Is physical activity possible and beneficial for patients with hepatitis C receiving pegylated interferon and ribavirin therapy?

L’activité physique est-elle possible et bénéfique chez les malades atteints d’hépatite chronique virale C traités par interféron pégylé et ribavirine

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Summary The great majority of patients with chronic viral hepatitis C are treated with pegylated interferon-ribavirin therapy. The aim of this study was to demonstrate that these patients were able to have some form of physical exercise, and that this activity can lead to an improvement in their quality-of-life. Twelve volunteer patients with hepatitis C, who were either sedentary or had become sedentary and who had been treated by combination therapy for the past few weeks, were recruited at hepatology clinics in the Midi-Pyrénées region of France early in 2006. All patients attended a sports medicine consultation for an initial evaluation: maximal aerobic power and maximal oxygen consumption tests, maximum heart rate (MHR), search for contraindications for participation in the proposed program of physical exercise. The patients were given a heart rate monitor so they could measure their heart rate during physical exercise and check that they exercised under safe conditions and remained within the so-called ‘’endurance’’ zone. The patients came to a sports facility daily for 5 days for the exercise program. The activities were divided into four sessions each day: an individual physical exercise selected by the patient, team physical exercise, recreational physical exercise, lectures on the different types of hepatitis and their treatment, on nutrition and on sports medicine assessments. Data on hepatitis, results of the cardiorespiratory examination and personal history and record of past physical activity were collected for each patient. Quality-of-life (SF36) was assessed at enrolment in the study and one month after the training sessions. At the initial

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Introduction

The announcement of hepatitis C virus (HCV) infection has a profound effect on patients who associate the disease with diminished physical capacity, leading to a loss of self-confidence [1]. A study conducted by the SOS hepatitis association entitled “Living with viral hepatitis” demonstrated that 64% of patients believe HCV infection is fatal; 50% have difficulty accepting their disease. Two-thirds of the patients reported that the disease affected their occupational, familial, relational and sexual lives, with 82% fearing they could not tolerate the antiviral treatment [2]. When compared with other populations affected by a chronic disease, patients with chronic hepatitis feel their physical and psychic capacities are significantly diminished [3–5]. This decline in quality-of-life is observed at the announcement of the diagnosis [6] and is more related to comorbid conditions and knowledge of the diagnosis than with transaminase level, viremia, genotype or degree of fibrosis, excepting cases of complicated cirrhosis [7–9]. Pegylated interferon plus ribavirin, the gold standard treatment of HCV infection, is poorly perceived by patients and healthcare professionals (general practitioners, non-hospital nurses) because it is a long with many adverse effects [10–14]. Problems in coping with the treatment are sometimes incriminated as the cause of dose reduction or poor observance, known to be prognostic factors of treatment efficacy [15,16]. Observance is not a natural human behavior [17]. Hepatologists consider that more than 95% of patients comply with pre-
scriptions, but information gathered from discussion groups and phone-in services reveals that patients readily adapt their treatments, lowering doses [18]. Achievement of virological response with a second treatment similar to a first treatment associated with non-response is an illustration of the impact of observance on treatment efficacy [19]. In order to improve patient quality-of-life and compliance with treatment, the 2002 consensus workshop recommended the development of units for patient education and treatment management [3,20—24]. The beneficial effect of physical exercise has been demonstrated in diverse pathological conditions [25—36], particularly after myocardial infarction [37].

The purpose of this pilot study was to evaluate the effectiveness of a 5-day physical activity program designed for patients with HCV infection taking pegylated interferon plus ribavirin for 12 weeks and to determine whether this intervention can improve quality-of-life as assessed by SF36 (Short Form 36 Health Survey Questionnaire) [38].

Patients and methods

Patient selection and inclusion criteria

Practitioners in hepatology clinics in the Midi-Pyrénées region of southern France recruited participants among their patients with HCV infection. During routine visits, participation in the study was proposed to patients aged 30 to 55 years taking a first treatment with pegylated interferon plus ribavirin for at least 12 weeks. Depending on the genotype, anti-HCV treatments were scheduled for 48 weeks. Volunteers capable of participating in individual or team sports, even if they had been sedentary for several months, were included sequentially. The participants were invited to attend a free consultation at the sports medicine center in order to ensure the absence of any contraindication for physical exercise and sports activities (see below). Using tests designed for persons wanting to resume or continue their physical activity, the sports medicine physicians determined the aptitude of the patients to participate in the proposed physical activity program and established an individualized program to renew or develop the patient’s physical activities. Exclusion criteria were: legal safeguard status, decompensated cirrhosis or beta-blocker treatment, treatment associated with non-response is an illustration of any contraindication for physical exercise and sports activities (see below). Using tests designed for persons wanting to resume or continue their physical activity, the sports medicine physicians determined the aptitude of the patients to participate in the proposed physical activity program and established an individualized program to renew or develop the patient’s physical activities. Exclusion criteria were: legal safeguard status, decompensated cirrhosis or beta-blocker treatment, treatment associated with non-response.

Baseline evaluation

Before inclusion in the study, the patients were seen by a sports medicine specialist who determined their aptitude for physical exercise. History taking and physical examination were conducted using a validated questionnaire [39]. The purpose of this visit was to detect any condition which might affect, limit, or contraindicate a specific type of physical activity. Patients performed a cardiorespiratory exercise test with measurement of gas exchanges in order to obtain an overall assessment of their tolerance to muscular exercise and evaluate their endurance capacity. Maximum oxygen uptake (\(V_{O2,max}\)) was determined. The protocol for muscle exercise tests proposed by the French Societies of Sports Medicine and Pneumology was applied. Briefly, after setting the position of the ergometric bicycle and installing the monitoring equipment (12-lead and CM5 ECG) the patient performed a 3-minute warm-up at 30% theoretical \(V_{O2}\) and corresponding maximal aerobic power. Exercises were then performed with an increment load of 20% theoretical maximal aerobic power every two minutes until reaching \(V_{O2,max}\) and the corresponding maximal aerobic power. The notion of symptom-limited \(V_{O2,sl}\) was used when a peak \(V_{O2}\) was measured but was sustained insufficiently to retain the qualification of \(V_{O2,max}\). Beyond \(V_{O2,max}\) or \(V_{O2,sl}\), the patients continued for a 3-minute period of active recovery at 30% maximal aerobic power followed by two minutes of passive recovery. Exercise load to heart rate ratio was noted during the test.

Spirometry was performed before and after exercise in order to measure variations in airflow, and particularly to search for exercise-induced bronchospasm. During the exercise test, gas exchange was measured to determine the thresholds of ventilatory adaptation and inadaptation as defined by Beaver et al. [40]. Borg’s scale was used to assess patient-perceived exercise level [41]. A standard definition was retained for “difficult exercise level” using software applying the tangents method to the intensity-score curve.

The modalities for applying the reference intensities to optimize training were then applied. According to Krollen’s principle, reserve heart rate is defined as the difference between maximal heart rate and resting heart rate, which is strongly correlated with exercise load. The patients were familiarized with heart rate monitoring so it could be used to establish an individualized exercise level and a relatively precise training program adapted to heart rate. The devise was calibrated for each patient as a function of the initial tests. The concept of heart rate reserve was applied to personalize the training program for each patient without the requirement of a maximal exercise test, coupled with gas exchange measurements, as long as the maximal theoretical heart rate was not too far from the real value.

The precise determination of the adaptation zones during muscle exercise using the Beaver ventilatory threshold method et al. [40] was used to validate the choice of the reference intensity level which was based on a chosen percentage of the reserve heart rate coupled to the index of perceived exercise level measured according to Borg [41].
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Quality-of-life assessment

The SF36 is a self-administered questionnaire used to determine a health-related quality-of-life profile, irrespective of the disease involved. The 36 items comprise eight subscales for the preceding month: physical activity (10 items), everyday life and relations with others (two items), physical pain (two items), perceived health (five items), vitality (four items), physical limitations (four items), mental health (five items), and evolution of perceived health (one question). Results are expressed as a standardized score for each subscore. The total score ranges from 0 to 100, a higher score corresponding to better quality-of-life [38].

Exercise program

Patients participated in the exercise program, which was organized daily in a sports facility for 5 days. Physical activities were divided into four categories:

- individual physical activity selected by the patient (walking, running, swimming), time allotted = 1h30;
- physical activity in a team setting (frisbee, racket sport, badminton, volleyball), time allotted = 1h30;
- recreational activity (ballroom dancing, African dancing, archery), time allotted = 1h30;
- lectures on the topic of hepatitis and treatments, evaluation in sports medicine, history of jaundice.

Data collected for each patient included: data on the liver disease, medical history, sports history, results of cardiorespiratory examination, SF36 results. A diary was used to check regular attendance, good tolerance, and quality of the physical exercise sessions. The following items were noted in the diary: day and time of the physical exercise session; physical status (shape) before starting the exercise session; type of physical exercise performed and duration of the session; general tolerance to muscular exercise during the session noted as average, best level, and worst level of tolerance perceived during the session using the Borg scale of perception of physical exertion.

Statistical analysis

Because of the sample size (n < 30 patients), items on the SF36 were analyzed using Student’s t test for paired data; p < 0.05 was considered significant.

Results

Between September 2005 and April 2006, 12 patients, eight men and four women, mean age 45.6 ± 12 years were included in this study. These patients were recruited from hepatology clinics of the Montauban hospital (seven patients), the Toulouse university hospital (three patients), the Albi hospital (one patient), and the Cèdres clinic of Cornebarieu (one patient). Among the 12 patients included, eleven completed the entire exercise program. One patient was excluded the first day of the program after the scheduled tests had ruled out any contraindication for physical activity because he presented purulent sinusitis. The main characteristics of the study population are summarized in Table 1.

During the sports medicine visit before the exercise sessions, all patients reached the maximal heart rate and were considered capable of performing the proposed physical activity. The results of the sports medicine visit are presented in Table 2. VO2max was 1.62 l/mn on average (range 1—2.7); maximal heart rate was 156 bpm on average (range 122—175).

All participants performed the three types of physical activity (individual, team, recreational) with no problem. There was a trend to improved quality-of-life one month after these patients resumed physical activity (Table 3). The “general perception” item of the SF36 improved from 63 ± 8 on day 0 to 71 ± 12 at one month (p = 0.07).

Discussion

The usefulness of physical activity was studied in the 1980s in patients with acute viral hepatitis (mainly hepatitis B) who performed training exercises on an ergometric bicycle. The authors were unable to identify any beneficial or deleterious effects of physical exercise on the course of the liver disease [42]. The only study conducted in patients with HCV infection treated with pegylated interferon plus ribavirin was reported in an abstract. That study showed a decrease in perceived fatigue during treatment in patients participating in physical exercises [43]. Physical exercise, when started in a well-controlled context, is beneficial and free of risk for patients with chronic diseases such as diabetes or multiple sclerosis for example [25,29—36] or after myocardial infarction [27]. Because of these findings, physical exercise has become an important part of management practices for chronic disease [44]. We thus wanted to test the hypothesis that resumption of physical activity in patients treated with pegylated interferon and ribavirin for HCV infection would be free of risk and might have a beneficial effect. Considering the potential risk for patients, we wanted first to conduct a study in a small number of patients. Since all of the patients included in the present study were able to perform the initial physiological tests with no problem, these results suggest that physical activity is possible, and free of risk, in this context. This study thus allows the recommendation that patients treated with pegylated interferon plus ribavirin should continue or resume their physical activities. Although the statistical power is weak, our results show a trend for improved quality-of-life in patients who participate in physical activities. These results are in agreement with those obtained in studies conducted in patients with chronic disease practicing a physical activity [26—37]..

We decided to report a relatively short follow-up of the SF36 quality-of-life assessment. This was because with treatment, certain patients eliminate the HCV definitively while others retain a certain viremia; this fact might introduce a major confounding factor for the statistical analysis. In addition, the effects of physical exercises are not sustained over time if the training sessions are not pursued [45]. Several reports have demonstrated that, because of the diff-
### Table 1  Baseline characteristics of patients included in the study.
*Principales caractéristiques des malades inclus dans l’étude.*

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Gender</th>
<th>Body mass index (kg/m²)</th>
<th>Viral genotype</th>
<th>Viral load (Copies/ml[^b])</th>
<th>Metavir score before treatment</th>
<th>Serum hemoglobin (g/100ml)</th>
<th>Sustained virological response (6 after treatment withdrawal)</th>
<th>Type of pegylated interferon</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37</td>
<td>M</td>
<td>23.87</td>
<td>1</td>
<td>14,383,160</td>
<td>A3F3</td>
<td>13.1</td>
<td>Non response</td>
<td>Alfa 2b</td>
</tr>
<tr>
<td>2</td>
<td>46</td>
<td>M</td>
<td>24.60</td>
<td>1</td>
<td>14,452,812</td>
<td>A2F2</td>
<td>11.3</td>
<td>Relapse</td>
<td>Alfa 2a</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>M</td>
<td>21.60</td>
<td>1</td>
<td>12,949,793</td>
<td>A2F4</td>
<td>12.3</td>
<td>Non response</td>
<td>Alfa 2a</td>
</tr>
<tr>
<td>4</td>
<td>59</td>
<td>F</td>
<td>22.31</td>
<td>1</td>
<td>900,564</td>
<td>A1F2</td>
<td>10.1</td>
<td>Relapse</td>
<td>Alfa 2a</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>F</td>
<td>19.53</td>
<td>1</td>
<td>450,678</td>
<td>A0F0</td>
<td>12.3</td>
<td>Prolonged response</td>
<td>Alfa 2a</td>
</tr>
<tr>
<td>6</td>
<td>36</td>
<td>F</td>
<td>22.26</td>
<td>1</td>
<td>2,296,490</td>
<td>A1 F1</td>
<td>12.1</td>
<td>Relapse</td>
<td>Alfa 2a</td>
</tr>
<tr>
<td>7</td>
<td>57</td>
<td>M</td>
<td>22.32</td>
<td>4</td>
<td>4,778,675</td>
<td>A3F2</td>
<td>11.3</td>
<td>Prolonged response</td>
<td>Alfa 2a</td>
</tr>
<tr>
<td>8</td>
<td>24</td>
<td>F</td>
<td>21.21</td>
<td>1</td>
<td>450,000</td>
<td>A2F1</td>
<td>11.8</td>
<td>Prolonged response</td>
<td>Alfa 2b</td>
</tr>
<tr>
<td>9</td>
<td>59</td>
<td>M</td>
<td>22.02</td>
<td>1</td>
<td>2,453,456</td>
<td>A2F2</td>
<td>11.6</td>
<td>Non response</td>
<td>Alfa 2a</td>
</tr>
<tr>
<td>10</td>
<td>35</td>
<td>M</td>
<td>21.91</td>
<td>1</td>
<td>2,987,230</td>
<td>A2F2</td>
<td>11.3</td>
<td>Lost to follow-up</td>
<td>Alfa 2a</td>
</tr>
<tr>
<td>11</td>
<td>47</td>
<td>M</td>
<td>23.48</td>
<td>1</td>
<td>5,789,563</td>
<td>A1F2</td>
<td>10.5</td>
<td>Non response</td>
<td>Alfa 2a</td>
</tr>
</tbody>
</table>

[^a]: M = Male; F = Female.
[^b]: Taqman Roche Technique.

### Table 2  Characteristics of patients included in the study.
*Caractéristiques des patients inclus dans l’étude.*

<table>
<thead>
<tr>
<th>Patient</th>
<th>$V_{O_{2}}$ max (l/mn) % Theoretical value</th>
<th>Maximum heart rate (beats/mn)</th>
<th>Maximum blood pressure at peak exercise (mmHg)</th>
<th>Endurance zone (beats/mn)</th>
<th>Threshold of ventilatory adaptation Load/heart rate (beats/mn)</th>
<th>Threshold of ventilatory inadaptation Load/heart rate (beats/mn)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.5</td>
<td>100</td>
<td>175</td>
<td>180/75</td>
<td>135—160</td>
<td>100/135—140</td>
</tr>
<tr>
<td>2</td>
<td>1.3</td>
<td>77</td>
<td>139</td>
<td>170/80</td>
<td>105—125</td>
<td>45/105—110</td>
</tr>
<tr>
<td>3</td>
<td>1.4</td>
<td>90</td>
<td>153</td>
<td>Not determined</td>
<td>100—125</td>
<td>40/100—105</td>
</tr>
<tr>
<td>4</td>
<td>1.2</td>
<td>98</td>
<td>156</td>
<td>185/75</td>
<td>95—120</td>
<td>30/95—100</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>70</td>
<td>122</td>
<td>130/80</td>
<td>100—110</td>
<td>45/110—115</td>
</tr>
<tr>
<td>6</td>
<td>1.2</td>
<td>90</td>
<td>167</td>
<td>230/95</td>
<td>115—140</td>
<td>35/110—115</td>
</tr>
<tr>
<td>7</td>
<td>2.5</td>
<td>114</td>
<td>167</td>
<td>235/80</td>
<td>115—140</td>
<td>50/115—120</td>
</tr>
<tr>
<td>8</td>
<td>1.1</td>
<td>60</td>
<td>154</td>
<td>150/100</td>
<td>110—120</td>
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<tr>
<td>9</td>
<td>2.7</td>
<td>113</td>
<td>154</td>
<td>195/90</td>
<td>85—115</td>
<td>55/80—85</td>
</tr>
<tr>
<td>10</td>
<td>1.7</td>
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<td>167</td>
<td>170/100</td>
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<td>1.3</td>
<td>92</td>
<td>165</td>
<td>150/90</td>
<td>100—120</td>
<td>30/100—105</td>
</tr>
</tbody>
</table>

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To improve treatment observance and efficacy [3], physical activity should be more than just suggested. It should be favored and actively supported for these patients since this type of activity can be expected to improve treatment observance and efficacy [3].

This study demonstrated that patients with HCV infection receiving pegylated interferon plus ribavirin can participate in an active well-controlled program of physical exercises without undue risk. In our patients, participation in an exercise program led to a considerable change in their perception of their disease helping them cope with the problems of a difficult treatment schedule.

Conflicts of Interest

Conflicts of interest: Jean-Louis Payen: no conflicts of interest; Fabien Pillard: no conflicts of interest; Véronique Mascarel: no conflicts of interest; Daniel Rivière: no conflicts of interest; Patrice Couzigou: no conflicts of interest, Natalia Kharlov: conflicts of interest with Roche laboratory.

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