

Safety Recommendations for Laboratory Values in Specific Product Characteristics (SPC) of Peginterferon alfa-2a (PEG) and Ribavirin (RBV). What Happens Under Real Life Conditions?

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INTRODUCTION

- The "Association of German Gastroenterologists in Private Practice" (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.
- Recommendations of Specific Product Characteristics (SPC) are derived from forced conditions in pivotal trials. A very important part concerns haematological laboratory data at start and during therapy. However, data on the adherence to SPC recommendations are missing.

- adults with detectable HCV RNA. The nature of this study allowed dosing and duration of both peginterferon alfa-2a (40KD) and RBV to be at the discretion of the physician.
- The study procedure includes a screening of all incoming patients with hepatitis C and, in case of treatment with peginterferon alfa-2a (40KD) (PEGASY[®]) plus ribavirin, a documentation of the therapy.
- 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.
- Laboratory parameters being specified at screening and during therapy (week 2, 4, 8, 12, 24 and 48) were neutrophils, platelets and haemoglobin.
- 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.

RESULTS

Patients

- A total of 10,326 treatment naive patient screenings have been completed and 4,377 of these patients (42.4%) have been treated with peginterferon alfa-2a (40KD), in almost all cases plus ribavirin.
- The demographic data of the 4,377 patients are demonstrated in Table 1.

Table 1: Demographic Data

	Patients
N	4,377
Age (yrs)	41.2 ± 12.1
Gender male/female	61.3% / 38.7%
BMI (kg/m ²)	24.9 ± 4.2
Duration of infection (yrs)	11.2 ± 8.7
Genotype 1	57.6%
2 / 3	39.3%
4 / 5 / 6	3.1%

Baseline Parameters

- In a small part of the patients HCV treatment was initiated despite baseline values below the recommended haematological parameters (see Figure 1):
 - Neutrophils: 2.7% had neutrophils < 1,500 /µl.
 - Platelets: 2.7% had platelets < 90,000 /µl.
 - Haemoglobin: 3.4% had haemoglobin < 12 g/dl.
- In 7.5% of the patients the HCV treatment was initiated although at least one of the above laboratory parameter was below the recommended cut-off of the SPC (see Figure 1).

OBJECTIVE

- The main aim of this ongoing study on the treatment of HCV patients is to perform an evaluation of clinical routine treatment in everyday practice beyond controlled studies. This analysis provides data describing the treatment behaviour if laboratory data achieve or exceed recommended cut-off values of the SPC.

METHODS

- This evaluation is part of a large ongoing German multicentre, open-label observational study including anti-HCV-positive

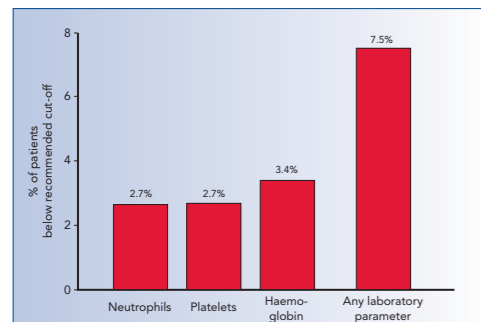


Fig. 1. Baseline parameters below the recommended cut-off of the SPC

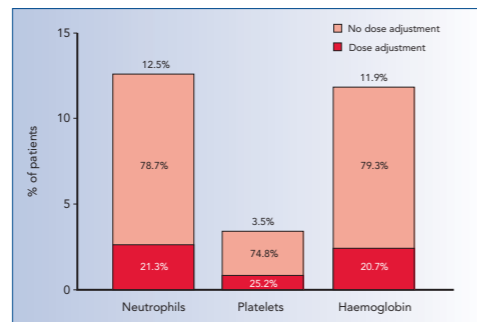


Fig. 2. Patients with laboratory parameters below the recommended cut-offs of the SPC during treatment and rates of dose adjustments of PEG and/or RBV

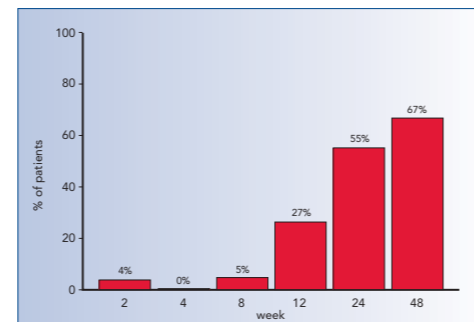


Fig. 3. Discontinuations of HCV treatment according to neutrophils below cut-off (< 500 /µl)

Dose Adjustment

- During the entire treatment period, the following results were observed (see Figure 2):
 - Neutrophils: In 12.5% neutrophils decreased to < 750 /µl at any time. No adjustment of PEG in 78.7%.
 - Platelets: In 3.5% platelets decreased to < 50,000 /µl (but ≥ 25,000 /µl) at any time. No adjustment of PEG in 74.8%.
 - Haemoglobin: In 11.9% haemoglobin decreased to < 10 mg/dl (but ≥ 8.5 mg/dl) at any time. No adjustment of RBV in 79.3%.
- Rates of patients with laboratory values below the recommended range and dose adjustments during the course of treatment are demonstrated in Table 2.

Table 2: Laboratory Data and Dose Adjustments

	week					
	2	4	8	12	24	48
Neutrophils*	2.8	4.8	5.1	5.7	4.6	3.1
% PEG not adjusted	78.9	77.6	73.7	81.3	78.5	68.8
Platelets**	0.9	1.5	2.3	2.2	1.8	1.5
% PEG not adjusted	67.7	67.3	68.4	77.6	70.0	80.8
Haemoglobin***	0.9	3.6	5.2	5.9	6.8	7.0
% RBV not adjusted	82.8	83.5	77.8	80.3	84.2	80.0

* % of patients with neutrophils < 750 /µl
 ** % of patients with platelets < 50,000 and ≥ 25,000 /µl
 *** % of patients with haemoglobin < 10 and ≥ 8.5 mg/dl

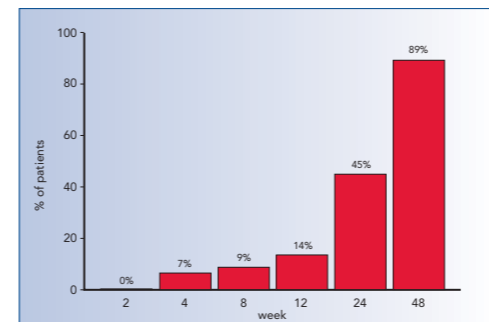


Fig. 4. Discontinuations of HCV treatment according to platelets below cut-off (< 25,000 /µl)

Treatment Discontinuations

- Neutrophils: During the entire treatment, in 3.0% of the patients neutrophils decreased to < 500 /µl (up to 1.2% per visit):
 - Weeks 2, 4 and 8: The discontinuation rate for these patients was 5% or less.
 - Weeks 12, 24 and 48: At week 12 the discontinuation rate was 27% and increased to 67% at week 48 (see Figure 3).
- Platelets: During the entire treatment, in 1.2% of the patients platelets decreased to < 25,000 /µl (up to 0.6% per visit):
 - Weeks 2, 4, 8 and 12: The discontinuation rate for these patients was 14% or less.
 - Weeks 24 and 48: At week 24 the discontinuation rate was 45% and increased to 89% at week 48 (see Figure 4).
- Haemoglobin: During treatment, in 1.6% of the patients haemoglobin decreased to < 8.5 mg/dl (up to 0.9% per visit):
 - Weeks 2, 4, 8 and 12: The discontinuation rate for these patients was 31% or less.
 - Weeks 24 and 48: At week 24 the discontinuation rate was 64% and increased to 93% at week 48 (see Figure 5).

Virological Response

- Neutrophils:
 - Neutrophils ≥ 750 /µl: SVR (Sustained Virological Response) 60.6% (N=1037/1711).
 - Neutrophils < 750 /µl: SVR 60.8% (N=161/265).
 - Neutrophils < 500 /µl: SVR 55.8% (N=29/52).
- Platelets:
 - Platelets ≥ 50,000 /µl: SVR 61.9% (N=1161/1877).
 - Platelets < 50,000 and ≥ 25,000 /µl: SVR 38.4% (N=28/73).
 - Platelets < 25,000 /µl: SVR 34.6% (N=9/26).

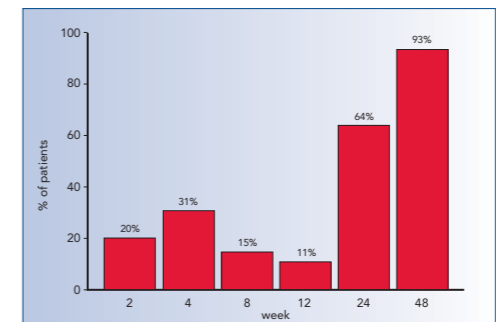


Fig. 5. Discontinuations of HCV treatment according to haemoglobin below cut-off (< 8.5 mg/dl)

- Haemoglobin:
 - Haemoglobin ≥ 10 mg/dl: SVR 61.2% (N=1025/1675).
 - Haemoglobin < 10 and ≥ 8.5 mg/dl: SVR 57.8% (N=149/258).
 - Haemoglobin < 8.5 mg/dl: SVR 47.2% (N=17/36) (see Figure 6).

Adverse Events

- The incidence of adverse events was 10% higher in patients with dose adaption than without:
 - Patients with dose adaption: 67.6% (N=48/71).
 - Patients without dose adaption: 57.8% (N=259/448).

CONCLUSIONS

- The CHC-treatment with peginterferon alfa-2a (40KD) (PEGASY[®]) plus ribavirin was initiated according to SPC in more than 93% of the patients.
- However, if the laboratory parameters neutrophils, platelets or haemoglobin fall below the cut-off values of the SPC, the recommended dose adjustments were more rarely than expected.
- This could be a consequence of the 4 weekly visit schedule: After registration of lowered laboratory values a nearby second appointment is required to change dose, but this is often not feasible.
- Nevertheless, the SVR rates of these patients (except for platelets) are similar to those of patients with „normal“ values.

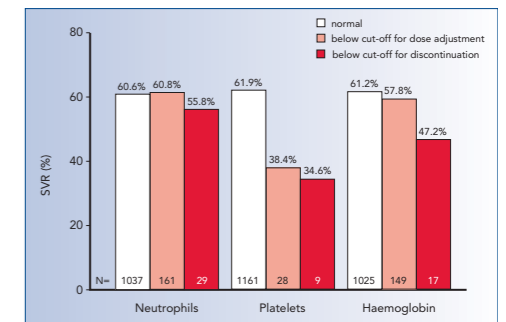


Fig. 6. Virological result of the treatment with Peginterferon alfa-2a (40KD) (Pegasy[®])