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RIBAVIRIN PRIMING HAS NO BENEFICIALE EFFECTS FOR CHRONIC HEPATITIS C PATIENTS

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ABSTRACT

AIM. The aim of this study is to assess the efficacy of an initial dose of ribavirin administered before a 48-week course of treatment with peg-IFN + ribavirin in treatment-naïve patients and in patients after previous failure of CHC treatment.
MATERIAL AND METHODS. A total of 103 patients with chronic hepatitis C infected with genotype 1 HCV were qualified to the study. Study patients were randomised to receive one of two treatments: A- RBV for 4 weeks followed by combined therapy with peg-IFN alpha-2a +RBV for 48 weeks (n = 73), or B- combined therapy with peg-IFN alpha-2a +RBV for 48 weeks (n = 30).
RESULTS. SVR 24 was observed in 44% patients in group A and in group 40% patients in group B (40%), $p > 0.05$. Comparing subgroups of the naive patients, it was found that the SVR24 value was higher in group A than group B (57% vs. 47%, $p > 0.05$). In the re-therapy subgroups, higher treatment response rates in patients not responding earlier was found in group A than group B (39% vs. 16%, $p > 0.05$).
CONCLUSION. No significant advantage was found in the use of a priming method over a standard regimen. However, it could be recommended in patients with a total lack of response to peg-IFN and ribavirin when no other therapeutic options are available.

Key words: *chronic hepatitis C, treatment, ribavirin, priming*

INTRODUCTION

Chronic hepatitis C (CHC) is one of the fundamental problems faced by hepatology, both in Poland and worldwide. Approximately 250 million people around the world, and around 700 000 in Poland, are believed to be infected with HCV (1-2). In recent years, rapid progress has been made in the design of new methods of treating CHC. Standard treatment with peg-IFN and ribavirin has been found to be an effective cure for 45-50% patients with genotype 1 HCV (3,4). However, new methods of treatment using drugs which act directly on the virus (DAA) produce a sustained virological response in up to 80% of the patients (5,6). Unfortunately, despite the spectacular effects of these new therapeutic methods, their high prices prohibit their widespread use in many countries. Hence, in many regions of the world, treatment of HCV infection with DAA is possible only in limited indications (re-therapy, genotype TT with IL28B), and the standard treatment is still based on peg-IFN and Ribavirin for the majority of treatment-naïve patients.

Therefore, there is a need to continue the search for improved standard treatment efficacy, e.g. vitamin D3 supplementation in cases of deficiency (7) or concurrent treatment with statins (8). One way of modifying a current standard treatment regime is an initial 4-week treatment with ribavirin, before starting full therapy with peg-IFN + ribavirin (9). It has been observed that such a procedure may significantly increase SVR in patients with CHC during re-therapy (9,10) and probably also in patients after liver transplantation (11). The effectiveness of such procedures observed on small groups of patients was attributed to the immunomodifying effect of ribavirin. Although ribavirin does not present an

anti-viral effect in monotherapy, the effect does become significantly more pronounced when used in combination with peg-IFN (12,13).

The aim of this study is to assess the efficacy of an initial dose of ribavirin administered before a 48-week course of treatment with peg-IFN + ribavirin in treatment-naïve patients and in patients after previous failure of CHC treatment.

MATERIALS AND METHODS

The patients. A total of 103 patients with chronic hepatitis C infected with genotype 1 HCV were qualified to the study. All patients were treated in the Department of Infectious Diseases and Hepatology, Medical University of Lodz, in the period 2010-2012. All of the patients were confirmed to have chronic HCV infection in the compensated liver disease stage. Both treatment-naïve patients and patients previously unsuccessfully treated with peg-IFN + ribavirin for CHC were qualified to the study. Among the patients who had been previously treated, two groups were distinguished: non-responders (NR), in whom no decrease of HCV-RNA >2 log10 was seen in the 12th week of the previous therapy, and partial-responders and relapsers (PR/R), in whom a decrease of HCV-RNA <2 log10 was observed in the 12th week, despite not achieving sustained virological response (SVR24).

The inclusion criteria in this study were as follows:

1. adults aged 18 to 70 years;
2. genotype 1 HCV;
3. a history of positive HCV antibody and detectable HCV RNA 6 months before the screening;
4. chronic HCV infection confirmed by histopathological examination of liver biopsy material interpreted by a local pathologist, or Fibroscan < 20 kPa within 1 year prior to screening;
5. platelet count ≥90 000/mm^3, absolute neutrophil count ≥1200/mm^3, and hemoglobin ≥12.0 g/dL for women and ≥13.0 g/dL for men; creatinine clearance >70 mL/min;
6. glycosylated hemoglobin (A1c) levels ≤8.5% in diabetic patients;
7. normal or adequately controlled thyroid-stimulating hormone levels while on the prescribed medication;
8. alpha-fetoprotein levels within normal limits or hepatocellular carcinoma ruled out within 6 months prior to the screening;
9. inability to conceive or active use of appropriate birth control methods.

The patients were excluded from the study if they had a positive HIV or hepatitis B surface antigen serology; demonstrated signs of decompensated liver disease at any time before the study (ascites, variceal bleeding, liver encephalopathy); had used direct antiviral agents any time before the study; been diagnosed with severe psychiatric or neuropsychiatric disorders (e.g. severe depression, history of suicidal ideation); significant ischaemic or unstable heart disease; significant metabolic, haematologic, pulmonary, endocrine, ophthalmologic (including retinopathy) or immune-mediated disease; had undergone organ or bone marrow transplantation; had engaged in chronic use of immunosuppressive medications (>30 days), including steroids, in doses equivalent to ≥10 mg of prednisone 30 days before or anytime during the study; had a recent history of alcoholism or illicit drug use; been diagnosed with or treated for a malignancy within the preceding 5 years; or were breastfeeding or had received a positive pregnancy test result at any time during the study.

Written informed consent was obtained from all the patients prior to inclusion in the study. This trial was accepted by the Ethics Board of Medical University of Lodz.

Study design. Study patients were randomised to receive one of two treatment regimes: (i) 1000-1200 mg RBV (Roche, Switzerland) orally twice daily for 4 weeks followed by combined therapy with 1000-1200 mg RBV orally twice daily plus 180 μg peg-IFN alpha-2a (Pegasys, Roche, Switzerland) per week subcutaneously for 48 weeks (priming arm-group A, n = 73), or (ii) combined therapy with 1000-1200 mg RBV orally twice daily plus 180 μg peg-IFN alpha-2a (Pegasys) per week subcutaneously for 48 weeks (standard dosing arm-group B, n = 30). The patients in each group of study were monitored for 24 weeks and sustained viral response was evaluated after this period of time (SVR24).

Demographic information and baseline characteristics were summarized for all randomised patients. All patients underwent a clinical interview, physical examination and laboratory blood testing for haematological and biochemical factors at a number of time points: group A - Day 1 of RBV, Day 1 of combined therapy and then every 4 weeks during the study; group B - Day 1 of combined therapy and then every 4 weeks during the study. The plasma HCV RNA values were measured at day 1, at weeks 12, 24 and 48 of combined treatment and at the 24th week of the follow-up using the Cobas TaqMan HCV Quantitative Test v2.0 (Roche Diagnostics, Switzerland): sensitivity to 43 IU/mL.

The IL-28B genotype was estimated in most patients using the facilities of the Department of Biochemistry, Medical University of Lodz, Poland.

All laboratory tests were performed at a local laboratory at the Bieganski memorial Hospital, Lodz, Poland.

Statistical analysis. Descriptive statistics were used for continuous variables, and percentages were used for categorical measurements.

Table 1. Characteristics of the studied groups

Parameter	Priming arm - group A	Standard dosing arm-group B	p
Number of patients	73	30	
Naive patients in the group n(%)	35 (48)	17 (56)	NS(p=0.98)
Re-therapy patients (Non-responders/ Partial responders and Relapsers)	38 (18/20)	13 (6/7)	NS(p=0.93)
Advanced fibrosis and cirrhosis patients S3-4 n(%)	25 (34) Naïve- 11/35 (31) PR-8/20 (40) NR- 6/18 (33)	10(33) Naïve - 4 /17 (24) PR- 3/6 (50) NR- 3/7 (50)	NS(p=0.55) NS(p=0.66) NS(p=0.65)
Age (years)	42.6	41.5	
Male n(%)	48 (65.7)	18 (60)	NS(p=0.58)
IL-28B n(%) CC CT TT	69 (94) 15 (22) 37 (54) 17 (24)	28 (93) 6 (20) 16 (53) 8 (26)	 NS(p=0.97) NS(p=0.75) NS(p=0.68)

RESULTS

Patients. A total of 103 patients met the eligibility requirements and were randomized to priming arm-group A (n = 73) or standard dosing arm-group B (n = 30). The baseline patient structure is summarized in Table 1.

Group A consisted of 48 (65.7%) men and 25 women, aged 18 to 59 years: mean value 42.6 years old. Thirty-five (48%) patients had never been treated with anti-virals before (naïve), and of the remaining 38 patients, who had received previous treatment, 18 presented with total lack of response to the treatment, and 20 responded partially or relapsed after treatment. In 25 (34%) patients, advanced fibrosis or cirrhosis of the liver was confirmed. IL28B gene assessment was performed in 69 of 73 of patients from group A (94%): the CC/ CT/ TT proportion being 15 / 37 / 17 (Table 1).

Group B consisted of 18 (60%) men and 12 women, aged 19 to 56 years: mean value 41.5 years old. Seventeen (56%) patients had never been treated with anti-virals before (naïve). Among the remaining 13 patients in group B, who had experienced previous treatment, 6 presented with total lack of response to the treatment, and 7 respond partially or relapsed after treatment. Advanced fibrosis or cirrhosis of the liver was confirmed in 10 (33%) patients. IL28B gene assessment was performed in 28 of 30 of patients from the group (93%): the CC/ CT/ TT proportion being 6 / 16 / 8 (Table 1).

Efficacy. Twenty-four weeks after completion of combined therapy (SVR 24), a greater proportion of patients achieved an undetectable viral load (HCVRNA negative) in group A (44%) than in group B (40%) but this difference was not statistically significant (P > 0.05). Comparing subgroups of the naive patients, it was found that the SVR24 value was higher in group A than group B (57% vs. 47%, p > 0.05), however, this difference was also statistically insignificant. Comparing both re-therapy subgroups, no significant differences were found between groups A and B (32% vs. 30%, p > 0.05). In the re-therapy subgroups, higher treatment response rates in patients not responding earlier was found in group A than group B (39% vs. 16%, p > 0.05), however, the Chi-square and Fisch er's tests revealed no significant difference. In subgroups of partial-responders or relapsers, a more frequent response was found in group B (25% vs. 43%, p > 0.05), although without statistical significance (Table 2).

Safety. The incidence of adverse events was similar between the A and B treatment arms (10.2% vs. 10.5%)**,** and no significant difference was found in the proportions of the patients experiencing a haemoglobin decline less than 10 mg/dl: 5.0% vs. 5.3%. Furthermore, no significant differences were seen in the frequencies of other AEs between treatment arms. No treatments were discontinued due to adverse events in either of the arms.

DISCUSSION

No significantly increased SVR was found in the group of the patients treated with an initial 4-week dose of ribavirin before 48-week treatment with peg-IFN and ribavirin compared to those treated with the

Table 2. Results of treatment in study groups

Parameter	Group A	Group B	p
Number of SVR patients-**all groups** n (%)	**32/73 (44)**	**12/30 (40)**	NS(p=0.72)
Number of SVR naive patients n(%)	**20/35 (57)**	**8/17 (47)**	NS (p=0.49)
Number of SVR re-therapy patients (**non-responders/** partial responders and relapsers)	12/38 (32) **7/18 (39)** 5/20 (25)	4/13 (30) **1/6 (16)** 3/7 (43)	NS(p=0.95) NS(p=0.31) NS(p=0.37)

standard regimen. No significant differences were found between groups of treatment-naïve patients and those experiencing re-therapy. Interestingly, a higher percentage of the non-responders achieved SVR when treated with an initial dose of ribavirin: 39% vs. 16% for controls. However, the differences were not found to be statistically significant, probably because the number of patients in the B arm was too low.

Both *Ogawa* et al. and *Furusyo* et al.have previously indicated that priming methods similar to that used in this study have a positive immunomodifying effect on the treatment of HCV infection (14,15). *Ogawa* et al. describe that out of group of 17 patients, Th1/Th2 ratios significantly increased after the priming stage in patients with RVR from 13.9 +/-5.1 before treatment to 16.7 +/-6.2 after treatment ($P<0.05$) but did not change in those without RVR (14). The levels of Th2 cytokines (interleukin-10 and soluble CD30) significantly decreased, especially in the RVR group. The mean mutation rates of interferon sensitivity-determining region (ISDR) at the nucleotide level increased in the RVR group from 2.6 +/-0.9 sites/clone before treatment to 3.9 +/-1.6 sites/clone after treatment ($P<0.05$), but did not change in the non-RVR group. SVR was not described in this study. The authors conclude that ribavirin administration might increase the efficacy of interferon therapy in patients with chronic hepatitis C by stimulating the host immune system and promoting HCV gene mutation (14).

The most complex work published so far regarding priming methods is by Furusyo et al, who used a primer in 40 patients infected with genotype 1b HCV and compared the results of treatment with a group of 41 patients treated according to the current standard (15). Lymphocyte subpopulations Th1 and Th2 were monitored after an initial dose of ribavirin. However, no difference was found between the group treated with priming method over standard treatment with regard to SVR rates: 22.9% vs. 19.4%, respectively. Nevertheless, the results indicate that the mean Th1/Th2 ratio significantly increased from baseline to day 1 of combined treatment, as Th2 cells decreased, and then the ratio significantly decreased from day 1 to week 4 in the priming group, while no significant difference was found between baseline and day 1 in the standard group (15). In the priming group, 13 patients with HCV RNA clearance within 4 weeks demonstrated a significantly increased Th1/Th2 ratio, from 14.0 at baseline to 22.1 at day 0, and then a significantly decreased ratio, from 22.1 at day 0 to 15.0 at week 4, while no significant change was noted in the remaining patients (15).

These results confirm that ribavirin monotherapy exerts an immunomodifying effect in the mentioned group of the patients but is seems to be too weak to allow the statistically more frequent SVR. *Brillanti* et al. report priming treatment demonstrated increased effectiveness in patients who did not respond to standard treatment with peg-IFN and ribavirin (16). In the group of 10 non-responders treated with a priming method, 5 (50%) achieved SVR24: a considerable improvement over standard re-therapy, which returns values between 5% and 17% (16).

Tox et al. achieved 100% SVR in the patients treated with the method mentioned above, however, those patients were found to have genotype 2/3 and there only 3 people were included in the study group (9). The use of priming in patients with genotype 2 and 3 HCV may bring about significant improvement of SVR, however, in the 17 patients with genotype 1, the achieved SVR was no different from that which could be expected for standard treatment: 41% (9).

Merli et al. describe a study on a group of 13 patients after liver transplantation because of cirrhosis, who were primed with an 8-week initial treatment with Ribavirin (11). In total, 6 out of 13 patients (46%) achieved SVR, 4 of whom were infected with genotype 2/3 HCV (11). The results were probably slightly better than in the patients after liver transplantation treated with standard regimen. However, no statistical comparisons were possible due to the small size of the group (11).

Palmer et al. report the use of an initial dose of Taribavirin (Ribavirin prodrug) in the treatment of 23 patients infected with HCV vs. 18 patients treated with a standard regimen (17). A slightly greater HCV viral load reduction of 32% in the primed group vs. 22% in the standard regimen was noted in the 24th week of treatment, however, these results are not statistically significant and the SVR results were not published (17).

A group of 103 patients with CHC was treated in the present study, 73 of whom were given initial dose of ribavirin. Neither of the studies published so far have included such a large group: *Furusyo* et al. (15) incorporated 40 patients in the priming group, 23 in *Palmer* et al. (17) 13 in *Merli e*t al. (11) 20 in *Tox* et al. (9). Although improvements were noted in SVR rates after initial doses of ribavirin were administered, the small size of the studies prevented statistical comparisons from being performed, or the results appeared statistically insignificant. Indeed, in all cases, the authors recommend using larger study groups.

The present study not only uses the largest group to be treated with a priming method, but also compares treatment with an initial dose of Ribavirin with a standard regimen, and compares the effects of both methods in groups of naïve and non-naïve patients. Although greater SVR rates were found when using a priming method in groups of naïve patients (57% vs.47%) and non-naïve patients (39% vs. 16%), as well as when all patients were taken into consideration (A - 44% vs. B - 40%), no significant advantage was found in the use of a priming method over a standard regimen. Hence,

there would seem to be little value in using this method of treatment. However, it could be recommended in patients with a total lack of response to peg-IFN and ribavirin when no other therapeutic options are available (*Direct Antiviral Agent* – DAA).

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Received: 25.04.2014
Accepted for publication: 9.07.2014

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ERRATA

W Przeglądzie Epidemiologicznym nr 2/2014 w artykule: N Parda, Ł Henszel, M Stępień: Hepatitis C in Poland in 2012, s.267 wydrukowano niewłaściwą rycinę (Fig.1).

Poniżej zamieszczamy właściwą rycinę 1 (Fig.1), do której odnosi się tekst w prawej kolumnie, 10 wiersz, s.267: The highest incidence for males and females was reported in the following age groups 45-49 (12.45) and 55-59 (15.4), respectively (Fig.1).

Redakcja Przeglądu Epidemiologicznego

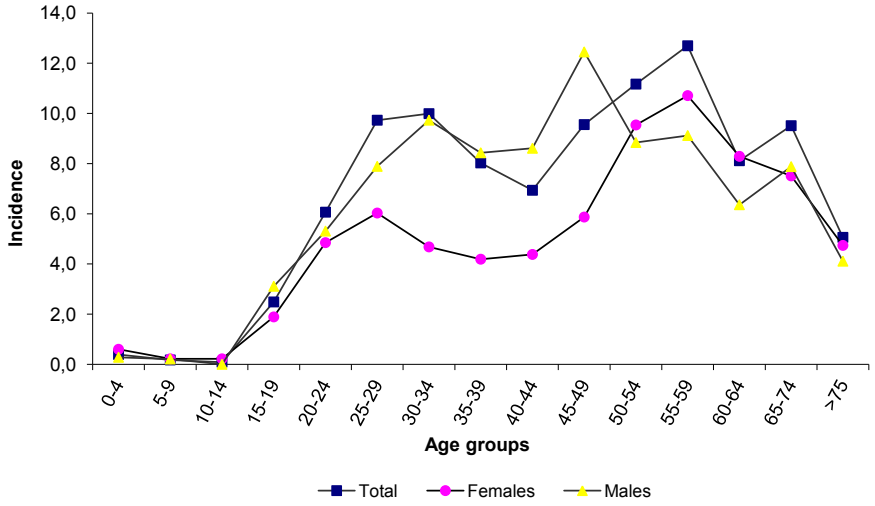

Fig.1. Hepatitis C in Poland in 2012. Incidence per 100,000 population by age group and gender.