Efficacy and safety of pegylated interferon α and ribavirin in patients monoinfected with HCV genotype 4

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Gastroenterology Rev 2018; 13 (1): 22–29
DOI: https://doi.org/10.5114/pg.2018.74558

Key words: pegylated interferon, HCV genotype 4, sustained virological response.

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Abstract

Introduction: Dual therapy (PegIFN and ribavirin) (DT) was the standard of care in patients infected with HCV genotype 4 (HCV-4) until 2014. Nowadays, new treatment options are available including interferon (IFN)-based and other IFN-free regimens.

Aim: To assess the efficacy (SVR24) and safety of DT and the selected predictor factors of SVR in HCV-4 infected patients.

Material and methods: One hundred and twelve patients (62 men) of median age 23 years were treated with DT for 48/72 weeks (107/5) in the years 2006–2014. Most of them were treatment naïve (80.4%) and with fibrosis F ≤ 2 (83.1%). To select a subset of independent predictors of SVR Logistic Regression Analysis was applied.

Results: SVR24 was achieved in 46/112 (41.1%) patients. The mean viral load was 5.55 $\log_{10}$ IU/ml. Lack of therapy experience increases the odds of achieving SVR (OR = 4.17; 1.04–16.67), whereas more advanced fibrosis and higher baseline viral load tend to decrease the probability of SVR (OR = 0.05; 0.01–0.52 and OR = 0.44; 0.17–1.13, respectively). In contrast, the weight loss is associated with higher probability of virological response (OR = 4.31; 1.37–13.60). Two hundred and seventy-nine adverse events (AEs) were reported in 96 individuals. The rates and types of AEs were similar in patients treated with PegIFN-α2a/RBV and PegIFN-α2b/RBV. Overall, 3 (2.7%) patients discontinued therapy prematurely because of serious AEs.

Conclusions: SVR24 was low. Loss of weight was a new positive predictive factor of SVR found in our study. Most of the AEs were typical of those previously reported for DT.

Introduction

Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease worldwide. It is estimated that 2.35% of the world population is chronically infected with HCV [1]. Hepatitis C virus prevalence across Europe ranges between 0.4% and 3.5%, with wide geographical variation [2, 3]. Poland belongs to the countries with medium prevalence of HCV infection; approximately 1.9% of the population is infected [4]. HCV genotype 4 (HCV-4) is most frequent in the Middle East, and North and sub-Saharan Africa [5]. In Europe, HCV-4 prevalence ranges from 1% (Turkey, Hungary, Sweden) to above 10% (Switzerland, Belgium, Spain, Greece, Montenegro, Albania) [2, 6]. In Poland, HCV-4 is recognised in 4.9% of HCV-infected patients [4]. Dual therapy (DT) with pegylated interferon α (PegIFN) and ribavirin (RBV) had been the standard of care in chronic HCV-4 until the beginning of 2014 [7]. Nowadays, new treatment options are available, some of them interferon (IFN)-based and other IFN-free regimens [8, 9]. New studies show that the IFN-containing composition has high efficacy and low rate of relapse, even in patients with advanced fibrosis [10]. Moreover, in children DT remains the only possible treatment option.

Aim

The aim of our retrospective study was to assess the efficacy, i.e. sustained virological response at post-treatment week 24 (SVR24) and safety of DT in HCV-4-infected patients. The secondary objective was to assess a selection of predictive factors of SVR24.

Material and methods

Patients

One hundred and thirty-two consecutive patients with confirmed chronic HCV-4 infection started DT at the two liver centres between January 2006 and December 2014. One hundred and twelve patients fulfilled the inclusion criteria and were enrolled in the analysis. The group included 50 women and 62 men aged 18–80 years, who underwent therapy with PegIFN-α2a + RBV (54 patients) or PegIFN-α2b + RBV (58 patients). The inclusion criteria were presence of chronic HCV infection defined as detectable levels of HCV RNA in serum together with positive anti-HCV antibodies for more than 6 months and typical changes for chronic hepatitis C in liver biopsy performed within 2 years before the start of DT. The fibrosis stage was assessed by percutaneous liver biopsy in Metavir score. Patients with other hepatic diseases (e.g. active HBV infection, Wilson's disease, alcoholic liver disease, autoimmune hepatitis, drug-induced hepatitis), HIV coinfection, decompensated cirrhosis, and other known contraindications to DT were excluded. PegIFN and RBV type was prescribed at the discretion of the doctor. Patients received PegIFN-α2a (Pegasys®, Roche, Grenzach-Wyhlen, Germany) 180 µg subcutaneously once weekly and RBV (Copegus®, Roche, Grenzach-Wyhlen, Germany) orally twice daily, adjusted to patients' weight (1000 mg for < 75 kg, 1200 mg for ≥ 75 kg). PegIFN-α2b (PegIntron®, MSD, Herdfordshire, GB) was injected subcutaneously at a dose of 1.5 µg/kg once a week, and RBV (Rebetol®, MSD, Herdfordshire, GB) was given orally twice daily at a dose adjusted to patients' weight (800 mg for < 65 kg, 1000 mg for 65–85 kg, 1200 mg for > 85 kg). The planned treatment duration was 48 or 72 weeks. Futility rules were defined in compliance with the international and local guidelines valid in a given treatment period [6, 7, 11]. Safety was assessed through the monitoring of patient-reported adverse events (AEs) and by clinical and laboratory test results. This study was retrospective and conducted with respect to the Declaration of Helsinki principles. Analysis of medical records of patients was used to collect the study data. All patient data were de-identified.

Methods

Biochemical laboratory tests (alanine aminotransferase (ALT) activity, haemoglobin level, platelet and leukocyte counts, TSH) and HCV RNA levels were determined in all patients at baseline, treatment weeks 4, 12, 24, 48, or 72, and 24 weeks after the end of treatment. Quantitative PCR assays were used to measure HCV RNA: Roche COBAS TaqMan v.2.0 (lower limit of quantification (LLOQ) of 15 IU/ml) or Abbott RealTime System (LLOQ of 12 IU/ml). HCV genotype was determined using INNO-LiPA HCV assay (Immunogenetics®, Belgium) or Linear Array HCV Genotyping Test (LA HCV GT) reagents from Roche. Anti-HCV antibodies were analysed using Elisa Murex HCV v.4.0 assay.

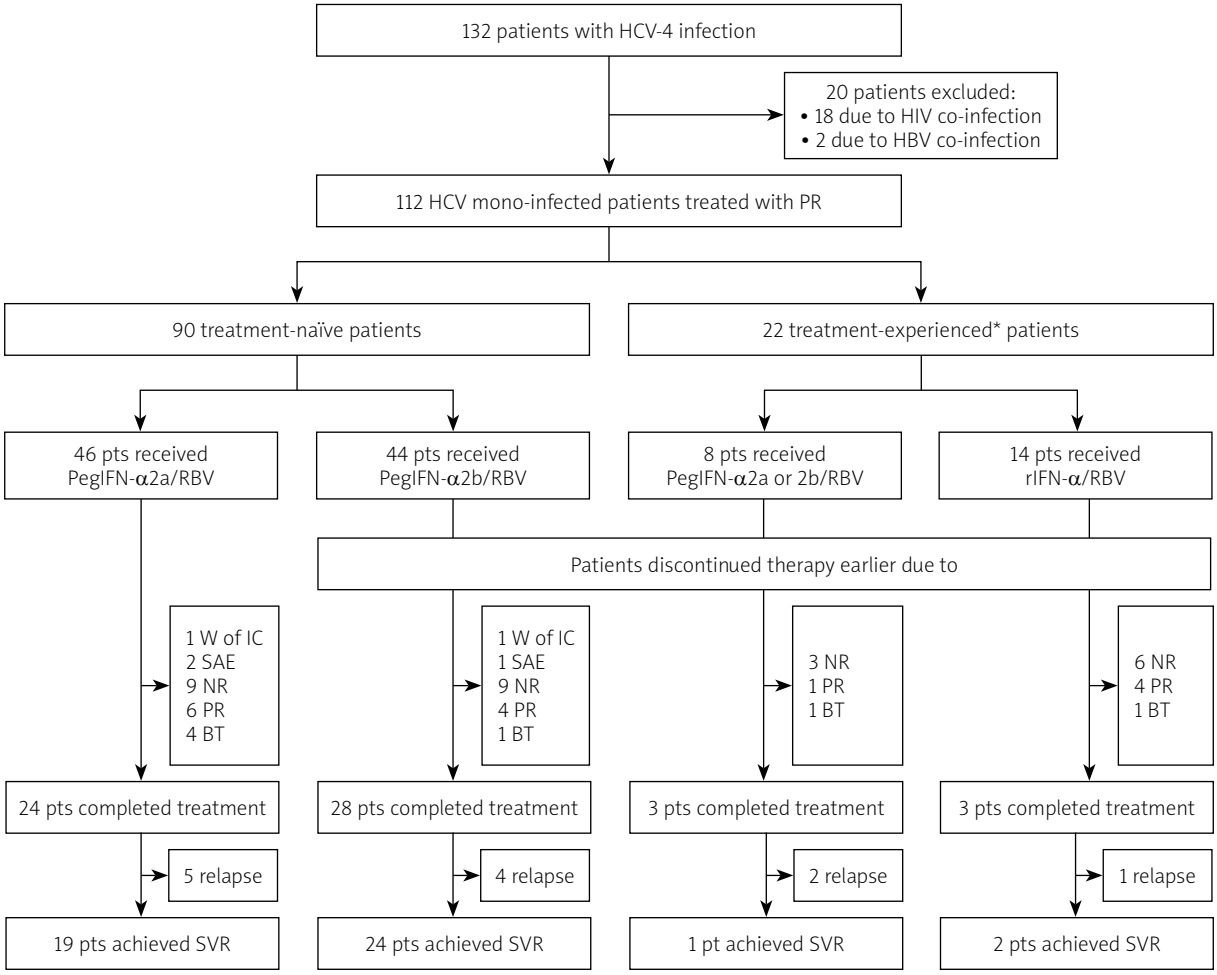
Statistical analysis

The summary statistics for normally distributed continuous variables are presented as mean ± standard deviation (SD) or as median with range for non-normally distributed variables. Categorical variables are presented as frequencies. Differences between continuous normally distributed variables were analysed by the *t* test or by the Wilcoxon test for non-normally distributed variables. Differences for categorical variables were assessed using the χ^2 or Fisher exact test for independence. Logistic Regression Analysis was used to find the independent predictors of SVR24. Variables significant at the 0.2 level in the univariable models were considered for inclusion into the multivariable model. The backward elimination feature selection procedure was applied for selection of the most significant subset of predictor variables. The results were considered as statistically significant when the *p*-value was lower than 0.05. The statistical analysis was performed with the use of R-software, version 3.0.3.

Results

Baseline patients' characteristics

One hundred and twelve patients fulfilled the inclusion criteria and were further analysed (Figure 1). Patients' demographic and clinical characteristics are presented in Table I. The median age of patients was 23 years and the majority were men (55.4%). Also, the vast majority (80.4%) were treatment naïve. Risk factor analysis confirmed nosocomial and health-care-associated transmissions as the major routes of transmission (49.1%). The mean viral load was 5.55 $\log_{10}$ IU/ml. Forty-one (36.6%) patients had increased ALT activity. Mild fibrosis (F0-F2) was present in 93 subjects, and 3/15 patients with advanced fibrosis (F3–F4) had compensated liver cirrhosis. The most common reasons for premature discontinuation was lack of efficacy (49 patients), serious AEs (3 patients), or withdrawal of consent (2 patients).



*PR – pegylated interferon-α2a/α2b and ribavirin, pt/pts – patient/patients, W of IC – withdrawal of informed consent, SAE – serious adverse event, NR – null response, PR – partial response, BT – breakthrough, SVR – sustained virological response at post treatment week 24, *patients with previous history of unsuccessful therapy with recombinant/pegylated interferon α and ribavirin, rIFN-α – recombinant interferon α.*

Figure 1. Flow chart of study enrolment and disposition of patients

Factors associated with sustained virological response

Overall, SVR24 was achieved in 46/112 (41.1%) patients treated for 48 or 72 weeks. Gender, baseline ALT activity, and PegIFN type did not demonstrate any association with the applied DT response, while younger age (≤ 39 years) (p = 0.001), lower pretreatment viral load (≤ 2 × 10^5 IU/ml) (p = 0.024), less advanced fibrosis (F ≤ 2) (p = 0.004), platelet count > 140 × 10^9/l (p = 0.044), and haemoglobin level within the normal range (p = 0.040) were associated with good response to DT. SVR rate was significantly higher in treatment-naïve patients than in those treatment-experienced (47.8% vs. 13.6%; p = 0.004). Additionally, loss of weight, defined as > 10% loss of baseline weight over the first 24 weeks of treatment, was associated with higher SVR rate (p = 0.038) (Table II). To select a subset of independent predictors Logistic Regression Analysis was applied (Table III). Lack of therapy experience increases the odds of achieving SVR (OR = 4.17; 1.04–16.67), whereas more advanced fibrosis and higher baseline viral load tend to decrease the probability of SVR (OR = 0.05; 0.01–0.52 and OR = 0.44; 0.17–1.13, respectively). In contrast, the weight loss is associated with higher probability of virological response (OR = 4.31; 1.37–13.60).

Safety of treatment

Among 112 patients assigned to the therapy, 279 adverse events were reported in 96 individuals: 43 of 54 (79.6%) in the group treated with PegIFN-α2a + RBV, and 53 of 58 (91.4%) in the group treated with PegIFN-α2b + RBV. Overall, 3 (2.7%) patients discontinued therapy prematurely because of serious AEs: thrombocytopaenia with bleeding, chronic inflammatory demyelinating polyneuropathy, and increased ALT activity > 10× above the upper limit of normal.

Table I. Baseline demographic and clinical characteristics of the patients

Parameter	Dual therapy (*N* = 112) *n* (%)	Parameter	Dual therapy (*N* = 112) *n* (%)
Gender: female	50 (44.6)	ALT activity [U/l]	49 (13–498)*
Age [years]:	23 (18–80)*	Hb level (12–18 g/dl)	14.5 (1.5)**
≤ 39	79 (70.5)	Platelet count (140–440 × 10^9/l)	218 (63.6)**
> 39	33 (29.5)	Leukocyte count (4–10 × 10^9/l)	5.96 (1.53)**
Route of transmission:		Liver fibrosis (METAVIR score):	
Nosocomial and health-care associated transmission	55 (49.1)	F0–F1	60 (53.6)
IVDU	2 (1.8)	F2	33 (29.5)
Blood transfusion before 1993	9 (8)	F3	12 (10.7)
Perinatal transmission	2 (1.8)	F4	3 (2.7)
Non-medical procedure	1 (0.9)	Unknown	4 (3.6)
Occupational exposure	2 (1.8)	Treatment – naïve	90 (80.4)
Household contact	2 (1.8)	Treatment – experienced	22 (19.6)
Unknown	39 (34.8)	Planned treatment duration:	
Type of PegIFN-α:		48 weeks	107 (95.5)
PegIFN-α2a	54 (48.2)	72 weeks	5 (4.5)
PegIFN-α2b	58 (51.8)	Premature PR discontinued	54 (48.2)
HCV RNA level ($\log_{10}$ IU/ml):	5.55 (0.65)**		
≤ 5.3 $\log_{10}$ (2 × 10^5 IU/ml)	35 (31.2)		
> 5.3 $\log_{10}$ (2 × 10^5 IU/ml)	77 (68.7)		

**Median (range), **mean (SD), IVDU – intravenous drug use, PegIFN-α – pegylated interferon α, ALT – alanine aminotransferase, Hb – haemoglobin, PR – pegylated interferon and ribavirin.*

Most AEs were typical of those previously reported for DT. As shown in Table IV, the rates and types of them were similar in patients treated with both types of PegIFN. Influenza-like symptoms, fatigue, and loss of body weight were the most common AEs. Initiation of antidepressant treatment in 17 patients with depression helped them to continue with the therapy. Interferon-induced thyroiditis occurred in 11 patients, of whom 5 had hypothyroidism, 4 had hyperthyroidism, and 2 had destructive thyroiditis. Infections were observed in 14 patients. Most of them were bacterial respiratory tract infections (8 patients), urinary tract infections (4 patients), or a gastrointestinal tract disorder (acute appendicitis in 1 patient). Fever blister was recognised in one case. The most common laboratory abnormalities were anaemia and a decrease in absolute neutrophil counts < 750 cells/mm^3. One patient with haemoglobin level < 7.5 g/dl needed blood transfusion.

Discussion

HCV-4 infection is not common among native residents of Europe, especially in its northern region. Higher HCV-4 prevalence may be noted in western but mainly southern European countries, where it is mostly recognised in intravenous drug (IVD) users, HCV/HIV-coinfected patients, immigrants from endemic countries, and returning expatriate communities who lived in Africa [2, 12, 13]. The prevalence of HCV-4 as well as response to DT in Central and Eastern Europe are poorly documented. HCV-4 infection does not occur in the Czech Republic and Russia, is very low in Hungary (1.7%), medium in Austria (5.2%), and for Romania, Lithuania, Estonia, Belarus, and Ukraine there is no data available [2, 14]. In Poland, HCV-4 is recognised in 4.9%, 24.0%, and 4.8% of HCV-monoinfected, HCV/HIV-coinfected, and HCV/HBV-coinfected individuals, respectively [4]. Our data confirm this, as well:

Table II. Factors associated with sustained virological response

Factors	SVR = no (*N* = 66) *n* (%)	SVR = yes (*N* = 46) *n* (%)	*P*-value
Gender:			0.689
Female	31 (62.0)	19 (38.0)	
Male	35 (56.5)	27 (43.5)	
Age [years]:	25 (18–73)*	21 (18–80)*	0.007
≤ 39	39 (49.4)	40 (50.6)	
> 39	27 (81.8)	6 (18.2)	0.001
Fibrosis:			
F ≤ 2	51 (54.8)	42 (45.2)	
F > 2	14 (93.3)	1 (6.7)	0.004
Type of PegIFN-α:			
PegIFN-α2a	34 (63.0)	20 (37.0)	
PegIFN-α2b	32 (55.2)	26 (44.8)	0.518
Reduction of PegIFN-α:			
No	45 (58.4)	32 (41.6)	
Yes	21 (60.0)	14 (40.0)	1
Reduction of PegIFN-α due to thrombocytopenia:			
No	57 (55.9)	45 (44.1)	
Yes	9 (90.0)	1 (10.0)	0.045
Reduction of PegIFN-α due to neutropaenia:			
No	57 (58.2)	41 (41.8)	
Yes	9 (64.3)	5 (35.7)	0.885
Reduction of RBV:			
No	45 (56.2)	35 (43.8)	
Yes	21 (65.6)	11 (34.4)	0.485
Treatment – experience:			
No	47 (52.2)	43 (47.8)	
Yes	19 (86.4)	3 (13.6)	0.004
HCV RNA [IU/l]:			
≤ 2 × 10^5	15 (42.9)	20 (57.1)	
> 2 × 10^5	51 (66.2)	26 (33.8)	0.024
ALT activity:			
> ULN**	46 (64.8)	25 (35.2)	
Normal value	20 (48.8)	21 (51.2)	0.113
Hb:			
< LLN***	7 (100)	0 (0)	
Normal value	59 (56.2)	46 (43.8)	0.040
Platelet:			
< LLN#	9 (90)	1 (10)	
Normal value	56 (55.4)	45 (44.6)	0.044
Leukocyte:			
< LLN&	7 (77.8)	2 (22.2)	
Normal value	59 (57.3)	44 (42.7)	0.304
ILS:			
No	37 (63.8)	21 (36.2)	
Yes	29 (53.7)	25 (46.3)	0.338
Loss of body weight:			
No	56 (64.4)	31 (35.6)	
Yes	10 (40.0)	15 (60.0)	0.038

*SVR – sustained virological response, *median (range), PegIFN-α – pegylated interferon α, RBV – ribavirin, ULN** – upper limit of normal (ALT ≥ 33 U/l for female and ≥ 41 U/l for male), Hb – haemoglobin, LLN*** – low limit of normal (Hb equal to 12 g/dl for female and 14 g/dl for male), LLN# for platelets 140 × 10^9/l, LLN& for leukocyte 4 × 10^9/l; ILS – influenza-like symptoms.*

Table III. Predictive factors of SVR24 identified by Simple and Multiple Logistic Regression

Parameter	Unadjusted OR (CI)	*P*-value	Adjusted OR (CI)	*P*-value
Age ≤ 39 vs. > 39 years	4.54 (1.82–14.29)	0.002		
Liver fibrosis > 2 vs. ≤ 2	0.17 (0.03–0.67)	0.026	0.05 (0.01–0.52)	0.012
ALT activity: ULN* vs. normal	0.52 (0.24–1.13)	0.099		
Haemoglobin level < LLN vs. > LLN**	0.09 (0.0–1.86)	0.118		
Platelet count < 140 × 10^9/l vs. > 140 × 10^9/l	0.1 (0.01–0.78)	0.029		
PegIFN dose reduction due to thrombocytopaenia	0.14 (0.02–1.15)	0.068		
Naïve vs. TE	5.88 (1.82–25.0)	0.006	4.17 (1.09–16.67)	0.037
HCV RNA level > 2 × 10^5 vs. ≤ 2 × 10^5 IU/ml	0.38 (0.17–0.87)	0.022	0.44 (0.17–1.13)	0.089
Loss of body weight	2.71 (1.09–6.75)	0.032	4.31 (1.37–13.60)	0.013

ALT – alanine aminotransferase, ULN – upper limit of normal (ALT activity ≥ 33 U/l for women and ≥ 41 U/l for men), LLN** – lower limit of normal for haemoglobin of 12 and 14 g/dl for women and men, respectively; TE – treatment – experienced, OR (CI) – odds ratio with 95% confidence interval.*

Table IV. Adverse events reported during therapy with PegIFN-α2a + RBV or PegIFN-α2b + RBV for 48 or 72 weeks

Adverse events	All patients (*N* = 112) *n* (%)	Patients treated with PegIFN-α2a + RBV (*N* = 54) *n* (%)	Patients treated with PegIFN-α2b + RBV (*N* = 58) *n* (%)	*P*-value
Any SAE	5	3 (5.5)	2 (3.4)	
SAE leading to discontinuation	3	2 (3.7)	1 (1.7)	0.608
Clinical AE:				
Fatigue	33 (29.5)	15 (27.8)	18 (31)	0.836
ILS	55 (49.1)	22 (40.7)	33 (56.9)	0.094
Depression	17 (15.2)	8 (14.8)	9 (15.5)	1
Insomnia, anxiety, or irritability	25 (22.3)	10 (18.5)	15 (25.9)	0.374
Rash, pruritus	10 (8.9)	7 (13)	3 (5.2)	0.192
Loss of hair	12 (10.7)	4 (7.4)	8 (13.8)	0.364
Loss of weight	25 (22.3)	9 (16.7)	16 (27.6)	0.181
Cough	2 (1.8)	2 (3.7)	0 (0)	0.230
Infections:	14 (12.5)	6 (11.1)	8 (13.8)	0.561
Bacterial	13 (11.6)	6 (11.1)	7 (12.1)	0.763
Viral	1 (0.9)	0 (0)	1 (1.7)	1
Oligomenorrhoea	3 (2.7)	2 (3.7)	1 (1.7)	0.608
IIT	11 (9.8)	5 (9.3)	6 (10.3)	1
Anorexia	1 (0.9)	1 (1.8)	0 (0)	0.482
Laboratory AE:				
ALT activity > 10 × ULN	1 (0.9)	0 (0)	1 (1.7)	1
Anaemia (Hb 10–8.5 g/dl)	32 (28.6)	16 (29.6)	16 (27.6)	0.837
ANC < 750 cells/mm^3	29 (25.9)	13 (24.1)	16 (27.6)	0.829
Platelet count < 50 × 10^9/l	9 (8.0)	6 (11.1)	3 (5.2)	0.309
RBV dose reduction due to anaemia	32 (28.6)	16 (29.6)	16 (27.6)	0.837
PegIFN dose reduction:	41 (36.6)	22 (40.7)	19 (32.7)	0.316
Due to ANC < 750/mm^3	29 (25.9)	13 (24.1)	16 (27.6)	0.829
Due to anaemia	3 (2.7)	3 (5.6)	0 (0)	0.109
Due to platelet count < 50 × 10^9/l	10 (8.9)	7 (13)	3 (5.2)	0.309

SAE – serious adverse event, AE – adverse event, PegIFN-α2a – pegylated interferon α2a, PegIFN-α2b – pegylated interferon α2b, ILS – influenza-like symptoms (fever, myalgia, arthralgia), IIT – interferon-induced thyroiditis, ALT – alanine aminotransferase, ULN – upper limit of normal, Hb – haemoglobin, ANC – absolute neutrophil counts, RBV – ribavirin.

18 out of 20 patients withdrawn from the analysis were HIV-coinfected while only two carried also HBV. The analysed group consisted mostly of young individuals where the most common mode of transmission was nosocomial and health-care associated contact, mainly in childhood. This stands in opposition to the studies from other countries where median age of patients was higher (45 years in France, 44 years in Greece, 39 years in Spain), and the predominant route of HCV transmission was IVD abuse [12, 13, 15–18]. In our group, a low percentage of patients with advanced fibrosis (F3–F4), recognised only in 13.4% of the treated individ-

uals, is particularly striking. The proportion of patients with advanced fibrosis was higher in Spanish (21%), French (24.2%), and Greek patients (58.4%) [12, 13, 15]. Two prospective studies from Austria SVR24 achieved 50% and 43.5% of patients treated with PegIFN-α2a + RBV for 48 or 72 weeks, respectively [19]. The limitation was the small HCV-4-infected patient groups. In the French group presented by Roulot *et al.*, 40.3% of patients achieved SVR24 [12]. Papastergiou *et al.* received a similar result in Greek patients (43.6%) [13]. By contrast, in a Spanish study 52.7% of treated patients achieved SVR24 [17]. Here, the response rate was lower, and only 41.1% of patients had SVR24. Interestingly, except for Spaniards, there is a similar SVR24 rate in the majority of European groups, regardless of their country of origin. In the multivariable analysis, we found the following factors to be independently associated with SVR: less advanced fibrosis, lower pretreatment viral load, lack of previous treatment experience, and loss of weight. There is no unequivocal consensus on positive predictors of SVR in HCV-4-infected patients. According to the available results of European studies, the most commonly listed is absence of advanced liver fibrosis and lack of previous history of HCV treatment [12, 13, 18]. Our results confirm this as well. As determined in the studied population, an additional predictive factor of SVR not analysed in the available literature was loss of body weight. Weight loss during therapy without a concurrent RBV dose reduction may result in blood RBV concentration increase. It was demonstrated that in patients receiving RBV at a dose > 10.6 mg/kg, regardless of viral genotype or its load, the response rate was significantly higher than in patients receiving RBV at a dose ≤ 10.6 mg/kg. Patients receiving RBV at a dose > 13.2 mg/kg achieved the highest SVR. Probably we observed the same effect in the studied population.

Conclusions

This is the first study presenting the DT results in Polish adult patients infected with HCV-4. While we are aware that the era of interferon-based regimens has already passed and they are no longer the main focus of scientists and physicians supervising treatments in HCV-infected patients, we still consider identification of a homogenous group of HCV-infected patients from Europe and its detailed characteristics to be an important contribution to the general knowledge on the infection epidemiology on the European continent. Also, we demonstrate differences in the demographic characteristics and severity of the condition among Polish patients and those of other European countries. The SVR rate achieved in HCV-4-infected patients in our study was low. The following factors were demonstrated to be independently associated with SVR: less advanced fibrosis, lower pretreatment viral load, lack of previous treatment experience, and body weight loss.

Conflict of interest

Dorota Kozielewicz: speaking and teaching: Roche, Gilead, BMS, AbbVie. Grzegorz Madej: speaking and teaching: Roche, AbbVie. Anna Grabińska and Magdalena Wietlicka-Piszcz do not have any disclosures to report.

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Received: 1.12.2016
Accepted: 18.04.2017