® Postepy Hig Med Dosw (online), 2012; 66: 339-347
e-ISSN 1732-2693

www.phmd.pl
Original Article

Received: 2012.02.15
Accepted: 2012.05.25
Published: 2012.06.12

Results of antiviral treatment of patients with chronic hepatitis C: experience of Poznan centre

Wyniki leczenia przeciwwirusowego pacjentów z przewlekłym zapaleniem wątroby typu C – doświadczenia ośrodka poznańskiego

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Maciej Bura[ABCDEF], Arleta Kowala-Piaskowska[BEF], Agnieszka Adamek[ABCDEF], Aleksandra Bura[BCDE], Arkadiusz Czajka[BD], Katarzyna Hryckiewicz[ABD], Iwona Bereszyńska[AB], Iwona Mozer-Lisewska[ABCDEFG]

Department of Infectious Diseases, Poznan University of Medical Sciences, Poland

Summary

Introduction: Hepatitis C virus (HCV) infection in Poland affects approximately 750 thousand persons. The prevention of cirrhosis and hepatocellular carcinoma, of which approximately 20% of patients with chronic hepatitis C virus are at risk, aims at eradication of the virus by applying antiviral treatment with pegylated interferon alpha with ribavirin.

Material/Methods: In this paper the results of the standard treatment of chronic hepatitis C in a population of 169 adult patients in whom it was started in the period of 01.01.2007–30.06.2008 are analyzed. Moreover, the influence of various clinical, biochemical and viral factors on achieving therapeutic success in the form of the sustained virological response (SVR) was studied.

Results: In the group of 128 patients who received the full course of antiviral treatment, the SVR was achieved by 67.2% of patients (86 persons), whereas regarding all 169 patients who started the therapy, the sustained disappearance of viremia was found in 53.2% of patients (90 persons).

Regarding 155 persons in whom the treatment was not interrupted for reasons others than virology, this value was 55.5%.

For the sustained disappearance of viremia the following was favorable: genotype 3 virus, age under 40 years, body mass up to 75 kg, correct value of body mass index (BMI), low gamma-glutamyl transpeptidase (GGTP) activity before the treatment, minimum advancement of liver fibrosis in a liver biopsy (S1), complete early biochemical response (cEBR), and moreover, the achievement of negation of viremia after 12 weeks of the treatment in a group of patients infected with genotype 1 (complete early virological response, cEVR). These factors were strongly correlated with each other and that is why an analysis by the method of logistic multiple regression was impossible.

Adverse reactions to the treatment and other health problems were the reasons for earlier discontinuation of the standard therapeutic scheme in 14 patients, whereby the lack of an SVR occurred in 10 of them (71.5% which is 5.9% of the studied population).

Key words: **hepatitis C • treatment • interferon • ribavirin**

Streszczenie

Wstęp: W Polsce zakażenie HCV dotyczy około 750 tys. osób. Zapobieganie marskości wątroby oraz rakowi wątrobowokomórkowemu, którymi zagrożonych jest prawie 20% pacjentów z przewlekłym

zapaleniem wątroby (pzw C) polega na dążeniu do eradykacji wirusa poprzez stosowanie leczenia przeciwwirusowego preparatami pegylowanego interferonu alfa z rybawiryną.

Materiał/Metody: W pracy przeanalizowano wyniki standardowego leczenia pzw C w grupie 169 dorosłych pacjentów, które rozpoczęto w okresie 01.01.2007–30.06.2008 r.; ponadto zbadano wpływ różnych czynników klinicznych, biochemicznych i wirusologicznych na uzyskanie sukcesu terapeutycznego pod postacią utrwalonej odpowiedzi wirusologicznej (SVR).

Wyniki: W grupie 128 pacjentów, którzy otrzymali pełen kurs leczenia przeciwwirusowego, SVR osiągnęło 67,2% chorych (86 osób), natomiast biorąc pod uwagę wszystkich 169 pacjentów, którzy rozpoczęli terapię – utrwalony zanik wiremii stwierdzono u 53,2% chorych (90 osób). W odniesieniu do 155 osób, u których nie przerywano leczenia z przyczyn innych niż wirusologiczne, wartość ta wyniosła 55,5%.

Utrwalonemu zanikowi wiremii sprzyjały: genotyp 3 wirusa, wiek poniżej 40 rż., masa ciała do 75kg, prawidłowa wartość wskaźnika masy ciała (BMI), niska aktywność gamma-glutamylotranspeptydazy (GGTP) przed leczeniem, minimalne zaawansowanie włóknienia wątrobowego w bioptacie wątroby (S1), całkowita wczesna odpowiedź biochemiczna (cEBR), ponadto – uzyskanie negatywizacji wiremii po 12 tygodniach leczenia w grupie chorych zakażonych genotypem 1 (całkowita wczesna odpowiedź wirusologiczna, cEVR). Czynniki te były silnie skorelowane ze sobą, dlatego niemożliwa była analiza metodą logistycznej regresji wielokrotnej.

Działania niepożądane leczenia oraz inne problemy zdrowotne były przyczyną wcześniejszego zaprzestania stosowania standardowego schematu terapeutycznego u 14 chorych, przy czym brak SVR wystąpił u 10 z nich (71,5%, co stanowi 5,9% populacji badanej).

Słowa kluczowe: **hepatitis C • treatment • interferon • ribavirin**

Full-text PDF: http://www.phmd.pl/fulltxt.php?ICID=1000332

Word count: 3204
Tables: 5
Figures: 3
References: 19

Author's address: Maciej Bura MD, PhD, Department of Infectious Diseases, Poznan University of Medical Sciences, ul. Szwajcarska 3, 61-288 Poznan, Poland

Introduction

The hepatitis C virus (HCV) infection is currently a leading issue of infectious hepatology in industrialized countries, on a world scale as well as in Poland. Its significance – as a problem important from the point of view of public health – results from several premises, namely:

– the occurrence frequency (notably it is a consequence of exposure of a significant percentage of the population in the past in relation to among other things transfusion of infected blood or blood products and procedures connected with the break in continuity of tissue),
- possible clinical consequences of chronic hepatitis C,
- the occurrence of extrahepatic manifestations of HCV infection which can decrease the quality of life of the patients,
- economic consequences for the health care systems (direct liability, i.e. costs of hospitalization and treatment of the patients, including liver transplantations and indirect, i.e. the loss of productivity, rehabilitation and annuity benefits),
- patients infected with HCV are a reservoir of the virus and in certain situations a potential epidemiological danger for the community.

According to the assessments of numerous experts, the intensity of essential health problems connected with HCV infection (cirrhosis together with its complications, hepatocellular carcinoma) will increase in the world at least for the next two or three decades [5,14,17].

In diagnosing HCV infection a crucial role is played by specific tests, i.e. serological and molecular tests. The biochemical significance of non-specific tests, i.e. activity of aminotransferases (mainly alanine transaminase, ALT), is smaller. Moreover, the knowledge of HCV genotype has an influence on the length of therapy and is significant for predicting the chances of an infected patient receiving the sustained virological response (SVR) after antiviral treatment with pegylated interferon alpha (PEG-IFN-α) with ribavirin (RBV).

For many years various factors having significance for prognosing hepatitis C therapy (among other things genotype, viremia, the length of infection duration, coexisting diseases, coinfections, sex, age, race, body mass, ALT activity and others) have been searched for.

The aim of this paper was:
- characterization of the course of a standard antiviral therapy in patients with chronic hepatitis C,

- analysis of the results of antiviral therapy (virological and biochemical response) of chronic hepatitis C with PEG-IFN-α with RBV in patients not treated earlier,
- an attempt to determine factors conditioning the achievement of SVR in adult patients infected with HCV, undergoing antiviral treatment.

Material and Methods

The study comprised 169 patients who were not treated earlier, including 70 women and 99 men infected with HCV, aged 18 to 73 (mean: 41.3±12.8 years, median: 42 years) in whom the therapy of chronic hepatitis C with PEG-IFN-α with RBV in doses adjusted to their body mass was started in the period from 01.01.2007 to 30.06.2008. The body mass of the patients ranged from 44 kg to 120 kg (mean: 76.5±15.2 kg, median: 76.7 kg), and the body mass index (BMI) ranged from 18 to 41 kg/m^2 (mean: 25.9±4.5 kg/m^2, median: 25.5 kg/m^2).

Chronic hepatitis C was diagnosed according to generally accepted criteria.

In the studied group of patients 87 (51.5%) received PEG-IFN-α-2b and the remaining 82 patients (48.5%) received PEG-IFN-α-2a, in both cases with RBV.

Definitions useful for the assessment of virological response depending on the time of its execution:

EVR – early virological response: at least 100-fold (2 $\log_{10}$) decrease of concentration of HCV-RNA after 12 weeks of the treatment compared to pre-therapeutic value; two kinds of EVR were distinguished:
a) cEVR – complete early virological response: non-detectability of HCV-RNA by the qualitative test,
b) pEVR – partial early virological response: HCV-RNA detectable by the qualitative test.

EVR was not assessed in patients infected with genotype 3.

EOTVR – end of treatment virological response: non-detectability of HCV-RNA directly after completion of the antiviral therapy, verified by the qualitative test.

SVR – sustained virological response: non-detectability of HCV-RNA directly after completion of the antiviral therapy and 24 weeks after completion of the antiviral therapy, verified by the qualitative test.

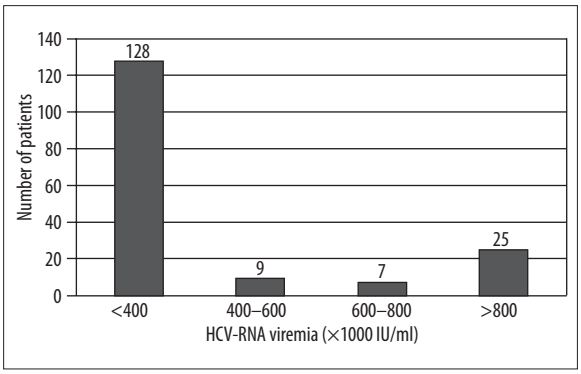

Fig. 1. HCV RNA viremia in the blood serum of patients before implementing the antiviral treatment (n=169)

cEBR – complete early biochemical response: normalization of ALT activity after 12 weeks of the treatment compared to pre-therapeutic value.

In patients infected with the virus of genotype 3 the treatment was 24 weeks; in patients infected with other genotypes of HCV the time of treatment was 48 weeks, on the condition of receiving EVR in the 12th week of the treatment and of the lack of occurrence of serious adverse reactions.

In the studied group of patients the genotype distribution was as follows: 1a → n=5 (3.0%), 1b → n=131 (77.5%), 1a + 1b → n= 3 (1.8%), 3a → n=29 (17.1%), 1b+3a → n=1 (0.6%).

At the moment of initiation of the antiviral therapy the initial viremia HCV-RNA fluctuated from 50–599 IU/ml (the positive result of qualitative determination of HCV-RNA, the quantitative test of sensitivity 600 IU/ml showed viremia below this threshold) to 1.36×10^8 IU/ml (Fig. 1).

The activity of alanine transaminase (ALT), gamma-glutamyl transpeptidase (GGTP) and the selected parameters of complete blood count in the analyzed population at the moment of initiation of the antiviral treatment is presented in Table 1. The normal initial GGTP activity was found in 52 women and 74 men, which was 74.6% of persons in the studied group of patients.

The results of liver biopsy obtained from 154 patients concerning the inflammation activity (G, grading) and the stage of fibrosis (S, staging) are presented in Figures 2 and 3.

Table 1. ALT activity and the value of selected parameters of complete blood count at the beginning of the treatment

Parameter	Range	Mean ±SD (IU/l)	Median (IU/l)
ALT (IU/l)	16–279	79.8±50.0	65
GGTP (IU/l)	9–524	69.6±68.1	48
WBC (G/l)	4.0–12.6	6.6±1.7	6.4
HGB (g/dl)	11.9–18.9	15.1±1.4	15.3
PLT (G/l)	78–391	201±56	204
NEUT (G/l)	2.0–10.6	4.3±1.6	4.0

WBC – White blood cells; HGB – Hemoglobin; PLT – Platelets; NEUT – Neutrophils.

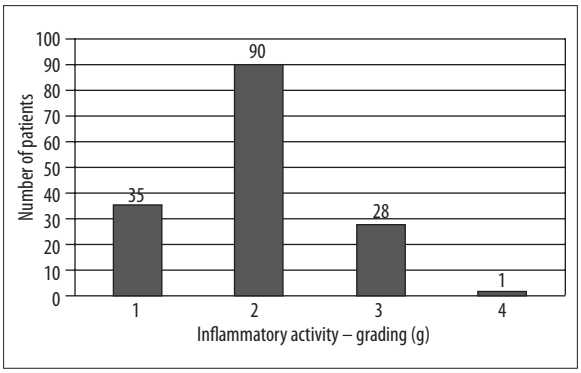

Fig. 2. Inflammatory activity in the studied group of patients (n=154)

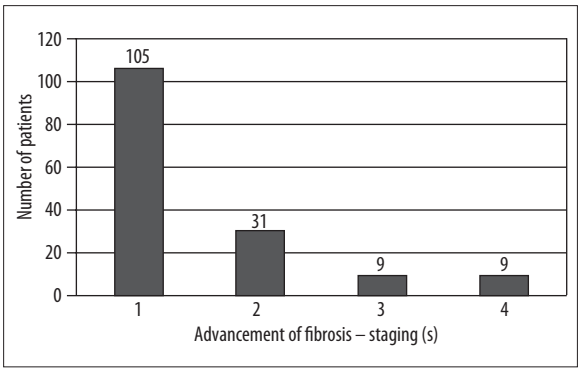

Fig. 3. The advancement of fibrosis in the studied group of patients (n=154)

The pathomorphological assessment of preparations was performed according to the criteria established in "Podsumowanie wstępne dotyczące wypracowania standardu oceny histopatologicznej bioptatów w przebiegu przewlekłych zapaleń wątroby – Katowice 15.04.1999" [Preliminary summary concerning the standard of histopathological assessment of bioptates in the course of the chronic hepatitis] in the scale 0–4 points [9].

The initial doses of PEG-IFN-α drugs per kilogram of body mass of the patient were: for PEG-IFN-α-2a, 1.57–3.74 μg (mean: 2.40±0.47 μg, median: 2.27 μg); and for PEG-IFN-α-2b, 1.25–1.68 μg (mean: 1.48±0.08 μg, median: 1.48 μg).

The initial dose of RBV was 6.31–20.79 mg/kg (mean: 14.15±1.97 mg/kg, median: 13.9 mg/kg).

The statistical assessment was performed in the Poznan Medical University Department of Computer Science and Statistics.

Results

Early virological response (EVR)

Out of the group of 169 patients, 161 patients received the 12-week course of treatment (in 8 patients the therapy was stopped before this time). EVR was assessed in 132 patients infected with a virus of non-3 genotype. This parameter was not analyzed in 29 patients infected with a virus of genotype 3. EVR was achieved by 105 among 132 patients (79.5%) infected with a virus of genotype non-3. In 85 cases the disappearance of HCV-RNA (cEVR) was found, and in another 20 patients it came to at least 100-time reduction of viremia, but it was possible to detect HCV-RNA in the blood serum (pEVR), and 27 patients did not fulfill the criteria of EVR, so the therapy was interrupted at this stage.

End of treatment virological response (EOTVR)

128 patients received the complete course of antiviral treatment depending on the HCV genotype, including 99 individuals infected with a virus of genotype "non-3" and 29 infected with a virus of genotype 3. In total EOTVR was obtained by 114 patients (89.1%), remaining 14 patients (10.9%) did not reach non-detectability of HCV-RNA at this point. 100% of patients (n=29) with genotype 3 obtained EOTVR, while in patients with genotype "non-3" 85 among 99 assessed (85.8%) received a negative result of HCV-RNA determined by the qualitative method. In patients with "non-3" genotype who reached cEVR, the EOTVR was found in 91.4% (74 among 81 patients who completed therapy), while in patients with pEVR, the EOTVR reached 61.1% (11 among 18 patients who completed therapy).

Sustained virological response (SVR)

Among 114 patients without detectable viremia within the time of the assessment of the EOTVR, 6 months later this state was confirmed in 75.4% of this population, which means that the SVR was reached in 86 out of a group of 128 patients (67.2%) who received the complete, dependent on the genotype, course of standard treatment. Therapeutic success was achieved by 61.6% of persons (61 patients) with "non-3" genotype and 86.2% (25 patients) infected with genotype 3. In patients with "non-3" genotype who received cEVR, SVR was found in 70.4% (57 among 81 patients who completed therapy), while in patients with pEVR, SVR was observed in 22.2% from this group (4 among 18 patients who completed therapy). In total, among 169 patients who started the therapy, SVR was achieved by 90 patients (53.2%), while among patients with "non-3" genotype this value was 46.4% (65/140 patients of initial population).

For the purposes of the analysis of the treatment results, out of the population of 169 patients a group of 155 persons in whom the treatment was not interrupted for reasons other than virological (called the comprehensive group) was distinguished. It comprised 128 patients who completed the full course of antiviral therapy and a group of 27 patients who did not reach EVR and did not continue the treatment.

A comparison of the assessment of the SVR assessed in various groups of patients is presented in Table 2.

ALT activity

The ALT activity analysis was performed at the moment of implementation of treatment (T_0), in the 12th week of therapy (T_{12}), at the end of the therapy (T_{EOTVR}) and 24 weeks after the therapy completion (T_{SVR}) during the SVR assessment. This parameter was analyzed only in patients who received the complete course of the antiviral therapy (n=128) and is presented in Table 3.

Table 2. Summary of the SVR assessment in various groups of patients

Population of patients	Number of patients with SVR	% of patients with SVR in a given population
The complete course of the standard antiviral treatment, all (n=128)	86	67.2
The complete course of the standard antiviral treatment, genotype 3 (n=29)	25*	86.2*
The complete course of the standard antiviral treatment, genotype non-3 (n=99)	61	61.6
Patients who started PEG-IFN-α + RBV therapy (n=169)	90	53.2
Patients who started PEG-IFN-α + RBV therapy, genotype non-3 (n=140)	65	46.4
Patients in whom the standard antiviral treatment was not interrupted due to other reasons than virological, all – the so called comprehensive group (n=155)	86**	55.5**
Patients in whom the standard antiviral treatment was not interrupted due to other reasons than virological, genotype non-3 (n=126)	61**	48.4**

* – SVR values for patients infected with genotype 3 are the same in all analyzed populations of patients because all of them received the complete course of a standard antiviral treatment (24 weeks);
** – estimated value which was obtained by assuming that even if the patients without EVR were treated further, none of them would fulfill the criterion of the sustained virological response; in reality SVR in the group of patients without the EVR reaches the values from 0 to 3% (see: Discussion) and because 27 patients did not achieve the EVR, then assuming that at most 3% of them achieved the therapeutic success in the form of the sustained disappearance of viremia with the antiviral therapy prolonged by 48 weeks, the absolute number of patients with the SVR in this population would be as follows: $27 \times 0.03 = 0.81$; due to the clear reasons this value can be round off 1 which means that at most 1 person from the discussed group would reach the SVR, if the rule of the 12th week (interrupting the treatment in patients infected with HCV of worse prognosing genotypes in the case of not achieving by them the EVR) was not applied and then the percentage of the SVR in this group of patients would be 49.2%.

Table 3. ALT activity in patients who received the complete course of antiviral treatment with PEG-IFN-α with RBV (n=128)

Group of patients	ALT (T_0) IU/l	ALT (T_{12}) IU/l	ALT (T_{EOTVR}) IU/l	ALT (T_{SVR}) IU/l
In total n=128	Range 16–250 Mean ±SD 76.1±48.4 Median 64 Norm* – 30 (23.4%)	Range 6–164 Mean ±SD 37.4±31.2 Median 28 Norm* – 94 (73.4%)	Range 6–174 Mean ±SD 37.0±31.2 Median 26 Norm* – 94 (73.4%)	Range 6–454 Mean ±SD 40.5±50.5 Median 25 Norm* – 90 (70.3%)
Genotype non-3a n=99	Range 16–235 Mean ±SD 67.4±42.2 Median 57 Norm* – 28 (28.3%)	Range 6–164 Mean ±SD 33.2±23.6 Median 27 Norm* – 74 (74.7%)	Range 7–142 Mean ±SD 34.4±26.7 Median 25 Norm* – 75 (75.7%)	Range 6–454 Mean ±SD 41.7±53.9 Median 26 Norm* – 67 (67.7%)
Genotype 3a n=29	Range 33–250 Mean ±SD 106.0±56.6 Median 97 Norm* – 2 (6.7%)	Range 14–161 Mean ±SD 51.5±46.9 Median 30 Norm* – 20 (69%)	Range 6–174 Mean ±SD 46.0±42.4 Median 29 Norm* – 19 (65.5%)	Range 8–168 Mean ±SD 36.3±36.7 Median 25 Norm* – 23 (79.3%)

* Norm – number (and percentage) of patients with ALT activity to 40 IU/l.

The influence of various clinical, virological and biochemical factors for reaching SVR was assessed in 155 patients in whom the treatment was not interrupted for reasons other than virological (the comprehensive group). The results of this analysis are presented in Table 4.

In Table 5 the adverse reactions are specified as well as other essential health events that were the reason for modifying doses of antiviral drugs or stopping therapy. As can be seen from the data presented in Table 5, among 169 patients who started the antiviral therapy, in 94 patients doses of antiviral drugs were modified or the standard treatment was abandoned before completing a 12-week therapeutic course. Among patients treated over 12 weeks similar interventions were necessary in 95 cases. Moreover, in 56 patients thyroid function disorders manifesting as incorrect TSH (thyroid stimulating hormone) values were found.

Table 4. Influence of clinical, virological and biochemical factors on achieving the SVR in the population of patients from the comprehensive group (n=155)

Criterion	Ratio of number of patients fulfilling the criterion who achieved the SVR to the number of all patients fulfilling the criterion	Ratio of number of patients not fulfilling the criterion who achieved the SVR to the number of all patients not fulfilling the criterion	Is the difference in achieving the SVR in the group of patient fulfilling *vs.* not fulfilling the criterion statistically significant?
Male gender	53/93 (57.0%)	33/62 (53.2%)	No, p>0.05
Age to 40 years	53/76 (69.7%)	33/79 (41.8%)	**Yes, p=0,0006**
Body mass to 75 kg	46/70 (65.7%)	40/85 (47.1%)	**Yes, p=0,0213**
BMI to 24.99 kg/m^2	53/75 (70.6%)	33/80 (41.3%)	**Yes, p=0.0003**
Cryoglobulinemia	35/69 (50.7%)	37/58 (63.8%)	No, p>0.05
Genotype 3 HCV	25/29 (86.21%)	61/126 (48.41%)	**Yes, p=0.0003**
Initial viremia >400 000 IU/ml	24/38 (63.1%)	62/117 (53.0%)	No, p>0.05
Anemia after 12 weeks of the treatment	29/45 (64.44%)	57/110 (51.82%)	No, p>0.05
Tobacco smoking	28/51 (54.90%)	58/104 (55.77%)	No, p>0.05
Flue-like syndrome	53/101 (52.5%)	8/11 (72.7%)	No, p>0.05
Modification of drug doses before the 12th week of therapy	38/72 (52.78%)	48/83 (57.83%)	No, p>0.05
Fibrosis S1	61/99 (61.6%)	18/43 (41.9%)	**Yes, p=0.0316**
Inflammation G1	19/32 (59.37%)	60/109 (55.04%)	No, p>0.05
Inflammation G2	49/85 (57.64%)	30/56 (53.57%)	No, p>0.05
Inflammation G3	11/24 (45.83%)	68/117 (58.12%)	No, p>0.05
Liver steatosis	15/24 (62.50%)	64/118 (54.24%)	No, p>0.05
Complete EBR	46/72 (63.9%)	20/52 (38.5%)	**Yes, p=0.0059**
PEG-IFN-α-2a	51/77 (66.23%)	35/78 (44.87%)	**Yes, p=0.0303**
Initial dose of PEG-IFN-α-2a from 2.4 µg/kg upwards	26/30 (86.67%)	25/47 (53.19%)	**Yes, p=0.0033**
Initial dose of PEG-IFN-α-2b from 1.5 µg/kg upwards	17/38 (44.7%)	18/40 (45.0%)	No, p>0.05
Initial dose of RBV >10.6 mg/kg	83/152 (54.6%)	3/3 (100.0%)	No, p>0.05
ALT-0 Norm	22/33 (66.7%)	64/122 (52.5%)	No, p>0.05
AST-0 Norm	42/71 (59.1%)	44/84 (52.4%)	No, p>0.05
GGTP-0 Norm	76/115 (66.1%)	10/40 (25.0%)	**Yes, p=0.00001**

Discussion

Despite numerous studies on drugs which could be used in the antiviral therapy of chronic hepatitis C the standard still remains combination therapy using IFN-α (the preferred option is due to comfortable dosing and better treatment results PEG-IFN-α) and RBV.

Among the studied patients the permanent disappearance of viremia was achieved by 86 among 128 persons who received the complete course of the standard PEG-IFN-α with RBV therapy (66.2%). However, it seems that the more realistic value for effectiveness of the applied treatment is the result achieved in the group of 155 patients (the comprehensive group), considering also 27 persons without EVR. In the mentioned population the estimated SVR was 55.5%. The reason for such an attitude is the results of the studies in which the patients without the early virological response were treated to the end of the 48 week treatment period. The sustained disappearance of viremia was reached in such cases only by 0–3% among them. Based on the above data, in the group of patients in whom it did

Table 5. Significant events (including adverse reactions) which are the reason for modifying the doses of the antiviral drugs or interrupting PEG-IFN-α and RBV therapy

n=169 (before the 12th week of therapy)	N=134 (after the 12th week of therapy)
Anemia* – 52 (30.8%)	Anemia* – 39 (29.1%)
Neutropenia* – 13 (7.7%)	Neutropenia* – 16 (11.9%)
Bad clinical tolerance of the treatment (subjective afflictions of the patient)* – 10 (5.9%)	Bad clinical tolerance of the treatment (subjective afflictions of the patient)* – 9 (6.7%)
Organizational considerations – 7 (4.1%)	Organizational considerations – 8 (6.0%)
Skin lesions* – 4 (2.4%)	Thrombocythemia* – 6 (4.5%)
Thrombocytopenia* – 4 (2.4%)	Infection treated with antibiotic – 5 (3.7%)
Lymphadenopathy – 1 (0.6%)	Depression* – 3 (2.2%)
Hyperbilirubinemia– 1 (0.6%)	Injuries – 3 (2.2%)
Intracerebral hematoma after fall from height* – 1 (0.6%)	Hyperbilirubinemia – 2 (1.5%)
Vein thrombosis of the lower limb* – 1 (0.6%)	Increased creatinine level – 1 (0.7%)
	Proteinuria – 1 (0.7%)
	Autoimmune reaction[a,] * – 1 (0.7%)
	Postmenopausal bleeding – 1 (0.7%)

[a] Autoimmune hepatitis and autoimmune thyroiditis (in the same female patient); * adverse reaction which were the reason for a definite interruption of the treatment or the replacement of IFN to nonpegylated.

not result in at least 100-fold decrease in concentration of HCV-RNA after 12 weeks of the therapy, at most one person would have the chance to obtain final success of the treatment (27×0.03=0.81), which would increase the SVR value in the group of assessed patients by only 0.6%.

In summary, the results of antiviral treatment in this group of patients compared with the SVR values obtained by other researchers both domestic [12,13] and foreign [1,4,7,10,15,18] are similar.

It should be stressed that among the 169 patients who started the PEG-IFN-α with RBV therapy, a low percentage of patients was burdened with serious coexisting diseases that could influence the course and results of the antiviral therapy of chronic hepatitis C, and in almost 60% of them no additional pathology was found. Also the fact of a low percentage of patients participating in the study with advanced liver disease (18/154, i.e. 11.7% persons who had biopsy of this organ) is significant.

The standard antiviral therapy was abandoned in 14 among 169 patients who started it (8.3%). This is a relatively low value compared to the frequency of this kind of event provided by authors of the main studies registering the described treatment in the United States, i.e. 10–16% [8,10,15].

The most common adverse reactions requiring changes to the initially set treatment scheme (dose, preparation) were: hemolytic anemia induced by RBV and the results of myelosuppressive activity of interferon, which corresponds well with the data from the literature [8,15]. Serious health events both connected with and those most probably independent of therapy (intracerebral hematoma after fall from height) were rare.

In reference to the patients infected with non-3 HCV genotype (in this analysis these were practically patients infected with genotype 1 of the virus) the carried out study only confirms the relative significance of EVR for predicting chances for the achievement of final therapeutic success. The higher value of the discussed parameter within this range after considering the variety of the kind of the early virological response (complete *vs.* partial EVR, respectively in 64.3% and 22.2%) remains in accordance with the data presented among other people by Berg et al. [3] and Fried et al. [7]. It should be stressed here that a significantly better prediction indicator of reaching SVR is confirmation of the so-called rapid viral response (RVR), defined as non-detectability of viremia 4 weeks after the moment of giving the first PEG-IFN-α injection [6].

Data concerning the significance of gender as a predictive factor for success of the antiviral therapy of chronic hepatitis C are ambiguous. The studies by Manns et al. [15] and Fried et al. [8] in which PEG-IFN-α drugs were used did not confirm the beneficial influence of the female gender in this aspect. Similar conclusions result from the assessment carried out in the current paper.

Younger patients (<40 years) have a greater chance for successful completion of the therapy, which is a commonly recognized fact. This also concerned patients assessed in this analysis. The negative influence of a more advanced age on achieving the SVR can be explained by among other things alleged longer mean duration of HCV infection and the greater average number of health burdens among older people. This may be the reason for more advanced liver damage compared to the children's population.

HCV genotype is a commonly recognized, essential single prognostic factor concerning SVR. Its influence on the therapeutic success is explicitly determined, at least for the most commonly met genotypic variants of the virus [8,10,11,15]. This paper confirms the significance of this parameter; patients infected with genotype 3 HCV had greater chances for achieving permanent disappearance of HCV-RNA than patients infected with genotype 1 despite the shorter period of treatment. The basis for variation of the virological response depending on the genotype of the virus was so far not determined.

Otherwise than it results from the current opinions about the significance of viremia before the treatment in determining the probability for achieving the sustained negation of HCV-RNA in blood serum under the influence of antiviral therapy [2,16,19] the significant difference in achieving the mentioned aim was not found in groups of patients with low (defined as HCV-RNA to 400 000 IU/ml) or high (HCV-RNA >400 000 IU/ml) viremia. The reasons for such a juncture are not clear.

It is known that overweight and obesity contribute to the more rapid liver fibrosis progression in patients with chronic hepatitis C. It results from the registration trials of PEG-IFN-α drugs that the lower body mass beneficially influences the chance for achieving SVR. There are also data about a similar BMI significance [3]. Based on the assessment of these two parameters in reference to our patients it should be recommended that the more credible variable in this population was the body mass index odds ratio (OR=3.43 *vs.* 2.15 for body mass), contrary to body mass as a feature which differentiates the chances for achieving therapeutic success in both groups of patients. So the BMI maintained its prognostic value in the aspect of predicting the success of an antiviral therapy also in the group of patients achieving EVR.

By judging the role of the initial values of such biochemical parameters as the activity of ALT and AST as well as GGTP in prognosing the chances for achieving the SVR, divergent results were obtained. The significance of aminotransferase in this range was not confirmed. But it was found that the normal activity of GGTP before the treatment occurred significantly more frequently in patients in whom the therapy was successful. These results are in accordance with the data from the literature [3]. Based on our own observations a thesis can be proposed about undervaluing this simple and routine biochemical parameter in daily clinical practice. It is worth mentioning in this context that in the group of 155 patients, comprising all patients treated with the complete course of standard therapy and 27 persons in whom the treatment was interrupted due to the lack of EVR, the value of the (OR) for achieving the SVR with the activity of GGTP before implementation of PEG-IFN-α with RBV within the range of the reference band (*vs.* increased) conceded only OR for the genotype and was 5.85. The possibility of an influence of a regular alcohol intake on the value of this parameter in patients infected with HCV should be also considered.

The role of a low grade of advancement of hepatic fibrosis as a positive predictive indicator for achieving eradication of HCV infection can be confirmed by a statistically significant difference of frequency of SVR among patients with minimum increase of fibrosis (S1) compared with persons of a greater extent of this histological indicator of advancement in liver damage. This refers to those patients in whom the therapy was not interrupted due to other reasons than virological (n=155). Among patients without the EVR it was possible to identify 13.1% of persons from the group of minimum fibrosis in comparison with 27.9% from the group of patients with the extent of fibrosis within S2-4. This is explained by the lack of a significant difference in achieving the SVR depending on the discussed variable in patients who received the complete course of a standard treatment (n=128).

The percentage of patients who did not receive the complete (dependent on the HCV genotype) course of an antiviral treatment due to other reasons than virological was similar in this analysis to the values found in literature comprising big groups of studied patients with the chronic hepatitis C.

Conclusions

1. The combination standard treatment of chronic hepatitis C leads to the sustained disappearance of viremia in two thirds of patients who completed therapy.
2. There is a correlation between the analyzed clinical, biochemical and virological parameters and the effectiveness of therapy.
3. The antiviral treatment of patients with chronic hepatitis C should aim at individual determination of therapy conditions considering the changes in kinetics of viremia, and also aiming at comprising the treatment of the highest possible number of young people.

Reeferences

[1] Bain V.G., Lee S.S., Peltekian K., Yoshida E.M., Deschênes M., Sherman M., Bailey R., Witt-Sullivan H., Balshaw R., Krajden M.: Canadian PEGASYS Study Group. Clinical trial: exposure to ribavirin predicts EVR and SVR in patients with HCV genotype 1 infection treated with peginterferon alpha-2a plus ribavirin. Aliment. Pharmacol. Ther., 2008; 28: 43–50

[2] Berg T., von Wagner M., Hinrichsen H., Heintges T., Buggisch P., Goeser T., Rasenack J., Pape G.R., Schmidt W., Kalinowski B., Klinker H., Spengler U., Alshuth U., Zeuzem S.: Definition of pre-treatment viral load cutoff for an optimized prediction of treatment out- come in patients with genotype 1 infection receiving either 48 or 72 weeks of peginterferon alfa-2a plus ribavirin. Hepatology, 2006; 44 (Suppl. 1): 321A

[3] Berg T., von Wagner M., Nasser S., Sarrazin C., Heintges T., Gerlach T., Buggisch P., Goeser T., Rasenack J., Pape G.R., Schmidt W.E., Kallinowski B., Klinker H., Spengler G., Martus P., Alshuth U., Zeuzem S.: Extended treatment duration for hepatitis C virus type 1: comparing 48 versus 72 weeks of peginterferon-alfa-2a plus ribavirin. Gastroenterology, 2006; 130: 1086–1097

[4] Bourliere M., Ouzan D., Rosenheim M., Doffoel M., Marcellin P., Pawlotsky J.M., Salomon L., Fagnani F., Hayem C., Lonjon-Domanec I., Vray M.: Efficacy of of peginterferon alfa-2a and ribavirin in 2102 patients with HCV infection in real-life clinical practice: results of the French HEPATYS study. Hepatology, 2007; 46(Suppl.1): 366A

[5] Deuffic-Burban S., Poynard T., Sulkowski M.S., Wong J.B.: Estimating the future health burden of chronic hepatitis C and human immunodeficiency virus infections in the United States. J. Viral. Hepat., 2007; 14: 107–115

[6] Ferenci P., Fried M.W., Shiffman M.L., Smith C.I., Marinos G., Gonçales F.L. Jr., Häussinger D., Diago M., Carosi G., Dhumeaux D., Craxì A., Chaneac M., Reddy K.R.: Predicting sustained virological responses in chronic hepatitis C patients treated with peginterferon alfa-2a (40 KD)/ribavirin. J. Hepatol., 2005; 43: 425–433

[7] Fried M.W., Hadziyannis S.J., Shiffman M., Messinger D., Zeuzem S.: Rapid viral response is a more important predictor of sustained virological response (SVR) than genotype in patients with chronic hepatitis C virus infection. J. Hepatol., 2008; 48(Suppl.2): 5A

[8] Fried M.W., Shiffman M.L., Reddy K.R., Smith C., Marinos G., Gonçales F.L. Jr., Häussinger D., Diago M., Carosi G., Dhumeaux D., Craxi A., Lin A., Hoffman J., Yu J.: Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N. Engl. J. Med., 2002; 347: 975–982

[9] Gabriel A., Miętkiewski J., Stolarczyk J., Szczepański W., Wawelska-Zielecka., Ziółkowski A.: Podsumowanie wstępne dotyczące wypracowania standardu oceny histopatologicznej bioptatów w przebiegu przewlekłych zapaleń wątroby – Katowice 15.04.1999. Pol. J. Pathol., 1999; 50(Suppl.1):31–32

[10] Hadziyannis S.J., Sette H. Jr., Morgan T.R., Balan V., Diago M., Marcellin P., Ramadori G., Bodenheimer H. Jr., Bernstein D., Rizzetto M., Zeuzem S., Pockros P.J., Lin A., Ackrill A.M.: PEGASYS International Study Group. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann. Intern. Med., 2004; 140: 346–355

[11] Jacobson I.M., Brown R.S. Jr., Freilich B., Afdhal N., Kwo P.Y., Santoro J., Becker S., Wakil A.E., Pound D., Godofsky E., Strauss R., Bernstein D., Flamm S., Pauly M.P., Mukhopadhyay P., Griffel L.H., Brass C.A.: WIN-R Study Group. Peginterferon alfa-2b and weight--based or flat-dose ribavirin in chronic hepatitis C patients: a randomized trial. Hepatology, 2007; 46: 971–981

[12] Juszczyk J., Baka-Ćwierz B., Beniowski M., Berak H., Bolewska B., Boroń-Kaczmarska A., Cianciara J., Cieśla A., Dziambor A. Gąsiorowski J., Gietka A., Gliwińska E., Gładysz A., Gonciarz Z., Halota W., Horban A., Inglot M., Janas-Skulina U., Janczewska-Kazek E., Jaskowska J., Jurczyk K., Knysz B., Kryczka W., Kuydowicz J., Łakomy E.A., Logiewa-Bazger B., Łyczak A., Mach T., Mazur W., Michalska Z., Modrzewska R., Nazzal K., Pabjan P., Piekarska A., Piszko P., Sikorska K., Szamotulska K., Śliwińska M., Świętek K., Tomasiewicz K., Topczewska-Staubach E., Trocha H., Wasilewski M., Wawrzynowicz-Syczewska M., Wrodycki W., Zarębska-Michaluk D., Zejc-Bajsarowicz M.: Pegylowany interferon α-2a z rybawiryną w leczeniu przewlekłego wirusowego zapalenia wątroby typu C (raport końcowy z badań). Przegl. Epidemiol., 2005; 59: 651–660

[13] Juszczyk J., Białkowska J., Bolewska B., Boroń-Kaczmarska A., Gładysz A., Halota W., Inglot M., Janas-Skulina U., Jabłkowski M., Jabłońska J., Jurczyk K., Kryczka W., Kuydowicz J., Łakomy E.A., Łyczak A., Mach T., Michalska Z., Moczko J., Modrzewska R., Nazzal K., Pabjan P., Pawłowska M., Piszko P., Sikorska K., Świętek K., Tomasiewicz K., Topczewska-Staubach E., Wawrzynowicz-Syczewska M., Zarębska-Michaluk D., Zejc-Bajsarowicz M.: Pegylowany interferon α-2b i rybawiryna w leczeniu przewlekłego wirusowego zapalenia wątroby typu C. Pol. Merkur. Lekarski, 2004; 94: 353–357

[14] Lehman E.M., Wilson M.L.: Epidemic hepatitis C virus infection in Egypt: estimates of past incidence and future morbidity and mortality. J. Viral. Hepat., 2009; 16: 650–658

[15] Manns M.P., McHutchison J.G., Gordon S.C., Rustgi V.K., Shiffman M., Reindollar R., Goodman Z.D., Koury K., Ling M., Albrecht J.K.: Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet, 2001; 358: 958–965

[16] Martinot-Peignoux M., Ripault M., Maylin S., Boyer N., Giuily N., Castelnau C., Asselah T., Marcellin M.: Optimal pretreatment viral load cut-off to predict treatment outcome in patients with chronic hepatitis C treated with peginterferon α-2a plus ribavirin. J. Hepatol., 2007; 46(Suppl.1): S234

[17] Sypsa V., Touloumi G., Papatheodoridis G.V., Tassopoulos N.C., Ketikoglou I., Vafiadis I., Hatzis G., Tsantoulas D., Akriviadis E., Koutsounas S., Hatzakis A.: Future trends of HCV-related cirrhosis and hepatocellular carcinoma under the currently available treatments. J. Viral Hepat., 2005; 12: 543–550

[18] Witthöft T., Möller B., Wiedmann K.H., Mauss S., Link R., Lohmeyer J., Lafrenz M., Gelbmann C.M., Hüppe D., Niederau C., Alshuth U.: Safety, tolerability and efficacy of peginterferon alpha-2a and ribavirin in chronic hepatitis C in clinical practice: The German Open Safety Trial. J. Viral Hepat., 2007; 14: 788–796

[19] Zehnter E., Mauss S., John C., Heyne R., Moller B., Lutz T., Bokemeyer B., Kihn R., Moog G., Alshuth U., Hueppe D.: Better prediction of SVR in patients with HCV genotype 1 (G1) with peginterferon alfa--2a (PEGASYS®) plus ribavirin: improving differentiation between low (LVL) and high baseline viral load (HVL). Hepatology, 2006; 44(Suppl.1): 328A

The authors have no potential conflicts of interest to declare.