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Fatigue before, during and after antiviral therapy of chronic hepatitis C: Results from the Virahep-C study

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Background & Aims: Fatigue is the most frequent and often debilitating symptom of chronic hepatitis C. It is unclear whether successful therapy of hepatitis C leads to its clinical improvement. In the Virahep-C study, patients with hepatitis C virus (HCV) genotype 1 infection were treated with peginterferon alfa-2a and ribavirin for up to 48 weeks while undergoing assessment of viral kinetics and clinical symptoms.

Methods: Fatigue measurements were conducted, before, during and after therapy, as 'presence' (yes/no) and 'severity' (visual analog scale: 0–100 mm). The clinical, histologic, and virologic features that correlated with the presence and degree of fatigue were assessed focusing upon changes associated with sustained virological response (SVR).

Results: At baseline, 52% (n = 401) of participants reported having fatigue, which was more common in women than men (59% *vs.* 48%, $p = 0.02$) and slightly more severe (30 *vs.* 22 mm, $p = 0.056$). Fatigue was frequent and worse in cirrhotics versus those with lesser fibrosis (66% *vs.* 49%; 34 *vs.* 24 mm). Fatigue did not correlate with other parameters. The proportion of patients and median fatigue scores increased on treatment (52–78%; 25–40 mm, $p < 0.0001$) with higher fatigue noted amongst those who ultimately achieved SVR ($p < 0.0001$). On achieving SVR, there was a significant decrease in both frequency and severity of fatigue compared to their baseline (53–33%; 27–13 mm, both $p < 0.0001$).

Conclusions: Fatigue is common in patients with chronic hepatitis C but is poorly associated with biochemical parameters. Sustained response is accompanied by substantial improvement of fatigue.

Keywords: Liver; Anti-viral therapy; Tiredness; Cirrhosis; Peginterferon; Ribavirin; Side-effects.

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Abbreviations: HCV, hepatitis C virus; AA, African American; CA, Caucasian American; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; SVR, sustained virological response; NR, non-response; VAS, visual analog scale; HRQoL, health related quality of life.

Introduction

Fatigue is the most frequent symptom of liver disease and has a major effect on quality of life and daily activity in patients chronically infected with hepatitis C virus (HCV) [1–6]. However, the degree of fatigue varies considerably among patients and often correlates poorly with the severity of disease. In many instances, it is unclear whether fatigue is caused by hepatitis C and, if so, whether it is due to the chronic viral infection or to the degree of liver inflammation, injury or dysfunction [2,3,7]. A better understanding of the nature of fatigue in liver disease is hampered by (1) the fact that it is a subjective experience and difficult to measure and quantify; (2) is often multifactorial; and (3) its quality and severity are similar among the different etiologies.

Many clinical trials in liver disease have tried to capture the effects of medical treatments on fatigue using self-report instruments, with variable success [2,3,8–12]. Estimating the presence and severity of fatigue is particularly important in studies of interferon-based therapies for hepatitis C [7]. Even with recent advances in treatment for this disease, regimens still include peginterferon, administered for 24–48 weeks, based upon viral genotype and viral response [13–16]. During interferon therapy, fatigue is the most common side effect and can lead to early termination of therapy and treatment failure [7,17,18].

Perhaps just as important as capturing the degree of fatigue that occurs during therapy, is whether eradication of HCV ultimately leads to improvement in symptoms. While several studies have evaluated and noted improvements in quality of life (QoL) with successful therapy [18–20], the typical QoL construct can be diffuse, encompassing mental, physical, social, occupational and role functioning, without a detailed analysis of changes in specific symptoms. While the rationale for interferon treatment is usually to prevent long-term complications of hepatitis C, another reason is to improve clinical symptoms and quality of life.

The data from the Viral Resistance to Antiviral Therapy of Hepatitis C (Virahep-C) study offered a unique opportunity to

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evaluate the effect of therapy on fatigue in hepatitis C patients. Virahep-C enrolled 401 African-Americans (AAs) and Caucasian Americans (CAs), with HCV genotype 1 who were treated with peginterferon and ribavirin for up to 48 weeks while undergoing careful and extensive longitudinal evaluation of clinical, biochemical, virologic, immunologic factors, and clinical symptoms [21–24], including fatigue. Fatigue severity was measured using a visual analog scale (VAS), which is easy to administer, understand and not restricted by literacy levels [25,26]. Notably, VASs have been used in multiple clinical contexts to study fatigue, including liver diseases [27–31], and are highly correlated with other validated fatigue measurements [25,28,31,32]. The aim of this study was to assess whether fatigue was associated with disease severity and whether fatigue improved with successful treatment.

Materials and methods

The Virahep-C study design

Virahep-C was a prospective clinical study conducted at 8 U.S. medical centers between 2002 and 2005 in which 196 AAs and 205 CAs patients with chronic hepatitis C, genotype 1, were treated with the standard antiviral regimen of peginterferon alfa-2a (Pegasus, Roche Pharmaceuticals; Nutley, NJ) and ribavirin (Copegus, Roche) while undergoing extensive studies of HCV viral kinetics, immune function, genetics, and interferon signaling pathways [21–24,33]. The major aims of Virahep-C were to define response rates to conventional therapy among AA versus CA patients and investigate factors associated with non-response in the two racial groups. Details of Virahep-C are described elsewhere [21]. All patients provided fully informed written consent and the study design and all details were approved by local Institutional Review Boards.

Patients were evaluated and had blood tests taken twice before therapy (Screening Visits 1 and 2), at treatment weeks 1, 2, 4, 8, 12, 16, 20, 24, 32, 36, 40, 44, and 48, and 4, 12, and 24 weeks after treatment discontinuation. Patients completed symptom questionnaires and were asked about side effects at Screen 2 and at all the treatment and the follow-up weeks. Blood samples were taken for routine liver tests (including serum alanine and aspartate aminotransferase levels: ALT, AST), blood counts and HCV RNA concentrations, which were measured centrally using an assay with a lower limit of sensitivity of 500 IU/ml (COBAS Amplicor Hepatitis C Virus Monitor Test, version 2.0 assay: Roche Molecular Diagnostics, Alameda CA).

Patients who remained HCV RNA positive after 24 weeks of therapy stopped treatment and were considered non-responders (NR) whereas those who were HCV RNA negative at week 24 (responders) continued treatment for a total of 48 weeks. Patients who remained HCV RNA negative for at least 24 weeks after treatment were considered to have a sustained virological response (SVR), while those who had rebound of HCV RNA positivity were considered to have had a relapse (if it occurred after treatment) or breakthrough (if while on treatment). For the current analyses, the major focus was on the responder versus the non-responder populations and especially those who achieved SVR.

Assessment of 'presence' of fatigue ('fatigue presence')

The presence or absence of fatigue was assessed directly by study personnel (usually a research nurse coordinator) asking, "Do you have fatigue?" Patients were asked to respond "Yes" or "No.".

Assessment of 'severity' of fatigue ('fatigue severity')

A VAS for fatigue was administered at each clinic visit (Supplementary Fig. 3). The scales were displayed on a computer screen and patients were asked to touch a point along a 10 cm line between "None" and "Worst ever", the position of which best reflected how much fatigue they had experienced during the previous week. The results were sent directly to the Data Coordinating Center, and study personnel were masked to patient responses. The degree of fatigue was scored from 0 to 100 mm by measuring from the start of the line to the patient mark.

Depression was also measured at each clinic visit using a VAS (Depression VAS). Analyses of depression during Virahep-C have been published [33].

Statistical methods

The prevalence of fatigue at baseline by categorical patient characteristics was summarized using frequency and percent and the associated p values were obtained from univariate logistic regression. Fatigue severity was summarized using median and quartiles. Due to its non-normality, fatigue severity between two groups was compared using Wilcoxon rank-sum test and across multiple groups using Kruskal–Wallis test. Univariate and multivariate logistic regression was used in assessing the association between incidence of fatigue (binary) and patient characteristics. Wilcoxon rank sum test was used in assessing the association between fatigue presence (non-normal) and patient characteristics; signed rank test was used to assess significant changes in fatigue presence between any two time points. All analyses were conducted using SAS 9.3 (SAS Institute Inc., Carey, NC).

Results

Baseline results

At the time of screening, 207 of 401 (52%) study participants reported the presence of fatigue (Table 1). Fatigue was more common among women (59%) than men (48%) ($p = 0.02$). There were no statistically significant differences in the presence of fatigue by age, race, body mass index (BMI), ALT or AST level, viral subtype (1a *vs.* 1b), HCV RNA concentration, or any other baseline variable (Table 1). Liver histology taken within one year before enrollment was available from 399 patients and the presence of fatigue did not vary by inflammatory scores, but was more common in patients with cirrhosis (Ishak fibrosis score 5–6: 66%) than those with minimal (Ishak 0–2: 49%) or moderate fibrosis (Ishak 3–4: 53%) although not statistically significant ($p = 0.25$). Multivariable logistic regression analysis at screening showed that no variables, except gender, have had a significant association with the presence of fatigue.

The severity of fatigue was measured at baseline by the fatigue VAS (n = 390), and the median fatigue VAS score was 25 mm. Of 390, 205 patients (53%) reported having fatigue, of which 181 (88%) patients marked a score of greater than 10 mm on the fatigue severity VAS. Fatigue severity was slightly higher for women than men (median 30 *vs.* 22 mm: $p = 0.056$) (Table 2). Baseline fatigue severity was similar between AA and CA patients, and did not vary consistently by BMI, HCV RNA levels or histological inflammatory scores. Again noted was fatigue severity higher among patients with cirrhosis than in those with minimal or moderate fibrosis (median 34 *vs.* 24 and 25 mm), although not statistically significant ($p = 0.62$). Interestingly, fatigue severity was worse among patients with normal ALT levels (<40 U/L: 37 mm) than in those with mild (40–100 U/L: 25 mm) or moderate-to-high ALT elevations (>100 U/L: 21 mm) ($p = 0.02$). In contrast, fatigue scores did not vary by AST levels. In multivariable analysis at screening, controlling for sex, race, baseline viral level and Ishak score, younger age and lower ALT were associated with more severe fatigue ($p < 0.05$ for both).

To better classify fatigue severity, fatigue VAS scores (n = 390) were grouped into three categories: no or minimal fatigue (0–10 mm: n = 120), mild-to-moderate fatigue (>10–40 mm: n = 115) and severe fatigue (>40–100 mm: n = 155). The clinical, demographic, biochemical and histologic features of patients with these three degrees of fatigue are tabulated in Table 2. Those with cirrhosis had a significantly higher proportion with severe fatigue compared to those with lesser degree of fibrosis (48% *vs.* 38%: $p = 0.005$).

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Table 1. Presence of fatigue at the time of enrollment by selected clinical, virological, and histologic features.

	n	Fatigue (n, %)	*p* value
Total	401	207 (52%)	
Gender:			
Male	261	124 (48%)	0.02*
Female	140	83 (59%)	
Race:			
White	205	113 (55%)	0.15
Black	196	94 (48%)	
Age:			
<40 yr	49	25 (51%)	
>40 yr	352	182 (51%)	0.93
BMI:			
<25	95	46 (48%)	
25-30	149	78 (52%)	0.64
>30	150	77 (51%)	0.86
ALT:			
<40 U/L	68	36 (53%)	
40-100 U/L	220	116 (53%)	0.77
>100 U/L	111	55 (50%)	0.58
AST:			
<30 U/L	58	30 (52%)	
30-100 U/L	283	147 (52%)	0.97
>100 U/L	58	30 (52%)	0.98
HCV genotype:			
1a	210	115 (55%)	
1b	148	73 (49%)	0.98
HCV RNA:			
>400,000	31	18 (58%)	
<400,000	368	188 (51%)	0.46
HAI score:			
1-5	34	17 (50%)	
5-10	163	86 (53%)	0.71
11-18	202	103 (51%)	0.95
Fibrosis:			
0-2	253	125 (49%)	
3-4	117	62 (53%)	0.49
5-6	29	19 (66%)	0.14

*p <0.05.

On treatment results

During treatment, the proportion of patients who admitted to having fatigue increased from 52% at baseline to 78% at week 4 (p <0.0001), and remained at this level for the duration of treatment (range: 67% to 79%) (Fig. 1A). The median fatigue severity score increased during the first 4 weeks of therapy (from 25 to 40 mm, p <0.0001) and remained at this higher level for the duration of treatment (range: 29–43 mm).

Patterns of changes in fatigue severity on treatment were assessed in subgroups of patients during treatment; comparing women *vs.* men (Supplementary Fig. 1), AA *vs.* CA participants (Supplementary Fig. 2). Fatigue severity was greater amongst women than men (p <0.001: Supplementary Fig. 1) and amongst CA compared to AA patients during therapy (p <0.001: Supplementary Fig. 2). In addition, both the frequency and severity of fatigue were greater among participants who ultimately achieved SVR *vs.* NRs (p <0.001: Fig. 2A and B, respectively).

After treatment results

Once therapy terminated, the proportion of patients who admitted to feeling fatigued decreased. By 12 weeks after discontinuation, the proportion of patients with fatigue was lower than that at baseline (36% in responders, 42% non-responders *vs.* 52% at baseline, Fig. 1A). The median fatigue VAS scores were also lower (11 mm in responders, 17 mm in non-responders *vs.* 25 mm at baseline: Fig. 1B).

The improvement in fatigue was greater among patients who achieved an SVR than in those who never became HCV RNA negative (non-responders). Overall, the proportion of SVR patients who admitted to having fatigue decreased from 53% at baseline to 33%, 24 weeks after treatment (p <0.0001; n = 161), and the median VAS fatigue score decreased from 27 mm to 13 mm (p <0.0001; n = 158). These changes were especially profound in patients who at baseline had severe levels of fatigue (fatigue VAS score >40 mm), in whom the median fatigue VAS score decreased from 64 mm at baseline to 21 mm at follow-up week 24 (p <0.0001, n = 66; Fig. 3A). Among non-responders, the presence and severity of fatigue decreased but not significantly between baseline and 24 weeks after treatment regardless of the initial score (p >0.05, Fig. 3B). Furthermore, there was no significant change in fatigue presence or severity among patients who had virologic relapse (n = 60) or breakthrough (n = 21) (data not shown).

As expected, fatigue score was associated with depression, (Spearman correlation coefficients, r_s = 0.53 at baseline; 0.66 at treatment week 24; and 0.73 at follow-up week 24; all p <0.0001). Controlling for the presence of depression did not alter the significance of the changes in fatigue severity after successful completion of therapy compared to baseline (p <0.0001).

Discussion

Fatigue is perhaps the most common symptom among patients with chronic hepatitis C and is a troublesome side effect of its therapy [1,2,4,7,9,34,35]. In this study, half of the patients enrolled in a study of antiviral therapy of HCV admitted that they had some degree of fatigue, of whom two-thirds rated it as moderate or severe. The current literature suggests that the presence and severity of fatigue correlate poorly with disease activity although it may be somewhat more common and severe in patients with cirrhosis [1,9,19,36]. In the current study, the differences in frequency and severity of fatigue in patients with cirrhosis compared to those with lesser degrees of fibrosis were not statistically significant; however, the data were limited by numbers of patients with more advanced disease (n = 29: 7% of the cohort) but it was notable that more cirrhotics had worse fatigue than those with minimal fibrosis.

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Table 2. Median and 75% interquartile range of fatigue VAS scores and their distribution by baseline clinical, virologic, and histologic features.

	n	Fatigue VAS median (Q1, Q3)	*p* value	Fatigue(%)		
				None to mild (VAS 0-10)	Moderate (VAS 10-40)	Severe (VAS 40-100)
Total	390	25 (6, 55)		33	29	38
Gender:						
Male	261	22 (5, 49)	0.06	35	30	35
Female	140	30 (9, 68)		29	26	45
Race:						
White	205	24 (9, 55)	0.48	26	37	37
Black	196	27 (5, 56)		39	20	40
Age (yr):						
<40	49	39 (15, 70)	0.12	22	29	49
>40	352	24 (5, 53)		34	29	37
BMI:						
<25	95	23 (5, 55)	0.85	35	28	37
25-30	149	24 (5, 51)		32	30	39
>30	150	27 (6, 60)		33	27	40
ALT:						
<40 U/L	68	37 (6, 63)	0.02*	31	22	47
40-100 U/L	220	25 (6, 55)		31	27	41
>100 U/L	111	21 (5, 44)		36	36	28
AST:						
<30 U/L	58	28 (3, 60)	0.89	40	17	43
30-100 U/L	283	25 (6, 55)		31	29	39
>100 U/L	58	21 (6, 46)		31	38	31
HCV genotype:						
1a	210	29 (6, 55)	0.4	31	27	42
1b	148	24 (5, 59)		33	30	36
HCV RNA:						
>400,000	368	33 (5, 47)	0.58	33	29	38
<400,000	31	25 (6, 56)		32	23	45
HAI score:						
1-5	34	24 (3, 67)	0.99	44	21	35
5-10	163	26 (8, 55)		31	31	39
11-18	202	25 (6, 55)		32	29	40
Fibrosis:						
0-2	253	24 (4, 54)	0.62	36	26	38
3-4	117	25 (8, 63)		29	32	39
5-6	29	34 (21, 55)		14	38	48

*p <0.05.

As expected, fatigue became more troublesome during interferon therapy [9,14,15,18]. Fatigue worsened during the first 4 weeks of therapy, then plateaued, and did not completely resolve or return to baseline until 12 weeks after stopping therapy. The cause of fatigue induced from interferon therapy is likely multifactorial, but may include the systemic effects of cytokines, secondary effects of treatment-related side effects such as anemia [37–40], as well as the psychosocial stress of having to maintain occupational and family responsibilities while undergoing medical treatment. Thus, although attributing the cause of fatigue to a specific set of genes or proteins is an attractive and parsimonious notion, an interlinked pathway involving multiple genetic, biochemical, and environmental processes is a more realistic probability [41], and an area for future research.

Importantly, the presence and severity of fatigue ultimately declined in patients with sustained clearance of HCV. The results remained consistent even after controlling for depression, a common cofounder of fatigue. These findings indicate that therapy of HCV can result in significant and sustained improvement in clinical symptoms, and that the measurement of fatigue using VASs is successful in capturing these changes. Improvements in fatigue were most convincing in patients with moderate to severe levels of fatigue at baseline. Thus, patients with relatively non-significant biochemical or histologic disease, but who have troublesome symptoms such as fatigue, should be considered for antiviral therapy.

The likely cause for the improvement of fatigue with eradication of HCV is unclear. It is also unclear whether certain aspects of

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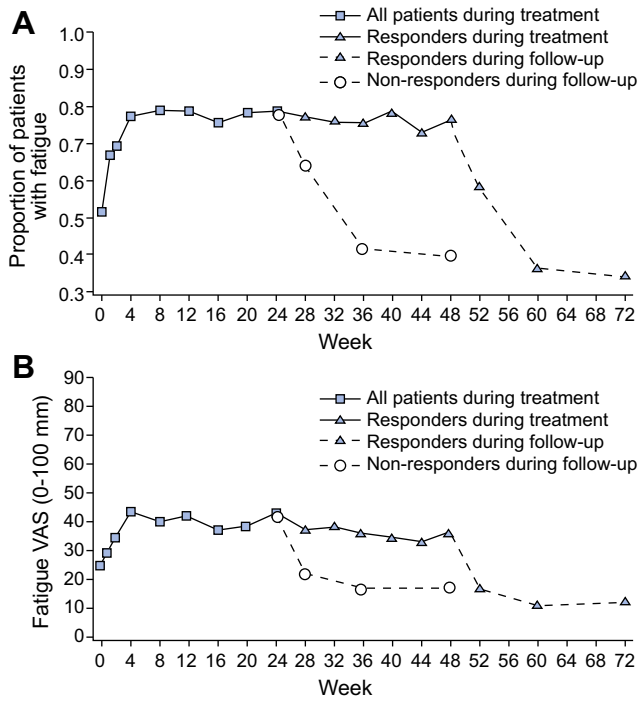

Fig. 1. 'Presence of' and 'severity' of fatigue at baseline, on treatment and follow-up of all patients. (A) Proportion ('yes/no') of patients with fatigue and (B) the severity of fatigue (VAS), at baseline, on treatment and follow-up. Each point marks the week of patient evaluation and fatigue measurement: at screening visit 2, treatment weeks 1, 2, 4, 8, 12, 16, 20, 24, 32, 36, 40, 44 and 48 (until week 24 for non-responders), and at follow-up at 4, 12 and 24 weeks after treatment discontinuation.

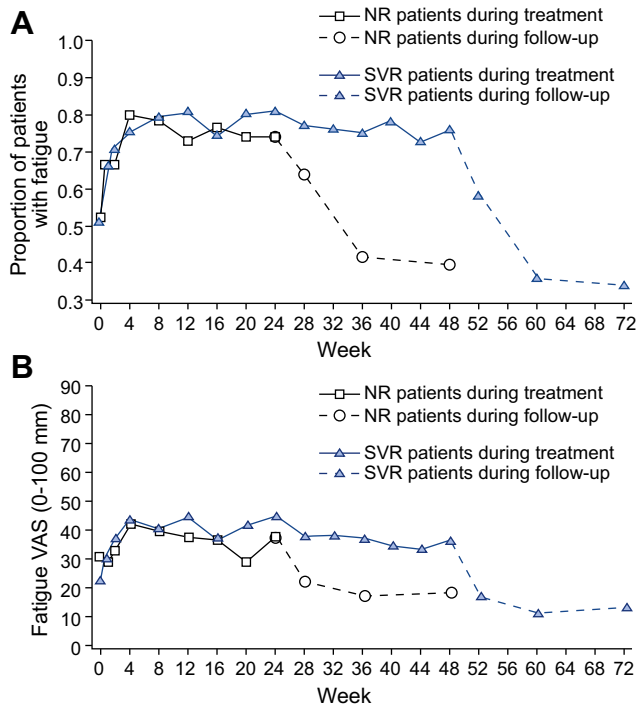

Fig. 2. 'Presence of' and 'severity' of fatigue at baseline, on treatment and follow-up amongst those achieving SVR versus NR. (A) Proportion of patients with fatigue and (B) severity of fatigue among those who achieved sustained virologic response (SVR) versus non-responders (NR).

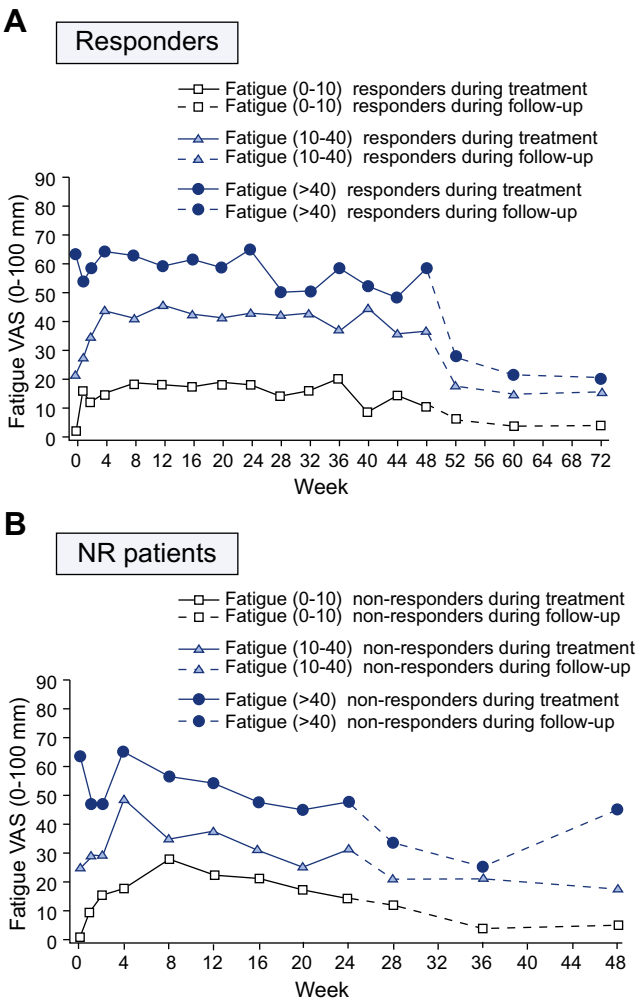

Fig. 3. Severity of fatigue categorized by baseline fatigue status in responders and non-responders (NR). Severity of fatigue by baseline fatigue status in (A) responders and (B) NR patients.

fatigue (i.e., physical, mental or cognitive) fare better, as the VAS is a quantitative measure rather than a qualitative one. While patient awareness of virological response could have a beneficial psychological effect on perceptions of fatigue, fatigue assessments were obtained before the results of virological testing were known, and improvements in fatigue were achieved well before knowledge of SVR was given to patients.

A few limitations of this study should be noted. The cohort tested was a relatively biased sample of patients with HCV infection, as these subjects all had genotype 1 and all were sufficiently motivated to undergo a rigorous, prolonged medical therapy with notable adverse side effects. Another caveat to consider is that the improvements in fatigue scores were observed predominantly among patients who had moderate or severe levels of fatigue before treatment, and there was little or no improvement in patients who initially reported minimal fatigue. Such findings suggest that there is little room for improvement in fatigue among those with lower levels at baseline, or that the VAS is not sensitive enough to detect minor improvements.

In conclusion, use of a simple fatigue VAS demonstrated that at least half of the patients with chronic hepatitis C who participated

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in a clinical trial had complaints of fatigue at baseline, however, fatigue significantly improved in those who achieved viral eradication. Further analyses of the quality of fatigue in chronic liver disease, as well as the biologic and psychosocial pathways associated with this subjective symptom are needed to improve management of chronic liver disease and assessment of the benefits of antiviral therapy, whether curative or ameliorative in nature.

Conflict of interest

D.M.E. had grant funding from Roche/Genentech and served as advisor for Vertex in the last 12 months. The other authors have no conflicts of interest to report.

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Supplementary data

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