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Hepatitis C infection: eligibility for antiviral therapies

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Abstract

Background Current treatments of chronic hepatitis C virus (HCV) are effective, but expensive and susceptible to induce significant side effects.

Objectives To evaluate the proportion of HCV patients who are eligible for a treatment.

Methods In a database comprising 1726 viraemic HCV patients, the files of 299 patients who presented to the same hepatologist for an initial appointment between 1996 and 2003 were reviewed.

Results Patients' characteristics were age 43.1 ± 15.6 years, 53% male and 92% Caucasian. The main risk factors were transfusion (43%) and drug use (22%). Genotypes were mostly genotype 1 (66%), genotype 3 (12%) and genotype 2 (10%). These characteristics were not different from those of the whole series of 1726 patients. A total of 176 patients (59%) were not treated, the reasons for non-treatment being medical contraindications (34%), non-compliance (25%) and normal transaminases (24%). In addition, 17% of patients declined therapy despite being considered as eligible, mainly due to fear of adverse events. Medical contraindications were psychiatric (27%), age (22%), end-stage liver disease (15%), willingness for pregnancy (13%), cardiac contraindication (7%) and others (16%). Only 123 patients (41%) were treated. A sustained viral response was observed in 41%. The treatment was interrupted in 16% for adverse events.

Conclusions The majority of HCV patients are not eligible for treatment. This implies that, with current therapies, only 17% of patients referred for chronic HCV become sustained responders. Some modifications of guidelines could extend the rate of treatment (patients with normal transaminases), but an important barrier remains the patients' and the doctors' fear of adverse events.

Keywords : hepatitis C ; treatment ; interferon alfa ; cost ; adverse events ; epidemiology ; contraindication

Introduction

Hepatitis C virus (HCV) is an important cause of chronic liver disease worldwide with a significant global mortality and morbidity. The World Health Organization estimates that about 3% of the world population is currently infected with HCV. In the United States, the estimated prevalence is 1.8% [1]. In Europe, among blood donors, the prevalence of HCV ranged from very low (< 0.1%) in the United Kingdom and Scandinavia, to low (0.1-0.5%) in the rest of Western Europe and moderate (0.6%) in Southern Europe [2]. In a sample of the general population in Belgium, the seroprevalence was 0.87% [3]. More than 70% of newly infected patients progress to chronic infection with its attendant complications of cirrhosis, liver failure and hepatocellular carcinoma. Furthermore, the health-related quality of life is significantly compromised in persons with chronic HCV compared with the general population [4]. At present, the management of patients with hepatitis C largely focuses on combination antiviral treatment using a 24-week or 48-week course of peginterferon and ribavirin [5]. These therapies proved to be effective. They are susceptible, however, to inducing significant adverse effects. In addition, they are expensive, and entail a substantial socioeconomic burden. It has been shown that the therapy was cost-effective, in particular, in US [6], Spanish [7], German [8] and Belgian settings [9-11]. Beyond the

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problem of the cost-effectiveness ratio, however, the global cost estimation of a treatment for a country depends on the number of patients actually treated per year. There is a huge discrepancy between the number of patients that could be potentially treated in regards of the disease prevalence and the number of patients that are actually treated. For Belgium, for example, only around 1000 patients are treated every year for an estimated population of about 90 000 infected persons. It has been suggested that a large number of patients are still unaware of their seropositivity. Furthermore, under-reporting by healthcare professionals is common, and many high-risk individuals do not have easy access to health care. Another explanation is that only a small proportion of patients that are seeking medical care are eventually treated. In the United States, it has been shown in the Veterans' population infected with HCV that 30% only of referred patients were considered eligible for therapy [12,13]. In this population, the most common contraindication was psychosocial factors [12]. Although the findings in HCV-infected US Veterans may not be directly applicable to other HCV populations (because they are more likely than HCV-infected US non-Veterans to have a history of alcoholism, active substance abuse, post-traumatic stress disorder and antidepressant therapy [14]), a few studies in the general population in the United States also reported that many patients were not eligible for therapy [15-17]. To date, such figures are not available for Europe. We therefore investigated the overall antiviral treatment rate and the reasons for non-treatment in a population of HCV-infected patients in Belgium.

Methods

From 1992 to 2003, the Centre for Molecular Diagnosis of Liège, Belgium has depicted 1726 viraemic HCV patients (i.e. those found positive for HCV-RNA by polymerase chain reaction) [18]. From that database, we reviewed the charts of patients who presented to the Academic Hospital Sart Tilman, Liège, Belgium, between 1996 and 2003, for an initial appointment with the same hepatologist. The year 1996 was chosen because effective therapies combining interferon and ribavirin became available at that time in this hospital. Only patients for whom the polymerase chain reaction was requested by this hepatologist were taken into account in the analysis. This attitude was taken to reduce the potential bias of an over-assessment of the treatment rate due to a referring of patients initially evaluated in another centre and sent to the academic hospital in order to initiate the therapy. All patients were evaluated by the same hepatologist, who decided to treat or not to treat on the basis of classical guidelines. For all patients, the following information was gathered: demographics, medical history, modes of contamination and viral genotype. For treated patients, the rate of sustained viral response, of relapse after the end of therapy or of non-response was assessed, as well as the rate of premature discontinuation of therapy. For each untreated patient, we documented reasons for not initiating therapy such as medical contraindications, mood disorders, current pregnancy or desire of pregnancy, refusal, non-adherence to medical evaluation (defined as missing two or more clinic appointments or not attending the appointment for liver biopsy) and normal alanine aminotransferase (ALT) levels.

This study was approved by the Ethics Committee of the University of Liège, Belgium.

Statistical analysis

Comparisons were analysed by either the chi-square test or the Student's *t*-test. The statistical results were considered to be significant at the level of 5%.

Results

The files of 299 patients were reviewed. The mean age was 43.1 ± 15.6 years; 157 patients (53%) were male. Most patients (274 patients) were Caucasians (92%), 22 patients (7%) were Africans and three patients (1%) were Asians.

Risk factors for HCV acquisition were transfusion before 1992 for 127 patients (43%), intravenous drug use for 66 patients (22%), needle-stick injury for four patients (1%), sexual for three patients (1%) and of unknown origin for 102 patients (33%).

Genotypes were determined in 134 patients. Genotype 1 was the most common (89 patients, 66%). Genotype 2 was found in 13 patients (10%), genotype 3 in 16 patients (12%), genotype 4 in 13 patients (10%) and genotype 5 in three patients (2%).

The characteristics of these 299 patients did not differ from those of the 1726 patients of the whole series as far as gender, age, proportion of genotype 1 versus non-genotype 1 and proportion of transfused patients versus non-transfused patients were considered. Actually, 176 patients (59%) were not treated (Table 1).

The reasons for not fulfilling therapy criteria were: normal ALT levels (*n* = 43, 24%), non-adherence to evaluation procedures (*n* = 44, 25%) and medical contraindications (*n* = 60, 34%). The medical contraindications were: psychiatric (*n* = 16, 27%), age (*n* = 13, 22%), end-stage liver disease (*n* = 9, 15%), willingness of pregnancy (*n* = 8, 13%), significant coronary artery disease (*n* = 4, 7%), neoplasm other than hepatocellular carcinoma (*n* = 4, 7%), haematological disturbances (*n* = 3, 5%), autoimmune disease (*n* = 2, 3%) and retinopathy (*n* = 1, 1%). The psychiatric factors included: alcohol abuse (*n* = 4), current or recent drug abuse (*n* = 6), current or recent depressive symptoms (*n* = 4) and other psychiatric disorders (*n* = 4) including bipolar disorder or schizophrenia. The median age of patients excluded from therapy due to their age was 71 years (64-82 years). These patients were considered too old to be treated on a case-by-case decision.

Table 1: *Follow-up of 299 patients evaluated for the treatment of chronic hepatitis C*

Treated (*n* = 123, 41%)	Untreated (*n* = 176, 59%)
Sustained response, *n* = 50 (41%)	Medical contraindication, *n* = 60 (34%)
Non-response, *n* = *48* (39%)	Non-adherence, *n* = 44 (25%)
Relapse, *n* = *5* (4%)	Normal alanine aminotransferase level, *n* = 43 (24%)
Stop treatment, *n* = 20 (16%)	Patient choice, *n* = 29 (17%)

Table 2: *Comparison between treated patients and patients eligible for therapy but who refused to be treated*

	Patients who refused to be treated	**Treated patients**	***P***
n	29	123	
Male/female	12/17	71/52	NS
Age (years) (mean±SD)	47± 13.6	41 ± 14.1	0.026
Risk factor			
Transfusion	12	52	
Intravenous drug use	6	20	NS
Unknown	11	42	
Genotype			
Genotype 1	14	48	NS
Non-genotype 1	6	25	
Metavir score			
Score 0-2	16	74	
Score 3-4	3	31	NS

There was no significant difference between treated patients and patients who refused to be treated except for age.

Despite being considered eligible for treatment, 17% (*n* = 29) of patients declined therapy. Personal circumstances (e.g. currently in school, in search of a new job, living most of the time abroad) were the reasons to delay treatment in a few patients (*n* = 3). In most cases (*n* = 26), however, the patient's decision to delay therapy was the fear of adverse events. These 26 patients, theoretically eligible but who refused therapy, did not differ from the 123 patients who accepted therapy as far as gender, risk factors for HCV acquisition, genotype or stage of fibrosis were considered (Table 2). They were, however, slightly older (47 ± 13 versus 41 ± 14 years, *P* = 0.026) than patients who accepted therapy. Although most refusals could not be considered *a priori* as definitive, no patient who initially refused to be treated changed his or her mind even after some years of follow-up and despite the improvement in the efficacy of therapies.

Eventually, only 123 patients (41%) were treated. The treatment regimens documented during the 7-year period included interferon and ribavirin or pegylated interferon and ribavirin. A sustained viral response was obtained in 41% of patients. The treatment was interrupted in 16% because of side effects.

Discussion

Combination therapy of peginterferon alfa-2a or alfa-2b together with ribavirin has significantly advanced the treatment of chronic hepatitis C and represents the current standard of care. Several large randomized clinical trials have demonstrated that the majority of patients achieve a sustained viral response with this combination therapy [19-21]. However, it appears that in the United States only a small proportion of infected patients benefit from these therapies. Rowan *et al.* [13] in a series of 580 Veterans, and Muir and Provenzale [12] in a series of

100 Veterans, showed that 70% and 68%, respectively, of their HCV patients had not been considered as eligible for therapy. Rocca *et al.* [17] retrospectively reviewed a series of 366 HCV patients listed in the Olmsted County Hepatitis C registry. For these patients, a discussion on treatment was performed for only 234 patients (64%). Among them, 179 (77%) remained finally untreated. In a series of 293 viraemic patients attending a teaching county hospital, Falck-Ytter *et al.* [15] showed that the rate of non-treatment was 72%. The populations of these series, however, were particular, with high proportions of African-Americans (24-51%) and intravenous drug users (43-74%) (Table 3). It was postulated that these American series could not be compared with the population of patients seen in Europe. Epidemiological characteristics and risk factors in our series of patients attending a Belgian academic hospital effectively differed from those of the American series, while being very close to those observed in France in a cohort of 1872 patients [22] (Table 3). Although there were statistically less drug users in our series than in this latter series, the distribution of risk factors in our series did not differ significantly from that described in another French cohort of 6664 patients [23]: 37% of transfusion-related transmission (versus 43% in our series) and 25% of drug addicts (versus 22%).

We found that most (59%) patients evaluated for a treatment were actually not treated. Although we treated significantly more patients than in the aforementioned American series (Table 3) (probably in relation to the academic nature of our hospital [16] and also to the difference in patients' characteristics), a majority of patients were considered non-eligible for therapy.

The most frequent reasons for not treating were medical contraindications, normal transaminases or refusal of therapy by the patient. Among motives for not initiating a treatment, 34/176 (19%) were definitive (end-stage liver disease, cardiac contraindications, leucopenia, age, retinopathy, neoplasia). The others could either be improved (non-compliance, refusal to be treated, drug abuse), be transient (pregnancy) or be related to guidelines' criteria (normal ALT). The recent demonstration, indeed, that the therapy is as effective in patients with normal ALT as in patients with elevated transaminases [24] probably will increase the rate of eligible patients.

Table 3: *Comparison of European and US series versus the Belgian series*

	Delwaide *et al.* (Belgium) [present study]	**Martinot-Peignoux *et al.* (France) [22]**	***P***	**Rowan *et al.* (US Veterans) [13]**	***P***	**Rocca *et al.* (US community) [17]**	***P***	**Falck-Ytter *et al.* (US academic) [15]**	***P***	**Muir and Provenzale (US Veterans) [12]**	***P***
n	299	1872		580		366		293		100	
Age (years) (mean ± SD)	43.1 ± 15.6	43 ± 4	NS	51 ±5	S	40.2 ± na	na	50± na	na	47.3 ± 5.6	S
Ethnic origin											
Caucasians	274 (92%)	976/1059 (92%)		251 (43%)		277 (76%)		158 (54%)		49 (49%)	
Africans	22 (7%)	83/1059 (4%)	NS	250 (43%)	S	89 (24%)	S	102 (35%)	S	51 (51%)	S
Risk factor											
Transfusion	127 (43%)	655 (35%)		114/537 (21%)		89 (24%)		35 (1 2%)		13/74 (1 8%)	
Intravenous drug use	66 (22%)	599 (32%)	S	343/537 (63%)	S	156 (43%)	S	1 93 (65%)	S	55/74 (74%)	S
Genotype											
Genotype 1	89/134 (66%)	851 (46%)		na		na		na		na	
Non-genotype 1	45/134 (34%)	611 (54%)	NS	na		na		na		na	
Treatment											
Treated	123	na		174		55		83		32	
Untreated	1 76 (59%)	na		406 (70%)	S	1 79 (77%)	S	210 (72%)	S	68 (68%)	NS

S, significant difference with the Belgian series at the $P<0.05$ level; na, data not available. Patients in the US series were older and more likely to be African-Americans and intravenous drug users than those in the Belgian series. The proportion of untreated patients was higher in the US series. Belgian patients were, on the contrary, similar to French patients as far as age, ethnic origin or genotype distribution were concerned.

The most frequent reason for the patient refusing therapy was the fear of potential adverse events. Neither the results of genotype determination nor of liver biopsy were predictive of acceptation of therapy in patients theoretically eligible for therapy (Table 2). The side-effect profile of peginterferon versus non-pegylated interferon being quite similar, it is not surprising that most patients who initially refused therapy maintained their position over the 7 years of this study despite the demonstration during these past years of an increased probability of sustained viral response afforded by peginterferon. The side effect profile of the current regimen of treatment of hepatitis C thus remains a serious barrier to therapy.

The overall rate of sustained viral response (41%) observed in the treated patients from 1996 to 2003 was very

similar to that (40%) observed in academic hospitals from 1997 to 2001 in the United States [25]. The rate of discontinuation of treatment (16%) was also similar to those observed in registration trials of pegylated interferon and ribavirin [5,26]. This means that only 50 patients out of 299 referred for chronic hepatitis C (17%) became sustained responders, a figure very close to what has been reported in a teaching county hospital in the United States (13%) [15].

In real life, the majority of patients with chronic hepatitis C are not eligible for interferon plus ribavirin-based therapies. An important barrier to treatment remains the safety profile of these therapies. That emphasizes the need to continue to explore alternative treatment options or strategies for these patients.

Conflict of interest

None declared.

Authors' contributions

Jean Delwaide designed the study. Refaat El Saouda was involved in the acquisition of data. Jean Delwaide, Refaat El Saouda and Christiane Gérard analysed the data and wrote the paper. Jacques Belaïche critically reviewed the manuscript for important intellectual content.

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