Therapy of chronic hepatitis C with PEG-IFN α-2b plus ribavirin in patients with genotype 2 or 3: 16 versus 24 weeks, clinical outcome and direct cost analyses

Paolo Fabris[a], Antonio Carlotto[b], Tiziana Del Bianco[c], Federica Malfatti[d], Andrea Tramarin[a], Marco A. Miotti[a], Vincenzo Baldo[e], Annarosa Floreani[f], Maria Teresa Giordani[a] and Alessandro Grasso[d]

Introduction **Short antiviral therapy has been proposed for patients with chronic hepatitis C, easy genotypes, low fibrosis score, low viral load at baseline, and rapid virological response (RVR). However, this approach is not completely accepted.**

Objectives **The aims of this study were (a) to evaluate the sustained virological response (SVR) in noncirrhotic patients with genotype 2 or 3, achieving an RVR, randomized to receive pegylated-interferon (IFN) α-2b plus ribavirin for either 16 or 24 weeks and (b) to carry out direct cost analysis comparing patients treated for 16 versus 24 weeks.**

Results **Of the 142 initially evaluated patients, 130 were enrolled according to the selection criteria, but independent of the viral load. According to the intention-to-treat analysis, SVR was achieved in 104 patients (80%). Logistic regression analysis showed that RVR ($P<0.001$) and genotype 2 ($P<0.03$) were the most important factors independently associated with SVR. Among patients with RVR, SVR was comparable between patients treated for 16 weeks and those treated for 24 weeks (86.2 vs. 89.7%, P=NS). The mean direct costs were €4003.7 for patients treated for 16 weeks and €5676.7 for those treated for 24 weeks, with a 30% difference between the two arms.**

Conclusion **In patients achieving an RVR, a 16-week treatment with pegylated-interferon plus ribavirin was comparable to a 24-week treatment. Short treatment in patients with RVR allows us to save 30% of the direct costs, independent of the viral load at baseline. *Eur J Gastroenterol Hepatol* 25:1396–1401 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

European Journal of Gastroenterology & Hepatology 2013, **25**:1396–1401

Keywords: cost analysis, genotypes 2 and 3, hepatitis C virus therapy

[a]Department of Infectious Diseases and Tropical Medicine, S. Bortolo Hospital, [b]Department of Infectious Diseases, Schio, Vicenza, [c]Gastroenterology Unit, Gorizia Hospital, Gorizia, [d]Department of Gastroenterology, AASL2, San Paolo Hospital, Savona, [e]Institute of Hygiene and [f]Department of Surgery, Oncology and Gastroenterology, University of Padova, Padova, Italy

Correspondence to Paolo Fabris, MD, Department of Infectious Diseases and Tropical Medicine, S. Bortolo Hospital, Viale Rodiolfi 38, 36100 Vicenza, Italy
Tel: +39 0444 753624; fax: +39 0444 753405; e-mail: pfabris@yahoo.com

Received 2 February 2013 **Accepted** 26 April 2013

Introduction

Hepatitis C virus (HCV) infection affects ~170 million individuals worldwide. It is one of the leading causes of liver cirrhosis and hepatocellular carcinoma and is also an indication for liver transplantation. At present, the standard of care (SOC) for patients with genotype 2/3 is the combination of pegylated-interferon (PEG-IFN) and ribavirin. The clearance of HCV with SOC depends on several factors including viral load, HCV genotype, liver fibrosis, etc. Sustained virological response (SVR) with SOC is achieved quite easily in patients with genotypes 2 and 3. The SVR range is between 70 and 85% of patients treated for 24 weeks. Further, several studies have shown that treatment with SOC can be reduced to 12 or 14 weeks without compromising the SVR rate [1–6]. However, other authors have reported a better efficacy of the standard therapy protocol (i.e. PEG-IFN α-2a plus ribavirin) for 24 weeks compared with 16 weeks [7,8]. Side effects of therapy are common and sometimes serious. Further, in the current scenario of the global economic crisis, it is mandatory to tailor the treatment to achieve the best balance between cost and effectiveness. In this study, we evaluated the efficacy and the direct costs of the treatment on the basis of rapid virological response (RVR) for patients with chronic hepatitis C and genotype 2 or 3, treated for 16 or 24 weeks.

Materials and methods

Men and women older than 18 years of age, with chronic hepatitis C, monoinfected with either genotype 2 or 3 were enrolled in this study. None of the patients evaluated had double infection (i.e. two different genotypes). All patients had persistently altered alanine aminotransferase levels. The first patient was enrolled in October 2009 and the last in July 2011. Inclusion criteria were neutrophil and platelet counts within the normal range. The study was carried out in three different centers (Infectious Diseases and Tropical Medicine, Vicenza; Infectious Diseases Unit, Schio; and Department of Internal Medicine, Savona, Italy) after obtaining approval from the respective ethics committees. The study has been codified as SF3PEG-RIBA and regularly

0954-691X © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/MEG.0b013e328362dc22

Table 1 Characteristics of the patients enrolled in the study according to group

Characteristics	Total	RVR		No RVR
		16-week arm	24-week arm	
Number of patients	130	58	58	12
Age (years) [mean (SD)]	45.4 (12.4)	44.8 (13.5)	45.1 (12.2)	46.3 (6.4)
Sex [*n* (%)]				
Male	85 (65.4)	34 (58.6)	40 (69)	9 (75.0)
Female	45 (34.6)	24 (41.4)	18 (31)	3 (25.0)
IVDU [*n* (%)]	74 (56.9)	30 (51.7)	29 (50.0)	5 (41.7)
Other source of transmission [*n* (%)]	56 (43.1)	28 (48.3)	29 (50.0)	7 (58.3)
BMI [mean (SD)]	23.9 (3.1)	23.4 (2.7)	24.1 (3.5)	25.1 (2.2)
AST (IU/ml) [mean (SD)]	65.3 (51.2)	61.7 (45.2)	65.9 (47.8)	81.9 (87.6)
ALT (IU/ml) [mean (SD)]	123.3 (112.1)	126.9 (117.4)	117.1 (93.2)	135.9 (168.0)
GGT (IU/ml) [mean (SD)]	46.2 (39.8)	39.7 (32.1)	46.3 (42)	77.8 (51.9)
HCV [*n* (%)]				
Genotype 2	67 (51.5)	31 (53.4)	31 (53.4)	3 (25.0)
Genotype 3	63 (48.5)	28 (48.3)	26 (44.8)	9 (75.0)
Viral load (IU/ml) [mean (SD)]	1 847 982.7 (2 673 523.7)	1 664 454.6 (2 438 672.2)	2 068 972.9 (3 023 537.2)	1 760 305.8 (2 208 741.6)
Viral load [*n* (%)]				
$\leq$ 800 000 IU/ml	67 (51.5)	29 (50)	33 (56.9)	5 (41.7)
>800 000 IU/ml	63 (48.5)	29 (50)	25 (43.1)	7 (58.3)
PEG-IFN [mean (SD)]				
Daily (μg)	88.8 (15.3)	85.5 (16.2)	92.6 (14.3)	86.7 (13.0)
μg/kg/week	1.3 (0.3)	1.2 (0.2)	1.3 (0.2)	1.2 (0.2)
Ribavirin [mean (SD)]				
Daily (mg)	879.7 (123.8)	886.2 (130.4)	879.3 (123.9)	850.0 (90.5)
mg/kg/day	12.6 (2.6)	13.2 (1.7)	12.6 (2.2)	11.3 (1.6)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase; HCV, hepatitis C virus; IVDU, intravenous drug user; PEG-IFN, pegylated-interferon; RVR, rapid virological response.

registered on the website of Agenzia Italiana del Farmaco (*http://oss-sper-clin.agenziafarmaco.it*) in the clinical observatory division of drug experimentation with the name and number assigned by the European Agency of Drugs, EudraCT 2007-000270-40.

Patients with any other cause of liver disease; HIV and/or coinfections; metabolic, cardiovascular, renal, neurologic, or psychiatric diseases; those who concomitantly administered immunosuppressive medication; and those with evidence of daily intake of alcohol of more than 20 g/day were excluded. Further exclusion criteria were pregnancy and lactation. In addition, patients with cirrhosis were excluded from this study according to the following criteria: APRI score greater than 1.5 (AST/platelets $\times$ 100) [9], liver biopsy obtained within 1 year from the enrollment compatible with cirrhosis (using the Ishak staging score > 4), or elastometry (Fibroscan; Echosens, Paris, France) showing liver stiffness greater than 12 kPa. Informed and written consent was obtained from each patient before enrollment. The main characteristics of the patients studied are reported in Table 1. HCV genotype was determined by reverse hybridization (Inno Lipa HCV; Innogenetics, Gent, Belgium).

Study design

This randomized study compared the efficacy and direct costs of 16 versus 24 weeks of treatment with PEG-IFN α-2b plus ribavirin in naive patients who were infected with genotype 2 or 3. Patients were treated with PEG-IFN α-2b (1.5 μg/kg subcutaneously weekly) plus ribavirin (Copegus; Hoffman-La Roche AG, Basel, Switzerland). Ribavirin dose was based on body weight at study entry (< 65 kg: 800 mg/day; 65–85 kg: 1000 mg/day; >85 kg: 1200 mg/day).

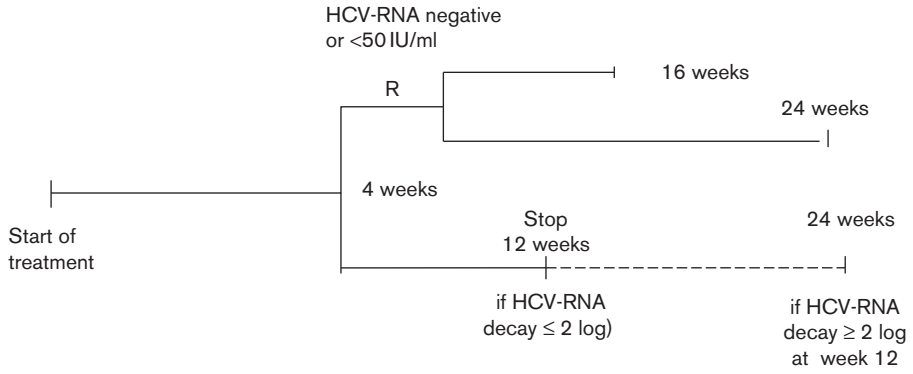
Patients with RVR (HCV-RNA negative or viral titer <50 IU/ml after 4 weeks of treatment; Amplicore monitor version 2.0; Roche Molecular Systems, Mannheim, Germany) were randomized to receive either 16 or 24 weeks of treatment. Randomization was performed using a random number generated by a computer. In contrast, patients with viremia over 50 IU/ml were randomized to receive standard therapy (24 weeks). The sample size of the study was calculated as follows: with the hypothesis of a difference between the groups of 0.3, with an α type 1 error of 5% and a power (1 – β) of 80%, with a test with two sides, 176 patients had to be enrolled in each group. Treatment was stopped in patients with a less than 2 log decrease in the viral load with respect to baseline after 12 weeks of therapy. In contrast, patients with greater than 2 log decay in the viral titer at week 12 (early virological response) continued treatment for 12 more weeks (24 weeks of treatment). The design of the study is reported in Fig. 1

Direct cost analysis

Direct cost analyses were carried out by considering the costs of blood tests, the costs of drugs, and the costs of consultations.

The following blood tests were performed for each patient at baseline, after 15 days, and then monthly until

Fig. 1



Design of the study. HCV, hepatitis C virus; R, randomization.

the end of treatment and 6 months of follow-up: determination of blood count and levels of aspartate aminotransferase, alanine aminotransferase, γ-glutamyltransferase, total bilirubin, thyroid-stimulating hormone, and alkaline phosphatase. ECGs were obtained for all patients before treatment. Non-organ-specific autoantibodies (antinuclear, anti-smooth muscle, anti-liver-kidney microsomes) and thyroid antibodies were tested for at baseline and after 3 months; quantitative HCV-RNA was tested for at baseline and after 4, 12, and 24 weeks of treatment; they were tested for at 12-week intervals after therapy until 6 months of follow-up. The costs of each blood test and ECG were determined from the regional tariff system. PEG-IFN α-2b and ribavirin were distributed and administered only at the hospital. Hence, the costs of PEG-IFN α and ribavirin were the official prices determined by the National Drug Agency (AIFA).

Statistical analysis

Data were analyzed using the χ^2-test (uncorrected and Fisher's exact test) and Student's *t*-test as appropriate. A *P*-value of 0.05 was considered significant. A stepwise multiple regression analysis was carried out for each variable under study to determine which characteristics were associated independently with SVR. Analyses were carried out using SPSS (v 18.0; SPSS Inc., Chicago, Illinois, USA).

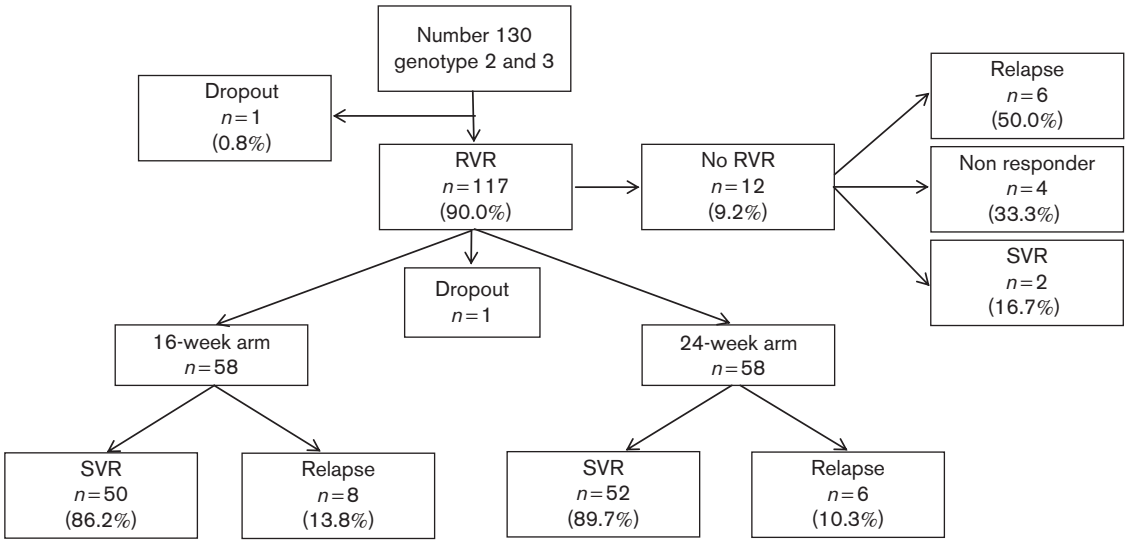
Clinical findings

Of the 142 patients initially selected, 130 fulfilled the inclusion criteria and were enrolled in the study. The enrollment was interrupted in June 2011 after an interim analysis and because of the difficulty in recruitment of new cases at our centers. The clinical characteristics of the patients are shown in Table 1. The mean histological score for staging was 2.2±9 and the mean stiffness obtained on elastometry was 8.9 kPa (range 4.5–9.2). All patients enrolled had an APRI score of less than 1.5 (mean 0.8±0.3). Among the 130 patients enrolled in the study, 117 (90%) achieved an RVR (Fig. 2) and were randomized in the short arm (16 weeks) or the standard protocol (24 weeks) of treatment. No statistically significant differences were found on comparing patients of the two groups that achieved an RVR with those of the group that did not achieve an RVR (Table 1). Intention-to-treat analysis (including the two dropout patients) indicated an overall SVR rate of 80% (104/130 patients). SVR was achieved in 102/117 (87.2%) patients with an RVR and in 2/12 (16.7%) patients without an RVR (Fig. 2). The SVR rate was not significantly different between patients treated for 16 weeks and those treated for 24 weeks (86.2 vs. 89.7%, respectively, P = NS). Further, the comparison of relapse rates and the difference between two RVR arms according to characteristics failed to show any significant difference (Table 2). Four patients (viral decay < 2 log after 3 months of therapy) were classified as nonresponders and treatment was withdrawn. On univariate analysis, SVR was significantly associated with genotype 2 compared with genotype 3 (89.6 vs. 69.8%, $P < 0.01$); this finding was independent of the dosage of either PEG-IFN α-2b or ribavirin and the duration of treatment as well. Logistic regression analysis showed that SVR was significantly associated with genotype 2 ($P < 0.03$, odds ratio 5.3, 95% confidence interval 1.1–24.5); however, RVR was the most important variable associated independently with SVR ($P < 0.0001$, odds ratio 61.4, 95% confidence interval 6.1–612.9; Table 3).

Side effects

Side effects were similar in the group treated for 16 weeks and in the group treated for 24 weeks. However, alopecia was reported only in the group treated for 24 weeks. Indeed, hypothyroidism with an increase in both thyroid antibodies and thyroid-stimulating hormone was observed in two patients in the short arm and three patients treated for 24 weeks (P = NS). Interestingly, spontaneous normalization of thyroid function was observed after IFN withdrawal in both patients treated in the short arm and only one patient treated for 24 weeks. Occurrence of flu-like symptoms was

Fig. 2



Main results according to rapid virological response (RVR). SVR, sustained virological response.

Table 2 Relapse rates and difference between the two rapid virological response arms according to characteristics

	Total patients [*n* (%)]		
Characteristics	14-week arm	24-week arm	Difference in the relapse rates
Age			
<40	2/20 (10)	2/24 (8.3)	1.7
≥ 40	6/38 (15.8)	4/34 (11.8)	4.0
Sex			
Males	7/34 (20.6)	5/40 (12.5)	8.1
Females	1/24 (4.2)	1/18 (5.6)	−1.4
HCV			
Genotype 2	2/29 (6.9)	2/33 (6.1)	0.8
Genotype 3	6/29 (20.7)	4/25 (16)	4.7
Viral load			
≤ 800 000 IU/ml	3/29 (10.3)	3/32 (9.4)	0.9
>800 000 IU/ml	5/29 (17.2)	3/26 (11.5)	5.7

HCV, hepatitis C virus.

Table 3 Multivariate regression analysis carried out on 130 patients enrolled: dependent variable sustained virological response (yes vs. no)

			95% CI	
Variables	*P*	Adjusted OR	Inferior	Superior
Age	0.925	1.003	0.938	1.073
Sex (women vs. men)	0.057	5.344	0.948	30.115
BMI	0.653	0.942	0.725	1.223
Baseline viral load (<800 000 vs. ≥ 800 000)	0.862	0.887	0.230	3.422
RVR (positive vs. negative)	0.000	61.495	6.170	612.957
Genotype (2 vs. 3)	0.030	5.385	1.180	24.571
Duration of therapy (24 vs. 16 weeks)	0.103	1.725	0.895	3.325
Dose of PEG-IFN administered	0.228	0.967	0.915	1.021
Dose of ribavirin administered	0.179	1.004	0.998	1.010
AST (continuous variable)	0.063	0.969	0.937	1.002
ALT (continuous variable)	0.049	1.014	1.000	1.028
GGT (continuous variable)	0.875	1.002	0.978	1.027

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; GGT, γ-glutamyltransferase; PEG-IFN, pegylated-interferon; OR, odds ratio; RVR, rapid virological response.

Table 4 Direct cost analysis according to protocol (mean±SD) in patients achieving rapid virological response

Variables	16-week arm	24-week arm	*P*
Mean cost of IFN administration (€)	247.8±304.2	3972.7±427.0	<0.001
Mean cost of ribavirin (€)	412.8±50.8	616.2±86.3	<0.001
Mean cost of drugs (IFN + ribavirin) (€)	2919.7±361.3	4552.8±586.1	<0.001
Mean costs of blood tests and consultations (€)	1074.5±102.5	1107.9±123.5	NS
Mean cost for patient (€)	4003.7±382.7	5676.7±586.1	<0.001

IFN, interferon; NS, not significant.

comparable in the two randomized groups but disappeared promptly only in the 16-week treatment group after treatment withdrawal. Depression was observed in only one patient treated for 24 weeks.

Direct cost analysis

The cost analysis was carried out considering blood tests, consultations, and drugs administered. As for PEG-IFN α-2b, the dose actually administered for each patient was considered for at least 80% of the stipulated period. Therefore, the dose reduction of both PEG-IFN and ribavirin during treatment was included in the analysis. Notably, the mean doses of PEG-IFN and ribavirin administered were lower than those scheduled (mean PEG-IFN 1.2 μg/kg/week in the patients treated for 16 weeks and 1.3 μg/kg/week in those treated for 24 weeks, P = NS); similarly, the mean dose of ribavirin administered was 886.2 and 879.3 mg/day in patients treated for 16 and 24 weeks, respectively (Table 1). The reduction of ribavirin was because of anemia in the majority of patients (80% of patients), whereas PEG-IFN reduction was because of neutropenia. Drug reductions were prescribed in all patients after the first 4 weeks of treatment. We did not use either erythropoietin or granulocyte growth factor to control anemia and neutropenia.

The direct cost for patients who dropped out after the first month was €1009.2, whereas the direct cost for patients who dropped out between the second and third months of treatment was €1405, and the direct cost for the four nonresponders treated for 3 months was €7447. For treated patients who achieved an RVR and those treated for 16 or 24 weeks, the results are reported in Table 4. The mean direct cost for patients treated for 16 weeks was €4003.7 for each patient (ranging from €3112 to €5017), whereas the mean direct cost for patients treated for 24 weeks was €5676.7 (ranging from €4164 to €6742), according to the body weight. Overall, the direct cost for the 58 patients randomized to receive 24 weeks of treatment was €329 208.5 plus the cost of €1662 for the patient who dropped out (total €330 870.3).

The direct cost for the 58 patients treated for 16 weeks was €232 214.6, with a difference of €96 993.9. In other words, on using the short-arm strategy, 30% of direct costs were saved in the treatment of patients with chronic hepatitis C with genotype 2 or 3.

Discussion

These results deserve several considerations and address several points of importance to public health.

First, only naive patients without cirrhosis, with so-called 'easy-to-treat genotypes' (genotypes 2 and 3) were enrolled, and the design of the study was according to the practice guidelines for the treatment of hepatitis C published by the Italian Association for the Study of the Liver; the Italian Society for Infectious, Tropical Disease; and the Italian Society for the Study of Sexually Transmitted Diseases [10]. According to these guidelines, the duration of treatment can be shortened to 12–16 weeks in a subgroup of patients with either genotype 2 or 3 who have developed RVR. To do this safely without compromising SVR rates, the following conditions should be fulfilled: the presence of RVR, the absence of advanced fibrosis, cirrhosis, or any other cofactor/comorbidity known to reduce the efficacy of antiviral therapy; and adequate adherence to PEG-IFN and ribavirin. In contrast to the current guidelines and other studies, we did not consider baseline viral titers to randomize the patients achieving an RVR [11,12]. Despite this approach, our findings are comparable to those reported by other authors [1–6], showing, once again, that RVR is the most important predictor for achieving an SVR. RVR, as expected, was the most important factor associated with SVR in the logistic regression analysis. The lack of a correlation between baseline viral titers and SVR in patients achieving an SVR may be partially explained by the characteristics of the patients enrolled: absence of advanced liver disease, low BMI, and absence of cofactors.

This is also true considering the reduction in the dose of ribavirin and PEG-IFN after the first 4 weeks of treatment. In fact, in the present study, the mean dose of ribavirin was 13.2 and 12.6 mg/kg/day in the short arm and the standard protocol, respectively. The doses of both PEG-IFN and ribavirin were reduced in 25% of the cases after 4 weeks. This approach was determined on the basis of neutropenia (< 500 ml/mmc^3) and in four patients on the basis of a decreased platelet count ($< 50\,000$). The mean doses actually administered are shown in Table 1. None of the patients were treated for neutropenia with growth factors and none received erythropoietin for anemia. In these patients, a ribavirin dose reduction (generally 200 mg/day) or a reduction in the PEG-IFN

dose could ameliorate neutropenia, anemia, and platelet count. The cost–benefit analysis supports the short-arm regimen for both the easy genotypes. The probability of achieving an SVR was the same in the two arms (86.2 vs. 89.7%) and the relapse rate was similar (13.8 vs. 10.3%).

Finally, logistic regression analysis showed that besides RVR, genotype 2 was correlated significantly with SVR. This finding is in agreement with those of other authors, confirming that it is not appropriate to combine genotypes 2 and 3 [13]. The higher rate of SVR in patients with genotype 2 than in those with genotype 3 treated with SOC has been explained by a different induction of interferon-stimulated genes. Interferon-stimulated genes promote antiviral, antiproliferative, and immunoregulatory signals in the host, which can contribute toward viral eradication [13].

Data on the analysis of polymorphisms of interleukin 28b were not available at our centers when the study was commenced; in addition, that analysis was primarily limited to genotype 1 only. Second, we did not use this marker to further reduce the cost of treatment. However, as reported recently in the literature, it is reasonable to expect a high prevalence of the rs12979860 CC genotype of interleukin 28b in our patients with genotype 2 or 3 with RVR [14,15]. As only two patients dropped out, the costs of unsuccessful treatment were determined by the relapser and the nonresponder patients. In our study, adherence was almost 100%. Adherence has been proven with an accurate check at each visit, counting the remaining tables of ribavirin and vials of PEG-IFN.

Taking into account the inclusion of patients with easy genotypes and without advanced disease, the costs of treatment for patients who were enrolled in the long duration arm were comparable to those for patients enrolled in the study by Helsper *et al.* [16], who considered the real-life costs of standard therapy of hepatitis C treatment. The results of our study indicate that the mean direct costs for patients with an easy genotype and RVR were €4003.7 if they were treated for 16 weeks and €5676.7 if they were treated for 24 weeks. Treatment resulting in dropout for nonresponse increased the cost by €1662 per patient. Although the conclusions are similar, in our study, the mean direct costs were lower than those reported by De Compadri *et al.* [17]. The differences have several explanations: we considered the actual doses of drugs administered; we did not evaluate for psychiatric disorders in each patient before treatment; and we managed side effects by ourselves, on the basis of our experience, in our clinics, without specialist consultations. Further, we did not evaluate the costs of liver biopsy and/or liver elastography (Fibroscan).

Conclusion

Our findings support a good balance between cost and effectiveness of short-term treatment in patients with HCV of genotypes 2 and 3 with noncirrhotic disease and achieving an RVR, independent of viral titer at baseline. Efforts should be made in the future to estimate the actual cost saving involved in the treatment of new cases of HCV by evaluating not only the direct costs but also the indirect costs of therapy.

Acknowledgements

The authors would like to thank Dr Giampietro Pellizzer for his assistance.

Conflicts of interest

There are no conflicts of interest.

References

1 Mangia A, Santoro R, Minerva N, Ricci GL, Carretta V, Persico M, *et al.* Peginterferon alfa-2b and ribavirin for 12 vs. 24 weeks in HCV genotype 2 or 3. *N Engl J Med* 2005; **352**:2609–2617.
2 Dalgard O, Bjoro K, Hellun KB, Myrang B, Ritiand DS, Shaug K, *et al.* Treatment with pegylated interferon and ribavirin in HCV infection with genotype 2 or 3 for 14 weeks: a pilot study. *Hepatology* 2004; **40**:1260–1265.
3 Dalgard O, Mangia A. Short-term therapy for patients with hepatitis C virus genotype 2 or 3 infection. *Drugs* 2006; **66**:1807–1815.
4 Andriulli A, Dalgard O, Bjøro K, Mangia A. Short-term treatment duration for HCV-2 and HCV-3 infected patients. *Dig Liver Dis* 2006; **38**:741–748.
5 Slavemburg S, Weggelaar I, van Oijen MG, Drenth JP. Optimal length of antiviral therapy in patients with hepatitis C virus genotype 2 and genotype 3: a meta-analysis. *Antivir Ther* 2008; **14**:1139–1148.
6 Dalgard O, Bjoro K, Ring-Larsen H, Verbaan H. In patients with HCV genotype 2 or 3 infection and RVR 14 weeks treatment is noninferior to 24 weeks. Pooled analysis of two Scandinavian trials. *Eur J Gastroenterol Hepatol* 2010; **22**:552–556.
7 Diego M, Mitchell L, Shiffman ML, Bronowichi JP, Zeuzem S, Rodriguez-Torres M, *et al.* Identifying hepatitis C virus genotype 2/3 patients who can receive a 16 week abbreviated course of peginterferon alfa-2a (40KD) plus ribavirin. *Hepatology* 2010; **51**:1897–1903.
8 Shiffman MI, Suter F, Bacom BR, Nelson D, Harley H, Solà R, *et al.* Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3. *N Engl J Med* 2007; **357**:124–134.
9 Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, *et al.* A simple non invasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology* 2003; **38**:518–526.
10 Prati D, Gasbarrini A, Mazzotta F, Sagnelli E, Carosi G, Abrescia N, *et al.* Practice guidelines for the treatment of hepatitis C: recommendations from an AISF/SIMIT/SIMAST Expert opinion meeting. *Dig Liver Dis* 2010; **42**:81–91.
11 von Wagner M, Huber M, Berg T, Hinrichsen H, Rasenack J, Heintges 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**:522–527.
12 Craxí A, Pawlotsky JM, Wedemeyer H, Bjoro K, Flisiak R, Forns X, *et al.* EASL Clinical Practice Guidelines: management of hepatitis C virus infection. *J Hepatol* 2011; **55**:245–264.
13 Duarte-Rojo A, Heathcote EJ, Feld JJ. Easy to treat genotypes were not created equal: Can rapid virological response (RVR) level the playing field. *J Hepatol* 2011; **55**:466–473.
14 Sarrazin C, Susser S, Doehring A, Lange CM, Müller T, Schlecker C, *et al.* Importance of IL28B gene polymorphisms in hepatitis C virus genotype 2 and 3 infected patients. *J Hepatol* 2011; **54**:415–421.
15 Mangia A, Thompson AJ, Santoro R, Piazzolla V, Tillmann HL, Patel K, *et al.* An Il28B polymorphism determines treatment response of hepatitis C virus genotype 2 or 3 patients who do not achieve a rapid virological response. *Gastroenterology* 2010; **139**:821–827.
16 Helsper CW, Hellinga HL, van Essen GA, de Wit GA, Bonten MJ, van Erpecum KJ, *et al.* Real-life costs of hepatitis C treatment. *Neth J Med* 2012; **70**:145–153.
17 De Compadri P, Koleva D, Mangia A, Motterlini N, Garattini L. Cost minimisation analysis of 12 or 24 weeks of peginterferon alfa-2b + ribavirin for hepatitis C virus. *J Med Econ* 2008; **11**:151–163.