Assessment of quality-of-life in chronic hepatitis C: effect of treatment

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SUMMARY

Objectives — To study Quality of Life during chronic hepatitis C infection in patients recruited by hospital-based or private hepatologists and to assess the effect of antiviral therapy.

Methods — A self-administered quality of life questionnaire (SF36) was proposed before, during, and 6 months after the end of treatment. The quality of life scales were assessed according to treatment response.

Results — 599 patients filled in the questionnaire before treatment and 168 patients 6 months after the end of treatment. After 6 months of therapy, patients with treatment response (n = 54) showed increased scores in all SF-36 scales, this increase reaching more than 25% for “Role Physical”, “General Health Perception” and “Vitality” scores. Non-responders (n = 70) had an impairment of physical scores but a general improvement of Mental Health.

Conclusion — This study confirms that sustained virological response is associated with an improved quality of life in hepatitis C patients. However, non-responders still have a positive “General Health Perception”. Together with the development of new therapies, these observations could help to convince reluctant patients to be treated.

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Introduction

Chronic hepatitis C virus (HCV) infection is frequent and often a fortuitous discovery of screening tests. At diagnosis, less than half of patients are symptomatic. When present functional signs are usually nonspecific, mainly fatigue which is difficult to assess objectively [1]. The Fatigue Impact Scale introduced in 1994 was the first specific questionnaire to be validated [2]. The physical and mental impact of disease can be assessed by measuring the patient’s quality-of-life (QoL) and perception of general health determined as “the functional impact of a disease and its treatment as perceived by the patient”. Four dimensions can be distinguished: physical and occupational activity, emotional status, social life, somatic sensations [3]. QoL scores, which can be monitored over time, provide an objective measure of the impact of a disease. QoL assessment has become a commonly used tool to evaluate the impact of treatment in many chronic conditions [4, 5].

Assessing QoL requires an adapted questionnaire. A wide variety of QoL questionnaires have been proposed, hindering comparisons between studies [6, 7]. The Short Form 36 (SF-36) [8] is however a widely used self-administered questionnaire which provides a reliable assessment of health-related QoL. The French version has been validated [9].

In hepatogastroenterology, QoL is a relatively new concept [10]. Recent French and European consensus conferences on HCV infection have underlined its importance [11, 12]. Before treatment, and irrespective of the evaluation technique, most published studies have reported a significant decline in physical and emotional status in patients with chronic HCV infection in comparison with control populations free of chronic disease [13, 14]. Patients experience impaired physical capacity and vitality and altered emotional and social life [15-17]. Loss of appetite, reduced occupational and daily activities, and limited capacity to recover have been described [18]. Impact on sexual life and fear of the future have also been reported [19]. Several studies suggest that impairment in physical and mental health in subjects with chronic HCV infection could be greater than observed in subjects with other chronic diseases such as hepatitis B virus (HBV) infection [16], hypertension, and insulin-dependent diabetes mellitus [15]. The physical impact is comparable to that observed in depression [15]. It is essential to evaluate the influence of treatment on QoL in patients with chronic HCV infection to assess the impact of side effects and treatment response [20]. In naïve patients, six months after treatment end, responders exhibit an improvement in most of the QoL scores in comparison with nonresponders [21]. In subjects who relapse after a first treatment, significant improvement in vitality and social life is observed among those with sustained virological response or histological improvement six months after terminating a new treatment [22, 23].

The objective of this multicentric French study was to evaluate QoL and impact of treatment on QoL in patients with chronic HCV infection recruited by 189 hospital-based or private hepatogastroenterologists.

Patients and methods

Study population

For this multicentric prospective survey, 189 hospital-based or private hepatogastroenterologists recruited 599 patients between January 1997 and January 1999. These patients had histologically proven HCV infection and were naive to antiviral treatment. There was an indication for treatment.
treatment in all patients. The patients were managed in the routine setting and were generally given standard monotherapy with interferon in compliance with the marketing approval recommendations at the time of study onset. Some patients were also given combination therapy with an interferon–ribavirin regimen. Demographic, epidemiological, biological, virological and histological data were collected at inclusion (M0). The following data were noted in the context of routine patient management: age, gender, source and duration of infection, serum ALAT and GGT, qualitative and quantitative PCR, genotype, overall and associated Knodell score. The survey was designed to record available biological and virological data at treatment onset, at six months treatment (M6) and at twelve months treatment (M12) as well as six months after treatment end.

To study the impact of treatment on changes in QoL, data were required at M0 and six months after treatment and to retain patients for analysis, irrespective of the reason for interrupting the treatment or its duration. Response or nonresponse to treatment were determined from biological data (ALAT) and virological data (qualitative PCR) recorded six months after treatment end. Response was defined as ALAT $<$ upper limit of normal (ULN) and PCR negative for HCV RNA. Nonresponse was defined as ALAT $\geq$ ULN and PCR positive for HCV RNA.

Methodology

QUALITY-OF-LIFE QUESTIONNAIRE

The survey was prospective. QoL was assessed with a self-administered questionnaire at M0, M6, M12 and six months after treatment end. To limit the bias effect of announcing treatment follow-up results, the patient was asked to complete the questionnaire at the beginning of the follow-up consultations. The questionnaire included the 36-item SF36 and a specific 7-item form widely used to assess QoL in patients with HCV infection and designed to assess changes in health. The French version of SF-36 has been validated and is widely used to assess QoL in diverse populations [9, 24-27]. The 36 items of the SF-36 were grouped in eight scales: physical activity, physical role (limitations in usual activities because of physical health problems), bodily pain, general health perception, vitality (energy and fatigue), social role (limitations in social activities because of physical or emotional problems), emotional role (limitations in activities because of emotional problems), and general mental health (psychological distress and well-being). A supplementary item was used to assess changes in the patient’s perception of general health. Summary scores were calculated using a method defined for the purposes of this study: physical component score (PCS) and mental component score (MCS) established from the first four scales of the SF-36 and mental component score (MCS) established from the last four scales of the SF-36. Scores for the eight SF-36 scales could range from 0 (lowest level of QoL) to 100 (highest theoretical QoL). The mean reference value for PCS and MCS was 50 [28]. Change in general health was scored 0 to 5.

Statistical analysis

To search for relationships between QoL scores and clinical data, nominal variables were compared between groups of patients using the chi-square test or the exact Fisher test as appropriate and ordinal variables were compared between groups of patients using the Mann-Whitney-Wilcoxon or the Kruskal-Wallis test as appropriate. P < 0.05 variables were compared between groups of patients using the Mann-Whitney-Wilcoxon test or the exact Fisher test as appropriate and ordinal nominal variables were compared between groups of patients using the Mann-Whitney-Wilcoxon test as appropriate. P < 0.05.

Results

Patient characteristics

POPULATION AT M0

The study population at M0 included 599 HCV RNA-positive patients. Mean age was 42 ± 13 years (mean ± standard deviation); 62% were men and 38% women.

Statistical analysis

To search for relationships between QoL scores and clinical data, nominal variables were compared between groups of patients using the chi-square test or the exact Fisher test as appropriate and ordinal variables were compared between groups of patients using the Mann-Whitney-Wilcoxon or the Kruskal-Wallis test as appropriate. P < 0.05 was considered statistically significant. The statistical analysis was performed with SAS software (version 6.12).

The presumed route of infection was blood transfusion for 163 patients (27.2%), intravenous drug use for 230 (38.4%), another route (known or not) for 191 (31.9%), blood transfusion and intravenous drug use for 8 patients (1.3%), and an undetermined route for 7 (1.2%). Estimated duration of infection was 13.1 ± 8.2 years. Mean serum ALAT was 2.6 ± 2.3 ULN and mean serum GGT was 1.6 ± 2.5 ULN. The overall Knodell score was 8.2 ± 4.4, and the activity and fibrosis scores were 6.5 ± 2.2 and 1.7 ± 1.2 respectively. Cirrhosis was present in 9.5% of patients. The viral genotype was known for 234 patients: genotype 1a or 1b (N = 119), genotype 3 (N = 80), other genotype (N ≤ 35).

POPULATION AT STUDY END

Six months after treatment end, 431 patients did not attend consultations or had missing data. QoL scores were available at M0 and six months after treatment end for 168 patients. Among these 168 patients, 54 were complete responders, 70 were nonresponders, and 44 had discordant biological and virological results (ALAT $\leq$ ULN and HCV RNA+, or ALAT $>\geq$ ULN and HCV RNA-). These latter patients were excluded from the analysis.

Quality-of-life scores

ACCEPTABILITY

There were no missing data for 82% of the questionnaires. The mean number of missing data per questionnaire per patient was 0.5.

QUALITY-OF-LIFE AT INCLUSION

The scores of the eight SF-36 scales and PCS and MCS are presented in Table I for patients included in the analysis and for responders and nonresponders.

There was no significant difference in the summary scores (PCS, PCS, and change in health) between responders and nonresponders (Wilcoxon test: P = 0.37 for PCS, P = 0.68 for MCS, and P = 0.17 for change in health).

QUALITY-OF-LIFE AT M6, M12 AND SIX MONTHS POST-TREATMENT (TABLE II)

For responders, the scores of the eight SF-36 scales increased, more than 25% for physical role, general health perception, and vitality. In nonresponders, certain scores also improved, mainly those related to emotional and mental health: emotional role, mental health, and mental component score (MCS). An improvement in vitality and general health perception was also observed.

CHANGES IN QUALITY-OF-LIFE FROM M0 TO SIX MONTHS POST-TREATMENT (FIGURE 1)

In responders, the summary scores (PCS and MCS) declined after six months treatment, then progressively improved up through six months post-treatment. In nonresponders, the PCS was lower after six months of treatment and remained low throughout the study. Conversely, the MCS varied little during the period of treatment. In each population, the sign rank test was applied to compare change in the summary scores (PCS and MCS) and change in health (between M0 and six months post-treatment versus absence of change). In responders, there was a significant improvement in the three scores (PCS, MCS, and change in health). On the contrary PCS exhibited a significant decline (table III).
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### Table I – Quality-of-life scores at inclusion. Scoring of the eight scales may range from 0 (lowest level of quality-of-life) to 100 (highest theoretical score). Physical component score (PCS) and mental component score (MCS) have a mean reference value of 50. Change in Health is assessed using a score ranging from 0 to 5.

<table>
<thead>
<tr>
<th>Scale</th>
<th>Included patients N = 599</th>
<th>Responders N = 54</th>
<th>Nonresponders N = 70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical activity</td>
<td>Mean ± SD</td>
<td>Median</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Physical role</td>
<td>82.1 ± 21.5</td>
<td>90</td>
<td>81.4 ± 22.7</td>
</tr>
<tr>
<td>Emotional role</td>
<td>58.8 ± 40.6</td>
<td>66.7</td>
<td>64.2 ± 34.9</td>
</tr>
<tr>
<td>Social role</td>
<td>65.1 ± 24.5</td>
<td>62.5</td>
<td>63.7 ± 22.7</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>68.0 ± 26.1</td>
<td>72</td>
<td>68.7 ± 24.7</td>
</tr>
<tr>
<td>Mental health</td>
<td>55.6 ± 20.1</td>
<td>56</td>
<td>55.9 ± 20.3</td>
</tr>
<tr>
<td>Perception of general health</td>
<td>54.1 ± 19.9</td>
<td>55</td>
<td>50.3 ± 20.2</td>
</tr>
<tr>
<td>Vitality</td>
<td>45.0 ± 20.2</td>
<td>45</td>
<td>42.3 ± 22.2</td>
</tr>
<tr>
<td>Physical component score</td>
<td>47.8 ± 9.2</td>
<td>49.7</td>
<td>46.8 ± 9.4</td>
</tr>
<tr>
<td>Mental component score</td>
<td>39.2 ± 11.1</td>
<td>40.0</td>
<td>39.3 ± 10.1</td>
</tr>
<tr>
<td>Change in health</td>
<td>2.88 ± 0.81</td>
<td>3</td>
<td>2.65 ± 0.74</td>
</tr>
</tbody>
</table>

### Comparison of scores by response status

Changes in the QoL, scores between M0 and six months post-treatment were compared between responders and nonresponders. There was a significant difference for PCS and change in health, but no difference for MCS (table IV).

### Discussion

The impact of disease and treatment on the patient’s QoL has become an important medical concern. Several studies evaluating QoL in patients with HCV infection have demonstrated that patients have a good perception of their altered well-being [16]. This alteration in health status involves physical [29] and mental and emotional components [21, 30]. The presence of co-morbid conditions [31, 32] or extrahepatic manifestations such as arthralgia, myalgia, pruritus, or sicus syndrome [33] or possible effect of HCV on the central nervous system may also play an important role [34-36]. It is also demonstrated that knowledge of the diagnosis of HCV infection can have in itself a negative effect on QoL [37]. Knowledge of risks (cirrhosis, hepatocellular carcinoma) undoubtedly has an important impact on QoL. The epidemiological characteristics of our study population of nearly 1000 patients included in the present study are similar to those of other studies concerning QoL in patients with HCV infection [30].

### Table II – Quality-of-life scores at M0, M6, M12 and six months after the end of treatment in sustained responders (SR, N = 54) and nonresponders (NR, N = 70) and changes in these scores between M0 and six months after the end of treatment. Score of the eight SF-36 scales may range from 0 (lowest quality-of-life) to 100 (highest theoretical score). PCS (physical component score) and MCS (mental composite score) have a mean reference value of 50. Change in Health is assessed using a score ranging from 0 to 5.

<table>
<thead>
<tr>
<th>M0</th>
<th>M6</th>
<th>M12</th>
<th>6 months post-treatment</th>
<th>Change between M0 and 6 months post-treatment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SR</td>
<td>NR</td>
<td>SR</td>
<td>NR</td>
<td>SR</td>
</tr>
<tr>
<td>Physical activity</td>
<td>81.4</td>
<td>80.4</td>
<td>71.5</td>
<td>79.8</td>
</tr>
<tr>
<td>Physical role</td>
<td>60.7</td>
<td>66.6</td>
<td>52.7</td>
<td>59.8</td>
</tr>
<tr>
<td>Emotional role</td>
<td>64.2</td>
<td>57.1</td>
<td>50.7</td>
<td>57.3</td>
</tr>
<tr>
<td>Social role</td>
<td>63.7</td>
<td>68.4</td>
<td>57.5</td>
<td>67.9</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>8.7</td>
<td>67.6</td>
<td>58.6</td>
<td>64.4</td>
</tr>
<tr>
<td>Mental health</td>
<td>55.9</td>
<td>55.6</td>
<td>51.7</td>
<td>60.1</td>
</tr>
<tr>
<td>Perception of general health</td>
<td>50.3</td>
<td>57.4</td>
<td>50.7</td>
<td>62.0</td>
</tr>
<tr>
<td>Vitality</td>
<td>42.3</td>
<td>46.6</td>
<td>41.5</td>
<td>47.6</td>
</tr>
<tr>
<td>Physical component score</td>
<td>46.8</td>
<td>48.4</td>
<td>44.3</td>
<td>47.2</td>
</tr>
<tr>
<td>Mental component score</td>
<td>39.9</td>
<td>39.8</td>
<td>37.4</td>
<td>41.3</td>
</tr>
<tr>
<td>Change in health</td>
<td>2.65</td>
<td>2.84</td>
<td>3.43</td>
<td>3.37</td>
</tr>
</tbody>
</table>
600 patients were similar to those described in the survey of 6 664 patients with chronic HCV infection performed for the French Ministry of Health [38]. To date, most published series have been selected among specialized center recruitment which could induce an overestimation of the proportion of patients with severe forms of the disease. The population in our study, recruited by 189 hospital-based or private hepatogastroenterologists (62% and 38% of patients respectively), was thus probably representative of the general population of HCV-infected subjects. One could expect that the homogenous nature of therapeutic trial populations could induce a bias in the QoL assessment. Inclusion-exclusion criteria, as well as the follow-up schedule can have an effect, particularly on QoL. The rate of response to the self-administered questionnaire (greater than 80%) also emphasizes the reliability of QoL assessment in a population of patients recruited in a routine care setting. The results indicate that the QoL scores before treatment were very similar to those reported in the literature. For the eight SF-36 scales, the scores were significantly lower than those reported in other studies or in patients with another type of infection such as HBV [16]. These results, as well as those reported for a sample of type 2 diabetes patients [15, 21] thus confirm that chronic HCV infection as a significant though often “silent” impact on QoL [39]. This impact is independent of therapeutic effects and thus a direct consequence of the disease itself.

In a North American study including 912 patients [40], McHutchison et al. compared QoL scores before and after combination interferon-ribavirin antiviral treatment. Their assessment was based on the SF-36 questionnaire and specific questions for HCV infection and disclosed that before treatment, patients with HCV infection present deteriorated QoL. The results also indicated that most of the scores returned to normal in patients who achieved sustained therapeutic response but not in nonresponders. Our findings are in agreement and show a significant difference in the time course of PCS and change in health between responders and nonresponders. Virological response sustained for six months after the end of the antiviral treatment is associated with improved QoL. All scores do not improve in nonresponders but these patients do perceive an improvement in their general and emotional health. The slight improvement in the scores from M12 to six months post-treatment is probably related to treatment withdrawal. It would be reasonable to predict that improved therapeutics allowing a higher rate of sustained virological response will have a positive impact on the QoL of these patients. Regarding the changes in QoL during interferon treatment, several studies have demonstrated a deterioration of depression scores the first three months [41]. A study of a French cohort of 354 patients given interferon alone for 12 months showed that fatigue increased during the first three months of treatment, then stabilized and finally declined at treatment end, independently of response [42]. Another study using the Nottingham Health Profile (NHP) questionnaire also demonstrated lower QoL scores in patients taking interferon [43]. This study emphasized the importance of using a specific questionnaire to detect sometimes minimal changes in health status. Pilot studies have indicated that the impact of monotherapy using pegylated interferon [44-46] or combination therapy with ribavirin [47] is significantly less than that observed with standard interferon given in combination or not with ribavirin. Certain studies have also demonstrated that patient compliance and drop out are directly associated with QoL [48]. Here again, our study confirms earlier results demonstrating that responders have a significant improvement in the three summary scores (PCS, MCS, change in health). This difference observed between responders and nonresponders cannot be explained by differences in the two groups since there was no difference at inclusion (M0). These observations together with therapeutic advances suggest that certain reluctant patients will be encouraged to undergo treatment. A probable improvement in QoL in patients with sustained virological response could be a supplementary argument for proposing treatment in patients with minimal histological lesions.

**Table III** – Change in quality-of-life summary scores between M0 and six months post-treatment in responders and nonresponders to antiviral therapy.

<table>
<thead>
<tr>
<th></th>
<th>Responders N=54</th>
<th>P</th>
<th>Nonresponders N=70</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical component score</td>
<td>3.32</td>
<td>0.0028</td>
<td>-2.47</td>
<td>0.0037</td>
</tr>
<tr>
<td>Mental component score</td>
<td>4.57</td>
<td>0.0042</td>
<td>2.21</td>
<td>0.076</td>
</tr>
<tr>
<td>Change in health</td>
<td>1.33</td>
<td>0.000001</td>
<td>0.57</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

**Table IV** – Comparison of changes in summary scores, Physical and Mental Component scores, and Change in Health between responders and nonresponders.

<table>
<thead>
<tr>
<th></th>
<th>Responders N=54</th>
<th>Nonresponders N=70</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical component score</td>
<td>3.32</td>
<td>-2.47</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Mental component score</td>
<td>4.57</td>
<td>2.21</td>
<td>0.0977</td>
</tr>
<tr>
<td>Change in health</td>
<td>N</td>
<td>N</td>
<td>0.001</td>
</tr>
</tbody>
</table>


**Fig. 1** – Evolution of the Physical Component Score (PCS) and Mental Component Score (MCS) in responder and non-responder patients.
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