-IFN-α-2b varies according to the patient's weight, the standard dosage regimen being 1.5 μg/kg per week.

IFN-β

Interferon-β is a natural IFN that can be used in a non-pegylated form, and is approved as monotherapy and in combination with ribavirin for medical insurance coverage. It is administered at least three times per week as an i.v. injection or i.v. infusion. Although IFN-β binds to the same type I IFN receptor as IFN-α, and has a similar antiviral effect to IFN-α, their adverse reaction profiles differ. A retrospective study of natural human IFN-β + ribavirin combination therapy in the treatment of 40 cases with genotype 1b HCV infections reported fewer discontinuations due to adverse reactions, and only mild decreases in platelet counts.[25] Even patients with a history of discontinuing IFN-α therapy due to depression tolerated IFN-β + ribavirin combination therapy well in terms of depressive symptoms and other adverse reactions.[26–28] IFN therapy with natural human IFN-β is therefore recommended in patients in whom IFN-α therapy is not tolerated, for example, those with a history of depression.

Anti-IFN-α neutralizing antibodies were detected in 15% of non-responders to Peg-IFN-α + ribavirin therapy in one study.[29] Anti-IFN-α neutralizing antibodies do not block IFN-β activity, so a changeover to natural human IFN-β should be considered in cases of non-response to Peg-IFN-α + ribavirin due to these neutralizing antibodies.

Natural human IFN-β can be administered twice daily in divided doses, providing a more potent antiviral effect than once daily dosing as measured by the HCV dynamics.[30] Divided dosing IFN-β induction prior to Peg-IFN-α + ribavirin therapy has been trialed.[31]

Antiviral effects of IFN[32–34]

IFN acts through binding to type I IFN receptors on the target cell membrane. Type I IFN receptors are common to IFN-α and IFN-β, and binding of either IFN type to the receptor causes activation of the tyrosine-protein kinase, Janus kinase 1 (JAK1). This induces phosphorylation of tyrosine residues in the intracellular domain of the receptor, resulting in phosphorylation and formation of dimer complexes of signal transducer and activator of transcription 1 (STAT1), which transmit signal to the cell nucleus. This in turn induces and upregulates expression of IFN-stimulated genes (ISG). The family of ISG includes a wide variety of antiviral and immunoregulatory genes, and the antiviral effects of IFN are thought to derive from proteins induced by ISG.

Adverse reactions

Adverse reactions to IFN therapy are experienced by almost all patients. The most common are influenza-like symptoms, such as general malaise, fever, headache and aching joints, and are reported by 60–95% of patients. Most influenza-like syndrome can be controlled with anti-inflammatory analgesic medication. Blood tests show leukopenia, with white blood cell counts <1000/mm^3 seen in approximately 60% of patients. Serious infections associated with neutropenia are, however, considered rare.[35] White blood cell, neutrophil and platelet counts tend to decrease for the first 4 weeks of IFN therapy, then often remain stable without further decline. Neuropsychiatric symptoms such as depression and insomnia occur in 5–10% of patients, and are more

common in those with pre-existent neuropsychiatric symptoms or a history of depression.[36] Neuropsychiatric symptoms are classified into depression-specific symptoms and depression-related autonomic nervous symptoms, with selective serotonin re-uptake inhibitors (SSRI) reported to be useful in treating the former.[37–39] IFN can also trigger or aggravate autoimmune diseases such as chronic thyroiditis, so the utmost caution is required when administrating IFN to patients with autoimmune diseases. Interstitial pneumonia, another reported adverse reaction to IFN therapy, can be serious and even life-threatening. It usually occurs after 2 months of therapy, or in the later stages of treatment. A rapid and appropriate management is required following the onset of respiratory symptoms such as a dry cough or dyspnea, including an immediate chest CT scan. Determination of serum KL-6 levels is also useful in the diagnosis of interstitial pneumonia. Other reported adverse reactions to IFN therapy include cardiomyopathy and fundal hemorrhage.

The adverse reaction profile of Peg-IFN differs somewhat to that of non-pegylated-IFN. In a Japanese clinical trial of Peg-IFN-α-2a monotherapy, the adverse reactions with a higher reported frequency than non-pegylated-IFN-α-2a were skin reactions such as erythema at the injection site and hematological reactions such as decreases in the white blood cell counts or platelet counts. On the other hand, mild to moderate adverse reactions such as influenza-like syndrome, including fever and joint pains, or malaise and loss of appetite, were milder than with standard non-pegylated-IFN-α-2a.[40]

Recommendations:

1 ***Reported adverse reactions to IFN therapy include influenza-like syndrome, decrease of blood cell counts, neuropsychiatric symptoms, autoimmune phenomena, interstitial pneumonia, cardiomyopathy and fundal hemorrhage.***
2 ***Pegylation stabilizes serum IFN levels, ameliorating influenza-like syndrome such as fever and joint pains.***
3 ***Patients self-injecting of natural human IFN-α at night minimizes influenza-like syndrome.***
4 ***IFN-β should be considered in patients unable to tolerate IFN-α due to depression or other causes.***

Is there any difference between Peg-IFN-α-2a and Peg-IFN-α-2b therapeutic efficacy and adverse reactions?

In Japan at present, two Peg-IFN formulations are available for use in Peg-IFN + ribavirin therapy, Peg-IFN-α-2a and Peg-IFN-α-2b. McHutchison *et al.* conducted a large multi-center study comparing the efficacy of these two agents. In this randomized controlled trail (RCT) conducted at 118 institutions, with 3070 patients with IFN-naive genotype 1 HCV infection, the SVR rate in the Peg-IFN-α-2a 180-μg group was 40.9% and that in the Peg-IFN-α-2b group 39.8%, with no difference seen between groups, and no significant difference was seen between groups in terms of tolerability.[41] On the other hand, two Italian single-center studies with 441 and 320 patients with IFN-naive genotype 1–4 HCV infection, respectively, found no significant difference between groups in the incidence of adverse events, but reported significantly higher SVR rates in the Peg-IFN-α-2a group than in the Peg-IFN-α-2b group.[42,43] A recent systematic review examining 12 RCT of the efficacy and safety of these two agents found no difference between them in terms of adverse events causing discontinuation. The overall SVR rates based on 8 RCT were 47% for the Peg-IFN-α-2a group and 41% for the Peg-IFN-α-2b group, significantly higher in the former (risk ratio, 1.11; 95% confidence interval [CI], 1.04–1.19; $P = 0.004$).[44] However, a conclusion has not been reached to recommend either agent, due to heterogeneity of the patient populations in HCV genotype, race and Peg-IFN-α-2b dosage in the different RCT, as well as problems with the quality of the RCT in terms of subject numbers and withdrawals, and only limited data concerning adverse events. In Japan, studies have been conducted comparing both agents, but the final results have yet to be published.

Accordingly, at present, Peg-IFN-α-2a and Peg-IFN-α-2b are considered similar from the viewpoints of efficacy and adverse reactions, and there is no definitive evidence supporting a recommendation of either formulation in clinical practice. To improve therapeutic efficacy further, more important considerations will be optimization of the dosage and duration of treatment with other agents, such ribavirin, for each individual patient, as well as formulation of a treatment plan with consideration of factors that influence therapeutic efficacy for each patient, and control of adverse reactions.

Inhibition of HCC by IFN monotherapy

Many reports have emerged from Japan regarding inhibition of hepatocellular carcinogenesis by IFN therapy. Ikeda *et al.*[6] performed a retrospective analysis of cumulative hepatocellular carcinogenesis rates in patients with chronic hepatitis C who underwent IFN monotherapy as initial treatment, stratified for therapeutic

efficacy. The 10-year hepatocellular carcinogenesis rate was 12.0% in the untreated group ($n = 452$), 15.0% in the IFN nonresponsive group, with no SVR and abnormal ALT levels ($n = 1076$) and 1.5% in the SVR group ($n = 676$), significantly lower in the latter. Even in the incomplete response group, with no SVR but normalization of ALT levels ($n = 298$), the 10-year hepatocellular carcinogenesis rate was 2.0%, indicating suppression of HCC.[6] Imai *et al.*[45] and Kasahara *et al.*[7] have reported similar results, with IFN therapy inhibiting hepatocellular carcinogenesis in the normalized ALT group. Furthermore, Yoshida *et al.*[8] conducted a large-scale retrospective study with 2890 patients, reporting that IFN therapy and resultant SVR reduce the risk of developing HCC, including patients in whom ALT levels improved to within two times the upper limit of normal. They further reported that the calculated rate of progression of hepatic fibrosis was −0.28/year in IFN responders, indicating amelioration of hepatic fibrosis associated with viral clearance, and even in patients who failed to respond to IFN, the rate of progression of −0.2/year indicated inhibition of progression of hepatic fibrosis.[8] Okanoue *et al.* also reported inhibitory effect on development of HCC dependent on the degree of progression of hepatic fibrosis, and amelioration of fibrosis with IFN therapy.[46] Nishiguchi *et al.* conducted a prospective study with patients with HCV-associated cirrhosis, finding HCV eradication or prolonged normalization of ALT levels by IFN therapy significantly reduced the risk of HCC and liver failure.[47]

Overseas, Di Bisceglie *et al.* conducted the Hepatitis C Antiviral Long-term Treatment Against Cirrhosis (HALT-C) trial, a prospective randomized controlled study of whether low-dose Peg-IFN-α maintenance therapy can reduce the rate of liver disease-associated events, including HCC, in non-responders to Peg-IFN-α + ribavirin therapy. They recruited a cohort of 1050 HCV-infected patients with bridging fibrosis or cirrhosis who had not had an SVR to previous therapy with Peg-IFN-α + ribavirin therapy, and randomly allocated them to a group administered Peg-IFN-α-2a 90 μg/week for 3.5 years or an untreated control group. They compared incidences during the observation period of outcome variables including the following: death, development of HCC, development of hepatic decompensation and exacerbation of histological fibrosis. After 3.8 years of observation in both groups, 157 patients reached one of the end-points, 34.1% of the treatment group and 33.8% of the control group, with no significant difference seen between groups (hazard ratio [HR], 1.01; 95% CI, 0.81–1.27).[48] They also examined the risk of hepatocellular carcinogenesis in this cohort, with 48 patients (4.8%) developing HCC during the observation period. The 5-year cumulative HCC rate was 5.4% in the treatment group and 5.0% in the control group, with no significant difference seen between groups ($P = 0.78$).[49] The conclusion was that, at this stage, low-dose Peg-IFN-α-2a maintenance therapy does not reduce the rate of liver disease-associated events, including HCC, in non-responders to Peg-IFN-α + ribavirin therapy. Similar results were achieved in a study using Peg IFN-α-2b.[50]

However, Lok *et al.* recently published the results of an extended analysis of the HALT-C cohort. Extending the observation period beyond the previous analysis to a median 6.1 years (greatest, 8.7 years), they reported HCC in 88 patients (8.4%). Including both patients with and without cirrhosis, the 7-year cumulative HCC rate was 7.2% in the treatment group and 9.6% in the control group, with no significant difference seen between groups (HR, 0.77; 95% CI, 0.51–1.18; $P = 0.24$), showing no clear inhibition of hepatocellular carcinogenesis by IFN therapy. If we limit the analysis to patients with cirrhosis, however, the 7-year cumulative HCC rate was 7.8% in the treatment group and 24.2% in the control group, showing a significant reduction in the risk of HCC with low-dose Peg-IFN-α-2a maintenance therapy (HR, 0.45; 95% CI, 0.24–0.83; $P = 0.01$). However, this effect was not significant in patients without cirrhosis, as the 7-year cumulative HCC rate was 8.3% in the treatment group and 6.8% in the control group, actually tending to be higher in the group administered Peg-IFN-α (HR, 1.44; 95% CI, 0.77–2.69; $P = 0.26$).[51]

Inhibition of hepatocellular carcinogenesis by low-dose Peg-IFN-α-2a monotherapy was also examined in Japan in a multicenter collaborative trial. The subjects were 59 patients administered Peg-IFN-α-2a monotherapy and a control group comprising 59 patients matched for age, sex, degree of fibrosis, platelet counts and serum bilirubin levels. They reported a significantly lower cumulative HCC rate in the Peg-IFN-α-2a monotherapy group ($P = 0.0187$) with a relative risk (RR) of 0.167. The reduction in risk of HCC was particularly marked in patients with advanced fibrosis (F3–4) (RR, 0.0847; $P = 0.0036$). Even in patients who failed to eradicate HCV RNA, the HCC rate was significantly lower in those who achieved either an ALT level <40 IU/L or AFP <10 ng/mL at treatment week 24.[19] Improvement in ALT and AFP levels with Peg-IFN-α-2a monotherapy has been reported in other Japanese studies.[52,53]

We can understand that with extension of the observation period, the results of the HALT-C trial confirm that low-dose Peg-IFN-α maintenance therapy reduces the risk of HCC in patients with cirrhosis. The effect was unclear on analysis of the entire cohort in patients without cirrhosis, however, and the results suggest that reduction in the risk of HCC did not emerge until after at least 4 years of low-dose Peg-IFN-α maintenance therapy. On the other hand, the above-mentioned Japanese studies confirmed that IFN therapy significantly reduced the incidence of HCC in patients with sustained normalization of ALT levels, even if SVR was not achieved. In the above-mentioned multicenter collaborative trial of Peg-IFN-α-2a monotherapy, a significant reduction in the HCC was seen, even when patients without cirrhosis were included, and with shorter observation periods. In this way, the results of the HALT-C trial do not agree with Japanese findings. Possible reasons for this discrepancy may include the fact that the average age of the HALT-C cohort was 52 years, younger than the average age of Japanese patients with chronic hepatitis C, and the low overall incidence of HCC. Asahina *et al.* reported that in Japanese patients with chronic hepatitis C, even with the same degree of fibrosis the risk of HCC is considerably higher in older patients, whereas in patients with cirrhosis, there is no significant difference in the risk of HCC associated with aging.[17] We cannot therefore exclude the possibility that differences between Japan and the USA in the ages of patients with chronic hepatitis C and the risk of HCC influenced the results of the HALT-C trial for patients without cirrhosis. Furthermore, there were a considerable number of deaths and liver transplantation events in the HALT-C cohort, the incidences of which were significantly different between patients on low-dose Peg-IFN maintenance therapy and control groups among patients without cirrhosis.[54] These deaths and liver transplantation events give rise to bias in analyses of the risk of HCC. From the above, a certain degree of caution is needed in interpreting the results of the HALT-C trial.

Inhibition of HCC by IFN monotherapy in the elderly

As mentioned above, Japanese patients with chronic hepatitis C are older than their Western counterparts, and the risk of developing HCC is higher in elderly patients, even after correction for other risk factors. Although the risk of HCC is significantly reduced with SVR, even in elderly patients, in comparison with younger patients they are more likely to fail to achieve SVR, and to discontinue treatment due to adverse reactions.[17] With these considerations of therapeutic efficacy and adverse reactions in mind, in Japan, long-term IFN monotherapy is widely used in elderly patients, the aim of treatment being inhibition of hepatocellular carcinogenesis by reducing inflammation rather than viral eradication.

Arase *et al.*[18] examined the reduction in hepatocellular carcinogenesis by IFN therapy in a study with 120 subjects aged ≥60 years with either chronic hepatitis C or liver cirrhosis. They were treated with natural IFN-α 3 MU three times weekly for an average of 2.47 years, and compared with an age- and sex-matched control group not administered IFN comprising 240 subjects. As a result, the 10-year HCC rate was 17.3% in the IFN group and 32.8% in the control group, with an RR of 0.3. AFP levels decreased significantly in the IFN group than in the control group, and the incidence of HCC was particularly low in patients with AFP levels <10 ng/mL.[18] Nomura *et al.* also conducted a study with 44 patients with genotype 1 HCV infection aged ≥60 years. They were treated with natural IFN 3 MU three times weekly for 3 years, and compared with a control group not administered IFN, matched for age, sex and hepatic histological findings, comprising 44 subjects. They reported a significantly lower cumulative rate of HCC in the IFN group.[55]

Recommendations:

1 *Eradication of HCV by IFN therapy lowers the risk of HCC.*
2 *Even if HCV cannot be eradicated, we can expect the risk of developing HCC to be reduced through lowering ALT or AFP levels by long-term natural IFN-α therapy or long-term Peg-IFN-α-2a monotherapy.*

Inhibition of HCC recurrence by IFN therapy

Not only is IFN administered with the aim of inhibiting hepatocellular carcinogenesis in patients with chronic hepatitis C and cirrhosis who have not yet developed HCC, it is also given to patients who have undergone complete ablation or resection of HCC nodules with the aims of preventing recurrence and improving survival rates. Shiratori *et al.*[56] randomly allocated patients who had undergone complete ablation of HCC nodules, using ethanol injection, to a group administered IFN for 48 weeks and an untreated control group, comparing recurrence rates and survival rates. They reported no significant difference between groups in the rate of first recurrence; however, the rates of second and subsequent recurrences were significantly lower in the IFN group, as

were survival rates. These results indicated the usefulness of IFN therapy following complete tumor ablation.[56] Sakaguchi *et al.*[57] and Kudo *et al.*[58] administered low-dose long-term IFN-α-2b or IFN-α-2a therapy to 127 patients with HCC who had undergone complete ablation. Comparison with an untreated control group matched for sex, age and platelet count showed a significant reduction in recurrences after the first recurrence, and a significant improvement in survival rates, the RR for survival being 0.21.[57,58] Another study of IFN + ribavirin therapy following hepatic arterial embolization or radiofrequency ablation reported viral eradication in half of patients, with lower tumor recurrence rates and prolonged survival.[59]

Recommendation:

IFN therapy following complete ablation of HCC can be expected to reduce tumor recurrence rates and improve survival rates.

Necessity of follow up of patients who achieved an SVR

SVR is defined as undetectable levels of serum HCV RNA 24 weeks after the completion of IFN treatment. HCV RNA clearance is usually sustained in cases of SVR, with HCV RNA remaining undetectable in 99–100% over the average 5.6-year observation period (range, 1–8.3 years) in patients with SVR to IFN + ribavirin therapy.[60,61] In studies conducted prior to 2000, however, a somewhat lower proportion at 96–98% of patients remained serum HCV RNA negative.[62–66] Possible causes for this discrepancy are that IFN monotherapy was the mainstay in the earlier studies, and that the sensitivity of testing for HCV RNA was lower at the time, suggesting the possibility of false-positive assessments of SVR.

As described above, achievement of SVR gives sustained clearance of HCV RNA, and significantly reduces the risk of HCC in patients with chronic hepatitis C.[6–8,45,46] However, HCC has been reported to develop during follow up even in patients who have achieved SVR. A number of Japanese studies have addressed hepatocellular carcinogenesis following SVR, with reported HCC rates of 0.9–4.2% over mean observation periods of 3.3–8.0 years. Risk factors for HCC include advanced age, male sex, advanced fibrosis, alcohol consumption, hepatic steatosis and insulin resistance. The interval between achieving SVR and detection of HCC is most often reported as being within 10 years, although some studies reported an interval of greater than 10 years.[8,17,46,67–71] There is a lack of consensus regarding how long patients should be screened for HCC following SVR, but depending on the risk factors for hepatocellular carcinogenesis in each individual patient, screening for HCC should continue for at least 5–10 years after achieving SVR.

Recommendation:

Risk factors for developing HCC in virological responders include advanced age, male sex, advanced fibrosis, alcohol consumption, hepatic steatosis and insulin resistance. Even following SVR, screening for HCC should continue with consideration of the known risk factors for each individual.

3.2 Ribavirin

Ribavirin, a purine nucleotide analog with a chemical structure resembling guanosine, shows antiviral activity against a wide range of RNA and DNA viruses.[72] Proposed mechanisms for the actions of ribavirin include T-helper cell 1 dominant immune induction, induction of viral mutagenesis, inhibition of RNA polymerase and depletion of intracellular guanosine triphosphate pools.[73] Ribavirin monotherapy for chronic hepatitis C improves ALT levels, but does not decrease HCV RNA or improve liver histology.[74–76] However, IFN-α-2b + ribavirin combination therapy is superior to IFN-α-2b monotherapy in terms of viral clearance and improved ALT levels.[77]

Ribavirin is generally used in combination with one of the Peg-IFN preparations, Peg-IFN-α-2a or Peg-IFN-α-2b. In comparison with Peg-IFN monotherapy, higher end-of-treatment HCV RNA clearance rates are achieved with Peg-IFN + ribavirin combination therapy, but most importantly, the addition of ribavirin markedly decreases the risk of relapse following completion of treatment.[78,79] Presently in Japan, apart from the Peg-IFN preparations, ribavirin can also be used in combination with standard non-pegylated-IFN-α-2a or IFN-β. When the pretreatment hemoglobin (Hb) level is ≥14 g/dL, the daily dose of ribavirin is 600 mg for patients weighing ≤60 kg, 800 mg for 61–80 kg and 1000 mg for >80 kg.[80,81]

Therapeutic results

The efficacy of Peg-IFN + ribavirin combination therapy was confirmed in two Japanese phase III clinical trials.[82,83] In Japanese clinical studies with patients with genotype 1b chronic hepatitis C with high viral loads (>100 kIU/mL), the SVR rate with 48 weeks of Peg-IFN-α-2b + ribavirin therapy was 48% (121/254), and that for 48 weeks of Peg-IFN-α-2a + ribavirin therapy was

59% (57/96).[83,84] In another study, other than with genotype 1b and high viral loads, a high SVR rate of 89% (40/45) was achieved with 24 weeks of Peg-IFN-α-2b + ribavirin therapy.[85]

Adverse reactions

Ribavirin is administered p.o. twice daily, after breakfast and dinner. The peak plasma concentration is reached 1–2 h after ingestion, and with repeated administration plasma levels reach equilibrium after 4–8 weeks of treatment. Ribavirin accumulates in the body, remaining in the liver, muscle and within erythrocytes for long periods. Ribavirin is mostly eliminated by the renal route, and caution is required when prescribing to patients with renal disease or impaired renal function. It is contraindicated in patients with a creatinine clearance ≤50 mL/min. Ribavirin is not eliminated by dialysis, so it is generally contraindicated in patients with renal failure on dialysis.

The main adverse reaction to ribavirin is hemolytic anemia, so caution is required when considering ribavirin therapy in patients with anemia or heart conditions (e.g. ischemic heart disease, heart failure, arrhythmia). In a Japanese clinical trial of Peg-IFN-α-2b + ribavirin combination therapy, treatment was discontinued in 8–11% of patients, and the ribavirin dose reduced in 20%, due to anemia. Dose reduction was more common in patients with a pretreatment Hb <14 g/dL, neutrophil count <2000/μL or platelet count <120 000/μL, and in females. In particular, a reduction in the dose of Peg-IFN or ribavirin was required in 80% of patients aged ≥65 years with a pretreatment Hb ≤13 g/dL. The rate of discontinuation of treatment was high in patients with a decline in Hb ≥2 g/dL at 2 weeks from the start of treatment, so the authors suggest reducing the ribavirin dose by 200 mg/day at this point.[86] The criteria for ribavirin dose reduction or discontinuation when a decline in Hb occurs during treatment (in patients without heart conditions) are: reduce the daily dose by 200 mg (400 mg if started at 1000 mg) for Hb <10 g/dL, and discontinue if Hb is <8.5 g/dL.[80,81] In one of the above-mentioned Japanese clinical studies, the SVR rate was 62.5% when no reduction in the IFN or ribavirin dose was needed, 45.7–53.3% when a dose reduction or temporary withdrawal was needed, falling to 19.2% when treatment was discontinued.[83] Accordingly, to achieve SVR it is important to control any decline in Hb appropriately, complete the treatment without discontinuation and as much as possible avoid any dose reductions or temporary withdrawals.

It has become evident that two functional variants in the inosine triphosphatase (*ITPA*) gene on chromosome 20 (rs7270101 and rs1127354) are associated with severe anemia during Peg-IFN + ribavirin therapy.[87,88] Of the *ITPA* polymorphism (rs1127354), the CC genotype (major-homo) was strongly associated with treatment-induced anemia in comparison with the CA + AA genotypes, and the CC genotype was an independent risk factor for ribavirin dose reduction.[89] Accordingly, patients with the CC genotype and low Hb need to be monitored for further decline in Hb during treatment.

Other adverse reactions associated with ribavirin include lymphopenia, hyperuricaemia, pruritus, rashes, cough and nasal congestion. Teratogenicity has been reported in animal studies with ribavirin, so it is contraindicated in pregnant women, women who may be pregnant and breastfeeding women. Transfer into the seminal fluid cannot be ruled out, so when ribavirin is administered to women who might become pregnant, or men whose partner might become pregnant, they should be advised to use contraception during treatment and for 6 months after its completion.

Recommendations:

1 *In comparison with Peg-IFN monotherapy, HCV RNA is more likely to be undetectable at the end of treatment with Peg-IFN + ribavirin combination therapy, and the risk of relapse following completion of treatment is markedly decreased.*
2 *The main adverse reaction to ribavirin is hemolytic anemia, so caution is required when considering ribavirin therapy in patients with anemia or heart conditions.*
3 *To achieve SVR it is important to control any decline in Hb appropriately, complete the treatment without discontinuation, and as much as possible avoid any dose reductions or temporary withdrawals.*
4 *SNPs (rs7270101 and rs1127354) in the ITPA gene are associated with severe anemia during Peg-IFN + ribavirin therapy.*
5 *Due to concerns regarding teratogenicity, ribavirin is contraindicated in pregnant and breastfeeding women. Women who might become pregnant, and men whose partner might become pregnant, should be advised to use contraception.*

3.3 Telaprevir

Telaprevir, discovered through optimization of α-ketoamide scaffolds, is an antiviral agent that can be administered p.o.[90] A protease inhibitor, telaprevir

directly inhibits NS3-4A serine protease, a HCV gene non-structural protein that plays an important role in HCV replication, thereby strongly inhibiting viral replication.[91] Telaprevir inhibits replication of the HCV genotype 1 particularly strongly, and was approved in September 2011 for use in Japan in combination with Peg-IFN and ribavirin in the treatment of genotype 1 chronic hepatitis C with a high viral load (≥5.0 log IU/mL).

Therapeutic results

Treatment-naive patients. The duration of telaprevir + Peg-IFN-α-2b + ribavirin triple therapy is 24 weeks, with all three agents for the first 12 weeks, then Peg-IFN-α-2b + ribavirin dual therapy for the remaining 12 weeks. In a Japanese phase III clinical trial of 24 weeks of triple therapy for IFN-naive patients (aged ≤65 years), the SVR was 73% (92/126), significantly higher than that of 49% (31/63) for the control group, given Peg-IFN-α-2b + ribavirin dual therapy for 48 weeks (Table 1). The relapse rate was 17% (21/126), the breakthrough rate 3% (4/126) and the non-response rate 1% (1/126). No correlation was seen between sex or viral load at commencement and SVR, whereas the SVR rate was higher in patients aged <50 years than in those aged ≥50 years (85% vs 67%, $P = 0.034$).[11]

Analysis of therapeutic efficacy according to adherence showed that the SVR rate in patients who discontinued none of the three agents was 84% (66/79), 60% (12/20) in those who discontinued telaprevir alone and 52% (14/27) in those who discontinued all three agents. The SVR rate was high at 79% (85/108) in patients with ≥60% adherence to telaprevir and 39% (7/18) in those with <60% adherence. Similarly, the SVR rate was high at 84% (68/81) in patients with ≥80% adherence to Peg-IFN-α-2b, and was less than 60% in those with <80% adherence. The SVR rate was high at 93% (13/14) in patients with ≥80% adherence to ribavirin, and although the SVR rate decreased as adherence declined, it was still 53% (8/15) in those with <20% adherence to ribavirin.[11]

In terms of virological kinetics, the SVR rate was 75% (81/108) in patients achieving a rapid virological response (RVR) (Table 2) and 61% (11/18) in those failing to achieve an RVR. The SVR rate was 80% (70/88) in patients achieving an extended RVR (eRVR) and 58% (22/38) in those failing to achieve an eRVR (Table 3).[11]

Relapsers and non-responders to previous treatment. A Japanese trial of 24 weeks' triple therapy for relapsers and non-responders to previous treatment yielded SVR rates of 88% (96/109) and 34% (11/32), respectively (Table 4). No correlation was seen between sex, age or viral load at commencement and SVR. Analysis of therapeutic efficacy according to adherence showed that the SVR rate was 91% (93/102) in relapsers with ≥40% adherence to telaprevir and 43% (3/7) in those with <40% adherence. In non-responders to previous treatment, the SVR rate was 40% (10/25) with ≥80% adherence to telaprevir and 17% (1/6) in those with 60–80% adherence. The SVR rate was ≥80% in relapsers to previous treatment with ≥40% adherence to Peg-IFN-α-2b and 48% (11/23) in non-responders to previous treatment only with ≥80% adherence. The SVR rate was high at ≥85% in relapsers with ≥20% adherence to ribavirin and 33–38% in non-responders even with 40–80% adherence to ribavirin.[9]

In terms of virological kinetics, among relapsers the SVR rate was 92% (90/98) in those achieving an RVR and 55% (6/11) in those failing to achieve an RVR. For non-responders to previous treatment, the SVR rate was 39% (9/23) in those achieving an RVR and 22% (2/9) in those failing to achieve an RVR. The SVR rate was 96% (84/88) in relapsers achieving an eRVR and 57% (12/21) in those failing to achieve an eRVR; whereas for non-responders to previous treatment the SVR rate was 47% (9/19) in those achieving an eRVR and 15% (2/13) in those failing to achieve an eRVR (Table 3).

Table 1 Therapeutic results for telaprevir + Peg-IFN-α-2b + ribavirin triple therapy in treatment-naive patients (SVR rate, %) (reproduced from [11])

	Telaprevir + Peg-IFN-α-2b + ribavirin triple therapy	Peg-IFN-α-2b + ribavirin dual therapy	*P*
SVR	73.0	49.2	0.002
Relapse	16.7	22.2	
Breakthrough	3.2	1.6	
Non-response	0.8	20.6	<0.0001

Peg-IFN, pegylated interferon; SVR, sustained viral response.

Recommendations:

1 ***The SVR rate was 73% in IFN-naive patients administered telaprevir + Peg-IFN-α-2b + ribavirin triple therapy for 24 weeks, significantly higher than that of 49% in the control group administered Peg-IFN-α-2b + ribavirin dual therapy for 48 weeks.***

2 *Telaprevir + Peg-IFN-α-2b + ribavirin triple therapy achieved SVR rates in relapsers and non-responders to previous treatment of 88% and 34%, respectively.*

Table 2 Virological response definitions

Virological response	Definition
Rapid virological response (RVR)	Serum hepatitis C virus (HCV) RNA undetectable at treatment week 4
Extended RVR (eRVR)	Serum HCV RNA undetectable at both treatment week 4 and 12
Early virological response (EVR)	cEVR or pEVR
Complete EVR (cEVR)	Serum HCV RNA undetectable at treatment week 12
Partial EVR (pEVR)	Serum HCV RNA detectable at treatment week 12 but decrease ≥2 $\log_{10}$ IU/mL
End of treatment response (ETR)	Serum HCV RNA undetectable at the end of treatment
Sustained virological response (SVR)	Serum HCV RNA undetectable 24 weeks after the completion of treatment
Breakthrough	Reappearance of HCV RNA at any time during treatment having once been undetectable
Relapse	Reappearance of HCV RNA following treatment having been undetectable during treatment
Non-responder	Serum HCV RNA never undetectable during treatment
Null responder	Serum HCV RNA decrease <2 $\log_{10}$ IU/mL at treatment week 12
Partial responder	Greater than 2 $\log_{10}$ IU/mL decrease in serum HCV RNA level from baseline at treatment week 12, but serum HCV RNA detectable at treatment week 24

N.B.: The 2009 American Association for the Study of Liver Diseases (AASLD) "Diagnosis, management, and treatment of hepatitis C: an update" define non-responder, null responder and partial responder as "failure to clear HCV RNA from serum after 24 weeks of therapy", "failure to decrease HCV RNA by <2 logs after 24 week of therapy" and "2 log decrease in HCV RNA but still HCV RNA positive at week 24", respectively.[116] However, the 2011 version, updated to include telaprevir and boceprevir, dropped the non-responder category, and redefined null responder and partial responder as "failure to decrease HCV RNA level by at least 2 log IU/mL at treatment week 12" and "decrease in HCV RNA level by at least 2 log IU/mL at treatment week 12 but HCV RNA still detected at treatment week 24", respectively.[101] In these guidelines, we define null and partial responder as per the 2011 AASLD guidelines, and further define non-responder as encompassing both null and partial responders.

Adverse reactions

The incidence of adverse reactions is greater for telaprevir + Peg-IFN-α-2b + ribavirin triple therapy than for Peg-IFN + ribavirin dual therapy. The most important adverse reactions are skin disorders and anemia.

In one study, skin disorders were reported in 85% (226/267) of patients, of greater severity than with dual therapy. The timing of onset was within 7 days after commencement of treatment in 56% (150/267) and within 28 days in 77% (205/267). More than 50% of the body surface was affected in 5% (19/355) of patients. Constitutional symptoms such as fever and lymphadenopathy were reported in 7% of patients, and serious skin disorders, including Stevens–Johnson syndrome, drug-induced hypersensitivity syndrome and erythema multiforme with mucosal involvement, in 1.5% (4/267).[92] Accordingly, strict attention should be given to any skin changes. A dermatologist should be consulted in the management of any treatment-induced skin disorders, and appropriate treatment promptly commenced in accordance with the symptom severity, topical corticosteroids and oral anti-allergic drugs for milder cases, and systemic corticosteroids for more severe cases. Most cases can be managed with topical corticosteroids and oral anti-allergic drugs. However, when skin disorders occur the hepatologist should not treat them his/herself, but should always consult a dermatologist colleague, even for mild symptoms, and follow their instructions regarding the possibility of exacerbation, and the use of topical and systemic medication to control symptoms. Subsequent collaboration is also important. The decision whether telaprevir therapy can be continued should also be made in consultation with the dermatologist, with due consideration of therapeutic efficacy and adverse reactions.

Anemia is an important adverse reaction to Peg-IFN-α-2b + ribavirin dual therapy, with a strong correlation between the SNP (rs1127354) of the ITPA gene and a decline in Hb during treatment.[87,88,93] The addition of telaprevir to dual therapy causes even more severe anemia. In the above-mentioned Japanese clinical trial for treatment-naive patients, the incidence of grade 1 anemia (Hb 9.5–11.0 g/dL) was 39.7% in the group administered telaprevir + Peg-IFN + ribavirin triple therapy and 50.8% in the group on Peg-IFN + ribavirin dual therapy, whereas the incidence of grade 2 anemia (Hb 8.0–9.5 g/dL) was 27.0% and 17.5%, respectively, and grade 3 anemia (Hb <8.0 g/dL) occurred only in the triple therapy group.[11] The rate of treatment discontinuation due to anemia is also high with triple therapy.

Table 3 Therapeutic results for telaprevir + Peg-IFN-α-2b + ribavirin triple therapy stratified by RVR and eRVR (SVR rate, %) (reproduced from [9,11])

	RVR		eRVR	
	Achieved	Not achieved	Achieved	Not achieved
Initial treatment	75% (81/108)	61% (11/18)	80% (70/88)	58% (22/38)
Relapse	92% (90/98)	55% (6/11)	96% (84/88)	57% (12/21)
Non-response	39% (9/23)	22% (2/9)	47% (9/19)	15% (2/13)

eRVR, extended rapid viral response; RVR, rapid viral response; SVR, sustained viral response.

Similarly to dual therapy, with triple therapy including telaprevir, significantly greater decreases in Hb early in the treatment period are seen with the CC genotype of the ITPA gene than with the CA/AA genotypes. Rapid decreases in Hb are seen up to treatment week 4 in patients with the CC genotype.[94] Risk factors for a Hb level <11.0 g/dL at treatment week 4 were female sex, body mass index <23, CC genotype of the ITPA gene and age ≥50 years. Risk factors for a Hb level <8.5 g/dL, one of the discontinuation criteria, were patients weighing <60 kg and aged ≥61 years. Patients with any of these risk factors should be carefully monitored for changes in Hb levels.

The response to a decline in Hb should be regular Hb measurements and an early reduction in the ribavirin dose. As mentioned above, in Japanese clinical trials of initial therapy and retreatment, reductions in the ribavirin dose had relatively little effect on therapeutic efficacy.[9,11] In particular, SVR rates ≥85% were achieved in relapsers as long as at least 20% of the intended ribavirin dose was administered.[9]

Some other noteworthy adverse reactions seen in the early treatment period that have come to light through post-marketing surveillance are raised serum creatinine (renal dysfunction) and hyperuricaemia. As these generally appear within the first week of treatment, patients should be monitored for rises in serum creatinine and uric acid soon after treatment commences. Japanese clinical trials of triple therapy including telaprevir did not include patients with cirrhosis, so its safety in these patients has not been established. Clinicians should be aware that triple therapy is not approved for patients with cirrhosis under the national medical insurance scheme.

Table 4 Therapeutic results for telaprevir + Peg-IFN-α-2b + ribavirin triple therapy in relapsers and non-responders to previous treatment (SVR rate, %) (reproduced from [9])

	Relapsers	Non-responders to previous treatment
SVR	88.1	34.4
Relapse	7.3	40.6
Breakthrough	0.9	18.8
Non-response	0.9	6.3

SVR, sustained viral response.

Recommendations:

1 ***Serious skin disorders can occur with telaprevir + Peg-IFN + ribavirin triple therapy. When skin disorders occur, the hepatologist should not treat them his/herself, but should always consult a dermatologist colleague, even for mild symptoms, and follow their instructions regarding the possibility of exacerbation, and the use of topical and systemic medication to control symptoms. The decision whether telaprevir therapy can be continued should also be made in consultation with the dermatologist, with due consideration of therapeutic efficacy and adverse reactions.***
2 ***A decline in Hb should be managed with regular Hb measurements and an early reduction in the ribavirin dose.***
3 ***Serum creatinine and uric acid levels may rise early in the treatment period.***
4 ***In patients with liver cirrhosis, the safety of triple therapy including telaprevir has not been established, and thus triple therapy is not approved for cirrhosis by national medical insurance in Japan.***

Drug interactions

Telaprevir strongly inhibits the CYP3A4/5 drug metabolizing enzyme, and may increase plasma levels of co-administered drugs that are also substrates of CYP3A4/5. Telaprevir is also metabolized by CYP3A4, so co-administration with inducers of CYP3A4 may lower plasma telaprevir levels. As a result, co-administration of a number of agents with telaprevir is contraindicated (Table 5) and caution is advised with

Table 5 Drugs contraindicated for co-administration with telaprevir with trade names (reproduced from [95])

Contraindicated drug (generic name)	Trade names
Quinidine sulfate hydrate	Quinidine sulfate
Bepridil hydrochloride hydrate	Vascor, Bepricor
Flecainide acetate	Tambocor
Propafenone hydrochloride	Rythmol, Pronon
Amiodarone hydrochloride	Cordarone, Ancaron
Pimozide	Orap
Ergotamine tartrate	Cafergot, Ergomar
Dihydroergotamine mesilate	Migranal, Dihydergot
Ergometrine maleate	Oxytocin
Methylergometrine maleate	Methergine, Utergin
Triazolam	Halcion, Hypam, Trilam
Lovastatin/simvastatin	Crestor/Zocor
Atorvastatin calcium hydrate	Lipitor, Caduet
Alfuzosin	Uroxatral
Vardenafil hydrochloride hydrate	Levitra
Sildenafil citrate (for treatment of pulmonary hypertension)	Viagra, Revatio
Tadalafil (for treatment of pulmonary hypertension)	Cialis, Adcirca
Blonanserin	Lonasen
Colchicine (when administered to patients with liver or kidney disease)	Colgout, Lengout
Rifampicin	Aptecin, Rifadin, Rimactane

many others.[95] The package insert should be referred to before administrating telaprevir.

Recommendation:

Telaprevir strongly inhibits the CYP3A4/5 drug metabolizing enzyme and is also a substrate, so co-administration of a number of agents is contraindicated or requires caution. The package insert should be referred to before administrating telaprevir.

Drug resistance

Telaprevir-resistant mutations (V36, T54, R155, A156, V170) have been reported in cases of viral breakthrough with telaprevir monotherapy,[96–98] as well as in cases on virological non-response and relapse with triple therapy.[99,100] The reported incidences of telaprevir resistance are 12% with initial therapy and 22% with retreatment. One study found telaprevir-resistant viruses in 80–90% of cases of viral breakthrough, virological non-response and relapse.[101] Resistance is more common in genotype 1a than genotype 1b HCV. In most cases, these telaprevir-resistant viruses become undetectable, reverting to wild type, over time.[97,98]

3.4 Initial treatment—Genotype 1 with high viral load

A number of new agents are under development for the treatment of HCV genotype 1 with a high viral load (≥5.0 $\log_{10}$ IU/mL using real-time PCR, HCV core antigen ≥300 fmol/L), which is often refractory to treatment. These include HCV-selective antiviral agents in the form of enzyme inhibitors (protease inhibitors, polymerase inhibitors, NS5A inhibitors), new IFN formulations, ribavirin prodrugs and immunopotentiation agents. At present, however, the only therapies available for clinical use in Japan are antiviral combinations based on an IFN formulation, in other words Peg IFN (IFN) ± ribavirin ± telaprevir. Peg-IFN + ribavirin therapy was approved available for use in Japan in 2004, improving therapeutic efficacy but with the addition of adverse reactions such as anemia. Subsequent detailed studies in a large number of IFN-treated subjects have identified correlations between viral, host and drug factors on the one hand and therapeutic effect and adverse reactions on the other hand. At present, we are moving away from uniform therapies in accordance with HCV genotype and viral load towards optimizing therapy for each individual patient, with the emphasis on response-guided therapy that adjusts the duration of treatment according to the response. In 2009, IFN-β + ribavirin therapy, which has a relatively good safety profile with fewer adverse reactions such as depression, gained approval under the national medical insurance scheme in Japan.

In 2011, telaprevir + Peg-IFN + ribavirin triple therapy became available for use in Japan. The addition of telaprevir to Peg-IFN + ribavirin improves the therapeutic efficacy, also shortening the treatment duration from 48 (or 72) weeks to 24 weeks, but with the addition of adverse reactions such as severe anemia and serious skin disorders. Japanese clinical trials of this triple therapy were conducted with patients aged ≤65 years with platelet counts ≥100 000/μL, so we need to gather scientific evidence regarding therapeutic efficacy and adverse reactions in patients at high risk of developing HCC, including elderly patients and those with advanced hepatic fibrosis.

Recently interleukin (IL)-28B SNP and substitutions of amino acids in the HCV core and NS5A regions are widely recognized as important pretreatment predictors of therapeutic efficacy. Accordingly, although not