mortality is attributed to the frequent progression to cirrhosis and/or HCC in HCV-infected patients who receive hemodialysis.

Because RBV is excreted renally, it is currently contraindicated in patients with CKD who have a creatinine clearance of less than 50 mL/min. In addition, pharmacokinetic studies have shown that the clearance of IFN is lower in patients who undergo hemodialysis than in patients who have normal renal function.[126]

Studies of antiviral therapy in patients who undergo hemodialysis suggest that IFN monotherapy is generally well tolerated and that SVR rates are higher than those in patients with normal renal function.[127] The overall SVR rate was reported to be 33–37% in hemodialysis patients.[128] However, the number of subjects in these trials was too low to support confident conclusions. Adverse events are common in this population, and many patients discontinue therapy prematurely because of such events. A recent RCT showed in EASL 2008 that 135 μg/week of PEG-IFN-α-2a for 48 weeks achieved an SVR rate of 39% (23/38), whereas a dose of 90 μg/week produced an SVR rate of 35% (16/43). In 74% of the patients, treatment was completed as scheduled.

Another important point is when to initiate antiviral therapy in hemodialysis patients. IFN might induce allograft rejection and renal failure.[129] Therefore, IFN therapy should be considered before renal transplantation. The next issue to be resolved is the efficacy and safety of low-dose RBV combination therapy in hemodialysis patients.

In 2008, KDIGO proposed guidelines for the treatment of patients with CKD.[130] In Japan, a committee including hepatologists and specialists for CKD is planning a clinical trial for HCV-infected patients with CKD.

Recommendation 18: 3 MIU of IFN thrice weekly or 90 or 135 μg of PEG-IFN-α-2a weekly is recommended for patients with CKD. (Level 2a, Grade B.)

Patients with acute HCV infection

Acute HCV infection progresses to chronic infection in approximately 70% of patients.[131] Antiviral treatment should therefore be considered for this group of patients. On the other hand, it is difficult to identify patients with self-limited disease not requiring therapy. The results of previous studies indicate that anti-HCV treatment should be initiated if HCV RNA is detected continuously for more than 12–16 weeks. If treatment is initiated within this period, monotherapy with IFN or PEG-IFN achieves an SVR rate of more than 80% in patients with acute HCV infection.[132] Reliable evidence showing that additional treatment with RBV improves the SVR rate in such patients is not available.

Recommendation 19: Patients with acute HCV infection should be considered as candidates for antiviral therapy. If HCV RNA is detected continuously for 12 or 16 weeks from the onset, treatment with 6 MIU of IFN or 180 μg of PEG-IFN monotherapy should be initiated. (Level 2a, Grade B.)

Patients who receive curative treatment for HCC

Hepatocellular carcinoma frequently recurs in HCV-infected patients, even after curative therapy for HCC. Prevention of the recurrence of HCC is essential in such patients. Several RCT showed that the incidence of HCC was low in an IFN-treated group, compared to a control group (Table 4).[133,134] For example, Kubo *et al.* reported that 3 MIU IFN monotherapy thrice weekly for 96 weeks inhibited the recurrence of HCC in patients who had undergone a curative resection.[134] Furthermore, Shiratori *et al.* performed an RCT in 74 patients who had received curative percutaneous ethanol injection therapy for HCC. They reported that second and third recurrences of HCC were less frequent in patients who received IFN.[135] In an Italian study of 150 patients who had undergone curative resection, the recurrence rate of HCC 2 years after operation was significantly lower among patients who received IFN.[136]

Japanese studies showed that the survival rate was also improved by IFN treatment owing to the suppression of HCC and/or the progression of hepatic failure.[137,138]

Recommendation 20: IFN therapy should be considered for patients after curative treatment for HCC. (Level 1, Grade A.)

Maintenance therapy for patients with advanced hepatic fibrosis

Previous studies of patients with advanced hepatic fibrosis, defined as a fibrosis score 3 or 4, showed that IFN monotherapy inhibited the occurrence of HCC, compared to patients who did not receive IFN.[64,139,140] In Japanese studies, IFN was effective not only in SVR patients, but also in non-SVR patients.[139,141] On the other hand, an Italian study showed that the incidence of HCC decreased only in cirrhotic patients in whom HCV was eradicated by IFN therapy.[75]

Case–control studies in patients older than 60 years showed that a low dose of IFN reduced ALT and AFP levels and decreased the incidence of HCC, compared to a control group.[142,143] RCT for IFN monotherapy non-

Table 4 Interferon monotherapy for patients after curative treatment for hepatocellular carcinoma

Author	Study design	No. of patients (IFN group vs non-IFN group)	Age (IFN group vs non-IFN group)	Interferon	Sustained virological response	Follow-up duration (months)	HCC recurrence (IFN group vs non-IFN group)	Survival (IFN group vs non-IFN group)
Ikeda *et al.*	RCT	10 vs 10	60 vs 65	beta	0	25	10% vs 70% $P = 0.0004$	
Kubo *et al.*	RCT	15 vs 15	62 vs 60	alpha	2 (13%)	54	60% vs 87% $P = 0.055$	80% vs 50% $P = 0.041$
Suou *et al.*	Pilot study	18 vs 22	61 vs 62	alpha	6 (33%)	60	28% vs 82% $P < 0.001$	100% vs 73% $P < 0.05$
Shiratori *et al.*	RCT	49 vs 25	61 vs 63	alpha	14 (29%)	60	80% vs 92%	68% vs 48%
Lin *et al.*	RCT	8 vs 6	61 vs 59	alpha	no data	27	63% vs 83% $P = 0.34$	
Jeong *et al.*	Prospective case–control study	16 vs 16	69 vs 68	alpha	2 (13%)	36	69% vs 80% $P = 0.157$	100% vs 88% $P = 0.45$
Sakaguchi *et al.*	Case–control study	24 vs 33	69 vs 67	alpha	1 (4%)	36	14% vs 73% $P = 0.011$	100% vs 94% $P = 0.25$
Mazzaferro *et al.*	RCT	76 vs 74	65 vs 67	alpha	2 (3%)	45	76% vs 94% $P = 0.49$	64% vs 52% $P = 0.47$
Akamatsu *et al.*	Retrospective study	53 vs 399	60 vs 68	no data	17 (32%)	72		88%, 71% vs 53.2% $P = 0.025$
Kudo *et al.*	Case–control study	43 vs 84	65 vs 66	alpha or pegylated IFN	2 (5%)	60	56% s 71% $P = 0.04$	86% vs 56% $P = 0.004$

IFN, interferon; HCC, hepatocellular carcinoma; RCT, randomized control study.

responders showed that histological fibrosis and activity was improved in the assigned IFN-treated group. In contrast, in the untreated group, the fibrosis score did not decline.[144] In Japan, several studies support the effectiveness of low-dose IFN maintenance therapy.[145–147] In the USA, an RCT of 53 patients in whom a histological response, but not a viral response was induced by 6 MIU of IFN showed that 3 MIU of IFN for 24 months improved the degree of hepatic fibrosis.

However, the Hepatitis C Antiviral Long-Term Treatment against Cirrhosis (HALT-C) trial found no difference in the progression of liver disease between a low-dose PEG-IFN group and a control group.[114] The large discrepancy in the effectiveness of IFN maintenance therapy between the HALT-C trial and Japanese trials might be attributed to several factors. First, the study designs differed. One of the most important differences was related to the patients' clinical characteristics. For example, patients enrolled in Japanese studies were older than those in the HALT-C trial. Elderly patients have a higher incidence of HCC than younger patients. It is suggested that the tumor-suppressive effect of IFN maintenance therapy might be more clearly demonstrated in a high-risk group, including elderly patients.[138]

Until more data become available, the decision to perform IFN maintenance therapy should be made on an individual basis.

Recommendation 21: IFN maintenance therapy is a treatment option that can inhibit the progression of liver disease in patients with advanced hepatic fibrosis, especially in those who are elderly. However, the effect of monotherapy with IFN or PEG-IFN remains uncertain in non-responders to combination therapy with PEG-IFN plus RBV. (Level 2a, Grade C.)

CONSENSUS ON THERAPEUTIC STRATEGY FOR CH-C

Indication of antiviral therapy

IKEDA *ET AL.* elucidated the necessities of antiviral therapy for elderly patients with chronic HCV infection.[132] At 5 and 10 years, hepatocarcinogenesis rates in the intermediate ($100–140 \times 10^9$/L) and low platelet ($<100 \times 10^9$/L) groups were 10.9% and 21.6% in the IFN group ($n = 217$) and 19.5% and 43.0% in the untreated group ($n = 459$), respectively ($P = 0.0005$). IFN independently decreased the risk of carcinogenesis risk with a hazard ratio of 0.56 ($P = 0.035$). On the other hand, in the high platelet ($\geq 150 \times 10^9$/L) group, no significant difference was found in 5- and 10-year carcinogenesis rates between the IFN-treated group ($n = 228$) and the untreated group ($n = 585$) ($P = 0.69$). Furthermore, IFN treatment significantly increased cumulative survival in the lower platelet subgroup ($P = 0.0001$) but did not affect the higher platelet subgroup ($P = 0.08$). Thus, the necessities of antiviral therapy are shown to be greater in elderly patients with advanced fibrosis, although adverse effects of IFN are reported to be more frequent and the efficacy of IFN to be lower in such patients.[148–150]

Therefore, the indication of antiviral therapy should be considered in the following order: the necessity of treatment, first; safety of treatment, second; and efficacy of treatment for a patient, last. Antiviral therapy should not be given up because the expected SVR rate is low.

Recommendation 22: Antiviral therapy should be offered even to CH-C patients whose SVR rates are expected to be low if type C chronic liver disease is the prognostic determinant (prognosis is improved by HCV elimination) for the individual patient, and the expected adverse effects are tolerable to the patients. (Level 6, Grade B/C.)

Effect of drug adherence of PEG-IFN and RBV on virological response

The relationship between drug exposure and antiviral effect of PEG-IFN plus RBV combination therapy has been reported in several papers.[101,151–155] McHutchison *et al.* revealed that the SVR rate in patients who received 80% or more of their total planned doses of PEG-IFN-α-2b and RBV for 80% or more of the scheduled duration of therapy was significantly higher than that of patients who received less than 80% of one or both drugs (51% vs 34%) and also suggested that the impact of dose reduction was greatest in patients for whom the dose had to be decreased within the first 12 weeks of treatment.[152]

Recently, Oze *et al.* evaluated how reducing drug doses affects complete early virological response (c-EVR) defined as HCV RNA negativity at week 12, using 984 patients with CH-C genotype 1.[156] As a result, the mean dose of PEG-IFN-α-2b, and not RBV, during the first 12 weeks was the independent factor for c-EVR ($P = 0.02$), not RBV.

Hiramatsu *et al.* reported on whether dose reduction of RBV (or PEG-IFN) has an effect on virological relapse in PEG-IFN plus RBV treatment for patients with CH-C genotype 1.[157] In the analysis of 472 patients responding to PEG-IFN-α-2b plus RBV, stepwise reduction of the

RBV dose was associated with a stepwise increase in relapse rate from 11% to 60% (Fig. 3).

Improving the treatment tolerability for genotype 2 or 3 patients has focused on dose reduction of treatment drugs. Weiland *et al.* examined low-dose PEG-IFN-α-2a (135 μg/week) with a weight-based standard dose of RBV (11 mg/kg daily) for genotype 2 and 3 patients.[158] Recently, Inoue *et al.* reported neither PEG-IFN nor RBV drug exposure were critical in reaching rapid virological response and SVR.[159]

Recommendation 23: In genotype 1 patients, PEG-IFN is dose-dependently correlated with c-EVR, independent of RBV dose. The administration over 80% of the scheduled dose of PEG-IFN-α-2a or over 1.2 μg/kg per week of PEG-IFN-α-2b should be chosen as a starting dose: a marked dose reduction of PEG-IFN should not be risked at the start even for patients with disadvantage (e.g. aged patients). (Level 2b/3, Grade B.)

Recommendation 24: In genotype 1 patients, RBV shows a dose-dependent correlation with the relapse after treatment. Maintaining the RBV dose over 80% of the scheduled dose or over 10 mg/kg per day (12 mg/kg per day, if possible) during the complete treatment period can lead to suppression of the relapse in HCV genotype 1 patients responding to PEG-IFN-α-2b plus RBV, especially in c-EVR patients. (Level 2b/3, Grade B.)

Recommendation 25: In genotype 2/3 patients, reducing drug doses of PEG-IFN and RBV (down to 400 mg/day) has no significant effect on virological responses. (Level 2a, Grade B.)

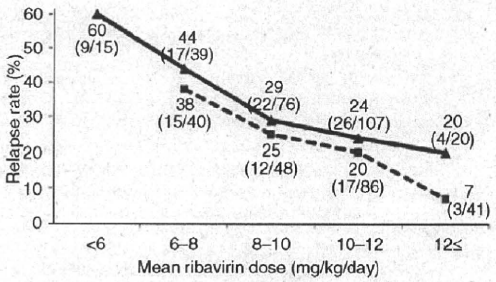


Figure 3 Relapse rate according to pegylated interferon (PEG-IFN)-α-2b and ribavirin doses during treatment of patients who completed treatment, which was stratified with the mean ribavirin doses (-▲-). Group with the mean PEG-IFN dose <1.4 μg kg/week (-■-). Group with the mean PEG-IFN dose ≥1.4 μg kg/week. There was no significant difference between the two PEG-IFN-α-2b-dose groups ($P = 0.17$).

Treatment for patients without elimination of HCV

Tarao *et al.* showed the rate of HCC appearance was significantly higher in HCV-related cirrhotic patients with a high ALT value (≥80 IU/mL) than in those with a lower ALT value (<80 IU/mL).[70] This suggested that suppression of inflammation in the liver with HCV infection is very important to prevent the hepatocarcinogenesis in patients with HCV-related cirrhosis.

Omata *et al.* assessed the effects of oral ursodeoxycholic acid (UDCA) on serum biomarkers. CH-C patients with elevated ALT were assigned randomly to 150 ($n = 199$), 600 ($n = 200$) or 900 mg/day ($n = 197$) UDCA intake for 24 weeks. As a result, the median changes in serum ALT at the end of treatment were shown to be −15.3, −29.2 and −36.2%, respectively, although serum HCV RNA did not change in any group.[160]

A glycyrrhizin product, Stronger Neo-Minophagen C (SNMC; Minophagen Pharmaceutical, Tokyo, Japan), is used widely in Japan and has been reported to improve ALT levels and liver inflammation.[161,162] Furthermore, Ikeda *et al.* reported liver carcinogenesis was suppressed by long-term administration of glycyrrhizin, using a cohort of 1249 patients, and its favorable effect on hepatocellular carcinogenesis in those patients with IFN-resistant CH-C.[163,164]

Repeated phlebotomy has been shown to be effective for the improvement of serum ALT as well as progression of fibrosis,[32] however, it remains controversial whether the effects of IFN improve with extensive phlebotomy.[165–169]

In Japan, Yano *et al.* showed the iron removal by repeated phlebotomy improved serum ALT levels in patients with CH-C.[170]

Recommendation 26: Patients whose HCV RNA was not eradicated by PEG-IFN plus RBV and whose ALT and/or AFP levels were not improved by IFN monotherapy or those without indication for IFN therapy should be treated with the liver-supporting therapy (SNMC, UDCA), and if the effect of this medication is inadequate, phlebotomy can be used in combination. (Level 3/6, Grade B/C.)

Treatment of patients with decompensated cirrhosis

The compensated patients who failed to eradicate HCV by antiviral therapy and decompensated patients should be referred for consideration of liver transplantation and liver supporting therapy should be performed. Long-

term nutritional supplementation with oral branched-chain amino acid (BCAA) has been shown to be useful to prevent progressive hepatic failure and to improve surrogate markers.[171,172] Early interventional with oral BCAA was shown to prolong the liver transplant waiting period by preserving hepatic reserve in cirrhosis.

Recommendation 27: Patients with compensated cirrhosis for the prevention of hepatocellular carcinogenesis, should be treated by not only IFN but also with liver supporting therapy (SNMC, UDCA) and/or phlebotomy and/or BCAA in order to improve the liver inflammation and AFP levels. (Level 3, Grade C.)

Novel antiviral drugs

Telaprevir, a protease inhibitor specific to the HCV nonstructural 3/4A serine protease, reduced HCV RNA levels rapidly in early studies. McHuthison *et al.* reported the improved SVR rate with triple therapy for 12 weeks followed by PEG-IFN-α-2a and RBV for 12 weeks.

Thus, the treatment for CH-C is progressing. Therefore, as a treatment strategy, PEG-IFN plus RBV combination therapy should be performed early for aged patients and the patients with the advanced fibrosis. However, the novel antiviral drugs, such as protease inhibitors and polymerase inhibitors, should be taken into account as a candidate of treatment for the patients who can wait for the oncoming drugs.

Recommendation 28: Novel antiviral drugs, such as a protease inhibitor or a polymerase inhibitor, in combination with PEG-IFN plus RBV, can improve the SVR rates in genotype 1 CH-C patients. (Level 2a, Grade A.)

REFERENCES

1 Ghany MG, Strader DB, Thomas DL *et al.* AASLD practice guidelines. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology* 2009; **49**: 1335–74.
2 Shiffman RN, Shekelle P, Overhage J *et al.* Standard reporting of clinical practice guidelines: a proposal from the Conference on Guideline Standadization. *Ann Intern Med* 2003; **139**: 493–98.
3 Pileri P, Uematsu Y, Campagnoli S *et al.* Binding of hepatitis C virus to CD81. *Science* 1998; **282**: 938–41.
4 Scarselli E, Ansuini H, Cerino R *et al.* The human scavenger receptor class B type I is a novel candidate receptor for the hepatitis C virus. *EMBO J* 2002; **21**: 5017–25.
5 Evans MJ, von Hahn T, Tscherne DM *et al.* Claudin-1 is a hepatitis C virus co-receptor required for a late step in entry. *Nature* 2007; **446**: 801–5.
6 Dubuisson J, Helle F, Cocquerel L. Early steps of the hepatitis C virus life cycle. *Cell Microbiol* 2008; 10: 821–7.
7 Ploss A, Evans MJ, Gaysinskaya VA *et al.* Human occludin is a hepatitis C virus entry factor required for infection of mouse cells. *Nature* 2009; **457**: 882–6.
8 Flint M, von Hahn T, Zhang J *et al.* Diverse CD81 proteins support hepatitis C virus infection. *J Virol* 2006; **80**: 11331–42.
9 Sumpter R Jr, Loo YM, Foy E *et al.* Regulating intracellular antiviral defense and permissiveness to hepatitis C virus RNA replication through a cellular RNA helicase, *RIG-I*. *J Virol* 2005; **79**: 2689–99.
10 Yoneyama M, Kikuchi M, Natsukawa T *et al.* The RNA helicase *RIG-I* has an essential function in double-stranded RNA-induced innate antiviral responses. *Nat Immunol* 2004; 5: 730–7.
11 Li K, Chen Z, Kato N, Gale M Jr, Lemon SM. Distinct poly(I-C) and virus-activated signaling pathways leading to interferon-beta production in hepatocytes. *J Biol Chem* 2005; **280**: 16739–47.
12 Kawai T, Takahashi K, Sato S *et al.* IPS-1, an adaptor triggering *RIG-I*- and Mda5-mediated type I interferon induction. *Nat Immunol* 2005; **6**: 981–8.
13 Sen GC. Viruses and interferons. *Annu Rev Microbiol* 2001; 55: 255–81.
14 Loo YM, Owen DM, Li K *et al.* Viral and therapeutic control of IFN-beta promoter stimulator 1 during hepatitis C virus infection. *Proc Natl Acad Sci USA* 2006; **103**: 6001–6.
15 Gale M Jr, Foy EM. Evasion of intracellular host defense by hepatitis C virus. *Nature* 2005; **436**: 939–45.
16 Bode JG, Ludwig S, Ehrhardt C *et al.* IFN-alpha antagonistic activity of HCV core protein involves induction of suppressor of cytokine signaling-3. *FASEB J* 2003; **17**: 488–90.
17 Alexander WS. Suppressors of cytokine signalling (SOCS) in the immune system. *Nat Rev Immunol* 2002; **2**: 410–6.
18 Polyak SJ, Khabar KS, Paschal DM *et al.* Hepatitis C virus nonstructural 5A protein induces interleukin-8, leading to partial inhibition of the interferon-induced antiviral response. *J Virol* 2001; 75: 6095–106.
19 Taylor DR, Shi ST, Romano PR *et al.* Inhibition of the interferon-inducible protein kinase PKR by HCV E2 protein. *Science* 1999; **285**: 107–10.
20 Noguchi T, Satoh S, Noshi T *et al.* Effects of mutation in hepatitis C virus nonstructural protein 5A on interferon resistance mediated by inhibition of PKR kinase activity in mammalian cells. *Microbiol Immunol* 2001; **45**: 829–40.
21 Moriya K, Nakagawa K, Santa T *et al.* Oxidative stress in the absence of inflammation in a mouse model for hepatitis C virus-associated hepatocarcinogenesis. *Cancer Res* 2001; **61**: 4365–70.
22 Okuda M, Li K, Beard MR *et al.* Mitochondrial injury, oxidative stress, and antioxidant gene expression are induced by hepatitis C virus core protein. *Gastroenterology* 2002; **122**: 366–75.

23 Korenaga M, Wang T, Li Y *et al.* Hepatitis C virus core protein inhibits mitochondrial electron transport and increases reactive oxygen species (ROS) production. *J Biol Chem* 2005; **280**: 37481–8.
24 Shintani Y, Fujie H, Miyoshi H *et al.* Hepatitis C virus infection and diabetes: direct involvement of the virus in the development of insulin resistance. *Gastroenterology* 2004; **126**: 840–8.
25 Kawaguchi T, Yoshida T, Harada M *et al.* Hepatitis C virus down-regulates insulin receptor substrates 1 and 2 through up-regulation of suppressor of cytokine signaling 3. *Am J Pathol* 2004; **165**: 1499–508.
26 Perlemuter G, Sabile A, Letteron P *et al.* Hepatitis C virus core protein inhibits microsomal triglyceride transfer protein activity and very low density lipoprotein secretion: a model of viral-related steatosis. *FASEB J* 2002; **16**: 185–94.
27 Moriishi K, Mochizuki R, Moriya K *et al.* Critical role of PA28gamma in hepatitis C virus-associated steatogenesis and hepatocarcinogenesis. *Proc Natl Acad Sci USA* 2007; **104**: 1661–6.
28 Nishina S, Hino K, Korenaga M *et al.* Hepatitis C virus-induced reactive oxygen species raise hepatic iron level in mice by reducing hepcidin transcription. *Gastroenterology* 2008; **134**: 226–38.
29 Miura K, Taura K, Kodama Y, Schnabl B, Brenner DA. Hepatitis C virus-induced oxidative stress suppresses hepcidin expression through increased histone deacetylase activity. *Hepatology* 2008; **48**: 1420–9.
30 Veldt BJ, Chen W, Heathcote EJ *et al.* Increased risk of hepatocellular carcinoma among patients with hepatitis C cirrhosis and diabetes mellitus. *Hepatology* 2008; **47**: 1856–62.
31 Ohata K, Hamasaki K, Toriyama K *et al.* Hepatic steatosis is a risk factor for hepatocellular carcinoma in patients with chronic hepatitis C virus infection. *Cancer* 2003; **97**: 3036–43.
32 Kato J, Kobune M, Nakamura T *et al.* Normalization of elevated hepatic 8-hydroxy-2′-deoxyguanosine levels in chronic hepatitis C patients by phlebotomy and low iron diet. *Cancer Res* 2001; **61**: 8697–702.
33 Furutani T, Hino K, Okuda M *et al.* Hepatic iron overload induces hepatocellular carcinoma in transgenic mice expressing the hepatitis C virus polyprotein. *Gastroenterology* 2006; **130**: 2087–98.
34 Romero-Gomez M, Del Mar Viloria M, Andrade RJ *et al.* Insulin resistance impairs sustained response rate to peginterferon plus ribavirin in chronic hepatitis C patients. *Gastroenterology* 2005; **128**: 636–41.
35 Harrison SA, Brunt EM, Qazi RA *et al.* Effect of significant histologic steatosis or steatohepatitis on response to antiviral therapy in patients with chronic hepatitis C. *Clin Gastroenterol Hepatol* 2005; **3**: 604–9.
36 Martinot-Peignoux M, Boyer N, Cazals-Hatem D *et al.* Prospective study on anti-hepatitis C virus-positive patients with persistently normal serum alanine transaminase with or without detectable serum hepatitis C virus RNA. *Hepatology* 2001; **34**: 1000–5.
37 Castera L, Vergniol J, Foucher J *et al.* Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gastroenterology* 2005; **128**: 343–50.
38 Strader DB, Wright T, Thomas DI, Seeff LB. Diagnosis, management, and treatment of hepatitis C. *Hepatology* 2004; **38**: 1147–71.
39 Tsubota A, Chayama K, Ikeda K *et al.* Factors predictive of response to interferon-α therapy in hepatitis C virus infection. *Hepatology* 1994; **19**: 1088–94.
40 Lau JY, Davis GL, Kniffen J *et al.* Significance of serum hepatitis C virus RNA in chronic hepatitis C. *Lancet* 1993; **341**: 1501–4.
41 Yamada G, Takatani M, Kishi F *et al.* Efficacy of interferon alfa therapy in chronic hepatitis C patients depends primarily on hepatitis C virus RNA level. *Hepatology* 1995; **22**: 1351–4.
42 Enomoto N, Sakuma I, Asahina Y *et al.* Comparison of full-length sequences of interferon-sensitive and resistant hepatitis C virus 1b. *J Clin Invest* 1995; **96**: 224–30.
43 Enomoto N, Sakuma I, Asahina Y *et al.* Mutations in the nonstructural protein 5A gene and response to interferon in patients with chronic hepatitis C virus 1b infection. *N Engl J Med* 1996; **334**: 77–81.
44 Pascu M, Martus P, Hohne M *et al.* Sustained virological response in hepatitis C virus type 1b infected patients is predicted by the number of mutations within the NS5A-ISDR: a meta-analysis focused on geographical differences. *Gut* 2004; **53**: 1345–54.
45 Shirakawa H, Matsumoto A, Joshita S *et al.* Pretreatment prediction of virological response to peginterferon plus ribavirin therapy in chronic hepatitis C patients using viral and host factors. *Hepatology* 2008; **48**: 1753–60.
46 El-Shamy A, Nagano-Fujii M, Sasase N *et al.* Sequence variation in hepatitis C virus nonstructural protein 5A predicts clinical outcome of pegylated interferon/ribavirin combination therapy. *Hepatology* 2008; **48**: 38–47.
47 Akuta N, Suzuki F, Sezaki H *et al.* Association of amino acid substitution pattern in core protein of hepatitis C virus genotype 1b high viral load and non-virological response to interferon-ribavirin combination therapy. *Intervirology* 2005; **48**: 372–80.
48 Akuta N, Suzuki F, Kawamura Y *et al.* Predictive factors of early and sustained responses to peginterferon plus ribavirin combination therapy in Japanese patients infected with hepatitis C virus genotype 1b: amino acid substitutions in the core region and low-density lipoprotein cholesterol levels. *J Hepatol* 2007; **46**: 403–10.
49 Donlin MJ, Cannon NA, Yao E *et al.* Pretreatment sequence diversity differences in the full-length hepatitis

C virus open reading frame correlate with early response to therapy. *J Virol* 2007; 81: 8211–24.
50 Akuta N, Suzuki F, Kawamura Y *et al.* Amino acid substitutions in the hepatitis C virus core region are the important predictor of hepatocarcinogenesis. *Hepatology* 2007; 46: 1357–64.
51 Fishman SL, Factor SH, Balestrieri C *et al.* Mutations in the hepatitis C virus core gene are associated with advanced liver disease and hepatocellular carcinoma. *Clin Cancer Res* 2009; 15: 3205–13.
52 Ogata S, Florese RH, Nagano-Fujii M *et al.* Identification of hepatitis C virus (HCV) subtype 1b strains that are highly, or only weakly, associated with hepatocellular carcinoma on the basis of the secondary structure of an amino-terminal portion of the HCV NS3 protein. *J Clin Microbiol* 2003; 41: 2835–41.
53 Nishise Y, Saito T, Sugahara K *et al.* Risk of hepatocellular carcinoma and secondary structure of hepatitis C virus (HCV) NS3 protein amino-terminus, in patients infected with HCV subtype 1b. *J Infec Dis* 2007; 196: 1006–9.
54 Mattsson L, Sonnerborg A, Weiland O. Outcome of acute symptomatic non-A, non-B hepatitis: a 13-years follow-up study of hepatitis C virus markers. *Liver* 1993; 13: 274–8.
55 Barrera JM, Bruguera M, Ercilla MG *et al.* Persistent hepatitis C viremia after self-limitng posttransfusion hepatitis C. *Hepatology* 1995; 21: 639–44.
56 Amoroso P, Rapicetta M, Tosti ME *et al.* Correlation between virus genotype and chronicity rate in acute hepatitis C. *J Hepatol* 1998; 28: 939–44.
57 Tanaka E, Kiyosawa K. Natural history of acute hepatitis C. *J Gastroenterol Hepatol* 2000; 15: E97–104.
58 Seeff LB, Buskell-Bales Z, Wright EC *et al.* Long-term mortality after transfusion-associated non-A, Non B hepatitis. *N Engl J Med* 1992; 327: 1906–11.
59 Seeff LB, Miller RN, Rabkin CS *et al.* 45-year follow-up of hepatitis C virus infection in healthy young adults. *Ann Intern Med* 2000; 132: 105–11.
60 Kenny-Walsh E, the Irish Hepatology Research Group. Clinical outcomes after hepatitis C infection from contaminated anti-D immune globulin. *N Eng J Med* 1999; 340: 1228–33.
61 Kiyosawa K, Sodeyama T, Tanaka E *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.
62 Tong MJ, El-Farra NS, Reikes AR *et al.* Clinical outcomes after transfusion-associated hepatitis C. *N Eng J Med* 1995; 332: 1463–6.
63 Ikeda K, Saitoh S, Koida I *et al.* A multivariate analysis of risk factors for hepatocellular carcinogenesis: a prospective observation of 795 patients with viral and alcoholic cirrhosis. *Hepatojogy* 1993; 18: 47–53.
64 Yoshida H, Shiratori Y, Moriyama M *et al.* Interferon therapy reduces the risk for hepatocellular carcinoma: national surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. IHIT Study Group. Inhibition of hepatocarcinogenesis by interferon therapy. *Ann Intern Med* 1999; 131: 174–81.
65 Okanoue T, Itoh Y, Minami M *et al.* Interferon therapy lowers the rate of progression to hepatocellular carcinoma in chronic hepatitis C but not significantly in an advanced stage: a retrospective study in 1148 patients. *J Hepatol* 1999; 30: 653–9.
66 Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METEVIR, CLINIVIR and DOSVIRC groups. *Lancet* 1997; 349: 825–32.
67 Shiratori Y, Imazeki F, Moriyama M *et al.* Histologic improvement of fibrosis in patients with hepatitis C who have sustained response to interferon therapy. *Ann Intern Med* 2000; 132: 517–24.
68 Persico M, Persico E, Suozzo R *et al.* Natural history of hepatitis C virus carriers with persistently normal aminotransferase. *Gastroenterology* 2000; 118: 760–4.
69 Okanoue T, Makiyama A, Nakayama M *et al.* A follow-up study to determine the value of liver biopsy and need for antiviral therapy for hepatitis C virus carriers with persistently normal serum aminotransferase. *J Hepatol* 2005; 43: 599–605.
70 Tarao K, Rino Y, Ohkawa S *et al.* Association between high serum ALT and more rapid development and higher rate of incidence of hepatocellular carcinoma in patients wit5h hepatitis C virus-associated cirrhosis. *Cancer* 1999; 86: 589–94.
71 Kumada T, Toyoda H, Kiriyama S *et al.* Relation between incidence of hepatic cardcinhogenesis and integration value of alanine aminmotransferase in patients with hepatitis C virus infection. *Gut* 2007; 56: 738–9.
72 Kumada T, Toyoda H, Kiriyama S *et al.* Long-term follow-up of patients with hepatitis C with a normal alanime aminotransferase. *J Med Virol* 2009; 81: 446–51.
73 Suruki R, Hayashi K, Kusumoto K *et al.* Alanine aminotransferase level as a predictor of hepatitis C virus-associated hepatocellular carcinoma incidence in a community-based population in Japan. *Int J Cancer* 2006; 119: 192–5.
74 Makiyama A, Itoh Y, Kasahara A *et al.* Characteristics of patients with chronic hepatitis C who develop hepatocellular carcinoma after a sustained response to interferon therapy. *Cancer* 2004; 101: 1616–22.
75 Bruno S, Stroffolini T, Colombo M *et al.* Sustained virological response to interferon-alpha is associated with improved outcome in HCV-related cirrhosis: a retrospective study. *Hepatology* 2007; 45: 579–87.
76 George S, Bacon BR, Brunt EM *et al.* Clinical, virologic, histologic, and biochemical outcomes after successful HCV therapy: a 5-year follow-up of 150 patients. *Hepatology* 2009; 49: 729–38.

77 Iino S, Okita K, Omata M *et al.* Clinical efficacy of PEG-Interferon alfa-2b and ribavirin combination therapy for 48 weeks in chronic hepatitis C patients with genotype 1 and high viral load –retrospective comparison with Interferon alfa-2b and ribavirin combination therapy for 24 weeks. *Kantansui* 2004; **49**: 1099–121.
78 Yamada G, Iino S, Okuno T *et al.* Virological response in patients with hepatitis C virus genotype 1b and a high viral load: impact of peginterferon-alpha-2a plus ribavirin dose reductions and host-related factors. *Clin Drug Investig* 2008; **28**: 9–16.
79 Akuta N, Suzuki F, Hirakawa M *et al.* A matched case-controlled study of 48 and 72 weeks of peginterferon plus ribavirin combination therapy in patients infected with HCV genotype 1b in Japan: amino acid substitutions in HCV core region as predictor of sustained virological response. *J Med Virol* 2009; **81**: 452–8.
80 Mangia A, Santoro R, Minerva N *et al.* Peginterferon alfa-2b and ribavirin for 12 vs. 24 weeks in HCV genotype 2 or 3. *N Engl J Med* 2005; **352**: 2609–17.
81 Sezaki H, Suzuki F, Kawamura Y *et al.* Poor response to pegylated interferon and ribavirin in older women infected with hepatitis C virus of genotype 1b in high viral loads. *Dig Dis Sci* 2009; **54**: 1317–24.
82 Kogure T, Ueno Y, Fukushima K *et al.* Pegylated interferon plus ribavirin for genotype lb chronic hepatitis C in Japan. *World J Gastroenterol* 2008; **14**: 7225–4230.
83 Akuta N, Suzuki F, Kawamura Y *et al.* Predictors of viral kinetics to peginterferon plus ribavirin combination therapy in Japanese patients infected with hepatitis C virus genotype 1b. *J Med Virol* 2007; **79**: 1686–95.
84 Mizuta T, Kawaguchi Y, Eguchi Y *et al.* Whole-body insulin sensitivity index is a highly specific predictive marker for virological response to peginterferon plus ribavirin therapy in chronic hepatitis C patients with genotype 1b and high viral load. *Dig Dis Sci* 2010; **55**: 183–9.
85 Tsukada H, Ochi H, Maekawa T *et al.* A Polymorphism in MAPKAPK3 Affects Response to Interferon Therapy for Chronic Hepatitis C. *Gastroenterology* 2009; **136**: 1796–805.
86 Asahina Y, Izumi N, Hirayama I *et al.* Potential relevance of cytoplasmic viral sensors and related regulators involving innate immunity in antiviral response. *Gastroenterology* 2008; **134**: 1396–405.
87 Asahina Y, Izumi N, Umeda N *et al.* Pharmacokinetics and enhanced PKR response in patients with chronic hepatitis C treated with pegylated interferon alpha-2b and ribavirin. *J Viral Hepat* 2007; **14**: 396–403.
88 Sezaki H, Suzuki F, Kawamura Y *et al.* Evaluation of long-term biochemical responses to combination therapy of interferon plus ribavirin in those infected with hepatitis C virus genotype 1b and high baseline viral load. *Hepatol Res* 2007; **37**: 787–92.
89 Berg T, von Wagner M, Nasser S *et al.* Extended treatment duration for hepatitis C virus type 1: comparing 48 versus 72 weeks of peginterferon-Alfa-2a plus ribavirin. *Gastroenterology* 2006; **130**: 1086–109.
90 Sanchez-Tapias JM, Diago M, Escartin P *et al.* Peginterferon-alfa2a plus ribavirin for 48 versus 72 weeks in patients with detectable hepatitis C virus RNA at week 4 of treatment. *Gastroenterology* 2006; **131**: 451–60.
91 Ferenci P, Laferl H, Scherzer TM *et al.* Customizing treatment with peginterferon alfa-2a (40kD) (PEGASYS®) plus ribavirin (COPEGUS®) in patient with HCV genotype 1 or 4 infection: interim results of a prospective randomized trial. *Hepatology* 2006; **44**: 336a.
92 Pearlman BL, Ehleben C, Saifee S. Treatment extension to 72 weeks of peginterferon and ribavirin in hepatitis c genotype 1-infected slow responders. *Hepatology* 2007; **46**: 1688–94.
93 Buti M, Lurie Y, Zakharova NG *et al.* Extended treatment duration in chronic hepatitis C genotype 1-infected slow responders: final results of the SUCCESS study (abstract #141). *J Hepatol* 2009; **50** (Suppl 1): S58.
94 Ide T, Hino T, Ogata K *et al.* A randomized study of extended treatment with peginterferon alpha-2b plus ribavirin based on time to HCV RNA negative-status in patients with genotype 1b chronic hepatitis C. *Am J Gastroenterol* 2009; **104**: 70–5.
95 von Wagner M, Huber M, Berg T *et al.* Peginterferon-alpha-2a (40KD) and ribavirin for 16 or 24 weeks in patients with genotype 2 or 3 chronic hepatitis C. *Gastroenterology* 2005; **129**: 522–7.
96 Shiffman ML, Suter F, Bacon BR *et al.* Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3. *N Engl J Med* 2007; **357**: 124–34.
97 Dalgard O, Bjøro K, Ring-Larsen H *et al.* Pegylated interferon alfa and ribavirin for 14 versus 24 weeks in patients with hepatitis C virus genotype 2 or 3 and rapid virological response. *Hepatology* 2008; **47**: 35–42.
98 Lagging M, Langeland N, Pedersen C *et al.* Randomized comparison of 12 or 24 weeks of peginterferon alpha-2a and ribavirin in chronic hepatitis C virus genotype 2/3 infection. *Hepatology* 2008; **47**: 1837–45.
99 Yu ML, Dai CY, Huang JF *et al.* A randomised study of peginterferon and ribavirin for 16 versus 24 weeks in patients with genotype 2 chronic hepatitis C. *Gut* 2007; **56**: 553–9.
100 Mangia A, Minerva N, Bacca D *et al.* Determinants of relapse after a short (12 weeks) course of antiviral therapy and re-treatment efficacy of a prolonged course in patients with chronic hepatitis C virus genotype 2 or 3 infection. *Hepatology* 2009; **49**: 358–63.
101 Manns MP, McHutchison JG, Gordon SC *et al.* Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001; **358**: 958–65.

102 Fried MW, Shiffman ML, Reddy KR *et al.* Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002; 347: 975–82.

103 Hadziyannis SJ, Sette H Jr, Morgan TR *et al.* Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 2004; 140: 346–55.

104 Helbling B, Jochum W, Stamenic I *et al.* HCV-related advanced fibrosis/cirrhosis: randomized controlled trial of pegylated interferon alpha-2a and ribavirin. *J Viral Hepat* 2006; 13: 762–9.

105 Bergmann JF, Vrolijk JM, van der Schaar P *et al.* Gamma-glutamyltransferase and rapid virological response as predictors of successful treatment with experimental or standard peginterferon-alpha-2b in chronic hepatitis C non-responders. *Liver Int* 2007; 27: 1217–25.

106 Diago M, Crespo J, Olveira A *et al.* Clinical trial: pharmacodynamics and pharmacokinetics of re-treatment with fixed-dose induction of peginterferon alpha-2a in hepatitis C virus genotype 1 true non-responder patients. *Aliment Pharmacol Ther* 2007; 26: 1131–8.

107 Carr C, Hollinger FB, Yoffe B *et al.* Efficacy of interferon alpha-2b induction therapy before retreatment for chronic hepatitis C. *Liver Int* 2007; 27: 1111–8.

108 Mathew A, Peiffer LP, Rhoades K *et al.* Sustained viral response to pegylated interferon alpha-2b and ribavirin in chronic hepatitis C refractory to prior treatment. *Dig Dis Sci* 2006; 51: 1956–61.

109 Jacobson IM, Gonzalez SA, Ahmed F *et al.* A randomized trial of pegylated interferon alpha-2b plus ribavirin in the retreatment of chronic hepatitis C. *Am J Gastroenterol* 2005; 100: 2453–62.

110 Herrine SK, Brown RS Jr, Bernstein DE *et al.* Peginterferon alpha-2a combination therapies in chronic hepatitis C patients who relapsed after or had a viral breakthrough on therapy with standard interferon alpha-2b plus ribavirin: a pilot study of efficacy and safety. *Dig Dis Sci* 2005; 50: 719–26.

111 Shiffman ML, Di Bisceglie AM, Lindsay KL *et al.* Peginterferon alfa-2a and ribavirin in patients with chronic hepatitis C who have failed prior treatment. *Gastroenterology* 2004; 126: 1015–23.

112 Jensen DM, Marcellin P, Freilich B *et al.* Re-treatment of patients with chronic hepatitis C who do not respond to peginterferon-alpha2b: a randomized trial. *Ann Intern Med* 2009; 150: 528–40.

113 Poynard T, Colombo M, Bruix J *et al.* Peginterferon alfa-2b and ribavirin: effective in patients with hepatitis C who failed interferon alfa/ribavirin therapy. *Gastroenterology* 2009; 136: 1618–28.

114 Di Bisceglie AM, Shiffman ML, Everson GT *et al.* Prolonged therapy of advanced chronic hepatitis C with low-dose peginterferon. *N Engl J Med* 2008; 359: 2429–41.

115 McHutchison JG, Gordon SC, Schiff ER *et al.* Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. Hepatitis Interventional Therapy Group. *N Engl J Med* 1998; 339: 1485–92.

116 Poynard T, Marcellin P, Lee SS *et al.* Randomised trial of interferon alpha2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. International Hepatitis Interventional Therapy Group (IHIT). *Lancet* 1998; 352: 1426–32.

117 Davis GL, Esteban-Mur R, Rustgi V *et al.* Interferon alfa-2b alone or in combination with ribavirin for the treatment of relapse of chronic hepatitis C. International Hepatitis Interventional Therapy Group. *N Engl J Med* 1998; 339: 1493–9.

118 Reichard O, Norkrans G, Frydén A *et al.* Randomised, double-blind, placebo-controlled trial of interferon alpha-2b with and without ribavirin for chronic hepatitis C. The Swedish Study Group. *Lancet* 1998; 351: 83–7.

119 Zeuzem S, Feinman SV, Rasenack J *et al.* Peginterferon alfa-2a in patients with chronic hepatitis C. *N Engl J Med* 2000; 343: 1666–72.

120 Lindsay KL, Trepo C, Heintges T *et al.* A randomized, double-blind trial comparing pegylated interferon alfa-2b to interferon alfa-2b as initial treatment for chronic hepatitis C. *Hepatology* 2001; 34: 395–403.

121 Pockros PJ, Carithers R, Desmond P *et al.* Efficacy and safety of two-dose regimens of peginterferon alpha-2a compared with interferon alpha-2a in chronic hepatitis C: a multicenter, randomized controlled trial. *Am J Gastroenterol* 2004; 99: 1298–305.

122 Akuta N, Suzuki F, Tsubota A *et al.* Efficacy of interferon monotherapy to 394 consecutive naive cases infected with hepatitis C virus genotype 2a in Japan: therapy efficacy as consequence of tripartite interaction of viral, host and interferon treatment-related factors. *J Hepatol* 2002; 37: 831–6.

123 Iwasaki Y, Shiratori Y, Hige S, NIshiguchi S *et al.* A randomized trial of 24 versus 48 weeks of peginterferon a-2a in patients infected with chronic hepatitis C virus genotype 2 or low viral load genotype 1: a multicenter national study in Japan. *Hepatol Int* 2009; 3: 468–79.

124 Masuko K, Okuda K, Meguro T *et al.* Hepatitis C virus antibodies, viral RNA and genotypes in sera from patients on maintenance haemodialysis. *J Viral Hepat* 1994; 1: 65–71.

125 Fabrizi F, Martin P, Dixit V, Bunnapradist S, Dulai G. Meta-analysis: effect of hepatitis C virus infection on mortality in dialysis. *Aliment Pharmacol Ther* 2004; 20: 1271–7.

126 Rostaing L, Chatelut E, Payen JL *et al.* Pharmacokinetics of alphaIFN-2b in chronic hepatitis C virus patients undergoing chronic hemodialysis or with normal renal function: clinical implications. *J Am Soc Nephrol* 1998; 9: 2344–8.

127 Russo MW, Goldsweig CD, Jacobson IM, Brown RS Jr. Interferon monotherapy for dialysis patients with chronic hepatitis C: an analysis of the literature on efficacy and safety. *Am J Gastroenterol* 2003; **98**: 1610–5.
128 Fabrizi F, Dixit V, Messa P, Martin P. Interferon monotherapy of chronic hepatitis C in dialysis patients: meta-analysis of clinical trials. *J Viral Hepat* 2008; **15**: 79–88.
129 Kamar N, Ribes D, Izopet J, Rostaing L. Treatment of hepatitis C virus infection (HCV) after renal transplantation: implications for HCV-positive dialysis patients awaiting a kidney transplant. *Transplantation* 2006; **82**: 853–6.
130 KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of hepatitis C in chronic kidney disease. Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int Suppl* 2008; **109**: S1–99.
131 Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. *J Viral Hepat* 2006; **13**: 34–41.
132 Ikeda K, Arase Y, Kawamura Y *et al.* Necessities of Interferon Therapy in Elderly Patients with Chronic Hepatitis C. *Am J Med* 2009; **122**: 479–86.
133 Ikeda K, Arase Y, Saitoh S *et al.* Interferon beta prevents recurrence of hepatocellular carcinoma after complete resection or ablation of the primary tumor-A prospective randomized study of hepatitis C virus-related liver cancer. *Hepatology* 2000; **32**: 228–32.
134 Kubo S, Nishiguchi S, Hirohashi K *et al.* Effects of long-term postoperative interferon-alpha therapy on intrahepatic recurrence after resection of hepatitis C virus-related hepatocellular carcinoma. A randomized, controlled trial. *Ann Intern Med* 2001; **134**: 963–7.
135 Shiratori Y, Shiina S, Teratani T *et al.* Interferon therapy after tumor ablation improves prognosis in patients with hepatocellular carcinoma associated with hepatitis C virus. *Ann Intern Med* 2003; **138**: 299–306.
136 Mazzaferro V, Romito R, Schiavo M *et al.* Prevention of hepatocellular carcinoma recurrence with alpha-interferon after liver resection in HCV cirrhosis. *Hepatology* 2006; **44**: 1543–54.
137 Kubo S, Nishiguchi S, Hirohashi K, Tanaka H, Shuto T, Kinoshita H. Randomized clinical trial of long-term outcome after resection of hepatitis C virus-related hepatocellular carcinoma by postoperative interferon therapy. *Br J Surg* 2002; **89**: 418–22.
138 Shiratori Y, Ito Y, Yokosuka O *et al.* Antiviral therapy for cirrhotic hepatitis C: association with reduced hepatocellular carcinoma development and improved survival. *Ann Intern Med* 2005; **142**: 105–14.
139 Nishiguchi S, Kuroki T, Nakatani S *et al.* Randomised trial of effects of interferon-alpha on incidence of hepatocellular carcinoma in chronic active hepatitis C with cirrhosis. *Lancet* 1995; **346**: 1051–5.
140 Ikeda K, Saitoh S, Arase Y *et al.* Effect of interferon therapy on hepatocellular carcinogenesis in patients with chronic hepatitis type C: a long-term observation study of 1,643 patients using statistical bias correction with proportional hazard analysis. *Hepatology* 1999; **29**: 1124–30.
141 Imai Y, Kawata S, Tamura S *et al.* Relation of interferon therapy and hepatocellular carcinoma in patients with chronic hepatitis C. Osaka Hepatocellular Carcinoma Prevention Study Group. *Ann Intern Med* 1998; **129**: 94–9.
142 Arase Y, Ikeda K, Suzuki F *et al.* Prolonged-interferon therapy reduces hepatocarcinogenesis in aged-patients with chronic hepatitis C. *J Med Virol* 2007; **79**: 1095–102.
143 Nomura H, Kashiwagi Y, Hirano R *et al.* Efficacy of low dose long-term interferon monotherapy in aged patients with chronic hepatitis C genotype 1 and its relation to alpha-fetoprotein: A pilot study. *Hepatol Res* 2007; **37**: 490–7.
144 Shiffman ML, Hofmann CM, Contos MJ *et al.* A randomized, controlled trial of maintenance interferon therapy for patients with chronic hepatitis C virus and persistent viremia. *Gastroenterology* 1999; **117**: 1164–72.
145 Saito Y, Saito H, Tada S *et al.* Effect of long-term interferon therapy for refractory chronic hepatitis c: preventive effect on hepatocarcinogenesis. *Hepatogastroenterology* 2005; **52**: 1491–6.
146 Arase Y, Ikeda K, Suzuki F *et al.* Interferon-induced prolonged biochemical response reduces hepatocarcinogenesis in hepatitis C virus infection. *J Med Virol* 2007; **79**: 1485–90.
147 Akuta N, Suzuki F, Kawamura Y *et al.* Efficacy of low-dose intermittent interferon-alpha monotherapy in patients infected with hepatitis C virus genotype 1b who were predicted or failed to respond to pegylated interferon plus ribavirin combination therapy. *J Med Virol* 2008; **80**: 1363–9.
148 Imai Y, Kasahara A, Tanaka H *et al.* Interferon therapy for aged patients with chronic hepatitis C: improved survival in patients exhibiting a biochemical response. *J Gastroenterol* 2004; **39**: 1069–77.
149 Iwasaki Y, Ikeda H, Araki Y *et al.* Limitation of combination therapy of interferon and ribavirin for older patients with chronic hepatitis C. *Hepatology* 2006; **43**: 54–63.
150 Hiramatsu N, Oze T, Tsuda N *et al.* Should aged patients with chronic hepatitis C be treated with interferon and ribavirin combination therapy? *Hepatol Res* 2006; **35**: 185–9.
151 Davis GL, Wong JB, McHutchison JG, Manns MP, Harvey J, Albrecht J. Early virologic response to treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C. *Hepatology* 2003; **38**: 645–52.
152 McHutchison JG, Manns M, Patel K *et al.* Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C. *Gastroenterology* 2002; **123**: 1061–9.

153 Shiffman ML, Ghany MG, Morgan TR *et al.* Impact of reducing peginterferon alfa-2a and ribavirin dose during retreatment in patients with chronic hepatitis C. *Gastroenterology* 2007; **132**: 103–12.
154 Reddy KR, Shiffman ML, Morgan TR *et al.* Impact of ribavirin dose reductions in hepatitis C virus genotype 1 patients completing peginterferon alfa-2a/ribavirin treatment. *Clin Gastroenterol Hepatol* 2007; **5**: 124–9.
155 Shiffman ML, Salvatore J, Hubbard S *et al.* Treatment of chronic hepatitis C virus genotype 1 with peginterferon, ribavirin, and epoetin alpha. *Hepatology* 2007; **46**: 371–9.
156 Oze T *et al.* Pegylated interferon alpha-2b affects early virologic response dose-dependently in patients with chronic hepatitis C genotype 1 during treatment with Peg-IFN alpha-2b plus ribavirin. *J Viral Hepat* 2009; **16**: 578–85.
157 Hiramatsu N *et al.* Ribavirin dose reduction raises relapse rate dose-dependently in genotype 1 patients with hepatitis C responding to pegylated interferon alpha-2b plus ribavirin. *J Viral Hepat* 2009; **16**: 586–94.
158 Weiland O, Hollamder A, Mattsson L *et al.* Lower-than standard dose peg-IFN alfa-2a for chronic hepatitis C caused by genotype 2 and 3 is sufficient when given in combination with weight-based ribavirin. *J Viral Hepat* 2008; **15**: 641–5.
159 Inoue Y, Hiramatsu N, Oze T *et al.* Factors affecting efficacy in patients with genotype 2 chronic hepatitis C treated by pegylated interferon alpha-2b and ribavirin: reducing drug doses has no impact on rapid and sustained virological responses. *J Viral Hepat* (in press).
160 Omata M, Yoshida H, Toyota J *et al.* A large-scale, multicentre, double-blind trial of ursodeoxycholic acid in patients with chronic hepatitis C. *Gut* 2007; **56**: 1747–53.
161 Suzuki H, Ohta Y, Takino T *et al.* Effects of glycyrrhizin on biochemical tests in patients with chronic hepatitis. Double blind trial. *Asian Med J* 1983; **26**: 423–38.
162 Wildhirt E. Experience in Germany with glycyrrhizinic acid for the treatment of chronic viral hepatitis. In: Nishioka K, Suzuki H, Mishiro S, Oda T, eds. *Viral Hepatitis and Liver Disease*. Tokyo, Springer-Verlag, 1994; 658–61.
163 Arase Y, Ikeda K, Murashima N *et al.* The long term efficacy of glycyrrhizin in chronic hepatitis C patients. *Cancer* 1997; **79**: 1494–500.
164 Ikeda K, Arase Y, Kobayashi M *et al.* A long-term glycyrrhizin injection therapy reduces hepatocellular carcinogenesis rate in patients with interferon-resistant active chronic hepatitis C: a cohort study of 1249 patients. *Dig Dis Sci* 2006; **51**: 603–9.
165 Piperno A, Sampietro M, D'Alba R *et al.* Iron stores, response to alpha-interferon therapy and effects of iron depletion in chronic hepatitis C. *Liver* 1996; **16**: 248–54.
166 Fong TL, Han SH, Tsai NC *et al.* A pilot randomized, controlled trial of the effect of iron depletionon long-term response to alpha-interferon in patients with chronic hepatitis C. *J Hepatol* 1998; **28**: 369–74.
167 Herrera JL. Iron depletion is not effective in inducing a virologic response in patients with chronic hepatitis C who failed to respond to interferon therapy. *Am J Gastroenterol* 1999; **94**: 3571–5.
168 Fontana RJ, Israel J, LeClair P *et al.* Iron reduction before and during interferon therapy of chronic hepatitis C: results of a multicenter, randomized, controlled trial. *Hepatology* 2000; **31**: 730–6.
169 Di Bisceglie AM, Bonkovsky HL, Chopra S *et al.* Iron reduction as an adjuvant to interferon therapy in patients with chronic hepatitis C who previously not responded to interferon: a multicenter, prospective randomized, controlled trail. *Hepatology* 2000; **32**: 135–8.
170 Yano M, Hayashi H, Yoshioka K *et al.* A significant reduction in serum alanine aminotransferase levels after 3-month iron reduction therapy for chronic hepatitis C: a multicenter, prospective, randomized, controlled trial in Japan. *J Gastroenterol* 2004; **39**: 570–4.
171 Marchesini G, Bianchi G, Merli M *et al.* Nutritional supplementation with branched-chain amino acids in advanced cirrhosis: a double-blind, randomized trial. *Gastroenterology* 2003; **124**: 1792–801.
172 McHutchison JG, Everson GT, Gordon SC *et al.* Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. *N Engl J Med* 2009; **360**: 1827–38.

C型肝炎に対するペグインターフェロン・リバビリン併用療法

インターフェロン・リバビリンの使い方

平松　直樹　　小瀬　嗣子　　林　　紀夫

medicina
第47巻　第3号 別刷
2010年3月10日　発行

医学書院

C 型肝炎に対するペグインターフェロン・リバビリン併用療法

インターフェロン・リバビリンの使い方

平松 直樹・小瀬 嗣子・林 紀夫

ポイント

★1 型高ウイルス量症例(1H)のウイルス陰性化には Peg-IFN，再燃には RBV が用量依存性に関与する．

★1H で 12 週以降にウイルスが陰性化した症例では，72 週投与が有効である．

★1H 以外の症例では約 80% が著効となり，高齢者でも治療効果は良好である．

C 型慢性肝炎に対する抗ウイルス療法は，ペグインターフェロン(pegylated interferon：Peg-IFN)/リバビリン(ribavirin：RBV)併用療法の登場によって飛躍的な治療効果の向上を認めた[1]．しかし，難治性である genotype 1 型高ウイルス量症例では，通常の治療法での著効率は 40～50% と，半数以上でウイルス排除ができていない．

Peg-IFN/RBV 併用療法の標準薬剤投与量は，Peg-IFNα2b(ペグイントロン®)1.5 μg/kg，または Peg-IFNα2a(ペガシス®)180 μg 週 1 回皮下投与，RBV(レベトール®またはコペガス®)〔600 mg(体重 40～60 kg)/800 mg(60～80 kg)/1,000 mg(80～100 kg)〕連日経口投与で，標準治療期間は genotype 1 型高ウイルス量では 48 週投与，genotype 1 型高ウイルス量以外では 24 週投与であるが，薬剤投与量の調節や投与期間の延長を行うことにより，より高い治療効果が得られる可能性がある．

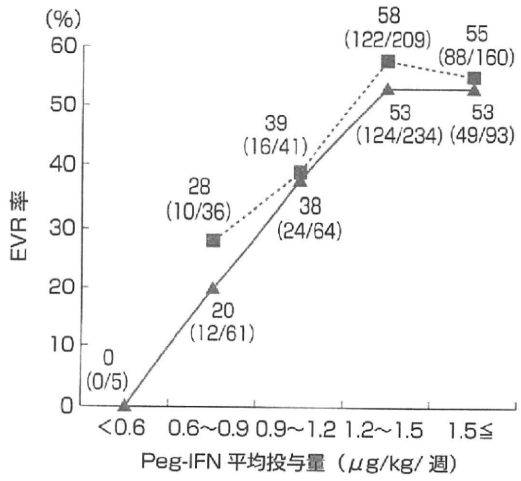
本稿では，大阪大学を中心とした OLF(Osaka Liver Forum)参加施設における Peg-IFN α2b/RBV 併用療法の解析結果を中心に，Peg-IFN/RBV の目標とすべき治療期間，薬剤投与量について述べる．

薬剤投与量と治療効果

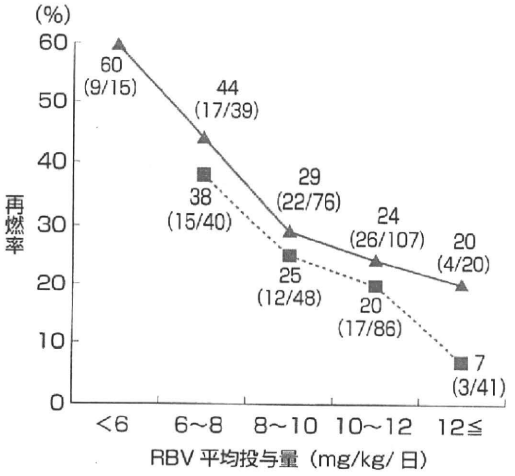
genotype 1 型に対する Peg-IFN/RBV 併用療法では，薬剤投与量(adherence)が治療効果に関連する重要な因子である．McHutchison らは，genotype 1 型において，著効を得るためには予定投与期間(48 週)の 80% 以上の期間において Peg-IFN，RBV ともに 80% 以上の投与量を維持することが重要であると報告した．また，OLF における検討から，早期ウイルス陰性化(early virologic response：EVR)の達成〔12 週までの HCV-RNA 陰性化(<50 IU/m*l*)〕には，RBV 投与量には関連がなく，Peg-IFN 投与量が用量依存性に関与することが明らかとなった[2](**図 1**)．ウイルス陰性化のためには，Peg-IFN 投与量 1.2 μg/kg/週を目標投与量とすることが重要であり，高齢などの理由で半量にて投与開始することは極力避けるべきである．一方，24 週までにウイルスが陰性化した症例における治療後の再燃率は，Peg-IFN 投

ひらまつ なおき，おぜ つぎこ，はやし のりお：大阪大学大学院医学系研究科消化器内科学 〒565-0871 大阪府吹田市山田丘 2-2

0025-7699/10/¥500/論文/JCOPY



【図 1】 投与開始後 12 週までの Peg-IFN 平均投与量と EVR 率（RBV 投与量別）（文献 2 より）
■……■：RBV 平均投与量 ≧10.6mg/kg/ 日
▲——▲：RBV 平均投与量 <10.6mg/kg/ 日
RBV 平均投与量 10.6mg/kg/ 日は中央値



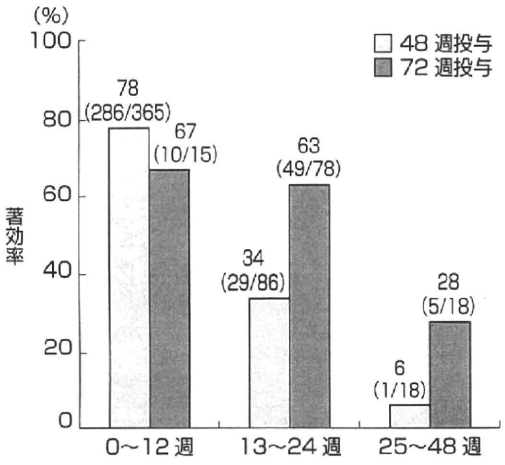
【図 2】 投与開始後 48 週までの RBV 平均投与量と再燃率（Peg-IFN 投与量別）（文献 3 より）
■……■：Peg-IFN 平均投与量 ≧1.4μg/kg/ 週
▲——▲：Peg-IFN 平均投与量 <1.4μg/kg/ 週
Peg-IFN 平均投与量 1.4μg/kg/ 週は中央値

与量には関連がなく，RBV 投与が用量依存性に関与している[3]（**図 2**）．治療後の再燃率低下のためには，48 週間の RBV 平均投与量 10 mg/kg/日（できれば 12 mg/kg/日）以上を目標投与量とすることが重要である．特に EVR 例では，RBV 12 mg/kg/日以上が投与された場合の再燃率は 3% ときわめて低率であった．逆に 12 週までに Peg-IFN 1.2 μg/kg/週以上を投与されて EVR が得られた症例では，12 週以降に Peg-IFN を減量しても再燃率は増加していない〔12 週以降の Peg-IFN 投与量別再燃率：1.2 μg/kg/ 週 以 上：19%(39/201)，0.9～1.2 μg/kg/週：21%(4/19)，0.9 μg/kg/週未満：20%(2/10)〕．

一方，genotype 2 型では，4 週の HCV-RNA 陰性化のみが著効に寄与する因子で，ある程度の薬剤減量では治療効果は低下しないことが報告されているため，特に 4 週陰性化例では，副作用の程度により減量も考慮に入れる必要がある[4]．

薬剤投与期間と治療効果

1 型高ウイルス量症例に対する HCV RNA 陰性化（<50 IU/ml）時期は，治療開始 4 週まで（rapid virologic response：RVR）が 6%，12 週まで（EVR）が 50%，13～24 週の陰性化（late virologic response：LVR）が 23% であった（OLF データ）．48 週治療の結果，RVR 例では全例が著効に至り，以後，5～8 週陰性化例で 83%，9～12 週で 69% と，陰性化時期が早いほど著効率が高く，逆に陰性化時期が遅い LVR 例では，著効率は低値となった．欧米の臨床試験において，LVR 例に対して長期投与が有用であることが示されているが，OLF においても，EVR 例に対する 72 週投与の著効率は 48 週投与と変わらなかったが，LVR 例では 48 週投与の 34% に比し，72 週投与で 63% と治療効果が向上した[5]（**図 3**）．このように，1 型高ウイルス量症例に対する標準治療では 48 週投与を基本とするが，治療開始後 13～24 週で陰性



【図3】 HCV-RNA陰性化時期別の著効率
(genotype1型高ウイルス量症例，48週投与 vs 72週投与)（文献5より）

化するlate responderでは72週の長期投与が有用である．厚生労働省の「C型慢性肝炎に対する初回投与のガイドライン」では，genotype 1型において，リアルタイムPCR法で，12週以降36週までの陰性化例に対する72週延長投与を推奨しており，こうした症例では医療費助成期間も延長されている．

genotype 1型に対する治療中止基準は，HCV RNAが12週で前値の2 log未満の低下にとどまる(1/100以下にならない)症例である．24週でウイルス陰性化が得られない症例では48週治療では著効が得られないが，24週時点でALTが正常である場合は，治療後もALT正常が持続することがあるため，48週まで治療を継続する意義はあり，必ずしも中止する必要はない．36週までにHCV-RNAが陰性化して72週投与を行うことができれば著効が得られる可能性もある．

一方，genotype 2型では，RVRが達成されれば，12～16週の短期投与を行っても治療効果は下がらないという報告が散見されるが，逆の報告もあり，副作用が強くなければ通常24週治療を行うことが望ましい．

文献

1) 平松直樹：C型慢性肝炎に対する抗ウイルス療法の新たな展開—Peg-IFN/Ribavirin併用療法と新規抗ウイルス療法．日内会誌 97：75-81，2008
2) Oze T, et al：Peginterferon alfa-2b affects early virologic response dose-dependently in patients with chronic hepatitis C genotype 1 during treatment with pegylated interferon alfa-2b plus ribavirin. J Viral Hepat 16：578-585, 2009
3) Hiramatsu N, et al：Ribavirin dose reduction raises relapse rate dose-dependently in genotype 1 patients with chronic hepatitis C responding to pegylated interferon alfa-2b plus ribavirin. J Viral Hepat 16：586-594, 2009
4) Inoue Y, Hiramatsu N, Oze T：Factors affecting efficacy in patients with genotype 2 chronic hepatitis C treated by pegylated interferon alpha-2b and ribavirin：Reducing drug doses has no impact on rapid and sustained virological responses. J Viral Hepat(in press)
5) Oze T, et al：Extended treatment with peginterferon alfa-2b and ribavirin combination therapy can suppress the relapse rate after treatment of chronic hepatitis genotype 1 patients with late viral response. Hepatology 48(Suppl)：853A, 2008

カレントテラピー

別刷

月刊カレントテラピー［別刷］2010 Vol.28 No.8 8月号

C型慢性肝炎に対する抗ウイルス薬

林 紀夫[*1]・小瀬嗣子[*2]・平松直樹[*3]

abstract

C型肝炎に対する抗ウイルス療法は，ペグインターフェロン/リバビリン（Peg-IFN/RBV）併用療法からさらなる治療効果向上を目指して，C型肝炎ウイルス（hepatitis C virus：HCV）選択的抗ウイルス剤である酵素阻害剤（protease阻害剤，polymerase阻害剤）や免疫賦活作用を有する薬剤などの開発が進んでいる．Protease阻害剤であるtelaprevirとPeg-IFN/RBVの3剤併用療法の大規模臨床試験では，Telaprevir/Peg-IFN/RBV12週+Peg-IFN/RBV12週の投与において，初回投与例で約60%，前治療再燃例で約70%，無効例で約40%の著効率が得られたとの報告がなされ，今後の臨床応用が待たれる．また，protease阻害剤（R7227）とpolymerase阻害剤（R7128）の2剤併用療法では，14日間投与により約5 log_{10}IU/mLのHCV-RNA減少が得られるなど，非常に強い抗ウイルス効果が示されており，今後の大規模臨床試験の結果が待たれる．

I はじめに

C型慢性肝炎に対する抗ウイルス療法は，インターフェロン（interferon：IFN）単独療法の時代から，IFN徐放剤であるペグインターフェロン（Pegylated interferon：Peg-IFN）と経口抗ウイルス剤であるリバビリン（ribavirin：RBV）の併用療法が標準的な治療法となって，治療効果は飛躍的に向上した[1),2)]．しかし，同療法においても，難治性であるgenotype 1型高ウイルス量症例では，約半数にC型肝炎ウイルス（hepatitis C virus：HCV）排除が得られず，ウイルス感染が持続している現状があり，さらなる治療効果向上を目指して新薬の開発が進んでいる．

現在のところ，新たなC型肝炎治療薬として，新しいIFN製剤[3)]や，RBVのプロドラッグ[4)]，HCV選択的抗ウイルス剤である酵素阻害剤[5)~22)]，免疫賦活作用の増強を目的とした各種薬剤[23)~30)]などが開発中である．本稿では，最も開発が進んでいる酵素阻害剤について，protease阻害剤[5)~17),22)]，polymerase阻害剤[18)~22)]を中心に最近の知見を紹介する．

II Protease阻害剤

HCVは肝細胞に進入すると約3,000のアミノ酸からなるウイルスのpolyproteinを合成し，このpolyproteinはウイルスおよび宿主のproteaseにより10種類のpolypeptideに切断される．これらのウイルス蛋白のひとつが非構造性蛋白NS3で，serine protease活性を有しHCVの増殖に重要な役割を果たしている．NS3/4 serine protease阻害剤は，protease活性部位に結合することにより酵素活性を阻害し，ウイルス増殖を直接抑制する作用がある．NS3/4 protease阻害剤として開発中の主な薬剤とし

*1 関西労災病院病院長
*2 大阪大学大学院医学系研究科消化器内科学
*3 大阪大学大学院医学系研究科消化器内科学講師

て，VX-950（telaprevir）[5)~12)]，SCH503034（boceprevir）[13)]，TMC435[14)]，MK7009[15)]，BI201335[16)]，SCH900518（narlaprevir）[17)] などが挙げられる．

1 Telaprevir

TelaprevirのC型慢性肝炎患者に対する第Ⅰb相試験[5)]では，genotype 1型（HCV-RNA≥100KIU/mL）の28例（うち23例は前治療無効例）を対象として，450mg×8時間ごと，1,250mg×12時間ごと，750mg×8時間ごとの3群比較（14日間投与）が行われた．この結果，全例において2 log_{10}IU/mL以上，約9割（26/28）に3 log_{10}IU/mL以上，最も効果の高かった750 mg投与群では，4.4 log_{10}IU/mL（中央値）のHCV-RNA量低下を認め，transaminase値も投与終了時点で全例低下を認めた．しかし，高率に変異ウイルスが出現することも報告されており[6)]，各症例の治療前ならびに治療終了時の血清サンプルから抽出された各々約80クローンのHCV-RNAについて，NS3領域のN末端543塩基（181アミノ酸）の変異が解析された結果，治療終了時点で4カ所（36，54，155，156）のアミノ酸変異が同定された．最も頻度の高い変異パターンは，V36A/M，T54A，R155K/T，A156V/T/Sのsingle mutationと36+155，36+156のdouble mutationであった．このうち，軽度薬剤耐性（野生株の25倍未満）はV36A/M，T54A，R155K/T，A156S変異株にみられ，高度薬剤耐性（野生株の60倍超）はA156V/T，36+155，36+156に認められた．

以上のように，Telaprevirは強い抗ウイルス活性を有するが，早期に薬剤耐性変異が生じる．したがって，単独療法では完全なウイルス排除は期待できず，現在，Peg-IFNやRBVとの併用を中心に臨床試験が行われている[7)~12)]．

このうち，Telaprevir（750mg×8時間ごと）/Peg-IFNα2a（180μg/週）/RBV（1,000～1,200mg/日）3剤併用療法の第Ⅱ相試験が終了しているPROVE 1，PROVE 2およびPROVE 3について紹介する[10)~12)]．PROVE 1 study[10)]では，初回治療のgenotype 1型C型慢性肝炎250例に対して，対照をPeg-IFNα2a/RBV 48週投与群（PR48）として，Telaprevir/Peg-IFNα2a/RBV3剤併用12週投与群（T12PR12），3剤併用12週投与後Peg-IFNα2a/RBV 12週投与群（Telaprevir 12週/PR24週：T12PR24），3剤併用12週投与後Peg-IFNα2a/RBV 36週投与群（Telaprevir 12週/PR48週：T12PR48）を比較している（**図1A**）．この結果，HCV-RNA陰性化（<10IU/mL）は，治療開始4週時点において，PR 48：11%，T12PR12：59%，T12PR24：81%，T12PR48：81%，12週時点において，PR48：45%，T12PR12：71%，T12PR24：68%，T12PR48：80%とTelaprevir併用群において高率であり，著効率も，PR48：41%，T12PR12：35%，T12PR24：61%，T12PR48：67%と，3剤併用の後にPeg-IFN/RBV投与を継続した群において有意に高率であった（p=0.02，p=0.002）．また，3剤併用後のPeg-IFN/RBV併用が12週と36週の群の治療効果がほぼ同等であったことから，現在，3剤併用12週投与後Peg-IFN/RBV 12週投与を基本に臨床研究が進められている．

PROVE 2 study[11)]は，初回治療のgenotype 1型C型慢性肝炎323例に対し，対照をPeg-IFNα2a/RBV 48週投与群（PR48）として，telaprevir/Peg-IFNα2a 12週投与群（T12P12），3剤併用12週投与群（T12PR12），3剤併用12週投与後Peg-IFNα2a/RBV 12週投与群（T12PR24）を比較し，telaprevir併用療法におけるRBVの有用性について検討している（**図1B**）．この結果，HCV-RNA陰性化（<10 IU/mL）は，治療開始4週時点において，PR48：13%，T12P12：50%，T12PR12：80%，T12PR24：69%，12週時点において，PR48：43%，T12P12：62%，T12PR12：80%，T12PR24：73%とTelaprevir併用群において有意に高率であった．著効率は，PR48：46%，T12P12：36%，T12PR12：60%，T12PR24：69%と，3剤併用群で高く，RBVを併用しないT12P12では最も低率であった．これは，T12P12において，治療中のHCV-RNA再上昇を24%（19/78），治療後再燃を48%（22/46）に認め，3剤併用群（T12PR12とT12PR24）の治療中のHCV-RNA再上昇率（3%：5/163），治療後再燃率（T12PR12：30%，T12PR24：14%）に比し，有意に高率であったことが主因である．したがって，Telaprevirによる治療では，Peg-IFNのみならず，RBVを含んだ3剤併

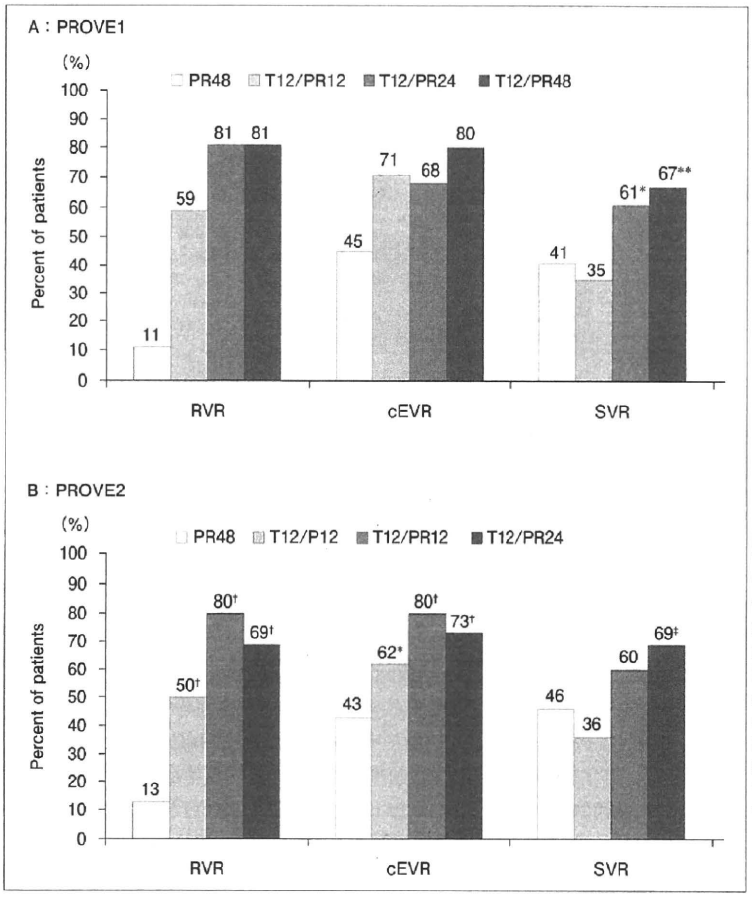


図1
Telaprevir/Peg-IFNα2a/RBVの第Ⅱ相試験
T：Telaprevir,
P：Peg-IFNα2a, R：RBV
RVR：Rapid viral response（治療開始4週時点でのHCV-RNA陰性化）
cEVR：Complete early viral response（治療開始12週時点でのHCV-RNA陰性化）
SVR:Sustained viral response(著効)
*：p=0.02 vs. P/R 48週
**：p=0.002 vs. P/R 48週
†：p<0.001 vs. P/R 48週
‡：p=0.004 vs. P/R 48週
〔参考文献10), 11)より引用改変〕

用が必要であることを示している.

以上2つの第Ⅱ相試験の結果を受けて，現在わが国において，3剤併用12週投与後Peg-IFN/RBV 12週投与群とPeg-IFN/RBV 48週投与群を比較する第Ⅲ相試験が行われている.

PROVE 3 study[12]は，Peg-IFN/RBV併用療法において著効が得られなかったgenotype 1型C型肝炎（代償性肝硬変を含む）453例に対する，telaprevir（750mg×8時間ごと）/Peg-IFNα2a（180μg/週）/RBV（1,000～1,200mg/日）3剤併用療法の第Ⅱ相試験である．対照をPeg-IFNα2a/RBV 48週投与群(PR48)として，telaprevir/Peg-IFNα2a 24週投与群（T24P24），telaprevir/Peg-IFNα2a/RBV3剤併用12週投与後Peg-IFNα2a/RBV 12週投与群（T12PR24），3剤併用24週投与後Peg-IFNα2a/RBV 24週投与群（telaprevir24週/PR48週：24PR48）を比較するもので，2009年11月米国肝臓学会において結果が報告された．治療終了時点でのHCV-RNA陰性化率は，対照群に比しtelaprevirを併用した群で高率であり，著効率も，PR48：14%，T24P24：24%，T12PR24：51%，T24PR48：53%と特に3剤併用群で高率であった．また，前治療効果別では，Peg-IFN/RBV併用療法の再燃例において，T12PR24：69%，T24PR48：76%と高率な著効率を認め，無効例においても，T12PR24：39%，T24PR48：38%と比較的良好な治療効果が得られた（**図2**）．以上の結果は，Peg-IFN/RBV併用療法において著効が得られなかった

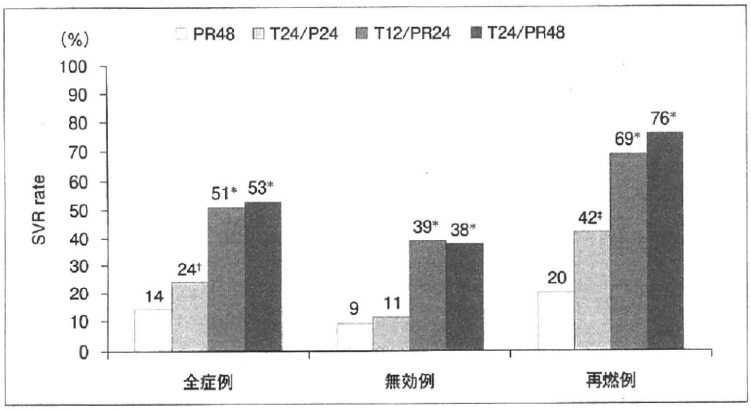


図2
Peg-IFN/RBV併用療法にて著効が得られなかった症例に対するtelaprevir/Peg-IFNα2a/RBVの第Ⅱ相試験（PROVE3）
T：Telaprevir,
P：Peg-IFNα2a, R：RBV
SVR:Sustained viral response(著効)
*：p<0.001 vs. P/R 48週
†：p=0.035 vs. P/R 48週
‡：p=0.029 vs. P/R 48週
〔参考文献12）より引用改変〕

症例においても，telaprevirを含む3剤併用療法は治療効果が期待できることを示している．

2 Boceprevir

Bocepreviについても，boceprevir（800mg×3/日）/Peg-IFNα2b（1.5μg/kg/週）/RBV（800～1,400mg/日）3剤併用療法の第Ⅱ相試験[13]が行われている．SPRINT-1 studyは，初回治療のgenotype 1型C型慢性肝炎に対し，対照をPeg-IFNα2b/RBV 48週投与群として，boceprevir/Peg-IFNα2b/RBV 3剤併用28週あるいは48週投与する群，Peg-IFNα2b/RBV 4週間先行投与の後に3剤併用24週あるいは44週投与する群の5群を比較する試験である．この結果，著効率は，対照群の38%に対し，Peg-IFNα2b/RBVの先行投与の有無にかかわらず28週投与群で54～56%と高率であり，48週投与群では，Peg-IFNα2b/RBV先行投与のない群で67%，先行投与を行った群では75%と，Peg-IFNα2b/RBV 4週間先行投与後に3剤併用44週投与群が最も高率であった．また，Peg-IFNα2b/RBV 4週間先行投与の2群においては，治療開始4週時にHCV-RNA陰性化が得られた場合の著効率は，3剤併用24週群で82%，3剤併用48週群で94%，治療開始12週時のHCV-RNA陰性化が得られた場合の著効率はそれぞれ68%，91%であった．3剤併用44～48週投与における主な副作用は，Peg-IFNα2b/RBV併用療法での副作用と同様，倦怠感，軽度の貧血，頭痛などであり，telaprevir併用でみられる重篤な皮疹や高度な貧血などの副作用の出現は認めなかったと報告されている．こうしたことから，boceprevirはtelaprevirより長期投与できる可能性があり，今後，Peg-IFNα2b/RBV4週間投与後の3剤併用24週あるいは44週投与に対する第Ⅲ相試験が行われる予定である．

3 その他のprotease阻害剤

上述したtelaprevirやboceprevirは1日3回の内服を必要とするが，1日1回の内服で同等の抗ウイルス効果を示すprotease阻害剤の開発が進んでいる．TMC435については，現在，TMC435/Peg-IFNα2a（180μg/週）/RBV（1,000～1,200mg/日）3剤併用療法の第Ⅱ相試験が行われている[14]．対照をPeg-IFNα2a/RBV 48週投与群として，TMC（25mg, 75mg, 200mg）/Peg-IFNα2a/RBV3剤併用4週投与後Peg-IFNα2a/RBV44週投与を比較する試験であるが，治療開始4週時点のHCV-RNA減少量およびHCV-RNA陰性化（<10 IU/mL）は，TMC25mg群で4.74 log_{10}IU/mL，33%（3/9），75mg群で5.52 log_{10}IU/mL，89%（8/9），200mg群で5.54 log_{10}IU/mL，70%（7/10）であったと報告されている．

MK7009の初回治療のgenotype 1型C型慢性肝炎患者に対する第Ⅱ相試験[15]は，対照をPeg-IFNα2a/RBV 48週投与群として，用量・用法の異なるMK7009（300mg×2/日，600mg×2/日，600mg/日，800mg/日）/Peg-IFNα2a/RBV3剤併用4週投与後Peg-IFNα2a/RBV44週投与を比較する試験であるが，治療開始4週および12週時点の