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Efficacy and tolerability of peginterferon alfa-2a or alfa-2b plus ribavirin in the daily routine treatment of patients with chronic hepatitis C in Germany: The PRACTICE Study

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SUMMARY. In randomized clinical trials, treatment with peginterferon plus ribavirin (RBV) results in a sustained virological response (SVR) in around half of hepatitis C virus genotype 1-infected and 80% of genotype 2/3-infected individuals. This study aimed to evaluate efficacy and tolerability of peginterferon alfa-2a plus RBV compared with peginterferon alfa-2b plus RBV for the treatment of chronic hepatitis C in routine clinical practice. The intent-to-treat cohort consisted of 3414 patients treated with either peginterferon alfa-2a plus RBV (Group A) or peginterferon alfa-2b plus RBV (Group B) in 23 centres participating in the large, multicentre, observational PRACTICE study. Collected data included baseline characteristics, treatment regimen, RBV dose and outcome. Rates of early virological response, end of treatment response and SVR were 76.6%, 75.7% and 52.9% in Group A, and 70.2%, 65.6% and 50.5% in Group B, respectively. In patients matched by baseline parameters, 59.9% of patients in Group A and 55.9% in Group B achieved an SVR ($P \leq 0.051$). In genotype 1-infected patients matched by baseline parameters and cumulative RBV dose, SVR rates were 49.6% and 43.7% for Group A and Group B, respectively ($P \leq 0.047$); when matched by baseline parameters and RBV starting dose, SVR rates were 49.9% and 44.6%, respectively ($P = 0.068$). Overall, 21.8% of group A and 29.6% of group B patients discontinued treatment ($P \leq 0.0001$). The efficacy and tolerability of peginterferon plus RBV in this large cohort of patients treated in routine daily practice was similar to that in randomized clinical trials. In matched pairs analyses, more patients achieved an SVR with peginterferon alfa-2a compared with peginterferon alfa-2b.

Keywords: chronic hepatitis, HCV, PCR, pegylated interferon, ribavirin, sustained virological response, viral load.

Hepatitis C virus (HCV) infection is a major public health problem, with around 170 million individuals infected worldwide [1]. Up to 85% of infected individuals go on to develop chronic HCV (CHC) infection, with an associated risk of progression to cirrhosis, end-stage liver disease and hepatocellular carcinoma. Despite improvements in blood transfusion safety and healthcare conditions, the increase in numbers of intravenous drug users and immigration from endemic areas have led to an increase in the incidence of HCV infection in Europe over recent years [2,3]. Peginterferon plus ribavirin (RBV) represents the gold standard treatment for CHC. The primary measure of treatment success is sustained virological response (SVR), i.e. negative HCV RNA 6 months after the cessation of therapy, which is associated with a >99% chance of being virus-free 5 years later [4]. In large randomized controlled trials (RCTs), SVR was achieved by almost half of genotype 1-infected and around 80% of genotype 2/3-infected individuals [5–7]. Results from such trials form the basis of national and international guidelines that provide recommendations on dosing, treatment duration and patient management [8–12]. However patients included in RCTs are necessarily subject to strict inclusion and exclusion criteria that may not reflect

Abbreviations: BMI, body mass index; CHC, chronic HCV; EOT, end of treatment; EVR, early virological response; HVL, high viral load; IDEAL, Individualized Dosing Efficacy vs. flat dosing to Assess optimaL pegylated interferon therapy; ITT, intent to treat; LVL, low viral load; RBV, ribavirin; SVR, sustained virological response.

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the more complex clinical picture seen in patients in the 'real-life' setting. In addition, the clinical trial situation provides a high level of medical and support care that tends to maximize patient compliance. This, together with controlled management of side effects and dose reductions, potentially contributes to improved compliance that is known to influence the success of treatment [13,14]. Given these factors, it is possible that results may vary between RCT results and those seen in clinical practice.

Two forms of peginterferon, peginterferon alfa-2a (40KD) and peginterferon alfa-2b (12KD), are commercially available, which differ in terms of their pharmacokinetic, viral kinetic and tolerability profiles [15,16]. Evaluation of any differences in efficacy between the two compounds is difficult because of the lack of direct comparability between clinical trials and issues around trial design in direct comparison studies. A range of factors are known to affect response to peginterferon plus RBV, including baseline characteristics such as HCV genotype, viral load, age and degree of fibrosis [17]. In addition, RBV dose has also been shown to affect outcome, particularly in genotype 1-infected patients [6,14,18–20]. RBV dose can be a confounding factor in comparative trials. In the Individualized Dosing Efficacy vs. flat dosing to Assess optimaL pegylated interferon therapy (IDEAL) trial [21], for example, differences in RBV starting dose and dose reduction regimens introduce bias that prevents direct comparison between the two peginterferons. Recommended combination treatment regimens for each peginterferon use different RBV dosing [22,23], and therefore studies that use recommended regimens cannot provide a direct, head-to-head comparison, although they do offer comparisons between the specific combination regimens. To overcome the bias introduced by RBV dosing regimen, a recent Italian study gave all patients treated with either peginterferon the same RBV dose based on body weight, with RBV dose reduction being managed identically in both groups of patients [24]. However, if the two peginterferons are to be directly compared, baseline and treatment-related factors must be taken into account [25].

The Pegylated Interferons and RBV: Analysis of CHC Treatment In Centres of Excellence (PRACTICE) study is a German nationwide retrospective, observational study analysing the response to hepatitis C treatment in routine clinical practice. PRACTICE includes patients treated between 2000 and 2007 in 23 gastroenterological centres with excellent treatment expertise (at least 20 CHC patients treated per year). This retrospective study provides an important source of information regarding a cross section of HCV patients treated under real-life conditions. Such patients are likely to be exposed to factors that may potentially influence outcome which are not experienced by patients participating in highly controlled clinical trials. Using data from the PRACTICE cohort, we aimed to evaluate the efficacy and tolerability of peginterferon alfa-2a plus RBV and peginterferon alfa-2b plus RBV for the treatment of CHC patients in a 'real-world' clinical setting compared to that seen in clinical trials. We also aimed to assess response and tolerability in patients matched in terms of baseline characteristics and RBV dose to directly compare the effects of the two peginterferons.

METHODS

PRACTICE is a retrospective study of patients with CHC managed at 23 German gastroenterological centres with high treatment rates (≥20 patients/year) between 2000 and 2007. This study investigated patients from the total PRACTICE data set who had undergone treatment with either peginterferon alfa-2a (40KD) (PEGASYS®; Roche, Welwyn Garden City, UK) plus RBV (Copegus®; Roche, Grenzach-Wyhlen, Germany) or peginterferon alfa-2b (12KD) (PegIntron®; Schering-Plough, Bruxelles, Belgium) plus RBV (Rebetol®; Schering-Plough). As this study was retrospective, dosing and treatment duration were not controlled but reflected the clinical practice of the physician and/or treatment centre at the time the patient was treated. Patient selection for submission to the database was entirely at the clinician's discretion; no restrictive parameters were set other than diagnosis of CHC. Data collection was performed via an online e-CRF. Baseline parameters included sex, age, weight/body mass index (BMI), duration of infection, histology at baseline, concomitant diseases, drug abuse and concomitant medication; virological parameters included HCV genotype, viral load, early virological response (EVR [≥2-log10 drop in HCV RNA and/or HCV RNA ≤50 IU/mL and/or HCV RNA qualitatively undetectable at week 12]), end of treatment response (EOT) and SVR (HCV RNA ≤50 IU/mL and/or HCV RNA undetectable after 24 weeks of follow-up).

Statistics

The statistical analysis was descriptive to reflect the clinical routine as intended by the clinicians. Summary statistics (mean, median, standard deviation, 25th percentile, 75th percentile, minimum, maximum, number of values) or frequencies and proportions were assessed for all collected parameters. A matched pairs population was created to control the variability of baseline characteristics that influence response. A second matched pairs population was created to control for baseline characteristics and RBV dose. Analyses were calculated with SPSS for Windows Release 12.0.2 (Chicago, IL, USA), Testimate Version 6.4.27 (Institute for Data Analysis and Study Planning, Gauting/Munich, Germany) and Matched Version 1.1 (Institute for Medical Statistics and Documentation, Erlangen, Germany).

Matched pairs

Patients were matched in pairs, one from each treatment group: Group A included those patients treated with peginterferon alfa-2a and Group B those treated with peginterferon alfa-2b.

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Matched Pairs I

To account for variations in response to peginterferon that may result from baseline characteristics, patients were matched according to the following criteria: age difference ≤3 years; HCV genotype (based on predominant infecting genotype); category of viral load (low viral load or high viral load; cut-off: ≤400.000 IU/mL); BMI (difference ≤2 kg/m^2); previous treatment history (monotherapy, interferon-RBV-combination therapy, peginterferon-RBV-combination therapy, virological nonresponse, inadequate previous treatment); presence of drug substitution treatment and presence of HIV co-infection.

Matched Pairs II

To account for the effects of variations as a result of RBV dose, a further analysis was performed. In addition to the criteria of Matched Pairs I, patients were matched according to cumulative RBV dose (≤60/>60–80%/>80–100%/>100%), where 100% dose was based on that given by the specific RBV prescribing recommendation [22,23].

RESULTS

Patients

A total of 3470 patients (Group A = 1784, Group B = 1686) included in the PRACTICE cohort who had undergone treatment with peginterferon plus RBV were identified. Patient disposition is shown in Fig. 1. Among all, 56 patients subsequently diagnosed with acute hepatitis C and not chronic hepatitis C were excluded from the analysis. The intent-to-treat population therefore consisted of 3414 patients: 1755 in Group A and 1659 in Group B. Patients were then assigned to matched pairs based on the criteria given earlier. Those patients who could not be allocated to a pair were excluded from the analysis. The resulting Matched Pairs I dataset consisted of 2378 patients (1189 from Group A and 1189 from Group B); of these 1672 (836 from each Group) were included in the Matched Pairs II analysis.

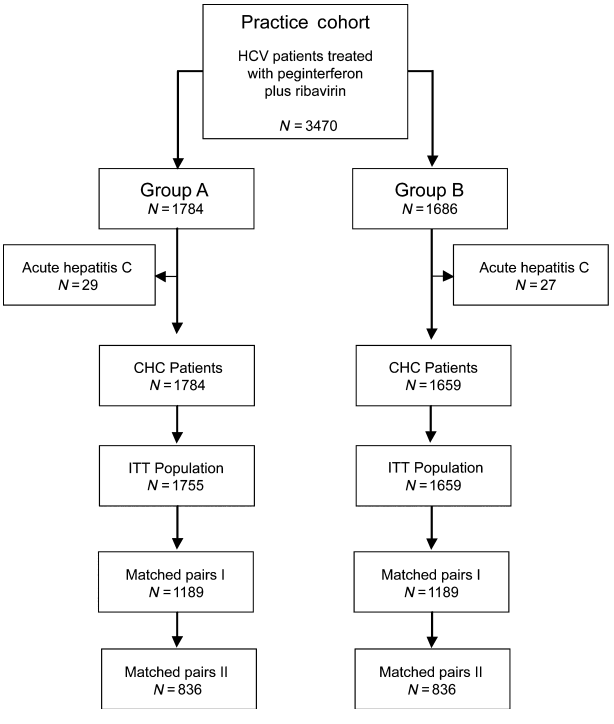

Fig. 1 Patient disposition.

Groups A and B were well matched in terms baseline and demographic data (Table 1) and in terms of concomitant medication (Table 2). The majority of patients were treatment naive [89.0%, intent to treat (ITT)]; 5.8% had relapsed, 4.9% were nonresponders and 0.3% had been both relapsers and nonresponders (≥2 previous treatments). The most common known sources of HCV infection were intravenous drug use (35.7%, ITT analysis) and transfusion (18.0%, ITT analysis). The source of infection was unknown in 33.0% of the patients.

The mean duration of therapy is shown in Table 3. The percentage of patients who received ≤80% cumulative dose of peginterferon and of RBV (based recommended dosing schedule) is shown in Table 4.

Virological response

Virological responses to treatment in the various groups are shown in Table 5. In the ITT analysis, the rate of EVR, EOT response and SVR was higher in patients in Group A compared with group B, although this did not reach statistical significance for any measure. In the Matched Pairs I analysis, the overall SVR was lower in Group B patients (55.9%) than in Group A patients (59.9%), and this difference showed a trend in favour of peginterferon alfa-2a (P = 0.051; Fig. 2). There was no significant difference in SVR between Group A and Group B when analysed by genotype (Table 5; Fig. 1). In the Matched Pairs II analysis, the overall SVR was again higher in Group A patients compared with Group B patients (59.1% *vs* 54.4%, respectively; P = 0.054). For genotype 1-infected patients, the percentage of patients with an SVR in Group A was significantly higher than for Group B (49.6% *vs* 43.7%, respectively; P = 0.047) (Fig. 3). There was no significant difference for genotype 2/3-infected patients.

Rates of EVR, EOT and SVR response were lower in patients co-infected with HIV (n = 148) compared with those with HCV infection only. In the ITT population, 29.4%, 47.4% and 34.7% of genotype 1 co-infected patients with HIV achieved EVR, EOT response and SVR, respectively. For genotype 2/3 co-infected patients, EVR, EOT response and SVR rates were 85.7%, 79.2% and 58.5%, respectively. SVR rates were higher in patients in Group A compared with Group B (36.7% *vs* 31.6%, respectively, for genotype-1 co-infected patients, and 63.0% *vs* 53.9%, respectively, for genotype-2/3 co-infected patients).

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Table 1 Baseline characteristics

	Group A: PEG-IFN alfa-2a			Group B: PEG-IFN alfa-2b		
	ITT	MP I	MP II	ITT	MP I	MP II
N	1755	1189	836	1659	1189	836
Sex (% male/female)	59.7/40.3	57.0/43.0	57.5/42.6	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 ± 11.7	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/m^3)	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						
Genotype 1	59.9	61.6	66.3	57.3	61.6	66.3
Genotype 2/3	37.3	37.1	32.5	39.0	37.1	32.5
Genotype 4/5/6	2.8	1.2	1.2	3.7	1.3	1.2
Viral load (%LVL/HVL)						
Genotype 1	33.8/66.2	37.1/62.9	36.3/63.7	38.3/61.7	37.1/62.9	36.3/65.7
Genotype 2/3	41.2/58.8	42.2/57.8	45.2/54.8	41.4/58.6	42.4/57.8	45.2/54.8
Genotype 4/5/6	25.4/64.6	40.0/60.0	30.0/70.0	57.6/42.4	40.0/60.0	30.0/70.0
Histology, fibrosis score (%)						
With baseline biopsy	26.9	27.2	29.7	29.6	29.3	30.5
F0-1/F2-3/F4	53/40/5	55/40/5	54/40/5	56/38/6	54/40/5	55/41/5
Concomitant disease (%)*	52.4	48.4	46.2	51.9	47.3	45.3
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	8.3	8.5	7.8	7.1	7.1	7.9
Chronic respiratory	6.3	7.5	6.5	5.1	3.9	3.2
Chronic 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 hepatitis A	9.4	9.2	8.5	15.4	14.8	13.2
Hepatitis B co-infection	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 co-infection	9.1	3.6	3.1	7.4	3.7	3.2
Thyroid conditions	5.5	6.4	6.7	5.9	5.2	5.3
Skin conditions	5.3	5.0	6.2	5.0	5.9	5.3

ITT, intent to treat; MP, matched pairs; BMI, body mass index; HVL, high viral load (>400 000 IU/mL); LVL, low viral load (≤400 000 IU/mL). *Present in >5% of overall population.

Treatment discontinuations (ITT analysis)

Overall, significantly fewer patients discontinued therapy before the EOT in Group A compared with Group B (21.8% *vs* 29.6%; $P \leq 0.0001$). The main reasons for withdrawal were (multiple reasons were possible for each patient) virological nonresponse (Group A 12.7%; Group B 19.3%); poor tolerability (Group A 4.0%; Group B 4.3%); patient request (Group A 2.2%; Group B 3.1%) and noncompliance (Group A 1.9%; Group B 1.2%).

Ribavirin dose and dose adjustment – Matched Pairs III

In the Matched Pair II analysis, where patients were matched according to cumulative RBV dose as defined by prescribing information, significantly more genotype 1-infected patients in Group A achieved an SVR compared with Group B. However, as the prescribed RBV starting dose and dose reduction regimens are different for the two different RBV preparations [22,23], this method may not have resulted in matching in terms of absolute RBV dose. We therefore performed an additional analysis of genotype 1-infected patients matched by the criteria of Matched Pairs I plus initial RBV dose, which included the evaluation of any dose reductions and dose reduction strategy (i.e. amount of reduction). The potential effect of body weight on RBV starting dose was controlled as patients were matched for BMI deviation <2 kg/m^2 as per Matched Pair I criteria. In all, 579 matched pairs were included in this analysis (Matched Pairs III). Starting dose of RBV was 600 mg in 0.2%, 800 mg in

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Table 2 Concomitant medication

	Group A: PEG-IFN alfa-2a			Group B: PEG-IFN alfa-2b		
	ITT	MP I	MP II	ITT	MP I	MPII
Antiretroviral HIV-treatment (%)	4.8	1.8	1.4	3.9	1.8	1.4
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
Antacids	1.5	1.1	0.6	0.8	0.7	0.5
Antispasmodics/anticholinesterases	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
Gynaecological	1.8	0.9	0.7	1.5	1.3	1.2
Antibiotics	1.5	0.8	0.6	0.8	0.7	0.8
Anti inflammatories/anti rheumatics	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. *In >1% of cohort.

26.4%, 1000 mg in 54.7% and 1200 mg in 18.6% of patients in each Group. The majority of patients (90.2% in Group A and 87.2% in Group B) did not require RBV dose reduction; 20 (3.5%) and 19 (3.3%) patients in Group A and Group B, respectively, received RBV dose reductions of ≥400 mg, and 31 (5.4%) and 52 (9.0%), respectively, received RBV dose reductions of 200 mg ($P = 0.1148$ for difference in dose reduction between groups). Average time to first dose reduction was similar between both groups (92.1 days in Group A and 94.5 days in Group B). In the Matched Pairs III analysis, a higher proportion of genotype 1-infected patients achieved SVR in Group A compared with Group B when matched by RBV starting dose, although this did not reach statistical significance (49.9% *vs* 44.6%, respectively; $P = 0.068$).

DISCUSSION

In this large open-label cohort study of patients with chronic hepatitis C treated in clinical community settings over a period of 7 years, treatment with peginterferon plus RBV resulted in a cure (SVR) in over half of all patients, a figure similar to that reported in pivotal clinical trials [5–7]. Good SVR rates were achieved despite the fact the study included patients such as HIV infected patients and intravenous drug abusers who are generally considered to be less easy to treat and would have been excluded from clinical trials. The overall rates of EVR, EOT and SVR were higher in those patients treated with peginterferon alfa-2a plus RBV compared with peginterferon alfa-2b plus RBV. In patients matched by baseline characteristics, treatment with peginterferon alfa-2a plus RBV was associated with a higher rate of SVR than peginterferon alfa-2b plus RBV. In addition, when patients were matched in terms of RBV dose, both by starting dose and as a proportion of cumulative dose based on prescribing information, more genotype 1-infected patients achieved SVR with peginterferon alfa-2a plus RBV compared with peginterferon alfa-2b plus RBV.

Data from randomized clinical trials form the basis of treatment guidelines and inform clinicians and healthcare workers on individual patient management. However, clinical trial populations by necessity are defined and restricted, and the trial process itself involves the use of clear protocols, for example, concerning dose reductions or treatment. The support and monitoring a patient receives during a clinical trial is also more likely to improve compliance with treatment, which is an important contributor to a successful outcome. As such, the clinical trial situation may not fully reflect real-life clinical practice with its more diverse, complex patient population, variability in access and support mechanisms, and possibly less well-defined protocols in routine practice. Cohort studies such as the current study are therefore important to assess how well clinical trial data transfer to routine practice. In the current study, 57.9%

Table 3 Mean duration of therapy*

Genotype	Matched Pair group	Group A: PEG-IFN alfa-2a	Group B: PEG-IFN alfa-2b
1/4	MP 1	40.2 (13.26)	37.5 (14.16)
	MP 2	40.7 (12.53)	37.3 (14.25)
2/3	MP 1	24.6 (5.95)	24.8 (6.75)
	MP 2	23.8 (5.68)	24.5 (6.93)

MP, matched pair. *Weeks (SD).

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Table 4 Patients (%) who received ≤80% cumulative dose of peginterferon or ribavirin (RBV) dose

Genotype	Matched Pair group	Cumulative peginterferon dose ≤80%		Cumulative RBV dose ≤80%	
		Group A: PEG-IFN alfa-2a	Group B: PEG-IFN alfa-2b	Group A: PEG-IFN alfa-2a	Group B: PEG-IFN alfa-2b
1/4	MP 1	33.9	51.7	26.4	14.6
	MP 2	30.9	54.4	13.5	13.5
2/3	MP 1	10.4	22.4	4.1	23.9
	MP 2	11.4	22.4	3.3	3.3

MP, matched pair.

of patients overall achieved an SVR: 46.5% of genotype 1-infected patients and 77.3% of genotype 2/3-infected. This compares favourably with pivotal clinical trials that reported rates of 42–46% in genotype 1-infected patients and 76–82% in genotype 2/3-infected patients [5–7,26,27]. The findings of this study are also in line with those from other retrospective analyses of HCV-infected patients treated in routine clinical practice where overall SVR rates of 49–66% have been reported, with rates of 37–61% in genotype 1-infected and around 70% of genotype 2-infected patients [28–32]. The SVR rates achieved by HIV/HCV co-infected patients in the current study not only were lower than those in HCV monoinfected patients as would be expected, but also compared favourably to those achieved in clinical trials [33,34].

Treatment with peginterferon plus RBV was well tolerated in the current study. Rates of discontinuation of therapy were similar to that reported in pivotal clinical trials (14–21%) [5–7] and were within the range reported by other cohort studies of peginterferon plus RBV in clinical practice (11–33%) [28,31,32]. This current study therefore adds to the growing volume of data demonstrating that the efficacy and tolerability of peginterferon plus RBV can be similar in everyday clinical practice as that reported in highly controlled clinical trials.

The current study also suggests that treatment with peginterferon alfa-2a may result in a higher rate of SVR in patients treated under routine clinical conditions. For a valid comparison of peginterferon regimes to be made, it is important to match patient groups not only according to baseline factors but also according to RBV dose. Genotype and viral load are the most significant factors associated with SVR, but other baseline factors such as CHC treatment history, co-infection with HIV, BMI and age have also been shown to influence response [17,31,35,36]. RBV dose is also important both to early viral decline and EVR, and to the prevention of relapse and so SVR [35]. There is evidence that RBV dose at the start of and early in the course of treatment is predictive of SVR [19,20] and that maintenance of RBV dose during therapy is also an important factor in attaining SVR, particularly in genotype 1-infected patients [14,37]. Interestingly, RBV has also been shown to be important to SVR in recent studies of triple antiviral regimens [38] – the so-called specifically targeted antiviral therapy for hepatitis C or STAT-C – further underlining its importance in interferon-based treatment regimens. We found that EVR, EOT and SVR rates were all higher for peginterferon alfa-2a compared with peginterferon alfa-2b, although this did not reach significance in the ITT analysis. Where patients were matched by potentially confounding baseline characteristics,

Table 5 Virological response

	Group A: PEG-IFN alfa-2a			Group B: PEG-IFN alfa-2b		
	ITT	MP I	MP II	ITT	MP I	MP II
EVR (%)	76.6	79.4	79.8	70.2	71.5	69.5
EOT (%)	75.5	76.8	75.6	65.6	66.4	64.4
SVR (%)						
Total cohort	52.9	59.9*	59.1†	50.5	55.9*	54.4†
Genotype 1	43.2	48.7	49.6‡	39.3	44.1	43.7‡
Genotype 2/3	68.2	78.7	79.3	67.9	76.0	76.8

EVR, early virological response; EOT, end of treatment; SVR, sustained virological response; ITT, Intent to treat; MP, Matched pairs; *P* values for A vs. B.
Underlined *P* values reflect 5% level of significance: **P* = 0.051; †*P* = 0.054; ‡*P* = 0.047.

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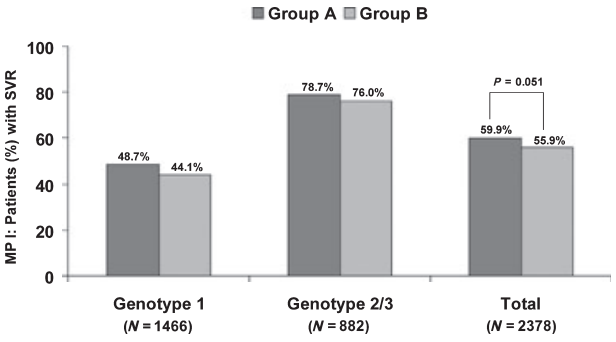

Fig. 2 Sustained virological response in Matched Pair I analysis (matched by baseline factors).

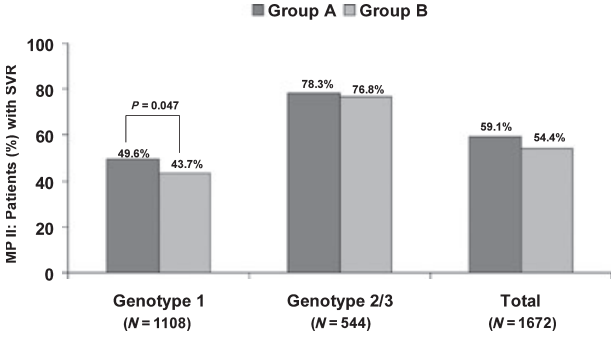

Fig. 3 Sustained virological response in Matched Pair II analysis (matched by baseline factors and cumulative ribavirin dose).

more patients achieved an SVR with peginterferon alfa-2a plus RBV compared to peginterferon alfa-2b plus RBV in a real-life setting, and this difference approached significance. When matched by cumulative RBV dose, significantly more genotype 1-infected patients treated with peginterferon alfa-2a achieved an SVR. Similar results were also seen when patients were matched in terms of baseline characteristics and RBV starting dose, although this did not reach significance, possibly as a result of the lower patient numbers in the Matched Pairs III analysis. As the majority of patients did not require on-treatment dose reductions, and as reduction strategies appeared to be similar in those that did, it is unlikely that differences in RBV dose affected our findings. Interestingly, in line with results from the APRICOT and RIBAVIC studies [33,34], we found a higher rate of response rate in HCV/HIV co-infected patients treated with peginterferon alfa-2a compared with those treated with peginterferon alfa-2b in the ITT population of this 'real-life' study. Unfortunately, because of the small number of patients in the Matched Pairs groups, it is not possible to interpret this finding further. The reasons behind the different responses obtained using the different peginterferons is unclear. Differences in pharmacokinetics and viral kinetics may impact on virological response [15,16], while differences in side-effect profiles may affect adherence and so SVR. There was a significantly higher discontinuation rate with peginterferon alfa-2b compared with peginterferon alfa-2a in the current study, predominantly as a result of higher virological nonresponse, although the rate of 'poor tolerability' was similar between groups. Consensus Guidelines for the treatment of CHC with peginterferon plus RBV have been available since 2002 [8,9,11,12], with German guidelines being published in 2004 [10]. The findings from this study suggest that, overall, clinicians who took part in PRACTICE were largely following guidelines in terms of treatment duration, with a mean duration of therapy of around 24 weeks for genotype 2/3 patients and 40 weeks for genotype 1 patients, although the mean duration of therapy in genotype 1 patients was shorter in the peginterferon alfa-2b group. In addition, the number of genotype 1 patients who received ≤80% cumulative interferon dose was higher at over 50% in the peginterferon alfa-2b group, which may also have contributed to poorer outcome.

Several recent trials have also reported higher SVR rates with peginterferon alfa-2a plus RBV compared with peginterferon alfa-2b plus RBV. A prospective, randomized, independent Italian study, in which a standard initial dose of RBV and consistent strategies for dose reduction were used for both peginterferons, found that more patients treated with peginterferon alfa-2a plus RBV significantly achieved SVR compared with those treated with peginterferon alfa-2b plus RBV (68.7% *vs* 54.4%, respectively; $P = 0.008$) [24]. The randomized open-label Milan Safety Tolerability study also reported significantly higher SVR rates with peginterferon alfa-2a plus RBV compared with peginterferon alfa-2b plus RBV (66% *vs* 54%, respectively; $P = 0.02$) [39]. However, in the IDEAL study, SVR rates in genotype 1-infected patients were reported to be similar between the two different peginterferons plus RBV [40]. The study reported higher EOT response with peginterferon alfa-2a plus RBV, as was also seen in the current study, but this was offset by a greater relapse rate in IDEAL that resulted in the similar rate of SVR. In a subanalysis of African American patients, a particularly difficult to treat population, included in the IDEAL trial, although SVR rates were similar, treatment with peginterferon alfa-2a plus RBV resulted in higher rates of rapid virological response, EVR and EOT response [41]. Given the importance of RBV to both early and SVR, particularly in genotype 1 patients, this effect may be explained by the different RBV dosing and side-effect management strategies that were used in the different treatment arms of IDEAL, where RBV dose reductions of 200–400 mg/day were used for those patients treated with peginterferon alfa-2b, whereas those patients treated with peginterferon alfa-2a received an RBV dose reduction of 600 mg/day (as recommended in the prescribing guidelines). Such differences make direct comparisons between the individual peginterferons alone impossible to make with confidence from this study. In our study, initial RBV dose

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and dose reduction management were at the discretion of the treating clinician and presumably reflected current treatment guidelines. However, it is interesting to note that, in genotype 1-infected patients matched for initial RBV dose and for BMI, RBV dose reductions on-treatment were very similar between patient groups treated with peginterferon alfa-2a or peginterferon alfa-2b. The majority of patients received dose reductions of 200 mg, independent of the prescribing information that recommends reduction of 600 mg. These findings therefore suggest that differences in RBV dose reduction did not contribute to the differences seen in SVR and also that a more conservative RBV dose reduction strategy is employed in routine practice than is recommended in prescribing recommendations. Overall, therefore, data from our study support those of studies which suggest that patients treated with peginterferon alfa-2a may be more likely to achieve an SVR compared with those who receive peginterferon alfa-2b. Further evaluation is required to investigate possible reasons for the apparent differences in treatment success in the current study.

Although retrospective studies are subject to a range of limitations compared with prospective studies, they do provide an important source of descriptive information pertaining to treatment under 'real-life' conditions and over longer time periods. In particular, they provide the opportunity to assess whether success rates (in this case SVR) obtained in clinical trials can also be obtained under real-life conditions where patients are exposed to factors not encountered in clinical trials. The major strengths of this study include its large size and the long time period over which data had been collected. Unlike the controlled clinical trial population, this study examined an unselected cross section of CHC patients treated under routine 'real-life' conditions and therefore is more reflective of clinical practice. The use of matched pairs of patients allows for more comparability between treatment groups by accounting for variation in baseline factors and RBV dose that may impact on outcome. Limitations of the study include the fact that is not possible to completely rule out potential selection bias in different centres when assessing suitability for treatment and in selecting treatment regimens, although the use of matched pairs of patients should help overcome the latter. Clinicians were free to decide which patients they selected for inclusion in the study, and data regarding any patients not selected for inclusion and the reasons for any such noninclusion are not available. As with all retrospective studies, another potential bias may be caused by missing data, as only data that were documented by the clinicians in the patient records were available for inclusion in the study. However, substantial data for the evaluation of the HCV therapy were available for most baseline characteristics, and the majority of patients had EVR and EOT as well as SVR data. With regard to differences between the two treatment regimens, this is not a controlled head-to-head study but offers comparisons between the specific combination regimens used in daily practice in patients matched for possibly confounding baseline parameters.

In this large, multicentre study of patients treated with peginterferon plus RBV over 7 years in 'real-world' clinical conditions, efficacy and tolerability were similar to that described in industry-sponsored registration trials, despite the high selection and support provided to patients enrolled in such trials. When patients in this study were matched in terms of baseline characteristics and according to RBV dose, both of which are known to affect the outcome of peginterferon therapy, data suggest that more patients treated with peginterferon alfa-2a in routine daily practice achieve SVR compared with peginterferon alfa-2b.

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STATEMENT OF INTERESTS

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