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Clinical Characteristics and Treatment Efficasy of Chronic HCV Infection Among Intravenous Drug Users in Tuzla Canton

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ABSTRACT

Introduction: Chronic HCV infection is chronic inflamatory liver disease caused by hepatitis C virus. Anti HCV prevalence among intravenous drug users (IVDU) is very high and it accounts 40% -90% (60%-90%) with the risk of 80% of developing the chronic infection. **Aim:** The aims of this study were: a) to compare clinical characteristics of chronic HCV infection among IVDU and non-users population and to detect their impact to treatment outcome ; b) to investigate the treatment efficacy comparing sustained viral response (SVR) in these two populations in Tuzla Canton. **Patients and methods:** The study was retrospective-prospective and included 45 IVDU of both sexes from Tuzla Canton which were treated from chronic HCV infection with Pegilated interferon 2a/2b + ribavirin in the Clinic for Infectious Diseases and Clinic for Internal Disease of University Clinical Centre in Tuzla. The control group were presented by non-users who completed therapy in both Clinics. For statistical analyses it was used statistical package SPSS 20,0 (SPSS Inc, Chicago, IL, USA) with tests of descriptive statistics with measures of central tendency and dispersion. Quantitative variables were tested by t-test or by Mann-Whitney test. Qualitative variables were tested by hi-square test or by Fisher´s test. The standard analyse of level´s risk was used too. The analyse of predictive value of EVR for achieving the ETR and SVR was done by cross-tabulation. The impact of known factors for achieving the SVR was evaluated by logistic regression analyses. All tests were done with statistical level of significance of 95% (p=0,05). **Results:** Men were more dominant in the test group (93,3% / 61,7%), also younger age (p<0,001) and lower BMI (p=0,019). The test group had significant higher basal values of Le, Hb, Plt and ALT and tendency to lower stages of fibrosis (p=0,08). The difference in genotype frequencies was statistically significant (p=0,001) with clearly dominance of G3 and G4 among IVDU. Treatment was not complited by two patients in both groups (4,4% /3,3%). EVR was significantly higher in test group (p=0,001) so did the ETR (p=0,002) and SVR (p<0,001). Predictive factors for SVR were: age (negative predictive factor), male sex, absence of reduction of pegilated interferon and ribavirin, Metavir stage of fibrosis and presence of EVR. **Conclusion:** Population of IVDU were adherent to treatment protocol and with excellent treatment response they justified the hope of health care workers for success treatment of this population.

Keywords: chronic hepatitis C, drug users, treatment efficacy.

1. INTRODUCTION

Chronic hepatitis C (CHC) is chronic inflamatory viral disease caused by hepatitis C virus. About 50%-90% of new detected HCV infections are in relations with intravenous drug users (IVDU) so do mostly cases of chronic HCV infection, especialy in developed countries (1). The main organ for viral replication is liver and some extrahepatic viral reservoars are Ly in peripheral blood, intestinal epithelial cells and central nervous sistem (2).

Globally G1 is dominated by 44% of all HCV infections, G3 by 25% and G4 by 15%. Regarding to genotype distribution the most frequent in Bosnia and Herzegovina is G1b-69,3%, G3-21,3%, G1a and G2-4% each of them whereas G4-1,3% (3). In the EU countries anti HCV prevalence of more than 60% among IVDU is very high. Factors that increase transmission risks among IVDU are age, duration and frequency of drug application, suplies exchange, multidrugs applications, HCV prevalence among IVDU in

local area, homelessness and prisoners (4).

The goal of treatment is infection eradication and prevention the complications with eventually letal outcome. In general treatment respond is determined by laboratory tests (ALT value normalisation), virological (negative HCV RNA in serum by polymerase chain reaction-PCR) and histological parameters (decrease of >2 degreess of necroinflamation without worsening of fibrosis).

Estimated prevalence of chronic HCV infection in 2015 was 71,1 million people (62,5-79,4) with estimated prevalence of viremic HCV infections of 1,0% (95% CI 0,8-1,1) (3) with 2,3 million HIV/HCV coinfected (5, 6). The prevalence of chronic HCV infection among recent IVDU were 50% (8% of all infections globally), representing 5,6 million IVDU with chronic HCV (5, 7). Most drug users (DU) in the last years rest without social and health care of HCV infection and only few of them were treated. Most of them were denied of laboratory tests obligated for implementation the treatment and haven't get the preposition for viral testing. It could be emphasized that less DU have chance to cure chronic hepatitis C than all other populations infected with HCV (8, 9). The main risk factors for transmission of infection is needle and siringes exchange so do changing the accessoires for preparing and drug application (11, 12, 13).

In Bosnia and Herzegovina there is no many studies about HCV infection among IVDU. Many doctors were afraid of treatment of infected IVDU, because of possible missing adherence to treatment, agravation of psychological troubles, uncertainty to the treatment outcome and possibility of reinfection. HCV reinfection rates after sucessful interferon based treatment among IVDU are 0-5 cases per 100 person- years, but studies are limited by small sample sizes and heterogeneity in injecting risks after treatment (14, 15). Only one quarter of people with history of injecting drug use are estimated to continue injecting (16).

2. AIM

The aim of this study was: a) To compare clinical charasteristic of chronic HCV infection (genotype, Metavir-score, AST, ALT) among IVDU and non users and test their impact on the treatment respond; b) Test the efficacy of HCV infection treatment comparing SVR among IVDU and non users in Tuzla Cantoon.

3. PATIENTS AND METHODS

This retrospective study included 45 IVDU of both sex with chronic HCV and treated with combination of pegylated interferon α and ribavirin in the Clinic for Infectious Diseases and Clinic for Internal Diseases in University Clinical Center Tuzla (UCC Tuzla). The beginning of the study was 1.1.2012. Control group was presented with 60 non-users that finished treatment in the same Clinics. A total of 32 IVDU and 50 non-users were treated with peg-interferon α 2a 180 μgr/week + ribavirin but 11 IVDU and 8 non-users with peg-interferon α 2b 1,5 μgr/kg/week + ribavirin. Ribavirin was administered in the recommended doses according to weight. The duration of therapy in G 1 and 4 was 48 weeks but in G 2 and 3 it was 24 weeks. The study was approved by the Ethics Committee of the UCC Tuzla. Data of clinical and epidemiological characteristics of HCV infected patients were stored in hospital archives; missed datas were colected later by patient's visit the Clinic for Infectious diseases.

Tests of serological and molecular diagnostics were:

a) HCV-antibodies - Ortho Clinical Diagnostics Tests; b) PCR HCV RNA - qualitative test - Cobas Amplicor Hepatitis C Virus Test, version 2.0 - Roche Molecular Diagnostics; c) RT PCR HCV RNA- quantitative test- Cobas TaqMan HCV Test, version 2.0 - Roche Molecular Diagnostics; d) Genotyping - HCV GenoType 2.0 Assay (LiPA)- Bayer Health Care (Simmens).

Laboratory tests for detection liver function failure and tests for autoimmune hepatitis were done.

Histology by needle liver biopsy where Knodell and Metavir scoring system were used as an indicator for histological activity.

Regular psychiatric reports of psychosomatic condition of IVDU and their eligibility for HCV treatment.

All tests were realised in the Department for laboratory, microbiology and patology of UCC Tuzla. Results of these tests were evaluated on Consilium of UCC Tuzla and by the Federal group of Ministry for Health for cure chronic viral hepatitis. SVR was defined as undetectable HCV RNA at 24 weeks after the end of treatment.

An ethycal approval was received from the Ethics Committee of Clinic for Infectious Disease, Tuzla, Bosnia and Herzegovina.

Statistical analysis

For statistical analysis statistical package SPSS 20,0 (SPSS Inc, Chicago, IL, USA) was used. Standard tests descriptive statistics with central tendency and dispersion were done. All variables were tested to normall distribution using Kolmogorov-Smirnov test. Quantitative variables with normal distribution were tested by student t-test and Man-Whitney test in the case of asimetric distribution. For qualitative variables it was used hi-square test, respectively Fisher exact test for analyses in which frequency solid cells were less than 6. Standard risk analyses with detection relative and absolute risk was used including testing relative risk reduction with interval reliability of 95%. Impact of known risk for SVR attendance was evaluated by logistic regressive analyses. All tests were done with level of statistical significance of 95% ($p<0.05$).

3. RESULTS

A total of 105 patients were included in the study from which 45 (42.9%) presented the test group (IVDU) while the rest of 60 (57.1%) were control group (general population).

Discrepancy in sexual distribution has been evident with great domination of mail in test group (42/45; 93.3%) regarding the control group (37/60; 61.7%). As it was expected the patients in test group were much younger ($p<0.001$) than patients in control group, average 17.14 years (95% CI=13.17-21.10). BMI was higher in control group with mean difference of 2.2 (95%CI=0.2-4.2) ($p=0.019$). IVDU had significantly higher basal values of hemoglobin, leucocytes and thrombocytes (Table 1). Generally it hasn't been speciall differences of basal laboratory parameters between two groups except of mean higher ALT among IVDU; globulin and INR was less than in control group (Table 2).

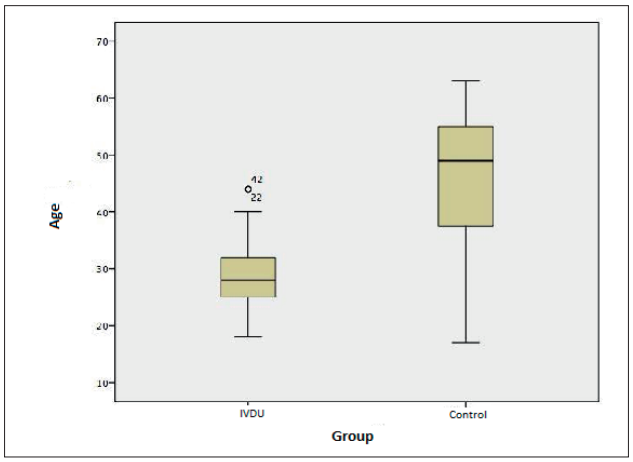

Figure 1. Age distribution in the populations

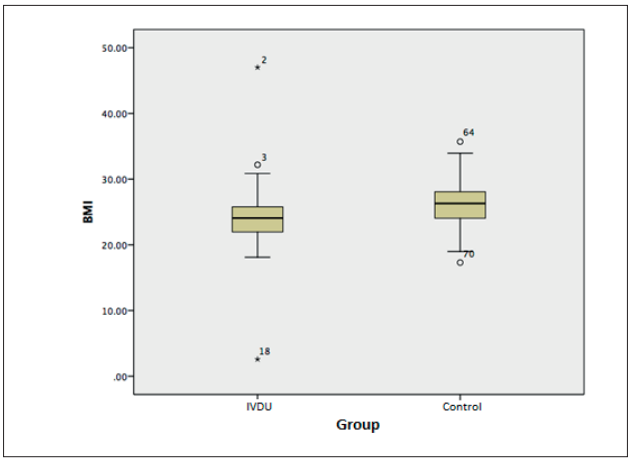

Figure 2. Body mass index (BMI) in the populations

Liver biopsy was used for assessement of disease activity and fibrosis according Metavir scale. According to activity it hasn't been found significant differences between groups (p=0.72) but fibrosis had significant differences (p=0.027).

The comparation of median fibrosis scores between groups was analysed with Man-Whitney test. Althoug this analyse has limited significance (p=0.08) obvious tendency to less values of F-scor among IVDU has been present (Figure 3). Mean values of HCV RNA between the groups hasn't had statistical difference (p=0.38). Moreover, as it was expected the significant difference in special genotypes distributions has been present (p<0.001) respectively to the groups with strong domination of G 3 (62.2%) and 4 (15.6%) among IVDU. In control group the most frequent was G1 (86.7%) than G3 (10%). In both groups treatment wasn't completed by 2 patients that meant 4.4% among IVDU and 3.3% in control group.

Significant higher frequency of EVR was noticed among IVDU than in control group (p<0.001) so do ETR (p= 0.002) and SVR (97.7% among IVDU) but in control group it was

	Group	AS	SD	p-value
Er	IVDU	8.34	22.82	0.3
	Control	4.81	0.53	
Hgb	IVDU	140.32	42.03	0.04
	Control	121.91	49.72	
MCV	IVDU	87.04	15.00	0,5
	Control	88.73	5,2	
Htc	IVDU	3.48	14.93	0.69
	Control	2.54	9.31	
Le	IVDU	7.35	1.65	0.001
	Control	6.22	1.79	
Ne	IVDU	35.65	24..3	0.954
	Control	35.38	23.36	
Ly	IVDU	26.18	18.81	0,446
	Control	29.16	18.79	
Tr	IVDU	222.89	50.32	<0,001
	Control	177.70	59.14	

Table 1. Basal haematological values in both groups

	Group	AS	SD	p-value
ALT	IVDU	173.63	244.83	0.03
	Control	97.34	83.21	
AST	IVDU	89.14	18.79	0.33
	Control	65.31	39.02	
GGT	IVDU	65.88	53.05	0.39
	Control	58.01	39.88	
BUN	IVDU	4.62	1.45	0.2
	Control	4.97	1.35	
CREA	IVDU	79.09	14.3	0.16
	Control	74.76	16.35	
TBIL	IVDU	12.54	5.32	0.86
	Control	12.71	4.28	
Fe	IVDU	21.89	7.28	0.38
	Control	46.88	188.35	
Feritin	IVDU	140.88	97.61	0.3
	Control	168.21	148.87	
TPROT	IVDU	77.07	5.11	0.18
	Control	78.47	5.35	
ALB	IVDU	42.44	4.4	0.17
	Control	41.12	5.22	
GLOB	IVDU	34.62	5.61	0.03
	Control	36.85	4.88	
AFP	IVDU	5.11	7.79	0.07
	Control	8.5	8.5	
INR	IVDU	1.6	0.09	0.009
	Control	1.11	0.09	
a-PTT	IVDU	25.19	10.75	0.69
	Control	26.18	11.68	

Table 2. Basal laboratory parameters in the groups

	ETR (%)			SVR (%)		
	All	IVDU	Contr	All	IVDU	Contr
Sensitivity	88	98	79	91	98	81
Specificity	84	100	80	53	100	52
PPV	96	100	92	81	100	59
NPV	56	50	57	74	50	76
LR+	25	-	11,33	4,2	-	1.47
LR-	0,77	1	0.75	0.35	1	0.31

Table 4. Paremeters of diagnostic validity on ETR and SVR prediction.

Parameter	Odds Ratio (OR)	95%CI	p-value
Age	0.898	0.860-0.939	<0.001
Mail	2.85	1.10-7.36	0.03
ALT	1.002	0.998-1.007	0.312
BMI	0.95	0.86-1.04	0.25
Hgb	1.002	0.994-1.011	0.63
Without reduction RIB	2.7	1.11-6.54	0.028
Without reduction IFN	3.27	1.25-8.57	0.016
Metavir fibrosis	0.52	0.32-0.86	0.011
Metavir activity	0.73	0.44-1.22	0.235
EVR	11.9	4.01-35.32	<0.001

Table 5. Predictive factors for SVR

46.6% (p<0.001). Risk analyses showed that IVDU had relative risk for treatment failure of 0.12 (95% CI=0.03-0.5) with relative risk reduction of 87.6% for treatment failure in comparison to control group. The SVR frequency relating to the group and viral genotype was also analysed. Besides the dominant G3 among IVDU the treatment efficasy wasn't insufficient among genotypes marked as „hard to treat" with reserve of analysed small sample. Also, significant difference wasn't observed (p>0.50) with type of implemented treatment (Pegylated interferon α 2a vs. Pegylated interferon α 2b). EVR was positive predictive factor for SVR in 81% of total sample, among IVDU in 100% but in control group in 59%. Negative EVR in total sample (23 patients) in 74% of cases was negative predictive factor fo SVR; among IVDU in 50% but in control group in 76% of cases. The parameters of diagnostic validity was noticed in Table 4. The predictive influence of known factors for SVR was evaluated in the sample by logistic regressive analyses (Table 5).

Obviously significant SVR prediction were age, male sex, absence of treatment reduction (ribavirin and interferon), stages of fibrosis according Metavir and EVR presence.

Age was a negative predictor with the chance for SVR decreased 1.12 times (1/0.89) with each next year of life.

Male sex increased chance for SVR 2.85 times relating to female. Absence of dosage reduction of ribavirin and PEG-IFN during the treatment increased the chance for SVR 2.7 times vs. 3.7 times regarding to those with treatment reductions. Each additional stages of fibrosis according Metavir scale on the basal biopsy reduced the chance for SVR 2 times regarding previously stage although EVR was a strong predictor for SVR with the chance of 11.9 times higher.

4. DISCUSSION

Host factors which influenced the decision to treat chronic HCV were age, bichemical values of liver enzymes, histological stage of disease and comorbidities that could worsen patient's health condition and influenced the treatment results.

Our test group regarding the origin of infection was younger for 17.14 years with statistical significancy (p<0.001). Similar statistical significant difference was noted by the other authors in their studies (p=0.0001; p<0.001; p<0.001) (17, 18, 19). In other sudies the age of IVDU was 21-59 years and male was present by 65.9%-94% (20-25). In both populations of actuell study mail was dominant with higher frequency in test group in relation to higher risk behaviours among male but, also, in control group that was noticed by other authors (Kurelac et al. with statistical significant difference- p=0.0001; Papadopoulos et al. with p<0.001). Regarding to genotype distribution in our test and control group the frequency had statistical significant difference with p<0.001 and strong domination of G3 and G 4 in test group that was expected. Dominant G3 among IVDU was reported in other studies (20). In actuell study G1 was found by 20,0% of IVDU. BMI in test group (24.2 ± 5.8) was less for 2.2 than in control group with statistical significant difference (p= 0.019) unlikely the Greek study by Papadoupoulos where IVDU had less BMI without statistical significant difference (p=0.152). Normal BMI in IVDU noted by Schulte was 22.4 (16.9-28.7) (21). Basal hematological values (leucocytes, hemoglobins and thrombocytes) in this relatively health population had higher values than in general population in our study with p=0.001; p=0.04; p<0.001 and in the literature too (21, 26). In our laboratory tests the ALT value among IVDU was higher considering the younger age and more intensive reaction of inflamation, but globulin and INR (shorter time of infection) was some lower in relation to general population that is similar the results in the literature (21, 27). In the French study ALT value >3x of normal range had 21.8% of patients and viremia ⩽ 400000 IU 30.2% of patients (29). The mean value of viremia (<106IU) in the same population group reported in the literature corresponds to results of current work (20, 21).

On the liver biopsy Metavir A1 in the test and control group didn't have statistical significance (p=0.72) opposite the fibrosis which had more frequent lower stage of fibrosis among IVDU with statistical significant difference (p=0.027). Camma et al. in their study among 644 examiners with 43.4% IVDU were reported higher activity scores and stages of fibrosis, Poynard et al. in their study among general population was noticed A2-3 within 55% examiners, F3 - 10% but F4 at 9% examiners. Many authors the mechanisms for disease progression explain by advanced ages regarding to higher sensitivity to environmental conditions. Special roles had oxidative stress, circulatory insufficiency and limited mitochondrial or immunological capacity. Authors reported protective estrogen effect to fibrogenesis by inhibition activity on stellate cells proliferation (28, 29). EVR in our IVDU group was higher related to

84% in the same population that was noticed by Fried, but in the same time it was lower than excellent 100% among drug users in the study by Alvarez-Uria et all. ETR in the same population group was higher than ETR noticed in the studies of other authors (68%-90.1%) (20, 21, 26, 30) such as the SVR value in the literature (48.4% - 70.75%) (8, 17, 19, 20, 24, 25, 30-33). SVR among general population in the literature have had some higher value (51.04% - 66.7%) relating to our study (17, 23, 26, 29, 34). SVR in test group based on genotype distribution was found of 100% in all genotypes except of G4 - 85.7%. SVR among IVDU with G3 noticed 54.6% to 91% (21, 31, 34) but in the study of the maior IVDU population HCV monoinfected and co-infected with HIV SVR was reported by 60.5% and 51.4% (35).

In the treatment by peg- interferon α 2a + ribavirin and peg-interferon α 2b + ribavirin SVR in actuell study was almost more eficassy relating to SVR that was reported by Kurelac and all. Study which included 118 centers in USA reported significant statistical difference in EVR (p=0.01), ETR (p< 0.001), but in SVR there was no statistical significant difference (p=0.57) between the same treatment options (36). In the paper of brasilian authors peg- interferon α 2b was in negative association with SVR attainment (35).

EVR was a positive predictive factor (PPF) for ETR by 96% in total population group of our study; among IVDU and in control group it was by 100% and 92%. EVR was a PPF for SVR by 81% in our total population group; among IVDU and in control group it was by 100% and 59%. Negative EVR in total population group (23 patients) was a NPF for SVR by 74%; among IVDU and in control group it was by 50% and 76%. Our EVR positive correlation for SVR among IVDU were better in relation to data by Fried and all. where PPV of EVR for SVR was by 71% but NPV was by 91% (20).

Significant predictors for SVR found by logistic regressive analyses were age (negative predictor), male (increase chance for SVR 2,85 times relating to female), the absence of reduction of ribavirin and peg-interferon (increased chance for SVR 2.7 v.s. 3.27 times relating to patients with dose reduction), fibrosis stage according to Metavir scale (each stage reduce chance 0.52 times relating to previous stage) and achieved EVR (strong predictor with chance 11.9 times higher irrespective to patients without EVR).

Brasillian authors the most higher SVR were noticed among patients with F3 (67%) then with F0 and F1 (59%) (35). By multivariant regressive analyses Marcellin and al. reported statistical significant relation between SVR and absence of cirrhosis, higher values of Tr and ALT, less values of viremia and AST, lower BMI, younger age and treatment by peg- interferon α 2a among patients with G1. Similar results were noted by Greecs authors where independent predictors of SVR were genotypes 2/3 and younger age (p=0.002) (19). Age limit ⩽ 40 years (OR:4.2; p<0.0001) was un independent factor for SVR in the literature so were basal viremia ⩽ 8x105 IU (OR: 3.4; p<0.0001) and rapid viral respond (RVR) (OR: 11; p<0.0001) (23, 37). Significant predictors by multivariate analyses were age < 40 years (OR:2,98; p=0.0017), G2 and G3 (OR: 25.40; p=0.0016) (17). Zeuzem and al. reported that low viremia had 77% better chance for SVR than high viremia among 422 patients, but it hasn't had statistical significant efficacy for SVR in non G1 population. An undepedent variable, age ⩽ 40 years correlated positively with SVR (OR 2,31, 95% CI), meaning that patients with that age limit had 26% higher possibility achieving SVR (38).

5. CONCLUSION

Basal characteristic of IVDU that contributed to the successful treatment were lower age, higher male frequency and strong domination of G3 and G4. Important predictive factors for SVR were age, male, reduction of peg-interferon and ribavirin, stage of fibrosis and EVR. As it is reported in the literature treatment of chronic HCV by peg-interferon/ribavirin still present acceptable treatment option besides better treatment choice (35). That is important for the countries where DAA treatment wasn't completely implemented. IVDU population had good adherence to treatment and with good virological responce it justified the expectance for successful treatment.

- **Author's contribution:** J.P. and N.S. gave substantial contribution to the conception or design of the work and in the acquisition, analysis and interpretation of data for the work. M.H., S.A., R.J. also gave the contribution in the acquisition of the data. J.P., N.S., S.A., A.S-N. , D.P. and H.P-J. had role in drafting the work and revising it critically for important intellectual content. Each author gave final approval of the version to be published and they are agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
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