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BRIEF ARTICLE

nse predicts the success of short-herapy for chronic hepatitis C

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AIM: rt-term peg-interfer ronic hepatitis C patien virological response.

METHODS: ate virological response (IVR)" epatitis C virus (HCV) RNA 7 d after th ation of PEG-IFN , we conducted a 12-wk PEG-IFN 2a monotherapy without the addition of ribavirin for 38 patients who had low pretreatment HCV RNA load and exhibited IVR. The patients included 21 men and 17 women, whose ages ranged from 22 to 77 years (mean ± SD: 52.0 ± 17.8 years). There were 4 patients with HCV genotype 1b, 23 patients with genotype 2a and 4 patients with genotype 2b. HCV genotype was not determined for the remaining 7 patients. Patients were categorized into a sustained virological response (SVR) HCV RNA remained treatment

relapsed with serum HCV RNA 12 wk after the end of treatment. Two patients (5.3%) withdrew from the study during the 24-wk follow-up period. With regard to the HCV RNA genotype, the SVR rates were 100% (4/4) for genotype 1b, 95.7% (22/23) for genotype 2a and 100% (4/4) for genotype 2b. The SVR rate in 7 patients, whose HCV RNA genotypes were not determined, was 71.4% (5/7).

CONCLUSION: Short-term PEG-IFN 2a monotherapy is highly effective for chronic hepatitis C patients who have low pretreatment HCV RNA load and exhibit IVR.

Key words: Chronic hepatitis C; Immediate virological response; Interferon therapy

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INTRODUCTION

combination therapy with peg-interferon (PEG-IFN) and ribavirin (RBV) is the first-line therapy used to eliminate HCV in patients with chronic hepatitis C. The duration of treatment is determined based on the viral genotype, with treatment administered for 48 wk in patients with genotype 1 and 24 wk in patients with genotypes 2 or 3[1,2]. However, long-term administration of IFN and RBV increases the cost of treatment and the risk of severe adverse events.

The efficacy of IFN therapy depends on the HCV genotype, pretreatment viral load and early viral kinetics[3-7]. Thus, IFN therapy must be individualized and optimized according to the virological and clinical status of each patient. Several studies have shown that the duration of IFN therapy could be shortened in patients who achieve serum HCV RNA negativity during the early stages of treatment[7-9]. Therefore, it is essential that we reduce the treatment duration for patients who exhibit a quick virological response to IFN therapy. In the present study, we focused on the initial response to PEG-IFN administration and studied the efficacy of short-term PEG-IFN 2a monotherapy for patients who had low pretreatment HCV RNA load.

MATERIALS AND METHODS

Definition of IVR and protocol for PEG-IFN 2a therapy

We defined an "immediate virological response (IVR)" as the loss of serum HCV RNA 7 d after the first administration of PEG-IFN . Patients with low pretreatment HCV RNA load (< 1.0×10^5 IU/mL) were monitored for HCV RNA in the serum 7 d after the first administration of PEG-IFN 2a. We scheduled a 12-wk treatment course of PEG-IFN 2a without the addition of RBV for patients who achieved IVR. The patients received subcutaneous injection of 180 g of PEG-IFN 2a (Pegasys, Roche) once per week. According to the circumstance of each patient, the dose was reduced to 90 g or the treatment course was terminated.

Patients

We administered PEG-IFN 2a without the addition of RBV to a total of 59 patients with low HCV RNA load from December 2004 to November 2007. They were monitored for serum HCV RNA 7 d after the first administration of PEG-IFN 2a. Among these, 38 patients who achieved IVR were enrolled in this study. The age, gender, HCV genotype, serum HCV RNA level, ALT level, hemoglobin (Hb), and the neutrophil and platelet (PLT) counts before treatment are shown in Table 1. The patients included 21 men and 17 women, whose ages ranged from 22 to 77 years (mean ± SD: 52.0 ± 17.8 years). There were 4 patients with genotype 1b, 23 patients with genotype 2a and 4 patients with genotype 2b. HCV genotype was not determined for the remaining 7 patients. Among the 38 patients enrolled in this study, 37 received IFN therapy for the first time for HCV infection. Pt. 16 is the same patient as Pt. 3, who received the same treatment course for HCV genotype 2a infection at 26 years of age. After the initial successful treatment, the patient was infected with genotype 2b HCV and re-treated at 28 years of age. Pt. 25 had been treated for hepatocellular carcinoma prior to this IFN treatment course.

Determination of serum HCV RNA load and the HCV genotype

Pretreatment serum HCV RNA levels were determined by RT-PCR using an Amplicor HCV monitor v2.0 series kit (Roche Diagnostics Co.), which had a detection limit of 5.0×10^3 IU/mL. When the serum HCV RNA level was below the detection limit, qualitative analysis of the HCV RNA was performed by RT-PCR using a COBAS Amplicor HCV test kit v2.0 (Roche Diagnostics Co.), which had a detection limit of 50 IU/mL. Qualitative analysis of HCV RNA was performed 7 d after the first administration for the evaluation of IVR, and at 24 wk after the end of treatment for the evaluation of the SVR. HCV genotype was determined using an HCV Genotyping SMITEST kit (Roche Diagnostics Co.).

Evaluation of the efficacy of PEG-IFN 2a therapy

Patients were categorized into the sustained virological response (SVR) group, if serum HCV RNA remained negative for 24 wk after the end of PEG-IFN 2a therapy. Patients were categorized into the relapse group if serum HCV RNA reappeared after the end of the treatment course.

Informed consent

All patients provided informed consent prior to their participation in this study. The study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice.

RESULTS

Completion of treatment

Figure 1 presents the dose and duration of PEG-IFN 2a administration for each patient. Of 38 patients enrolled in this study, 26 (Pts. 1-26, 68.4%) completed a 12-wk treatment course. It was necessary to reduce the dose of PEG-IFN 2a in 5 (Pts. 22-26) of these 26 patients. Twelve patients (Pts. 27-38, 31.6%) discontinued treatment prior to completion of the 12-wk course. In 6 (Pts. 30, 31 and 35-38, 15.8%) of these 12 patients, either self-withdrawal or financial problem was the cause for discontinuation. In 3 cases (Pts. 27, 28 and 32), the dose was reduced during the treatment, but the treatment was discontinued before completion of the 12-wk course.

Efficacy of the therapy

An intention-to-treat analysis was performed. Two patients (Pts. 27 and 35, 5.3%) withdrew from this study

Table 1 Patient characteristics

Pt. No.	Age (yr)	Gender	Genotype	Viral load (IU/mL)	ALT (IU/L)	Hb (g/dL)	Neutrophil (/mm^3)	PLT (× 10^3/mm^3)	Naive/ re-treatment
1	51	M	2a	2.4×10^4	83	10.5	2729	254	Naive
2	56	M	1b	7.6×10^3	14	14.0	2565	268	Naive
3	26	F	2a	2.7×10^4	157	15.6	5217	284	Naive
4	67	M	2a	$< 5.0 \times 10^3$	63	15.2	3940	159	Naive
5	48	F	2a	1.1×10^4	121	12.1	1851	146	Naive
6	48	F	2a	7.0×10^4	48	12.7	3084	244	Naive
7	70	M	2a	5.3×10^4	119	13.7	2002	157	Naive
8	64	M	ND	$< 5.0 \times 10^3$	65	14.5	2200	148	Naive
9	22	M	ND	$< 5.0 \times 10^3$	51	15.3	5003	308	Naive
10	40	F	2a	1.1×10^4	198	14.2	2424	190	Naive
11	68	F	2a	9.3×10^3	31	11.8	3567	212	Naive
12	60	M	2a	$< 5.0 \times 10^3$	18	14.9	1520	265	Naive
13	68	F	2a	1.8×10^4	112	13.4	3338	190	Naive
14	76	M	2a	1.8×10^4	39	13.6	2540	272	Naive
15	25	F	2a	8.6×10^4	181	12.2	2649	260	Naive
16	28	F	2b	1.9×10^4	19	14.4	3522	324	Re-treatment
17	23	M	ND	$< 5.0 \times 10^3$	456	15.0	3483	257	Naive
18	57	F	2b	5.9×10^3	97	14.2	2080	306	Naive
19	48	M	2a	6.4×10^4	41	15.1	1688	235	Naive
20	56	M	2b	5.1×10^4	124	15.1	3810	82	Naive
21	34	F	2a	2.8×10^4	72	13.4	4004	98	Naive
22	32	F	2a	1.7×10^4	41	12.5	1853	259	Naive
23	74	M	ND	$< 5.0 \times 10^3$	37	10.6	1784	92	Naive
24	45	M	2a	1.0×10^4	41	16.3	4606	147	Naive
25	76	F	2a	$< 5.0 \times 10^3$	54	10.9	2948	192	Naive
26	53	F	1b	5.0×10^3	13	11.9	3438	204	Naive
27	27	F	ND	$< 5.0 \times 10^3$	46	15.1	2205	169	Naive
28	71	F	ND	5.0×10^3	40	14.1	2022	98	Naive
29	70	M	2a	5.1×10^4	81	14.5	2894	125	Naive
30	60	M	1b	5.7×10^3	40	15.1	1502	297	Naive
31	57	M	2a	2.8×10^4	61	15.5	3154	137	Naive
32	77	M	2a	$< 5.0 \times 10^3$	68	10.3	1430	125	Naive
33	69	F	1b	1.6×10^4	21	12.8	2772	186	Naive
34	37	F	2a	$< 5.0 \times 10^3$	42	13.1	2343	314	Naive
35	23	M	ND	$< 5.0 \times 10^3$	46	14.6	2772	238	Naive
36	36	M	2a	1.3×10^4	26	14.5	5126	242	Naive
37	57	F	2b	4.7×10^4	50	14.9	1628	130	Naive
38	71	M	2a	3.5×10^4	102	14.4	3852	109	Naive
mean ± SD	52.0 ± 17.8				76.8 ± 77.6	13.7 ± 1.5	2838.20 ± 972.50	212.9 ± 79.1	

ND: Not determined; ALT: Alanine transaminase; Hb: Hemoglobin; PLT: Platelet.

during the 24-wk follow-up period because they did not attend the hospital appointments. Thirty-five patients (92.1%) were negative for serum HCV RNA 24 wk after the end of treatment and were categorized into the SVR group (Figure 2). One patient (Pt. 6, 2.6%) was positive for serum HCV RNA 24 wk after the end of treatment and was categorized into the relapse group.

With regard to the HCV RNA genotype, the SVR rates were 100% (4/4) for genotype 1b, 95.7% (22/23) for genotype 2a and 100% (4/4) for genotype 2b (Figure 2). The SVR rate in 7 patients, whose HCV RNA genotypes were not determined, was 71.4% (5/7), as we could not evaluate the treatment effect for 2 patients because of self-withdrawal during the follow-up period.

Adverse events

The most frequent adverse events were flu-like symptoms, such as fever and pain. Fatigue appeared as the second most frequent. Other adverse events are summarized in Table 2. Some patients who complained of insomnia were treated with hypnotics. Thrombocytopenia (< 50 000/mm^3) occurred in 1 case (Pt. 23) and the dose was reduced for the 4th and 5th administration during the treatment course. Neutropenia (< 750/mm^3) appeared in 3 cases, and in 1 case (Pt. 32) it was necessary to reduce the dose of PEG-IFN 2a from the 2nd to 5th administration. Anemia (Hb < 8.5 g/dL) did not occur in any of the patients. In 6 cases, it was necessary to reduce the dose of PEG-IFN 2a because of fatigue (Pts. 22, 25 and 28), emotional lability (Pts. 26 and 27) or vertigo (Pt. 24). None of the patients discontinued the treatment course because of bone marrow suppression. In 5 cases it was necessary to discontinue the treatment course for the following reasons: 2 with fatigue (Pts. 28 and 34), 1 with stomatitis (Pt. 27), 1 with skin symptoms and diarrhea (Pt. 29) and the other with viral influenza infection (Pt. 32). These adverse events were not particularly severe. One case (Pt. 33) discontinued the treatment

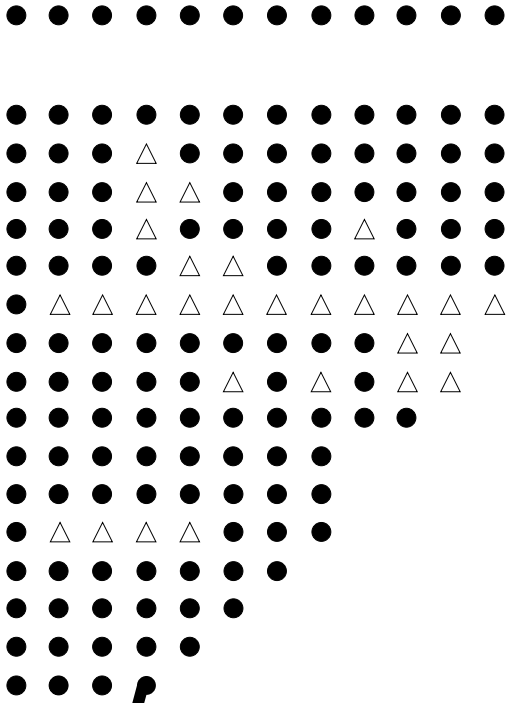

Figure 1 Administration of peg-interferon (PEG-IFN) 2a. The patients received subcutaneous injections of 180 g of PEG-IFN 2a (rotundity) once per week. Twenty-one patients (Pts. 1-21) completed a 12-wk treatment course without dose reduction. In 17 patients (Pts. 22-38), the dose was reduced to 90 g (triangle) or the treatment was terminated before completion of the 12-wk course.

course because of bacterial pneumonia, and recovered after antibiotic administration.

DISCUSSION

In the present study, we defined an "immediate virological response (IVR)" as the loss of serum HCV RNA 7 d after the first administration of PEG-IFN . We then conducted a 12-wk treatment course of PEG-IFN 2a in a population of patients who had low pretreatment HCV RNA load and who achieved IVR. This short-term PEG-IFN 2a monotherapy without the addition of RBV exhibited an extremely high SVR rate.

The current standard therapy to eliminate HCV in patients with chronic hepatitis C is combination therapy with PEG-IFN and RBV. While the SVR rate for 24 wk of PEG-IFN /RBV therapy in patients with genotypes 2 and 3 is 78%-93%, the SVR rate for 48 wk of treatment for genotype 1 is 40%-51%[1,2,10-13]. New methods of determining the adequate dose and duration of PEG-IFN /RBV administration have been devised to increase the probability of SVR in the treatment for patients with genotype 1 and high pretreatment viral load[9,14]. High dose and long-term IFN treatments, however, are expensive and contribute to additional risk for many adverse events.

Major contributory factors for SVR are viral genotype (except genotype 1), low pretreatment viral load (< 1.0 × 10^5 IU/mL) and early loss of serum HCV RNA[3-7]. Early virological response (EVR) and rapid virological response (RVR), which are indicated by loss of serum HCV RNA at weeks 12 and 4, respectively, are closely related to the SVR rate[6,7,15,16]. Furthermore, Mangia *et al*[8] have reported that 12 wk of administration of PEG-IFN /RBV to patients with HCV genotype 2 or 3 and who achieve RVR, results in a high probability of SVR. Tabaru *et al*[17] reported that the SVR rate was 100% after treatment with IFN 2b for 6 wk for patients infected with HCV genotype 2a and low viral load. Establishing the minimum, and yet sufficient, IFN therapy period is important in terms of financial efficiency and for reduction of the risk of adverse events. Therefore, it is essential to establish a guideline to make the treatment period shorter than the standard length for patients who have a high probability of achieving SVR. For patients with low pretreatment HCV RNA load, the current standard IFN therapy which is allowed by Japanese National Medical Insurance, is 24-48 wk of PEG-IFN 2a monotherapy without the addition of

RBV. RBV causes hemolytic anemia, and severe anemic symptoms sometimes appear in PEG-IFN /RBV combination treatment[18]. PEG-IFN monotherapy can avoid these adverse events induced by RBV.

Thus, in the current study, we studied the efficacy of short-term PEG-IFN 2a monotherapy for patients who had a low pretreatment HCV RNA load and exhibited IVR. Remarkably, 35 (97.2%) out of 36 cases that we were able to follow up to 24 wk after the last administration, were categorized into the SVR group. With regard to the HCV RNA genotype, SVR rates were 100% (4/4) for genotype 1b, 95.7% (22/23) for genotype 2a and 100% (4/4) for genotype 2b (Figure 2). These data might suggest that the efficacy of short-term PEG-IFN 2a monotherapy for patients exhibiting IVR is independent of HCV genotype. Further analyses with a large population of patients should be conducted for each genotype of HCV, because the number of patients enrolled in this study, especially for genotype 1b, was small.

The patient (Pt. 6) who relapsed during this treatment course subsequently received 24 wk of PEG-IFN 2a therapy and succeeded in achieving SVR. We consider that if short-term treatment failed to induce SVR, those non-SVR patients could be re-treated with long-term PEG-IFN monotherapy (24-48 wk) or PEG-IFN /RBV combination therapy. Thus, it is suggested that we should select short-term monotherapy at the first approach for patients with low pretreatment HCV RNA load and IVR.

Nine out of 35 cases who achieved SVR received less than 9 wk (4-8 wk) of drug administration. Therefore, there is the possibility that the treatment period could be shortened to less than 12 wk for a certain group of patients. Further analyses in randomized controlled trials with a large population of patients should be conducted to examine the efficacy of shorter treatment courses, such as 4 wk or 8 wk.

Frequent adverse events that generally appear during IFN therapy were seen in this study group of patients. However, no severe events were observed. None of the patients required discontinuation of therapy because of bone marrow suppression. While 1 case exhibited bacterial pneumonia as a severe complication, the patient recovered with antibiotic treatment. Thus, we consider that short-term monotherapy is safe.

PEG-IFN monotherapy clearly has the advantage of avoiding adverse events induced by RBV. However, we have to consider the possibility that adding RBV to this short term PEG-IFN therapy could offer shorter treatment duration or higher SVR rates. This option should be investigated in larger studies.

In conclusion, short-term PEG-IFN 2a monotherapy is highly effective for chronic hepatitis C patients who have low pretreatment HCV RNA load and exhibit IVR. IVR is a simple and useful indicator of early viral kinetics to predict the high probability of SVR.

COMMENTS

Background

The efficacy of interferon (IFN) therapy for chronic hepatitis C depends on the hepatitis C virus (HCV) genotype, pretreatment viral load and early viral kinetics. Therefore, IFN therapy must be individualized and optimized according to the virological and clinical status of each patient.

Research frontiers

Focusing on the initial response to PEG-IFN administration, the authors proposed a new concept, the "immediate virological response (IVR)". Then the efficacy of short-term PEG-IFN 2a monotherapy was investigated for patients who had low pretreatment HCV RNA load and exhibited IVR.

Innovations and breakthroughs

A 12-wk treatment course of PEG-IFN 2a without the addition of RBV was highly effective for patients who achieved IVR. SVR rate for all patients in this study was 92.1% (35/38).

Applications

The present study has shown that short-term PEG-IFN 2a monotherapy is an excellent treatment regimen for chronic hepatitis C patients who have low pretreatment HCV RNA load and exhibit IVR. It is also suggested that IVR is a simple and useful indicator of early viral kinetics to predict the high probability of SVR.

Terminology

An "IVR" was defined as the loss of serum HCV RNA 7 d after the first administration of PEG-IFN .

Peer review

Yada *et al* reported that a 12-wk treatment course of PEG-IFN 2a alone in a population of patients who had low pretreatment HCV RNA load and achieved immediate virological response results in extremely high SVR rates. The data are encouraging and important from a cost-effectiveness point of view.

REFERENCES

1 **Seeff LB**, Hoofnagle JH. National Institutes of Health Consensus Development Conference: management of hepatitis C: 2002. *Hepatology* 2002; **36**: S1-S2

2 **Manns MP**, Wedemeyer H, Cornberg M. Treating viral hepatitis C: efficacy, side effects, and complications. *Gut* 2006; **55**: 1350-1359

3 **Yoshioka K**, Kakumu S, Wakita T, Ishikawa T, Itoh Y, Takayanagi M, Higashi Y, Shibata M, Morishima T. Detection of hepatitis C virus by polymerase chain reaction and response to interferon-alpha therapy: relationship to genotypes of hepatitis C virus. *Hepatology* 1992; **16**: 293-299

4 **Matsumoto A**, Tanaka E, Suzuki T, Ogata H, Kiyosawa K. Viral and host factors that contribute to efficacy of interferon-alpha 2a therapy in patients with chronic hepatitis C. *Dig Dis Sci* 1994; **39**: 1273-1280

5 **Nomura H**, Kimura Y, Tada H, Hisano C, Morita C, Okamoto O, Shiraishi G, Kashiwagi S. Predictive factors of a response to interferon therapy in chronic hepatitis C. *J Clin Gastroenterol* 1996; **23**: 185-190

6 **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**: 645-652

7 **Jensen DM**, Morgan TR, Marcellin P, Pockros PJ, Reddy KR, Hadziyannis SJ, Ferenci P, Ackrill AM, Willems B. Early identification of HCV genotype 1 patients responding to 24 weeks peginterferon alpha-2a (40 kd)/ribavirin therapy. *Hepatology* 2006; **43**: 954-960

8 **Mangia A**, Santoro R, Minerva N, Ricci GL, Carretta V, Persico M, Vinelli F, Scotto G, Bacca D, Annese M, Romano M, Zechini F, Sogari F, Spirito F, Andriulli A. Peginterferon alfa-2b and ribavirin for 12 vs. 24 weeks in HCV genotype 2 or 3. *N Engl J Med* 2005; **352**: 2609-2617

9 **Satoh T**, Masumoto A. Accordion Index: A new tool for the prediction of the efficacy of peg-interferon-alpha-2b and ribavirin combination therapy for chronic hepatitis C. *Hepatol Res* 2008; **38**: 315-318

10 **Manns MP**, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, Koury K, Ling M, Albrecht JK. 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**: 958-965

11 **Fried MW**, Shiffman ML, Reddy KR, Smith C, Marinos G, Gonçales FL Jr, Häussinger D, Diago M, Carosi G, DhumeauxD, Craxi A, Lin A, Hoffman J, Yu J. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002; **347**: 975-982

12 **Hadziyannis SJ**, Sette H Jr, Morgan TR, Balan V, Diago M, Marcellin P, Ramadori G, Bodenheimer H Jr, Bernstein D, Rizzetto M, Zeuzem S, Pockros PJ, Lin A, Ackrill AM. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 2004; **140**: 346-355

13 **Zeuzem S**, Hultcrantz R, Bourliere M, Goeser T, Marcellin P, Sanchez-Tapias J, Sarrazin C, Harvey J, Brass C, Albrecht J. Peginterferon alfa-2b plus ribavirin for treatment of chronic hepatitis C in previously untreated patients infected with HCV genotypes 2 or 3. *J Hepatol* 2004; **40**: 993-999

14 **Berg T**, von Wagner M, Nasser S, Sarrazin C, Heintges T, Gerlach T, Buggisch P, Goeser T, Rasenack J, Pape GR, Schmidt WE, Kallinowski B, Klinker H, Spengler U, Martus P, Alshuth U, Zeuzem S. Extended treatment duration for hepatitis C virus type 1: comparing 48 versus 72 weeks of peginterferon-alfa-2a plus ribavirin. *Gastroenterology* 2006; **130**: 1086-1097

15 **Yu JW**, Wang GQ, Sun LJ, LixG, Li SC. Predictive value of rapid virological response and early virological response on sustained virological response in HCV patients treated with pegylated interferon alpha-2a and ribavirin. *J Gastroenterol Hepatol* 2007; **22**: 832-836

16 **Poordad F**, Reddy KR, Martin P. Rapid virologic response: a new milestone in the management of chronic hepatitis C. *Clin Infect Dis* 2008; **46**: 78-84

17 **Tabaru A**, Narita R, Hiura M, Abe S, Otsuki M. Efficacy of short-term interferon therapy for patients infected with hepatitis C virus genotype 2a. *Am J Gastroenterol* 2005; **100**: 862-867

18 **Martin P**, Jensen DM. Ribavirin in the treatment of chronic hepatitis C. *J Gastroenterol Hepatol* 2008; **23**: 844-855

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