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TREATMENT OF ELDERLY PATIENTS WITH CHRONIC HEPATITIS C: A RETROSPECTIVE COHORT STUDY

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SUMMARY – The prevalence of chronic hepatitis C increases in elderly patients. The aims of this study were to identify the factors associated with hepatocellular carcinoma (HCC) and end-stage liver disease development and to evaluate the efficacy and safety of pegylated interferon (PEG-IFNα) plus ribavirin (RBV) therapy in elderly patients. A retrospective cohort study included all consecutive patients with hepatitis C virus (HCV) infection treated with PEG-IFNα+RBV between 2003 and 2013. Elderly patients had a higher frequency of poor prognostic factors including genotype 1 infection, high fibrosis, and high fibrosis index based on four factors (FIB-4) score. The sustained virologic response (SVR) rate for genotype 1 was significantly lower (35.8% *vs*. 57.1%), while the frequency of PEG-IFNα (27.2% *vs*. 7.8%), RBV dose reduction (19.6% *vs*. 9.7%) and treatment discontinuation (13.0% *vs*. 4.1%) was significantly higher in elderly patients. However, age was not associated with SVR in multivariate analysis, and comparable SVR rates were achieved when adjusted for fibrosis score (Ishak ≤3: 66.7% *vs*. 69.8%). During the follow-up, HCC was diagnosed in 18 elderly patients (3 SVR+, 4 SVR- and 9 untreated patients). In conclusion, selected elderly patients can achieve comparable SVR rates as younger patients, but with a higher rate of side effects. Since complications of HCV infection occur more frequently in elderly patients, they should be given priority for antiviral therapy.

Key words: *Hepatitis C, chronic – treatment; End stage liver disease; Aged; Hepatitis C – prognosis; Pegylated interferon alpha; Immunotherapy; Antiviral agents*

Introduction

Chronic hepatitis C (CHC) continues to be a major public health problem. Despite the limited number of population-based studies on the age-specific prevalence, HCV prevalence increases with age, and currently the age group with the peak prevalence in Europe is the 55-65 age group[1, 2]. While the mean life expectancy in the European Union (EU) is 19.8 years once a man reaches the age of 65 (according to the EuroStat), it is expected that HCV related liver cirrhosis and hepatocellular carcinoma (HCC) will dramatically increase in the following years, particularly in the elderly population[3].

Aging is considered as an unfavorable factor for liver disease progression; adults older than 60 more often present with complications of cirrhosis and HCC as initial manifestations of HCV infection; older age at the time of initial infection is associated with more rapid progression to fibrosis, cirrhosis and infectious complications; elderly patients are at an increased risk of HCC, even if they achieve sustained viral response (SVR) in the absence of significant fibrosis or cirrhosis[4-6]. Although this age group was excluded from the initial pegylated interferon plus ribavirin (PEG-

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IFNα+RBV) registration trials, these studies identified age ≥60 years to be associated with poorer treatment response[7,8]. The safety and efficacy of HCV therapies have been extensively studied in patients between the ages of 18 and 60, but elderly patients remain an understudied and difficult-to-treat population. The 'real-life' studies of PEG-IFNα+RBV treatment in elderly individuals are scarce. Although generally thought as a negative predictor of SVR, the published results of therapy efficacy in elderly patients are disagreeing. While some studies showed the treatment to be well tolerated and there was little or no difference in SVR, other showed marked reduction in SVR rates[6,9-12]. Nevertheless, older age is still associated with a lower likelihood of being considered for antiviral therapy[13,14].

Not long ago, direct acting antiviral agents (DAAs) that markedly increase SVR have been licensed, but the efficacy and toxicity of these drugs in elderly population is still unknown. Importantly, due to the price concerns, it is unlikely that this treatment will soon become widely available in low-income countries. Thus, the ways of stratifying patients that might benefit from PEG-IFNα+RBV backbone therapy are of high importance.

Therefore, we performed a retrospective cohort study to examine disease progression in elderly patients treated with PEG-IFNα+RBV as compared with treatment naïve elderly patients and to identify factors associated with HCC and end-stage liver disease (ESLD) development. The secondary aim was to evaluate PEG-IFNα+RBV treatment response and safety in elderly patients (≥60 years).

Patients and Methods

Study design and population

In order to analyze treatment response and safety profile of PEG-IFNα and RBV combination therapy in elderly population, a retrospective cohort study that included 577 consecutive adult, treatment-naïve patients that started combination therapy between January 2003 and January 2013 was conducted at the Croatian Reference Center for Viral Hepatitis, Zagreb, Croatia. Patients were stratified by age into two groups: those aged ≥60 (n=92, 15.9%) and those aged <60 years (n=485, 84.1%).

To determine the impact of PEG-IFNα+RBV treatment and achievement of SVR on the clinical outcomes of HCV infection in elderly population (≥60 years), all consecutive CHC patients enrolled between 2003 and 2013 were included in the study. In total, 142 patients were included in the cohort that was followed for 3.56±1.87 years. Patients were stratified in three categories: SVR group, non-SVR group and untreated patients. Selected endpoints were development of HCC, ESLD, and progression of liver disease, as measured by the aspartate aminotransferase-to-platelet ratio index (APRI) and fibrosis index based on four factors (FIB-4) scores.

Data collection and definitions

Records of all patients treated at the Department of Viral Hepatitis, University Hospital for Infectious Diseases, Zagreb (UHID) during the study period were extracted and used for collection of clinical and laboratory data. Patients were treated either with PEG-IFNα2a 180 μg/week (n=334, 57.9%) or PEG-IFNα2b 1.5 μg/week (n=243, 42.1%) plus weight-adjusted RBV. The duration of therapy in HCV genotypes 1 and 4 was 48 weeks, and in genotypes 2 and 3 it was 24 weeks. Therapy was discontinued in patients with genotype 1 and genotype 4 if the viral load decreased by less than 2 log HCV RNA copies/mL at week 12 compared with baseline values and if HCV RNA was still detectable at week 24.

The following demographic and laboratory data were analyzed: age, gender, baseline hemoglobin concentration, white blood cell count (WBC), absolute neutrophil count (ANC), platelet count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total serum protein and serum albumin, pretreatment HCV viremia, and genotype. HCV RNA quantification was performed by COBAS Ampliprep/COBAS TaqMan HCV test (Roche Diagnostics, Diagnostic Systems, Pleasanton, CA, USA). HCV genotyping was performed by VERSANT HCV Genotyping assay (LIPA, Bayer Diagnostics, Puteaux, Cedex, France). Liver biopsy was performed in a total of 427 patients and the Ishak scoring system was used as an indicator of histologic activity[15]. The APRI and FIB-4 scores were calculated for all patients and were used as a surrogate marker of disease severity[16,17]. The primary outcome measured was SVR achievement defined as undetectable HCV RNA at 24 weeks after the end of

antiviral therapy. Secondary outcomes were rates of adverse events, rates of PEG-IFNα and/or RBV dose modifications and treatment discontinuation. In order to evaluate disease progression in elderly patients, data on the development of HCC, APRI, FIB-4 score and ESLD were retrieved from medical records of all patients that had ≥60 years at the time of diagnosing HCV at UHID between 2003 and 2013. The diagnosis of HCC was confirmed on the basis of a verified focal liver lesion by imaging techniques in accordance with the European Association for the Study of the Liver guidelines[18]. This study was conducted according to the ethical guidelines of the Declaration of Helsinki and was approved by the UHID Ethics Committee.

Statistical analysis

Demographic and clinical characteristics and laboratory data were evaluated and presented descriptively. The χ^2-test with Yates correction, Fisher exact test and Mann Whitney U test were used to compare the groups, as appropriate. All tests were two-tailed; a $p<0.05$ was considered statistically significant. Binary logistic regression analysis was used to assess the independent predictors of SVR. Cumulative incidence of HCC was estimated by the Kaplan-Meier method. The prognostic relevance of clinical variables and HCC occurrence was evaluated by univariate analysis with the log-rank test and by multivariate Cox regression analysis. The time frame for each outcome was defined as the time from diagnosing HCV infection until the onset of the event. Data were censored when individuals died from non-liver-related causes, received a liver transplant, or were lost during follow-up. The strengths of association were expressed as odds ratio (OR) and the corresponding 95% confidence interval (95%CI). Statistical analyses were performed using Prism (ver. 5.0) statistical software (Graphpad Software, San Diego, CA, USA) and MedCalc for Windows®, ver. 11.5.1.0 (MedCalc Software, Mariakerke, Belgium).

Results

Baseline characteristics of treated patients

A total of 346 men and 231 women aged 18-73 years (44.18±12.6) were included in the study. Patients aged ≥60 comprised 15.9% of the study population. There were six patients younger than 20, 249 (43.2%) patients aged 20-39, 118 (20.5%) patients aged 40-49, 112 (19.4%) patients aged 50-59, 81 (14.0%) patients aged 60-69, and 11 (1.9%) patients aged >70. Patient baseline characteristics are shown in Table 1.

Elderly patients were more often infected with HCV genotype 1 (88.0%), had more severe histologic activity of the disease, as well as higher FIB4-score and lower platelet count and hemoglobin level. Importantly, elderly patients more frequently had comorbidities (65.2%), including hypertension (n=42, 45.7%), diabetes (n=9, 9.8%), chronic obstructive pulmonary disease (n=10, 10.9%), hyperlipidemia (n=24, 26.1%), coronary disease (n=13, 14.1%), and osteoporosis (n=7, 7.6%). Although six (6.5%) patients had chronic renal impairment, none of our patients was treated with chronic dialysis.

Treatment safety, modifications and discontinuation

Therapy had to be adapted in a substantial number of elderly patients. Reduction of PEG-IFNα and RBV was more frequently required and treatment was more frequently prematurely discontinued due to side effects in elderly patients. Data on treatment discontinuation and side effects are summarized in Table 2.

Neutropenia (≤1500 cells/μL), anemia and thrombocytopenia ($\leq 50 \times 10^9$/L) more frequently developed in the elderly group. In addition, during the course of treatment, a decreased level of hemoglobin, ANC and platelets was more pronounced than in younger patients. The mean decrease in hemoglobin was 39.73±25.71g/L in elderly *versus* 26.46±12.33g/L in younger patients (p=0.0265). The incidence of both anxiety and insomnia was higher in elderly patients. There was no lethal outcome in either group during the treatment or in the 6-month follow-up period.

Treatment outcome

The analysis included data on all patients who received at least one dose of medication (intention-to-treat analysis). In the whole group, SVR was achieved in 339 (62.4%) patients; SVR rate was 53.8% for genotype 1 and 80.1% for genotype 3.

In elderly patients, SVR rate was significantly lower for genotype 1 (35.8% *vs.* 57.1%, p=0.0007), while there was no statistical significance for genotype 3

Table 1. Baseline patient characteristics

	≥60 years (n=92)	<60 years (n=485)	p value[b]
Male sex	41 (44.57%)	305 (62.89%)	0.0016
Age (years)	63.8±3.7	40.4±10.1	<0.0001
Body weight (kg)	73.5±13.43	75.77±16.82	0.5151
Comorbidities	60 (65.22%)	96 (19.79%)	<0.0001
Duration of infection (years)[a]	19.86±12.31	12.35±9.91	0.0009
Risk factors			
Blood transfusion	42 (45.65%)	97 (20.00%)	0.0001
Intravenous drug use	12 (13.04%)	193 (39.79%)	
Surgery/wounding	15 (16.30%)	43 (8.87%)	
Sexual behavior	0 (0.00%)	20 (4.12%)	
Other	1 (1.09%)	31 (6.39%)	
Unknown	22 (23.91%)	101 (20.82%)	
Liver biopsy (n=427)			
Ishak score			
Ishak 0,1	4 (6.15%)	18 (4.97%)	0.0001
Ishak 2,3	19 (29.23%)	230 (63.54%)	
Ishak 4,5	37 (56.92%)	108 (29.83%)	
Ishak 6	5 (7.69%)	6 (1.66)%	
Histology Activity Index (HAI)			
HAI 1-8	24 (36.92%)	222 (61.33%)	0.0006
HAI 9-12	26 (40.00%)	100 (27.62%)	
HAI 13-18	15 (23.08%)	40 (11.05%)	
Liver steatosis	39 (60.00%)	175 (48.34%)	0.1055
Moderate/severe steatosis	21 (32.31%)	78 (21.55%)	0.0779
Genotype			
Genotype 1	81 (88.04%)	303 (62.47%)	<0.0001
Genotype 1a	8 (8.70%)	79 (16.29%)	
Genotype 1b	59 (64.13%)	156 (32.16%)	
Genotype 3	7 (7.61%)	156 (32.16%)	
Other	4 (4.35%)	26 (5.36%)	
HCV RNA, log10, IQR	5.85 (5.49-6.3)	5.84 (5.23-6.31)	0.3481
<600,000 IU/mL	36 (44.44%)	173 (46.51%)	0.8060
>600,000 IU/mL	45 (55.56%)	199 (53.49%)	
Biochemical activity			
AST (IU/mL)	40.9±27.21	69.78±71.13	0.0001
ALT (IU/mL)	51.31±49.65	108.2±125.1	<0.0001
Platelets (x10^9/L)	185.0±72.86	241.0±299.1	0.0038
Hemoglobin (g/L)	140.0±12.37	147.5±14.59	0.0107
APRI score	0.68±0.58	0.79±0.98	0.8552
FIB-4 score	2.39±1.43	1.24±1.03	<0.0001

[a]Data available for 345 patients; [b]Fisher exact test or Wilcoxon rank sum test, as appropriate; APRI = aspartate aminotransferase-to-platelet ratio index; FIB-4 = fibrosis index based on four factors

Table 2. Treatment safety and tolerability

	≥60 years	<60 years	p value[a]
Reported side effects during PEG-IFNα therapy[b]			
Neutropenia, n (%)	23 (25.00%)	53 (10.93%)	0.0006
mean±SD ($x10^9$/L)	2.5±0.91	3.2±1.14	0.0015
Anemia, n (%)	29 (31.52%)	89 (18.35%)	0.0069
mean±SD (g/L)	107.9±17.77	117.9±14.65	0.0018
Thrombocytopenia, n (%)	32 (34.78%)	45 (9.28%)	0.0001
mean±SD ($x10^9$/L)	98.7±48.62	124.7±46.96	0.0116
Arthralgia/ myalgia	12 (13.04%)	89 (18.35%)	0.2941
Dermatologic	11 (11.96%)	61 (12.58%)	1.0000
Respiratory	3 (3.26%)	27 (5.57%)	0.4520
Hypo/ hyperthyroidism	3 (3.26%)	11 (2.27%)	0.4764
Flu-like symptoms	29 (31.52%)	203 (41.86%)	0.0649
Anxiety	42 (45.65%)	61 (12.58%)	0.0001
Depression	4 (4.35%)	19 (3.92%)	0.7743
Insomnia	48 (52.17%)	39 (8.04%)	0.0001
Headache	23 (25.00%)	103 (21.24%)	0.4120
Therapy modification and discontinuation			
RBV dose reduction	18 (19.57%)	47 (9.69%)	0.0107
PEG-IFNα dose reduction	25 (27.17%)	38 (7.84%)	0.0001
PEG-IFNα and RBV dose reduction	14 (15.22%)	13 (2.68%)	0.0001
Therapy discontinuation	12 (13.04%)	20 (4.12%)	0.0019

[a]Fisher exact test or Wilcoxon rank sum test; PEG-IFNα = pegylated interferon alfa; RBV = ribavirin

(57.1% *vs*. 82.0%, p=0.1271). Virologic response in young and elderly patients is summarized in Table 3.

However, since the majority of elderly patients had genotype 1 infection and significant fibrosis (Ishak >3), subgroup analysis was performed and showed no statistical differences in genotype-1 SVR rates when adjusted for fibrosis score (Ishak ≤3: 66.7% (14/21) *vs*. 69.8% (169/73), p=0.8016, and Ishak ≥4: 29.7% (11/36) *vs*. 43.6% (44/101, p=0.1714).

Table 3. Treatment response

	≥60 years	<60 years	p value
Genotype 1			
SVR	29 (35.80%)	173 (57.10%)	0.0007
Lost to follow-up	3 (3.70%)	13 (4.29%)	1.0000
Genotype 3			
SVR	5 (71.43%)	128 (82.05%)	0.6136
Lost to follow-up	0 (0.00%)	13 (8.33%)	1.0000

Fisher exact test; SVR = sustained virologic response

Factors associated with sustained viral response

In order to identify if age ≥60 is independently associated with lower SVR, we performed multiple logistic regression analysis taking confounders into account. All predictors were entered in a backward stepwise logistic regression model with the SVR being the dependent variable (antiviral therapy (PEG-IFNα2a *vs.* PEG-IFNα2b), age (<60 years *vs.* ≥60 years), gender, body weight (≤75 kg *vs.* >75 kg), HCV-genotype 3 *vs.* non-3, extent of fibrosis (mild fibrosis: Ishak 0-3 *vs.* significant fibrosis: Ishak 4-6)). Statistically non-significant predictors were progressively excluded based on the likelihood ratio test. Multivariable model showed that age had no significant influence on SVR. As expected, the best SVR predictor was genotype 3, while significant fibrosis and RBV reduction were negatively associated with SVR, as shown in Table 4.

Similar results were obtained in subgroup analysis that focused on genotype 1, significant fibrosis and RBV reduction. When only genotype 1 patients were included, fibrosis (OR 0.26, 95%CI 0.15-0.45, p<0.0001) and RBV reduction (OR 0.37, 95%CI 0.18-0.77, p=0.0074) had a negative impact on SVR, while PEG-IFNα-2a treatment was positively associated with SVR (OR 1.99, 95%CI 1.15-3.43, p<0.0132). Next, we performed subgroup analysis on patients with significant fibrosis (Ishak ≥4). The final multivariable model included genotype 3 (OR 17.75, 95%CI 2.06-152.28), PEG-IFNα reduction (OR 0.09, 95%CI 0.01-0.75) and female sex (OR 2.62, 95%CI 1.26-6.70), but again age was not found to be an independent predictor of SVR.

Table 4. Factors associated with sustained virologic response

	Univariate analysis		Multivariate analysis	
	Odds ratio (95%CI)	p value	Adjusted odds ratio (95%CI)	p value
Age ≥60	0.22 (0.11-0.44)	<0.0001		
FIB-4 >3.25	0.14 (0.02-0.93)	0.0418		
Fibrosis (Ishak ≥4)	0.34 (0.22-0.54)	<0.0001	0.34 (0.20-0.56)	0.0001
Genotype 3	6.89 (3.81-12.45)	<0.0001	8.68 (3.83-19.64)	<0.0001
PEG-IFNα-2a	1.50 (1.02-2.20)	0.0390		
RBV reduction	0.34 (0.21-0.56)	<0.0001	0.46 (0.24-0.90)	0.0238
PEG-IFNα reduction	0.37 (0.20-0.68)	0.0016		

PEG-IFNα = pegylated interferon alfa; RBV = ribavirin; 95%CI = 95% confidence interval

Incidence of heptatocellular carcinoma and disease progression in elderly patients

Of the 577 patients that received PEG-IFNα+RBV treatment in the study period, 256 (44.4%) patients were followed-up for more than 12 months after the end of treatment (98 SVR+ and 158 SVR- patients, with the mean follow-up of 4.57±2.71 years). Seventeen patients developed HCC at the mean age of 56.21±11.66 years, corresponding to the incidence rate of 1.95 *per* 100 person-years. HCC was diagnosed in four patients that achieved SVR; in two patients within 1 year after SVR, and in the other two at 3 and 4 years, respectively, after achieving SVR. HCV RNA was tested at the diagnosis of HCC in all four of these patients, and they all were negative; two patients had Ishak fibrosis score 3, one patient had Ishak 4 and one Ishak 5; none had varices or decompensated liver disease at the time of HCC diagnosis. FIB-4 score >3.25 (HR 4.57, 95%CI 1.65-12.61, p=0.0035) and age ≥60 (HR 10.56, 95%CI 2.64-42.15, p=0.0009) were found to significantly influence HCC incidence.

To further determine the impact of PEG-IFNα+RBV treatment on the clinical outcomes of HCV infection in elderly population, we collected additional data from untreated CHC patients that were aged ≥60 at the time of first presentation at UHID between 2003 and 2013 and that were followed-up for at least 12 months. Overall, 142 patients were identified and included in the cohort (76 untreated and 66 treated) that was followed-up for 3.56±1.87 years. During the follow-up, HCC developed in three patients with SVR, four patients from non-SVR group and nine untreated patients, corresponding to the incidence of 3.6, 4.7 and 5.0 *per* 100 person-years, respectively. Cox proportional hazard regression analysis identified only baseline FIB-4 >3.25 (HR 12.1, 95%CI 3.78-38.71, p<0.0001) to be independently associated with HCC development, while sex, PEG-IFNα+RBV treatment and SVR were not associated with HCC in elderly patients.

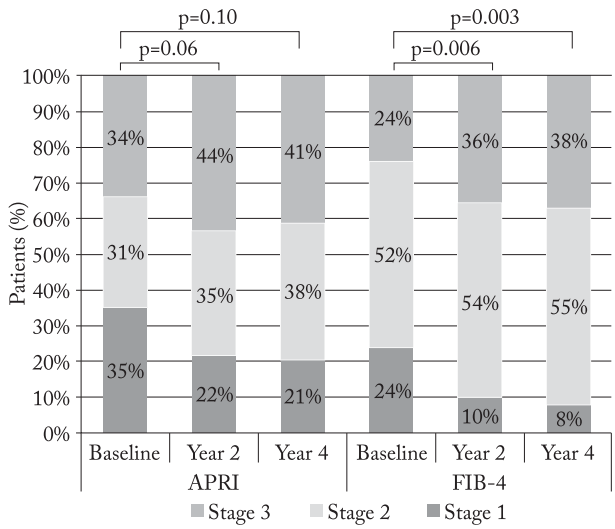

Fig. 1. Progression of liver disease in elderly patients as measured by APRI and FIB-4 score.

Frequencies of HCV infected elderly patients (combined SVR negative and treatment naïve) in different APRI and FIB-4 stages at baseline, year 2 and year 4 of follow-up are shown. A significant increase in stage 3 FIB-4 score was recorded between baseline and year 2 (p=0.006, χ^2-test) and year 4 (p=0.003).
APRI: stage 1 <0.5, stage 2 ≥0.5<1.0, stage 3 ≥1.0;
FIB-4: stage 1 <1.45, stage 2 ≥1.45<3.25, stage 3≥3.25.
APRI = aspartate aminotransferase-to-platelet ratio index; FIB-4 = fibrosis index based on four factors

Of 142 patients enrolled, 111 (78.1%) and 86 (60.5%) patients had both year 2 and year 4 APRI and FIB-4 levels available, respectively. There were no significant differences in APRI and FIB-4 progression between non-SVR and untreated patients; during 4 years, the proportion of patients with stage 3 APRI (>1.0) and FIB-4 (>3.25) increased from 34% and 24% at baseline to 41% and 38% at year 4, respectively (Fig. 1). Any event of disease decompensation (ascites, encephalopathy and/or variceal bleeding) developed in one patient from non-SVR group and in seven (9.21%) untreated patients.

Discussion

The combination of pegylated interferon and ribavirin still remains the backbone or even standard therapy in many resource-limited settings. Since the access to IFN free treatment is restricted, the way of prioritizing patients for treatment is of high importance. Interestingly, neither EASL nor AASLD in recently updated HCV treatment guidelines highlight elderly population for early treatment, reflecting the deficiency of studies performed in this understudied group[19,20].

While the safety and efficacy of PEG-IFNα+RBV therapy have been extensively reviewed, the perception of poorer outcomes and the potential difficulties associated with adherence and drug interactions have resulted in limited access for elderly patients. Results of our study show that older age is associated with several negative predictors of treatment response, such as higher fibrosis score, FIB-4 score, genotype 1 infection and longer duration of infection. This is in clear contrast to other risk groups in Croatia, traditionally considered 'difficult-to-treat', such as war veterans or intravenous drug users[21,22]. In addition, more comorbidities have been observed in elderly patients, mainly metabolic and cardiovascular diseases. According to multivariate analysis, significant fibrosis, RBV reduction and genotype 1, but not the age, were associated with SVR. Response rates were high among elderly patients with genotype 1 infection and mild fibrosis (66%) and comparable with younger group. Similar results have been reported from France, Italy, Canada and the USA[6,10,12,23]. Meanwhile, reports from Japan consistently report lower SVR rates in elderly patients[11,13]. Although some of these studies had been performed before IL28B genotyping was recommended, this difference in response rates might be explained with differences in gene polymorphisms. Since the majority of patients from our cohort had been treated before IL28B genotyping was introduced, we did not include IL28B genotype in our analysis.

Huang *et al*. suggest that poor adherence is the major reason for treatment inferiority in elderly patients and that SVR of 67% and 80% can be reached in genotype 1 infected elderly patients, if their treatment lasts for ≥80% of its expected duration and if they achieve rapid virologic response (RVR), respectively[24]. In addition, analysis of our genotype 1 subgroup showed that fibrosis, RBV dose reduction and treatment with PEG-IFNα-2a, but not the age, were independent factors associated with treatment efficacy.

The results of our study also confirmed that elderly patients had a higher incidence of dose reduction, mainly due to neutropenia, thrombocytopenia and anemia[10,23,24]. The most frequent age-specific side effects were anxiety and insomnia in up to 52% of elderly patients, but in contrast to other studies, severe depression occurred in a minority of elderly patients (4%)[23-25]. Importantly, treatment completion rate in our study was 86.9% in the elderly and 95.9% in the younger group. These rates are significantly higher than previously reported in similar 'real-life' studies that had treatment discontinuation rate of 21% to 53%[10,24]. Overall, it seems that selected elderly patients can be treated with PEG-IFNα+RBV therapy, and achieve similar response rates as younger patients, with careful monitoring and management of more frequent side effects. Nevertheless, PEG-IFNα+RBV still remains an option for genotype 1 infected patients with positive predictors of treatment response (RVR, F1-F2 fibrosis and IL28 CC genotype) in many countries.

The long-term benefits of virologic cure are well known; SVR is associated with a more than 70% reduction in the risk of HCC and 90% reduction in the risk of liver-related mortality and liver transplantation[26-28]. However, the impact of age on HCV eradication and HCC development is still debatable. The mean age of HCC patients has been progressively increasing over the last decades and in Europe it is currently reaching a peak at 70 years[18]. We examined the occurrence of HCC in our treated cohort that corresponds to the incidence of 1.95 *per* 100 person-years. While FIB-4 score >3.25 and age ≥60 were significantly associated with HCC development, SVR did

not significantly reduce the incidence of HCC. Several studies have previously reported that advanced age at HCV eradication is a risk factor for HCC development in SVR patients[5,26,27]. Bruno *et al.* report that male sex and age >54 have a higher risk of developing HCC after SVR, suggesting that host-related factors and duration of the infection increase the risk of HCC[29]. Similarly, a study from Japan identified age >55 at HCV eradication and heavy alcohol intake to be independently associated with the development of HCC within 5 years after HCV eradication, but long-term risk of developing HCC remains for up to 15 years[30]. Our study showed that in elderly population, the risk of HCC was higher in both treated and naïve patients as compared with younger patients, thus highlighting this population and the importance of early antiviral treatment in this group. Importantly, a proportion of patients with FIB-4 >3.25 significantly increased in a 4-year period, increasing this risk even more. Recent reports argue the earlier initiation of treatment in patients with Metavir F0 and F1, which are recognized in current guidelines as a group in which treatment can be postponed; a long-term follow-up study recorded significantly better 15-year survival rates for SVR patients than for those whose treatment had failed or for those who remained untreated[31].

The retrospective nature of this study may have represented a potential source of selection bias that might overestimate the incidence of HCC and SVR rates since our Center serves as the Referral Center for Viral Hepatitis in Croatia. The significant number of lost-to-follow-up might represent information bias. However, the rates of SVR and HCC incidence in our study were consistent with those obtained in similar studies, as stated above.

In conclusion, the risk of disease progression and HCC development in elderly patients with CHC underscores the need for early treatment of this 'difficult-to-treat' group. Although elderly patients often have worse prognostic factors and more frequent side effects to PEG-IFNα+RBV therapy, a subset of elderly patients can be safely treated with close monitoring, and may achieve comparable SVR rates as younger patients. Since older age is strongly associated with faster fibrosis progression, HCC and reduced quality of life, elderly patients should not be excluded from assessment for treatment *a priori*. In the Croatian HCV treatment guidelines, elderly patients are now prioritized for antiviral therapy. Due to the persistent long-term risk of HCC in elderly patients, even after achievement of SVR, surveillance should be continued over a prolonged period.

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Sažetak

LIJEČENJE STARIJIH BOLESNIKA S KRONIČNIM HEPATITISOM C: RETROSPEKTIVNO KOHORTNO ISTRAŽIVANJE

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Učestalost kroničnog hepatitisa C (KHC) raste u starijim dobnim skupinama. Ciljevi ovoga istraživanja bili su utvrditi čimbenike povezane s razvojem hepatocelularnog karcinoma (HCC) i dekompenzirane jetrene bolesti te procijeniti učinkovitost i sigurnost terapije pegiliranim interferonom (PEG-IFNα) i ribavirinom (RBV) u starijih bolesnika. Retrospektivna kohortna studija je uključila sve bolesnike s KHC koji su liječeni PEG-IFNα + RBV između 2003. i 2013. godine u Klinici za infektivne bolesti "Dr. Fran Mihaljević". Bolesnici u dobi od >65 godina češće su imali nepovoljne prognostičke čimbenike, tj. HCV-1 genotip, uznapredovali stadij fibroze i viši zbir indeksa fibroze zasnovan na četiri čimbenika (*fibrosis index based on four factors*, FIB-4). Trajni virusološki odgovor (*sustained virologic response*, SVR) je bio značajno niži (35,8% prema 57,1%), dok je učestalost smanjenja doze PEG-IFNα (27,2% prema 7,8%), RBV (19,6% prema 9,7%) i prekida liječenja (13,0% prema 4,1%) bila značajno češća u starijih bolesnika. Dob nije bila povezana sa SVR u multivarijatnoj analizi, a stariji bolesnici su imali podjednaki SVR kao i mlađi bolesnici ovisno o stadiju fibroze (Ishak ≤3: 66,7% prema 69,8%). Tijekom praćenja HCC je dijagnosticiran u 18 bolesnika u dobi od >65 godina (3 SVR+, 4 SVR-, 9 neliječenih). Zaključno, stariji bolesnici imaju podjednaku vjerojatnost postizanja SVR kao i mlađi, ali uz češće nuspojave. Budući da se komplikacije infekcije virusom hepatitisa C češće javljaju u ovoj populaciji, stariji bolesnici trebaju imati prednost u primjeni antivirusne terapije.

Ključne riječi: *Hepatitis C, kronični – terapija; Terminalni stadij jetrene bolesti; Starija osoba; Hepatitis C – prognoza; Pegilirani interferon alfa; Imunoterapija; Antivirusni lijekovi*