CHARACTERISTICS OF CHRONIC HEPATITIS C AMONG INTRAVENOUS DRUG USERS: A COMPARATIVE ANALYSIS

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Abstract

Hepatitis C virus (HCV) usually evades the host's immune system and persists as a chronic infection. Intravenous drug users (IVDU) represent the majority of patients infected with HCV. Combined therapy of chronic hepatitis C (CHC) with peginterferon α-2a and ribavirin can be successful even when patients continue the intravenous drug use. In this study, we compared the characteristics of age, gender, genotype, and stage of fibrosis and the therapy outcome among IVDU and patients with no history of drug use. The study included 69 patients diagnosed with chronic hepatitis C, evaluated and treated at the Clinic for infectious diseases in Nis from 2005 to 2009. HCV RNA was detected by a polymerase chain reaction and the determination of genotypes was undertaken. Liver biopsies were examined histopathologicaly. Patients received a combined treatment of peginterferon alfa-2a and ribavirin. Therapy efficiency was evaluated based on the achievement of the sustained virological response (SVR). A comparison of characteristics was performed with the use of Mann–Whitney U test, chi-square (χ^2) test and logistic regression. IVDU were significantly younger than patients in the control group. Prevalence of stage 1 fibrosis was significantly higher among IVDU. The therapy outcome is influenced by the patient's age and HCV genotypes. Each year added to one patient decreased the therapy efficiency by 8.1%, while genotypes 2 and 3 experienced a therapy which was 2.08 times more efficient than in other cases. IVDU represent a specific population different from non-using patients. However, they can be treated effectively if an adequate patient-doctor relationship is established.

KEY WORDS: chronic hepatitis C, intravenous drug users, therapy, genotype, age

Introduction

Hepatitis C virus (HCV) is a blood-borne, hepatotropic, positive-strand RNA virus, which belongs to the *Flaviviridae family*. It is classified into 6 genotypes (1–6) and more than 70 subtypes. It is considered to be one of the most successful of all persistent human viruses. There are numerous ways HCV escapes clearance by the host's immune system: suppressive effects of viral proteins on CD4+ T cells, activation of regulatory T-cells that suppress HCV-specific CD8+-lymphocytes, and mutation in genes encoding viral coat proteins, which avoids detection by antibodies (1). Owing to that, HCV persists as a chronic infection in up to 70% of infected individuals, undermining virus–specific immunity while leaving the host's immunity to other infectious agents intact (2). Chronic hepatitis C (CHC) is a major cause of cirrhosis, liver failure and hepatocellular carcinoma. In Western countries, it is a leading indication for liver transplantation (3). Due to the improved blood transfusion safety and better healthcare conditions, injection drug use has became the main mode of viral transmission and accounts for more than 60% of prevalent cases in Europe (4). Intravenous drug users (IVDU) are frequently engaged in risky behaviour, favouring an extensive HCV spread. In addition, there is compelling evidence that morphine, and its synthetic product heroine, negatively affect both the immune system and hepatocytes. Morphine modulates the immune system either directly, by binding to μ-opioid receptors present on immune cells (T lymphocytes, B-lymphocytes, NK cells, monocytcs, macrophages), or indirectly, within the central nervous system. Opioids activate the descending pathways of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system. Activation of the hypothalamic-pituitary-adrenal axis starts the production of immunosuppressive glucocorticoids in the periphery, while the activation of the sympathetic nervous system triggers the release of noradrenalin. Both noradrenalin and glucocorticoids act on leukocytes and negatively modulate immune capability (5). Morphine, through interference with p38 signalling pathways, inhibits intrahepatic IFN-α expression. This is associated with the increased susceptibility of naive hepatic cells to HCV infection. Down-regulation of IFN-α–mediated innate immunity also favours HCV replication in hepatic cells. Opioids can also hamper the current IFN-α–based anti-HCV therapy (6). A combined therapy of CHC with peginterferon α-2a and ribavirin can be successful even when patients continue intravenous drug use, or if they are on the daily methadone regime. Methadone treatment extenuates risky behaviour and it is not a contraindication for CHC therapy (7). There may be differences in the virological evolution, immune response, therapy outcome and other characteristics between patients who acquired HCV through ongoing drug use with contaminated needles, compared to the immune response in patients with no history of drug use. The aim of this study was to assess characteristics of CHC and the therapy outcome between IVDU and non-using patients.

Materials and Methods

The study included 69 patients diagnosed with chronic hepatitis C, evaluated and treated at the Clinic for infectious diseases in Nis from 2005 to 2009. Among them, there were 48 men and 21 women. Based on the intravenous substance abuse, patients were divided into the experimental and control group. The experimental group included patients with a substantial history of past or present use of drugs through injection, while the control group consisted of patients who reported never using drugs intravenously. The average age of the patients was 33,4 in the experimental group and 46,2 in the control group. All participants displayed an elevated transaminase activity 6 months prior to the inclusion in the study. HCV RNA was detected by the polymerase chain reaction (PCR, Roche Amplicor) before therapy commencement. The number of HCV copies in the serum was 109 830 – 12 231 000/ml (x = 1 5480 630). The determination of HCV genotypes was undertaken in all samples. Liver specimens were formalin-fixed and paraffin embedded for histological evaluation, and analyzed by experienced pathologists. The degree of fibrosis was graded using the METAVIR scale. None of the patients had hepatitis B or HIV co-infection. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Patients with HCV genotypes 1 and 4 were treated with peginterferon alfa-2a and ribavirin for 48 weeks, and the patients with HCV genotypes 2 and 3 received treatment for 24 weeks. 180 μg of peginterferon alfa-2a was administered once a week, and the ribavirin dosage was from 800 to 1200mg/day. Doses were adjusted, when side effects such as leucopoenia, thrombocytopenia or anaemia occurred. Therapy efficiency was evaluated based on the achievement of the sustained virological response

(SVR). SVR was confirmed by undetectable serum HCV-RNA 6 months after the completion of treatment.

Statistical methods. The Mann-Whitney U test was used to compare values of noncategorical parameters (age, time until therapy begun). The Chi square test or Fisher exact test were used to compare categorical parameters between groups. Logistic regression analysis was performed to determine whether covariates (IVDU, gender, age, time until therapy commenced) significantly associated successful therapy. OR values with 95% confidence intervals were presented. The analyses were carried out using SPSS 10.0 for Windows, Microsoft Excel 2003 and STATCALC computer statistical packages. Significance levels were set at p<0,05.

Results

Characteristics of IVDU and control group were compared. IVDU were significantly younger than patients in the control group (33,4 ± 4,2; 46,2 ± 9,8 years of age), and the time until therapy had started was shorter (2,9±1,3; 4,3±2,6 years of age). Treatment was successful in a significant number of patients of the experimental group (93,5%:52,6%) (Table 1.). Prevalence of stage 1 fibrosis was significantly higher among IVDU (41,9:10,5%). In the control group, 16 patients were without fibrosis (42,1%) and stage IV fibrosis was present in 6 patients (15,8%) which was significantly higher compared to IVDU where there were no patients without fibrosis and no patients with stage IV fibrosis (Table 2.). The differences of gender structure, presence of co infections, and number of copies at the beginning of therapy between the control and experimental group were not statisticaly significant (Table 1.). IVDU patients were more likely associated with successful therapy (OR=1,78) than patients of the control group (Table 3.). Patients with HCV genotypes 2 or 3 were more likely associated with successful therapy than the others. The chance for the successful therapy decreased by 8,2% for every year of age. Multivariate logistic regression analysis isolated patient's age and genotypes 2 and 3 as factors that affect therapy outcome (Table 4.). Each year added to one patient decreased the therapy efficiency by 8,1%, while genotypes 2 and 3 experienced a therapy which was 2.08 times more efficient than in other cases.

Baseline characteristic	Groups		*P*
	Experimental (N=31)	Control (N=38)	
Gender			
male	25 (80,6)	23 (60,5)	0,071
female	6 (19,4)	15 (39,5)	
age (years)	33,4±4,2	46,2±9,8	**<0,001**
Time until therapy begun (years)	2,9±1,3	4,3±2,6	**0,009**
Co infection	2 (6,4)	1 (2,7)	0,580
Genotype			
1or 4	14 (45,2)	24 (63,2)	0,211
2 or 3	11 (35,5)	12 (31,6)	0,932
mixed	6 (19,4)	2 (5,3)	0,150
Efficient therapy	29 (93,5)	20 (52,6)	**<0,001**
Relapse	-	2 (5,3)	0,498
Nº of copies at the beginning of therapy			
Up to 1 million	12 (38,7)	12 (36,4)	0,715
1 to 2 million	9 (29,0)	7 (21,2)	0,452
More than 2 million	10 (32,3)	14 (42,4)	0,886

TABLE 1. Comparison of CHC patients' baseline characteristics in the control and experimental group

Stage of liver fibrosis	Groups		*P*
	Experimental (N=31)	Control (N=38)	
No fibrosis	-	16 (42,1)	**<0,001**
I stage	13 (41,9)	4 (10,5)	**0,006**
II stage	9 (29,0)	6 (15,8)	0,301
III stage	9 (29,0)	6 (15,8)	0,301
IV stage	-	6 (15,8)	**0,029**

TABLE 2. The degree of fibrosis in the control and experimental group

Factor	OR	95% CI for OR limit	*P*
IVDU	1,780	1,301- 2,443	**<0,001**
Male gender	0,971	0,313 - 3,016	0,960
Female gender	1,029	0,332 - 3,196	0,960
Age	0,918	0,890 - 0,946	**<0,001**
Time until therapy commenced	0,857	0,677 - 1,085	0,199
No fibrosis	0,418	0,130 - 1,345	0,144
I stage fibrosis	2,266	0,573 - 8,964	0,243
II stage fibrosis	7,598	0,927 - 62,295	0,059
III stage fibrosis	0,525	0,158 - 1,741	0,292
IV stage fibrosis	0,370	0,068 - 2,011	0,250
Co infection	0,118	0,011 - 1,213	0,072
Genotype 1or 4	0,561	0,191 - 1,645	0,292
Genotype 2 or 3	3,904	1,009 - 15,101	**0,048**
Mixed genotype	0,356	0,079 - 1,591	0,176
Nº of copies at the beginning of therapy up to 1 million	1,041	0,343 - 3,158	0,944
Nº of copies at the beginning of therapy up to 2 million	1,364	0,377 - 4,932	0,636
Nº of copies at the beginning of therapy more than 2 million	0,759	0,253 - 2,271	0,621

TABLE 3. Odds Ratio values for assessment of successful therapy (univariate logistic regression)

Factor	OR	95% CI for OR˚limit	*P*
Age	0,919	0,896 - 0,942	**<0,001**
Genotype 2 or 3	2,081	1,198 - 7,931	0,037
Constant of regression	21,681		0,011

TABLE 4. Odds ratio values for assessment of successful therapy (multivariate logistic regression)

Discussion

With the worldwide population of IVDU between 15 and 21.5 million, the problem has become a prevalent global concern, unrestricted by a country's level of development or location (8). According to the literature, 90% of IVDU are infected with HCV (7). Since the majority of HCV infected individuals will develop chronic infection, IVDU is a persistent reservoir for transmission to other users and the non-using community. Treatment of chronic hepatitis C in patients with drug addiction requires the cooperation of specialists for Hepatology, addiction and psychiatry. The response might be improved significantly if patients take over 80% of the medication during 80% of the treatment time. The therapeutic outcome can be achieved by improving compliance, reducing side effects and by an interdisciplinary case management (9). This study compared characteristics of HCV infection among IVDU and non-using patients. Genotype 1 is the most frequent among both IVDU and patients of the control group. In the control group, it represents more than half of all infections. The prevalence of HCV genotypes in our hospital generally follows the European genotype pattern. Similar results are found in studies in Italy, Western Turkey, Greece and Slovenia (10, 11, 12 and 13). However, a study in Poland showed that genotype 3 constituted the majority of HCV infections in IVDU (14). IVDU were significantly younger than non-using patients, with higher rates of stage I fibrosis and a better therapy outcome. Experimental models showed that the repeated administration of morphine interferes with hepatic antioxidant defence, especially through modulation of glutathione synthesis and catabolism pathways. This pro-oxidant property would be responsible for induction of apoptosis in hepatocytes (15). The presence of stage IV fibrosis among non-using patients of the control group can be explained by the asymptomatic development of HCV infection. The viral genotype, low viral load, age of 40 or less and the stage of liver disease represent the most powerful predictive factors of SVR according to several studies (16, 17 and 18). Our findings that Genotypes 2 and 3 have a twice better therapy outcome are not only consistent, but higher than the results of the multicentric study performed in Germany in 2007, where more than 60 % of the patients with genotypes 2 and 3 had SVR (19). The IVDU in our study showed a better therapy outcome than in non-using patients. A recent German study showed that even severely dependent IVDU, on continuous heroin uptake, could achieve viral response rates comparable to those of the non-using population, and even better than in most studies under methadone maintenance (20). Younger people, absence of co morbidities, short interval between the HCV verification and therapy commencement and patient's compliance, might explain high percentage of therapy efficiency in our experimental group. Although the patients' gender has an impact on fibrosis progression, and the progression to cirrhosis is 10 times more rapid in men than in women (21), our study showed no significant gender influence on the therapy outcome The role of ageing in fibrosis progression is evident. It is related to the higher vulnerability to environmental factors (especially oxidative stress), reduction in blood flow, mitochondrial capacity or immune capacities. The estimated probability of progression per year for men aged 61–70 was 300 times greater than that for men aged 21–40 (22). However, certain studies show that a patient's age cannot be regarded as an independent predictor of therapy outcome. A Greek study made in 2008 showed that only the histological stage of liver disease had a significant impact on the SVR among older patients (23). Our results show that therapy efficiency decreases by more than 8% for every year added to a patient. This finding suggests that the treatment response of young CHC patients with mild liver disease or even without histologicaly proven liver disease, irrespective of the viral genotype, should be differentiated from the response of old CHC patients, even those infected with the "easy-to-treat" genotype 2 or 3. Given the often asymptomatic nature of the HCV-associated liver disease, IVDU may not experience symptoms associated with liver disease and may not seek treatment for HCV, due to the lack of knowledge about the potential long-term consequences of HCV and the availability of effective treatment. IVDU are often denied therapy due to the concerns about adherence, susceptibility to side effects (e.g. depression), and re-infection risks (24). We found that these problems can be surpassed by establishing high motivation among IVDU through a good doctor-patient relationship. A Norwegian Pilot Study showed 100% therapy compliance and 94% SVR among IVDU in OSLO, stating that the key to successful treatment is the support from the medical team (25).

Conclusion

IVDU represents an independent group of CHC patients with an age range and a stage of fibrosis different from the non-using patients. The therapy outcome of Genotypes 2 and 3 is better than in other cases. Since every year added to a patient decreases therapy efficiency, the patient's age should be taken into account in everyday clinical practice when predicting SVR and the therapy outcome. Despite the risks of non-compliance and side effects, IVDU can be treated successfully. Increasing the education on HCV and its treatment of both patients and physicians is important for future results. Any comprehensive approach to control an HCV epidemic must include a strategy that addresses this group. Effectively engaging marginalized individuals in HCV treatment is crucial for lowering the future HCV-related disease burden.

List of Abbreviations

HCV	–	Hepatitis C virus
IVDU	–	Intravenous drug users
CHC	–	Chronic hepatitis C
SVR	–	Sustained virological response
PCR	–	Polymerase chain reaction

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