Effectiveness and tolerability of pegylated interferon alfa-2b in combination with ribavirin for treatment of chronic hepatitis C : the PegIntrust Study

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Abstract

Background and study aims : Large international clinical trials conducted in the past 5 years rapidly improved the treatment of chronic hepatitis C; however, it is unclear whether the advances seen in clinical trials are being paralleled by similar improvements in routine clinical practice. PegIntrust is a Belgian community-based trial evaluating the sustained virological response.

Patients and Methods : Observational study of 219 patients receiving pegylated interferon alfa-2b (1.5 µg/kg/wk) and weight-based ribavirin (800-1200 mg/day) for 48 weeks. Primary study end point was sustained virological response (SVR), defined as undetectable HCV RNA 6 months after the completion of treatment.

Results : In total, 108 patients (49.3 %) had undetectable HCV RNA at the end of therapy, 91 (41.6%) attaining SVR. Of the 111 patients without an end-of-treatment response, 28 were non-responders, and 21 had virological breakthrough. In total, 134 patients attained early virological response (EVR); 88 (65.7%) of those patients attained SVR. In contrast, 82 (96.5 %) of the 85 patients who did not attain EVR also did not attain SVR. Age, fibrosis score and baseline viral load were identified as important predictors of treatment outcome. The most frequently reported serious adverse events resulting in treatment discontinuation were anemia (n = 10), fatigue/asthenia/malaise (n = 6) and fever (n = 3).

Conclusion : Our data indicate that treatment of chronic hepatitis C with PEG-IFN alfa-2b plus weight-based ribavirin results in favourable treatment outcomes in a Belgian cohort of patients treated in community-based clinical practice. (Acta gastroenterol. belg., **2010**, 73, **5-11**).

Keywords : community-based, hepatitis C virus, pegylated interferon alfa-2b, ribavirin, tolerability, treatment, SVR

Introduction

Hepatitis C virus (HCV) infection is a major global health problem. Worldwide approximately 170 million persons are infected with HCV; the overall prevalence is 3% to 5% (1). Because this infection frequently leads to progressive liver disease, cirrhosis, and hepatocellular carcinoma, hepatitis C is thought to be responsible for at least 20% of all deaths from chronic liver disease, amounting to 280,000 fatalities worldwide each year (2). Hepatitis C is a significant healthcare concern in Belgium. During the early 1990s, the seroprevalence was estimated at 0.9% (3) ; however, 10 years later, a second survey based on the presence of hepatitis C antibodies in oral fluid reported an overall prevalence of 0.12% (4). The profile of hepatitis C in Belgium is typical of many other European and Western countries in terms of risk factors and genotype distribution. Transfusion, intravenous drug use, and invasive medical procedures are responsible for most infections (5). Genotype 1, the most common HCV type, is responsible for approximately 60% of all infections. Genotypes 2, 3 and 4 are each responsible for 10% to 15% of cases (6). Genotype 4 originates from African countries, and its rising prevalence in Western Europe appears to be fueled, at least in part, by the immigration of African persons (6).

Pegylated interferon (PEG-IFN) alfa plus ribavirin combination therapy is the current gold standard treatment for chronic hepatitis C. In large multinational clinical trials, sustained virological response (SVR) is reported in 54% to 56% of patients, with rates higher (76%-82%) in genotype 2/3 patients and lower (42%-46%) in genotype 1 patients (7,8). However, because of the stringent protocols used in these studies, including careful patient selection and regular clinic visits that promote motivation and adherence, it is unclear how closely these data reflect the treatment of chronic hepatitis C in a community-based setting. General practice SVR rates are commonly thought to be lower than those attained in clinical trials, though clear evidence of this in the literature is sparse.

We have, therefore, evaluated the treatment of Belgian patients with chronic hepatitis C receiving PEG-IFN alfa-2b (PegIntron® ; Schering-Plough, Kenilworth, NJ) and ribavirin administered according to a weight-based dosing schedule (Rebetol® ; Schering-Plough) in a community-based setting.

Methods

We conducted a community-based study of the treatment of chronic hepatitis C between January 2003 and October 2004. The study protocol was approved by the ethics committee at each participating centre and in accordance with the principles set forth by the Declaration of Helsinki.

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Patients

The study enrolled treatment-naive patients with chronic hepatitis C, as defined by detectable serum HCV RNA and elevated ALT levels (> 1× upper limit of normal). All patients had to have genotype 1, 4 or 5 and were required to provide a liver biopsy specimen at baseline with a METAVIR score greater than F1.

Exclusion criteria included genotype 2, 3 & 6, decompensated liver cirrhosis or other chronic liver disease (hepatitis B, auto-immune hepatitis, haemochromatosis, alpha 1 antitrypsin deficiency, Wilson's disease). Patients co-infected with HIV, with active alcohol abuse (defined as more than 30 g/day), or active intravenous drug abuse were also excluded. Finally, patients with ribavirin contraindications (chronic renal failure, anemia (Hb ≤ 10 g/dL), haemoglobinopathy), leukocyte count less than 3000 cells/μL and platelet count less than 100,000 cells/μL were excluded.

Study design

All patients received subcutaneous PEG-IFN alfa-2b (1.5 μg/kg/wk) plus oral ribavirin (800-1200 mg/day), according to body weight (patients weighing less than 65 kg received 800 mg/day, patients weighing between 65 and 85 kg received 1000 mg/day, patients heavier than 85 kg received 1200 mg/day) for 48 weeks. Patients were evaluated as outpatients for efficacy and tolerability on a monthly basis.

The primary end point of the study was SVR, defined as undetectable HCV RNA 6 months after the completion of treatment. End-of-treatment (EOT) response was defined as undetectable HCV RNA levels after 48 weeks of therapy. Non-responders were patients with detectable HCV RNA at all assessments during the treatment period, and virological breakthrough was defined as undetectable and subsequent reappearance of HCV RNA in a patient receiving therapy.

The definition of early virological response (EVR) varied according to treatment center. Accordingly, two EVR definitions were used across the entire study cohort, as follows :

1. ≥ 2 $\log_{10}$ reduction or undetectable HCV RNA at week 12
2. Undetectable HCV RNA at week 24

The dual definitions were the result of the differences in estimating EVR among the treating physicians. During the early part of this study, most physicians used qualitative PCR at week 24 to assess EVR. Later, however, when data supporting the week 12 evaluation of EVR was published (9), the study procedure was amended to assess EVR at week 12, in line with evolving best practice.

Qualitative HCV RNA levels were measured with use of Roche Amplicor (Roche Molecular Systems, Pleasanton, OR, USA ; lower limit of quantification (LLOQ) = 200 copies/mL]. Quantitative HCV RNA was measured with use of Roche Monitor (Roche Molecular Systems ; LLOQ = 2000 copies/mL). HCV genotyping was performed with the use of InnoLipa (Innogenetics, Zwijnaarde, Belgium). Serum ALT activity was determined using commercial reagents on an automated analyzer. Liver biopsy specimens were assessed by a local experienced pathologist who was unaware of the clinical and biochemical data. Histological results were classified according the METAVIR system (10).

Statistical analyses

Statistical analyses were performed on an intention-to-treat analysis. Parametric (Student *t*) and non-parametric (Mann-Whitney *U*) tests were used according to the distribution of the population. $P < 0.05$ was considered significant.

Results

Patient characteristics and disposition

In total, 239 patients with chronic hepatitis C were screened by 64 physicians (internists and gastroenterologists) at 46 centres in Belgium. Twenty patients were excluded : 4 patients did not start treatment, 1 was ineligible because HCV RNA was undetectable at the start of treatment, 5 were infected with HCV genotype 2 or 3 after the study began and were subsequently removed, and 10 had METAVIR fibrosis scores of F0 or F1. The intention-to-treat-population, therefore, consisted of 219 patients who received at least 1 injection of PEG-IFN alfa-2b, 1 capsule of ribavirin, or both.

Most patients had genotype 1 HCV (83%), and 69% had a baseline viral load greater than 600,000 IU/mL (Table 1). Twenty-two patients were of African origin, and all were infected with genotype 4 HCV. All remaining patients were Caucasian. Twenty-three percent of patients had histories of drug abuse.

In total, 121 of 219 patients completed 48 weeks of treatment, and 98 patients discontinued therapy early. Of the patients who did not complete the full treatment period, 41 did not attain EVR at week 12, 41 were discontinued because of poor tolerability (18 serious adverse events and 23 adverse events) and 16 discontinued for other reasons (5 patient's decision, 4 lost to follow-up, 7 non compliant patients).

Sustained virological response

In total, 108 of 219 (49.3%) patients had undetectable HCV RNA at the end of 48 weeks of therapy (Table 2, Fig. 1). Of these, 18 (16.7%) patients had relapse with detectable HCV RNA during follow-up, and 91 (41.6%) attained SVR. Furthermore, 8 patients with SVR were not assessed for HCV RNA at week 48 ; thus, the virological status of these patients at the end of treatment is unknown. One patient with detectable HCV RNA at the end of treatment had undetectable HCV RNA 24 weeks after treatment.

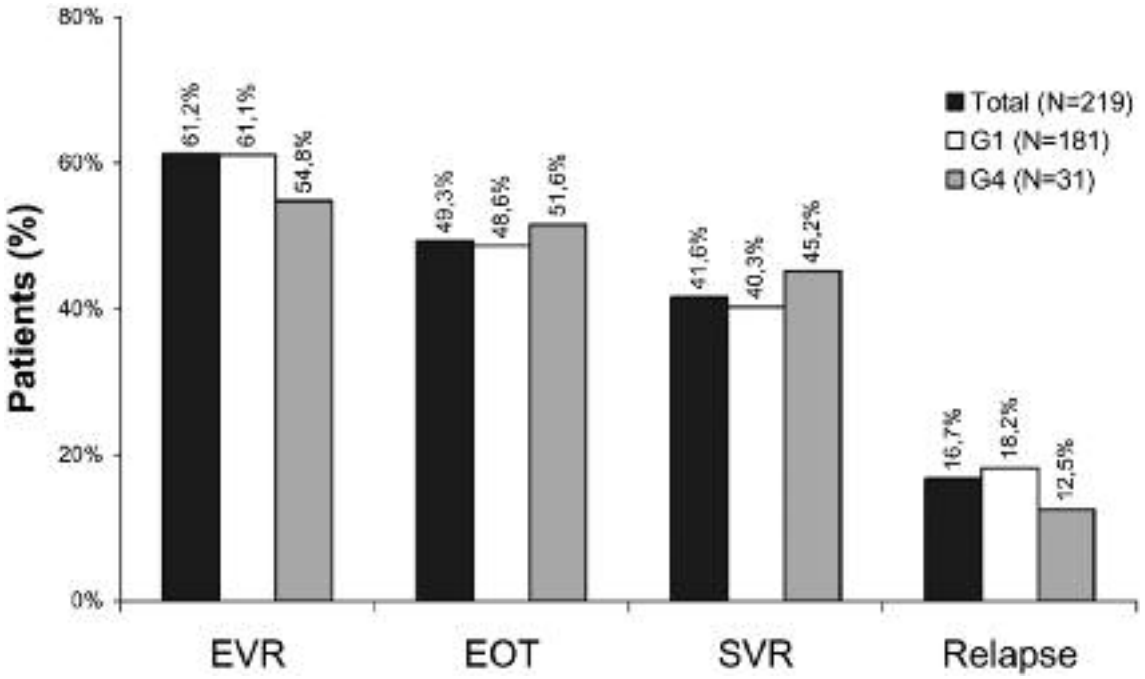

Fig. 1. — Treatment outcomes. EOT, end-of-treatment response ; EVR, early virological response ; G1, genotype 1 ; G4, genotype 4 ; NR, non-response ; SVR, sustained virological response.

Table 1. — **Patient demographics (mean ± SD)**

Variables	Total study population ($N = 219$)
Age, years (range)	51 (41-61)
Male, %	54
Weight, kg (range)	72 (63-82)
Body mass index, kg/m² (range)	25 (21-28)
Genotype, *n* (%)	
1	181 (83)
4	31 (15)
5	5 (2)
Unknown	1 (< 1)
Viral load, *n* (%)	
> 600,000 IU/mL	151 (69)
≤ 600,000 IU/mL	68 (31)
Percentage of fibrosis, *n* (%)	
F2	118 (54.0)
F3	45 (20.5)
F4	45 (20.5)
Unknown	11 (5.0)

Of the 111 patients who did not attain EOT response, 28 were non-responders with continuously detectable HCV RNA during the 48 week treatment period, 21 had virological breakthrough during treatment (i.e. reappearance of HCV RNA during therapy) and the remaining 62 had unknown virological status. Virology response data for genotype 1 and genotype 4 patients are also presented in Table 2.

Early virological response

EVR was assessed by 2 methods. In total, 199 subjects were assessed for EVR at week 12, week 24, or both. Overall, 51 patients were assessed for EVR at week 12 only, 33 patients were assessed for EVR at week 24 only, and 115 patients were assessed for EVR at week 12 and week 24 (Fig. 2). Of the 148 (68%) patients assessed for HCV RNA status at week 24, 47 had detectable HCV RNA and 101 patients had undetectable HCV RNA.

When considering week 12 and week 24 criteria, 134 of 219 patients were classified as having attained EVR ; of those, 105 had EOT responses and 88 attained SVR [positive predictive value (PPV), 65.7% ; Fig. 3]. In total, 87 of 88 patients with EVR who attained SVR had undetectable HCV RNA at the end of treatment. One patient who attained EVR but had detectable HCV RNA at the end of treatment also attained SVR (Fig. 2). In contrast, 82 of 85 patients who were not assessed or who did not attain EVR also did not attain SVR (negative predictive value (NPV), 96.5% ; 70 were non-responders, and 12 experienced virological breakthrough while on therapy). Of the 29 patients with EVR who did not attain EOT responses, 9 had virological breakthroughs while on therapy, and 20 had unknown virological status.

When considering week 12 EVR only, HCV RNA status was assessed in 166 patients ; of these, 52 patients did not attain EVR. Thus, 114 of 166 patients attained week 12 EVR; of those, 65 attained SVR. Thus, the PPV (proportion of EVR-positive patients who attained SVR) for the week 12 EVR assessment was 57%. Week 12 EVR was associated with an NPV of 92.

Predictors of response

Age, fibrosis score and baseline viral load were identified as important predictors of treatment outcome (Table 3). In the overall study population and in the

Table 2. — **Virological responses**

	All patients (N = 219)	Genotype 1 (n = 181)	Genotype 4 (n = 31)
Early virological response, n (%)	134 (61.2)	112 (61.1)	17 (54.8)
End-of-treatment response, n (%)	108[a] (49.3)	88 (48.6)	16 (51.6)
Relapse, n (%)	18 (16.7)	16 (18.2)	2 (12.5)
Sustained virological response, n (%)	91[b] (41.6)	72 (40.3)	14 (45.2)

[a] Of these 108 patients, 105 patients attained early virological response but 3 patients did not.
[b] One patient had detectable HCV RNA at week 48 but undetectable HCV RNA 24 weeks after treatment ; 8 patients were not assessed at week 48 but attained sustained virological response.

Table 3. — **Predictors for sustained virological response in the entire population and in genotype 1 and genotype 4 cohorts**

	All patients (n = 219)			Genotype 1 (n = 181)			Genotype 4 (n = 31)		
	SVR (n = 91)	No SVR (n = 128)	P	SVR (n = 72)	No SVR (n = 109)	P	SVR (n = 14)	No SVR (n = 17)	P
Age, y (range[a])	46 (35-58)	54 (44-64)	**<0.001**	47 (36-58)	55 (45-64)	**<0.001**	37 (30-47)	49 (43-58)	**< .01**
Gender (n)									
Male	46	73	0.38	36	62	0.45	9	10	0.9
Female	45	55		36	47		5	7	
Weight, kg (range)	71.4 (62.5-81.0)	72.5 (64.0-82.0)	0.42	71 (62-80)	72 (63-82)	0.8	71 (67-82)	81 (73-92)	**0.01**
BMI, kg/m^2 (range)	24.6 (21.6-27.94)	25.2 (22.8-28.4)	0.26	24.7 (21.7-28.0)	24.9 (22.6-27.7)	0.74	23.4 (20.5-25.8)	27.3 (24.7–34.1)	**0.01**
Fibrosis, n (%)									
F2	66 (77)	52 (43)	**<0.001**	49 (72)	42 (41)	**<0.01**	12 (92)	10 (59)	0.1
F3-F4	20 (23)	69 (57)		19 (28)	61 (59)		1 (8)	7 (41)	
Viral load, n (%)									
> 600,000 IU/mL	46 (51)	85 (59)	**0.01**	39 (54)	73 (67)	0.08	5 (36)	10 (59)	0.18
≤ 600,000 IU/mL	33 (36)	27 (21)		24 (33)	19 (17)		8 (57)	4 (24)	

SVR, sustained virological response; BMI, body mass index
[a] Intraquartile, representing range between 25th and 75th quartiles.

genotype 1 cohort, the mean age was significantly lower among patients who attained SVR than among those who did not ($P < 0.001$). Baseline viral load and fibrosis score were also significant predictors of treatment outcome in the overall study population.

The use of a weight-based ribavirin dosing regimen benefited patients throughout the entire weight spectrum, and there was no influence of body weight or body mass index (BMI) on SVR rates in the overall population or the genotype 1 cohort (Table 3). In genotype 4 patients, BMI and body weight were significantly associated with treatment outcome ($P = 0.01$) ; however, these data should be viewed with caution given the very low numbers of patients included in this analysis.

Safety and tolerability

Fourty-one patients discontinued treatment early because of adverse events ($n = 23$) or serious adverse events ($n = 18$). Ten patients discontinued treatment during weeks 1 to 12, 16 patients discontinued treatment during weeks 12 to 24, and the remaining 15 patients discontinued treatment after week 24. The most frequently reported serious adverse events resulting in treatment discontinuation were anemia (Hb ≤ 10 g/dL) ($n = 11$), fatigue/asthenia/malaise ($n = 6$) and fever ($n = 3$).
Adverse events were classified as hematological (anemia, $n = 11$; neutropenia, $n = 2$; pancytopenia, $n = 2$; thrombocytopenia, $n = 3$), general ($n = 15$), neuropsychiatric (5 depressions, 2 with suicidal thoughts) ($n = 5$), cutaneous ($n = 5$), optical neuropathic ($n = 2$) and gastrointestinal ($n = 2$).

Six deaths occurred during the treatment period (median patient age, 61 years ; intraquartile range, 55-77 years). Causes of death were cardiovascular event (1 patient), sepsis (1 transplanted patient for hepatocellular carcinoma), hepatocellular carcinoma (1 patient), multiple organ failure after lung infection (1 patient), and unknown (2 patients). None of the deaths were considered related to the study except the cardiovascular event in a 69 year patient, which was considered by the investigator to be probably related to PEG-IFN alfa-2b plus ribavirin treatment.

Discussion

Our data suggest that the SVR rates attained in large-scale clinical trials provide a realistic indication of the

SVR rates achievable in a community-based setting. In our exclusively genotype 1 and genotype 4 population, SVR rates were remarkably akin to those reported for similar cohorts in large clinical trials (42% vs 42%-52%) (7,8,11). Interestingly, the final results of a large Canadian community-based study (POWeR), which incorporated a weight-based ribavirin administration schedule (800-1200 mg/day according to body weight) in combination with PEG-IFN alfa-2b, also supports a close relationship between SVR rates in clinical trials and those attained in a community-based setting (12). SVR rates were similar in genotype 1 patients in POWeR and in the present study (42% *vs* 40%). Furthermore, the findings of AWB (13) in a community-based surveillance study that also made use of weight-based ribavirin dosing (800-1200 mg/day according to body weight) with PEG-IFN alfa-2b (1.5 µg/kg/wk) in Germany, support the use of a weight-based ribavirin regimen. A recent interim analysis of this study reported highly favorable SVR rates of 66% in a predominantly genotype 1, 4, 5, 6 population. Collectively, these data are encouraging and may help to dispel the perception that SVR rates reported in large clinical trials are generally not attainable in routine clinical practice.

Weight-based ribavirin dosing appears to be a critical factor in the success of community-based studies such as POWeR and AWB and also in the present study. The benefits associated with weight-based dosing of ribavirin were first suggested by Manns *et al.* (8). Logistic regression analysis of data from patients receiving PEG-IFN alfa-2b plus ribavirin at a fixed dose of 800 mg/day indicated that baseline body weight is an important predictor of SVR. These authors found that an increasing ribavirin dose per unit body weight was positively correlated with SVR to a threshold of approximately 13 mg/kg/day, after which further increases in ribavirin dose were not paralleled by increasing SVR rates (8). Manns *et al.* (8) conclude that a ribavirin dose range of between 11 and 15 mg/kg/day provides an effective balance between safety and efficacy. More recently, the merits of weight-based ribavirin dosing have received further affirmation from the results of the WIN-R study, which incorporated a structured, weight-based ribavirin schedule plus PEG-IFN alfa-2b into a large community-based prospective clinical trial (14). In genotype 1 patients, SVR rates were significantly higher among those receiving weight-based ribavirin (800-1400 mg/day) than in those receiving a fixed 800 mg/day dose (34% *vs* 29% ; $P = 0.004$). Weight-based dosing of ribavirin was approved in 2001 by the European Medicines Evaluation Agency, encouraging the wider adoption of this regimen into routine clinical practice. In our study, the absence of body weight or BMI as a predictor of treatment outcome, coupled with SVR rates that are comparable to previous clinical trial data, suggests that weight-based ribavirin dosing is an effective treatment approach in the community setting.

Age, baseline viral load, and fibrosis score were identified as significant predictors of treatment outcome. Again, these observations closely parallel previous clinical trial data that have also identified these characteristics as related to treatment outcome (7,8,11,15]. Zeuzem (15) suggested that because these factors are independently associated with treatment outcome, they have a cumulative effect on treatment outcomes when they exist in tandem. The least favorable population from the perspective of treatment outcomes would include genotype 1, 4, 5 or 6 HCV, high baseline viral load, age > 40 years, male gender, and septal fibrosis or cirrhosis (15,16). In this context, our overall SVR rate of 42% is particularly impressive. Eighty-three percent of patients in the present study had genotype 1 HCV, 69% had baseline viral load greater than 600,000 IU/mL, more than 75% were older than 40 years, 54% were male, and more than 40% had bridging fibrosis or cirrhosis. Similar demographics were also reported for the POWeR study cohort (approximately 60% genotype 1, 52% with viral load > 600,000 IU/mL, 40% with bridging fibrosis or cirrhosis) (12) possibly indicating that these difficult-to-treat patients are more frequently encountered in routine clinical practice and are generally under-represented in clinical trials.

Treatment discontinuation may also be more prevalent in the community-based management of chronic hepatitis C than in large-scale clinical trials in which patients can benefit from frequent physician visits and motivational support. In total, 18% of patients in the present study discontinued therapy because of poor tolerability, similar to rates reported in clinical trials (14%-22%) (7,8,11). Again, these data contradict the popular theory that patients in general clinical practice do not receive the same level of motivational support than patients enrolled in clinical trials receive, and this translates to lower adherence and higher dropout rates in community-based settings.

The predictive value of EVR in this study is difficult to determine because of the change in practice that occurred during the conduct of the study. Once it was realized that week 12 evaluation of HCV RNA levels provided an accurate prediction of treatment outcome, we modified our approach to accommodate this important treatment advance ; unfortunately, this change also confounded the analysis of our data. Nevertheless, some basic conclusions can be drawn from our data. In total, 92% of patients who did not attain an EVR at week 12 also did not attain SVR. Our subanalysis of only those patients with HCV RNA levels assessed at week 12 is, therefore, consistent with previously reported data highlighting the very high NPV of this assessment and validating its use as an early stopping rule. This reinforces the strategies of assessing EVR at week 12 and of withdrawing from treatment patients who have detectable HCV RNA at week 24. Both approaches are now regarded as integral elements of the individualized approach to the treatment of patients with chronic hepatitis C (17).

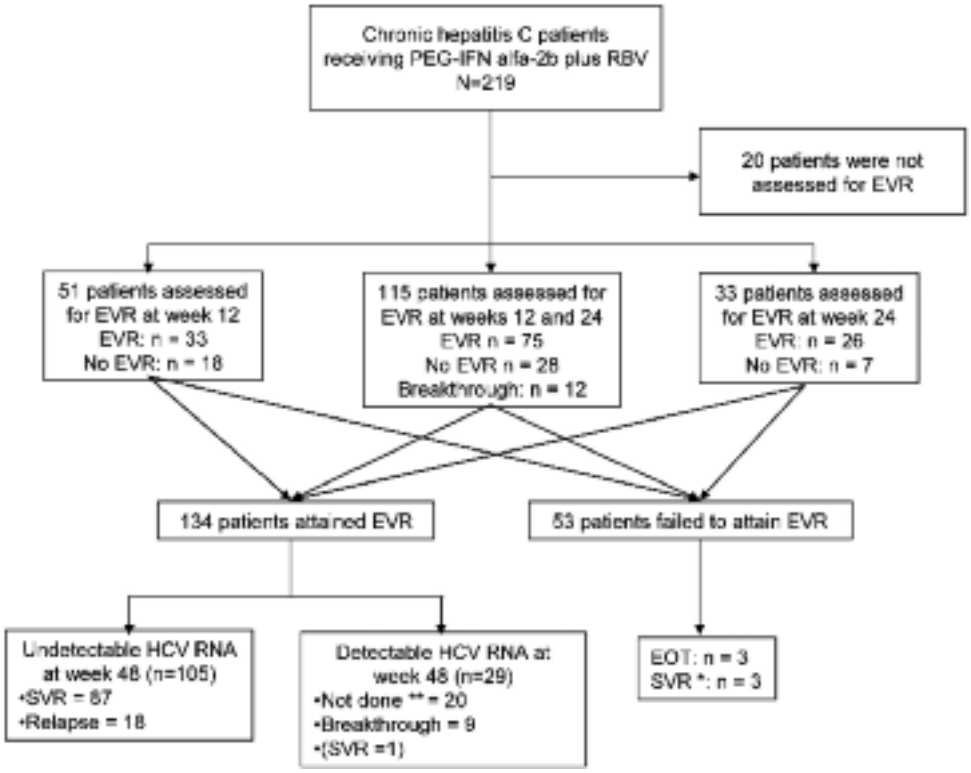

Fig. 2. — Assessment of early virological response. Patients with breakthrough viremia had undetectable HCV RNA at week 12 of therapy but detectable HCV RNA later during therapy. * Three patients who did not attain EVR attained EOT response and SVR. EVR, early virological response ; PEG-IFN, pegylated interferon ; RBV, ribavirin ; SVR, sustained virological response ; EOT, end of treatment.

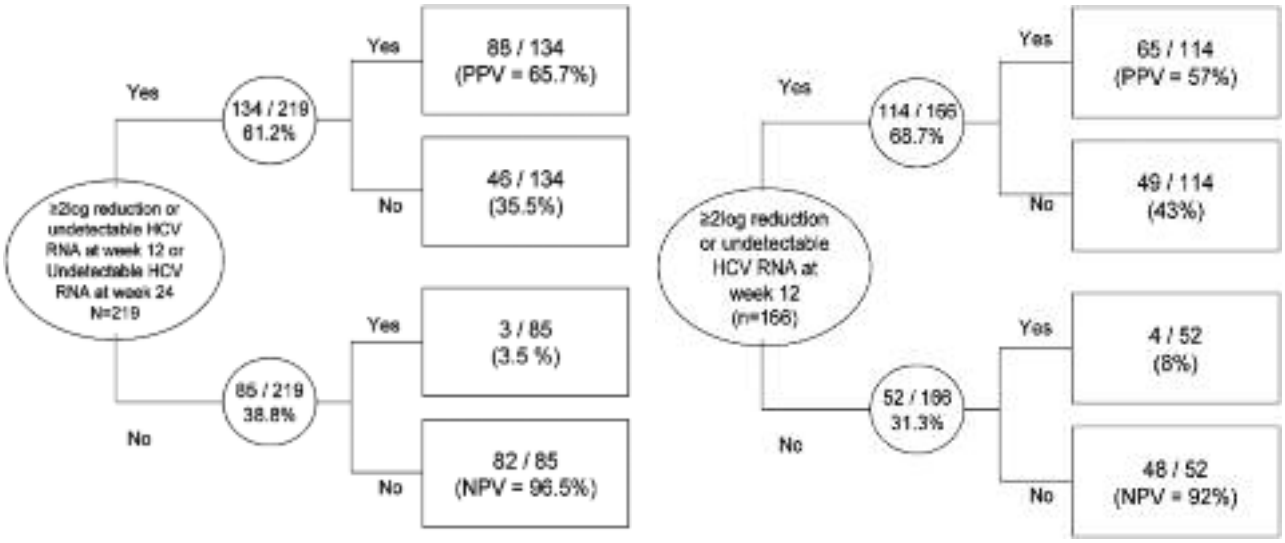

Fig. 3**. —** Early virological response as predictor of treatment outcome. (A) All patients, weeks 12 and 24 EVR criteria. (B) Week 12 EVR subanalysis. EVR, early virological response ; HCV, hepatitis C virus ; PPV, positive predictive value ; NPV, negative predictive value.

In conclusion, our data indicate that PEG-IFN alfa-2b plus weight-based ribavirin therapy for chronic hepatitis C resulted in favourable treatment outcomes in general clinical practice in a Belgian cohort. Enrolment of patients in trials testing new molecules has to be encouraged and these trials should be more accessible. Community -based studies of therapy for chronic hepatitis C are also required to distinguish the differences and similarities in findings between clinical trials and routine practice and to help provide relevant, evidence-based treatment regimens within a community-based setting.

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Appendix 1. — Alphabetical list of investigators

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Prof. M. Adler	CHU Erasme, Brussels
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Dr. N. Botembe	CH de l'Ardenne, Libramont
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Dr. S. Bourgeois	AZ Stuivenberg, Antwerp
Dr. C. Braxel	Privé - Eedverbondkaai, Gent
Dr. R. Brenard	Hôpital St.-Joseph, Gilly
Dr. C. Brixko	CHR de la Citadelle, Liège
Dr. M. Cabooter	AZ St-Jan, Bruges
Dr. M Castelain	Clin. des 2 Alice, Brussels
Dr. J. Coche	Clin. St.-Pierre
Dr. J. Colin	Clin. Europe St-Michel, Brussels
Prof. I. Colle	UZ Gent
Dr. C. De Galocsy	Clin. St. Anne / St. Rémi, Brussels
Dr. X. De Koninck	Clin. St.-Pierre, Brussels
Dr. M. De Maeyer	AZ St Elisabeth, Herentals
Dr. J. Delwaide	CHU Sart Tilman, Liège
Dr. J. Delwaide	CHR La Tourelle, Verviers
Dr. C. Denié	CHU Hornu, Frameries
Dr. J. Dewyspelaere	Stedelijk Ziekenhuis, Roeselare
Dr. B. D'Harveng	CHU Mouscron
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Dr. J.Henrion	Hôpital de Jolimont, Haine-St-Paul
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Dr. P. Holvoet	AZ Campus Middelheim, Antwerp
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Dr. J. Hulstaert	AZ Jan Portaels (b.v.b.a. Gastric), Vilvoorde
Dr. G. Lambrecht	AZ Damiaan Oostende
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Dr. L. Lasser	CHU Brugmann, Brussels
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Dr. V. Lefèbvre	CHR Namur
Prof. P. Michielsen	UZ Antwerpen
Dr. M. Moulart	CH Hornu, Frameries
Dr. JP. Mulkay	CHU St. Pierre, Brussels
Dr. JP.Mullier	CHU Joseph Bracops, Brussels
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Dr. H. Orlent	AZ St-Jan, Bruges
Dr. G. Paul	Clin. Europe St-Michel, Brussels
Dr. J. Ponette	St-Marie ZH, Halle
Dr. H. Reynaert	UZ, Brussels
Dr. G. Robaeys	ZOL, Genk
Dr. F. Sermon	UZ, Brussels
Dr. C. Solbreux	Clin. St.-Joseph, Liège
Dr. D. Sprengers	AZ St. Augustinus, Antwerp
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Prof. W. Van Steenbergen	UZ Gasthuisberg, Leuven
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Prof. H. Van Vlierberghe	UZ Gent
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Dr. P. Warzee	CHNDRF, Charleroi
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