Evaluation of a Predictive Model of Individual Chance for Sustained Virological Response in Patients with Chronic Hepatitis C Treated with Peginterferon alfa-2a and Ribavirin

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INTRODUCTION

- Success of HCV treatment is known to be dependent on various factors. By counseling a patient before therapy these variables play a crucial role. For this a response calculator based on baseline variables as well as RVR and EVR may be helpful to guide treatment decisions.
- Recently, Martens et al.[1] presented a response calculator derived from data of 949 patients treated in various German multi-center clinical trials. Three models were proposed using defined baseline factors and, if available, serum HCV RNA at week 4 and week 12 to predict sustained virological response (SVR) for individual patients. The models showed good predictive values for patients treated under study conditions (area under ROC 0.77, 0.84 and 0.86, respectively).

OBJECTIVE

- Aim of this analysis is to evaluate the proposed response calculator for the success of the treatment of cHC-patients in an unselected cohort under routine clinical practice.

METHODS

- We applied the proposed response calculator on data of 7266 patients included in a nationwide observational study conducted by the Association of German Gastroenterologists in Private Practice (bng) together with Roche to evaluate the predictive value of this calculator for an unselected cohort of patients treated with Peginterferon alfa-2a and ribavirin under real life conditions.
- The data base of this evaluation is part of a large ongoing German multicentre, open-label observational study including anti-HCV-positive adults with detectable HCV RNA. The nature of this study allowed dosing and duration of both peginterferon alfa-2a (40KD) and ribavirin to be at the discretion of the physician.
- The screening data include age, sex, weight, height, duration and source of infection, prior antiviral treatment, clinical symptoms, histology, genotype, viral load, concomitant diseases and social status.
- This data set includes patients who completed treatment with peginterferon alfa-2a (40KD) plus ribavirin. The data collection was performed online via the internet. The documented data should reflect the clinical routine as intended by the doctors in charge.
- Due to the ongoing character of the study, the status of data was frozen on September 1st, 2008, including queries solved.
- For the evaluation of the response calculator the calculation procedure of Martens et al.[1] was used. This procedure included estimation steps in case of missing data.
- The evaluation was performed for two data sets:
  - ALL: All patients (N=7266) representing real life data.
  - STUDY: Selection of patients representing „study conditions" (N=4522): treatment naiv, non-HIV, non-HBV and treated according to consensus recommendations (treatment duration, discontinuation only because of non-response or poor tolerability and EOT/SVR data available).

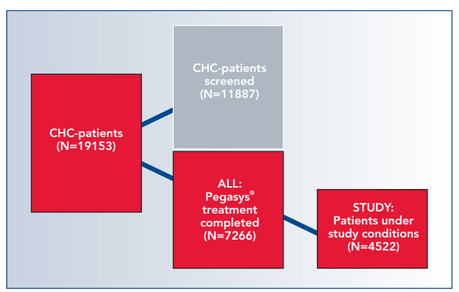

Figure 1. Study patients

Table 1: Baseline data

	Patients treated with PEG + RBV
N	N=7266
Sex (male / female)	61.4% / 38.6%
Age (mean ± SD in years)	42.0 ± 12.0
BMI (mean ± SD in kg/m²)	25.0 ± 4.2
Duration of infection (mean ± SD in years)	12.1 ± 8.9
Genotype 1	57.4
2	7.9
3	31.2
4	3.1
5	0.2
6	0.2

RESULTS

Patients

- Until September 2008 the online data documentation has been completed for a total of 19153 cHC patients including:
  - 11887 patients with screening data and
  - 7266 patients with completed treatment with peginterferon alfa-2a (40KD) in almost all cases plus ribavirin.

  (see figure 1)
- The demographic data for the 7266 CHC-patients being treated are shown in Table 1.

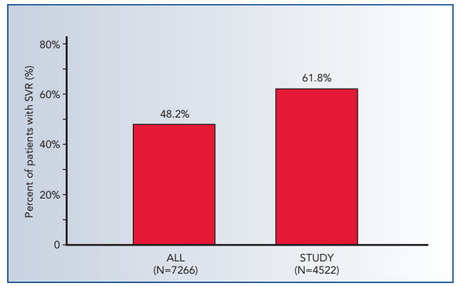

Figure 2. Sustained virological response (SVR)

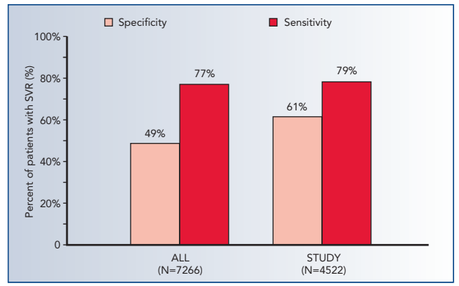

Figure 3. Specificity and sensitivity

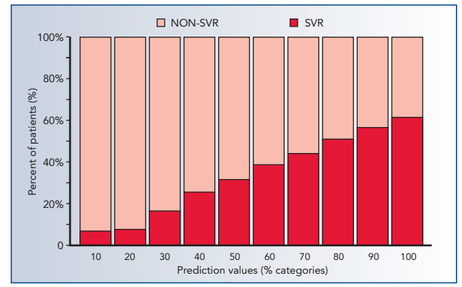

Figure 4. Comparing SVR rates with prediction values (ALL)

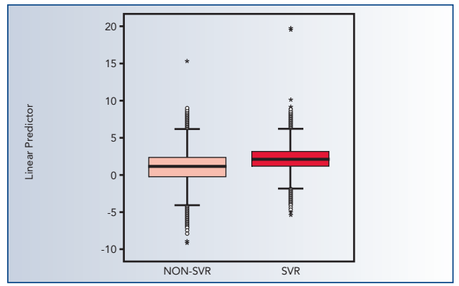

Figure 5. Boxplots of linear predictor (ALL)

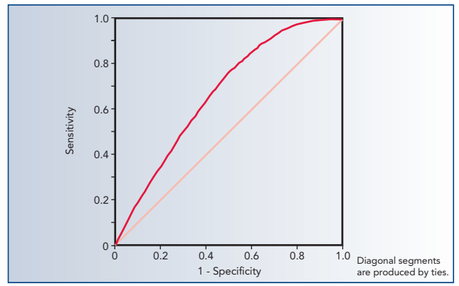

Figure 6. Area under ROC (ALL)

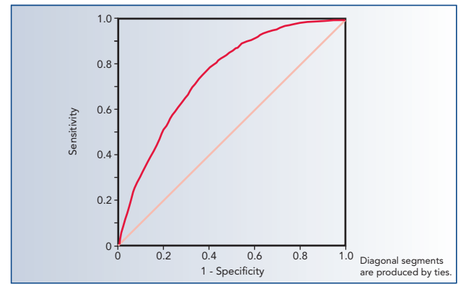

Figure 7. Area under ROC (STUDY)

Evaluation ALL

- The SVR rate over all patients (N=7266) was 48.2% (see Figure 2).
- The prediction of SVR by the response calculator yielded a specificity of 49% and an sensitivity of 77% (see Figure 3). The predictive behaviour is shown in Figure 4.
- Boxplots of predicting SVR vs. Non-SVR are shown in Figure 5.
- Evaluation of the model in this cohort yielded an area under ROC of 0.67 (see Figure 6).
- Evaluation in defined subgroups demonstrated that these factors were addressed adequately by the algorithm:
  - GT 1/4/5/6 vs. GT 2/3,
  - HCV RNA ≤400,000 IU/mL vs. >400,000 IU/mL,
  - age ≤40 years vs. >40 years,
  - total cholesterol ≤180 mg/dL vs. >180 mg/dL,
  - fibrosis yes vs. no,
  - ALT normal vs. high,
  - GGT normal vs. high.
- Furthermore, potential factors not included in the prediction showed similar area under ROC values with consistently lower rates of SVR for all analyzed populations:
  - with/without concomitant diseases (area under ROC 0.68/0.65),
  - with/without HIV co-infection (area under ROC 0.69/0.67),
  - with/without diabetes mellitus (area under ROC 0.66/0.67),
  - IVDU yes/no (area under ROC 0.67/0.67),
  - patients with essential hypertension (N=165; area under ROC 0.77).
- This indicates comparable predictive values for all these subgroups of patients and a lower probability of SVR in this real life cohort (overall SVR rate was 48.2% in the observational study compared with 59.6% in the study patients).

Evaluation STUDY

- To confirm the results of Martens et al., the response calculator was evaluated in a selected group of patients from the cohort simulating „study conditions" as described in methods.
- The SVR rate for the STUDY-patients (N=4522) was 61.8% (see Figure 2).
- The prediction of SVR by the response calculator yielded a specificity of 61% and an sensitivity of 79% (see Figure 3).
- In the STUDY-group the evaluation of the model yielded an area under ROC of 0.76 (see Figure 7).

CONCLUSIONS

- Evaluation of a response calculator derived from study data in an unselected cohort showed a lower predictive value than for study patients.
- Evaluating the response calculator in a selected group of patients from the cohort simulating „study conditions" showed better predictive values coming nearer to the results of study data.
- In routine clinical practice the lack of structured patient selection may result in the introduction of additional factors influencing treatment success and may shift the relative weight of the variables of the response calculator developed in study patients.
- Further analysis is necessary to include these factors in the model.

References

[1] Martens S et al. Poster presented at the EASL 2007, Barcelona

Presented at the Digestive Disease Week (DDW), May 30-June 4, 2009, Chicago, Illinois, USA.

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