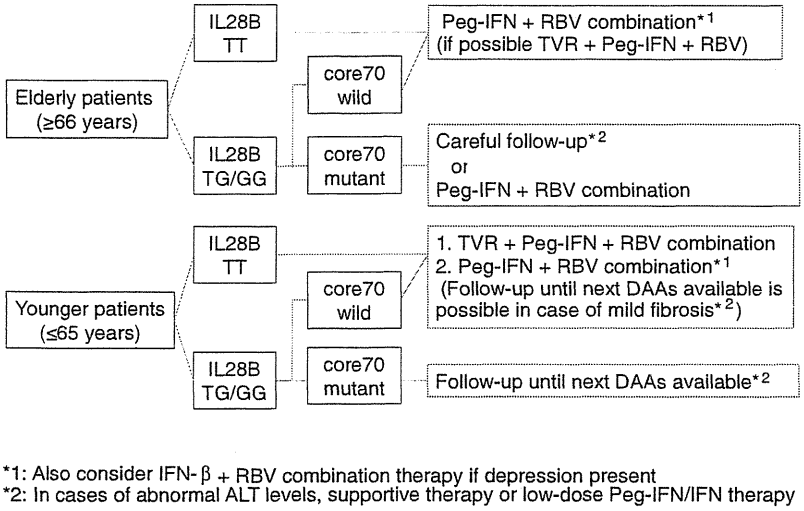


Figure 2 Patients with chronic hepatitis C genotype 1, high viral load; Principles of treatment in treatment-naive cases, when IL28B SNP/HCV core amino acid 70 substitution can be tested.

careful follow-up, with no antiviral therapy, is an option. If therapy aimed at SVR is not administered, but ALT levels are abnormal, then the above-mentioned low-dose long-term Peg-IFN or IFN therapy or supportive therapy (e.g. SNMC, UDCA) may be administered. In anemic patients (Hb <12 g/dL), Peg-IFN (IFN) therapy without ribavirin may be considered.

Recommendations:

1 *Elderly patients are at high risk of developing HCC, and should commence antiviral therapy promptly.*
2 *Antiviral therapy for elderly patients should be selected with due consideration of the anticipated therapeutic efficacy and adverse reactions, and the possibility that viral eradication may not be successful should be fully explained to the patient in advance.*
3 *As a general rule, Peg-IFN + ribavirin combination therapy is the first-line treatment for treatment-naive elderly patients.*
4 *If IL-28B minor alleles and amino acid 70 substitutions in the HCV core region have been detected in an elderly patient, careful follow-up is an option. If ALT levels are abnormal, low-dose long-term Peg-IFN/IFN therapy or supportive therapy may be administered.*

Non-elderly patients. In non-elderly patients with a relatively low risk of HCC, testing for IL-28B SNP and amino acid substitutions in the HCV core region and ISDR should be performed if possible. Treatment with the highest possible expected therapeutic efficacy, including next generation DAAs, should be considered. More aggressive therapy is required in patients with advanced fibrosis.

In practice, the treatment of first choice is telaprevir + Peg-IFN + ribavirin triple therapy. When tolerability is a concern, and in patients with advanced fibrosis, Peg-IFN + ribavirin combination therapy should be considered. Also, consider IFN-β + ribavirin combination therapy in patients with depressive symptoms. For some patients with mild fibrosis and a low risk of HCC, follow-up until new therapies with higher anticipated efficacies become available is an option. Testing of IL28B SNPs and amino acid 70 substitutions in the HCV core region is useful when it is difficult to decide whether antiviral therapy should be commenced in an individual patient. If IL-28B minor alleles and amino acid 70 substitutions in the HCV core region have been detected, as a general rule, aggressive antiviral therapy is not recommended.

Recommendations:

1 *In non-elderly patients with a relatively low risk of HCC, then testing for IL-28B SNP, amino acid substitutions in the HCV core region and ISDR should be performed if possible. Treatment with the highest possible expected therapeutic efficacy, including next generation DAAs, should be considered. More aggressive therapy is required in patients with advanced fibrosis, as with elderly patients, but follow-up until new therapies with higher anticipated efficacies become available is an option in non-elderly patients with mild fibrosis.*

2 *The treatment of first choice in non-elderly patients is telaprevir + Peg-IFN + ribavirin triple therapy. When tolerability is a concern and in patients with advanced fibrosis, Peg-IFN + ribavirin combination therapy should be considered.*
3 *If IL-28B minor alleles and amino acid 70 substitutions in the HCV core region have been detected, as a general rule, aggressive antiviral therapy should not be administered.*

3.5 Initial treatment—Genotype 1 with low viral load, and Genotype 2

In patients with chronic hepatitis C, genotype 1 with low viral load and genotype 2, administered Peg-IFN + ribavirin combination therapy, little difference is seen in SVR rates according to genotype or viral load. In the United States and Europe, Peg-IFN + ribavirin combination therapy is the treatment of first choice, whereas in Japan treatment-native patients with low viral loads are given IFN monotherapy as first choice.

Genotype 1, low viral load

Patients with genotype 1 and a low viral load (<5.0 $\log_{10}$ IU/mL using real-time PCR, HCV core antigen <300 fmol/L) administered Peg-IFN monotherapy achieve ≥50% of SVR rates.[40,134] Approximately 50% of SVR rates can be achieved with standard IFN monotherapy for 24–48 weeks as well.[135] Peg-IFN + ribavirin combination therapy has been reported to yield SVR rates ≥80% in this patient group,[136] but is not approved by Japanese national medical insurance.

Genotype 2, low virus load

Patients with genotype 2 and a low viral load administered Peg-IFN monotherapy achieve SVR rates of approximately 90%.[134,137] Similarly high SVR rates are also seen with standard IFN monotherapy. Although not approved by medical insurance in Japan, even higher SVR rates can be achieved with Peg-IFN + ribavirin combination therapy. The standard treatment duration is 24 weeks, but this can be shortened to 8–16 weeks if HCV RNA becomes undetectable by treatment week 1 or 2.[138]

Genotype 2, high viral load

Peg-IFN + ribavirin combination therapy shows high efficacy in patients with genotype 2 and a high viral load.[85,139] If HCV RNA is <1000 kIU/mL (6.0 $\log_{10}$ IU/mL), viral clearance can also be expected with Peg-IFN monotherapy. In particular, if HCV RNA becomes undetectable by treatment week 4–8, SVR rates ≥80% can be achieved.[137]

Recommendations:
1 *For treatment-naive patients with genotype 1 and a low viral load, Peg-IFN monotherapy for 24–48 weeks or standard IFN monotherapy for 24 weeks is recommended.*
2 *For treatment-naive patients with genotype 2 and a low viral load, Peg-IFN monotherapy for 24–48 weeks or standard IFN monotherapy for 24 weeks is recommended. This can be shortened to 8–16 weeks if HCV RNA becomes undetectable by treatment week 1 or 2.*
3 *For treatment-naive patients with genotype 2 and a high viral load, Peg-IFN + ribavirin combination therapy or IFN-β + ribavirin therapy for 24 weeks is recommended. If there are problems with using ribavirin, Peg-IFN monotherapy may be administered for 24–48 weeks.*

3.6 Retreatment—Genotype 1 with high viral load

Response to the previous therapy is the best indicator of the therapeutic efficacy of retreatment in patients who fail to respond to IFN/Peg-IFN + ribavirin combination therapy.[140–142] Failure to respond to previous therapy is broadly divided into "relapse" (HCV RNA became undetectable during treatment but reappeared following treatment) and "non-response" (HCV RNA did not become undetectable during treatment). Furthermore, "non-response" is divided into "null response", with almost no response (<2 log decrease in HCV RNA at treatment week 12) and "partial response" (HCV RNA did not become undetectable during treatment, but ≥2 log decrease at treatment week 12) (Table 2).[101] When combination therapy including ribavirin is administered to patients who did not have ribavirin in their previous therapy, namely, the previous therapy was IFN or Peg-IFN monotherapy, the response to previous therapy is not a strong predictor of efficacy. As a general rule, in these cases the therapy protocol in treatment-naive patients applies. If the details of previous treatment are unknown, again the therapy protocol in treatment-naive patients applies.

The Epic study, mainly conducted in Western countries, trialed the retreatment with 48 weeks' Peg-IFN + ribavirin combination therapy in patients who failed to respond to previous IFN/Peg-IFN + ribavirin combination therapy (genotype 1, METAVIR score F2–F4). They reported an SVR rate of 23% (56/243) in

relapsers of the previous treatment, and the even lower rate of 4% (19/431) in non-responders.[142] In the REPEAT study of the efficacy of extended treatment durations of Peg-IFN-α-2a + ribavirin combination therapy in patients who failed to respond to previous IFN/Peg-IFN-α-2b + ribavirin combination therapy, the SVR rate of 16% in the 72-week treatment group was higher than that of 8% for the 48-week treatment group.[140] In a study of response-guided retreatment of Peg-IFN + ribavirin combination therapy in patients who previously failed to respond to the same therapy, the SVR rate in relapsers was 63% (20/32) and 13% (3/24) in non-responders, whereas none of the 16 null responders achieved SVR.[141] In this way, in order to achieve SVR with retreatment with Peg-IFN + ribavirin combination therapy in a patient who failed to respond to previous combination therapy containing ribavirin, it is necessary that the patient not be a null responder to the previous treatment. It is also desirable that the previous treatment was not extended in duration.

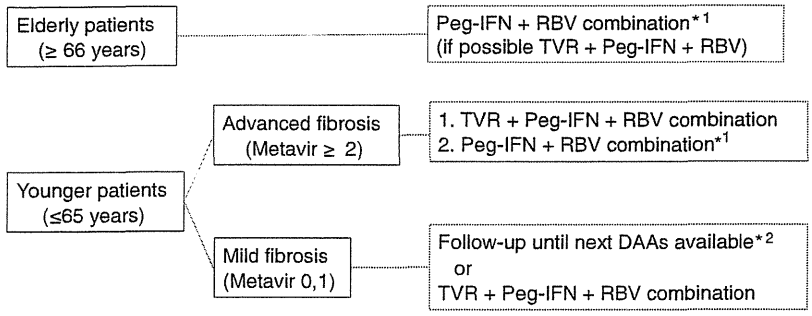
The response to previous therapy is also extremely important for retreatment with telaprevir + Peg-IFN + ribavirin triple therapy. When patients with genotype 1 chronic hepatitis C who failed to respond to previous Peg-IFN + ribavirin combination therapy were administered standard telaprevir therapy (telaprevir + Peg-IFN + ribavirin triple therapy for 12 weeks, followed by Peg-IFN-α-2a + ribavirin dual therapy for 12 weeks; T12PR24) as retreatment, the SVR rate in relapsers of Peg-IFN + ribavirin combination therapy was 69% (29/42), and lower in non-responders at 39% (26/66) (PROVE 3 study).[13] In a Japanese clinical trial, if we consider only patients whose previous treatment was Peg-IFN + ribavirin combination therapy, the SVR rate was 86% (68/79) in relapsers and 28% (8/29) in non-responders.

Another clinical trial administered telaprevir + Peg-IFN + ribavirin triple therapy for 48 weeks to patients with genotype 1 chronic hepatitis C who failed to respond to previous Peg-IFN + ribavirin combination therapy (REALIZE study). They allocated patients to a group administered telaprevir + Peg-IFN + ribavirin triple therapy for 12 weeks, followed by Peg-IFN-α-2a + ribavirin dual therapy for 36 weeks (T12PR48); a group administered Peg-IFN-α-2a lead-in monotherapy for 4 weeks followed by telaprevir + Peg-IFN-α-2a + ribavirin triple therapy for 12 weeks then Peg-IFN-α-2a + ribavirin dual therapy for 32 weeks (Lead-in T12PR48); and a control group administered Peg-IFN-α-2a + ribavirin therapy for 48 weeks (PR48). The SVR rates for the T12PR48/Lead-in T12PR48/PR48 groups according to response to previous therapy to Peg-IFN + ribavirin combination therapy were 83%/88%/24% for relapsers, 59%/54%/15% for partial responders and 29%/33%/5% for null responders, indicating that response to previous therapy is a strong predictor of the efficacy of triple therapy, regardless of lead-in.[100] A study of the relationship between IL-28B SNPs and therapeutic effect according to response to previous treatment found that for the same previous response, SVR rates were similar for major (CC) and minor (CT or TT) alleles at the IL-28B SNP (rs12980275) (relapser, 88%/85%/85%; partial responder, 63%/58%/71%; null responder, 40%/29%/31%).[143] In a clinical trial of retreatment with telaprevir + Peg-IFN + ribavirin triple therapy for patients with genotype 1 chronic hepatitis C who failed to respond to Peg-IFN + ribavirin combination therapy, null responders and those who failed to achieve eRVR were administered extended therapy (T12PR48), and others standard telaprevir therapy (T12PR24). The SVR rates were 97% (28/29) in relapsers, 55% (16/29) in partial responders and 37% (19/51) in null responders.[144]

In this way, we can see that the response to previous therapy is also an extremely important prognostic factor for retreatment with telaprevir + Peg-IFN + ribavirin triple therapy. The SVR rate for null-responders to previous therapy is only of the order of 30% for 48 weeks with telaprevir + Peg-IFN + ribavirin triple therapy, and lower SVR rates can be anticipated in Japan with 24 weeks' treatment. There are particular concerns regarding adverse reactions in elderly null-responders to previous therapy, so caution is required in considering triple therapy in this patient group.

Selection of antiviral therapy for retreatment: Genotype 1 with high viral load (Figs 3,4)

Elderly patients. In general, retreatment should be with Peg-IFN + ribavirin combination therapy, although telaprevir + Peg-IFN + ribavirin combination therapy should be considered if it can be tolerated. Therapeutic efficacy has been reported for retreatment with Peg-IFN + ribavirin combination therapy in non-responders to IFN + ribavirin combination therapy,[145,146] but SVR cannot be expected with Peg-IFN + ribavirin combination therapy in null responders to IFN + ribavirin combination therapy. Telaprevir + Peg-IFN + ribavirin combination therapy can be commenced in null responders to previous therapy, with due consideration of the discontinuation criteria. Due to concern about adverse reactions, and the fact that the anticipated therapeutic efficacy is not high, in general it is preferable to



*1: Also consider IFN-β + RBV combination therapy if depression present
*2: In cases of abnormal ALT levels, supportive therapy or low-dose Peg-IFN/IFN therapy

Figure 3 Patients with chronic hepatitis C genotype 1, high viral load; Principles of treatment in retreatment cases, when details of previous treatment are unknown. If IL28B SNP/core amino acid 70 substitutions can be tested, follow the treatment guidelines in treatment-naive patients.

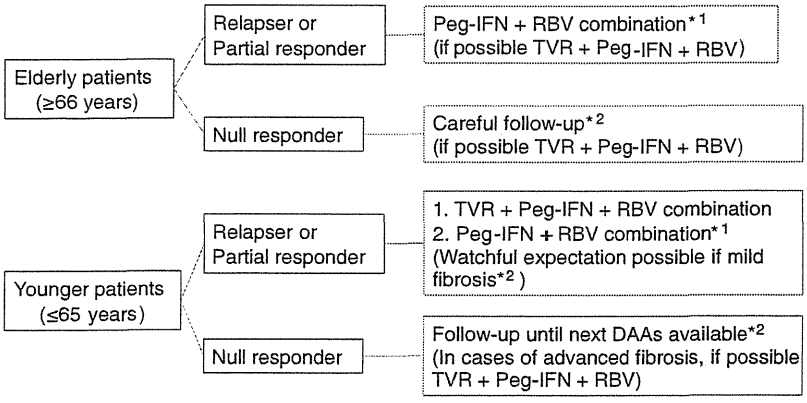
wait for the next generation DAAs. On the other hand, elderly patients are at high risk of developing HCC, so if viral clearance cannot be achieved, low-dose long-term Peg-IFN or IFN therapy, or supportive therapy (e.g. SNMC, UDCA) should be administered with the aims of biochemical improvement and inhibiting hepatocellular carcinogenesis.

Non-elderly patients. As mentioned above, in Japanese studies, retreatment with triple therapy in relapsers following previous Peg-IFN + ribavirin combination therapy is highly efficacious, with an SVR rate of 86%.[9,147] In all non-responders to Peg-IFN + ribavirin combination therapy, the SVR rate was 28%, although better rates can be anticipated in partial responders. Accordingly, the treatment of first choice in relapsers and partial responders to previous therapy is telaprevir + Peg-IFN + ribavirin triple therapy. If triple therapy cannot be tolerated, retreatment with Peg-IFN + ribavirin combination therapy should be considered in patients with advanced fibrosis, although waiting for the next generation DAAs is an option in patients with mild fibrosis.

In null responders to previous therapy, the anticipated therapeutic efficacy for 24 weeks' triple therapy is rather low.[9] Accordingly, telaprevir + Peg-IFN + ribavirin triple therapy should be considered in patients with advanced fibrosis, but for patients with mild fibrosis in general we should wait for the next generation DAAs.

Recommendations:

1 *Response to the previous therapy is the best indicator of the therapeutic efficacy of retreatment in patients with chronic hepatitis C genotype 1 and a high viral load who failed to respond to previous*



*1: Also consider IFN-β + RBV combination therapy if depression present
*2: In cases of abnormal ALT levels, supportive therapy or low-dose Peg-IFN/IFN therapy

Figure 4 Patients with chronic hepatitis C genotype 1, high viral load; Principles of treatment in retreatment cases, when details of previous treatment are known.

IFN/Peg-IFN + ribavirin combination therapy. In general, follow the therapy protocol in treatment-naive patients for retreatment with combination therapy including ribavirin in patients previously administered IFN or Peg-IFN monotherapy.

2 *Retreatment in elderly patients with genotype 1 and high viral load: for relapsers and partial responders to previous therapy, retreatment should be with Peg-IFN + ribavirin combination therapy in general, although telaprevir + Peg-IFN + ribavirin combination therapy should be considered if it can be tolerated.*
3 *Retreatment in elderly patients with genotype 1 and high viral load: for null responders to previous therapy, as an adequate antiviral effect cannot be expected, careful follow-up should be considered. If ALT levels are abnormal, low-dose long-term Peg-IFN/IFN therapy or supportive therapy should be administered.*
4 *Retreatment in non-elderly patients with genotype 1 and high viral load: for relapsers and partial responders to previous therapy, the treatment of first choice is telaprevir + Peg-IFN + ribavirin combination therapy. If triple therapy cannot be tolerated, retreatment with Peg-IFN + ribavirin combination therapy should be considered in patients with advanced fibrosis, although waiting for the next generation DAAs is an option in patients with mild fibrosis.*
5 *Retreatment in non-elderly patients with genotype 1 and high viral load: for null responders to previous therapy, telaprevir + Peg-IFN + ribavirin triple therapy should be considered in patients with advanced fibrosis, if tolerated, but for patients with mild fibrosis, we should wait for the next generation DAAs.*

3.7 Retreatment—Genotype 1 with low viral load, and Genotype 2

Genotype 1, low viral load

If the previous treatment was IFN or Peg-IFN monotherapy, as a general rule, retreatment should be with Peg-IFN + ribavirin combination therapy. When Peg-IFN-α is contraindicated due to depression or depressive symptoms, IFN-β can be used instead of Peg-IFN.[26] When the previous therapy included ribavirin, telaprevir + Peg-IFN + ribavirin combination therapy should be used. If triple therapy cannot be tolerated, then consider retreatment with Peg-IFN + ribavirin combination therapy, although there is no clear evidence regarding the efficacy of this therapy as retreatment.

Genotype 2, high viral load

If the previous treatment was IFN or Peg-IFN monotherapy, retreatment should be with Peg-IFN + ribavirin combination therapy (24 weeks). When the previous therapy included ribavirin, treatment with Peg-IFN + ribavirin therapy (24–48 weeks) should be considered. SVR rates ≥50% have been reported.[141,148] When Peg-IFN-α is contraindicated due to depression or depressive symptoms, IFN-β can be used instead of Peg-IFN.[26]

Genotype 2, low viral load

If the previous treatment was IFN or Peg-IFN monotherapy, retreatment should be with Peg-IFN + ribavirin combination therapy (24 weeks). When the previous therapy included ribavirin, treatment with Peg-IFN + ribavirin therapy (24–48 weeks) should be considered. High SVR rates comparable to those achieved with initial treatment have been reported.[85,136] As with patients with genotype 2 and a high viral load, if Peg-IFN-α is contraindicated due to depression or depressive symptoms, IFN-β can be used instead of Peg-IFN.[26]

Recommendations:

1 *In patients with genotype 1 and a low viral load, if the previous treatment was IFN or Peg-IFN monotherapy, as a general rule, retreatment should be with Peg-IFN + ribavirin combination therapy. When the previous therapy included ribavirin, telaprevir + Peg-IFN + ribavirin combination therapy should be used. If triple therapy cannot be tolerated, then consider retreatment with Peg-IFN + ribavirin combination therapy in patients with advanced fibrosis.*
2 *In patients with genotype 2, regardless of the viral load, if the previous treatment was IFN or Peg-IFN monotherapy, retreatment should be with Peg-IFN + ribavirin combination therapy (24 weeks). When the previous therapy included ribavirin, treatment with Peg-IFN + ribavirin therapy (24–48 weeks) should be considered.*
3 *In any patient group, in patients unable to tolerate Peg-IFN-α due to depression or depressive symptoms, IFN-β + ribavirin combination therapy should be administered for 28–48 weeks.*

3.8 Treatment of patients with liver cirrhosis

IFN therapy for compensated cirrhosis

The state in which the hepatic functional reserve is preserved, and there is no evidence of liver failure such as jaundice, ascites, hepatoencephalopathy or esophageal varices (Child–Pugh class A) is called compensated

cirrhosis, and when there is evidence of liver failure (Child–Pugh class B, C), it is called decompensated cirrhosis. Patients with liver cirrhosis accompanying severe fibrosis are a high-risk group for hepatocellular carcinogenesis. Even if they avoid developing HCC, the prognosis is poor if they develop liver failure. Accordingly, the objective of treatment for liver cirrhosis is to prevent both HCC and liver failure, and aggressive antiviral therapy is highly necessary in patients with compensated cirrhosis. Viral eradication through IFN therapy in patients with compensated cirrhosis can be expected to reduce the risk of HCC and liver failure.[8] However, patients with advanced hepatic fibrosis are IFN-resistant, and pancytopenia associated with hypersplenism complicating liver cirrhosis impedes IFN therapy.[78,79] When a virological response is not achieved with IFN therapy, a changeover to low-dose long-term IFN therapy should be made with the improving ALT levels and inhibiting hepatocellular carcinogenesis. The safety of telaprevir + Peg-IFN + ribavirin triple therapy has not been established in patients with cirrhosis, and is not approved by national medical insurance for this patient group.

Peg-IFN + ribavirin combination therapy. For some time now, outside of Japan, the standard treatment for patients with compensated cirrhosis has been the same as for chronic hepatitis C, Peg-IFN + ribavirin combination therapy.[149,150] In a trial comparing Peg-IFN-α-2b (1.0 μg/kg per week) monotherapy and combination therapy including ribavirin (800 mg/day), mainly in patients with compensated cirrhosis, higher efficacy was seen with the latter (SVR rates, 9.8% vs 21.6%, $P = 0.06$). The SVR rate was 67% in patients with genotypes 2 and 3, significantly higher than that of 11% in patients with genotypes 1 and 4 ($P = 0.001$). Progression towards liver failure was significantly less in patients achieving SVR than in non-responders (6.2% vs 38.3%, $P = 0.03$).[151] In a clinical trial of Peg-IFN-α-2a 180 μg/kg/week and ribavirin 600–1200 mg/day combination therapy, solely with patients with compensated cirrhosis, a significantly higher SVR rate was seen with genotypes 2 and 3 than with genotypes 1 and 4 (32% vs 58%, $P = 0.04$).[150] In 2011, Peg-IFN-α-2b or Peg-IFN-α-2a + ribavirin combination therapy has been approved in Japan by national medical insurance for the treatment of patients with compensated cirrhosis, irrespective of viral load or genotype. In a Japanese clinical trial of Peg-IFN-α-2b 1.0 μg/kg/week in combination with ribavirin for 48 weeks in patients with compensated HCV cirrhosis, the SVR rate was 22% (15/69) in patients with genotype 1 and a high viral load, and 79% (26/33) in other patients, indicating high efficacy in all groups other than genotype 1 with a high viral load. In a study of 48 weeks of a combination of Peg-IFN-α-2a in two doses, 90 and 180 μg/week, with ribavirin, the SVR rate was 28% (17/61) in the 90-μg group, and 27% (17/63) in the 180-μg group, with no difference seen between groups. In the 90-μg group, the SVR was 21% (10/48) in patients with genotype 1 and 50% (6/12) in those with genotype 2, showing high efficacy against the latter.[152]

In patients with compensated cirrhosis, where the doses of Peg-IFN-α and ribavirin are limited by the high degree of fibrosis, extended courses of combination therapy are required to achieve SVR. The HCV RNA dynamics following commencement of Peg-IFN + ribavirin combination therapy are also a good indicator of SVR in patients with compensated cirrhosis.[153,154] Accordingly, as with chronic hepatitis C, response-guided therapy altering the duration of treatment in accordance with the response to Peg-IFN + ribavirin therapy is useful. If HCV RNA does not become undetectable by treatment week 12 and viral clearance cannot be achieved, as with chronic hepatitis C, consideration should be given to a changeover to low-dose long-term Peg-IFN therapy with the aim of inhibiting hepatocellular carcinogenesis. Adverse reactions to Peg-IFN + ribavirin combination therapy in patients with compensated cirrhosis such as influenza-like-syndrome, depression, lethargy and cytopenia are common, but there are no great differences with chronic hepatitis in terms of safety and tolerability.[149,150] However, pancytopenia associated with hypersplenism may be present in the background, so reduction in the dose of both agents is often required due to severe cytopenias, including anemia, neutropenia and thrombocytopenia.[151,153]

The standard dose for Peg-IFN-α-2b in the treatment of patients with compensated cirrhosis is 1.0 μg/kg/week, and the criteria for dose reduction and discontinuation during treatment are as follows: halve the dose in the case of a neutrophil count <750/μL or platelet count <50 000/μL; and cease both Peg-IFN-α-2b and ribavirin in the case of a neutrophil count <500/μL, platelet count <35 000/μL or Hb <8.5 g/dL.[155] When the pretreatment Hb 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. If the pretreatment Hb is <14 g/dL, the starting dose of ribavirin is reduced by 200 mg, irrespective of weight.

The criteria for ribavirin dose reduction or discontinuation when a decline in Hb occurs during treatment 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.[81]

The standard dose for Peg-IFN-α-2a in the treatment of patients with compensated cirrhosis is 90 μg/kg/week. The criteria for dose reduction and discontinuation during treatment are as follows: reduce the dose to 45 μg/mL in the case of a neutrophil count <1000/μL, and to 22.5 μg/mL in the case of a neutrophil count <750/μL; and cease both Peg-IFN-α-2a and ribavirin in the case of a neutrophil count <500/μL, platelet count <50 000/μL or Hb <8.5 g/dL.[156] The starting doses for ribavirin are as for co-administration with Peg-IFN-α-2b. The criteria for ribavirin dose reduction or discontinuation when a decline in Hb occurs during treatment are: reduce the daily dose by 400 mg (600 mg if started at 1000 mg) for Hb <11 g/dL during treatment weeks 1–4, or Hb <10 g/dL during treatment weeks 5–48. For patients with heart conditions or a history of the same, in addition to the above criteria, if a decline in Hb ≥2 g/dL in comparison to the pretreatment level persists for 4 weeks, reduce the daily dose by 400 mg (600 mg if started at 1000 mg). If Hb remains <12 g/dL 4 weeks after the dose reduction, cease ribavirin.[80]

IFN monotherapy. Apart from patients with genotype 1 and a high viral load, IFN monotherapy should be selected for patients unable to tolerate Peg-IFN + ribavirin combination therapy due to adverse reactions such as anemia or depression. At present, IFN-β and human lymphoblastoid IFN (HLBI), an IFN-α formulation, are approved for national medical coverage for the treatment of patients with compensated cirrhosis with HCV genotype 1 and a low viral load, and genotype 2. They are not approved for patients with genotype 1 and a high viral load (≥100 kIU/mL for IFN-β, ≥500 kIU/mL for HLBI). Japanese clinical trials of IFN-β in the treatment of patients with compensated cirrhosis with genotype 1 and a low viral load, and genotype 2, yielded SVR rates in the patients administered 126 doses of 44% (8/18) in the genotype 1 low viral load group (<1 Meq/mL), 19% (3/16) in the genotype 2 high viral load group (≥1 Meq/mL) and 46% (6/13) in the genotype 2 low viral load group.[157] In a Japanese multicenter collaborative trial of HLBI in the treatment of HCV compensated cirrhosis, SVR rates in the group administered HLBI 6 MU consecutive daily for 2 weeks, then 3 MU three times weekly for 46 weeks, were 50% (1/2) in the genotype 1 low viral load group (<100 kIU/mL), 25% (3/12) in the genotype 2 high viral load group (≥100 kIU/mL) and 67% (4/6) in the genotype 2 low viral load group.[158] In both studies, efficacy increased with increased treatment duration. Furthermore, greater efficacy was seen with genotype 2 than genotype 1, and with a low viral load than with a high viral load. The rate of discontinuation due to adverse reactions was similar to that with chronic hepatitis C, and although the incidence of influenza-like syndrome and abnormal laboratory test results was high, no cirrhosis-specific adverse events were reported. In an overseas trial of Peg-IFN monotherapy in the treatment of patients with cirrhosis, SVR rates and biochemical efficacy were both superior to standard IFN therapy. A randomized prospective study comparing standard non-pegylated-IFN-α and Peg-IFN-α-2a reported SVR rates in patients administered non-pegylated-IFN-α-2a 3 MU three times/week, Peg-IFN-α-2a 90 μg/week and 180 μg/week to be 8% (7/88), 15% (14/96) and 30% (26/87), respectively. No difference was seen between groups in terms of tolerability.[159]

HLBI therapy aiming for viral clearance comprises HLBI 6 MU weekly for 2 consecutive weeks, then 3–6 MU three times weekly. The criteria for dose reduction and discontinuation during HLBI treatment are as follows: reduce the dose or increase the interval between doses in the case of a platelet count ≥30 000/μL and <50 000/μL, and discontinue in the case of a white blood cell counts <1500/μL, platelet count <30 000/μL or ALT level ≥500 U/L.[160]

IFN-β therapy is usually commenced at 6 MU, and is administered 3–6 MU consecutive daily until treatment week 6, then 3 MU three times a week. The criteria for dose reduction and discontinuation during IFN-β treatment are as follows: reduce the dose or increase the interval between doses in the case of a white blood cell counts <1500/μL, neutrophil count <750/μL or platelet count <50 000/μL, and discontinue in the case of a white blood cell counts <1000/μL, neutrophil count <500/μL or platelet count <25 000/μL.[133] For both HLBI and IFN-β, if HCV RNA becomes undetectable before treatment week 12, as for chronic hepatitis C, the treatment period should be extended to 48–72 weeks.

Low-dose IFN maintenance therapy. If HCV RNA does not become undetectable before treatment week 12 with Peg-IFN + ribavirin combination therapy or IFN monotherapy, a changeover to low-dose IFN maintenance therapy should be made with the aim of improving ALT levels and inhibiting hepatocellular carcinogenesis. Low-dose IFN or Peg-IFN maintenance therapy is useful in patients with liver cirrhosis in preventing progression

of liver disease and the development of HCC.[19,47,51] It is not effective in all patients, however, and discontinuation of treatment should be considered if improvement is not seen in ALT levels (≤40 IU/L) or AFP levels (≤10 ng/mL) within 6 months.

IFN therapy for decompensated cirrhosis

Patients with decompensated cirrhosis are at high risk of death due to liver failure, and liver transplant is the most effective treatment in suitable cases. However, post-transplant recurrence of hepatitis C causes allograft failure in approximately 30% of recipients within 5 years, so in overseas countries, pretransplant IFN therapy is administered with the aim of HCV eradication or suppression.[161,162] Several studies have demonstrated the efficacy of Peg-IFN (± ribavirin) therapy in patients with HCV genotype 2.[163–165] Patients with decompensated cirrhosis are at high risk of thrombocytopenia, anemia, infections and liver decompensation, however, and treatment discontinuation due to severe cytopenias is common. Serious bacterial infections associated with IFN therapy have been reported to be more common in patients with patients with Child–Pugh C than in Child–Pugh A/B disease.[166]

Treatment of patients with thrombocytopenia

In patients with marked thrombocytopenia associated with hypersplenism, it is difficult to introduce Peg-IFN or ribavirin combination therapy. Measures such as splenectomy or partial splenic embolization (PSE) are employed to increase the platelet count before commencing IFN therapy.[167–169] In Japan, mainly in patients with Child–Pugh A disease, Peg-IFN (± ribavirin) therapy is commenced following splenectomy or PSE. An increase in the platelet count is seen in almost all patients following either procedure, and high SVR rates are seen in patients with HCV genotype 2. However, postoperative complications including overwhelming post-splenectomy infection, portal vein thrombosis and hepatic dysfunction have been reported following both splenectomy and PSE.[168–170] The thrombopoietin receptor agonist, eltrombopag, has been developed overseas as an oral agent that increases platelet counts,[171] but it is not yet available for clinical use in Japan.

Recommendations:

1 *In patients with compensated cirrhosis (Child–Pugh class A) associated with HCV, aggressive IFN therapy should be commenced with the aims of preventing hepatocellular carcinogenesis and liver failure. This patient group requires careful observation during treatment due to the high incidence of adverse reactions such as cytopenias.*
2 *Patients with compensated cirrhosis associated with HCV should be given Peg-IFN + ribavirin combination therapy, irrespective of genotype or viral load. The standard dose is 1.0 μg/kg/week for Peg-IFN-α-2b and 90 μg/week for Peg-IFN-α-2a. The usual treatment period is 48 weeks, although consideration should be given to response-guided therapy and the discontinuation criteria for chronic hepatitis C.*
3 *Patients with compensated cirrhosis associated with HCV genotype 1 and a lower viral load, or genotype 2, not suited to combination therapy with ribavirin, should be administered HLBI or IFN-β monotherapy. HLBI therapy commences with HLBI 6 MU consecutive daily for 2 weeks, then 3–6 MU three times weekly. IFN-β therapy is usually commenced with 6 MU daily for a week, followed by 3 MU daily for 5 weeks, then 3 MU three times a week from treatment week 7. For both HLBI and IFN-β, if HCV RNA becomes undetectable before treatment week 12, the treatment period should be extended to 48–72 weeks.*
4 *If HCV RNA does not become undetectable before treatment week 12 with Peg-IFN + ribavirin combination therapy or IFN monotherapy in patients with compensated cirrhosis associated with HCV, long-term HLBI therapy at a dose of 3 MU three times weekly should be commenced with the aim of inhibiting hepatocellular carcinogenesis. Treatment should be discontinued if improvement is not seen in ALT levels (≤40 IU/L) or AFP levels (≤10 ng/mL) within 6 months.*
5 *The efficacy of IFN therapy is low in patients with decompensated cirrhosis associated with HCV (Child–Pugh class B and C). In particular, patients with Child–Pugh class C do not tolerate IFN therapy well, and serious adverse reactions such as cytopenias and infections have been reported, so IFN therapy is not recommended in this patient group.*
6 *If IFN therapy is being considered in a patient with compensated HCV cirrhosis associated with a platelet count <50 000/μL, one option is to perform splenectomy or PSE before commencing IFN therapy.*

3.9 Management of patients with normal ALT levels

In a study of Peg-IFN + ribavirin combination therapy and hepatocellular carcinogenesis in 809 patients with chronic hepatitis C and normal pretreatment ALT levels (male/female, 269/540; average age, 57 ± 11

years; genotype 1/2, 550/247; mean observation period, 36.2 ± 16.5 months), in the group with platelet counts ≥150 000/μL ($n = 586$) no significant difference was seen in the incidence of HCC according to therapeutic effect, with 1.5% of non-responders developing HCC within 3 years. In the group with platelet counts <150 000/μL ($n = 323$), however, the cumulative incidence of HCC was high at 10.1% in non-responders, with no cases of HCC among the responders or relapsers. These results demonstrated that Peg-IFN + ribavirin therapy significantly inhibits hepatocellular carcinogenesis ($P < 0.001$).[172] The efficacy of Peg-IFN + ribavirin combination therapy is similar in patients with normal and elevated ALT levels.[173,174]

Accordingly, antiviral therapy should be considered even in patients with ALT levels ≤30 IU/mL if their platelet count is <150 000/μL. On the other hand, antiviral therapy does not need to be commenced immediately in patients with an ALT level ≤30 IU/mL and a platelet count ≥150 000/μL, and follow-up while waiting for the next generation DAAs is a reasonable option. ALT levels may rise during the follow-up period, however, and treatment is indicated if the patient has a strong desire to commence antiviral therapy. At present, the available evidence regarding patients with normal ALT levels is mainly related to Peg-IFN + ribavirin combination therapy, although high therapeutic efficacy can also be anticipated with telaprevir + Peg-IFN + ribavirin combination therapy in this patient group.

Recommendation:

Antiviral therapy for patients with normal ALT levels (ALT, ≤30 IU/mL) can be administered in the same way as for patients with elevated ALT levels. Aggressive therapy is particularly desirable in patients with platelet counts <150 000/μL.

4. PROTECTIVE THERAPY

THE AIM OF protective therapy is not HCV clearance, but rather to reduce inflammation and inhibit the progression of fibrotic change in the hepatic tissue. The indications for protective therapy in patients with chronic hepatitis C are: patients with abnormal ALT and AST levels unable to undergo IFN or other antiviral therapy; patients who failed to achieve viral clearance with antiviral therapy; and patients who do not wish to undergo antiviral therapy. UDCA and SNMC are the protective therapies that have been scientifically shown to be useful.

UDCA

Ursodeoxycholic acid is a bile acid formulation, approved for use in doses of 600–900 mg daily by national medical insurance. The main mechanism of action of UDCA in hepatitis is a hepatocytoprotective effect. Other postulated mechanisms of action include protection of the hepatocyte cell membrane by substitution of UDCA for other cytotoxic bile acids, antioxidative stress affects, immunoregulatory effects and anti-apoptotic effects.[175]

Improvement of liver function is seen from UDCA doses of 150 mg/day.[176,177] In a Japanese nationwide multicenter double-blind trial, significantly greater improvement was seen in AST, ALT and γ-glutamyl transpeptidase levels in the groups administered 600 and 900 mg/day than in those given 150 mg/day.[176] Accordingly, the UDCA dose for the treatment of chronic hepatitis C is generally 600 or 900 mg/day. Adverse reactions are mainly gastrointestinal symptoms such as epigastric discomfort, diarrhea and constipation, but these are generally mild. A retrospective study of inhibition of hepatocellular carcinogenesis by UDCA reported that it significantly reduced the incidence of HCC.[178]

SNMC

The main constituent of SNMC is glycyrrhizin, a compound extracted from the liquorice root. The mechanisms of action of SNMC in the treatment of hepatic dysfunction are derived from anti-inflammatory effects related to the steroid-like properties of glycyrrhizin, and hepatocyte cell membrane protective effects. These actions are considered to lead to improved ALT levels. In a Japanese double-blind trial of SNMC 40 mL daily for 1 month, significant improvement in AST and ALT levels was seen in the SNMC group in comparison with the placebo group.[179,180] Doses are 40–100 mL daily or alternate daily, although Japanese dosage comparison trials found significantly greater improvement in ALT levels with 100 mL than with 40 mL.[181,182] In another study, long-term administration of SNMC significantly inhibited progression to liver cirrhosis in comparison with the control group.[183] Adverse reactions to SNMC include hypokalemia and hypertension.

Studies of inhibition of hepatocellular carcinogenesis by SNMC found that the incidence of HCC was significantly lower in the treatment group than in the control group.[183,184] SNMC therapy has also been found to significantly reduce the incidence of HCC in non-responders to IFN therapy.[185,186]

UDCA + SNMC combination therapy

An RCT comparing SNMC monotherapy and UDCA + SNMC combination therapy found significantly greater improvement in ALT levels in the combination therapy group.[187] This combination is useful in reducing inflammation.

Recommendation:

Oral UDCA and i.v. SNMC, or both in combination, are recommended as protective therapy in patients with chronic hepatitis C.

5. THERAPEUTIC PHLEBOTOMY

IRON METABOLISM PLAYS an important role in patients with chronic hepatitis C. Iron is an essential metal, and a constituent of important proteins, including Hb. When iron is present in excess, however, cytotoxic hydroxyl radicals are produced, causing oxidative stress. Therapeutic phlebotomy was devised as a supportive therapy for patients with chronic hepatitis C because oxidative stress associated with iron overload is a factor in progression of liver disease. Restriction of dietary iron is also important in the management of patients undergoing iron reduction therapy. As for protective therapy, therapeutic phlebotomy is indicated in patients with chronic hepatitis C with abnormal ALT and AST levels unable to undergo IFN or other antiviral therapy, patients who failed to achieve viral clearance with antiviral therapy and patients who do not wish to undergo antiviral therapy.

In 1994, a Japanese study reported that therapeutic phlebotomy lowered ALT levels in patients with chronic hepatitis C.[188] A Japanese multicenter RCT also confirmed improvement in ALT levels with therapeutic phlebotomy.[189] Other studies have reported a 50% decrease in ALT levels in 80% of patients, and normalization of ALT levels in 40–70% of patients.[190,191] Histological studies have reported inhibition of progression,[192] and even improvement,[193] of histological changes. Long-term therapeutic phlebotomy has been reported to significantly inhibit hepatocellular carcinogenesis.[190]

In general, therapeutic phlebotomy involves removal of 200–400 mL blood at 1–2-week intervals with the aim of reducing the serum ferritin level to ≤20 ng/mL. If the Hb level drops below 9–10 g/dL, phlebotomies are discontinued to allow recovery of hematopoietic function. After the target has been reached, therapeutic phlebotomies are performed as appropriate with reference to ferritin and Hb levels. Adverse reactions are rare, involving bradycardia and hypotension associated with the vagal reflex.

An additive effect is seen when therapeutic phlebotomy is performed in conjunction with UDCA or SNMC therapy. Greater reduction in ALT levels was seen with UDCA in combination with therapeutic phlebotomy than with UDCA monotherapy.[194] In patients on SNMC therapy, further reduction in ALT levels was seen with the addition of small volume phlebotomies.[195] The combination of therapeutic phlebotomy with another therapy with a different mode of action provides additional improvement in ALT levels.

Recommendations:

Therapeutic phlebotomy is a useful therapeutic modality in patients with chronic hepatitis C. Its use in combination with a protective therapy, oral UDCA or i.v. SNMC should also be considered.

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Virological response and safety of 24-week telaprevir alone in Japanese patients infected with hepatitis C virus subtype 1b

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SUMMARY. Hepatitis C virus (HCV) subtype 1b, which infects approximately 70% of Japanese carriers, is likely to be more eradicable by a telaprevir regimen than subtype 1a because of the higher genetic barrier of Val^{36} and Arg^{155} substitutions. The aims of this exploratory study were to evaluate the virological response and safety of 24-week oral administration of telaprevir alone in chronic HCV subtype 1b infection. Fifteen treatment-naïve patients were treated with telaprevir 750 mg every 8 h for 24 weeks. All patients were Japanese whose median age was 58.0 years (range: 45–68), and six patients (40%) were men. Median baseline HCV RNA level was 6.80 $\log_{10}$ IU/mL (range: 3.55–7.10). The HCV RNA levels decreased to undetectable in five patients (33%) within 8 weeks. Three patients (20%) with negative HCV RNA by Week 4 achieved end of treatment response. One patient (7%) who achieved sustained virological response had a low baseline viraemia of 3.55 $\log_{10}$ IU/mL. Most of the adverse events including anaemia and skin disorders were mild to moderate. Developed variants were T54A and A156V/T/F/Y with or without secondary substitutions rather than V36M ± R155K. Telaprevir alone for 24 weeks in Japanese patients with HCV subtype 1b resulted in an sustained viral response rate of 7% (1/15) and was well tolerated for 24 weeks. These results will support the implementation of further studies on oral combination of telaprevir with other direct-acting antiviral agents in patients infected with HCV subtype 1b.

Keywords: hepatitis C virus, monotherapy, subtype 1b, telaprevir.

INTRODUCTION

The World Health Organization (WHO) estimates that approximately 170 million people are infected with hepatitis C virus (HCV) [1]. In Japan, it is estimated that more than 1.5 million people are chronically infected with hepatitis C.

Telaprevir is a novel peptidemimetic HCV NS3-4A protease inhibitor. The mechanism of inhibition involves the formation of a stable, reversible, covalent bond between the ketocarbonyl of telaprevir and the active site serine of NS3 protease. Recently, telaprevir was approved for patients with HCV genotype 1 infection in the United States (US), Canada, European Union (EU) and Japan. The Phase 3 studies showed that patients who received telaprevir in combination with pegylated interferon (PEG-IFN) and ribavirin (RBV) achieved significantly higher rates of sustained viral response (SVR) compared to those who received PEG-IFN and RBV alone, regardless of their prior treatment experience [2–4]. The Japanese Phase 3 studies of the telaprevir-based triple regimen also showed high SVR rates [5,6]. The most common side effects in the telaprevir-based triple regimen were anaemia, rash and IFN-induced systemic symptoms.

The epidemiology of HCV in Japan takes on a different aspect from US and EU; that is, the majority of patients are aged more than 55 years [7]. Accordingly, the RBV dose reduction rate and the frequency of discontinuation of telaprevir treatment in Japan are higher than those in US and EU [2–6]. Taking such problems with telaprevir in combination with PEG-IFN and RBV into consideration, IFN-free

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DAA, direct-acting antiviral agent; EU, European Union; HCV, Hepatitis C virus; LDL, low-density lipoprotein; LOQ, lower limit of quantification; PEG-IFN, pegylated interferon; RBV, ribavirin; SVR, sustained viral response; T-bil, total bilirubin.

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regimens may become very useful options and satisfy important unmet medical needs especially for intolerant patients with IFN-based regimens. Clinical trials of IFN-free therapy for patients with chronic hepatitis C would provide us with meaningful knowledge for the future development of HCV therapy. Interestingly, HCV subtype 1b, which infects approximately 70% of Japanese HCV carriers [8], is likely to be more eradicable by telaprevir regimens than subtype 1a because of the higher genetic barrier of Val^{36} and Arg^{155} substitutions [9,10]. When treating with direct-acting antiviral agent (DAA), HCV subtypes of genotype 1 are now an important factor that affects treatment response. The main aim of this exploratory study is to evaluate the virological response and safety of telaprevir as monotherapy for 24 weeks in Japanese patients infected with HCV subtype 1b.

PATIENTS AND METHODS

Study design and organization

This Phase 2, single-arm, open-label study was conducted from January 2008 to February 2009 at Sapporo Kosei General Hospital, Musashino Red Cross Hospital, Toranomon Hospital and Hiroshima University Hospital. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practices. Before starting the study, the protocol and informed consent forms were reviewed and approved by the institutional review board in each site. All patients provided written informed consent following sufficient explanation before participating in the study. All the patients received 750 mg telaprevir orally every 8 h (q8h) (2250 mg/day) after a meal for 24 weeks. Telaprevir was given as a 250-mg tablet. This study is registered in ClinicalTrials.gov NCT 00621296.

Patients

Participants enrolled in this study were treatment-naïve, male or female chronic hepatitis C patients with the characteristics shown in Table 1 who met the inclusion criteria and did not conflict the exclusion criteria described previously [11], except the age and HCV RNA levels at the time of enrolment; age from 20 to 70 years and HCV RNA levels were not defined.

Virological responses

Virological response to telaprevir was evaluated based on the HCV RNA kinetics in patients. Serum HCV RNA levels were measured using the COBAS TaqMan HCV test (Roche Diagnostics Co., Ltd., Tokyo, Japan). The linear dynamic range was 1.2–7.8 $\log_{10}$ IU/mL. A qualitative result below the lower limit of quantification (LOQ) was also determined as positive (1.0) and negative (0.5). Measurements were obtained on Week 4 before the first dose, Days 1 (prior to the first dosing) and 3, Weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24 of the treatment period, and Weeks 2, 4, 8, 12, 16, 20, and 24 of the follow-up period. Day 1 was defined as the date of starting telaprevir treatment.

Table 1 Patient characteristics, treatment duration and viral response

	Sex	Age	BMI (kg/m^2)	Baseline HCV RNA ($\log_{10}$ IU/mL)	Treatment duration (day)	HCV RNA Nadir ($\log_{10}$ IU/mL)	Virological response
1	M	67	25.2	5.85	169 (complete)	Undetectable	Relapse
2	M	59	24.5	3.55	169 (complete)	Undetectable	SVR
3	F	45	18.7	6.80	44*	2.8	Breakthrough
4	F	68	20.9	7.05	43†	<1.2 detectable	Partial responder
5	F	48	21.5	6.45	169 (complete)	Undetectable	Breakthrough
6	F	57	20.9	4.75	43*	1.8	Breakthrough
7	F	51	19.9	5.95	170 (complete)	Undetectable	Partial responder
8	F	58	19.2	6.85	105*	1.5	Breakthrough
9	M	62	20.4	6.25	14†	1.4	Partial responder
10	M	58	24.5	7.10	39*	3.1	Breakthrough
11	M	63	16.2	7.00	74*	<1.2 detectable	Breakthrough
12	F	53	25.0	7.10	169 (complete)	Undetectable	Relapse
13	F	60	19.7	5.00	10‡	<1.2 detectable	Breakthrough
14	F	55	23.8	6.95	78*	<1.2 detectable	Breakthrough
15	M	50	27.5	6.90	26‡	1.3	Partial responder

HCV, Hepatitis C virus; SVR, sustained viral response. Subjects discontinued telaprevir because of *viral breakthrough, †AE and ‡other reasons.

Sustained viral response was defined as an undetectable HCV RNA level at 24 weeks after the end of treatment. Relapse was defined as the reappearance of serum HCV RNA during the follow-up period from the state of undetectable serum HCV RNA at the end of treatment. Breakthrough was defined as the state when the viral level increased by 2 $\log_{10}$ IU/mL from nadir or a level of more than 3 $\log_{10}$ IU/mL after reaching undetectable levels during treatment. Partial responders were subjects whose HCV RNA level dropped by at least 2 $\log_{10}$ IU/mL during treatment but was still detected at the end of treatment.

Sequence analysis at HCV NS3 protease domain

HCV RNA was isolated from serum samples collected on the same day for the measurement of HCV RNA levels. A DNA fragment of 543 bases long (181 amino acids) from the NS3 protease domain was amplified by nested RT-PCR and cloned. At least 39 clones per specimen were sequenced bi-directionally. The limit of detection for the sequencing analysis was 3.0 $\log_{10}$ IU/mL.

Safety assessments

Safety of telaprevir was assessed by clinical laboratory tests, vital signs, abdominal ultrasonography and AEs. Twelve-lead electrocardiogram (ECG) examinations were performed once during the screening period. These safety parameters were reported at regular intervals from 4 weeks before the first dosing to the end of the follow-up period.

Statistical analysis

Statistical analyses were performed using the statistical software SAS Version 9.1.3 (SAS Institute Inc., Cary, NC, USA). Reported AEs were classified according to MedDRA/J version 12.0 (MedDRA Japanese Maintenance Organization, Tokyo, Japan).

RESULTS

Baseline characteristics

Fifteen treatment-naïve patients infected with HCV subtype 1b were enrolled in this study. Baseline characteristics of patients are shown in Table 1. All patients were Japanese whose median age was 58.0 years (range: 45–68); 6 (40.0%) patients were men. Patients over 54 years of age accounted for 66.7% (10 of 15). Median baseline HCV RNA level was 6.80 $\log_{10}$ IU/mL (range: 3.55–7.10). The median BMI was 20.9 kg/m^2 (range: 16.2–27.5).

Virological response

Telaprevir alone caused a rapid decrease in HCV RNA levels after the initiation of treatment in all patients. The average changes were −3.24 $\log_{10}$ IU/mL on Day 3 and −4.24 $\log_{10}$ IU/mL on Week 1 (Fig. 1). The average of maximum reduction in each patient was 5.01 $\log_{10}$ IU/mL. The HCV RNA levels became undetectable in 1, 3, 3 and 5 patients at Weeks 1, 4, 6 and 8, respectively. Three patients with negative HCV RNA after 4 weeks achieved end of treatment response (ETR), of whom one patient achieved a SVR. The patient who achieved SVR had the lowest baseline viral load (3.55 $\log_{10}$ IU/mL) among all the patients.

Ten of 15 patients discontinued the telaprevir treatment because of the following reasons: six patients because of viral breakthrough, two patients because of AEs, one patient because of own drug discontinuation and one patient who met the exclusion criteria after administration.

Safety

AEs observed in two or more patients in this study are shown in Table 2. During the study, 14 of 15 patients experienced 80 AEs in total and 62 events were judged as adverse drug reactions. The common AEs that occurred in

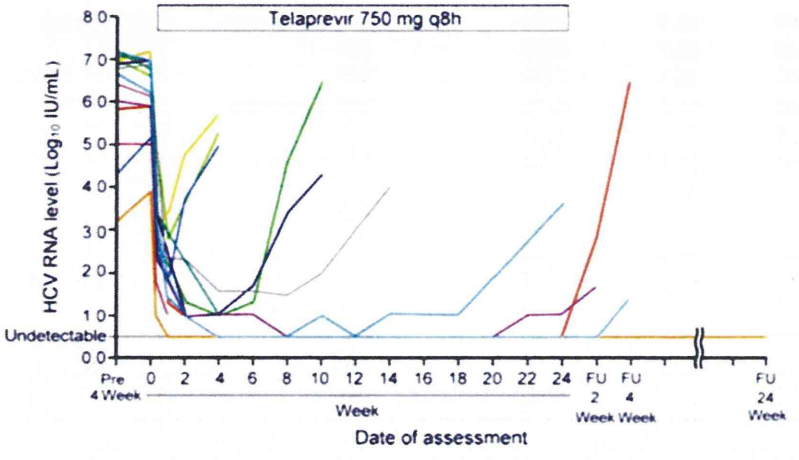

Fig. 1 HCV RNA kinetics during and after treatment with telaprevir monotherapy.