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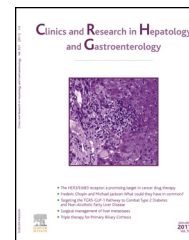
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ORIGINAL ARTICLE

Effects of preventive versus ‘on-demand’ nutritional support on paid labour productivity, physical exercise and performance status during PEG-interferon-containing treatment for hepatitis C[☆]



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Summary

Background and objective: Deterioration of nutritional status during PEG-interferon containing therapy for chronic hepatitis C can be ameliorated by preventive nutritional support. We aimed to explore whether such support also affects paid labour productivity, physical exercise and performance status.

[☆] This study was registered at ClinicalTrials.gov (identifier NCT00841243).

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Abbreviations: CHC, Chronic hepatitis C; PEG, Pegylated; SVR, Sustained virological response; RCT, Randomized controlled trial; HCV, Hepatitis C virus; KPS, Karnofsky performance status.

Methods: In this prospective randomized controlled trial (J Hepatol 2012;57:1069–75), 53 patients with chronic hepatitis C had been allocated to “on demand” support ($n=26$: nutritional intervention if weight loss $>5\%$) or preventive support ($n=27$: regular dietary advice plus energy- and protein-rich evening snack) during PEG-interferon-containing therapy. Paid labour productivity, physical exercise and performance status were evaluated at baseline, after 24 and (if applicable) after 48 weeks of treatment.

Results: At baseline, 46% of patients performed paid labour and 62% performed some kind of physical exercise. Furthermore, most patients were able to carry out normal activity with only minor symptoms of disease (mean Karnofsky performance score: 94). Decreases of paid labour productivity (-21% vs. -70% , $P=0.003$), physical exercise activity (-43% vs. -87% , $P=0.005$) and Karnofsky performance scores (-12% vs. -24% , $P<0.001$) were less in the preventive than in “on demand” group after 24 weeks of treatment. Effects of preventive nutritional support were even more pronounced after 48 weeks.

Conclusions: Preventive nutritional support markedly ameliorates decreases of paid labour productivity, physical exercise and performance status during PEG-interferon-containing treatment for chronic hepatitis C.

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Introduction

Chronic hepatitis C (CHC) is a leading cause of liver cirrhosis worldwide. Antiviral therapy for CHC has changed strongly over the past few decades and is nowadays highly effective. Until 2012, combined pegylated (PEG)-interferon plus ribavirin was the standard of care for CHC and resulted in a sustained virological response (SVR) in 40–90% of treatment-naïve patients [1–4]. Nevertheless, interferon containing antiviral therapy is associated with significant side effects, which may affect paid labour productivity, physical exercise activity and performance status.

Significant weight loss during interferon-containing antiviral therapy often occurs because of decreased appetite due to fatigue, fever, nausea, depression or taste changes during antiviral treatment [5]. Furthermore, interferon- α -based therapy delays gastric emptying, which could lead to upper abdominal discomfort and less appetite [6]. Average weight loss during treatment is reported to be approximately 7% of basal weight [5,7,8]. Weight loss may be even more pronounced with triple therapy containing protease inhibitors [9]. Severe weight loss during antiviral therapy is accompanied by a catabolic state and protein–energy malnutrition, which is also a frequent phenomenon in advanced hepatic disease [10]. A late-evening protein-rich nutritional supplement induces an anabolic state in patients with advanced liver disease [11]. In a recently published randomized controlled trial (RCT) [7], we found that preventive nutritional advice plus an energy- and protein-rich evening snack before bedtime also prevents deterioration of nutritional status of patients during PEG-interferon-containing antiviral treatment for CHC, with improved digestive symptoms and quality of life. Of note, such nutritional support also prevents catabolic state, as indicated by preserved handgrip strength according to Jamar [12–14], pinch grip strength and other parameters of nutritional state [7].

In previous studies, presence of CHC was associated with less work productivity and more absenteeism [15]. These findings were even more pronounced during PEG-interferon-containing therapy [16–19].

In the current study, we examine the effects of preventive versus “on-demand” nutritional advice plus supplementation on paid labour productivity, physical exercise and performance status during PEG-interferon-containing treatment for CHC.

Patients and methods

Patient and clinical characteristics

In a previously published RCT performed in the period 2008–2010, we evaluated potential beneficial effects of preventive nutritional support during PEG-interferon-containing antiviral treatment for CHC on nutritional state and quality of life [7]. Nevertheless, no data on paid labour productivity, physical exercise or performance status have been included in this previous publication. We therefore analyzed data on effects of preventive nutritional support on paid labour activity, physical exercise and performance status. These data had been prospectively collected and were all available in the database of this RCT. In total, 53 patients tested positive for serum hepatitis C virus (HCV)-antibodies and HCV RNA during at least 6 months and with an indication for antiviral treatment [20–22] were randomized for the “on demand” group ($n=27$) or the preventive group ($n=26$). Both groups received PEG-interferon alfa-2b 1.5 $\mu\text{g/kg/week}$ subcutaneously and oral ribavirin for 24 or 48 weeks depending on genotype and viral load. Ribavirin dose was 800, 1000, 1200, and 1400 mg/day for body weight <65 kg, 65–75 kg, 76–105 kg, and >105 kg, respectively. Duration of antiviral therapy was 29 ± 14 weeks in the “on demand” and 32 ± 12 weeks in the preventive group ($P=0.268$). Average PEG-interferon α -2b dosage (1.55 ± 0.23

and $1.41 \pm 0.3 \mu\text{g/kg/week}$) and ribavirin dosage (13.9 ± 1.6 and $14.5 \pm 2.1 \text{ mg/kg/day}$) did not differ between both groups [7]. In the preventive group, patients received dietary advice from a specialized nutritionist during their regular visits as well as an energy- and protein-rich evening snack to be taken daily before bedtime. Dietary advice included frequent energy and protein enriched meals with a high ratio of protein versus carbohydrates during the day. The prescribed Nutridrink protein® (Nutricia, Zoetermeer, The Netherlands) contains 20 g protein, 300 kcal and 25% of the advised daily amounts of all other essential nutrients. Only in case of significant ($>5\%$ of baseline) weight loss, patients in the “on demand” group received dietary advice and supplementation. The study was conducted according to recommendations of Good Clinical Practice and the Declaration of Helsinki. Written informed consent was provided by all patients and the protocol was approved by the medical ethical committees of all participating centres. This study was registered at ClinicalTrials.gov (identifier NCT00841243).

Paid labour productivity

For the assessment of paid labour productivity, we asked the patients to provide us with their productivity status at baseline and at the endpoint of 24 weeks and, if applicable, 48 weeks of treatment. Paid labour productivity was defined as paid full time or part time white collar (physically inactive) labour, blue collar (physically active) labour or none. Loss of paid labour productivity was based on percentage of baseline productivity at 24 weeks and, if applicable, 48 weeks of treatment, in only those patients who had any kind of paid labour productivity at baseline and separately for the total group (those with as well as those without paid labour activity at baseline). In addition, unpaid household activities were assessed in all patients without paid labour productivity at baseline.

Physical exercise

For the assessment of physical exercise (outside paid labour working hours), we asked the patients to provide us with their weekly physical exercise activity at baseline and at the endpoint of 24 weeks and, if applicable, 48 weeks of treatment. Patients were divided into the following subgroups according to their physical exercise activity per week:

- none;
- 60 to 150 minutes of low intensity exercise;
- >150 minutes of low intensity exercise;
- 60 to 150 minutes of high intensity exercise;
- >150 minutes of high intensity exercise.

Low intensity exercise was defined as walking and leisure cycling. High intensity exercise was defined as strength training, running and intense cycling. Loss of physical exercise was defined as percentage of baseline physical exercise activity at 24 weeks and, if applicable, 48 weeks of treatment, in only those patients with any level of physical activity at baseline and separately for the total group.

Performance status

The Karnofsky performance status (KPS) scale, which ranges from 0–100, was used to evaluate performance status outcomes of patients at baseline, at 24 weeks and, if applicable, 48 weeks of antiviral treatment [23].

Statistical analysis

Continuous data are given as means and standard deviations (SD) or, in case of a non-parametric distribution, as medians and ranges, and discrete variables as absolute and relative frequencies. Differences between the “on demand” and preventive groups were tested for statistical significance by independent *t*-test, Mann–Whitney *U*-test or Pearson χ^2 test, as appropriate. Pair-samples *t*-test was used to compare differences between time points in the same group. A two-sided *P*-value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 21.0 for Windows.

Results

Patient and clinical characteristics

Baseline characteristics of all 53 patients who were randomized for the “on demand” group ($n=27$) or the preventive group ($n=26$), and separately for those who reached the primary endpoint of 24 weeks of antiviral treatment ($n=22$ in both groups) are given in Table 1. Mean age was 49 years and majority of patients was male (72%). Furthermore, 87% of patients were treatment-naïve and half of patients (53%) had only mild liver disease (F0–2). In the patients who were treated for at least 24 weeks ($n=22$ in both groups), there were no significant differences in baseline host or viral characteristics between both treatment arms, except a higher proportion of co-morbidity in the preventive group (Table 1).

Effects of preventive nutritional support during antiviral treatment on paid labour productivity

At baseline, paid labour was performed by 24 of the 53 patients (46%): 15% performed full time white collar labour, 19% full time blue collar labour, 6% part time white collar labour and 6% part time blue collar labour. There were no significant differences in paid labour productivity between the “on demand” and preventive groups (Table 1). Of the patients without paid labour productivity at baseline ($n=29$), 13 patients (45%) performed unpaid household activities.

Data on paid labour productivity during antiviral therapy are given in Fig. 1A and B. After 24 weeks of treatment, paid labour productivity decreased in both groups, but loss of paid labour productivity was significantly larger in the “on demand” group (-70%) than in the preventive group (-21%) ($P=0.003$) (Fig. 1A and B), based on only those patients with any paid labour at baseline ($n=22$). After 48 weeks of treatment this difference was even greater: -89% in the “on demand” group vs. -17% in the preventive group ($P=0.023$) (Fig. 1A and 1B). When the total group ($n=44$) was taken

Table 1 Baseline characteristics of 53 chronic hepatitis C patients and separately for the patients with “on demand” nutritional support ($n = 22$) or preventive nutritional support ($n = 22$) who continued antiviral therapy during at least 24 weeks.

	All patients ($n = 53$)	“On demand” group ($n = 22$)	Preventive group ($n = 22$)	P -value ^b
Age (years), mean (SD)	49 ± 11	51 ± 9	45 ± 11	0.063
Male sex, n (%)	38 (72)	15 (68)	17 (77)	0.498
Weight (kg), median (range)	80 (46–105)	78 (69–83)	79 (69–81)	0.841
BMI (kg/m ²), mean (SD)	25.9 ± 4.0	25.5 ± 4.3	24.9 ± 3.4	0.751
HCV genotype, n (%)				0.365
1 or 4	30 (57)	10 (45)	13 (59)	
Other	23 (43)	12 (55)	9 (41)	
Naïve, n (%)	46 (87)	20 (91)	19 (86)	0.635
Liver disease, n (%)				0.761
F0–2	28 (53)	12 (55)	13 (59)	
F3–4	24 (45)	10 (45)	9 (41)	
Missing data	1 (2)	0 (0)	0 (0)	
Co-morbidity, n (%)	20 (38)	4 (18)	11 (50)	0.026
Cause of disease, n (%)				0.082
IV drug use	13 (25)	8 (36)	3 (14)	
Other	40 (75)	14 (64)	19 (86)	
Baseline viremia, n (%)				0.353
Low viral load (< 400,000 IU/mL)	25 (47)	12 (55)	15 (68)	
High viral load (> 400,000 IU/mL)	28 (53)	10 (45)	7 (32)	
Routine blood tests, median (range)				
AST (U/L)	54 (13–241)	54 (48–105)	70 (52–95)	0.808
ALT (U/L)	86 (29–417)	106 (81–169)	84 (74–127)	0.552
Alkaline phosphatase (U/L)	81 (25–156)	86 (73–94)	77 (68–97)	0.974
Albumin (g/L)	41.2 (30.7–48.0)	41.2 (39.1–42.7)	40.5 (38.7–42.2)	0.715
γ GT (U/L)	43 (15–371)	38 (30–76)	53 (29–127)	0.742
Bilirubin (μ mol/L)	16 (4–29)	14 (13–19)	16 (13–21)	0.783
INR	1.02 (0.95–1.48)	1.02 (1.01–1.08)	1.04 (1.02–1.17)	0.359
PTT (s)	13.7 (9.9–17.9)	13.7 (12.7–14.1)	13.7 (12.5–14.6)	0.977
Creatinine (μ mol/L)	75 (41–106)	72 (65–76)	75 (62–84)	0.172
Haemoglobin (mmol/L)	9.1 (7.4–10.6)	8.9 (8.5–9.4)	9.3 (9.0–9.8)	0.307
TSH (mIU/L)	1.2 (0.6–3.9)	1.1 (1.1–2.1)	1.6 (1.2–2.3)	0.759
Thrombocytes ($\times 10^9$ /L)	200 (43–371)	206 (179–236)	212 (170–257)	0.867
Paid labour productivity, n (%)				0.579
None	29 (54)	11 (50)	11 (50)	
Full time white collar	8 (15)	3 (14)	4 (18)	
Full time blue collar	10 (19)	6 (27)	4 (18)	
Part time white collar	3 (6)	0 (0)	2 (9)	
Part time blue collar	3 (6)	2 (9)	1 (5)	
Unpaid household activities ^a , n (%)	$n = 29$	$n = 11$	$n = 11$	0.193
Yes	13 (45)	6 (55)	3 (27)	
None	16 (55)	5 (45)	8 (73)	
Physical exercise, n (%)				0.953
None	20 (38)	6 (27)	8 (36)	
Low intensity, 60–150 min/week	5 (9)	2 (9)	2 (9)	
Low intensity, >150 min/week	16 (30)	7 (32)	7 (32)	
High intensity, 60–150 min/week	2 (4)	1 (5)	1 (5)	
High intensity, > 150 min/week	10 (19)	6 (27)	4 (18)	
KPS score, mean (SD)	94 (9)	94 (10)	94 (8)	0.913

Data are presented as n (%), mean ± SD and/or median (range). All routine blood tests are presented as median (range); KPS: Karnofsky performance status.

^a In only those patients without paid labour productivity at baseline ($n = 29$).

^b P -value applies to differences between the “on demand” and preventive groups.

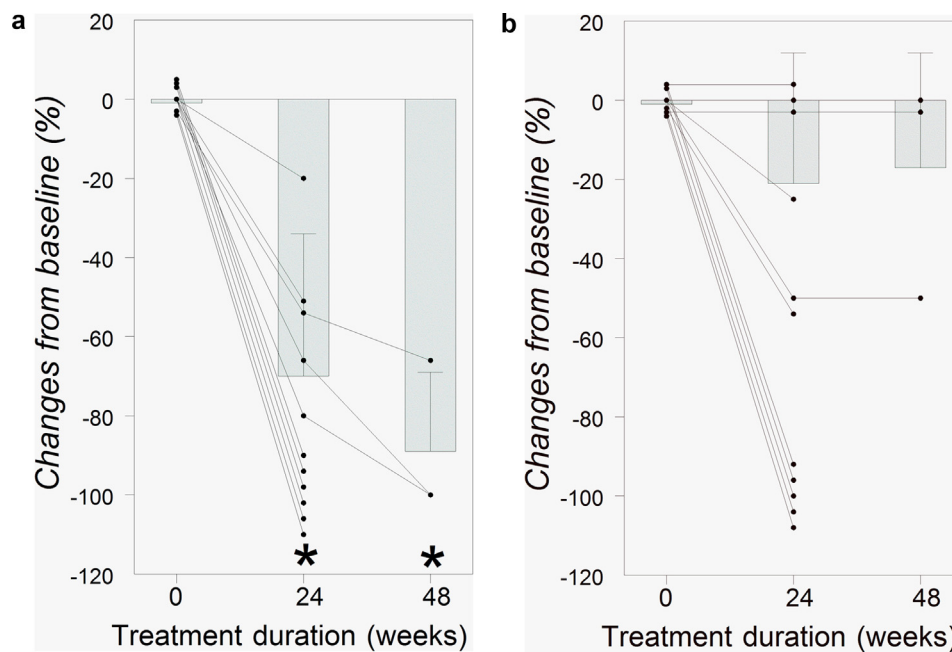


Figure 1 Paid labour productivity as percentage of baseline in patients with chronic hepatitis C with “on demand” nutritional support (a) or preventive nutritional support (b) at 24 and (if applicable) 48 weeks of antiviral treatment ($n=11$ in both groups, only patients with any paid labour activity at baseline included). Preventive nutritional support significantly decreases loss of paid labour activity. *Indicates significant decrease from baseline in the same group. Dots indicate individual patients connected with lines, bars indicate means with standard deviations. For clarity, some individual points at baseline are depicted slightly above or below zero and error bars positioned upward.

into account regardless of paid labour productivity at baseline, mean paid labour productivity changed with -35% vs. -6% after 24 weeks of treatment ($P=0.018$) and with -8% vs. 0% after 48 weeks of treatment in the “on demand” and preventive groups, respectively ($P=0.079$).

Of the six patients with only unpaid household activities at baseline in the “on demand” group, only one continued performing unpaid household activities during the first 24 weeks of treatment. After 48 weeks, all three patients in the “on demand” group stopped performing unpaid household activities. In contrast, in the preventive group, two of the three patients with only unpaid household activities at baseline continued performing unpaid household activities and the third patient even had started full time white collar paid labour during the first 24 weeks of treatment. After 48 weeks two of these patients still performed part time white collar labour or unpaid household activities, respectively.

Effects of preventive nutritional support during antiviral treatment on physical exercise

At baseline, many patients (38%) performed no physical exercise at all, 9% had 60 to 150 minutes of low intensity exercise per week, 30% had > 150 minutes of low intensity exercise per week, 4% had 60 to 150 minutes of high intensity exercise per week and 19% had > 150 minutes of high intensity exercise per week (Table 1). In patients who received at least 24 weeks of treatment no significant differences in baseline physical exercise activity were found between the “on demand” and preventive groups (Table 1). Degree of

physical exercise decreased after 24 and 48 weeks of treatment in both groups. Nevertheless, in the preventive group, this reduction was significantly smaller than in the “on demand” group. At 24 weeks of antiviral therapy, physical exercise had decreased with 87% in the “on demand” group and with 43% in the preventive group ($P=0.005$) (Fig. 2A and B). In the subgroup of patients with 48 weeks of therapy, decrease of physical exercise at 48 weeks was 90% in the “on demand” group and 0% in the preventive group ($P=0.027$) (Fig. 2A and B). These decreases were calculated based on only those patients with any physical exercise activity at baseline ($n=30$). When the total group ($n=44$) was taken into account regardless of physical activity at baseline, physical exercise was decreased with 64% and 25% at 24 weeks of treatment ($P=0.001$) and with 64% and 9% at 48 weeks of treatment ($P=0.090$) in the “on demand” and preventive groups, respectively.

Effects of preventive nutritional support during antiviral treatment on performance status

At baseline, there were no significant differences in performance status between patients in those “on demand” and preventive groups who received at least 24 weeks of treatment. Mean KPS score was 94 ± 10 in the “on demand” group and 94 ± 8 in the preventive group, indicating that most patients were able to carry out normal activity with only minor symptoms of disease (Table 1). After 24 weeks of treatment, performance status decreased in both groups, but this decrease was significantly higher in the “on demand group” (-24%) than in the preventive group

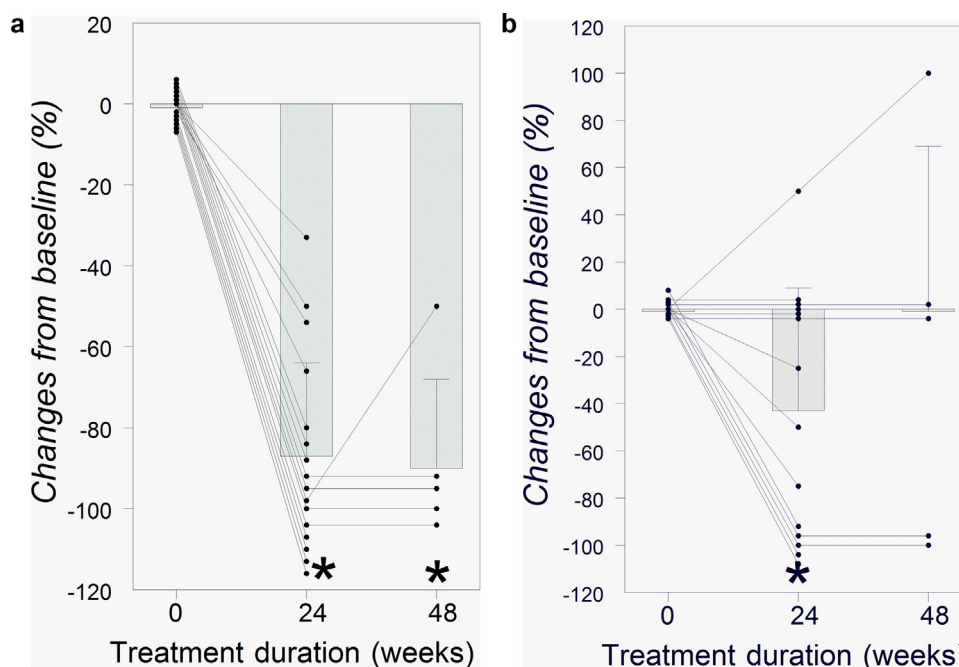


Figure 2 Physical exercise as percentage of baseline in patients with chronic hepatitis C with “on demand” nutritional support (a) or preventive nutritional support (b) at 24 and (if applicable) 48 weeks of antiviral treatment ($n=16$ and 14 “on demand” and preventive groups, only patients with any physical activity at baseline included). Preventive nutritional support significantly decreases loss of physical activity. *Indicates significant decrease from baseline in the same group. Dots indicate individual patients connected with lines, bars indicate means with standard deviations. For clarity, some individual points at baseline are depicted slightly above or below zero and error bars positioned upward.

(-12%) ($P < 0.001$). Similar results were found after 48 weeks of treatment (decrease of 28% in the “on demand” group and of 15% in the preventive group, $P = 0.017$).

Discussion

Presence of CHC is associated with significant impact on paid labour productivity, physical exercise and performance status with further deterioration during PEG-interferon-containing therapy, as underscored in the current work. A major finding of our study is that preventive nutritional advice plus supplementation decreases such loss of paid labour productivity, physical exercise activity and performance status during antiviral therapy for CHC. Interestingly, another study previously reported that acetyl-L-carnitine supplementation during PEG-interferon-containing anti-CHC therapy decreases fatigue and increases quality of life [24]. Recently, it was suggested that acetyl-L-carnitine supplementation also reduces loss of work productivity during anti-CHC therapy [25].

Several studies have investigated the impact of CHC infection on work impairment in a large number of participants [15,19,26–30]. Similar to our findings, proportion of CHC patients being unemployed in absence of antiviral therapy was high in these studies (range: 7–74%). Furthermore, CHC-infected workers reported higher levels of overall work impairment than controls [15,19,26–30]. Other studies evaluated the effect of anti-CHC therapy on work impairment. In line with our results, work productivity decreased strongly in patients receiving interferon-containing antiviral therapy.

During anti-CHC treatment, patients reported more absence days and lower productivity compared to baseline or untreated CHC patients [15–17,31,32]. For example, Aggarwal et al. reported a mean increase in number of absence days of 3 days compared to baseline during the previous month after 12 weeks of anti-CHC therapy. Furthermore more than 50% of patients reported decreased productivity [17]. Brook et al. [16] reported lower numbers: CHC-employees who received antiviral treatment had 0.52 more health-related work absence days than non-treated CHC-employees, missing an average of 1.27 workdays monthly. Furthermore, treated CHC employees had 12% fewer units processed per hour worked than those without treatment, but this difference was not statistically significant [16]. On the other hand, reaching SVR resulted in improvement of paid labour productivity with less absenteeism than in non-responders [15,31,33]. Previous studies also demonstrated that CHC-patients in general perform less physical exercise than non-CHC subjects [28,30]. In our study, proportion of patients who performed no physical exercise at baseline was 38%. During antiviral therapy, physical exercise and Karnofsky performance status decreased strongly in patients without preventive nutritional support. These findings are in line with other studies reporting a decrease in the physical component score of the SF-36 quality of life questionnaire during interferon-containing treatment for CHC [31,32].

In general, productivity is defined as an overall measure of the ratio of the volume of output to the volume of inputs (i.e. units of work processed per hour). Measurement of labour input can therefore be seen as a rough estimation of labour productivity. The true productivity depends on

multiple factors [34]. Moreover, similar to the current study, most studies regarding impact of CHC infection and antiviral therapy on work impairment used patient reported instead of objective measures, which may introduce measurement error and bias [15].

Results of the current study were validated in a retrospective group of 111 CHC patients under care in our hospital in the period 2011–2014. In line with findings of the current study, only half of patients performed paid labour at baseline. Furthermore, there was also a strong decrease in paid labour productivity after 24 and 48 weeks of PEG-interferon-containing antiviral therapy (–51% and –57%, respectively). Most patients in this group performed physical exercise at baseline. However, there was a dramatic decrease in physical exercise: proportion of patients without any physical exercise increased from 14% at baseline to 54% and 77% after 24 and 48 weeks of treatment, respectively. Although percentages slightly differ between this group and the current study, decreases in paid labour productivity and physical exercise during antiviral therapy are large.

The potential underlying mechanisms for the beneficial effects of nutritional support during antiviral therapy on paid labour productivity, physical exercise and performance status may be an improved nutritional state and higher quality of life, as demonstrated previously [7]. In the “on demand” group of our RCT, there was a trend towards a higher loss of paid labour productivity after 24 weeks of treatment in those patients who performed blue collar labour at baseline than in those with white collar labour (data not shown).

Preventive nutritional support during antiviral therapy and its beneficial effect on paid labour productivity may theoretically be cost-effective. According to the current study, nutritional advice and supplementation during antiviral treatment may reduce costs due to loss of paid labour productivity with 49%. Based on an average income of 28,400 euro in 2010 in The Netherlands (data from Central Bureau of Statistics), nutritional advice and support would lead to a reduction in costs due to loss of paid labour productivity of 6436 euro per patient per 24 weeks of treatment. On the other hand, in the Netherlands total costs for preventive nutritional advice plus evening supplementation during 24 weeks of antiviral therapy are only approximately 660 euro per patient.

Paid labour status is influenced by multiple factors, such as patient preference, co-morbidity and age. Indeed, patients with CHC may have several comorbidities that limit ability to work. For example, IV drug use is a common mode of transmission of CHC and is associated with psychiatric conditions [35]. Furthermore, in the current study, two patients had haemophilia and these patients may be restricted by joint problems to perform blue collar labour. Only one patient in the “on demand” group and none in the preventive group was ≥ 65 years of age and did not have paid labour at baseline.

Recently, several new generation direct-acting antivirals (DAAs) have been approved. Therefore, interferon-free treatment strategies for CHC are nowadays possible, which are more effective and better tolerated [36–39]. As a result, the role of interferon-containing therapy in CHC treatment will be limited in the future. However, in specific geographical regions, such as developing countries and other

economically deprived regions, interferon-containing antiviral therapy may still be a reasonable option due to excessive costs of the new DAAs [39]. Furthermore, results of the new treatment regimens in genotype 3-infected patients have been suboptimal [40].

According to a recent publication [41], work productivity may be less affected by dual therapy with sofosbuvir and ribavirin than with triple therapy with sofosbuvir, ribavirin and PEG-interferon. Nevertheless, proportion of patients with paid labour did not decrease during treatment in either group. Impairment in work productivity disappeared within 12 weeks after end of treatment, but recovery took longer in patients who received interferon-containing therapy [41]. Based on analyses of four phase 3 clinical trials of sofosbuvir, the new interferon-free treatment regimens lead to only a minor decrease in health-related quality of life, including the physical component score [42].

Our study has several strengths and limitations. Most important, this study revealed the significant impact of preventive nutritional advice and support on paid labour productivity, physical exercise activity and performance status during PEG-interferon-containing antiviral therapy for CHC, which was not well appreciated in the past. Data was prospectively collected and patients were randomly assigned to the preventive vs. “on demand” groups. On the other hand, as mentioned above, data on paid labour status, physical exercise and performance status relied on patient-reported measures. Finally, dietary advice combined with dietary supplementation is more effective in enhancing short-term weight gain and in preventing deterioration of the nutritional status than dietary advice alone [43]. Since our preventive group received both, it cannot be concluded from our data, which component was responsible for the beneficial effects.

In conclusion, preventive nutritional advice and support decreases loss of paid labour productivity, physical exercise and performance status during PEG-interferon-containing treatment for CHC.

Disclosure of interest

On behalf of all authors, I declare that we have the following potential conflicts of interest:

EJH, SvM, PDS, CMJvN: declare that they have no conflicts of interest concerning this article.

BvH: advisory board of Abbvie, Bristol-Myers Squibb, Janssen.

HvS: advisory board Bristol-Myers Squibb, Gilead, Abbvie, Janssen, Merck Sharp and Dohme.

JEA: Advisory board Janssen, Merck Sharp and Dohme, Abbvie, ViiV, Bristol-Myers Squibb, Gilead: Speakers Bureau Gilead.

KJvE.: advisory board of Bristol-Myers Squibb, Gilead, Abbvie.

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