The Role of Cholesterol on Sustained Virological Response (SVR) in the Treatment of Genotype 1-Infected Hepatitis C (CHC) Patients with Peginterferon alfa-2a (PEG) and Ribavirin (RBV)

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INTRODUCTION

- HCV life cycle is associated with cholesterol metabolism in host cells. So, cholesterol lowering drugs as statins are under discussion to inhibit HCV RNA replication. Otherwise, clinical researchers recently found that higher cholesterol levels are significant positive predictive factors on Sustained virological response (SVR).
- 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.

OBJECTIVE

- Aim of this analysis is to evaluate the role of cholesterol in the treatment of cHC-patients with genotype 1 under real life conditions.

METHODS

- 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. Therefore, the statistical analysis remains descriptive.
- Due to the ongoing character of the study, the status of data was frozen on May 15th, 2007, including queries solved.

RESULTS

Patients

- Until May 2007 the online data documentation has been completed for a total of 13590 cHC patients including:
  - 9532 patients with screening data and
  - 4058 patients with completed treatment with peginterferon alfa-2a (40KD) in almost all cases plus ribavirin.
- Cholesterol was specified in 2432 of the 4058 patients:
  - Cholesterol was normal in 1783 patients and
  - Cholesterol was elevated (>200 mg/dl; >5.2 mmol/l) in 649 patients.
- In 1429 of the 2432 patients genotype (GT) 1 was specified.
- The proportion of GT1-patients was lower in patients with normal cholesterol (999 of 1783 patients; 56.0%) than in patients with elevated cholesterol (430 of 649 patients; 66.3%).
- Two populations were defined:
  - Group N: cholesterol was normal in 999 GT1-patients (69.9%) and
  - Group E: cholesterol was elevated (>200 mg/dl; >5.2 mmol/l) in 430 GT1-patients (30.1%; see Figure 1).

Baseline data

- Baseline data were: mean age 44.4 (N) vs. 45.3 (E) years, rate of male patients 61.4% (N) vs. 53.7% (E), mean BMI 25.3 kg/m² for both groups, rate of patients with concomitant diseases 52.7% (N) vs. 56.3% (E). Baseline data for both groups are presented in Table 1.
- In the group with elevated cholesterol more female patients (46% for E vs. 39% for N) were included.
- The mean duration of infection was 12.5 years for group N and 12.9 years for group E.
- Sources of infection were: i.v. drug abuse 34.2% (N) vs. 33.3% (E), transfusion 22.4% (N) vs. 23.7 (E), medical action 9.7% (N) vs. 13.5% (E), unknown 27.6% (N) vs. 25.1% (E) (multiple answers possible).
- A high viral load (cut-off 400.000 IU/ml) was found in 56.9% of group N and in 57.8% of group E (see Figure 2).
- Histologic findings were available in about 1/3 of the patients: A fibrosis (≥2 acc. to Desmet-Scheuer) was specified in 49.9% (N) in contrast to 33.3% (E) (p≤0.001; see Figure 2).

Virological response

- Rapid virological response (RVR): A RVR (defined as HCV RNA ≤50 IU/ml and/or HCV RNA qualitatively undetectable) was achieved in 14.3% of group N and in 21.6% of group E (see Figure 3).

Table 1: Baseline data of genotype 1-patients with completed treatment

	Group N (Cholesterol normal)	Group E (Cholesterol >200 mg/dl)
N	N=999	N=430
Sex (male / female)	61.4% / 38.6%	53.7% / 46.3%
Age (mean ± SD in years)	44.4 ± 12.5	45.3 ± 11.8
Weight (mean ± SD in kg)	75.6 ± 14.6	74.7 ± 12.9
BMI (mean ± SD in kg/m²)	25.3 ± 4.4	25.3 ± 3.8
Duration of infection (years)	12.5 ± 9.5	12.9 ± 9.0

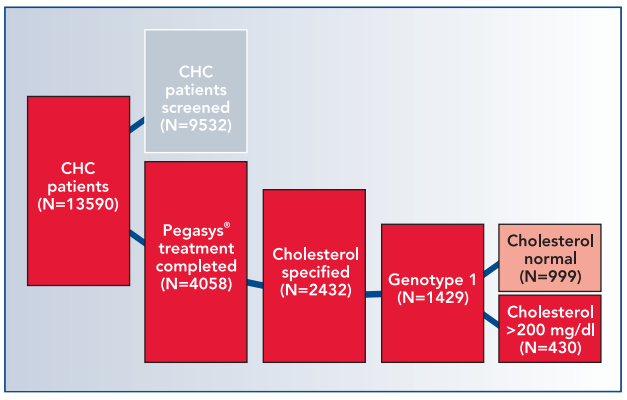

Figure 1. Study patients

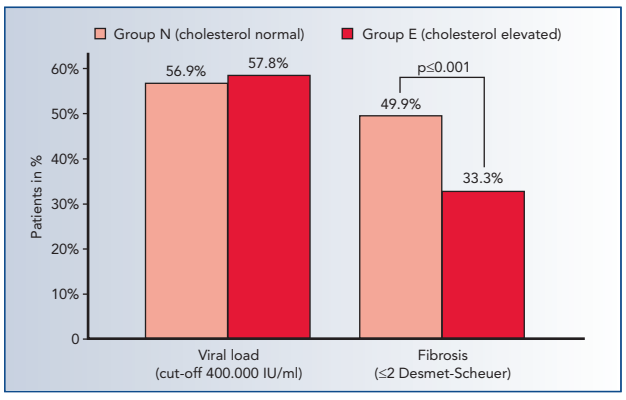

Figure 2. Baseline data

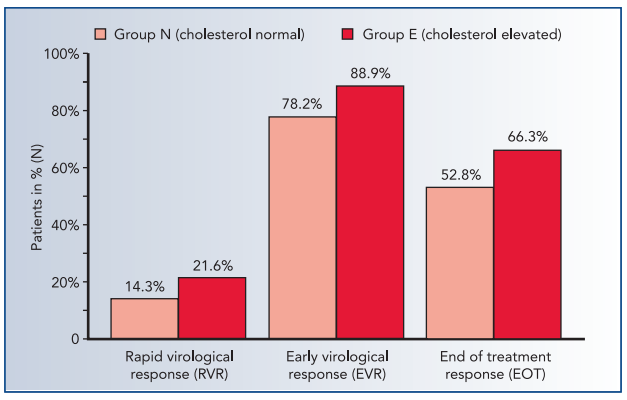

Figure 3. RVR, EVR and EOT

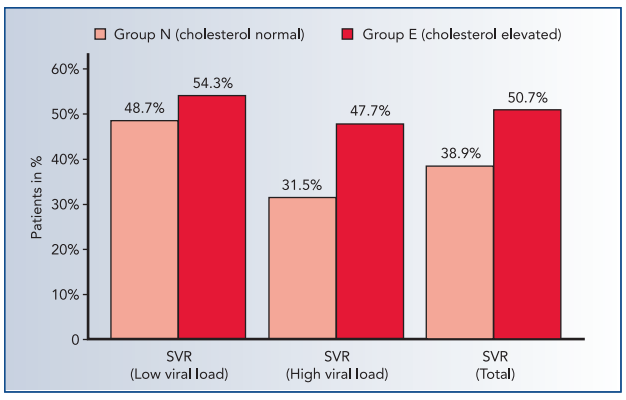

Figure 4. SVR

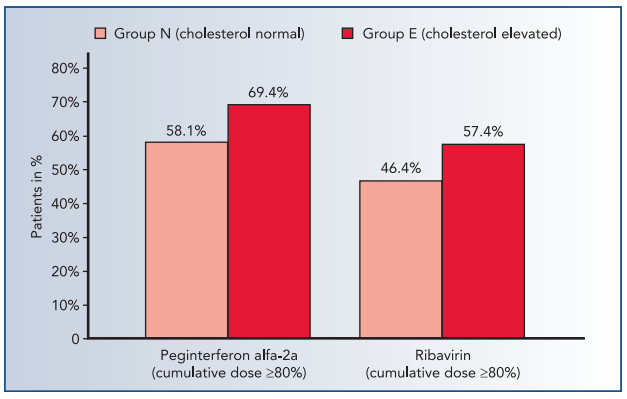

Figure 5. Cumulative doses

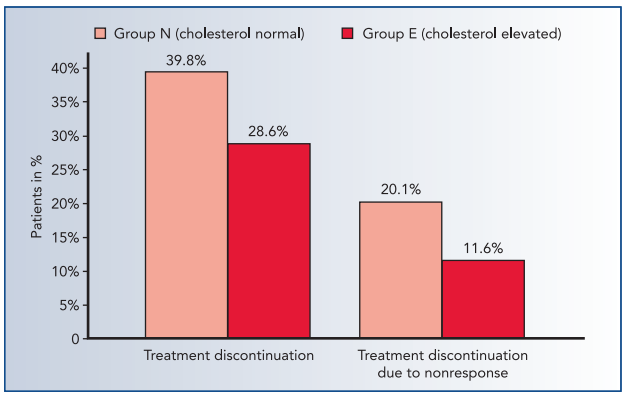

Figure 6. Discontinuation rates

- Early virological responses (EVR): An EVR (defined as ≥2-$\log_{10}$ drop in HCV RNA and/or HCV RNA ≤50 IU/ml and/or HCV RNA qualitatively undetectable) was achieved in 78.2% of group N and in 88.9% of group E (see Figure 3).
- End of treatment response (EOT): An EOT (defined as HCV RNA ≤50 IU/ml and/or HCV RNA qualitatively undetectable) was achieved in 52.8% of group N and in 66.3% of group E (see Figure 3).
- Sustained virological response (SVR): a SVR (defined as HCV RNA ≤50 IU/ml and/or HCV RNA undetectable after 24 weeks of follow-up) was achieved in 38.9% of group N and in 50.7% of group E. The SVR results differ according to viral load:
  - High viral load: A SVR was achieved in 31.5% of group N vs. 47.7% in group E.
  - Low viral load: A SVR was achieved in 48.7% of group N vs. 54.3% in group E (see Figure 4).

Treatment

- Differences between patients with normal vs. elevated cholesterol were seen in the cumulative doses for 48 weeks:
  - Peginterferon alfa-2a: 58.1% of group N vs. 69.4% of group E received ≥80% of the recommended dose.
  - Ribavirin: 46.4% of group N vs. 57.4% of group E received ≥80% of the recommended dose (see Figure 5).

Treatment discontinuations

- Treatment was discontinued in 39.8% (N) vs. 28.6% (E) of patients.
- Discontinuation rates due to virological nonresponse were 20.1% for patients with normal cholesterol (group N) compared to 11.6% for patients with elevated cholesterol (group E). Other reasons for withdrawal were comparable between both groups.

CONCLUSIONS

- About one third of the patients had elevated cholesterol >200 mg/dl (>5.2 mmol/l).
- In patients with available liver biopsy, patients with elevated cholesterol had a lower proportion of patients with advanced fibrosis (33%) vs. patients with normal cholesterol (50%) (p≤0.001).
- Despite the same viral load at baseline, better virological responses in patients with elevated cholesterol were observed. Apart from a direct biological effect in patients with higher cholesterol, additional causes may be a lower rate of advanced fibrosis and a better tolerance of interferon based therapy in patients with elevated cholesterol.

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