Management of hepatitis C patients:
a French population-based study

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SUMMARY

Aims — Our aim was to assess the proportion of patients in a well-defined population reaching specialized medical care after hepatitis C diagnosis.

Methods — Hepatitis C-positive patients recorded in the population-based registry of Côte-d’Or, an administrative district in France, constituted the study population.

Results — Between 1994 and 1999, new hepatitis C-positive serology was diagnosed in 847 patients, of whom 690 were eligible for this study. A total of 135 patients had not been given specialized medical care after diagnosis; among them, 50.4% had a normal serum alanine transferase level at diagnosis, 62.2% had risk factors related to lifestyle (drug addiction, sexual risk...), and 26.7% were current alcoholics. The 555 other patients were involved in specialized medical care after diagnosis: 42.7% had a liver biopsy and 27.0% were treated. Treatment was carried out more often in males than in females (OR: 1.67; P < 0.005), and in patients less than 65 years old (OR: 2.94; P < 0.0002). Nearly 30.5% of patients with a Metavir score greater than A1F1 did not undergo treatment.

Conclusion — This study shows that in a general population at least one patient out of five with hepatitis C infection remains outside the health care system. It also reveals that management practices vary with gender. Further surveys are needed to better understand this phenomenon.

RÉSUMÉ

Prise en charge des malades atteints d’hépatite chronique virale C dans la population générale

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Objectifs — Cette étude de population dans le département de Côte-d’Or avait pour objectif d’évaluer la prise en charge des mala- des après diagnostic d’une sérologie d’hépatite C positive.

Malades et méthode — L’étude rétrospective a été réalisée à partir des nouveaux cas de sérologie d’hépatite C positive recensés par le registre spécialisé de Côte-d’Or.

Résultats — Entre janvier 1994 et décembre 1999, 847 nouveaux cas ont été recensés ; 690 ont été étudiés. Dans 135 cas, aucun suivi médical n’a été fait : 50,4 % avaient une activité de l’alanine aminotransférase normale au moment du diagnostic, 62,2 % avaient un facteur de risque lié au mode de vie (toxicomanie, risque sexuel), 26,7 % étaient alcooliques. Parmi les 555 autres cas, 42,7 % ont bénéficié d’une biopsie hépatique, 27,0 % ont été traités. Les hommes étaient plus souvent traités que les femmes (OR : 1,67 ; P < 0,005) de même que les malades âgés de moins de 65 ans par rapport à ceux plus âgés (OR : 2,94 ; P < 0,0002). Près de 30 % des malades ayant un score Métavir supérieur à A1 F1 n’étaient pas traités.

Conclusion — Cette étude révèle qu’une personne sur cinq n’était pas prise en charge après le diagnostic. Des inégalités de prise en charge entre les deux sexes justifient des études complémentaires pour leur compréhension.

Introduction

Continuing improvement in the efficacy of anti-viral treatments [1, 2] and the results of anti-hepatitis C campaigns conducted for more than a decade have improved our capacity to screen viral carriers in an asymptomatic population and to treat patients expected to benefit from treatment and thus prevent serious complications of this disease (cirrhosis and hepatocellular carcinoma) [3, 4]. The importance of these two major objectives of the national anti-hepatitis C campaign was emphasized in the consensus conferences devoted to hepatitis C viral infections [5, 6].

The non-representative nature of patient populations attending specialized centers makes it difficult to evaluate management of patients in the general population from studies produced by these centers [7]. Such information is however crucial for appropriate organization of an anti-hepatitis C policy by the public health authorities.

The purpose of our study was to evaluate the quality of management of patients with a diagnosis of hepatitis C infection in a well-defined population.

Patients and methods

Study population

A registry of patients residing in the French administrative district Côte-d’Or (506,755 inhabitants) with a positive diagnosis of hepatitis C
infection was instituted in 1994. Data recorded in this registry essentially issue from the 43 private and public virology and biology laboratories operating in Côte-d’Or and neighboring communities where care may be given to patients residing in the district. Following permission from the patients, the laboratory physicians inform the registry of the name and address of all persons with a positive hepatitis C virus (HCV) serology as well as the name of the physician who prescribed the serology test. The two pathology laboratories in the district also send their biopsy reports on cases of chronic hepatitis C to the registry.

The registry sends an information sheet to the prescribing physician asking for information concerning the seropositive patient: date of birth, gender, occupation, residence (urban or rural), date of diagnosis, assumed date and mode of contamination, presence of risk factors for contamination, drinking habits (excessive alcohol intake defined as > 50 g/day), serum alanine aminotransferase (ALT) level at diagnosis, results of polymerase chain reaction (PCR) search for hepatitis virus C RNA or virus B DNA, and the presence of complications (cirrhosis and its severity, hepatocellular carcinoma). Patients not residing in the administrative district of Côte-d’Or and patients whose diagnosis was established before January 1994 were excluded from the present analysis.

A complementary survey was conducted using a questionnaire sent to the primary care physicians between October 2000 and February 2001 in order to study management practices employed after diagnosis (liver biopsy, anti-viral treatments) and development of complications. The medical files of hospitalized patients and attending hepatogastroenterologists of all seropositive patients were reviewed. The METAVIR score [8] was used to evaluate liver histology.

Correspondences analysis [7] was used to define three groups of risk factors for hepatitis C infection. This statistical method enabled grouping together patients with a large number of interlinked variables. The first group concerned patients whose infection was related to lifestyle: drug use by intravenous injection or nasal inhalation, sexual risk (infected partner, male homosexuality, multiple sexual partners), tattooing. The second group was a nosocomial risk group and included patients who had received a blood transfusion before 1990 or had a history of surgery, dialysis, sclerosis of lower limb varices, acupuncture, or health care occupation. The third group was constituted of individuals with no known risk factor. Patients whose risk factors fell into them in both groups 1 and 2 were classified in group 1 with the exception of subjects who had received a blood transfusion before 1990 and had no history of illicit drug use who were classed in group 2.

Statistical analysis

Univariate and multivariate analyses were used to search for correlation between the study variables and treatment. The actuarial method was used to establish the cumulative rate of treatment (endpoint February 2001) and the log-rank test was used to evaluate differences. Patients who died were censured at the date of death. The Cox model was used for multivariate analysis. Age, gender, risk factors, and period of diagnosis were included in the multivariate analysis even if univariate analysis did not demonstrate statistical significance. Co-variables demonstrating a P-value < 0.10 at univariate analysis were retained for the multivariate model. STATA software (Statacorp. 2001) was used for the statistical analysis.

Results

Between January 1994 and December 31, 1999, 847 new HCV-positive serologies were diagnosed in 492 men (mean age: 43.8 ± 18.5 years) and 355 women (mean age: 46.8 ± 20.0 years). The prescribing physician was a general practitioner for 32.3%, a hepatogastroenterologist for 16.3%, a psychiatrist for 9.2%, an infectious disease specialist for 4.7% and another specialist for the remainder. One hundred fifty-seven patients were excluded from the analysis: patients aged less than 15 years (N = 24), patients aged over 75 years (N = 48), patients with HIV co-infection (N = 49), patients with hepatocellular carcinoma at the time of diagnosis (N = 15), and patients who died within six months of diagnosis (N = 21).

The study group thus included 690 patients (figure 1) including 135 (19.6%) who were not given any medical care after diagnosis. Eighty-four (62.2%) of these 135 patients had a lifestyle-related risk factor and 36 (26.7%) were heavy drinkers. Normal serum ALAT level was recorded in 50.4%. Three hundred eighteen of the 555 patients (57.0%) were followed after the diagnosis but did not have a liver biopsy. Their mean age was 41.0 ± 9.0 years. Sixty-three (11.0%) had a contraindication for antiviral treatment, 19 (6.0%) had excessive alcohol intake, and 19 (6.0%) declined liver biopsy.

Among the 237 patients who had a liver biopsy, mean time between diagnosis and biopsy was 4.0 ± 0.3 months. This time was less than 9 months in 75% of patients. The histological lesions, which were not noted for 2 patients, were scored A1F1 in 174 patients (73.4%), more often in men (78.8%) than women (68.3%) (P < 0.07).

One hundred fifty (63.0%) of the 237 patients with a liver biopsy were treated representing 27% of the 555 included patients. Median time between diagnosis and treatment was 8.5 ± 0.8 months. Cumulative treatment rates at 6, 12, 24 and 48 months are presented in table I. The proportion of patients treated was higher among male than female patients; it was also higher among patients aged less than 65 years and was lower among heavy drinkers than non-drinkers. At multivariate analysis, male gender and age less than 65 years were associated with treatment, with elevated ALAT level, and with presence of C viral RNA. No interaction was observed between these two last elements (table II). The reasons for non-treatment put forward by the physicians were: normal ALAT level during follow-up (47.5%), absence of HCV-RNA in serum (12.6%), patient refusal (6.9%) and heavy drinking (6.4%) (table III).

Fifty-three patients among the 174 with a METAVIR score above A1F1 were not treated (table IV). At multivariate analysis, factors related with institution of treatment were age less than 65 years and fibrosis score 2 2. The reasons for non-treatment were presence of a contraindication for treatment (35.9%), loss to follow-up (18.9%), normal ALAT level (13.2%), patient refusal (11.3%), and heavy drinking (9.4%).

Discussion

This is the first population-based study analyzing management practices for patients with hepatitis C virus infection. We included in our population all persons with a new diagnosis among a population of 500,000 persons living in a district cov-

ABBREVIATIONS:

ALAT: alanine amino-transferase
RNA: ribonucleic acid
PCR: polymerase chain reaction
HCV: hepatitis C virus
HIV: human immunodeficiency virus

Fig. 1 – Study design.

Protocole d’étude.
### Tableau I. – Cumulated treatment rates (SE: standard error).

*Taux cumulés de traitement (ES : erreur standardisée).*

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Cumulated treatment rates</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 months</td>
<td>12 months</td>
</tr>
<tr>
<td></td>
<td>rate</td>
<td>SE</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>555</td>
<td>8.3</td>
<td>1.2</td>
</tr>
<tr>
<td>Sex</td>
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<td></td>
</tr>
<tr>
<td>Male</td>
<td>311</td>
<td>10.9</td>
</tr>
<tr>
<td>Female</td>
<td>244</td>
<td>4.9</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-24</td>
<td>42</td>
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<tr>
<td>25-34</td>
<td>127</td>
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</tr>
<tr>
<td>35-44</td>
<td>148</td>
<td>10.8</td>
</tr>
<tr>
<td>45-54</td>
<td>62</td>
<td>11.3</td>
</tr>
<tr>
<td>55-64</td>
<td>88</td>
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</tr>
<tr>
<td>65-75</td>
<td>88</td>
<td>4.6</td>
</tr>
<tr>
<td>Residence</td>
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<td></td>
</tr>
<tr>
<td>Rural</td>
<td>118</td>
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<tr>
<td>Small towns</td>
<td>98</td>
<td>9.2</td>
</tr>
<tr>
<td>Dijon</td>
<td>337</td>
<td>8.0</td>
</tr>
<tr>
<td>Year of Diagnosis</td>
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<tr>
<td>1994</td>
<td>106</td>
<td>8.5</td>
</tr>
<tr>
<td>1995</td>
<td>102</td>
<td>7.8</td>
</tr>
<tr>
<td>1996</td>
<td>114</td>
<td>8.7</td>
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<td>88</td>
<td>8.0</td>
</tr>
<tr>
<td>1998</td>
<td>86</td>
<td>9.3</td>
</tr>
<tr>
<td>1999</td>
<td>59</td>
<td>6.8</td>
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<tr>
<td>Risk factors</td>
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<tr>
<td>Lifestyle</td>
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<tr>
<td>Nasocomial</td>
<td>263</td>
<td>8.0</td>
</tr>
<tr>
<td>Absent or unknown</td>
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<td>4.7</td>
</tr>
<tr>
<td>Serum ALT</td>
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<td></td>
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<tr>
<td>Normal</td>
<td>226</td>
<td>4.4</td>
</tr>
<tr>
<td>Elevated</td>
<td>305</td>
<td>14.8</td>
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<tr>
<td>Unknown</td>
<td>24</td>
<td>0.0</td>
</tr>
<tr>
<td>HCV-RNA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>297</td>
<td>12.5</td>
</tr>
<tr>
<td>Absent</td>
<td>71</td>
<td>1.4</td>
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<tr>
<td>Unknown</td>
<td>187</td>
<td>4.3</td>
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<td>HBS Ag</td>
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<td>Present</td>
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<td>84</td>
<td>6.0</td>
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<tr>
<td>Alcoholism</td>
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<td></td>
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<tr>
<td>Current</td>
<td>114</td>
<td>6.1</td>
</tr>
<tr>
<td>Former</td>
<td>22</td>
<td>13.6</td>
</tr>
<tr>
<td>Absent</td>
<td>382</td>
<td>8.9</td>
</tr>
<tr>
<td>unknown</td>
<td>37</td>
<td>5.4</td>
</tr>
</tbody>
</table>

*a two homeless patients excluded.*
Tableau II. – Factors linked to treatment: multivariate analysis (555 patients monitored) a.

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.67</td>
<td>[1.16; 2.40]</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-34</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>35-64</td>
<td>1.15</td>
<td>[0.78 - 1.72]</td>
<td></td>
</tr>
<tr>
<td>65-74</td>
<td>0.34</td>
<td>[0.16 - 0.70]</td>
<td>0.0002</td>
</tr>
<tr>
<td><strong>HCV-RNA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent or unknown</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>2.30</td>
<td>[1.53 - 3.47]</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td><strong>Serum ALAT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated</td>
<td>7.93</td>
<td>[4.44 - 14.19]</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1.38</td>
<td>[0.31 - 6.24]</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td><strong>Alcoholism</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>0.45</td>
<td>[0.28 - 0.75]</td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>1.42</td>
<td>[0.71 - 2.84]</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1.36</td>
<td>[0.60 - 3.05]</td>
<td>0.0023</td>
</tr>
</tbody>
</table>

* the model was adjusted for the period of diagnosis and risk factors, not correlated with treatment.

ALAT = alanine aminotransferase.

Tableau III. – Reasons for not treating patients a.

<table>
<thead>
<tr>
<th></th>
<th>Total number of non-treated patients (N = 405)</th>
<th>Patients with METAVIR score ≤ A1F1 (N = 53)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Serum ALAT normal</td>
<td>192</td>
<td>47.4</td>
</tr>
<tr>
<td>HCV-RNA absent or unknown</td>
<td>51</td>
<td>12.6</td>
</tr>
<tr>
<td>Liver damage considered insufficient</td>
<td>35</td>
<td>8.6</td>
</tr>
<tr>
<td>Medical contraindication</td>
<td>54</td>
<td>13.3</td>
</tr>
<tr>
<td>Psychiatric contraindication</td>
<td>45</td>
<td>11.1</td>
</tr>
<tr>
<td>Patient lost to follow-up</td>
<td>52</td>
<td>12.8</td>
</tr>
<tr>
<td>Patient refusal</td>
<td>28</td>
<td>6.9</td>
</tr>
<tr>
<td>Active alcoholism</td>
<td>26</td>
<td>6.4</td>
</tr>
<tr>
<td>Patient considered too old</td>
<td>14</td>
<td>3.5</td>
</tr>
<tr>
<td>Active drug abuse</td>
<td>7</td>
<td>1.7</td>
</tr>
<tr>
<td>Decompensated cirrhosis</td>
<td>9</td>
<td>2.2</td>
</tr>
<tr>
<td>Physician unaware of diagnosis</td>
<td>6</td>
<td>1.5</td>
</tr>
<tr>
<td>Waiting for therapeutic progress</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>Infection too old</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>Associated hepatic autoimmune disease</td>
<td>1</td>
<td>0.2</td>
</tr>
</tbody>
</table>

* One or more reasons per patient.

The diagnosis of hepatitis C was made by a general practitioner for about one-third of patients, confirming the key role of general practice in screening for hepatitis C [9-11]. The high proportion of diagnoses made by psychiatrists concerned patients attempting to abstain from alcohol or illicit drug use.
Specialized medical care was not given to nearly one-fifth of the newly diagnosed patients. An earlier report concerning blood donors also found that management practices were insufficient [12, 13]. Half of the non-managed patients had a normal serum ALAT level at diagnosis. Both patients and physicians thus need to be informed that in the event of a normal serum ALAT level at diagnosis, ALT level should be re-assayed to obtain a time course and that complementary tests are indicated (RNA viral C levels). One-quarter of the patients who were not given specialized care were heavy drinkers, and are likely difficult to follow-up. The consensus conference held in February 2002 [5] nevertheless emphasized the need for improved management practices for these patients who could be expected to benefit from treatment due to their higher risk of cirrhosis because of the combined effect of alcohol and viral inflammation [14].

In patients given specialized care, the time from diagnosis to treatment was long: median 8.5 months. This is partially related to follow-up. The consensus conference held in February 2002 [5] nevertheless emphasized the need for improved management practices for these patients who could be expected to benefit from treatment due to their higher risk of cirrhosis because of the combined effect of alcohol and viral inflammation [14].

The proportion of treated patients, approximately 18%, is much lower than in hospital series. This is related to patient selection before referral to specialized centers, as we demonstrated in earlier work [7]. Considering the factors determining therapeutic management, i.e. patient age, elevated ALAT and presence of viral RNA, there is no obvious explanation for the higher frequency of treatment in men than women. This finding merits further exploration in a study taking into account the social and psychological dimensions of the therapeutic decision.

In a number of non-negligible patients, the absence of treatment could be related to fear (liver biopsy) as was demonstrated in the study conducted in another French administrative district, Poitou-Charentes [15]. The French consensus conference noted a few situations where treatment could be instituted without prior liver biopsy [5], a possibility which should increase the proportion of treated patients. Additional registration of patients should be helpful in clarifying this point. The high proportion of patients who were not treated after liver biopsy with evidence of liver damage greater than A1F1 is unexpected: nearly one-third of the patients fell into this category. Logically, patients who accepted biopsy would undergo treatment [5] when the biopsy results demonstrate moderate or severe liver damage. Many of the reasons for not treating which were put forward by the physicians are easily understandable: contraindication for treatment, elderly patients, normal ALAT. But if treatment could not be undertaken, why was the biopsy prescribed? We speculate that this situation occurs when the decision to treat is particularly difficult, for example for patients with borderline age or who have contraindications to treatment, or if the therapeutic risk would not be acceptable unless the patient presented severe histologically proven chronic hepatitis. For the other patients, late refusal of treatment emphasizes the importance of patient education and better awareness among health professionals concerning the sociological and occupational impact of hepatitis C treatment. Psychologists and specialized consultation nurses should play a key role in improving the quality of patient management and strengthening the efficacy of anti-viral programs.

**REFERENCES**