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CLINICAL STUDY

Anemia as a predictor of response to antiviral therapy in chronic hepatitis C

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Abstract: *Background:* The standard therapy for chronic HCV infection is the administration of pegylated interferons in combination with ribavirin. Anemia is a dose-dependent side-effect of ribavirin administration. The degree of anemia could be indicative of the individual exposure to ribavirin.
Aims: 1) To evaluate the correlation of HGB level decreases at specified time-points with a sustained virological response during the antiviral treatment. 2) To compare these parameters with the virological predictors for responses.
Methods: A retrospective analysis of cohort, which comprised 164 patients treated with standard therapy at a tertiary center in Prague, Czech Republic.
Results: We identified several predictive factors for a sustained virological response in females: baseline HGB level ≤140 g/l (p=0.025), maximum drop from baseline >40 g (p=0.039), and a HGB drop in week 4 >30 g (p=0.044). There was only one predictor identified for males: reaching the lowest HGB level after week 19 (p=0.021). The strongest positive predictor of response was a rapid virological response. A low viral load (<600 000 IU/ml) at baseline was not associated with a sustained response in either gender.
Conclusions: The parameters of HGB decrease during antiviral treatment are better correlated with a sustained response in females. None of these response predicting parameters was as significant as that of rapid virological response as that of rapid virological response *(Tab. 4, Fig. 1, Ref. 15).* Full Text in PDF *www.elis.sk.*
Key words: anemia, hepatitis C virus, pegylated interferon, ribavirin.

List of abbreviations: HCV – hepatitis C virus, HGB – hemoglobin, PEG-IFN – pegylated interferon, RBV – ribavirin, RVR – rapid virological response, cEVR – complete early virological response, pEVR – partial early virological response, EVR – early virological response, SVR – sustained virological response, ETVR – end of treatment virological response, HCV RNA – hepatitis C virus ribonucleic acid, RT-PCR – real-time polymerase chain reaction, LLD – lower limit of (qualitative) detection, BMI – body mass index, SNP – single nucleotide polymorphism.

A recommended by international (European Association for the Study of the Liver (EASL), American Association for the Study of Liver Disease (AASLD)) and national guidelines (), the standard therapy for untreated (naive) patients chronically infected with hepatitis C virus (HCV) infection is based on the administration of pegylated interferon alpha (PEG-IFN) in combination with ribavirin (RBV) (). This combination leads to virus elimination in approximately 60 % of all patients. The treatment's success is defined as a sustained virological response (SVR), which means no detectable HCV RNA by real-time polymerase chain reaction (RT-PCR) in serum in week 24, i.e. after stopping the administration of combined therapy. SVR rates are lower in genotypes 1+4 (approx. 30–40 %) than in genotypes 2+3 (80–85 %) (, ,). Numerous side-effects of this combination occur. The most common adverse events include flu-like symptoms, depression, anemia, and neutropenia. Anemia was of particular interest in our study. There are two possible mechanisms for the development of anemia during antiviral therapy: 1) the myelosuppressive effect of PEG-IFN, and 2) RBV accumulation in the red blood cells leading to hemolysis. The latter seems to be the most relevant mechanism (6, 7).

HCV genotype 1 patients require higher doses of RBV plus longer duration of treatment versus HCV genotype 2+3. Such higher doses lead to higher serum concentrations of RBV, as well as to higher rates of hemolytic anemia (which is a dose-limiting side-effect) (2). Anemia can be prevented by administering erythropoietin or darbopoietin but this is not a routine practice outside the clinical trials. Due to the side-effects mentioned above, the prediction of treatment success plays the key role in the management of each individual patient. This is especially important for HCV genotype 1 patients, as the SVR rate for this genotype is

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rather low. Several viral and host-dependent factors positively associated with SVR have been identified. Such factors may be used as predictors (positive or negative) of viral response to combination of PEG-IFN plus RBV. Among these viral factors, low baseline viremia (≤600 000 IU/ml), rapid virological response (RVR), and complete virological response (cEVR) are the strongest viral predictors of response (2, 8). Interleukin-28B (IL28B) single nucleotide polymorphism (SNP) has recently been described as the strongest host-dependent predictor of SVR (9). Only little information is available on the association of anemia with SVR. In the IDEAL study, the SVR rate was described to be higher among patients who had their hemoglobin level lower than 10 g/dl during the treatment with PEG-IFN + RBV (8).

Therefore, the aims of the present study were: 1) to assess the correlation of anemia (hemoglobin decrease in g/l or in % of the baseline value) at specified time-points with SVR in patients treated with PEG-IFN + RBV for chronic HCV infection; 2) to compare these parameters with the virological predictors of response (e.g. RVR).

Patients and methods

The inclusion criteria for the study were as follows: 1) documented anti-HCV or HCV RNA positive for at least 1 year before administration of treatment; 2) HCV genotype 1; 3) treatment duration of at least 12 weeks; 4) blood count results and HCV RNA were available ±5 days from all specified time-points, e.g. baseline, plus weeks 4, 12, 24, and 48 (or at the end of treatment if the therapy was discontinued prematurely); 5) HCV RNA result available at week 24, i.e. after the treatment; 6) absence of extrahepatic expressions of HCV infection. All patients were treated according to standard treatment recommendations. The treatment regimens were: 1) PEG-IFN alpha-2a (Pegasys, Roche, Switzerland): 180 µg once weekly; + RBV (Copegus, Roche Switzerland): 1000–1200 mg daily, according to body weight (1000 mg ≤75 kg, 1200 mg >75 kg) and 2) PEG-IFN alpha-2b (Schering-Plough CEAG): 1.5 µg/kg body weight once weekly; + RBV (Rebetol, Schering-Plough CEAG): 1000–1200 mg daily, according to body weight (1000 mg ≤75kg, 1200 mg >75 kg). Dose reductions were used according to SPC in each individual case. No erythropoietic growth factors (EGF) were co-administered.

A rapid virological response (RVR) was defined as undetectable HCV RNA by PCR (or real time PCR) at week 4 since baseline. An early virological response (EVR) was defined as ≥2 log drop in HCV RNA at week 12. A complete early virological response (cEVR) was defined as undetectable HCV RNA by PCR (or real time PCR) at week 12 since baseline. The end of treatment response was defined as undetectable HCV RNA by PCR (or real time PCR) at week 48 (or at the time of stopping the therapy, if this occurred prematurely). A sustained virological response (SVR) was defined as undetectable HCV RNA at week 24, after the therapy had been completed. The scheduled treatment duration was 48 weeks in cases of EVR. If EVR had not been achieved, patients were classified as non-responders, and the treatment was discontinued.

Anti-HCV reactivity was detected by the use of the commercially-available AxSYM diagnostic kit (Abbott). We used three different PCR techniques within the study period (2000–2008). Only one technique was used for HCV RNA measurements of every individual patient during the treatment and follow-up periods. We have used commercially available techniques as follows: 1) Cobas Amplicor (Roche, Switzerland, Lower Limit of Detection (LLD) = 50 IU/ml); 2) HCV Quantitative ASR (Abbott, LLD = 50 IU/ml), m2000rt (Abbott, LLD = 12 IU/ml); 3) Cobas Ampliprep/TaqMan (Roche, LLD = 15 IU/ml).

Statistical analyses

Initial values of the examined quantitative parameters were summarized by standard rank statistics: median, 5% - 95% percentiles. All comparative statistical testing was based on the robust rank Mann-Whitney U test, due to the asymmetric sample distribution of continuous variables. The frequency analysis and Maximum Likelihood chi-square test were used to summarize and compare the differences in categorical variables. Spearman's rank correlation coefficient was applied to evaluate the significance of relationship among examined variables. A universal significance level of p=0.05 was used as the statistical significance cut-off in all tests used. Both a univariate and multivariate logistic regression strategy was applied to quantify the predictive potential of examined factors, with SVR as the endpoint. The odds ratio with 95% confidence limits was estimated and tested in a Wald c2 test. The parameters with potential risk (providing at least $p<0.10$ in univariate logistic regression) were examined for mutual correlation, and the interaction terms were coded and tested for significantly correlated pairs of variables.

Results

Characteristics ofstudy patients

The study consisted of a total of 164 HCV RNA positive genotype 1 naïve patients, who were treated with a combination of PEG-IFN + RBV, and who fulfilled the inclusion criteria between 2000 and 2008. The baseline characteristics are shown in Table 1. Patients were considered having liver cirrhosis if this was clinically evident (abdominal sonography, portal hypertension, history of decompensation), or if the cirrhosis had been proven by liver biopsy. The average hemoglobin (HGB) level at baseline was 146.6 g/l (113–181 g/l).

Tab. 1. Baseline characteristics of patients.

Characteristic	n
Gender	
Male	97 (59.1%)
Female	67 (40.9%)
Baseline HCV RNA (IU/ml)	
<600000	68 (41.5%)
≥600000	92 (56.1%)
Liver cirrhosis	12 (7%)
Average age	38.6 (yrs)
Total [Caucasian]	164 (100%)

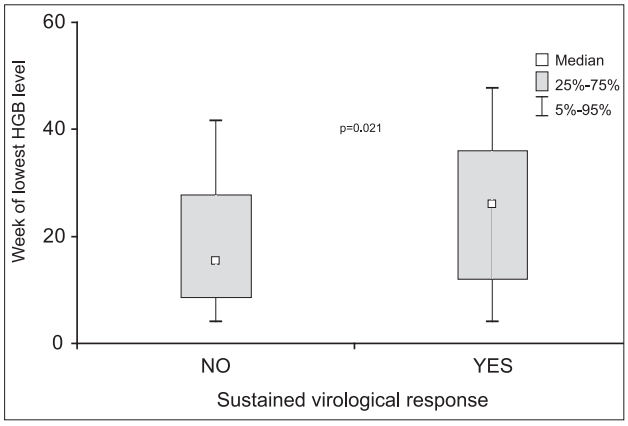

Fig. 1. Week of lowest HGB level according to SVR (sustained virological response).

Antiviral Efficacy

The overall SVR rate was 63 %. SVR was achieved in 61/97 of the males (63 %), and in 42/67 of the females (63 %). The RVR, cEVR, pEVR and non-response rates were 38 %, 70 %, 13 %, and 17 %, respectively. The SVR rate among males with low viral load (<600 000 IU/ml) was 68 %, while among males with high viral load (≥ 600 000 IU/ml), the SVR rate was 62 %. SVR in females was 72 % and 52 % for those with low and high viral loads, respectively.

Hemoglobin decrease within the treatment

The differences between baseline and week 12 HGB values are statistically significant (p< 0.001) for both males and females. The differences between baseline and week 4, as well as those between week 4 and week 12, did not reach the statistical significance in either gender (data not shown). Analysis of the absolute decreases in HGB levels (in g/l) and relative decreases (in % of the baseline value) proved that in week 12, the most common decrease in HGB level was up to 30 g/l for both genders (e.g. 36 % of male patients, and 48 % of females). On the other hand, the maximal drop in HGB level of >45 g/l during the therapy was observed in 29 % of males, but only in 13 % of the females. If the relative decrease in the percentage of baseline value was analyzed, the most prevalent decrease in week 12 was up to 20 % in both genders (39 % of males, and 43 % of females). A maximum drop of >40 % during the therapy was observed in 5 % of males and 6 % of females. The HGB decrease in g/l depends significantly on the baseline level for all time-points (week 4 p<0.001; week 12 p=0.001, and for the maximal decrease p<0.001). This is not the case for the relative decrease, where we only have proven a correlation between the baseline HGB level and week 4 (p=0.011). The percentage of decrease did not correlate with the baseline in week 12 (p=0.197), nor with the maximal decrease (p=0.148). At the end of follow-up, males with SVR achieved their minimal HGB level later (median = week 26), when compared with males without SVR (Fig. 1). This correlation was not achieved in females (p=0.729).

Predictors of SVR

Univariate logistic regression

Low viral load (HCV RNA <600 000 IU/ml) was not identified as a predictor of SVR in either gender (males p=0.535; females p=0.081). Age <35 years is a significant predictor of SVR for both genders. The overall predictive value of younger age is 70.7 % (OR 0.922, 0.894–0.951, p<0.001). The predictive values of younger age are 66.0 % and 77.6 % for males and females, respectively. RVR is the other significant predictor of SVR for both genders. The predictive value of RVR is 68.5 % (OR 13.391, 4.951–36.224, p<0.001).

Multivariate logistic regression

The results of the multivariate logistic regression analysis for males and females are shown in Tables 2 and 3 respectively. HGB levels as well as the parameters of HGB decrease seem to be more important in females than in males. The baseline HGB level ≤140 g/l was only identified as a significant predictor of SVR in females (not in males) in age-adjusted multivariate logistic regression (p=0.025). We have only identified one positive predictor in males: the lowest HGB level reached after week 19 of antiviral treatment (p=0.041; OR=2.274, (1.050–6.082)). Except for the predictors shown in Tables 2 and 3, we have also found significant associations of SVR with the parameters shown in Table 4 (age adjusted multivariate logistic regression for females).

Tab. 2. Multivariate logistic regression for males (n=97, backward stepwise).

Parameter	p	OR (95% IS)
Age at the begining of therapy >35 years	0.001	2.519 (0.825; 7.695)
RVR – not achieved	0.002	12.629 (2.585; 61.703)
Timepoint of lowest HB level >week 19	0.041	2.274 (1.050; 6.082)

Tab. 3. Multivariate logistic regression for females (n=67, backward stepwise).

Parameter	p	OR (95% IS)
Age at the begining of therapy >35 years	0.008	5.721 (1.589; 20.592)
RVR – not achieved	0.018	6.866 (1.395; 33.787)
Baseline HB level ≤140 g/l	0.025	4.877 (1.222; 19.457)
Maximum drop from baseline HB >40 g	0.039	0.275 (0.093; 0.917)
HB drop in week 4 >30 g	0.044	0.249 (0.107; 0.901)

Tab. 4. Age adjusted multivariate logistic regression for females (n=67).

Parameter combined with age	p	OR (95% IS)
HB drop in week 4 of therapy >30 g	0.041	0.238 (0.056; 0.925)
HB drop in week 12 of therapy >35 g	0.046	0.242 (0.091; 0.969)
Maximal drop in HB level >40 g	0.037	0.253 (0.070; 0.921)
% drop in HB level in week 4 of therapy >20 %	0.031	0.224 (0.057; 0.872)
% drop in HB level in week 12 of therapy >20 %	0.047	0.328 (0.123; 0.986)

Discussion

Anemia, which is mainly caused by hemolysis due to RBV administration, is a very well-known side-effect of standard antiviral therapy used for chronic HCV infection. The RBV dose has proven to be very important in regards to the SVR rate. Stepwise ribavirin reduction was associated with stepwise increase in re-

lapse rate from 11 % to 60 %. On the other hand, PegIFN dose could be reduced after week 12 with no relapse increment (10, 11).

In regular practice, i.e. outside the clinical trials, it is not usually possible to evaluate the plasma levels of RBVdue to high cost of the procedure. The IDEAL study (8) found a higher SVR rate among patients with HGB <100 g/l, and with RBV dose reductions (due to anemia; reductions defined by the trial protocol) during the treatment, when compared with those with HGB level ≥100 g/l (48.8 % vs 36.7 %, p<0.001). SVR was highly associated with the HGB decrease, namely: >3 g/dL, 43.7 %; ≤3 g/dL, 29.9 %; (p<0.001) (12). As anemia is a dose-dependent side-effect of ribavirin administration, we hypothesized that the degree of anemia could reflect the individual RBV exposure and therefore anemia might be a potential predictor of virological response.

To confirm this hypothesis, we have retrospectively analyzed those in our patient group treated with pegylated interferons in combination with RBV in 2000–2008. Solely the patients with recorded blood counts at defined time-points (±5 days) were included into the analysis, while the latter patients represent 62 % of all patients treated at our department in this particular period. We included the patients treated with both of available pegylated interferons into the study because we have used the same weighted limits for both variants for determining the RBV dose. In our overall group of patients, we have more than a 90 % prevalence of HCV genotype 1. Therefore, only the patients with this particular genotype have been included into the present study. The patients infected with non-1 HCV genotypes have been excluded. Due to local conditions, we had to change the PCR techniques used for HCV RNA detection several times within the study period. For the reproducibility of virological results, we have used only one PCR technique for the analysis of all the samples of any one individual patient within the study period (e.g. the sera of each patient were evaluated by only one technique). RBV dose reductions were applied in 16.5 % of all of our patients. This RBV reduction rate is lower than in the IDEAL study (30.2 %), or in the registration trials (3, 4) with PEG-IFN-2a (approx. 20 % in all sections, including placebo). This is likely due to strict rules for RBV dose reductions applied in the study protocol. In regular practice, the approach to anemia is not as rigorous as in clinical trials. On the other hand, we were not able to use EPO as a supportive treatment, as this is neither approved nor reimbursed in the Czech Republic.

To confirm our hypothesis, we have also performed several analyses of HGB decrease from the baseline level (absolute or relative HGB decrease), with respect to specified time-points. We have found that the parameters of HGB decrease are more significantly associated with SVR in females than in males. A baseline HGB level <140 g/l in both univariate and multivariate logistic regressions is a positive predictor of SVR only in women. We do not have a simple explanation for this finding. It is likely that multiple factors are involved. We had not measured the BMI or body surface of patients included into study, and both of these host-related factors have been associated with SVR. Lower amounts of liver iron deposits in women with lower HGB levels might as well play a role in this phenomenon. Liver iron has also been shown to be negatively associated with SVR (13).

In males, the only single parameter associated with SVR is the minimum HGB level reached after week 19 of antiviral treatment (Tab. 2 and Fig. 1). On the other hand, this was not the case in females. In females, we have identified a percentage of HGB decrease in weeks 4 and 12 (both absolute and relative) to be a significant positive predictor of response. All of these parameters were significantly associated with SVR (also in age-adjusted predictive models). In males, the OR for reaching the lowest HGB level after week 19 of treatment is comparable with the OR for younger ages (Tab. 2). In females, the comparable OR values were achieved for a baseline HGB level of ≤140 g/l, and age of ≤35 yrs. PPV and NPV were calculated for HGB levels slightly lower than average in week 12 for males and females. Data are not shown because the results do not allow us to recommend these HGB levels as a selection criterion for treatment decisions. Nevertheless, yet more convincing results of NPV were achieved for even lower HGB levels; still, this was lessened in significance by low numbers of patients in each subgroup.

We have also analyzed the standard virological factors known to be predictors of response, baseline viremia, and viral kinetics within the 12 weeks of antiviral treatment. We did not prove the positive predictive role of low baseline viremia (<600 000 IU/ml) for SVR. There was no significant difference in SVR rate in patients either with low or high baseline viremia (all patients: p=0.084; males: p=0.403; females: p=0.085). This unusual phenomenon might in part be caused by the changes in PCR techniques used within the study period for the evaluation of the baseline viremia. Less sensitive techniques used earlier could have under-evaluated the real levels of the viral load. This explanation is supported by the fact that we reached a statistically significant difference in SVR rate among patients with different types of early viral kinetics during the first 12 weeks of antiviral treatment. Both RVR and EVR are defined as a decrease from the baseline level, and thus as we have used the same technique in each particular patient, the relative error should be the same for all evaluations. RVR was proven as the strongest predictor of SVR for the entire group of patients, as well as for different subgroups (Tabs 2 and 3). Patients older than 35 years of age had a significantly lower SVR rate than younger ones (data not shown, all patients, males and females: p<0.001). As expected, the most important positive predictor of SVR was RVR. This was true for all subgroups of patients.

The low baseline viral load, as well as RVR, have been described as the most relevant predictors of SVR in many clinical trials. Zeuzem et al (14) has shown that HCV genotype 1 patients with low viral load (<600 000 IU/ml) may be treated for 24 instead of 48 weeks without any decrease in SVR rate. The overall SVR rate in this trial was 50 %. Ferenci et al (15) found that with the highest SVR rates in patients with RVR, the corresponding 74% NPV was however too low for any decision criterion. Among patients with RVR, their SVR rate was as high as 91 %.

The overall SVR rate in the present study was 63 %; the relapse rate was 18 %. The SVR rate in our study was higher than in registration trials with a combination of PEG-IFN + RBV (HCV genotype 1 patients: 46 % for PEG-IFN 2a + RBV, and 42 % for PEG-IFN 2b + RBV) (3, 4). The likely explanation for such a

high treatment efficacy is the demographic profile of our group of patients. We had younger patients (38 yrs vs 42 and 43 yrs); more than 40 % of them were former drug users with no comorbidities, and likely with shorter infection durations. In this retrospective analysis, we have not been able to verify the adherence to treatment; however, this is probably also much higher than in other populations and published trials. We believe that our group of patients was selected with regard to their generally good cooperation, high motivation, etc. In comparison with the registration trials, the most apparent objective difference is the percentage of patients with liver cirrhosis. In the present study, we had only 7 % of cirrhotics (32 % and 29 % in registration trials.

It has recently been shown that the most important host predictor of response to antiviral therapy in chronic HCV infections is the SNP of gene for IL28B (Thompson et al, 2010). Patients with CC genotype have a much greater likelihood of response than those with non-CC genotypes (CT or TT). It is estimated that this SNP is responsible for up to 60–70 % of all differences in SVR rates in different trials and geographic regions. Unfortunately, at the time we were designing our study, we did not have this information and therefore the genetic evaluation of IL-28B has not been included. As this SNP seems to play the key role among host-related predictive factors, the significance of all other parameters is smaller. However, we believe that our study brings greater insights to the matter of the development of anemia as a side effect of antiviral treatment of chronic hepatitis C.

Conclusions

The decrease in HGB parameters may serve as an additional predictive factor of SVR in patients with chronic HCV infection under antiviral treatment. This is particularly true for females. The most useful factors are a HGB decrease in weeks 4 and 12 of treatment. There was only one predictor identified for males, namely the reaching of the lowest HGB level after week 19. According to our results, these predictors might even be useful in the situation where the baseline viral load has a limited role in the prediction for SVR. On the other hand, the strongest predictor of SVR is still RVR. Therefore, the significance of early viral kinetics has been proven, even by our retrospective study.

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