Female patients in fertile age with chronic hepatitis C, easy genotype, and persistently normal transaminases have a 100% chance to reach a sustained virological response

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Background **Patients with chronic hepatitis C and persistently normal alanine transaminase levels have recently been included in the guidelines for antiviral treatment.**

Aim **To evaluate the efficacy of PEG-interferon α-2a and weight-based ribavirin doses in patients with these characteristics in a single Italian centre.**

Materials and Methods **Patients with chronic hepatitis C and at least three normal alanine transaminase values over a 12-month period were offered a treatment with PEG-interferon α-2a 180 mg/week and ribavirin (800 mg/day for weight <60 kg; 1000 mg/day for weight >60 and <75 kg; 1200 mg/day for weight >75 kg) for 24 weeks (according to genotype 2 or 3) or for 48 weeks (according to genotype 1 or 4). Each patient at baseline underwent liver stiffness (LS) examination using Fibroscan. Data were analysed according to the intention-to-treat criteria.**

Results **A total of 227 patients (55 men, 172 women) were enrolled into the study: 65 (28.6%) had genotype 1, 144 (63.4%) genotype 2, nine (4.0%) genotype 3 and nine (4.0%) genotype 4. Patients with genotype 2 or 3 (*N*=153 with easy genotypes) were allocated in group 1 and those with genotype 1 or 4 (*N*=74 with difficult genotypes) in group 2. According to the LS measurement, patients were classified as follows: 159 (70.0%) presented absent or mild fibrosis (LS=2.5–7.0 kPa), 61 (26.9%) patients had significant fibrosis (LS=7.1–9.5) and seven (3.1%) patients had severe fibrosis (LS >9.6). Twelve patients (5.3%) dropped out within 4 months because of side-effects, whereas 215 patients completed the study. Overall, 13 patients were considered nonresponders (5.7%) and six patients (2.6%) were relapsers to the therapy. The sustained virological response (SVR) rate was 85.4% and it was higher in 'easy' genotypes (2 or 3) compared with 'difficult' genotypes (1 or 4) (92.2 vs. 74.3%, *P*<0.001). No statistical difference was found in the SVR rate between patients presenting absent or mild fibrosis as against those with significant fibrosis. Multivariate analysis, including factors correlated with SVR, showed that easy genotype and female sex are significantly associated with a SVR.**

Conclusion **Patients with chronic hepatitis C and persistently normal transaminases have an 85.4% chance to clear the virus with conventional antiviral treatment. Female patients in fertile age with easy genotypes have a 100% chance to reach a SVR. *Eur J Gastroenterol Hepatol* 00:000–000 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Combination therapy with PEG-interferon (PEG-IFN) and ribavirin is the current strategy for the treatment of hepatitis C [1]. Over the last years, new concepts on the effectiveness of therapeutic strategy have emerged including predictors of response [particularly the early decline in viral load and the 'easy genotypes' (2 and 3 compared with genotype 1)]. Individualized treatment appears the best strategy for a rational use of resources [2,3].

Patients with persistently normal transaminases account for approximately 30% of the patients with chronic hepatitis C (CHC) [4]. These patients have significantly lower inflammation and fibrosis scores on liver biopsy examination than patients with elevated transaminase but almost two-thirds have portal fibrosis and 10% have bridging fibrosis [5]. In a large randomized, international controlled trial involving 70 centres, patients were randomized to receive PEG-IFN α-2a and ribavirin for 24 weeks, or the same dosage for 48 weeks, or no treatment. All patients included in the treatment group received a daily dose of ribavirin of 800 mg [6]. The sustained virological rate (SVR) was similar to that

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obtained in patients with elevated alanine transaminase (ALT) levels, suggesting that the indication for treatment of hepatitis C can be evaluated independently from baseline activity [6]. Another small study was conducted in 11 Italian centres and included 88 patients with CHC with persistently normal ALT levels [7]. Patients received PEG-IFN α-2a and weight-tailored ribavirin for 24 weeks (genotype 2 or 3) or 48 weeks (genotype 1). The conclusion of this study showed that combination therapy produces, in patients with normal ALT, virological response rates that are comparable to or even higher than those obtained in patients with elevated ALT.

More importantly, Deuffic-Burban *et al.* [8], using a Markov model to simulate progression of newly hepatitis C virus (HCV)-infected cohorts, have demonstrated that treatment of patients with CHC and persistently normal transaminases would decrease HCV morbidity and mortality. On the basis of these contributions, patients with CHC and normal transaminases should be considered as candidates for treatment just as others are. However, two important end-points need to be refined in the clinical practice: (a) the efficacy of weight-based ribavirin doses in association with PEG-IFN α-2a in a large cohort of patients; (b) the impact of sex on the SVR.

The aim of this study was to evaluate these points in patients with persistently normal transaminases and CHC treated with antiviral therapy in a single Italian centre.

Materials and methods

Study design

This study was designed as prospective, open-labelled, and noncontrolled for enrolment of patients with CHC and persistently normal transaminases. The study was approved by the local Ethical Committee, and written informed consent was obtained from each patient before being enrolled.

The inclusion criteria were as follows:

(1) Naive HCV-RNA-positive patients aged between 18 and 65 years (viral load > 1000 IU/ml by quantitative reverse-transcription PCR (Amplicor Monitor HCV v 2.0; Roche Molecular Systems, Mannheim, Germany).
(2) Normal ALT on at least four different occasions 3 months apart over a 12-month period.
(3) Neutrophil count and platelets at least 2000 ml and 90 000, respectively.
(4) Compensated chronic liver disease.

The exclusion criteria were as follows:

(1) Age below 18 years or above 65 years.
  (i) Coinfection with hepatitis B virus and/or HIV
  (ii) alcohol abuse (> 20 g/day for women, 40 g/day for men);
  (iii) a history of parenteral drug addiction unless they had abstained for at least 2 years.
(2) Decompensated liver disease.
(3) Concomitant liver disease of other aetiology (autoimmune hepatitis, cholestatic liver disease, or non-alcoholic fatty liver disease) and an alcohol intake of more than 20 g ethanol/day.
(4) Pregnancy or lactation.

All fertile women and men enrolled in the trial were strongly advised to use effective contraceptive methods during the treatment and for 6 months after the end of treatment. None of the female patients in menopausal stage was taking hormone replacement therapy (HRT).

Liver stiffness measurement

All patients at baseline underwent measurement of liver stiffness (LS) by transient elastography (TE) using a FibroScan (Echosens, Paris, France) as described in previous studies [9,10]. Measurements were performed in the right lobe of the liver trough intercostal spaces and the median depth of measurement was 55 mm. Ten validated measurements were obtained for each patient and the minimum success rate (ratio of the successful acquisition over the total number of acquisitions) was considered to be 60%. The final result of LS was the median of the 10 valid measurements and was expressed as kPa. The measurement of LS lasted less than 5 min.

Treatment

Eligible patients were offered a different treatment regimen according to HCV genotype:

(iv) PEG-IFN α-2a (40 kDa) (Pegasys; Roche, Basel, Switzerland) at a dose of 180 mg (0.5-ml prefilled syringe) subcutaneously once a week and a weight-based oral administration of ribavirin (Copegus, Roche) for 24 weeks in those with genotype 2 or 3;
(v) PEG-IFN α-2a (40 kDa) (Pegasys; Roche) at a dose of 180 mg (0.5-ml prefilled syringe) subcutaneously once a week and a weight-based oral administration of ribavirin (Copegus, Roche) for 48 weeks in those with genotype 1.

In both groups, ribavirin was administered orally in two daily doses for a total of 800 mg/day for patients weighing up to 70 kg, 1000 mg/day for patients weighing 71–80 kg, or 1200 mg/day for those weighing more than 80 kg.

The treatment was withdrawn if the patient failed to achieve a virologic response, defined as serum HCV-RNA undetectable by PCR 24 weeks after starting treatment; these patients were considered as nonresponders.

This end-point was based on the international guidelines [11]. Rapid virological response (RVR) was defined by undetectable HCV-RNA at week 4. End-of-treatment

virological response (ETR) was defined as a normalization of ALT and HCV-RNA negativity at the end of the treatment. Treatment duration was 48 weeks for patients with genotypes 1–4 and 24 weeks for those with genotypes 2–3.

SVR was defined as the absence of serum HCV-RNA and normal ALT 24 weeks after completing the treatment.

Follow-up

Each patient underwent a physical examination and liver function tests every month. Liver function tests included haemoglobin, white blood cell count, platelets, transaminases and γ-glutamyl-transpeptidase. Quantitative PCR for HCV was assessed at 1, 3, 6, 12 and 6 months after the end of treatment. Nonorgan-specific autoantibodies (antinuclear, antismooth muscle, antimitochondrial, anti-liver and kidney microsomes) and antithyroid antibodies were assessed at months 3 and 13 after treatment.

Statistical analysis

Data were analysed using the χ^2-test (Mantel Haenszel and Fisher exact test). A P value of 0.05 or less was considered significant, and the odds ratio with a 95% confidence interval was calculated for each parameter. A multivariate logistic regression analysis was performed to evaluate independent predictors of SVR. Analyses were performed with the Statistical Package for the Social Sciences (SPSS rel. 11.5, Chicago, Illinois, USA).

Results

A total of 227 (55 men, 172 women) patients fulfilled the criteria of inclusion in the study and were offered treatment according to the previously described protocol.

The risk factors for HCV infection were intravenous drug use (IVDU) in 15 patients (6.6%), previous blood transfusion in 85 (37.4%) and community-acquired infection in 127 patients (55.9%).

The demographic, biochemical and virologic characteristics of patients are listed in Table 1. Cirrhosis was recorded in two patients according to histological criteria. Table 2 shows the clinical details of female patients. Twelve patients (5.3%) dropped out within 4 months because of side-effects (three for severe anaemia, eight for depression and one for acute psychosis). Overall, 215 patients completed the study (Fig. 1).

Table 3 summarizes the virological results of treatment. RVR, EVR, ETR and SVR were significantly higher in group 1 than in group 2 [75.2 vs. 20.3% ($P < 0.001$), 92.2 vs. 66.2% ($P < 0.001$), 92.2 vs. 82.4% ($P = 0.028$), 92.2 vs. 74.3% ($P < 0.002$), respectively]. According to intention-to-treat analysis, the SVR was achieved in 92.2% of patients in group 1 and in 74.3% patients in group 2 ($P < 0.002$). Thirteen patients were considered non-responders (5.7%): among them, two stopped the treatment at month 3 for a decreased viral load less than 2 log, and the remaining 11 patients were considered nonresponders at the end of treatment. Six patients (all included in group 2) relapsed within 6 months after the end of treatment (Fig. 1).

Table 1 Demographic, biochemical and virologic characteristics at baseline

Characteristics	Group 1 ($n=153$) Genotype 2.3	Group 2 ($n=74$) Genotype 1.4
Sex		
Men	32	23
Women	121	51
Age (years)		
Mean ± SD	49.5 ± 11.8	42.9 ± 10.7
CI	47.7–51.4	40.6–45.3
BMI (kg/m^2)		
Mean ± SD	23.6 ± 3.3	23.0 ± 3.0
Range	23.1–24.1	22.4–23.7
ALT levels (IU/l)		
Mean ± SD	40.7 ± 30.3	40.3 ± 16.6
Range	36.0–45.4	36.6–43.9
GGT levels (IU/l)		
Mean ± SD	21.4 ± 22.9	28.5 ± 20.9
Range	17.8–24.9	23.9–33.1
HCV genotype		
1		65 (87.8%)
2	144 (94.1%)	
3	9 (5.9%)	
4		9 (12.2%)
HCV RNA, ($\times 10^6$ IU/ml)		
Mean ± SD	7.85 ± 7.73	4.26 ± 5.42
Range	6.64–9.05	3.06–5.47
Ferritin		
Mean ± SD	78.3 ± 85.9	72.9 ± 79.2
Range	64.9–91.7	55.3–90.5
Cirrhotic stage	1	1
Liver stiffness (kPa)		
2.5–7.0	105 (68.6%)	54 (73.0%)
7.1–9.5	45 (29.4%)	16 (21.6%)
>9.6	3 (2.0%)	4 (5.4%)
Median IQR (kPa)	0.9	1.1
Median success rate (%)	70	68

Normal values: serum ferritin: <300 ng/ml for men and <150 ng/ml for women; serum GGT: <38 IU/l for men and <29 IU/l for women; serum ALT<40 U/l for women, <50 U/l for men.
ALT, alanine transaminase; GGT, γ-glutamyl-transpeptidase; HCV, hepatitis C virus; IQR, interquartile range.

Overall, the SVR rate was 86.8%; it was 90.7% in women and 74.5% in men; the difference was statistically significant ($P = 0.002$) (Table 4). Women in the fertile age (< 50 years old) with 'easy genotypes' had an SVR rate of 100%, whereas patients in the menopausal stage (> 50 years old) had a probability of attaining an SVR rate of 90.1% ($P = 0.013$). Women in the fertile age with 'difficult genotypes' had an SVR rate of 82.2%, whereas those in the menopausal stage had a probability of attaining an SVR rate of 66.7%; the difference failed to reach any statistical significance.

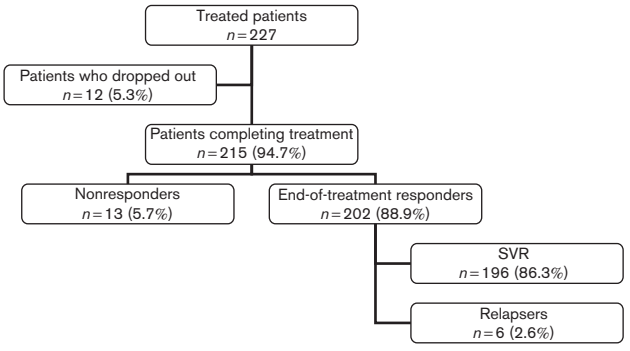
Analysing the response to treatment in relation to the degree of liver fibrosis evaluated by TE, no difference was found in the end-points of treatment (RVR, EVR, ETR and SVR) between the groups with an LS less than 9.5 kPa (corresponding to F0–F1–F2 METAVIR score)

Table 2 Demographic characteristics of the female patients

Characteristics	Group 1 ($n=121$) Genotype 2.3	Group 2 ($n=51$) Genotype 1.4
Age (years)		
Mean ± SD	49.6 ± 11.6	42.9 ± 10.7
≤ 50 years [*n* (%)]	61 (35.4%)	44 (25.6%)
≥ 50 years [*n* (%)]	60 (34.9%)	7 (4.1%)
BMI (kg/m^2)		
Mean ± SD	23.3 ± 3.4	23.0 ± 3.0
Range	22.7–23.9	22.4–23.7
ALT levels (IU/l)		
Mean ± SD	40.8 ± 32.0	40.3 ± 16.6
Range	35.1–46.5	36.6–43.9
GGT levels (IU/l)		
Mean ± SD	19.4 ± 22.0	28.5 ± 20.9
Range	15.5–23.3	23.9–33.1
HCV genotype		
1		46 (26.8%)
2	115 (66.8%)	
3	6 (3.5%)	
4		5 (2.9%)
HCV RNA, ($\times 10^6$)IU/ml		
Mean ± SD	7.85 ± 7.73	0.26 ± 5.42
Range	6.64–9.05	3.06–5.47
Ferritin		
Mean ± SD	59.0 ± 57.7	72.9 ± 79.2
Range	48.7–69.3	55.3–90.5
Cirrhotic stage	1	1
Liver stiffness (kPa)		
2.5–7.0	89 (73.6%)	35 (68.6%)
7.1–9.5	29 (24.0%)	13 (25.5%)
>9.6	3 (2.4%)	3 (5.9%)
Median IQR (kPa)	0.8	1.0
Median success rate (%)	75	72

Normal values for women: serum ferritin: <150 ng/ml; serum GGT: <29 IU/l; serum ALT <40 U/l.
ALT, alanine transaminase; GGT, γ-glutamyl-transpeptidase; HCV, hepatitis C virus; IQR, interquartile range.

Fig. 1



Design of the study.

and 9.5 kPa or more (corresponding to F3–F4 METAVIR), respectively (Table 5). Logistic regression analysis, including factors correlated with SVR, showed that an easy genotype and female sex were associated with SVR significantly (Table 5).

Analysing the factors associated with the SVR rates in 'difficult' or 'easy' genotypes, we found that none of the considered factors (sex, BMI, age, viral load, LS, serum ferritin and γ-glutamyl-transpeptidase) was independently associated with an SVR in patients with the 'difficult' genotype (Table 6), whereas female sex ($P = 0.006$), age below 50 years ($P = 0.008$) and a low viral load ($P = 0.018$) were significantly associated with an SVR in patients with the 'easy genotype' (Table 6).

Safety

Among the patients who completed the treatment ($N = 215$), 17 developed thyroid dysfunction (10 hypothyroidism and seven hyperthyroidism), three coeliac disease, one mild depression and one a moderate anaemia. A reduction of ribavirin dosage was performed in two patients (one with anaemia and the other one with hyperthyroidism).

None of the patients experienced a reduction in the PEG-IFN dosage.

Discussion

The results of our study indicate that CHC patients with persistently normal transaminases have an overall chance of achieving an SVR of 86.8%, but in the case of the 'easy genotype' the chance reaches 92.2% with the intention-to-treat analysis. Moreover, women with the 'easy genotypes' in fertile age have a 100% chance to reach an SVR to antiviral treatment. These rates of response were independent of the degree of fibrosis analysed before treatment by TE; finally, the logistic regression analysis showed that 'easy genotypes' and women in fertile age (< 50 years of age) were significantly correlated with SVR. These results deserve several comments. First of all, this is a study conducted in a single centre and includes a consistent number of patients with homogeneous characteristics. The risk for HCV acquisition was 6.6% for IVDU and 37.4% for previous blood transfusion; for the remaining patients, the risk was community-acquired infection. These risk factors are substantially similar to those recorded in the Italian multicentre study [7].

In the French multicentre study, IVDU risk was up to 30% higher [6]. With regard to the severity of liver disease, our

Table 3 Virological response (intention-to-treat analysis) to treatment according to different genotypes

Response	Group 1	Group 2	OR (95%CI)	*P*
Rapid virological response	115/153 (75.2%)	15/74 (20.3%)	11.90 (5.78–24.84)	$P<0.001$
Early virological response	141/153 (92.2%)	49/74 (66.2%)	5.99 (2.64–13.79)	$P<0.001$
End-of-treatment response	141/153 (92.2%)	61/74 (82.4%)	2.50 (1.01–6.27)	$P=0.028$
Sustained virological response	141/153 (92.2%)	55/74 (74.3%)	4.06 (1.73–9.60)	$P<0.002$

CI, confidence interval; OR, odds ratio.

Table 4 Sustained virological response rates in men and women

	SVR	OR (95% CI)	*P*
All patients (%)	197/227 (86.8%)		
Women	156/172 (90.7%)	3.33 (1.40–7.92)	0.002
Men	41/55 (74.5%)		
Women ≤ 50 years 'easy' genotype	60/60 (100%)	–	0.013
Women >50 years 'easy' genotype	55/61 (90.1%)		
Women ≤ 50 years 'difficult' genotype	37/45 (82.2%)	2.31 (0.24–19.45)	ns
Women >50 years 'difficult' genotype	4/6 (66.7%)		

CI, confidence interval; OR, odds ratio; SVR, Sustained virological response.

Table 5 Univariate analysis odds ratio and logistic regression analysis (adjusted odds ratio) of factors correlated with the sustained virological response

		SVR							
		Yes		No					
Factors	Total	*N*	(%)	*N*	(%)	OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Sex									
Men	55	41	74.5	14	25.5	0.30 (0.13–0.71)	0.002	0.37 (0.15–0.91)	0.032
Women	172	156	90.7	16	9.3				
BMI									
<25	161	139	86.3	22	13.7	0.87 (0.33–2.21)	0.755	1.03 (0.38–2.81)	0.953
≥ 25	66	58	87.9	8	12.1				
Age									
<50 years	128	119	93.0	15	11.7	1.53 (0.66–3.52)	0.280	0.40 (0.16–1.05)	0.063
≥ 50 years	93	78	83.9	15	16.1				
Genotype									
Easy	153	142	92.8	11	7.2	4.46 (1.87–10.78)	>0.001	4.99 (1.94–12.82)	>0.001
Difficult	74	55	74.3	19	25.7				
Viral load									
<800 000 IU/ml	38	32	84.2	6	15.8	0.78 (0.27–2.31)	0.608	2.04 (0.66–6.3)	0.213
≥ 800 000 IU/ml	189	165	87.3	24	12.7				
Liver stiffness									
<9.5 kPa	220	192	87.3	28	12.7	2.74 (0.35–17.14)	0.223	0.37 (0.06–0.92)	0.305
≥ 9.5 kPa	7	5	71.4	2	28.6				
Ferritin									
Normal	213	186	87.3	27	12.7	1.88 (0.39–7.96)	0.349	0.53 (0.11–2.46)	0.416
High	14	11	78.6	3	21.4				
GGT									
Normal	185	165	89.2	20	10.8	2.58 (1.01–6.48)	0.024	0.70 (0.26–1.90)	0.486
High	42	32	76.2	10	23.8				

Normal values: serum ferritin: <300 ng/ml for men and <150 ng/ml for women; serum GGT: <38 IU/l for men and <29 IU/l for women.
GGT, γ-glutamyl-transpeptidase; OR, odds ratio; SVR, Sustained virological response.

series was similar to both the French and the Italian series. In particular, our study and the previous studies included a negligible number of patients with advanced fibrosis.

The dosage of ribavirin was fixed in the French study (800 mg/day) [6]. In our study and in the Italian multicentre study [7] a weight-based regimen was utilized. We think that this is an important point to be stressed. In fact, when a weight-based regimen is introduced, the rate of SVR would be higher than in the case of a fixed dosage, as demonstrated by means of simulations and generalized additive models [12].

Finally, the response was independent of the degree of fibrosis evaluated by TE. In all, 70.0% of our patients had a low or absent grade of fibrosis. This rate is similar to that of the French study, in which fibrosis was absent or minimal at 66–69%. In our opinion, antiviral treatment should be offered to all infected patients who do not present contraindications to treatment. This is a crucial point that needs a prospective evaluation over the next decade, taking into account the fact that complications of CHC have a very slow progression. However, using a modeling approach, Deuffin-Burban *et al.* [8] showed for the first time that treating normal-transaminase populations would result in a decrease in morbidity and mortality from 2008 to 2025. Another important recommendation towards treatment comes from a Japanese study, which enrolled a cohort of 519 patients infected with HCV with normal ALT levels [13]. In a 10-year follow-up, 9.2% of the patients developed hepatocellular carcinoma, suggesting that patients with normal transaminases should also be considered as candidates for antiviral therapy.

Finally, our study showed that the SVR rate was significantly higher in women than in men ($P = 0.002$),

Table 6 Multivariate analysis of factors predicting an sustained virological response according to 'easy' and 'difficult' genotypes

	'Difficult' genotype		'Easy' genotype	
Factors	Adjusted or (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Sex				
Men	0.52 (0.15–1.87)	0.318	0.10 (0.02–0.51)	0.006
Women				
BMI				
<25	0.56 (0.14–2.19)	0.401	2.80 (0.54–14.51)	0.219
≥ 25				
Age				
<50 years	0.77 (0.20–2.98)	0.699	0.08 (0.01–0.51)	0.008
≥ 50 years				
Viral load				
<800 000 IU/ml	0.95 (0.21–4.27)	0.943	9.31 (1.46–59.29)	0.018
≥ 800 000 IU/ml				
Liver stiffness				
<9.5 kPa	0.70 (0.06–8.38)	0.780	0.06 (0.01–1.25)	0.070
≥ 9.5 kPa				
Ferritin				
Normal	0.23 (0.01–3.33)	0.282	0.63 (0.05–7.70)	0.716
High				
GGT				
Normal	0.61 (0.17–2.21)	0.448	1.70 (0.23–12.52)	0.599
High				

'Easy' genotype normal values: serum ferritin: <300 ng/ml for men and <150 ng/ml for women; serum GGT: <38 IU/l for men and <29 IU/l for women. CI, confidence interval; GGT, γ-glutamyl-transpeptidase; OR, odds ratio.

and that women in fertile age with easy genotypes have a 100% chance of obtaining an SVR. In contrast, women in the menopausal stage (with either the easy or the difficult genotypes) have a rate of SVR rate lower than women in fertile age. Data from a French study strongly suggest that long-term benefits of oestrogen exposure (premenopausal women or women in menopausal stage under HRT) have a slower rate of progression in liver fibrosis [14]. Another explanation for the high rate of SVR in female patients in fertile age may be the effect of the depletion of iron as a result of menstruation. This is an interesting but not completely explored field. It is well known that iron accumulation negatively affects the SVR in HCV patients treated with combination therapy [15]. Thus, menstruation can play an important role in reducing the 'toxic' effect of iron accumulation. However, logistic regression analysis failed to reveal a significant association between ferritin concentration and SVR. This observation has also been confirmed by the results of a multicentre study in Italy in which 442 women with CHC have been enrolled [16].

To our knowledge, this is the first time that a difference in SVR between women and men has been demonstrated. Indeed, over the last years, the role of oestrogens in liver fibrosis has been explored mostly in experimental studies, suggesting a possible antifibrotic and antiapoptotic role of oestrogens [17]. One limitation of our study is that the easy genotype group included mostly genotype 2 (96%), whereas genotype 3 was present in only 4%. Indeed genotype 2 is the easiest genotype to treat, reaching a higher rate of SVR than genotype 3 [18]. One limitation of our study was to calculate the menopausal cut-off rate arbitrarily (50 years). In a large cross-sectional study of the Italian Climateric Research Study Group, the observed mean age at menopause in the total population was 50.9 years [19]. However, none of our patients in menopausal stage was taking HRT during antiviral therapy. Thus, prospective and randomized studies in women with CHC are warranted to evaluate the role of oestrogens in ameliorating the SVR. Finally, because of the excellent result of SVR in the female population with 'easy genotypes', it may be speculated to shorten the duration of treatment. Another limitation of our study was not to address this specific point in our design of the study; this area is, however, important in order to obtain an individualized treatment according to the on-treatment virological response.

In conclusion, patients with CHC and with persistently normal transaminases have an 85.2% chance to clear the virus with conventional antiviral treatment. Female patients in the fertile age with easy genotypes have a 100% chance to reach an SVR.

Acknowledgement

Conflicts of interest

There are no conflicts of interest.

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