

# 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)

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## INTRODUCTION

- ▶ Baseline viral load has recently become a very important predictive factor in the development of a treatment algorithm in patients with genotype 1 (G1), but it is not clear whether the cut-off of 600,000 or 800,000 IU/ml is ideal. Both were derived from former 2 million cp/ml due to different factors of the used PCR assay.
- ▶ The "Association of German Independent Gastroenterologists" (bng, Berufsverband Niedergelassener Gastroenterologen Deutschlands e.V.) in cooperation with Roche, Germany, is conducting a nationwide observational study including screening and treatment phases to determine the quality of treatment for chronic hepatitis C (CHC) in routine clinical practice.
- ▶ In preceding analyses of our data on predictive factors (DDW 2006, # 219003), the categorized baseline viral load (800,000 IU/ml) was not significant neither in uni- nor in multivariate analyses.

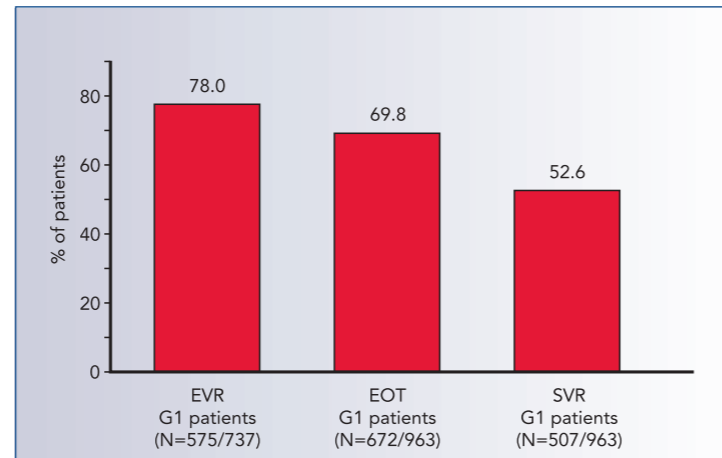


Figure 2. Virological response

- ▶ The documented data should reflect the clinical routine as intended by the doctors in charge. Therefore, the statistical analysis remains descriptive.
- ▶ Due to the ongoing character of the study, the status of data was frozen on May 31st, 2006, including queries solved.
- ▶ **Multivariate logistic regression (MLR) analyses:** To approximate the optimal cut-off for viral load, multivariate logistic regression analyses were performed in steps of 100,000 and subsequently 10,000 IU/ml. Statistical significance was evaluated by two-sided Fisher's exact test.
- ▶ **Receiver operating characteristic (ROC) curve:** The influence of logarithmized viral load on SVR was estimated as a continuous variable in univariate logistic regression (ULR) analysis and by analyzing the ROC curve. The optimized cut-off was then tested against both existing cut-offs in a MLR analysis.

## RESULTS

### Patients

- ▶ A total of 10326 treatment naive patient screenings (see Figure 1) have been completed and 4377 of these patients (42.4%) have been treated with peginterferon alfa-2a (40KD), in almost all cases plus ribavirin.
- ▶ Genotype 1 (G1) was diagnosed in 2522/4377 patients.
- ▶ In 1239/2522 G1 patients treatment documentation was finished. The mean age was 44.1 years. 58.1% of the patients were male. The mean BMI was 24.9 kg/m<sup>2</sup> and the mean duration of infection was 12.2 years.
- ▶ Sources of infection were (multiple answers possible): iv drug abuse 35.9%, transfusion 20.8% or medical measures 11.1%. The source of infection was unknown in 26.6% of the patients.
- ▶ In 118/1239 patients treatment was discontinued due to reasons not related to virological nonresponse or tolerability: lost-to-follow-up (n=49), personal reasons (n=30), lack of compliance (n=24), concomitant disease (n=5) or other reason (n=10).
- ▶ In 158/1239 patients the data cleaning process is still ongoing.
- ▶ The remaining 963 G1 patients formed the database for the following evaluation. These patients were treated according to the current consensus recommendations (i.e. treatment according to guidelines or

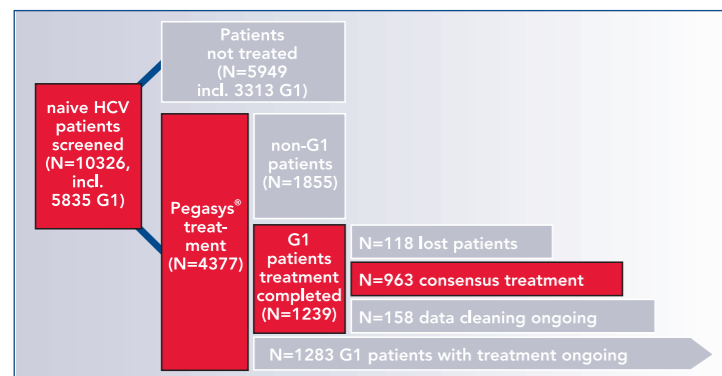


Figure 1. Study patients

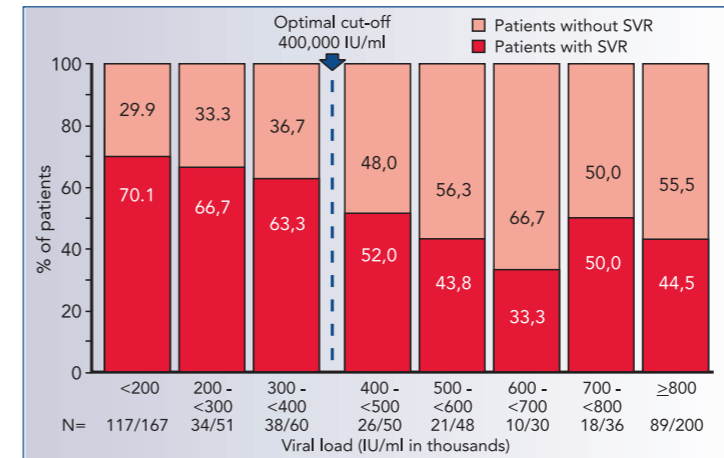


Figure 3. Cut-off categories and SVR rates

- discontinuation due to insufficient efficacy or tolerability). In 727/963 patients (75.5%) treatment was completed as planned. 236/963 patients (24.5%) discontinued treatment either due to insufficient efficacy (n=159, 16.5%) and/or to insufficient tolerability (n=89, 9.2%).
- ▶ Cut-off data set: In 642 patients viral load was documented in IU/ml.

### Virological response

- ▶ Early Virological Response: 575 of 737 G1 patients (78.0%) achieved an Early Virological Response at week 12 (EVR;  $\geq 2$ -log<sub>10</sub> drop in HCV RNA or HCV RNA undetectable; see Figure 2).
- ▶ EOT-Responses were achieved by 672 of 963 G1 patients (69.8%).
- ▶ Sustained Virological Response (SVR) was achieved by 507 of 963 G1 patients (52.6%).

### MLR analyses of viral load

- ▶ For the 642 patients of the cut-off data set, the optimal cut-off to discriminate between high and low viral load was 460,000 IU/ml (p<.0001).
- ▶ Figure 3 demonstrates the descriptive SVR rates for different cut-offs according to the cut-off categories of the first approximation of MLR analysis.

### ROC analysis of viral load

- ▶ In the ULR analysis continuous viral load was a strong predictor of SVR (p<.0001, OR=0.79, CI:0.69-0.89), but the effect of viral load was non-linear. The ROC-plot revealed a cut-off level of viral load of 5.6 log<sub>10</sub> IU/ml (~400,000 IU/ml).
- ▶ According to this result, an additional discrete cut-off level of 400,000 IU/ml in addition to the old ones (600,000 and 800,000 IU/ml) was compared by MLR analysis. 400,000 IU/ml was the best cut-off level (<.0001, OR=0.48, CI:0.37-0.63) between LVL and HVL.
- ▶ Using this cut-off of 400,000 IU/ml, G1 patients with LVL reached SVR rates of 62.0% and with HVL 43.7%. SVR-rates of other viral load cut-offs are shown in Figure 4. While SVR in patients with LVL increased with decreasing cut-off levels, SVR in patients using different HVL cut-offs remained at 43%. This result indicated that patients with higher viral load than 400,000 IU/ml had similar low SVR rates as patients with viral load of more than 800,000/ml and belong to the same category.

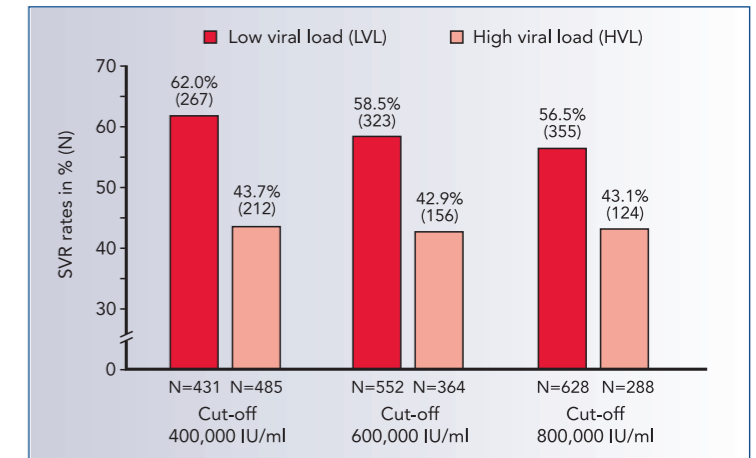


Figure 4. SVR in patients with LVL and HVL and different cut-offs

### Other predictive factors

- ▶ In order to identify other reliable predictive factors for the response to treatment, the following factors were estimated: age <40 years, BMI <25 kg/m<sup>2</sup>, sex (m/f), GPT male  $\geq 50$ , female  $\geq 35$  U/l, GGT male  $\geq 66$ , female  $\geq 39$  U/l, platelets  $\geq 150,000$  / $\mu$ l, serum ferritin <200  $\mu$ g/l (p>0.001) and VL (<400,000 IU/ml HCV RNA).
- ▶ In univariate analyses, all above predictions could be established significantly except for gender.
- ▶ In a multivariate analysis, age was the strongest independent significant predictive factor (p<.0001, OR=0.32, CI:0.19-0.52) controlled for the effect of GGT (p<.002, OR=0.48, CI:0.22-0.86), serum ferritin (p<.006, OR=0.49, CI:0.30-0.81), platelets (p<0.017, OR=0.43, CI:0.22-0.86) and VL (p<.022, OR=0.58, CI:0.37-0.93). GPT (p<.243), BMI (p<.592) and gender (p<.611) were non-significant.
- ▶ The best baseline predictors for chance of cure with antiviral therapy in HCV-patients are age <40 years, normal GGT, normal serum ferritin, normal platelets (>150,000) and a VL <400,000 IU/ml HCV-RNA. The determining of a new cut-off for low and high VL revealed that even under real life conditions VL is an important predictive factor of treatment outcome.

## CONCLUSION

- ▶ The well accepted formerly used cut-off of 2 million cp/ml translated with different factors into IU/ml was statistically optimized for treatment with standard interferon.
- ▶ The determining of a new cut-off for low and high VL revealed that even under real life conditions VL is an important predictive factor of treatment outcome.
- ▶ In the era of pegylated interferon this cut-off is not the best way to differentiate between LVL and HVL with regard to SVR. To use VL as a reliable predictor of successful treatment outcome in hepatitis C the optimized cut-off of 400,000 IU/ml should be adopted in the future.