PRELIMINARY REPORT

High virologic sustained response for former young intravenous drug users with chronic hepatitis C treated by pegylated interferon-α plus ribavirin

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Abstract: *Aims:* The aim of this clinical study was to assess virological response at end-of -treatment (ETR), sustained virological (SVR) and biochemical response in former drug users with chronic hepatitis C treated with PEG-IFN-α and R.
Patients: Ninety two former drug users (21 F, 71 M) average age 27 years (18 to 41 years) and previously not treated with IFN-α and R (naive patients, pts) were evaluated for their virological and biochemical response. Standard treatment regimen of either 24 or 48 weeks was applied in patients with genotype 3 or genotype 1, respectively. SVR was considered if viral tests (HCV RNA) were negative 24 weeks after the end of treatment.
Results: Overall SVR was attained in 87 (95 %) of 92 treated patients, and therapy failed in 5 pts with genotype 1. In genotype 1 patients ETR and SVR were 81 % and 86 %, respectively (p<0.001). In genotype 3 patients ETR and SVR were 98 % and 100 %, respectively (p<0.001). ALT levels decreased significantly after 12 weeks of therapy (ALT 1.61 vs 0.64 μkat/l, p<0.001) and were at normal levels during follow-up.
Conclusions: Crucial predictive factors resulting in high SVR were the younger age in combination with low stage of liver fibrosis, relatively short duration of viral infection, high proportion of genotype 3 and excellent adherence of patients to treatment regimen than previously not treated with IFN-α and R (naive patients). High proportion of SVR in former drug users has been achieved in patients with genotype 3 (100 %) and genotype 1 (86 %). The most decisive prognostic factor which favors high therapeutic efficacy appears to be young age and early onset of anti-HCV treatment (Tab. 3, Fig. 1, Ref. 33). Full Text (Free, PDF) www.bmj.sk.
Key words: chronic hepatitis C, former drug users, pegylated interferon-α, ribavirin, sustained viral response.

Infection with hepatitis C virus (HCV) is a global healthcare challenge. Approximately 3 % of the global population is infected with HCV, representing about 170 million persons worldwide. Although hepatitis C is a systemic disease that can affect most organs, the liver is the primary target for the HCV. HCV was first identified in 1989, and next was found to be the cause of 80 to 90 % of cases of Non-A, Non-B hepatitis (1). HCV is associated with significant morbidity and mortality. Study of the natural evolution of acute HCV infections has shown that approximately 30 % of cases result in spontaneous clearance whereas 70 % evolve towards chronic infection. In the past few years, the prevalence of hepatocellular carcinoma has increased in western countries, and cirrhosis related to HCV is the most common current cause of liver transplantation worldwide (2, 3). In industrialised countries, injecting drug use represents currently the most important risk factor for HCV infection, resulting in high prevalence rates of HCV among injectable drug users. The Hepatitis C European Network for C-operative research (HEN-CORE) group reported a prevalence of hepatitis C of 80 % among intravenous drug users (IDU) (4). The estimated prevalence of HCV infections among IDU in Slovakia is approximately 42 % (5). Identification of HCV-infected patients earlier in its natural course of disease will allow earlier interventions in targeted high-risk groups. The primary goal of treatment in patients with chronic hepatitis C is long-lasting eradication of virus. Those who remain HCV-RNA negative for 24 weeks after completion of therapy are defined as having achieved a sustained virological response (SVR). The use of interferon-α (IFN-α) in the treatment of chronic hepatitis C represents a milestone in the therapy of this disease. The approval of ribavirin (R) in combination

Tab. 1. Patients characteristics at baseline (n=92).

Mean age (years)	27±3.8
Range (years)	18-41
Males (n/%)	71/77
Female (n/%)	21/23
Mode of infection	
Intravenous drug (n/%)	92/100
Treatment	
Naive patients to PEG-IFN-α (n/%)	92/100
Patients treated with Pegylated IFN-α2a plus ribavirin (n/%)	66/72
Patients treated with Pegylated IFN-α-2b plus ribavirin (n/%)	26/28
Mean erythrocytes (x10^{12}/L)	4.81±0.40
Mean hemoglobin (g/L)	152±14
Mean leukocytes (x10^9/L)	6.6±1.7
Mean neutrophils (x10^9/L)	3.58±1.18
Mean platelets (x10^9/L)	198±48
Mean ALT (μkat/L)	1.55±1.17
Mean AST (μkat/L)	0.89±0.42
Mean GMT (μkat/L)	0.74±0.68
HCV genotype (n/%)	
1	36/39
2	0
3	56/61
4	0
Mean viral load SD, genotype 1, n=22	
HCV RNA (x10^6/mL copies)	2.3±39
Liver biopsy (n/%)	81/88
Liver histology *(n/%)* (fibrosis scale 0–5)	
Stage of fibrosis 0	17/21
Stage of fibrosis 1	47/58
Stage of fibrosis 2	16/20
Stage of fibrosis 3	1/1
Stage of fibrosis 4	0
Stage of fibrosis 5	0

Note: Data expressed as n±SD unless otherwise indicated.

therapy regimens with IFN-α dramatically improved the response. Another advance was the introduction of pegylated IFNs (PEG-IFN) which allows a once-weekly subcutaneous administration and show more favorable pharmacokinetics and greater efficacy. Male gender, more advanced fibrosis and older age are the factors associated with less favourable response to a combination of immunomodulatory and antiviral therapy (6, 7). Conversely, the young age of patients is one of the variables in favour of treatment (8). Few authors reported on SVR with IFN-α monotherapy or combined treatment in a specific group of patients – former IDU (9, 10, 11). The data on the efficacy of PEG--IFNs or in combination with R are still limited for this specific risk group of patients. We seek to identify predictos of SVR within this group.

The primary endpoint for this study was to assess the proportion of patients with SVR, defined as undetectable plasma HCV-RNA levels at 24 weeks following the end of treatment and to define the predictors of the treatment efficacy. The secondary endpoint was to determine early virological responses at 12 weeks of treatment (EVR) and at the end of treatment (ETR) as well as to assesses biochemical response in determined periods.

Patients and methods

Patients' selection

Ninety-two former IDUs aged 18–41 years (mean age 27±3.8) with compensated chronic HCV infection, not previously treated with IFN-α, R and/or amantadine were eligible for enrollment (Tab. 1). The criteria for treatment were a positive test result for HCV RNA (persistence of HCV RNA in the blood for 6 months or longer) and elevated serum alanine aminotransferase (ALT) on two occasions during the preceeding 6 months, compensated liver disease and liver biopsy specimen consistent with chronic hepatitis C obtained in the previous 12 months. Only former IDU subjects in long-term complete remission (absence of drug dependency for more than 6 months) were enrolled into the treatment. The patients were anti-HCV positive, and negative for hepatitis B surface antigen and antibody to human immunodeficiency viruses 1 and 2.

Leukocyte and platelet counts at entry visit had to be at least 3.000 and 80.000/μL, respectively. Hemoglobin values at entry visit had to be at least 12 g/dl for female and at least 13 g/dl for males. Patients with the following criteria were excluded, namely those with any other cause of liver disease or other relevant disorders including human immunodeficiency or hepatitis B virus coinfection, clinically significant hematologic, liver, metabolic, renal, reumatologic, neurological or psychiatric disease, anaphylatic reactions, clinically significant cardiac or cardiovascular abnormalities, organ grafts, systemic infection, clinically significant bleeding disorders, evidence of malignant neoplastic disease, average daily intake of alcohol exceeding 80 g of ethanol or drug abuse within past 6 months. Further exclusion criteria were pregnancy and lactation.

Study design

This single-arm, open-label, phase 4 prospective clinical study was designed to assess the efficacy of treatment with PEG-IFN-α2a (40kD) and PEG-IFN-α2b (12kD) plus R in former IDUs with chronic hepatitis C. Subjects with drug abstinence more than 6 months were enrolled into the treatment. The naive patients were recruited to treatment as outpatients and then evaluated in terms of therapeutic efficacy at two centres: at the National Reference Center for Treatment of Chronic Hepatitis located at the Slovak Medical University and at the Clinic of Infectology and Geographical Medicine in Bratislava. The selection of subjects and the whole study was performed in close collaboration with psychiatrists and psychologists. For ensuring good adherence of patients to therapy a close relationship between the patients and medical staff was developed. Patients were

thoroughly informed about the benefits and risks associated with the treatment. Education, encouragement and support from both the medical team and the patient's family and friends were crucial in helping the patients to maintain a positive attitude. All patients signed a written informed consent to participate in the study.

Treatment schedule

Administration of PEG-IFN-α2a 180 μg s.c. once weekly regardless of weight or PEG-IFN-α2b (12 kd) 1.5 μg/kg s.c. once weekly were administered. Dose of R was adjusted to patient's weight and type of genotype (800–1200 mg of R p.o. daily, in two divided doses, 1000 mg if <75 kg and 1200 mg if >75 kg of patient's weight for Copegus and 10.6 mg/kg/d for Rebetol). Patients with genotype 3 were treated for 24 weeks whereas patients with genotype 1 for 48 weeks.

Virological assays

Screening for anti-HCV was assessed by ELISA test (Innotest HCV IV Ab). Serial samples were tested for HCV RNA by qualitative HCV-RNA assay with a lower sensitivity of 100 copies per mililiter (50 IU) (Cobas Amplicor Monitor HCV Test, version 2.0 Roche Diagnostic Systems) in all patients at weeks 0, 12, 24 or 48 (in dependence of genotypes), and 24 weeks after completion of therapy. SVR was defined as undetectable level of hepatitis C virus RNA (<100 copies per mililiter) 24 weeks after completion of therapy.

Viral load was determined by the Versant HCV RNA 3.0 (bDNA) Assay, Bayer HealthCare, USA in patients with genotype 1 at baseline (at pre-treatment period). Viral genotypes were assessed by comercial line probe (INNO-liPATM HCV, Innogenetics, Belgium).

Liver biopsy

Liver biopsy specimens were assessed by experienced pathologists. Histological results were classified according to internationally standardized criteria (12). The degree of fibrosis was staged by using a scale from 0 to 5.

Response Rates

Responses to combination therapy were classified as biochemical (alanine aminotransferase levels within the range of normal) or virological (HCV RNA negative by PCR) as at EVR, ETR or SVR, respectively.

Assessment of efficacy

The primary efficacy end point was SVR defined as the absence of detectable HCV RNA at 24 weeks after completion of treatment assessed by PCR assay (Cobas Amplicor HCV Tests, version 2.0, lower limit of detection, 100 copies/50 IU/per mililiter). The secondary end point was the assessment of biochemical response during follow-up.

Safety assessments

Safety was assessed by physical examination and laboratory tests at weeks 2 and 4. Thereafter these assessments were perfor-

med at regular intervals every 4 weeks. All blood tests were performed at local laboratories. Monitoring included the evaluation of symptoms, side effects, routine liver tests and hematological tests.

The dose of R was reduced to 600 mg/d if a patient experienced laboratory abnormality, including the decrease in hemoglobin level to less than 100 g/L. R was discontinued in patients with hemoglobin level being lower than 85 g/L. Neutropenia is attributed to the IFN-α component of anti-HCV therapy and appears to occur at higher rates with PEG-IFNs than with standard IFN-α. Reduction of the dose of PEG-IFNs has been recommended for patients with neutrophil counts of less than 750 cells/mm^3. If the platelet counts decreased less than 60.000 cells/mm^3, the dose of PEG-IFNs has been adjusted.

Statistical analysis

The primary analysis was based on all 92 evaluated patients. Quantitative variables were expressed as means±SD. Univariate analysis was used for comparison between groups. To test for significant differences between two groups was used the Mann–Whitney two-sample test, and for differences between three groups Kruskal-Wallis test. The Pearson's chi-square test or Fisher exact test were used to compare proportions. McNemar test was used for comparing the treatment responses. Changes in ALT values were compared with the use of paired Student t-test or with the use of paired Wilcoxon test (when data were nonnormally distributed). A binary logistic regression was performed to identify the variables (genotype, sex, age, and fibrosis) associated with SVR.

SPSS 13.0 software was used for statistical analysis. All tests were done at significance level alfa=0.05.

Results

During the follow-up since January 2003 until July 2006, 92 patients aged 18–41 years completed combined therapy. Three patients (men) discontinued the treatment at week 12 because of non- compliance, 2 patients relapsed to drug abuse and 1 due to intolerance of side effect of treatment (depression). These patients were not included in the overall evaluation.

Baseline characteristics of the study population are shown in Table 1. A total of 92 naive patients (71 males, 21 females) who were former IDUs with the mean age of 273.8 years were evaluated.

A majority of patients had genotype 3 (56/61 %) compared with genotype 1 (36/39 %). Patients with genotypes 1 and 3 did not significantly differ in gender (in genotype 1, 25 % of females, and in genotype 3, 21 %, respectively). Sixty-two patients were treated with combined therapy PEG-IFN-α2a plus R and 26 with PEG-IFN-α2b plus R. Both PEG-IFNs did not differ significantly in therapeutic efficacy and tolerance.

In multivariable analyses to identify predictors of SVR among patients who recieved combined therapy, the following factors were included into the final logistic regression analy-

Tab. 2. Hematologic, biochemical and virologic response (n=92).

	12. week	End of therapy	24. week after therapy	P
Hematologic parameters				
Mean erythrocytes (x10^{12}/L)	4.23±0.47	4.22±0.5	–	<0.001
Mean hemoglobin (g/L)	132±13	132±15	–	<0.001
Mean leukocytes (x10^9/L)	3.8±1.3	3.95±1.78	–	<0.001
Mean neutrophils (x10^9/L)	1.83±0.98	2.03±1.28	–	<0.001
Mean platelets (x10^9/L)	140±43	153±52	–	<0.001
Biochemical parameters				
Mean ALT (µkat/L)	0.67±0.51	0.62±0.67	0.49±0.51	<0.001
Mean AST (µkat/L)	0.58±0.29	0.56±0.66	–	<0.001
Mean GMT (µkat/L)	0.67±0.85	0.63±0.66	–	n.s.
Virologic parameters				
Virologic response (n/%)	EVR	ETR	SVR	
Genotype 1	28/78[1]	29/81[2]	31/86[3]	<0.001[1,2,3]
Genotype 3	52/93[1]	55/98[2]	56/100[3]	<0.001[1,2,3]
Overall (genotype1+3)	80/87[1]	86/91[2]	87/95[3]	<0.001[1,2,3]

Note: Data expressed as n±SD unless otherwise indicated. Virologic response was indicated by undetectable HCV RNA in the qualitative assay. The percentage of response depending on the number of patients in Table 1. EVR – early viral response, assessed at 12 weeks of treatment, ETR – end-of-treatment response, SVR – sustained viral response – undetectable HCV RNA at 24 weeks after treatment. P1 – statistical significance of HCV RNA negativity for patients at baseline and EVR, P2 – statistical significance of HCV RNA negativity for patients at baseline and ETR, P3 – statistical significance of HCV RNA negativity for patients at baseline and SVR.

sis: sex, age, pretreatment (baseline) levels of ALT, pretreatment histologic diagnosis (stages of fibrosis) and HCV genotypes (1 vs 3).

Virological response

Overall EVR was achieved by 80 (87 %) of 92 patients: 28 (78 %) of 36 patients with genotype 1 and 52 (93 %) of 56 patients with genotype 3, (p<0.001 in all observed parameters). Overall ETR was achieved by 86 (91 %) of 92 patients: in groups of patients with genotype 1 and 3, the viral response was 29 (81 %) of

36 patients, 55 (98 %) of 56, respectively (p<0.001 in all observed parameters). Overall SVR was achieved in 87 (95 %) of 92 patients, whereas in the subset of patients with genotype 1, it was achieved in 31 (86 %) of 36 patients (p<0.001). All of the genotype 3 patients achieved SVR (56/100 %) (p<0.001) (Tab. 2, Fig. 1). Four patients with genotype 3 were treated 48 weeks due to positive HCV RNA at week 12 and negative at week 24 as they were considered to be slow responders.

Overall ETR was higher (86/91 %) when compared to 12-week data, however between the groups of patients with geno-
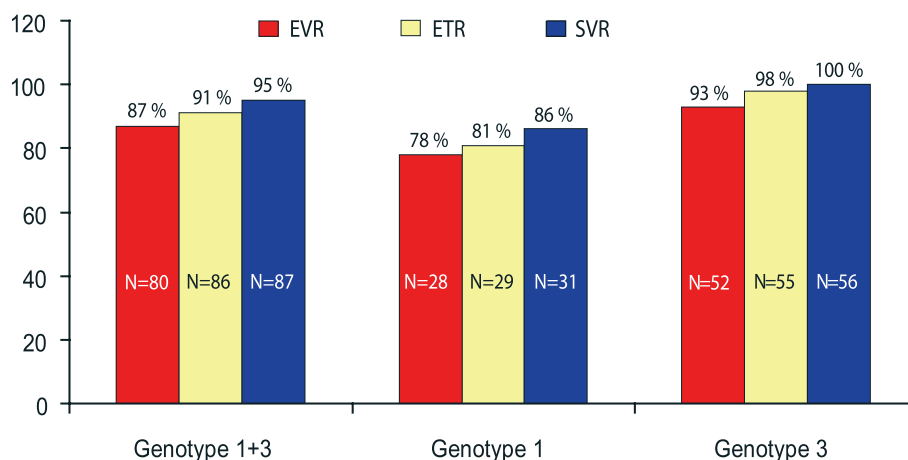
Fig. 1. Virological response in patients with chronic hepatitis C treated by PEG-IFNs and ribavirin. EVR – early viral response, ETR – end-of-treatment response, SVR – sustained viral response.

Tab. 3. Frequency of side effects in patients with chronic hepatitis C treated with PEG-IFNs and ribavirin (n=92).

Side effects	n/%
Flu-like syndrome fever, headache, chills, mylagia, fatigue	78/85
Gastrointestinal disorders nausea, anorexia, weight loss, diarrhea	74/80
Neuropsychiatric disorders depression, irritability	34/37
Skin disorders alopecia, pruritus, rash, dry skin	17/18
Bone marrow hypoplasia requiring dose modification, anemia, neutropenia, trombocytopenia	18/20

type 1 and 3, we did not notice any significant difference in the viral response 29 (81 %) vs 55 (98 %), respectively. The mean viral load assessed in a group of patients with genotype 1 at baseline was low (Tab. 1). We did not notice any correlation between viral load and SVR in this group of patients.

Taken together the majority of patients (87 %) were HCV RNA negative at week 12 of treatment and during the follow-up, the virological response increased gradually up to 95 %, when compared with baseline (p<0.001). An overall SVR was achieved in 95 % of the patients. In the group of patients with genotype 1 it was 86 %, and with genotype 3, 100 % (Tab. 2, Fig. 1).

Biochemical response

The levels of aminotranferases (ALT, AST) dropped significantly at week 12 of treatment and at the end of treatment in comparison with levels at baseline (p<0.001; p<0.001, respectively). At the end of treatment and at week 24 after the completion of therapy, the differences of ALT levels were not statistically significant; however both means measured parameters were already within reference limits (Tab. 2). The paired Student's test was used for statistical analysis.

Liver biopsy

The fibrosis response to HCV infection is variable. Fibrosis implies a possible progression to cirrhosis. Fibrosis, more than inflammation, predicts the progression to irreversible liver disease in HCV infection. Distribution of stages of liver fibrosis is shown in Table 1. Liver biopsies were performed in 81 (88 %) of the 92 patients. There were no biopsy-related complications in any patient. In a majority of patients (63) fibrosis stages 1 and 2 have been classified whereas fibrosis stage 0 was assessed in 17 patients. No patients with fibrosis stages 4 or 5 were classified in the study.

Hematologic parameters

Combined treatment with PEG-IFN-α and R is linked with expected adverse reactions in laboratory parameters. The levels

of hemoglobin, count of erythrocytes, leukocytes, neutrophils and platelets decreased significantly at week 12 of treatment when compared with baseline data (in all parameters p<0.001, respectively) (Tab. 2). It is generally accepted that changes in leukocytes and probably in platelets counts are caused by the immunosupressive effect of IFN-α on bone marrow, while changes in number of erythrocytes and hemoglobin levels are largely attributed to hemolysis induced by R although IFN-α may play a role to a lesser extent.

Predictors of response

Genders, HCV genotype, levels of ALT, stage of fibrosis were identified by single – variable analysis as potential predictors of response.

Relation between fibrosis and HCV RNA qualitative test

We did not notice a correlation between fibrosis and results of qualitative tests of HCV RNA (tested with chi-square test).

Relation between fibrosis and ALT levels

We compared the values of serum ALT in all observed periods in patients with fibrosis and in patients with different grade of fibrosis. The values of ALT did not differ significantly (Kruskal-Wallis test).

We compared the levels of ALT in all periods in patients with fibrosis and without fibrosis. The levels of ALT did not differ significantly (Mann-Whitney test).

Relation between genotypes and serum ALT levels

We compared the ALT values in all observed periods in both genotype groups. After completion of treatment, the ALT levels were significantly higher in patients with genotype 1 (p=0.025) (Mann-Whitney test).

Virologic response during treatment

We compared the number of HCV RNA-positive patients in all observed periods during the follow-up in patients with genotype 1 and 3, respectively. After week 12 of therapy, the difference was not significant (p=0.205), however after the completion of therapy, the ratio of HCV RNA-positive patients was in favour of patients with genotype 1 (p=0.005). Twenty-four weeks after completion of therapy, the number of HCV RNA-positive patients with genotype 1 was significantly higher (p=0.008) (Fischer's exact test) in comparison with genotype 3.

Relation between fibrosis and genotypes

No correlation between fibrosis and genotype 1 or 3 was found (chi-square test).

Proportion of gender in genotypes

Genotypes 1 and 3 did not differ in gender (25 % vs 21 %, respectively) (chi-square test) .

Relation between age and genotypes

The age of patients with genotype 1 did not differ from age of patients with genotype 3 (Mann-Whitney test).

Relation between SVR and genotypes

When we compared patients without SVR in relation to genotypes, we noticed that all patients without SVR were patients with genotype 1 (p=0.008) (Fischer's exact test).

Side effects

IFN-based therapy is associated with numerous side effects. The most common IFN-related side effects were symptoms consistent with a flu-like illness. This flu-like syndrome usually disappeared after 2 to 4 weeks of therapy. These symptoms were ameliorated by acetaminophen given before first two doseses of PEG-IFN-α. Long-term side effects included fatigue, anorexia, weight loss, neuropsychiatric symptoms, hematologic abnormalities and reversible alopecia. The frequency of side effects is presented in Table 3. The discontinuation of treatment was necessary in 1 patient due to intolerance of depression and refusal to recieve antidepressive therapy.

Discussion

Interferon-based regimens for treatment of chronic hepatitis C have become increasingly effective and currently are able to eradicate virus in more than half of cases and therefore should be considered the current standard of care. Data on the efficacy of PEG-IFNs or in combination with R are still limited especially for the group of young patients with the history of intravenous drug abuse. In this study, patients treated with PEG-IFNs and R experienced SVR that was higher than in previously published studies. The high proportion of SVR was achieved not only in the group of patients with genotype 3 (100 %) but also in the group with genotype 1 (86 %), respectively.

Contrary to our results, the major trials confirm that anti HCV drug treatment is effective in more than 50 % of all patients (54–63 %) and in approximately 70–80 % of patients with genotypes 2 or 3 (7, 13, 14, 15). What are the arguments to explain the differences in therapeutic efficacy of combined therapy presented in this study compared with those previously published?

It is generally accepted, that viral and patient-related factors are critical for the SVR rate. The HCV genome is characterized by significant genetic heterogeneity. Quasispecies diversity in individual HCV isolates and at least 6 major genotypes were found in different geographic areas. The major genotypes of HCV differ in their worldwide distribution. The most common genotypes in United States and Western Europe is the genotype 1 with the prevalence of 63–72 % in the HCV-positive population (risk group of IDUs), however some authors reported higher proportion of genotype 3 among the risk group of intravenous drug users. In England it is reported that fifty percent of all infections were genotype 1 with a higher percentage of genotype 3 among the IDUs (16, 17) and the same data were obtained in Slovakia (18). Our study also demonstrates higher proportion of genotype 3 in comparison with genotype 1 (61 % vs 39 %) in the group of former IDUs treated by combined therapy.

Our data documented that the treatment response is primarily driven by HCV genotype. The proportion of patients with genotype 3 in our study was higher in comparison with genotype 1. SVR rates in patients infected with HCV genotype 1 continue to be lower than those in patients harboring HCV genotypes 2 or 3 (7, 19, 20, 21).

High viral load is an independent predictive factor of unresponsiveness to anti HCV therapy. In our study we assessed the viral load only at baseline in patients with genotype 1, recruited by the National Reference Centre. We did not notice a correlation between high viral load (more than 2 million copies/mL) and unresponsiveness to therapy.

In this study, naive Caucasian patients were enrolled. Retreatment of patients who did not respond to IFN alone or in combination with R is associated with poor sustained virologic response rates in HCV-infected patients (22–27).

Compared with white patients, African-American patients are more frequently infected with HCV-1, are older when treated, weigh more, and have higher median Histological Activity Index Score (28).

Retrospective subanalyses of large randomized, multicenter trials have clearly demonstrated that age over 40 years is an independent predictor of nonresponse to IFN-based treatment of patients with hepatitis C (24, 29). In our study the mean age was 27 years, whereas in large clinical studies the mean age was more than 40 years (7, 13, 20, 21). Only in a study published by Neri et al, the mean age of patients was young (27 years), however the patients were treated by monotherapy with IFN-α-n2b (9). Mohsen (16) reported a close correlation between liver fibrosis and age. Multivariate analysis of risk factors demonstrated a strong correlation between fibrosis and age at biopsy, with patients over 50 years of age having 131-fold increased risk of fibrosis stage 3 or 4 compared with patients aged less than 30 years (95 % CI 4.4–253) (16, 30). This is consistent with our results. The treated population of former drug users was young (mean age 27 years) with the occurence of mild hepatitis in majority of patients. No patient with cirrhosis has been found among patients in our study. The absence of bridging fibrosis or cirrhosis, age less than 40 years and viral load less than 600 000 IU/ml were considered as independent predictive factors of SVR in the study performed by Dalgard et al (31). The correlation between the stage of fibrosis and the SVR was also emphasized by Parise et al. The rate of SVR among the subjects with fibrosis at an advanced stage (F3–F4) was 38 %, compared to 75 % for patients with fibrosis at an initial stage (F0–F2) (32).

In our study, we did not notice the correlation between female sex and higher therapeutic response rate; however some authors observed this phenomenon (23).

Adherence to therapy is critical in obtaining the best results. Retrospective analysis has documented that patients who receive more than 80 % of their total IFN doses and more than 80 % of their total R doses and more than 80 % of the duration of therapy had significantly higher SVR compared with those with lower adherence (33). In this study, patients experienced excellent adherence to therapy (higher than 80 % in all parameters). It was

achieved by close cooperation between medical staff and patients, education of patients and close clinical and laboratory monitoring of follow-up.

Taken together, the high SVR rate in this study was determined by best prognostic factors such as young age of patients with mild liver fibrosis, naive, not previously treated former DUs major proportion of patients subpopulation with genotype 3 and excellent adherence to combined therapy based on close cooperation between medical staff and patients. These results imply that patients' selection, education, and monitoring are critical in successful treatment of patients with chronic HCV infection.

Conclusion

The high SVR in former drug users treated by combined treatment was obtained by the best prognostic factors. Young-aged "naive", Caucasian patients with mild fibrosis and dominant proportion of genotype 3 with excellent treatment adherence based on close cooperation between medical staff and patients resulted in high response rate. High proportion of SVR in the group of former drug users has been achieved not only in subjects with genotype 3 (100 %) but also in those with genotype 1 (86 %), respectively. It seems that the most decisive prognostic factor which influences (favors) high therapeutic efficacy represent young age and early onset of anti-HCV treatment.

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