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Supplement 1

Effectiveness of combined treatment with pegylated interferon α-2a and ribavirin in chronic hepatitis C – study phase summary

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Summary

Background: *The aim of the study was to assess the effectiveness of treatment with pegylated interferon-α2a (PegIFN-α2a) PEGASYS® ROCHE at 180 μg dose administered 1 × week in combination with ribavirin (RBV) COPEGUS® at 800 mg/d dose administered every day for 48 weeks to patients with chronic hepatitis C within the framework of an open-label, non-randomized clinical study.*

Material and Methods: *The study was carried out in a group of 190 adult patients of both sexes, among them 167 had undergone liver biopsies. The treatment was completed by 181 subjects. In addition to standard biochemical tests, HCV-RNA, genotype and viremia level were determined. Control tests were carried out after 6 months of the end of treatment to assess sustained virological response (SVR).*

Results: *SVR was obtained in 58.2% of patients, without statistically significant difference between men and women; there was a difference between the group of patients over 50 years of age as compared with those below that age (43.2% vs. 62.4%, respectively;*

p= 0.040). Higher SVR rates (p=0.001) were observed in patients infected with non-1 HCV genotype in comparison with genotype 1 (85.7% vs. 52.8%). In patients with genotype 1 and viremia equal to, or lower than 800 000 lU/ml SVR was 61.3% while in patients with viremia greater than 800.000 IU/ml SVR was 41.9% (p=0.028). Such difference was not found for non-1 genotype patients. No significant differences in SVR values related to the stage of fibrosis were observed (patients with stage 1 and 2 according to 0–4 staging scale predominated: 73.6%). Higher SVR rates (p=0.034) were obtained in patients receiving ribavirin doses above 10.6 mg/kg b.w. (67.6% and 50%, respectively) without statistically significant difference between the patients treated with interferon and ribavirin doses, considered both jointly and separately, above and below 80% of the scheduled dose. Hemoglobin level, leukocyte and neutrophil counts decreased significantly during the therapy and returned to the reference values after its completion. There was a statistically significant decrease of AIAT activity during the treatment, both in patients with and without SVR, which was observed also 6 months after its completion. The treatment was not completed by 9 patients (5 because of adverse effects, and 4 for subjective reasons).

***Conclusions:** 1. The overall effectiveness of treatment, assessed 6 months after its completion, reached 58.2%, without taking into consideration HCV genotype and viremia level. 2. Patients infected with non-1 genotype responded significantly better than those with genotype 1 (85.7% vs. 52.8%). 3. Patients infected with genotype 1 with low viremia levels responded significantly better than those with genotype 1 and high viremia (61.3% vs. 41.9%). 4. The response to treatment was significantly better in patients below 50 years of age. 5. No significant differences in response were found with respect to: sex, previous antiviral treatment and the stage of fibrosis. 6. Patients treated with ribavirin doses ≥10.6 mg/kg responded significantly better than those receiving doses <10.6 mg/kg.*

Key words: chronic hepatitis C • combined pegylated interferon-α (IFN-α) and ribavirin (RBV) therapy • sustained virological response related to HCV genotype

BACKGROUND

The treatment of chronic hepatitis C has been the subject of intensive clinical studies during the recent years. They have resulted in increasing rates of sustained virological response (SVR). The effects of combined treatment with interferon-α (IFN-α) and ribavirin (RBV) have been especially promising [1]. It has been demonstrated, also in multicenter studies carried out in Poland [2], that after combined IFNα2b + RBV therapy, continued for 6 months, with efficacy assessment after the same time, SVR was obtained in 37% of patients. Marked improvement of therapeutic success rates was obtained after the introduction of combined therapy using pegylated interferons with polyethylene glycol of various molecular weight incorporated in the drug molecule. The pegylated interferon preparations include: PegIFN-α2b (12 kD m.w.; Schering-Plough) and PegIFN-α2a (40 kD m.w.; Roche). Such pharmacological formula prolongs the time of IFN-α activity and reduces the dosing frequency from three to one injection a week [review: 3]. 48-week treatment with Peg-IFNα and RBV has almost doubled the SVR rates, which ranged in international multicenter studies from 54% to 63% [4–6], and reached very high levels in patients infected with non-1 genotype – from 76% to 80% [4–6]. The presented paper is a study stage summary report concerning the effectiveness of combined PegIFN-α2a plus RBV therapy carried out in Polish clinical centers. It takes into consideration the SVR analysis related to HCV genotype, viremia level and extent of liver fibrosis, as well as other parameters. As the data concerning larger numbers of patients become available, the next report will be prepared.

MATERIAL AND METHODS

Recruitment of patients to the study was based on the following diagnostic criteria for chronic viral hepatitis C:

1) At least 6 months from the moment of anti-HCV detection.
2) HCV-RNA positivity in the serum.
3) Elevated alanine aminotransferase (AlAT) activity.
4) In liver biopsy: signs of chronic hepatitis C.

Table 1. Characteristics of patients included in the study.

Patients included in the study	n=190
Age	41 yrs ± 12 (18–69 yrs)
Females	n=64; (33.6%)
Males	n=126; (66.3%)
Mean age – females	42±10, (21–69 yrs)
Mean age – males	40±13, (18–65 yrs)
Previous treatment	n=59; (31.1%)
No previous treatment	n=131; (68.9%)
Body weight	n=178;76 kg ± 14 (41–126 kg)

The above criteria were met by 190 patients of mean age 41±12 (18–69) years, including 64 females: mean age 42±10 (21–69) years and 126 males: mean age 40±13 (18–65) years. Table 1 presents comprehensive characteristics of the patients included in the study.

In all the patients, on day: '0' (before inclusion in the study), and then in weeks 2-4-8-16-24-32-40-48 during the therapy and 24 weeks after its completion (week 72) the following laboratory parameters were determined:
- AlAT, AspAT and alkaline phosphatase activity;
- hemoglobin, bilirubin, albumin, creatinine, uric acid and triglyceride levels;
- erythrocyte, platelet, leukocyte and neutrophil counts;
- TSH.

Among the aforementioned parameters, AlAT activity, hemoglobin level and platelet, leukocyte and neutrophil counts were selected for further analysis.

HCV-RNA was determined using a COBAS AMPLICOR HCV Test v. 2.0 system of over 50 IU/ml sensitivity in the qualitative method, whereas a COBAS AMPLICOR

Table 2. Reasons for discontinuation of treatment.

Neutropenia	2 p. (410–680/mm^3) (week 40 and 41)
Thrombocytopenia	1 p. (32 thousand/mm^3) (week 30)
Suspicion of follicular carcinoma	1 p.(week 42)
Hyperthyroidism	1 p. (week 22)
Refusal to continue the therapy	3 p. (week 2, 20 and 29)
General poor tolerance (repeated syncopes)	1p. (week 30)

Table 3. Material: data availability.

HCV RNA availability in week 72	n=170
Liver biopsy	n=167
HCV RNA in week 72 + biopsy	n=148
ALT values + HCV RNA in week 72	n=146
Hb values + HCV RNA in week 72	n=150
Platelets + HCV RNA in week 72	n=145
Leukocytes + HCV RNA in week 72	n=149
Neutrophils + HCV RNA in week 72	n=136

HCV MONITOR Test v.1.5 system of 600–500 thousand IU/ml linearity was used for quantitative determinations. For HCV-RNA genotyping, a Versant HCV Genotype LiPA Assay system was used.

Quantitative and qualitative HCV-RNA determinations were performed before the commencement of treatment, immediately after its completion (*end of the treatment response*, ETR) and 24 weeks after its completion in order to determine sustained response to the therapy (*sustained virological response*, SVR).

Liver biopsies were performed with standard Menghini method. Various scales were used for histopathologic assessment, separate ones for inflammation (G, '*grading*') and fibrosis (S, '*staging*'). Because of their different character, the final analysis was carried out on the selected results obtained using a uniform 5-point (0–4) scale (according to 7), separately for hepatitis and fibrosis (G and S: 0–4 scores). However, because of a smaller number of obtained results concerning inflammation (G), as compared with fibrosis (S), the former parameter was not taken into account in the final analysis. The reduced number of data concerning hepatitis assessment resulted from the use of more complex assessment scales by some centers, which could not be converted into the 5-point scale.

Laboratory tests were performed according to the procedure which was unified in all the study centers.

The following tests were applied in statistical analyses: Fisher, McNemara, Wilcoxon and t-Student for related samples. The SPSS v. 8.0.1 statistical software package was used.

The *in tractu* and final assessed parameters included:
- *in tractu*: adverse effects (discussed in a separate publication);
- final: HCV-RNA undetectability in week 24 after the completion of treatment (SVR).

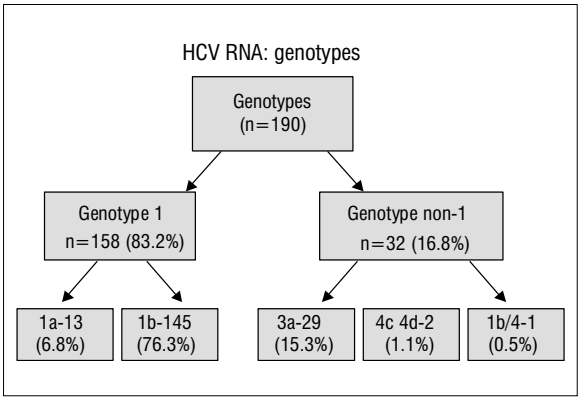

Figure 1. HCV RNA: genotypes.

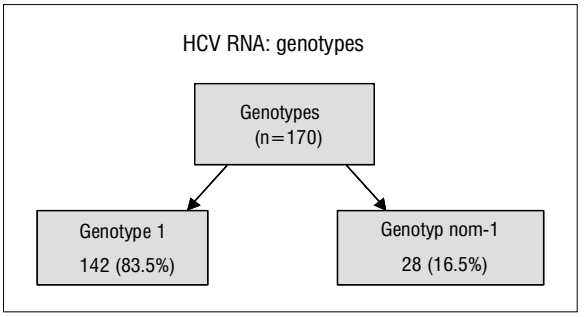

Figure 2. HCV RNA: genotypes.

Pegylated interferon-α2a (PegIFN-α2a) PEGASYS® ROCHE at 180 μg once a week with ribavirin (RBV) COPEGUS at 800 mg/d dose were used. The drugs were administered for 48 weeks with dose modifications dependent on tolerability.

RESULTS

The treatment was completed by 181 patients and discontinued by 9. The reasons for discontinuation are listed in Table 2.

The availability of results varied with respect to different tests, and the numbers of patients taken into account in the final analysis are presented in Table 3.

Unless another reason for the differences in numbers is stated in the discussion, they were caused by the lack of complete data in the database where the *in tractu* results were collected. With respect to some information, the reasons for differences will be specified, whereas the remaining ones for a specific parameter will result from the circumstances presented above.

Genotyping results in all patients included in the study (n=190) are presented in Figure 1, whereas those obtained in 170 patients who completed the treatment and their HCV-RNA results from week 24 after treatment were available – in Figure 2.

As it follows from the comparison of these two values, patients with genotype 1 were predominant (83.2% vs.

Table 4. Results of laboratory tests (x±SD; 95% confidence intervals).

Parameter	n	Treatment week						
		0	2	8	24	32	48	72
AlAT (IU/ml)	n=146	114±72.4 (102.1–125.8)	71.2±43.9 (64.–78.4)	55.0±31.4 (49.8–60.1)	43.8±37.7 (37.7–50)	45.2±38.5 (38.9–51.5)	47.7±48.4 (39.8–55.7)	50.0±55.6 (40.9–59.1)
Hb (g/dl)	n=150	14.8±1.4 (14.6–15.1)	14.1±1.5 (13.8–14.3)	12.9±1.5 (12.6–13.1)	12.5±1.4 (12.2–12.7)	12.6±1.3 (12.4–12.8)	12.6±1.4 (12.4–12.9)	14.7±1.6 (14.4–15.0)
Platelets ($\times 10^9$/L)	n=145	199.8±54.5 (190.9–208.8)	161.0±49.0 (153.0–169.1)	138.6±46.6 (130.9–146.2)	142.7±46.7 (135.0–150.4)	139.0±46.2 (131.4–146.6)	136.8±45.6 (129.3–144.3)	199.5±55.2 (190.4–208.5)
Leukocytes ($\times 10^9$/L)	n=149	6.1±1.3 (5.9–6.3)	4.3±1.4 (4.0–4.5)	3.4±1.3 (3.2–3.6)	3.2±1.1 (3.0–3.4)	3.2±1.0 (3.0–3.4)	3.1±1.2 (3.0–3.3)	5.8±1.6 (5.6–6.1)
Neutrophils ($\times 10^9$/L)	n=136	3.2±0.9 (3.0–3.3)	1.9±0.8 (1.7–2.0)	1.5±0.7 (1.4–1.6)	1.6±0.8 (1.5–1.7)	1.7±0.7 (1.5–1.8)	1.7±0.9 (1.5–1.8)	3.3±1.2 (3.1–3.5)

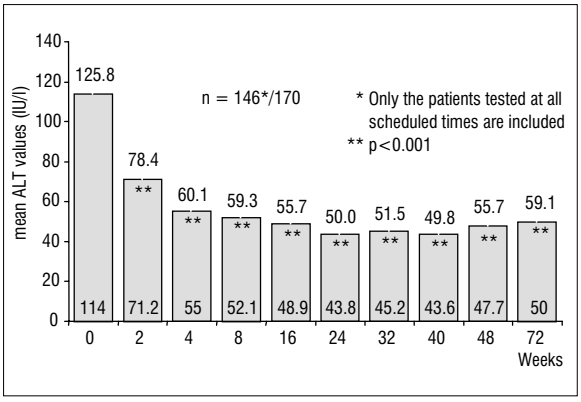

Figure 3. Mean values for ALAT.

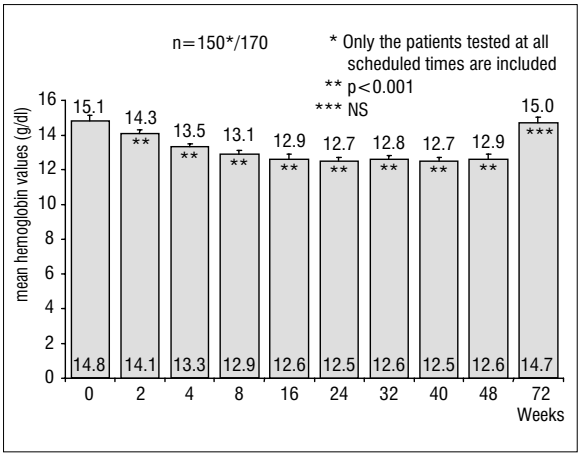

Figure 4. Mean values for hemoglobin.

83.5%) and patients with non-1 genotypes constituted a minority (16.8% vs. 16.5%). Among those infected with genotype 1, genotype 1b was the most frequent (76.3%), whereas among non-1 genotype infections genotype 3a predominated (15.3%).

Viremia levels were divided into two categories: over 800 thousand IU/mL (high viremia, HV) and equal to, or below 800 thousand IU/mL (low viremia, LV). For the whole population of 190 subjects, HV was found in 89/190 (46.8%) and LV in 101/190 (53.2%). If, the viremia values were calculated for genotype 1 (n=158) and separately for non-1 (n=32), in the genotype 1 subgroup HV accounted for 74/158 (46.8%), and LV for 84/158 (53.2%), and in the non-1 genotype subgroup for 15/32 (46.9%) and 17/32 (53.1%), respectively. As 170 patients were included in the final analysis, calculations analogous to the above demonstrated: HV 76/170 (44.7%) and LV - 94/170 (55.3%). If the viremia values were calculated for genotype 1 (n=142) and separately for non-1 (n=28), in the genotype 1 subgroup HV accounted for 62/142 (43.7%), and LV for 80/142 (56.3%), and in the non-1 genotype subgroup for 14/28 i.e. 50.0%, respectively. The decreased number of analyzed subjects by 20, from 190 to 170 (by 10.5%) did not affect the representativeness of the analyzed parameter in the final assessment.

Among 190 patients, 4 had no liver biopsies performed before the institution of treatment because of hemophilia. In the whole material of pre-treatment biopsies, with the relevant data available in the database (n=167), patients with stage 1 (36.5%) and 2 (38.3%) fibrosis, collectively accounting for 74.8% of hepatic lesions, were predominant, whereas in 7.2% of cases stage 0 was found, in 11.4 % – stage 3 and in 6.6% – stage 4. Among the patients who completed the treatment and whose liver biopsy results were available, it was possible to determine SVR in 148/167 (88.6%) patients, in whom pre-therapy liver bioptate assessments according to the 0–4 fibrosis staging scale were performed. The decrease of the number of analyzed data by 19 did not affect the proportions of fibrosis stage-related distribution in the particular subgroups, which results from the comparison of percentage values obtained for 167 initially analyzed patients and 148 ones subjected to the final assessment. Patients with stage 1 and 2 fibrosis were still predominant (35.8% and 37.8%, respectively, collectively – 73.6%). No signs of fibrosis were found in 11 (7.4%) and the same number had advanced stage fibrosis (S4).

The results of selected biochemical tests are presented in Table 4 and in Figures 3–7.

The dynamics of changes was as follows:

1) AlAT activity decrease was statistically significant ($p<0.001$) on all terms of tests carried out during the therapy and remained at that level for 24 weeks after its

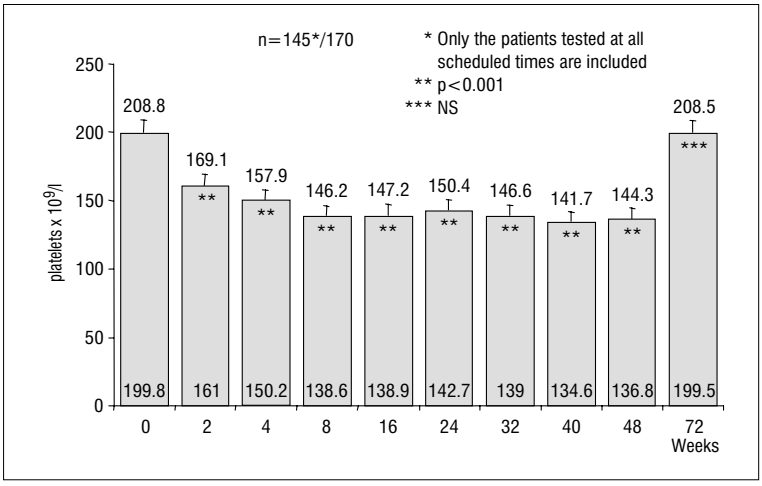

Figure 5. Mean values for plateles.

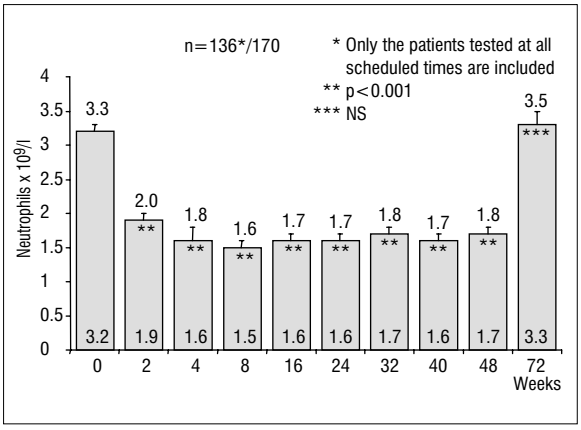

Figure 6. Mean values for neutrophils.

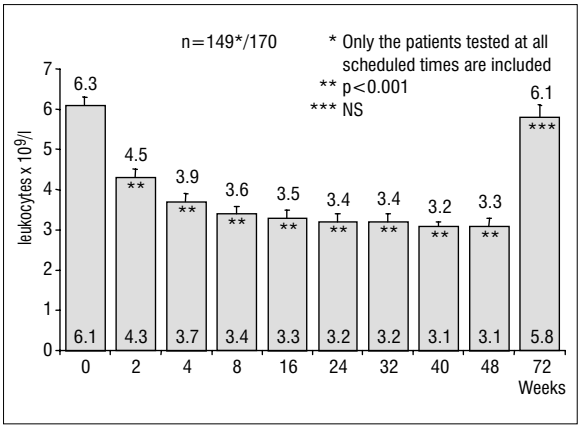

Figure 7. Mean values for leukocytes.

completion. This applied both to patients who had attained SVR as well as those with detectable HCV-RNA six months after termination of treatment.

2) Hemoglobin level, as well as platelet, leukocyte and neutrophil counts decreased significantly during the therapy ($p<0.001$) and increased to the values reaching no statistical significance in comparison with the baseline ('0' time).

It was possible to assess SVR in 170 cases. Among those, 99 (58.2%) demonstrated undetectable levels of HCV-RNA 6 months after the completion of the therapy. The analyzed group consisted of 58 women, 39 of whom obtained SVR (67.2%) and 112 men with SVR obtained in 60 (53.6%). The sex-related SVR frequencies reached no statistical significance ($p>0.05$). All the patients were divided into two age groups: below and over 50 years of age. In the first group, SVR was obtained in 83/133 cases (62.4%), and in the other one in 16/37 (43.2%). The difference is statistically significant ($p=0.04$): a higher percentage of subjects below 50 years of age benefited from the therapy.

The overall treatment efficacy assessed 6 months after its completion reached 58.2% for all the patients without taking into consideration HCV genotypes and viremia levels. Among patients with genotype 1, SVR was obtained in 75/142 (52.8%), and with non-1 – in 24/28 (85.7%), which is a statistically significant difference ($p=0.001$). However, such a difference was not observed in the comparison of patients with baseline viremia equal to or lower than 800 thousand IU/ml (60/94, i.e. 63.8%) with those having viremia levels above that value (39/76, i.e. 51.3%). In the genotype 1 subgroup, a statistically significant difference ($p=0.028$) between patients with high and low viremia was demonstrated according to the criteria described above (SVR – 26/62, i.e. 41.9% and 49/80, i.e. 61.3%, respectively). Such a difference was not observed among patients infected with non-1 genotype (SVR, 13/14 and 11/14, respectively).

No statistical significance was found in the presented material on the comparison of SVR in groups previously treated and untreated with antiviral therapy (35/53, i.e. 66% and 64/117, i.e. 54.7%, respectively, $p>0.05$).

No statistically significant differences ($p>0.05$) were found in SVR analyzed according to fibrosis stage. The highest rate of SVR (10/11) was obtained in patients with 0 stage fibrosis, the lowest (5/11) in those with maximum, stage 4 fibrosis. Similar distribution of SVR frequency was found in stage 1 (30/53, i.e. 56.6%), stage 2 (34/56, i.e. 60.7%) and stage 3 fibrosis groups (8/17).

The patients receiving RBV doses higher than 10.6 mg/kg b.w. throughout the whole treatment period, significantly more often ($p=0.034$) belonged to the group of responders (48/71, i.e. 67.6%) as compared with those receiving doses equal to, or lower than the above value (42/84, i.e. 50%).

There were no differences ($p>0.05$) between patients treated with PegIFNα-2a and RBV doses exceeding 80% of the scheduled dose (82/138, i.e. 59.4%) as compared with those receiving the doses of any drug lower than 80% (16/29, i.e. 55.2%). No such difference was also demonstrated when PegIFNα-2a and RBV were analyzed separately with the same dose threshold i.e. above and below 80%. For the former drug exceeding the 80% value, SVR was obtained in 14/27 (51.9%) vs. 84/140 (60.0%), and for the latter one, in 6/7 (85.7%) vs. 92/160 (57.5%), respectively. At this stage of analysis, in view of the lack of complete data obtained immediately after the completion of treatment, no analysis of results aimed at the determination of ETR was performed.

Discussion

Disappearance of HCV-RNA 6 months after completion of the therapy (SVR) was found in 58.2% of patients. The results are consistent with the range reported by international studies using the same type of PegIFNα2a with RBV (56–63%), and PegIFNα2b with RBV (54–61%), irrespective of HCV genotype [4–6], also using dosage, including that of RBV, adjusted to the patients' body weight. The predominance of men in our analysis is due to the fact that there are more representatives of that sex in the population of HCV-infected subjects and the criteria of recruitment (non-random) did not include the sex criterion. No statistically significant difference ($p>0.05$) in the SVR rates between women (67.2%) and men (53.6%) was demonstrated, although the percentages indicate the predominance of female gender. This is in agreement with data reported in the literature, according to which differences in treatment response between the sexes disappeared [5] when dosage of ribavirin per kg b.w. was taken into account, while others [6] did not indicate this difference at all. On the other hand, according to other authors [4–6], SVR was significantly more frequent ($p<0.05$) in patients below 50 years of age in comparison with those over that age limit, when such arbitrary division was applied (62.4% and 43.2%).

As presented in the results section, final analysis allowing to assess SVR in subjects with known fibrosis stages (S) was possible in 148 patients. In that group, extreme values, i.e. no fibrosis (S0) and the most advanced stage, morphologically equivalent to cirrhosis (S4) were represented by the same numbers of patients (11 in each group, i.e. 7.4%). Most patients were classified as S1 and S2 (73.6%), but 17 (11.5%) as S3. This indicates a non-homogeneous quantitative distribution of this characteristics with the predominance of subjects with mild forms of fibrosis. With high probability (low numbers of patients in S1 and S4 subgroups), this was the reason for obtaining no statistically significant differences in SVR frequency related to the stage of fibrosis. The literature data [4–6] indicate consistently that the lower the fibrosis stage, the higher SVR rates are obtained. No fibrosis or its mild form are mentioned as a positive prognostic factor. Some publications demonstrate that antiviral treatment, even resulting in no HCV-RNA elimination, causes inhibition or deceleration of both the inflammatory process and fibrosis, as well as that SVR patients may even demonstrate regression of previously existing cirrhosis [8]. Our study, for the reasons explained in the results section, did not take into account the stage of the inflammatory process. It will be included in a publication concerning a larger number of treated patients. The effect of the therapy on liver morphology parameters also could not be assessed because no control liver biopsies were performed.

HCV genotype is one of the most important prognostic factors in the treatment of chronic hepatitis C, because the SVR rates obtained in genotype 1-infected patients are always lower, irrespectively of PegIFNα type used with RBV, than those obtained in non-1 genotype patients. The above has been confirmed by our results: 52.8% and 85.7%, respectively ($p<0.05$). In both subgroups, the percentages are very slightly higher than the corresponding literature data [4–6]: within the 42–52% range for genotype 1 versus approximately 80% for non-1. As serum HCV-RNA was not determined in a sufficient number of patients immediately after treatment, with a reservation made for the possibility to return to this analysis in the subsequent publications, no immediate results of the end of treatment response (ETR) can be assessed. The above also means that it is impossible to calculate the frequency of relapses, i.e. transitions from negative HCV-RNA on ETR assessment date to repeated detection of HCV-RNA after six months from that date. The frequency of this phenomenon may amount to over ten per cent [5]. For the purpose of extended analysis, HCV-RNA determination after 12 weeks of treatment, not included in the study protocol, would also be very useful. With high probability (only 1.6% chance of obtaining SVR after continued treatment) the final outcome can be predicted on the basis of the above determination at such an early stage of the therapy [9,10].

Statistically significant difference in SVR concerned the patients infected with genotype 1 with viremia below 800 thousand IU/ml after division of the evaluated patients into two subgroups, compared with the value higher than, or equal to, the above threshold value (determinations performed prior to the commencement of the therapy). On the other hand, for all the treated patients and for those with non-1 genotype no such differences were demonstrated. According to the literature data, higher viremia levels resulted in a lower SVR frequency in patients infected with genotype 1 [4,6], those with non-1 genotype [4], as well as those without regard to genotype [4,5].

No statistical difference was demonstrated in the presented study with respect to the SVR rates obtained in patients previously treated and untreated with antiviral therapy. However, this conclusions is based on very weak grounds, i.e. very general information available in the database, resulting from the use of very simplified

criteria: treated – untreated. The patients characteristics did not include very important details such as time elapsed from the completion of previous treatment until the moment of inclusion in the analyzed study, the duration and type of previous treatment: non-pegylated IFNα monotherapy, or combined IFNα and RBV treatment. Therefore, the results discussed here should be interpreted very cautiously. Retreatment with non-pegylated IFNα and RBV of the patients who were non-responders to prior IFNα monotherapy, results in SVR rates no higher than 15% [11].

RBV, deposited in erytrocytes, causes generally mild hemolytic anemia [5], reflected by statistically significant decrease of Hb concentration, observed during the treatment of the discussed patients. In some patients, temporary reduction of RBV doses was necessary for this reason, but it did not lead to discontinuation of the therapy in any case. As reported by another team [5] patients who had received RBV doses above 10.6 mg/kg b.w. responded to the treatment better ($p=0.034$) than those treated with lower average doses (67.6% vs. 50%). As it was presented in the study results, dosage over and above 80% of the scheduled PegIFNα doses, both jointly with RBV, and separately, for both these drugs, does not demonstrate a statistically significant difference in SVR rates. Maintaining dosage of the combined treatment at a level greater than or equal to 80% increases its efficacy [12]. In the patients we treated, for whom we had full access to information, 29 of 167 patients (17.4%) received doses of any medication below this level, which is a relatively small proportion compared to those receiving doses greater than 80%.

The decrease of leukocyte, granulocyte and platelet counts is a result of moderate toxic effect of IFNα and Peg-IFNα on the bone marrow. Reduction of doses, usually temporary, allows to continue the therapy. The treatment was discontinued in 2 patients (week 40 and 41) because of persistent neutropenia (fall to the values of 410 and 680/mm^3). Persistent thrombocytopenia (the lowest value of 32 thousand/mm^3) was the reason for such decision in 1 patient (in week 30). Other authors discontinued treatment for that reason with similar frequency [5]. Decreased AlAT activity, as commonly interpreted in the literature, is associated with inflammation intensity decreased as a result of antiviral treatment.

The reasons for discontinuation of treatment in 9 patients (4.7%) in addition to the three mentioned above (thrombocytopenia and neutropenia) included, in three other cases: suspected carcinoma follicularis (week 42), hyperthyroidism (week 22), general poor tolerance with recurrent syncopes (week 30). Other 3 patients (weeks: 2, 20 i 29) withdrew from the treatment program despite the lack of any objective reasons. Other symptoms occurring in the course of treatment, which did not lead to its discontinuation, are discussed in a separate publication.

CONCLUSIONS

1. The overall treatment efficacy assessed 6 months after its completion reached 58.2% for all the patients without taking into consideration HCV genotypes and viremia levels.

2. Patients infected with non-1 genotype responded to the treatment significantly better than those with genotype 1 (85.7% vs. 52.8%).

3. Patients infected with genotype 1 with low viremia levels responded significantly better than those with genotype 1 and high viremia (61.3% vs. 41.9%).

4. The response to treatment was significantly better in patients below 50 years of life.

5. No significant differences in response were found with respect to: sex, previous antiviral treatment and the stage of fibrosis.

6. Patients treated with ribavirin doses $\geq$10.6 mg/kg responded significantly better than those treated with doses <10.6 mg/kg, reflecting the importance of dosing ribavirin by body weight in patients infected with genotype 1.

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