

How Severe Is Chronic Hepatitis with HCV Genotype 1b? A Study of 1,220 Cases on the Waiting List for Antiviral Therapy in Romania

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Abstract

Introduction. Chronic HCV infection represents a public health problem in Romania, with a prevalence of 3.23-4.56%, and more than 5,000 patients on the waiting lists for antiviral therapy. **Aim:** To perform an evaluation of the severity of chronic HCV infection genotype 1b, and a quantification of patients with a low viral load, in order to quantify the number of patients who may be considered for shortened treatment duration. **Material:** Histological assessment and viral load were performed in 1,220 consecutive patients from the waiting list for antiviral therapy in 2009. The severity of chronic hepatitis was assessed by histological evaluation (the necrotic-inflammatory index - Metavir and the fibrosis score - Metavir). Viral load was measured by PCR and 400,000UI/ml and 600,000UI/ml were defined as thresholds for low versus high viral load. We assessed the influence of age, sex, and viral load on necro-inflammatory activity and fibrosis. **Results:** The mean age of the patients included was 48 ±10.69 years and females predominated (58%). Many of them (60%) were in stage F3, with a high potential for disease progression in the next 10 years (necro-inflammatory activity was moderate to severe in over 90%). Almost half of the patients had low viral load, below 600,000 copies/ml. The viral load was significantly associated with the age ($p < 0.001$) and sex ($p < 0.001$) of the patients. **Conclusion:** Chronic HCV hepatitis in patients on the waiting lists for antiviral therapy in Romania has a high severity with important predictable consequences on the duration of life, complications and treatment costs. The strategy of shortening the duration of treatment would be beneficial for almost 50% of the patients.

Key words

Chronic hepatitis C – HCV genotype 1b – viral load – severity – histological scores.

Introduction

Chronic virus C hepatitis represents a public health problem in Romania. Recent studies have shown that the prevalence of the virus C chronic infection has reached 3.23-4.56%, which means between 600,000 to 800,000 people [1, 2]. Previously it was proven that almost all the infections are due to HCV genotype 1b [3]. Although controversy still exists, the genotype 1b is considered to be associated with higher levels of viral load, more severe liver injury, higher rates of progression towards liver cirrhosis and poorer response to antiviral therapy as compared to other genotypes of HCV [4-6]. Current predictions showed that requirements for liver transplantation in the patients with chronic HCV infection will increase significantly due to the high number of cases of liver cirrhosis, decompensated cirrhosis, hepatocarcinoma [7-9]. Such an assessment was recently performed by Gheorghe et al also in Romania [10], and it showed that the number of liver cirrhosis, cancers and deaths will increase by over 30% in the next 10 years. These estimations were motivated by the known natural history of HCV infection which showed that only about 20% of the cases of chronic hepatitis turned into liver cirrhosis, while most chronic hepatitis, which were mild to moderate, did not progress or progressed very slowly to cirrhosis [11, 12].

We considered the assessment of the severity of chronic HCV hepatitis necessary in order to assess the situation at present in our country and especially to predict its future consequences. The second task of this study was based on data from previously published studies which showed that the duration of antiviral treatment in the patients with genotype 1b (low viral load below 600,000 UI/ml or below 400,000 UI/ml) could be reduced to 24 weeks [13, 14]. This would allow the treatment of more patients, important because the national waiting list for therapy exceeds 5,000 patients [15]. Besides the financial benefits, shortening of the treatment time period would also minimize the side effects [16].

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Thus, the first goal of the present study was to perform an evaluation of the severity of chronic HCV infection genotype 1b in patients included on the waiting list for treatment. A second goal was the assessment of the percentage of patients with a low viral load in our population, in order to design a short term therapeutic strategy.

Material and method

The centralized system of antiviral therapy approval in Romania, which stipulates liver biopsy and viral load measurement as mandatory for the inclusion into the therapeutic protocol [17], made possible the evaluation of both the histological severity of chronic hepatitis requesting therapy and the proportion of patients with low viral load which could be included in the 24 weeks treatment program.

A number of 1,220 consecutive patients with HCV chronic hepatitis and liver cirrhosis were extracted from the database of antiviral therapy approval in the period January – May 2009. The patients were from all over Romania, as the National Health Insurance House (CNAS) regulations require processing by percentage according to the number of patients on the regional waiting lists. The latest CNAS protocol allowed the inclusion of patients with fibrosis ≥ 1 regardless of the intensity of inflammation or viral load [17]. The patients with co-infection (HBV or HIV) and alcohol intake more than 30 g/day were excluded.

The following parameters were studied:

- Histological grading (NIA – necro-inflammatory activity) of the patients based on the Metavir score, which assesses the extension of the necrosis and inflammation [18]. Category A1 included patients with absent or moderate interface hepatitis and minimal or moderate lobular necrosis; A2 – minimal to moderate hepatitis and moderate to severe lobular necrosis; A3 – severe piece-meal and lobular necrosis.

- Histological stage was also based on the Metavir score: F1 – periportal fibrosis; F2 – portal fibrosis with rare septa; F3 – portal fibrosis with septa and porto-central extension; F4 – cirrhosis [19]. Advanced liver disease was considered when fibrosis was F3 and F4 [20].

- Serum HCV-RNA levels were determined by PCR (real time polymerase chain reaction- Taqman HCV Test - Roche Molecular Systems), with a detection threshold of 50 UI/ml. The proportion of patients with viral load below 600,000 UI/ml and below 400,000 UI/ml was evaluated.

The correlations between viral load and inflammation, and between viral load and fibrosis were calculated, as well as the influence of age and sex on the level of viral load and histological severity.

Statistics

Significance was calculated by Fisher's exact test for categorical variable. Odds ratio and 95%CI were calculated. Normality of continuous data was assessed using the Kolmogorov-Smirnov test. The Student *t*-test was used for data comparison between the two groups. Bivariate

correlations between histological variables and viral load were evaluated using Spearman's *r* coefficient. Adjustments for confounding factors were performed. For all data analyses the Statistical Program for Social Sciences (SPSS V- 17.0) was used.

Results

Of the 1,220 consecutive patients, 1,128 underwent percutaneous liver biopsy (PLB). The remaining 92 patients (7%) underwent no PLB, mainly because of contraindications (hemophilia, hemangioma, thrombocytopenia, coagulation disturbances, obesity etc.). They were evaluated with non-invasive tests (Fibrotest, Fibromax, transient elastography - Fibroscan), two of the tests being required to be concordant for documenting liver disease severity in order to be approved for therapy [17].

The mean age of the patients was 48 ± 10.6 years (range 18 to 68). The female sex was predominant (710/1,220 - 58%), with the female:male ratio=1.39:1.

Histology

Activity of the hepatitis (NIA grading). Most cases of hepatitis were of moderate severity: A2 Metavir (n=919, 81.5%). A relatively small proportion (n=174, 15.4%) were grade A3, and only 35 patients (3.1%) were grade A1. A moderate/severe activity (A2+A3) had almost all our patients (n=1093, 97%) (Table I) .

Table I. Gender, histological aspect and viral load in the studied patients

	Total	Female	Male	p
Patients nr (%)	1,220	710 (58%)	510 (42%)	
With PLB	1,128	656 (58%)	472 (42%)	
Grading (Metavir)				
A1	35 (3.1%)	18 (3.6%)	17 (2.7%)	NS
A2	919 (81.5%)	537 (81.9%)	382 (80.9%)	NS
A3	174 (15.4%)	101 (15.4%)	73 (15.5%)	NS
Staging (Metavir)				
F1	43 (3.8%)	20 (4.9%)	23 (3%)	NS
F2	382 (33.9%)	223 (34%)	159 (33.8%)	NS
F3	675 (59.8%)	401 (61.1%)	274 (57.9%)	NS
F4	28 (2.5%)	12 (1.8%)	16 (3.4%)	NS
Viral load				
<400,000 UI/ml	475 (39%)	305 (43%)	170 (33.4%)	< 0.001
<600,000 UI/ml	585 (48%)	371 (52.3%)	214 (42.1%)	< 0.001

Liver fibrosis (staging). Most cases of hepatitis were in stage F3 (n=675, 59.8%), followed by cases of moderate fibrosis – F2 (n=382, 33.9%), F1 (n=43, 3.8%), and liver cirrhosis (n=28, 2.5%). Advanced liver disease was thus present in almost 2/3 of our patients.

Neither NIA nor fibrosis were significantly different in both sexes. The grade A3 was seen in 73/472 (15.5%) of males and 101/656 (15.4%) of females ($p=0.974$ - OR=0.995, CI 95%=0.717-1.380). The advanced fibrosis F3+F4 was noticed in 290/472 of males (61.3%) and 413/656 (63%) of females ($p=0.57$, OR=1.07, 95%CI=0.784-1.368).

Both NIA and fibrosis were correlated with the patients' age. Mean age was increased when fibrosis was more severe. The patients with A3 were 50.7 ± 9.8 years old, while those with NIA A1+A 2 were 47.6 ± 10.7 years old ($p < 0.001$). Similar results were obtained for fibrosis score: those with F3 + F4 were significantly older (48.5 ± 10.4 years old) than those with F1 + F2 (47.1 ± 10.4 years old) ($p = 0.026$).

Viral load

The viral load was below 600,000 UI/ml in 585 (48%) of the patients, and below 400,000UI/ml in 475 patients (39%) (Table II).

A viral load below 400,000 UI/ml and below 600,000UI/ml was more frequently seen in the younger ages ($p < 0.001$, OR -1.18, 95%CI= 1.08-1.31) (Table II).

A high viral load over 600,000 UI/ml was found in 295 (58%) of men, and in only 338 (47.7%) of women ($p < 0.001$, OR = 1.18, 95%CI = 1.07-1.29).

Necro-inflammatory activity was associated with the level of the viral load. An intense activity A3 was seen in 119/174 (68.4%) patients with viral load over 400,000UI/ml: and in 107/174 patients (61.5%) with viral load over 600,000 UI/ml ($p < 0.001$, OR=1.6, 95%CI=1.15-2.23.)

The level of the viral load was not associated with the fibrosis degree. The differences between patients with F1-F2 when compared to those with F3-F4 with high and, respectively low viral load, were not significant ($p=0.689$, OR-1.52, 95%CI= 0.82-1.345 for 400,000 UI/ml threshold and $p=0.699$, OR-1.05, 95%CI=0.828-1.34 for 600,000UI/ml threshold) (Table II).

Discussion

Our study group of 1,220 patients included mostly women (58%) and had a mean age of 48 years. Data in the literature showed that HCV genotype 1 belonged to patients infected before 1965 [7]. That is not true for our patients.

According to the Romanian patients' mean age, the infection took place most probably after 1965.

The severity of the HCV hepatitis was histologically assessed (NIA + fibrosis), given the fact that liver biopsy is the most accurate criterion of evaluation of patients in the perspective of antiviral therapy. Serum transaminases were not taken into account because no correlations were previously reported with severity, and because severe evolutions were also noticed in patients with normal transaminase levels [21, 22]. However, we assessed the viral load in order to investigate its possible influence on the histological severity and to measure the proportion of patients with a low viral load that might be included in a newly adopted therapeutic strategy. The influence of age was important for the disease course evaluation, and so was gender, since it is considered that chronic HCV hepatitis has a slower and more favorable course in women [22-24].

The great majority of our patients with chronic HCV infection presented advanced liver disease [18, 19]. The percentage of patients with F3 and F4 was almost 2/3 of the total (62.5%), most of them in stage F3 (60%).

At present, our study included 2.5% patients with cirrhosis, but in the next 10 years, with the progression of F3 cases who might develop cirrhosis [25], their number will increase 20 times and, as a result, so will the number of decompensations and complications. Moreover, the patients' duration of life would be reduced by 10-12 years, considering the estimations related to the age when cirrhosis is diagnosed [26]. The relatively young age of our patients is to be noted. The mean age of the 1,220 patients was 48 years, and it corresponds to the mean age of the patients with stage F3. This means that liver cirrhosis will probably occur at a younger age (under 60). Therefore, in Romania the antiviral treatment in patients with viral C hepatitis represents an emergency. Because the majority of our patients had advanced hepatic disease, the fibrosis stage should not be any more a priority criteria for treatment inclusion. The introduction of genetic criteria [27] based on IL28B assessment (ongoing study in Romania) could identify the patients with better probability of therapeutic response (CC genotype) and indicate the patients suitable for the actual antiviral treatment (pegInterferon + Ribavirin). For

Table II. Viral load and patients' age in relation with histology

	Viral load (UI/ml)					
	< 400,000	> 400,000	p	< 600,000	> 600,000	p
No. of patients (n, %)	475 (39%)	743 (61%)		585 (48%)	633 (52%)	
Age-years	46.6 (± 10.8)	49.3 (± 10.4)	< 0.001	47.0 (± 10.8)	49.3 (± 10.4)	< 0,001
Histology						
A1+A2	390 (87.6%)	562 (82.5%)	ns	477 (87.7%)	475 (81.6%)	ns
A3	55 (12.4%)	119 (17.5%)	< 0.02	67 (12.3%)	107 (18.4%)	< 0,001
F1+F2	171 (38.4%)	254 (37.2%)	ns	209 (38.3%)	216 (37.1%)	ns
F3+F4	274 (61.6%)	428 (62.8%)	ns	336 (61.7%)	366 (62.9%)	ns

the remainder of the patients, with TC or TT genotypes, the strategy “watch and wait” should be the strategy to follow [28], including the naïve patients, especially because in the near future new antiviral therapies (Telaprevir, Boceprevir) will be in use.

Contrary to other studies, we found no differences in severity between men and women, both for the NIA and the degree of fibrosis [11, 12, 14].

The level of the viral load was correlated with the patients' age and gender. Mean age of the patients with a viral load below 600,000UI/ml was significantly lower than of those with a viral load over 600,000UI/ml. Statistical significance was also noticed if the viral load threshold was 400,000 UI/ml. We have no explanation for this correlation [11, 14]. The viral load was higher in men (Table I). In the whole group, the viral load was low, almost 50% of the patients having below 600,000UI/ml (42% of men and over 52% of women), which might allow a short-term duration of the treatment (24 weeks) if the therapeutic response is rapid. This would have important economic consequences and also would reduce the side effects [13, 16, 29]. However, this strategy might be risky because recent studies showed that the relapse rate was higher in patients with a short treatment period of 24 weeks [29] and the immediate economic advantage could be diminished by the costs resulting from retreatment (including the new antiviral drugs).

Viral load was not associated with the degree of fibrosis. Ferreira Gonzales et al [30] had similar findings but, unlike their study, we found that viral load influenced NIA, most patients with A3 (Metavir) having a high viral load ($p < 0.001$) for both evaluated thresholds. A high degree of NIA (A2, A3) involves a relatively fast evolution of fibrosis. It is considered that patients with A2 and A3 have a fibrosis progression rate of 0.19 per year [14, 24]. This would reduce more the predictable period of the shift to cirrhosis of the 60% of our patients that have F3. The consequences are extremely serious, involving a considerable increase of hospital admissions and of the cost of treatment of liver cirrhosis and the complications of hepatic failure [31, 32]. This real-life study is much more pessimistic than the estimation based on the Markov model recently performed in Romania [10] or in the USA [6].

Conclusions

Chronic HCV hepatitis in patients on the waiting lists for antiviral therapy in Romania is very severe, almost 2/3 of the patients having advanced liver disease with F3 and F4 fibrosis (Metavir). This situation will result in an increase in the number of cases of decompensated cirrhosis in the next 10 years, with serious consequences on the number of hospitalizations and costs of therapy, as well as a marked reduction of the life duration of those infected by the HCV. These findings call for the increase of the number of patients being treated in order to prevent the evolution to liver cirrhosis. The important number of patients having viremia below 600,000 UI/ml (almost 50%) would allow

the optimization of financial resources, with the view of permitting access to therapy for a higher number of patients.

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Conflicts of interest

None to declare.

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