Efficacy and Tolerability of Peginterferon alfa-2a or -2b plus Ribavirin in the Routine Daily Treatment of Chronic Hepatitis C Patients in Germany: The PRACTICE Study

Witthoeft T[1], Hueppe D[2], John C[3], Goelz J[4], Meyer U[5], Heyne R[6], Moeller B[6], Link R[7], Teuber G[8], Sworszt S[9], Herrmann A[10], Wollschlaeger A[11], Baumgarten A[12], Simon K-G[13], Cordes J[14], Moog G[15], Dikopoulos N[16], Mauss S[17]

[1]Medical Department I, Div. of Gastroenterology, University Hospital Schleswig-Holstein Campus Luebeck, Luebeck; [2]Center of Gastroenterology, Herne; [3]Center of Gastroenterology, Berlin; [4]Practice Centre Kaiserdamm, Berlin; [5]Center of Internal Medicine, Berlin; [6]Center of Gastroenterology and Livercenter, Berlin; [7]Internal Medicine, St. Josef Clinic, Offenburg; [8]Johann Wolfgang Goethe University, Frankfurt/Main; [9]General Practice, Gelsenkirchen; [10]Friedrich Schiller University, Jena; [11]Hospital Dresden Friedrichstadt, Dresden; [12]General Practice, Berlin; [13]Center of Gastroenterology, Leverkusen; [14]Vitanus GmbH, Frankfurt/Main; [15]Center of Gastroenterology, Kassel; [16]Department for Internal Medicine I, University of Ulm, Ulm; [17]Center for HIV and Hepatogastroenterology, Duesseldorf; all Germany

INTRODUCTION

- The PRACTICE-study (Pegylated Interferons and Ribavirin: Analysis of CHC Treatment In Centres of Excellence) is a German nationwide retrospective observational study analysing the response to hepatitis C treatment in routine clinical practice between 2000 and 2007.
- The study included 23 gastroenterological centres with high treatment rates (>20/year) of chronic hepatitis C (CHC).

OBJECTIVE

- Aim of this analysis of retrospective data is to evaluate efficacy and safety of peginterferon alfa-2a plus ribavirin (A) compared to peginterferon alfa-2b plus ribavirin (B) the treatment of cHC-patients under real life conditions.

METHODS

- This evaluation is part of a large retrospective German multicentre, open-label observational study including anti-HCV-positive adults with detectable HCV RNA. According to the nature of this study, selection as well as dosing and treatment duration of peginterferon and ribavirin were at the discretion of the physician.
- The data set includes patients who completed treatment with peginterferon alfa-2a or alfa-2b plus ribavirin. The data collection was performed via an e-CRF 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.

Treatment

- Patients were treated either with:
  - **A**: Pegylated interferon alfa-2a (40KD) (Pegasys®) mostly plus ribavirin (Copegus®) or
  - **B**: Pegylated interferon alfa-2b (12KD) (PegIntron®) mostly plus ribavirin (Rebetol®).

Matched Pairs

- Matched Pairs I: To achieve comparability regarding interferon therapy, patients were matched acc. to the following criteria:
  - age difference ≤3 years,
  - same HCV genotype (only main type),
  - same category of viral load: LVL or HVL (cut-off: ≤400.000 IU/ml),
  - BMI difference ≤2 kg/m²,
  - same anamnesis of hepatitis C pretreatment incl. subcategories (monotherapy, IFN-RBV-combination therapy, PEG-RBV-combination therapy, virological non-response, not adequate pretreatment),
  - presence of substitution (yes / no),
  - presence of HIV-coinfection (yes / no).
- Matched Pairs II: To include ribavirin treatment, a second analysis of matched pairs was initiated: In addition to the criteria of Matched Pairs I, patients were matched acc. to:
  - cumulative ribavirin dose (≤60% / >60%-80% / >80%-100% / >100%).

RESULTS

Patients

- 3470 patients (A=1784, B=1686) treated with pegylated interferon plus ribavirin under real life conditions were documented between 2000 and 2007 from 23 large outpatient clinics:
  - Matched Pairs I: 2408 patients (A=1204; B=1204),
  - Matched Pairs II: 1696 patients (A=848; B=848).
- Patients with chronic hepatitis C (CHC): In order to evaluate only patients with chronic hepatitis C, 56 patients with acute hepatitis C (29 of group A and 27 of group B) were excluded from the analysis. Therefore, the following analysis is based on 3 data sets of patients with chronic hepatitis C:
  - Intent-to-treat (ITT): 3414 CHC-patients (A=1755; B=1659),
  - Matched Pairs I: 2378 CHC-patients (A=1189; B=1189),
  - Matched Pairs II: 1672 CHC-patients (A=836; B=836).
- Demographic data for the 3 data sets are shown in Table 1.
- Concomitant treatments are shown in Table 2.
- Most of the patients were treatment naïve (89.0%, ITT). 5.9% of the patients were relapsers, 4.9% non-reponders and 0.3% were both relapsers and non-responders (≥2 pretreatments).
- Sources of infection were (ITT; multiple answers possible): i.v. drug abuse (35.7%), transfusion (18.0%), medical action (6.1%). The source of infection was unknown in 33.0% of the patients.

Early virological response (EVR)

- 76.6% (A) vs. 70.2% (B) of the ITT-patients achieved Early virological responses at week 12 (≥2-$\log_{10}$ drop in HCV RNA and/or HCV RNA ≤50 IU/ml and/or HCV RNA qualitatively undetectable; see Table 3).

End of treatment response (EOT)

- End of treatment response (EOT) was achieved in 75.7% (A) vs. 65.6% (B) of the ITT-patients (HCV RNA ≤50 IU/ml and/or HCV RNA qualitatively undetectable) (see Table 3).

Sustained virological response (SVR)

- For group A-patients the SVR (HCV RNA ≤50 IU/ml and/or HCV RNA undetectable after 24 weeks of follow-up) was 52.9% in ITT analysis. The respective SVR for the group B-patients was 50.5% (see Table 3).

Table 1: Baseline data of patients with completed treatment

		A: PEG-IFN alfa-2a (40KD)			B: PEG-IFN alfa-2b (12KD)		
		ITT	MP I	MP II	ITT	MP I	MP II
N		N=1755	N=1189	N=836	N=1659	N=1189	N=836
Sex (%male / %female)		59.7 / 40.3	57.0 / 43.0	57.4 / 42.6	57.6 / 42.4	57.6 / 42.4	59.7 / 40.3
Age (mean ± SD in years)		42.3 ± 11.6	42.2 ± 11.3	42.4 ± 11.3	42.4 ± 11.7	42.2 ± 11.4	42.4 ± 11.3
Weight (mean ± SD in kg)		74.7 ± 14.2	73.6 ± 13.0	73.3 ± 12.4	74.3 ± 14.5	73.7 ± 13.0	73.8 ± 13.0
BMI (mean ± SD in kg/m²)		25.0 ± 4.2	24.7 ± 3.6	24.7 ± 3.5	24.9 ± 4.2	24.7 ± 3.6	24.7 ± 3.5
Duration of infection (years)		13.2 ± 8.7	13.6 ± 8.8	13.8 ± 9.1	13.9 ± 9.2	14.3 ± 9.2	14.0 ± 9.2
Genotype (%)	GT 1	59.9	61.6	66.3	57.3	61.6	66.3
	GT 2/3	37.3	37.1	32.5	39.0	37.1	32.5
	GT 4/5/6	2.8	1.3	1.2	3.7	1.3	1.2
Viral load (% LVL/HVL)	GT 1	33.8 / 66.2	37.1 / 62.9	36.3 / 63.7	38.3 / 61.7	37.1 / 62.9	36.3 / 63.7
	GT 2/3	41.2 / 58.8	42.2 / 57.8	45.2 / 54.8	41.4 /58.6	42.2 / 57.8	45.2 / 54.8
	GT 4/5/6	35.4 / 64.6	40.0 / 60.0	30.0 / 70.0	57.6 / 42.4	40.0 / 60.0	30.0 / 70.0
Histology (%)	baseline	26.9	27.2	29.7	29.6	29.3	30.5
	F0-F1 / F2-F3 / F4	53 / 42 / 5	55 / 40 / 5	54 / 40 / 5	56 / 38 / 6	54 / 40 / 5	55 / 41 / 5
Concomitant diseases (%)		52.4	48.4	46.2	51.9	47.3	45.3
incl. (>5%):	psychiatric	23.4	23.1	19.9	20.8	20.1	18.5
	cardiovascular	14.5	15.6	17.4	14.8	15.5	14.8
	diabetes mell.	8.3	8.5	7.8	7.1	7.1	7.9
	chron. respiratory	6.3	7.5	6.5	5.1	3.9	3.2
	chron. joint	5.1	5.0	5.2	5.1	4.8	5.8
	drug abuse	36.8	32.8	29.5	42.3	38.8	36.4
	alcohol abuse	6.3	6.6	5.4	8.5	9.6	9.0
	previous hep. A	9.4	9.2	8.5	15.4	14.8	13.2
	hep. B coinfection	2.1	2.1	2.1	1.0	1.4	1.6
	previous hep B	16.2	16.8	18.4	21.4	21.9	19.5
	HIV coinfection	9.1	3.6	3.1	7.4	3.7	3.2
	thyroid	5.5	6.4	6.7	5.9	5.2	5.3
	skin	5.3	5.0	6.2	5.0	5.9	5.3

ITT=Intent-to-treat; MP=Matched pairs; LVL=Low viral load (≤400 000 IU/ml); HVL=High viral load (>400 000 IU/ml)

Table 2: Concomitant medication during observation

		A: PEG-IFN alfa-2a (40KD)			B: PEG-IFN alfa-2b (12KD)		
		ITT	MP I	MP II	ITT	MP I	MP II
Antiretroviral HIV-treatment (%)		4.8	1.8	1.4	3.9	1.8	1.4
Substitutional medication (drug abuse, %)		9.4	5.4	3.7	8.5	5.4	3.7
Other concomitant medication (%)		95.8	97.1	97.7	96.2	96.4	97.0
incl. (>1%):	antacids	1.5	1.1	0.6	0.8	0.7	0.5
	antispas./anticholin.	1.1	0.6	0.2	0.8	0.9	0.7
	cardiac	1.9	1.0	0.8	1.6	1.4	1.3
	other gynecologicals	1.8	0.9	0.7	1.5	1.3	1.2
	antibacterials	1.5	0.8	0.6	0.8	0.7	0.8
	antiinflam./antirheum.	1.9	1.0	0.7	1.6	1.3	1.2
	joint/muscular	1.9	1.0	0.7	1.6	1.3	1.2
	analgesics	2.2	1.3	1.2	2.0	1.9	1.4
	psycholeptics	1.3	0.8	0.4	1.0	1.1	0.8
	psychoanaleptics	2.2	1.3	0.7	1.6	1.3	1.3

ITT=Intent-to-treat; MP=Matched pairs

Table 3: Virological response

		A: PEG-IFN alfa-2a (40KD)			B: PEG-IFN alfa-2b (12KD)		
		ITT	MP I	MP II	ITT	MP I	MP II
EVR (%)		76.6	79.4	79.8	70.2	71.5	69.5
EOT (%)		75.7	76.8	75.6	65.6	66.4	64.4
SVR (%, p-value)	Total	52.9 p=0.147	59.9 p=0.051	59.1 p=0.054	50.5 p=0.147	55.9 p=0.051	54.4 p=0.054
	Genotype 1	43.2 p=0.074	48.7 p=0.075	49.6 p=0.047	39.3 p=0.074	44.1 p=0.075	43.7 p=0.047
	Genotype 2/3	68.2 p=0.879	78.7 p=0.335	78.3 p=0.681	67.9 p=0.879	76.0 p=0.335	76.8 p=0.681

ITT=Intent-to-treat; MP=Matched pairs; p-values for A vs. B; underlined p-values reflect 5% level of significance

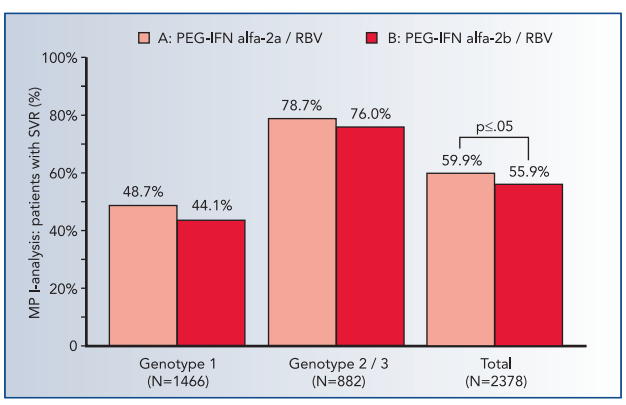

Figure 1. SVR in Matched Pairs I-analysis

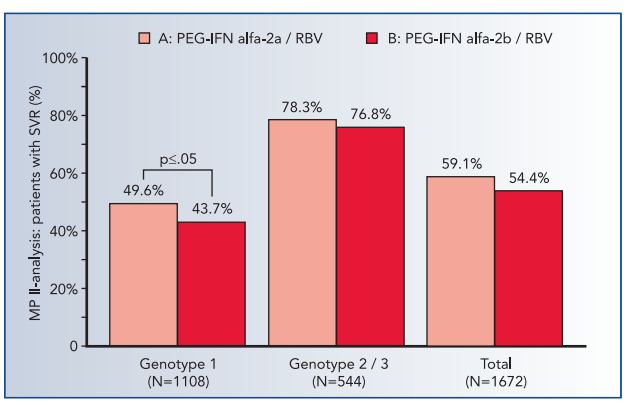

Figure 2. SVR in Matched Pairs II-analysis

- In the Matched pairs I-analysis the SVR was significantly lower in group B (55.9%) than in group A (59.9%) (p≤.05; see Fig. 1).
- In the Matched pairs II-analysis the SVR for genotype 1-patients of group A (49.6%) was significantly lower than for group B-patients (43.7%; p≤.05; see Figure 2).

Treatment

- The mean duration of therapy (weeks) was:
  - GT 1/4: MP I: 40.2 (A) vs. 37.5 (B), MP II: 40.7 (A) vs. 37.3 (B).
  - GT 2/3: MP I: 24.6 (A) vs. 24.8 (B), MP II: 23.8 (A) vs. 24.5 (B).
- Patients (%) who received cumulative interferon dose ≤80%:
  - GT 1/4 (48 weeks): MP I: 33.9 (A) vs. 51.7 (B), MP II: 30.9 (A) vs. 54.4 (B).
  - GT 2/3 (24 weeks): MP I: 10.4 (A) vs. 22.4 (B), MP II: 11.4 (A) vs. 22.4 (B).
- Patients (%) who received cumulative ribavirin dose ≤80%:
  - GT 1/4 (48 weeks): MP I: 26.4 (A) vs. 14.6 (B), MP II: 13.5 (A) vs. 13.5 (B).
  - GT 2/3 (24 weeks): MP I: 4.1 (A) vs. 23.9 (B), MP II: 3.3 (A) vs. 3.3 (B).

Treatment discontinuations (ITT)

- 21.8% of group A and 29.6% of group B discontinued therapy before end of treatment. Main reasons for withdrawal were (multiple answers possible):
  - virological nonresponse (A: 58.2%; B: 65.2%),
  - poor tolerability (A: 18.5%; B: 14.5%),
  - patient request (A: 9.9%; B: 10.6%) and
  - non-compliance (A: 8.9%; B: 4.1%).

CONCLUSIONS

- For a valid comparison of peginterferon regimes it is important to match patient groups not only according to baseline factors but also according to ribavirin dose.
- In our matched pairs analysis significantly more patients were cured with peginterferon alfa-2a (40KD) compared to peginterferon alfa-2b (12KD) in a real-life setting.
- Further evaluations will have a closer view to possible reasons of our results concerning the different treatment outcomes of both peginterferons

Presented at the 43rd Annual Meeting of the European Association for the Study of the Liver (EASL), April 23-27, 2008, Milan, Italy.

This research was supported by Roche Pharma AG, Grenzach-Wyhlen, Germany.