THE SUCCESS OF TREATMENT OF CHRONIC HEPATITIS C IN OPIATE ADDICTS IN CLINICAL CENTER OF VOJVODINA

SAŽETAK


KLJUČNE RЕČI: Hronični hepatitis C; Opijatski zavisnici; Adiktivno ponašanje; Antivirusni lekovi; Ishod lečenja; Interferon alfa; Ribavirin

Summary

Introduction: Chronic hepatitis C is a disease with a high prevalence in the population of intravenous drug users. Serious clinical course of the disease, which can lead to cirrhosis of the liver with all its complications, has a large epidemiological and clinical significance. This study was aimed at assessing the success of antiviral treatment of chronic hepatitis C in intravenous drug users and defining indicators of successful treatment in this population. Materials and Methods. This retrospective study included 316 patients treated with standard therapy for chronic hepatitis C, pegylated interferon and ribavirin, at the Department of Infectious Diseases, Clinical Center of Vojvodina in Novi Sad in the period from January 2007 to December 2012. The patients were divided into a group of intravenous drug users (n = 163) and a group of other modes of transmission of hepatitis C virus (n = 153). The indicators of successful treatment were measured in both groups. Results. A total 51.57% of the subjects belonged to the group of intravenous drug users. The therapy was successful in 87.15% of cases, while the success was achieved in only 53.47% of cases in the group of patients infected otherwise. The positive effect of therapy was associated with younger age, shorter duration of infection, low levels of fibrosis and a higher percentage of infected with hepatitis C virus genotypes 2 and 3. Conclusion. The population of intravenous drug users can be effectively treated with the standard therapy for chronic hepatitis C, even more successfully than the population infected in some other way.

Key words: Hepatitis C; Chronic; Opioid Related Disorders; Behavior, Addictive; Antiviral Agents; Treatment Outcome; Interferon-alpha; Ribavirin

Introduction

Hepatitis C is an inflammatory disease of the liver caused by the hepatitis C virus (HCV). The genome of this virus was identified in 1989. [1] Serological tests for its identification were introduced in most countries in 1991 [2, 3]. Identifying anti-HCV antibodies in our country began in late 1994 [4].
The hepatitis C virus is a small, single-stranded ribonucleic acid (RNA) virus and a member of the genus Hepacivirus of the Flaviviridae family [5]. Six genotypes were defined by analyzing the genomic sequences of HCV, labeled with numbers from 1-6, each with its subtypes and quasispecies [6]. Determining the genotype of the virus has epidemiological significance because certain types are specific to certain parts of the world and also have clinical significance since some genotypes are associated with the development of more severe form of the disease and its faster progression [7].

Pathogenesis of hepatitis C virus infection is still not fully understood. Immune mechanisms and direct cytopathic effect of the virus are reviewed as etiological factors [8, 9].

Epidemiological studies estimate that between 2.2% and 3% of the world population is currently infected with HCV, the total number being between 130 and 170 million people [10]. Data on the number of infected people in Serbia are not available. Since hepatitis C is a blood-transmitted disease, the majority of patients in developed countries belong to the group of injecting drug users (IDUs), the prevalence exceeding 90% [11]. The second most common group is the one that developed post-transfusion hepatitis C, also there is a group with sexual route of transmission, as well as iatrogenic transmission of infection during medical interventions (endoscopy, surgery), through dialysis, transplantation of organs and tissues, during tattooing, piercing and common use objects (scissors, razors, toothbrushes) [12]. Vertical transmission from mother to newborn is possible in 4-7% of cases [13].

Clinical manifestation of acute hepatitis, which develops after the incubation period of 6-7 weeks, runs inconspicuously in 75-80% of cases with nonspecific symptoms such as fatigue, loss of appetite, pain under the right costal margin and jaundice. The laboratory results record ten times more elevated activity of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), more elevated activity of alanine aminotransferase for more than six months and the persistent presence of HCV RNA in serum. It is either asymptomatic or has nonspecific symptoms. The chronic stage of disease is characterized by frequent presence of extrahepatic manifestations (arthralgia, myalgia, skin reactions, symptoms of renal impairment, a disorder of the thyroid gland function, and symptoms of diabetes). In the advanced stage of chronic HCV infection, the dominant symptoms and signs of the disease result from liver cirrhosis. Cirrhosis develops in 20-30% of the chronically infected patients within a period of 20-30 years, and the development of hepatocellular carcinoma (HCC) is possible [14-16].

The diagnosis is made according to anamnesis and epidemiological data, clinical features, laboratory findings and liver biopsy. Laboratory tests have significant pathological ALT activity, positive antibodies to hepatitis C virus (anti-HCV) and confirmed presence of HCV RNA by PCR technology [17]. Liver biopsy confirms the diagnosis of chronic liver inflammation and determines the intensity of necro-inflammatory process and the degree of liver fibrosis [18, 19].

Chronic HCV infections therapy is carried out by combining two specific antiviral drug: pegylated interferon α and ribavirin. There are two forms of pegylated interferon available on the market: pegylated interferon α2a, which is applied in a fixed dose of 180 mg and pegylated interferon α2b, which is administered at a dose of 1.5 mg per kg of body weight. Ribavirin is an antiviral agent from the group of nucleoside inhibitors, which is applied in the form of tablets of 200 mg and dosed according to the patient’s body weight, 800-1200 mg per day. The length of treatment depends on the genotype of HCV, being 24 weeks for genotype 2 and 3 and 48 weeks for the other genotypes [20].

The success of therapy was assessed by measuring the amount of HCV RNA in the serum by PCR method six months after its completion. It is believed that the therapy is successful if it has achieved a sustained viral response (SVR), there are no particles of HCV RNA in the serum of patients six months after completion of antiviral therapy. The patients who achieved SVR are considered cured because such findings are maintained in more than 99% of patients over time [21]. The combined administration of pegylated interferon with ribavirin has yielded positive results in over 60% of patients and in over 80% of selected patients [22].

Studies have shown that as many as 60-90% IDUs have chronic infection with hepatitis C [23, 24]. Despite great advances in the diagnosis and treatment of these diseases, there is a large number of IDUs with hepatitis C who are not treated [25]. The main problems in the treatment of this population are their inability to maintain abstinence from addictive substances, risk of re-infection, influence of the replacement therapy, alcohol abu-
se and bad adherence. Recent studies have shown that CHC can be effectively and safely treated in IDUs, especially in those receiving replacement therapy with methadone or other drugs [26, 27]. Therefore, treatment of CHC in population of IDUs should become a component of therapeutic guide in all health care systems, because there cannot be a reduction in the prevalence of CHC unless the infection is controlled in this group.

The aims of this study were:
To determine whether intravenous drug users with CHC can be effectively treated with standard dual therapy for this disease.
To compare the results of therapy within IDUs population with the results of treatment of patients infected otherwise.
To define indicators for successful treatment in the population of IDUs.

Material and Methods

The research was conducted as a retrospective study that included 316 patients with CHC, of whom 163 were injecting drug users, examined and treated at the Department for Infectious Diseases, Clinical Center of Vojvodina in Novi Sad from January 2007 to December 2012 year.

The diagnosis of CHC was based on clinical and laboratory findings including aminotransferases ALT and AST activity having at least double values, positive anti-HCV antibodies for more than six months, a positive qualitative and quantitative HCV RNA PCR test to determine the amount of viremia expressed in the number of copies of the virus per milliliter (cop/ml), HCV genotype and histopathological examination of liver biopsy.

Determination of HCV RNA was performed at the Virology Laboratory of the Institute for Infectious and Tropical Diseases, Clinical Center of Serbia in Belgrade. Cobas Amplicor HCV Test, version 2.0 (Roche Diagnostics, Menheim) was used as a qualitative test, with sensitivity of 50 IU/ml (135 cop/ml). The quantitative test was Cobas Amplicor HCV Monitor Test version 2.0 (Roche Diagnostics, Menheim), sensitivity of 600 IU/ml (1620 cop/ml). The genotype was determined by Linear Array HCV genotyping assay (Roche Diagnostics). All patients were tested before the introduction of antiviral therapy, as well as six months after the completion of therapy.

A blind liver biopsy was performed in all patients prior to therapy, except for those in whom this procedure was contraindicated. A sample of liver tissue was treated with standard histological techniques for small biopsies and stained with hematoxylin-eosin method. The degree of fibrosis was expressed by the modified Knodell’s numerical score.

The patients were treated with standard therapy for CHC, i.e. the combination of pegylated interferon α2a (Pegasys®) or α2b (Pegintron®) with ribavirin (Copegus® and Rebetol®). The therapy was considered successful when the stable virologic response was achieved (undetectable HCV RNA six months after the treatment). It was considered a failure if HCV RNA values had not been reduced by more than 2 logs compared to the initial ones (non-responders), and if the presence of HCV RNA was proved six months after the completion of treatment which was negative during the treatment (relapsers). The following factors were considered predictive for successful treatment: age, sex, body mass index (BMI), duration of infection, viral genotype and degree of liver fibrosis.

The duration of infection was determined on the basis of data on the presumed date of inoculation, while the duration of infection in patients with unknown mode of transmission of HCV was not taken into consideration.

All intravenous drug addicts were abstinent for at least 12 months prior to treatment, which was confirmed and documented with reports of psychiatrists.

Statistical analysis included descriptive statistics and tests of significance ($\chi^2$ and t-test) while the calculation was done by computer programs Excel and the Statistical Package for the Social Sciences (SPSS).

The statistical significance was determined by p-value, which represents the risk of concluding. The difference was considered statistically significant at p <0.05.

The results are expressed by the absolute numbers, percentages, tables and graphs with the accompanying text.

Results

Out of 316 patients with CHC included in the study, 163 were opiate addicts (51.57%) and 153 patients were infected with hepatitis C virus in some other way (48.43%).

Post-transfusion hepatitis was found in 43/316 (13.61%) patients, infection was sexually transmitted in 8/316 (2.53%) patients, tattoo and piercing caused infection in 11/316 (3.48%) patients, medical procedures (other than hemodialysis) resulted in infection in 8/316 (2.53%) patients, and hemodialysis caused infection in 9/316 (2.85%) patients, while the cause remained unknown in 74/316 (23.42%) patients. Distribution of patients according to the mode of transmission of hepatitis C virus infection is shown in Graph 1.

The success of antiviral therapy, estimated by the achievement of a SVR was found in 300/316 (94.94%) patients. The success of therapy remained undetermined in the patients who discontinued treatment themselves (5.06% of the patients, 16/316). The treatment was successful in 213/300 (71.0%) patients and failed in 87/300 (29.0%) patients. Among the unsuccessfully treated patients
there were 43/300 (14.33%) non-responders and 44/300 (14.67%) relapers (Graph 2).

The success of therapy was examined in 156 patients from the group of IDUs. Therapy was successful in 136/156 patients (87.18%), while it was unsuccessful in 20/156 (12.82%) cases. In the group of patients infected otherwise the success of therapy was assessed in 144 people and treatment was found to be successful in 77/144 (53.47%) and unsuccessful in 67/144 (46.53%) cases. A statistically significant difference was found in the distribution among the studied groups (p<0.05) (Graph 3).

Furthermore, some indicators of success of therapy were analyzed in both groups, as shown in Table 1.

As for gender, there were 128 (78.53%) males and 35 (21.47%) women in the group of IDUs and 96 (62.75%) males and 57 (37.25%) females in the control group. No statistically significant difference was found in the distribution of sex (p>0.05).

The average age of the group of IDUs and in the control group was 32.61 (SD± 6.52) years and 44.96 (SD±12.44) years, respectively. The difference was found to be statistically significant (p<0.05).

The average BMI in the group of IDUs and in the control group was 24.11 kg/m² and 25.45 kg/m², respectively. Obese patients with BMI above 30 kg/m² were not included in the study. The difference was found to be statistically significant (p<0.05).

The duration of infection in intravenous opiate drug addicts and in the group with the known cause of infection was on average 10.09 (SD± 6.04) years and 20.52 (SD±10.29) year, respectively. The difference was found to be statistically significant (p<0.05).

HCV genotyping was done in all patients. The group of opiate addicts had the highest number of genotype 1, 80/163 (49.07%), it was followed by genotype 3 in 75/163 (46.01%), genotype 4 in 4/163 (2.45%), genotype 2 in 2/163 (1.23%) and 2/163 (1.23%).

Table 1. Indicators of therapy success rate in both groups

<table>
<thead>
<tr>
<th>Drug addicts</th>
<th>Others</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>32.61</td>
<td>44.96</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.11</td>
<td>25.45</td>
</tr>
<tr>
<td>Genotype</td>
<td>2 and 3 (%)</td>
<td>47.24</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>F0, F1 and F2 (%)</td>
<td>90.8</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>F3 and F4 (%)</td>
<td>9.2</td>
</tr>
</tbody>
</table>

Graph 1. Mode of transmission of HCV infection

Graph 2. Therapy success rate in the total sample
(1.23%) patients had two or more genotypes. The control group had 110/153 (71.89%) patients with genotype 1; 30/153 (19.61%) patients had genotype 3; 7/153 (4.57%) patients had genotype 2; 1/153 (0.65%) patients had genotype 4 and 5/153 (3.27%) patients had two or more genotypes. Genotypes 5 and 6 were not identified. A statistically significant difference was found in the distribution between the groups (p<0.05).

Because of the different therapeutic modalities, the patients were divided into two groups: one group consisted of patients infected with HCV genotypes “2, 3”, which are considered easier to treat and achieve better therapy success, and another group of “1, 4” genotypes, classified as other genotypes, whose treatment is difficult and less successful. The number of patients with genotypes “2, 3” was 77/163 (47.24%) in the group of IDUs and 37/153 (24.18%) in the group of patients infected otherwise. The number of patients with “1, 4” genotypes in the group of addicts was 86/163 (52.76%), while in the group of otherwise infected patients it was 116/153 (75.82%). A statistically significant difference was found in distribution between the groups (p<0.05) (Graph 4).

Viral load was determined in all patients and the group of IDUs was found to have 11 517 733.8 cop/ml (±SD 21 997 317.28), and those infected in some other way had 9 859 044.95 cop/ml (SD± 14 734 036.56). There was no statistically significant difference (p=0.05).

Histopathological examination of liver biopsy specimens revealed liver fibrosis in 298 patients. Liver biopsy was contraindicated in 18/316 (5.7%) specimens revealed liver fibrosis in 298 patients. 734 036.56). There was no statistically significant difference (p> 0.05).

18/135 (13.33%), low degree, moderate and severe fibrosis was found in 39/135 (28.89%), 40/135 (29.63%), and 27/135 (20.0%), respectively and the signs of liver cirrhosis were present in 11/135 (8.14%) patients. A statistically significant difference was found in the distribution among the studied groups (p<0.05).

According to the presence and degree of fibrosis, which are the factors influencing the effectiveness of treatment, the patients were divided into the group without fibrosis or with signs of mild to moderate fibrosis (F0-2) and the group with signs of severe fibrosis and cirrhosis (F3-4). The treatment was successful in the former and less successful in the latter. There were 148/163 (90.8%) F0-2 patients and 15/163 (9.20%) F3-4 patients in the group of addicts. There were 97/135 (71.85%) patients with F0-2, and 28.15% with F3-4 in the group of patients infected in some other way. A statistically significant differences was confirmed in the distribution (p<0.05) (Graph 5).

Discussion

Chronic hepatitis C with liver cirrhosis as the final outcome is a major health issue mainly in the working-age population. Correlation between chronic HCV infection and opiate addiction, which is also intensifying, is becoming an obstacle to be yet overcome by modern medicine.

Treatment of CHC is still not efficient enough, although the development of new drugs and better selection of patients increase the treatment success rate. In our study, treatment of CHC was successful in 71.0% of cases from the whole study group, which is in accordance with most published studies, which have reported successful treatment of chronic hepatitis in 50-80% of cases [28, 30]. Worse treatment success than in our study was made in the studies which included previously unsuccessfully treated patients, patients with elevated BMI and patients who were not in stable abstinence from psychoactive substances and alcohol. These are the factors which have negative influence on antiviral treatment.

The report on successful treatment of CHC in our study is consistent with the published study of our colleagues Delic et al. who reported the effectiveness of treatment for CHC in 70.52% of cases [31]. Kulić-Kapulica et al. reported successful treatment of CHC in 55.5% of cases, which is less than in our study [32]. Their study sample had a smaller number of IDUs, who are known to be more responsive to antiviral therapy, which can explain lower treatment success rate in their study.

Intravenous opiate addicts represent the largest part of the population of patients treated for CHC at the Department of Infectious Diseases, Clinical center of Vojvodina in Novi Sad and they accounted for 51.57% of the subjects in this study. Jovancic et al. from the Department of Infectious Disea-
ses in Niš have reported the success of treatment of CHC in 93.5% of IDUs, which is very similar to our result of 87.18% [33]. Although their sample was much smaller (30 patients), the patients were selected for antiviral therapy according to the same principle, and they had very similar demographic and clinical characteristics and were treated by the same therapeutic protocol as ours. Only 30.46% of patients treated with standard viral therapy for CHC were opiate addicts who were included in the study of Kurelac et al. from the Croatian Reference Center for Viral Hepatitis [34]. They reported that successful therapeutic response in their study was achieved in only 57.10% of all patients with CHC, and in 70.75% of intravenous drug addicts. In our study, better therapeutic effects were achieved due to better selection of patients. Due to the current regulations of the Commission for Antiviral Therapy of CHC affiliated to the Republican Health Insurance Fund, our patients undergo more rigorous screening, taking into account predictors of successful treatment, and thus the success of treatment of CHC is higher. In addition, our study sample consisted mainly of patients with CHC virus infection, who had never been treated with antiviral therapy, and it is known that the success of treatment in these patients is greater than in previously unsuccessfully treated patients [35].

Our research has shown that IDUs have a better response to antiviral therapy, which is associated with predictors of successful treatment such as younger age, shorter duration of infection and lower degree of fibrosis.

In relation to the type of genotype in the group of IDUs, there was a significantly higher number of patients with genotypes 2 and 3, (47.24%) than in the group of patients infected with the other genotypes (52.76%), which is consistent with previously published reports in literature [36, 37].

Conclusions

The population of intravenous drug users can be effectively treated by standard dual antiviral therapy for chronic hepatitis C.

Injecting drug users have better therapy results than patients infected otherwise.

Indicators of successful treatment in injecting drug users are: younger age, shorter duration of infection and lower degree of fibrosis.

References