

The Role of Glomerular Filtration Rate (GFR) for Treatment with Peginterferon alfa-2A (40KD) and Ribavirin in Patients with Chronic Hepatitis C (CHC)

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INTRODUCTION

- Concerning importance of sufficient application of Ribavirin (RBV) the question was raised several times in the past whether dosing according to glomerular filtration rate (GFR) would be more optimal than to body weight.
- 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

- The aim of this observational study was to evaluate the influence of GFR in connection with standardised Ribavirin doses on sustained virological response (SVR), tolerability and Ribavirin dose-adjustment in everyday practice.

METHODS

- This evaluation is part of a large ongoing German multi-centre, 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 treatment naive patients who initiated 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 31st, 2006, including queries solved.
- To analyse GFR (in ml/min/1.73m²) the method of Mayo Clinic (Rule AD et al., Ann. Intern Med. 2004) was used according to KDOQI-categorisation.

GFR acc. to Mayo

$$\text{GFR} = \exp(1.911 + \frac{5.249}{\text{SCr}} - \frac{2.114}{\text{SCr}^2} - 0.00686 \times \text{Age} - 0.205 \text{ (if female)})$$

GFR = glomerular filtration rate (ml/min/1.73m²)

SCr = serum creatinine (mg/dl). If SCr < 0.8 mg/dl, use 0.8 for SCr.

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.
- In 3111/4377 patients treatment documentation was finished.
- In 1615/3111 patients a complete data set including GFR, SVR, Ribavirin dose, adverse events clinical symptoms and haemoglobin was available.
- The main focus was on 2 groups (see Table 1):
 - NORMAL:** 92.8% (N=1498/1615) of the patients had a GFR >90 ml/min/1.73m².
 - LOW-RENAL:** 6.6% (N=107/1615) of the patients had a GFR >60-90 ml/min/1.73m² indicating a minor confinement of renal function.
- 10 patients had GFR ≤ 60 ml/min/1.73m².

Baseline data

- Baseline data of both groups were: male sex 62.1% in **NORMAL** vs. 29.9% in **LOW-RENAL**; age (yrs) 40.1 in **NORMAL** vs. 57.3 in **LOW-RENAL**; BMI (kg/m²) 24.9 in **NORMAL** vs. 25.8 in **LOW-RENAL** (see Table 1).
- The duration of infection was 11.0 years in **NORMAL** and 16.7 years in **LOW-RENAL**.
- In **NORMAL** 55.5% (N=831/1498) had Genotype 1/4 whereas in **LOW-RENAL** 81.3% (N=87/107) Genotype 1/4-patients were found.
- A cirrhosis as a clinical finding was specified in 3.0% of the patients of **NORMAL** and in 9.3% of the patients of **LOW-RENAL** (see Figure 2).

Virological response

- Sustained virological response (SVR; HCV RNA undetectable) differs from 61.4% (N=920/1498) in **NORMAL** to 41.1% (N=44/107) in **LOW-RENAL** (see Figure 3).

Table 1: Baseline data

| | NORMAL (GFR* > 90) | LOW-RENAL (GFR* >60 - 90) | GFR* ≤60 | Total |
|---------------------------------------|------------------------------|-------------------------------------|-----------------|--------------|
| N | N=1498 | N=107 | N=10 | N=1615 |
| Sex (male / female) | 62% / 38% | 30% / 70% | 60% / 40% | 60% / 40% |
| Age (mean ± SD in years) | 40.1 ± 11.3 | 57.3 ± 13.1 | 44.9 ± 11.7 | 41.3 ± 12.2 |
| Weight (mean ± SD in kg) | 74.9 ± 15.0 | 72.1 ± 13.2 | 69.8 ± 9.9 | 74.7 ± 14.9 |
| BMI (mean ± SD in kg/m ²) | 24.9 ± 4.3 | 25.8 ± 4.5 | 24.5 ± 3.5 | 24.9 ± 4.3 |
| Duration of infection (years) | 11.0 ± 8.4 | 16.7 ± 11.3 | 7.3 ± 9.9 | 11.4 ± 8.8 |

* Glomerular Filtration Rate in ml/min/1,73m²

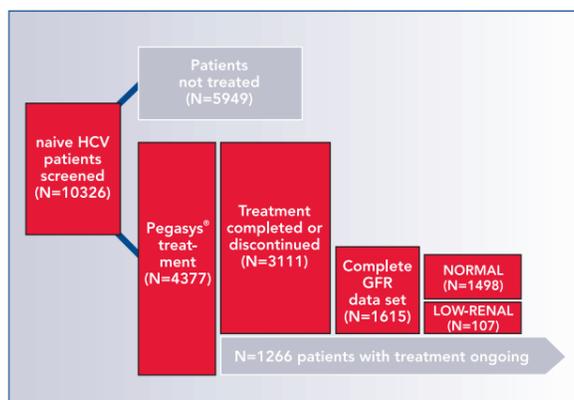


Figure 1. Study patients

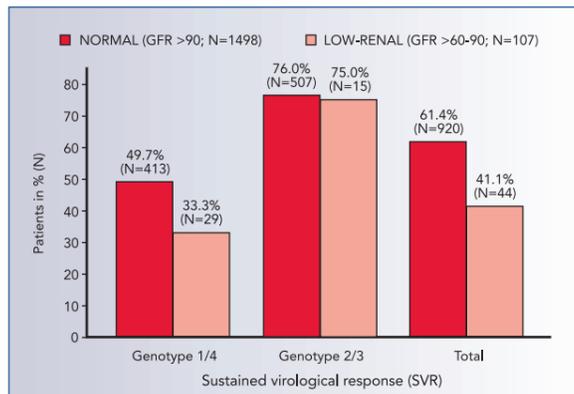


Figure 3. Sustained virological response

- Notably, Genotype 1/4-patients achieve only 33.3% in **LOW-RENAL** vs. 49.7% in **NORMAL**.

Safety

- The rate of discontinuation was 20.7% in **NORMAL** vs. 29.0% in **LOW-RENAL**.
- Concerning special side effects of Ribavirin, anaemia was more frequent in **LOW-RENAL** (35.5%) than in **NORMAL** (16.1%; see Figure 4).
- The same trend was found for skin alterations (**NORMAL**: 18.4%; **LOW-RENAL**: 27.1%) but not for cough (see Figure 4).

Ribavirin

- The mean initial dose of Ribavirin was 954.7 mg/d in **NORMAL** and 988.8 mg/d in **LOW-RENAL** (see Figure 5).
- However, the cumulative dose of Ribavirin was 88.2% of calculated dose according to guidelines in **NORMAL** versus 74.7% in **LOW-RENAL** (see Figure 6).

CONCLUSIONS

- Renal function measured by GFR plays an important role in achieving SVR. Distinct differences were found in genotype, sex and age but not in BMI and weight between patients with GFR <90 (**NORMAL**) and patients with GFR >60-90 (**LOW-RENAL**).
- Since weight based dosing of Ribavirin does not consider these facts, patients with constricted renal function suffer more side effects and get worse SVR rates maybe due to non-optimal Ribavirin dosing.
- A need for optimal RBV dosing is evident in **LOW-RENAL** GT1/4-patients with low SVR and high AE rates. Lower cumulative RBV-doses following comparable initial doses of RBV indicate dose reductions of RBV during treatment. It may be discussed, if a dose adjustment of RBV acc. to renal function would have optimised treatment success.

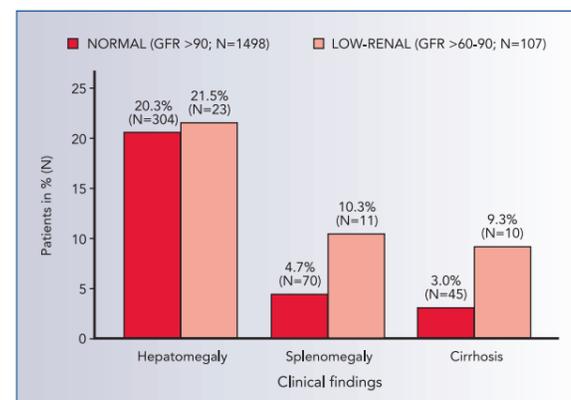


Figure 2. Clinical findings

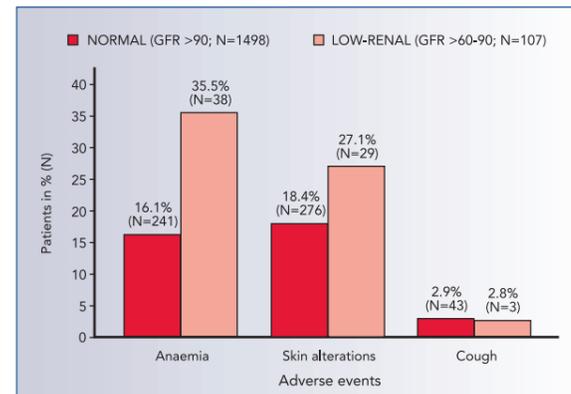


Figure 4. Adverse events

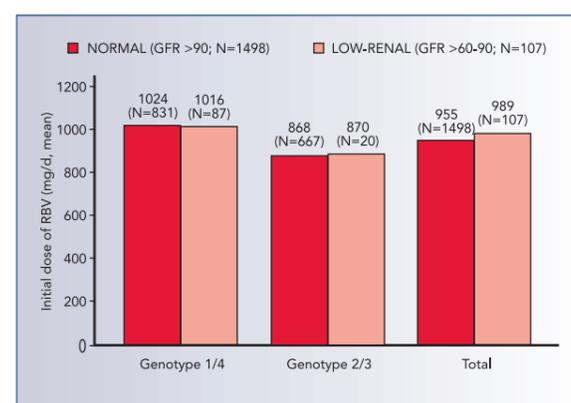


Figure 5. Initial dose of Ribavirin

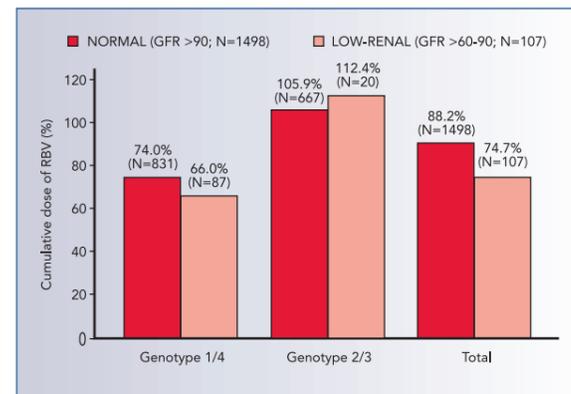


Figure 6. Cumulative dose of Ribavirin