



## Treatment of chronic hepatitis C in injecting drug users – A 5-year follow-up

### Lečenje hroničnog hepatitisa C kod intravenskih zavisnika – 5-godišnje praćenje

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#### Abstract

**Background/Aim.** Hepatitis C infection (HCV) is a systemic, generalised disease with the prevalence of inflammation in the liver. The aim of this study was to determine the success of treatment for chronic hepatitis C with pegylated interferon alfa 2a and ribavirin in injecting drug users. **Methods.** This a 5-year follow-up study included 30 patients [63.3% men and 36.7% women, average age 30.2 years (SD 7.1 years)] injecting drug users in one-year abstinence, with chronic hepatitis C, treated with the pegylated interferon  $\alpha$  2a and ribavirin. Complete history with possible route of infection, the standard biochemical tests, liver biopsy, quantification of the viral genome in sera and HCV genotyping and subtyping were done prior to the therapy initiation. Depending on the HCV genotype, the therapy was conducted over a period of 48 weeks for genotype 1 and 24 weeks for genotype non 1. Five years later all 30 patients were invited on control examination; 22 of them appeared at the check-up and quantification of the viral genome in their sera were analyzed. **Results.** The established degree of liver fibrosis was: F0 in 40%, F1 in 23.33%, F2 in 26.67%, F3 in 3.33% and F4 in 6.67% of the patients.

Genotype 3a was dominant (50.0%), 1b was registered in 40.0%, 1a in 6.66% and 2b in 3.33% of the patients. Sustained virologic response (SVR) was achieved in 86.7% of the patients, 10.0% of the patients were non-responders, while 3.33% of them revealed recurrence of HCV. Opiate abuse recurrence during antiviral therapy happened in 6.7% of the patients. Five years after the antiviral therapy 73.3% of the patients appeared at the check-up and all of them were in stable abstinence from opiate abuse. All of those, with a sustained viral response of five-year duration, had the negative PCR HCV RNA test ( $< 50$  IU ml<sup>-1</sup>). In the patients showing unsatisfactory therapy response 5 years before, antiviral therapy was repeated by the same therapeutic regimen, but without adequate therapeutic response. A total of 26.7% of the patients were lost from the records. **Conclusion.** In a 5-year follow-up period 73.3% of the patients used to come regularly to check-ups and among them neither the opiate abuse recurrence nor HCV infection recurrence were registered.

**Key words:**  
hepatitis c, chronic; interferon alfa-2a; ribavirin;  
substance abuse, intravenous; treatment outcome.

#### Apstrakt

**Uvod/Cilj.** Infekcija virusom hepatitisa C (*hepatitis C virus* – HCV) spada u sistemske generalizovanje bolesti sa prevalencijom zapaljenja jetre. Cilj istraživanja bio je da se ustanovi uspeh kombinovane antivirusne terapije pegilovanim interferonom  $\alpha$  2a i ribavirinom u lečenju hroničnog hepatitisa C u grupi zavisnika od opijata u apstinenciji, definisan periodom od 5 godina. **Metode.** Ova retrospektivno-prospektivna studija obuhvatila je 30 obolelih od hroničnog hepatitisa C [63,3% muškog, 36,7% ženskog pola, prosečne starosti 30,2 godine (SD 7,1 godina)], zavisnika od opijata u jednogodišnjoj apstinenciji, lečenih pe-

gilovanim interferonom  $\alpha$  2a i ribavirinom. Kod bolesnika su analizirani anamnestičko-epidemiološki podaci, klinički tok bolesti, patohistološki nalaz biopsije jetre, kao i serološki i virusološki parametri HCV infekcije (kvalitativni PCR HCV RNA i genotip HCV), pre uvođenja terapije. U zavisnosti od genotipa HCV sprovedena je terapija u trajanju od 48 za genotip 1, odnosno 24 nedelje za genotip *non* 1. Pet godina po završetku terapije svi bolesnici pozvani su na kontrolni pregled, 22 se odazvalo pozivu i kod njih je urađen kvalitativni PCR HCV RNA test. **Rezultati.** Prema klasifikaciji METAVIR utvrđen je stepen fibroze jetre: F0 kod 40%, F1 kod 23,33%, F2 kod 26,67%, F3 kod 3,33% i F4 kod 6,67% bolesnika. Genotip 3a bio je dominantan

(50,0%), 1b registrovan je kod 40,0%, 1a kod 6,66% i 2b kod 3,33% bolesnika. Stabilni virusološki odgovor je postignut kod 86,7% bolesnika, 10,0% bolesnika nije odgovorilo na terapiju, dok je kod 3,3% bolesnika ustanovljena relaps HCV ( $p > 0,05$ ). Do relapsa zloupotrebe opijata u toku antivirusne terapije došlo je kod 6,7% bolesnika. Pet godina po završetku antivirusne terapije na kontrolni pregled odazvalo se 73,3% bolesnika i svi su bili u stabilnoj apstinenciji od upotrebe opijata. Kod onih koji su postigli stabilni virusološki odgovor, 5 godina po završetku tera-

pije, PCR HCV RNA test bio je negativan ( $< 50$  IU ml<sup>-1</sup>). Ukupno 26,7% bolesnika bilo je izgubljeno iz evidencije. **Zaključak.** U 5-odišnjem periodu praćenja 73,3% bolesnika redovno se odazivala na kontrole i među njima nije zabeležen relaps zloupotrebe opijata, kao ni relaps HCV infekcije.

#### **Ključne reči:**

**hepatitis c, hronični; interferon alfa-2a; ribavirin; zloupotreba supstanci, intravenska; lečenje, ishod.**

## **Introduction**

Hepatitis C virus (HCV) infection is a systemic, generalized disease with the prevalence of inflammation in the liver. "Silent epidemic" of HCV infection is spread around the world, with an overall prevalence of approximately 3% of the infected<sup>1</sup>. It is well-known that in 80% of the cases HCV infection leads to chronic hepatitis with the progression to liver cirrhosis in 20% of the patients, and the emergence of primary hepatocellular carcinoma in 10% of the patients with liver cirrhosis<sup>2</sup>. However, it is believed that we will face the real consequences of this infection only in 2020, when there will be the manifestation of the HCV infection progression, in the most endangered population today, addicts to psychoactive substances<sup>3</sup>. With the contemporary treatment of chronic hepatitis C (CHC), pegylated interferon  $\alpha$  and ribavirin (peg IFN- $\alpha$  + rbv), eradication of the virus is achieved in 50%–80% of patients, the degree of fibrosis is reduced and the progression into liver cirrhosis is stopped<sup>4</sup>. There are conflicting views on the treatment of CHC injecting drug users in the world<sup>5</sup>. Today, the current antiviral therapy of peg IFN- $\alpha$  + rbv is extremely expensive – 30,000 to 40,000 dollars per patient<sup>6</sup>, so the question of investment in the treatment of the population, which is often socially and economically unproductive, is raised. There is a widespread opinion that the population of injecting drug users is unsuitable for the therapy due to the compliance problem and the possibility of reinfection<sup>7</sup>.

The aim of the research was to determine the success of the combined antiviral therapy (peg IFN- $\alpha$  2a + rbv) in the treatment of chronic hepatitis C in a group of injecting drug users in 1-year abstinence, defined with a period of 5-year follow-up.

## **Methods**

This 5-year follow up study included 30 patients with chronic hepatitis C, injecting drug users in 1-year abstinence, treated with the combined therapy peg IFN- $\alpha$  2a + rbv, (Pegasys®+Copegus®) in the Clinic for Infectious Diseases, Clinical Centre of Vojvodina, from January 1, 2004 to January 1, 2005. Complete history with a possible route of infection, physical examination, assessment of alcohol consumption, an abdominal ultrasound, standard biochemical liver functional tests, histological grades (activity) and stages (fibrosis) using the METAVIR scoring system, quantitative

PCR HCV RNA, HCV genotyping and subtyping were analysed in the patients prior to the therapy initiation.

In the whole cohort of the patients, there were 19 males and 11 females, aged from 22–40 years (mean  $\pm$  SD = 30.2  $\pm$  7.1 years). All the patients provided informed written consent, and the study was carried out in accordance with the declaration of Helsinki (2000) of the World Medical Association.

Depending on the HCV genotype, the therapy was conducted over a period of 48 weeks for genotype 1 and 24 weeks for genotype non-1. PegIFN- $\alpha$  2a (Pegasys®) was administered s.c. at a dose of 180 mcg once a week with daily ribavirin (rbv) (Copegus®) pill – taking at a dose of 800 mg a day for the patients with genotype non-1 HCV, regardless of body weight for 24 weeks, for genotype 1 HCV 1000 mg a day for the patients with body weight up to 75 kg, and 1200 mg a day for 48 weeks for the patients with body weight over 75 kg.

Data analysis was performed by the software SPSS version 10.0. Among the methods of descriptive statistics the measures of central tendency (mean,  $\bar{X}$ ), standard deviation (SD), as well as variability measures, absolute and relative frequency were used. The parametric tests (Student's *t*-test) and non-parametric tests (Mann-Whitney U, Kruskal-Wallis test,  $\chi^2$ -square test and Spearman's rho correlation coefficient) were used for data analysis. The chosen levels of significance were statistically highly significant ( $p < 0.01$ ) and not statistically significant ( $p > 0.05$ ).

## **Results**

Out of 30 injecting drug users in 1-year abstinence with chronic hepatitis C, 19 (63.3%) males and 11 (36.7%) were females, aged from 22 to 40 years ( $\bar{X} \pm$  SD, 30.2  $\pm$  7.1 years). The assumed average duration of infection was 8.9  $\pm$  7.4 years. All the infected patients had intravenous opiate addiction as a way of HCV transmission, and all of them had a psychiatric confirmation of a stable 1-year opiate abuse abstinence.

Before the antiviral therapy was administered in all the patients, a blind aspirational liver biopsy was done. According to METAVIR classification a degree of liver fibrosis was established: F0 in 12/30 (40%), F1 in 7/30 (23.33%), F2 in 8/30 (26.67%), F3 in 1/30 (3.33%) and F4 in 2/30 (6.67%) of the patients.

Genotype 3a was dominant in 15/30 (50.0%), 1b was registered in 12/30 (40.0%), 1a in 2/30 (6.66%) and 2b in 1/30 (3.33%) of the patients (Table 1).

**Table 1**  
**Distribution of hepatitis C virus (HCV) genotype**

HCV genotype	Patients n (%)
1a	2/30 (6.67)
1b	12/30 (40.00)
3a	15/30 (50.00)
2b	1/30 (3.33)
Total	30 (100)

A statistically significant difference between the degree of liver fibrosis and HCV genotype was not found ( $p > 0.05$ ).

A sustained viral response (SVR) (HCV RNA PCR test negative 6 months after the therapy) was achieved in 26/30 (86.7%) patients, 3/30 (10.0%) patients did not respond to the treatment and were marked as “non-responders” (NR) (HCV RNA PCR positive at the end of the therapy, as well as at the end of follow-up period), while 1/30 (3.33%) patients revealed recurrence of HCV (HCV RNA PCR negative at the end of the therapy, but positive at the end of a follow-up period) (Table 2)

increases with the duration of substance abuse, more frequent daily use of opiates, smoking “crack” and belonging to the so-called “shooting galleries”<sup>9</sup>. Among the male population, risk factors are primarily related to the careless use of opiates, while in women the risk of HCV infection transmission was increased by risky sexual behaviour<sup>10</sup>.

It is believed that HCV infection in 50%–80% occurs in the first year of intravenous drug use<sup>9</sup>. We hypothesized that inoculation with HCV in our patients was in the first year of intravenous use of opiates, so the likely duration of infection was 8.9 years.

Most patients surveyed did not have, or had just a low degree of liver fibrosis: F0 in 12/30 (40%), F1 in 7/30 (23.33%), F2 in 8/30 (26.67%), F3 in 1/30 (3.33%) and F4 in 2/30 (6.67%) of the patients. It is well-known that most important factors of liver fibrosis within the chronic hepatitis C are patient's age at the time of initial infection and the duration of infection<sup>11</sup>. The low level of fibrosis in our study stems exactly from the fact that these were young people, of the average age of 30.2 years and relatively short infection duration of 8.9 years on average.

**Table 2**  
**Sustained virological response (SVR)**

Clinical outcome	Patients (after the treatment)	Patients (after a 5-year follow-up)
	n (%)	n (%)
SVR	26/30 (86.7)	20/22 (90.9)
NR	3/30 (10.0)	2/22 (9.1)
Relaps	1/30 (3.3)	0
Lost from follow up		8/30 (26.7)
Total	30 (100)	30 (100)

NR – non responders.

Opiate abuse recurrence during antiviral therapy appeared in 2/30 (6.7%) patients. In both cases the treatment continued with psychiatric support.

Five years after the antiviral therapy 22/30 (73.3%) patients appeared at the check-up and all of them were in stable abstinence from opiate abuse. A total of 8/30 (26.7%) patients were lost from the records.

Among 22/30 (73.3%) of the patients who appeared at the check-up, 20/22 (90.9%) of the patients had SVR 6 months after the therapy. All of them, 20/20 (100.0%) had a sustained viral response of a 5-year duration, defined by the negative PCR HCV RNA test (Table 2). In 2/22 (9.1%) patients who 5 years before had an unsatisfactory therapy response, the antiviral therapy was repeated by the same therapeutic regimen, but without adequate an therapeutic response.

## Discussion

Out of 30 injecting drug users in 1-year abstinence, infected by HCV, included in the study, the ratio between men and women was equal, although recent studies have indicated that among newly diagnosed cases with chronic hepatitis in drug addicts, the percentage of women is greater<sup>8</sup>. It is obvious that the main route of transmission is sharing of needles, but it is estimated that the risk of HCV transmission

The dominant genotype in our study was genotype 3a (50.0%), followed by 1b (40.0%). The dominance of genotype 3 is consistent with the pattern of HCV genotypes distribution among risk groups in Western Europe, as in Serbia<sup>12–14</sup>. Clinical significance of determining HCV genotypes derived from the proved correlation between certain genotypes and the risk of developing severe degree of liver damage or the development of HCC<sup>15</sup>. A recent study conducted in Serbia confirmed that the patients infected with HCV genotype 1b had more frequently moderate or severe necroinflammatory activity of the disease, and a significantly higher grading score as compared with other genotypes<sup>16</sup>. However, we did not find a statistically significant difference between the degree of liver fibrosis and HCV genotype ( $p > 0.05$ ). A probable reason for this discrepancy is that this study included younger patients with shorter duration of HCV infection.

The aim of antiviral therapy is to achieve SVR. With the combined therapy, peg IFN  $\alpha$  2a + rbv, SVR was achieved in 70%–80% of the patients with genotype 2 or 3 and in 40%–50% of the patients with genotype 1 or 4<sup>17–19</sup>. SVR among the examined patients was noted in a significantly higher percentage (86.7%), and it is explained by a younger age, milder degree of liver damage, higher frequency of genotype 3, but the main reason probably was the short duration of HCV infection

among the examined patients. In fact, for every decade of the treatment postpone, the chance of obtaining SVR will decrease by approximately 10%<sup>20</sup>.

Opiate abuse recurrence and the possibility of HCV reinfection is one of the most important arguments "against" the treatment of HCV of injecting drug users<sup>21</sup>. It is well known that about 50% of the treated injecting drug users return to drug use even to a much worse form of addiction<sup>22</sup>. In our study opiate abuse recurrence occurred in 2 (6.7%) of the patients during the antiviral therapy. In both patients, with the psychiatric support the therapy was resumed, in one patient SVR was achieved, while the other patient did not respond to the antiviral therapy favourably.

The incidence of HCV reinfection after injecting drug abuse recurrence is 0–4 per 100 person-years of follow-up<sup>23</sup>. A lower incidence of HCV reinfection compared to the "primo" infection is explained by the prevention measures: intravenous addicts take care of their personal protection measured by using personal equipment for taking drugs<sup>21</sup>. Some authors believe that the lower infection incidence, and the recurrence of intravenous abuse of opiates, indicate the existence of partial cell-mediated immunity after the successful treatment of chronic hepatitis C<sup>24</sup>. In our study, the recurrence of injecting drug abuse (during a 5-year follow-up) was not registered and neither was HCV infection.

Five years after the antiviral therapy 8/30 (27.3%) patients were lost from the register in the Clinic for Infectious Diseases, so their abstinence from opiate abuse, as well as the status of chronic hepatitis C cannot be determined. A total of 22/30 (73.3%) patients came regularly for a check-up, and all of them were in stable abstinence from opiate abuse. All the patients who achieved SVR, maintained SVR 5 years after the therapy, so they can be considered cured.

Two patients (9.1%) with isolated genotype 1b, did not respond to the therapy adequately ("nonresponders"). Two years following the antiviral therapy peg IFN  $\alpha$  2a+rbv (Pegasys®+Copegus®) was reintroduced, but again with no adequate therapeutic response.

### Conclusion

This study indicates that opiate addiction does not influence the course of CHC nor the outcome of CHC therapy. The patients with CHC from the group of former drug addicts achieved a good virological response (86.67%) to the therapy peg IFN  $\alpha$  + rbv (Pegasys®+Copegus®). In a 5-year follow-up period 73.3% of the patients used to come regularly to check-ups and among them neither the opiate abuse recurrence nor HCV infection recurrence was registered.

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