Characteristics, treatment, and virologic responses of chronic hepatitis C patients treated with peginterferon alfa-2a and ribavirin in Belgium : a sub-analysis of the PROPHESYS study

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Abstract

Background and study aims : **PROPHESYS was a prospective, international cohort study of monoinfected, treatment-naive chronic hepatitis C patients treated with a combination of peginterferon alfa-2a or alfa-2b and ribavirin. It included worldwide 7,163 patients from 19 countries (including 384 patients from Belgium alone) and demonstrated that sustained virologic response rates in the real world were similar to those achieved in well-controlled clinical trials. The objective of this sub-analysis was to present an overview of the baseline characteristics, anti-hepatitis C drug treatment, and virologic responses of the patients treated in Belgium, infected with HCV genotype 1, 2, 3, or 4, and administered peginterferon alfa-2a. Moreover, the impact of ribavirin dosage on the response to treatment was studied.**

Patients and methods : **356 patients were included in this sub-analysis. All variables were summarized using descriptive statistics.**

Results : **Compared to the published data of the whole study population (1), the Belgian data presented some significant differences in terms of genotype distribution and response to treatment (e.g. lower prevalence of HCV genotype 1 infection, lower virologic response rates in HCV genotype 2 patients). Deviations from existing recommendations were identified (e.g. higher dose of ribavirin in HCV genotype 2 or 3 patients). Patients who received less than 80% of the target dose of ribavirin experienced a significantly weaker response to treatment.**

Conclusion : **This sub-analysis provided an interesting profile of the Belgian experience in the treatment of chronic hepatitis C.** (Acta gastroenterol. belg., **2014**, 77, **30-40**).

Key words : Hepatitis C, treatment, survey, Belgium.

Introduction

PROPHESYS was a prospective, international cohort study of monoinfected, treatment-naive chronic hepatitis C patients treated with a combination therapy consisting of peginterferon alfa-2a or alfa-2b and ribavirin, administered in accordance with country-specific legal and regulatory requirements (1). The study started in June 2007 and ended in March 2011. The objective of the study was to investigate the predictive value of a virologic response by weeks 2, 4 and 12 of treatment on sustained virologic response (SVR) in a routine clinical practice setting. SVR was defined as a HCV RNA level < 50 IU/mL at 24 weeks after end of treatment (EOT). The study included worldwide 7,163 patients from 19 countries and demonstrated that SVR rates achieved with peginterferon alfa-2a and ribavirin in the real world were similar to those achieved in well-controlled trials (2-6). 384 patients were enrolled and treated in Belgium. The overwhelming majority of them (95.1%) had been treated with peginterferon alfa-2a and a small minority (2.9%) were infected with HCV genotype 5 or 6. These findings explain why the population retained for this sub-analysis consisted only of patients infected with HCV of genotype 1, 2, 3, or 4 and treated with peginterferon alfa-2a and ribavirin. The objective of this sub-analysis was to present an overview of the baseline characteristics, drug treatment, and virologic responses of the patients treated in Belgium and to compare them with the data of the whole PROPHESYS study population, published by Marcellin P *et al* (1). In addition the impact of ribavirin dosage on the virologic response to treatment was studied.

Patients, material and methods

Patients

The primary analysis population consisted of all patients infected with HCV genotypes 1 to 4, treated in Belgium, who received ≥ 1 dose of peginterferon alfa-2a and ribavirin, had a baseline HCV RNA level ≥ 50 IU/mL, and had at least one post-baseline HCV RNA test result. The secondary analysis population included only patients with sufficient follow-up data. Patients were excluded from the secondary population if they had a HCV RNA level < 50 IU/mL at EOT, had no evidence of relapse and had no HCV RNA test done ≥ 140 days after EOT (for reasons not related to efficacy or safety). This study was conducted in accordance with the Declaration of Helsinki ; the protocol had been approved by the competent Institutional Review Boards and each patient had provided informed and voluntary consent to participate in the study.

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Submission date : 14/08/2013
Acceptance date : 07/12/2013

Anti-HCV Treatment

Patients were administered peginterferon alfa-2a (Pegasys®) in association with ribavirin (Copegus®). The overall duration of treatment, i.e. the period of time from start of treatment to last dose of peginterferon alfa-2a, was calculated in the primary population and patients were counted in each category of treatment duration (< 24, 24-25, > 25-< 48, 48-49 and > 49 weeks) for each HCV genotype. Patients were also counted in each category of start dose of anti-HCV drugs (180 or < 180 μg/week for peginterferon alfa-2a, and < 800, 800, 1,000, 1,200, or > 1,200 mg/d for ribavirin). The target dose of anti-HCV drugs was defined as the product of start dose and intended duration of treatment. The cumulative dose of anti-HCV treatment was defined as the product of start dose and calculated duration of treatment, taking into account possible dose modifications and/or treatment interruptions within this interval of time. Cumulative doses were presented as percentage (< 80% or ≥ 80%) of the target doses.

Outcomes

HCV RNA level was measured with the help of COBAS® AmpliPrep/COBAS® TaqMan® test. To allow comparisons with patients from countries using HCV RNA tests with a lower degree of sensitivity, HCV RNA level of 50 IU/mL (instead of 15 IU/ml which is actually the lower limit of detection of the COBAS® AmpliPrep/COBAS® TaqMan® test) was selected as cut-off value for the definition of a virologic response. Virologic responses were measured at baseline, by week 4 (i.e. at any time between Day 2 and Day 43), by week 12 (i.e. at any time between Day 2 and Day 99), at EOT (i.e. day of last drug intake ± 28 days) and at 24 weeks after EOT (i.e. ≥ 140 days after last drug intake) in both primary and secondary analysis populations. Virologic responses were not measured by week 2 as most physicians did not measure the viral load of HCV during the first two weeks of treatment. Time windows needed to be large because the aim of the study was document the actual behavior of the prescribers, in their routine clinical practice, without external constraint. Virologic responses were also analyzed in function of the cumulative dose of ribavirin taken by the patients (< 80% or ≥ 80% of the target dose). Treatment responses during the first 12 weeks of treatment were categorized as rapid (RVR), complete early (cEVR) and partial early (pEVR) virologic responses. RVR was defined as an HCV RNA test showing response at any time during the interval of time comprised between Day 2 and Day 43. cEVR was defined as an HCV RNA test showing response at any time during the interval of time comprised between Day 44 and Day 99 (but with no response between Day 2 and Day 43). pEVR was defined as a 2-$\log_{10}$ drop at any time during the interval of time comprised between Day 2 and Day 99, without RVR or cEVR. A patient was said to have experienced a virologic breakthrough if his HCV RNA level had decreased < 50 IU/mL during treatment but had rebounded before completion. A patient was said to have experienced a virologic relapse if his HCV RNA level had decreased and remained < 50 IU/mL during treatment but had become ≥ 50 IU/mL at 24 weeks after EOT. The number of patients with premature withdrawal from treatment, or with incomplete follow-up (i.e. without HCV RNA test result ≥ 140 days post-treatment), was calculated in the primary population and the reasons were documented. Positive predictive values (PPVs) and negative predictive values (NPVs) were calculated in both populations. PPV is the probability that a patient with given on-treatment virologic response by a given week will achieve an SVR. Conversely, NPV is the probability that a patient without a given on-treatment virologic response by a given week will not achieve an SVR. In the questionnaire to be completed by the physicians adverse events and deaths had to be reported without further description if they had consequences on the dosage of anti-HCV drug or the duration of treatment.

Results

Patients

Most patients treated in Belgium were infected with HCV genotype 1 (41.3%) and genotype 3 (32.6%). They were predominantly males (58.4%), white (76.4%), and younger than 45 (53.7%), with a body mass index (BMI) > 25 kg/m^2 (49.7%). Liver biopsy was the most frequent method to assess liver fibrosis in patients infected with HCV genotype 1 or 4 (95.2% and 96.4% respectively) and was performed in about one third of the patients with HCV genotype 2 or 3 (34.2% and 39.7% respectively). Cirrhosis or transition to cirrhosis was diagnosed in 23.0% of the patients whose liver fibrosis status had been assessed by an invasive or non-invasive method. The ALT ratio (i.e. actual ALT level divided by upper limit of normal for ALT) was ≤ 1 in 19.0% of the patients and the baseline HCV RNA level > 800,000 IU/mL in 56% of the patients. Except for two patients infected with HCV genotype 3, the duration of treatment anticipated by the physicians at baseline (48-49 weeks for HCV genotype 1 or 4, and 24-25 weeks for HCV genotype 2 or 3) complied with the recommendations of the summaries of product characteristics (SPCs) of both anti-HCV products. Baseline characteristic are summarized in Table 1.

Treatment

The calculated duration of treatment was on average 42.3 ± 13.4 and 43.2 ± 13.6 weeks in patients infected with HCV genotype 1 and 4 respectively (Table 2). In patients infected with HCV genotype 2 or 3, it was 21.2 ± 6.7 and 23.6 ± 5.5 weeks respectively. Table 2 provides the number and the proportion of patients whose duration of treatment complied with the SPC recommendations, or were longer or shorter than recommended. The start doses of peginterferon alfa-2a and ribavirin

Table 1. — **Baseline Characteristics**

Characteristics		**Genotype 1** [n = 147 (41.3%)]	**Genotype 2** [n = 38 (10.7%)]	**Genotype 3** [n = 116 (32.6%)]	**Genotype 4** [n = 55 (15.4%)]	**Total** [n = 356 (100%)]
Age [years, mean ± standard deviation [SD]]		46.7 ± 13.3	47.4 ± 12.4	40.6 ± 9.8	51.3 ± 12.8	45.5 ± 12.6
Age categorized (n)	≤ 45 years	74 (50.3%)	17 (44.7%)	82 (70.7%)	18 (32.7%)	191 (53.7%)
	> 45-65 years	61 (41.5%)	18 (47.4%)	32 (27.6%)	27 (49.1%)	138 (38.8%)
	> 65 years	12 (8.2%)	3 (7.9%)	2 (1.7%)	10 (18.2%)	27 (7.6%)
Sex (n)	Male	79 (53.7%)	23 (60.5%)	81 (69.8%)	25 (45.5%)	208 (58.4%)
	Female	68 (46.3%)	15 (39.5%)	35 (30.2%)	30 (54.5%)	148 (41.6%)
Ethnicity (n)	White	134 (91.2%)	29 (76.3%)	93 (80.2%)	16 (29.1%)	272 (76.4%)
	Black	3 (2.0%)	3 (7.9%)	1 (0.9%)	35 (63.6%)	42 (11.8%)
	Asian	4 (2.7%)	1 (2.6%)	12 (10.3%)	–	17 (4.8%)
	Other	6 (4.1%)	5 (13.2%)	10 (8.6%)	4 (7.3%)	25 (7.0%)
Weight [kg ± SD]		73.2 ± 15.5	75.1 ± 17.3	74.0 ± 14.2	77.8 ± 11.9	74.4 ± 14.8
Body Mass Index (BMI) [kg/m^2 ± SD]		25.34 ± 4.51	26.61 ± 6.45	25.02 ± 4.31	27.45 ± 4.60	25.70 ± 4.76
BMI categorized (n)	≤ 20 kg/m^2	9 (6.2%)	2 (5.3%)	11 (9.5%)	1 (1.8%)	23 (6.5%)
	> 20 -25 kg/m^2	66 (45.5%)	17 (44.7%)	55 (47.4%)	17 (30.9%)	155 (43.8%)
	> 25 kg/m^2	70 (48.3%)	19 (50.0%)	50 (43.1%)	37 (67.3%)	176 (49.7%)
Method used to assess liver fibrosis (n)	Biopsy	140 (95.2%)	13 (34.2%)	46 (39.7%)	53 (96.4%)	252 (70.8%)
	Non-invasive	5 (3.4%)	8 (21.1%)	23 (19.8%)	1 (1.8%)	37 (10.4%)
	Not assessed	2 (1.4%)	17 (44.7%)	47 (40.5%)	1 (1.8%)	67 (18.8%)
Result of liver fibrosis assessment (n)	Cirrhosis or transition	41 (27.9%)	12 (31.6%)	17 (14.7%)	12 (21.8%)	82 (23.0%)
	No cirrhosis	104 (70.7%)	9 (23.7%)	52 (44.8%)	42 (76.4%)	207 (58.1%)
	Not assessed/ missing	2 (1.4%)	17 (44.7%)	47 (40.5%)	1 (1.8%)	67 (18.8%)
Steatosis (n)	Yes	54 (36.7%)	10 (26.3%)	35 (30.2%)	25 (45.5%)	124 (34.8%)
	No	42 (28.6%)	8 (21.1%)	31 (26.7%)	18 (32.7%)	99 (27.8%)
	Not assessed/Missing	51 (34.7%)	20 (52.6%)	50 (43.1%)	12 (21.8%)	133 (37.4%)
Alanine aminotransferase [ALT] ratio categorized	≤ 1	35 (24.3%)	11 (28.9%)	10 (8.6%)	11 (20.4%)	67 (19.0%)
	> 1-3	83 (57.6%)	23 (60.5%)	75 (64.7%)	34 (63.0%)	215 (61.1%)
	> 3	26 (18.1%)	4 (10.5%)	31 (26.7%)	9 (16.7%)	70 (19.9%)
HCV-RNA (10^{5}IU/ml) categorized (n)	≤ 4	42 (29.2%)	8 (21.6%)	35 (30.2%)	29 (54.7%)	114 (32.6%)
	> 4-8	19 (13.2%)	3 (8.1%)	12 (10.3%)	6 (11.3%)	40 (11.4%)
	> 8	83 (57.6%)	26 (70.3%)	69 (59.5%)	18 (34.0%)	196 (56.0%)
Intended duration of treatment (n)	24 weeks	0 (0.0%)	38 (100%)	114 (98.3%)	0 (0.0%)	152 (42.7%)
	48 weeks	147 (100%)	0 (0.0%)	2 (1.7%)	55 (100%)	204 (57.3%)

The subtypes of HCV genotype 1 were identified in 122 patients. Subtype 1a only was found in 25 patients (20.5%), subtype 1b only was found in 95 patients (77.9%) and 1a and 1b in 2 patients (1.6%).

Table 2. — **Duration of treatment***
* From start of treatment to last dose of PEG INF alfa-2a

	Genotypes				
	G1 (n = 147)	G2 (n = 38)	G3 (n = 116)°	G4 (n = 55)	All genotypes (n = 356)[2]
Calculated duration of treatment in weeks					
Mean (SD)	42. 3 ± 13.4	21.2 ± 6.7	23.6 ± 5.5	43.2 ± 13.6	34.1 ± 14.5
Median	48.0	24.0	24.0	48.0	27.0
Min-Max	5-65	6-28	4-49	6-78	4-78
Number of patients in each category of calculated duration of treatment					
< 24 weeks	23 (15.6%)	12 (31.6%)	17 (14.8%)	8 (14.5%)	60 (16.9%)
24-25 weeks	3 (2.0%)	22 (57.9%)	84 (73.0%)	1 (1.8%)	110 (31.0%)
> 25-< 48 weeks	16 (10.9%)	4 (10.5%)	13 (11.3%)	7 (12.7%)	40 (11.3%)
48-49 weeks	88 (59.9%)	0 (0.0%)	1 (0.9%)	30 (54.5%)	119 (33.5%)
> 49 weeks	17 (11.6%)	0 (0.0%)	0 (0.0%)	9 (16.4%)	26 (7.3%)

° 115 and 355 patients for G2 and all genotypes respectively contributed to this information.

Table 3. — **Start dose of anti-HCV drugs**

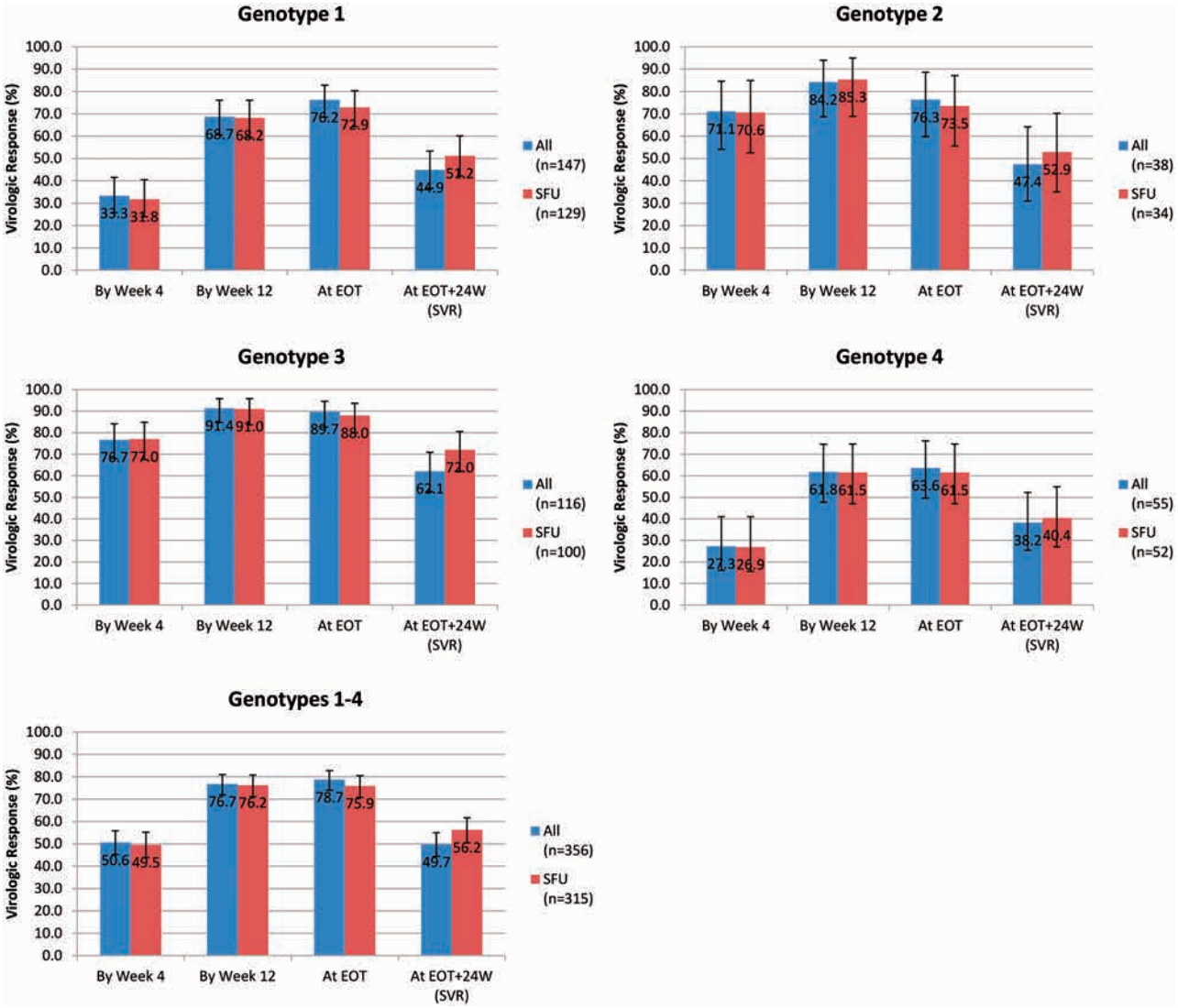
PEG-IFN a-2a (in μg/week)	Genotype						
	G1 (n = 147)		G2 (n = 38)	G3 (n = 116)	G4 (n = 55)		Overall population (n = 356)
	Number and Proportion of Patients						
180	146 (99.3%)		37 (97.4%)	116 (100%)	54 (98.2%)		353 (99.2%)
< 180	1 (0.7%)		1 (2.6%)	0 (0%)	1 (1.8%)		3 (0.8%)
Ribavirin (RBV) (in mg/d)	Genotype and Body Weight [BW] for G1 and G4						
	G1 BW < 75 Kg (n = 82)	G1 BW ≥ 75 Kg (n = 63)	G2 (n = 38)	G3 (n = 116)	G4 BW < 75 Kg (n = 21)	G4 BW ≥ 75 Kg (n = 34)	Overall population (n = 356)*
	Number and Proportion of Patients						
< 800	1 (1.2%)	0 (0.0%)	2 (5.3%)	2 (1.7%)	0 (0.0%)	1 (2.9%)	6 (1.7%)
800	6 (7.3%)	0 (0.0%)	25 (65.8%)	74 (63.8%)	1 (4.8%)	0 (0.0%)	106 (29.8%)
1,000	64 (78.0%)	9 (14.3%)	7 (18.4%)	23 (19.8%)	17 (81.0%)	7 (20.6%)	129 (36.2%)
1,200	11 (13.4%)	54 (85.7%)	4 (10.5%)	16 (13.8%)	3 (14.3%)	26 (76.5%)	114 (32.0%)
> 1,200	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.3%)

* Two G1 patients whose body weight was not recorded were treated with ribavirin at a dose of 1,000 mg/d. They were counted in the overall population column.

were examined in the light of the SPC recommendations as well. The start dose of peginterferon alfa-2a amounted to 180 μg/week in 99.2% of the patients, as recommended by the SPC of this drug (Table 3). Variations in the start dose of ribavirin were much more significant and are detailed in Table 3.

Outcomes

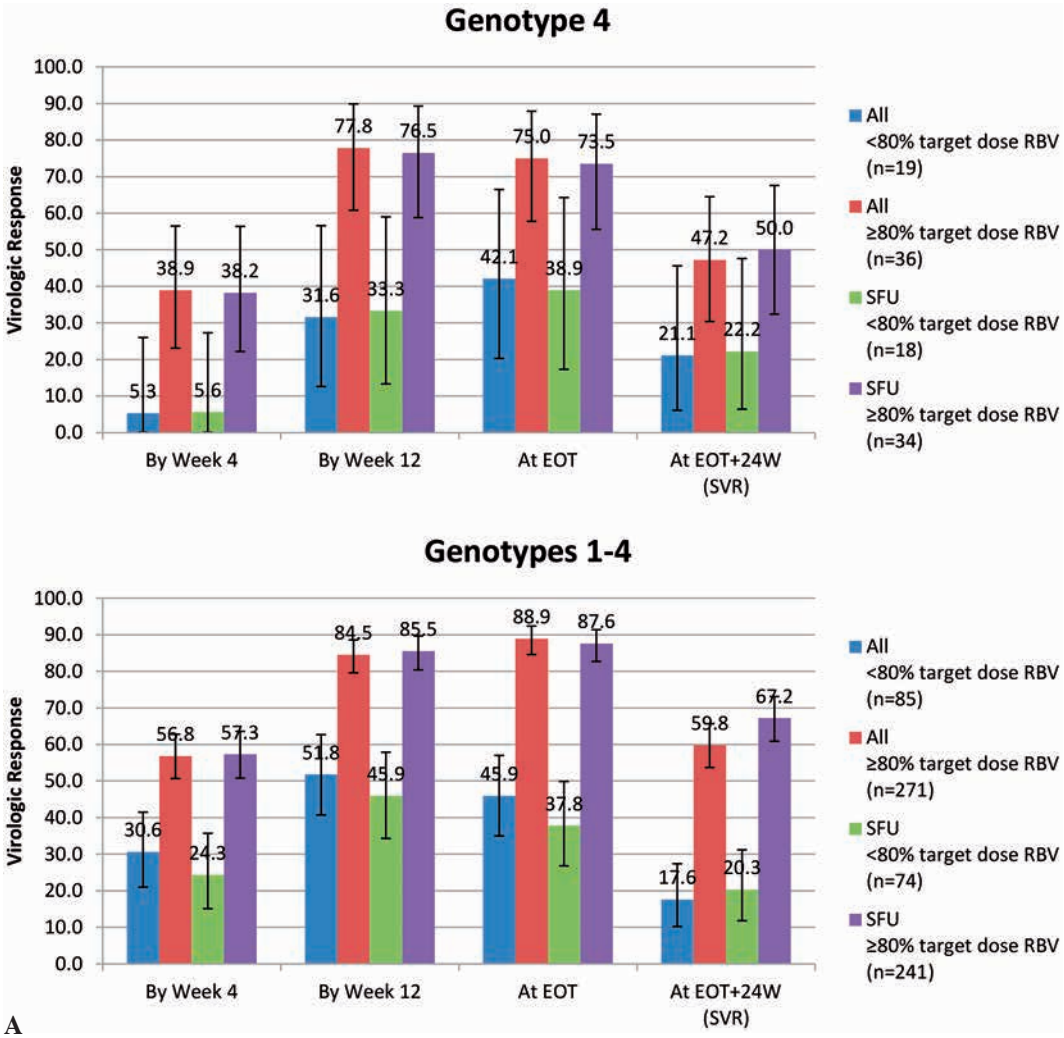
Across all genotypes the SVR rate was 49.7% (95%CI : 44.4%-55.0%) in the primary population and 56.2% (95%CI : 50.5%-61.7%) in the secondary population (Fig. 1). The mean SVR of the 38 patients infected with HCV genotype 2 was surprisingly low, with 47.4% (95%CI : 31.0%-64.2%) and 52.9% (95%CI : 35.1-70.2%) respectively. SVR rates were deeply influenced by the cumulative dose of ribavirin taken by the patients. Across all genotypes, SVR rates were reduced respectively to 17.6% (95%CI : 10.2%-27.4%) and 20.3% (95%CI : 11.8%-31.2%) in the primary and secondary population of patients administered ribavirin at a cumulative dose < 80% of the target dose, and increased respectively to 59.8% (95%CI : 53.7%-65.7%) and 67.2% (95%CI : 60.9%-73.1%) in both populations of patients administered ribavirin at a cumulative dose ≥80% of the target dose (Fig. 2). RVR was achieved in 33.3% of the



EOT = End of Treatment, EOT + 24W = 24 weeks after EOT, SVR = Sustained Virologic Response.

Fig. 1. — Virologic Response Over Time-All Patients and Patients with Sufficient Follow-up Data (SFU)

patients with HCV genotype 1, 71.1% of those with genotype 2, 76.7% of those with genotype 3 and 27.3% of those with genotype 4 (Table 4). cEVR was achieved in 35.4% of the patients with HCV genotype 1, but 13.2% only of those with genotype 2, 14.7% of those with genotype 3 and 34.5% of those with genotype 4. In patients whose cumulative dose of ribavirin was < 80% of the target dose, the percentages of RVR were reduced to 26.2% for HCV genotype 1, 60.0% for HCV genotype 3, and 5.3% for HCV genotype 4 (the percentage for genotype 2 was not calculated because the number of patients was too low). Virologic breakthrough was observed in only 3.0% (95%CI : 1.3%-5.9%) of the 263 patients (73.9% of the whole population) who were evaluable for this parameter (not shown). Relapses at 24 weeks after EOT were more frequent and were diagnosed in 24.4% (95%CI : 19.0%-30.4%) of the 234 patients (65.7% of the whole population) who were evaluable for this parameter (not shown). Across all genotypes, 21.1% of the patients were prematurely withdrawn from treatment (Table 5). The main reasons were : insufficient virologic response (5.9%), adverse events or death (6.2%), and patients failing to return (4.8%). One patient with HCV genotype 1 infection was treated for a period of time shorter than anticipated (and was therefore considered methodologically as prematurely withdrawn from treatment) because he had developed an early virologic response. Six patients (15.8%) with HCV genotype 2 infection were withdrawn for non-medical reasons (i.e failure to return or move to another trial). The percentage of premature withdrawal was similar between HCV genotype 1 and 4 infections (23.8% versus 23.6%), but clearly dissimilar between HCV genotype 2 and 3 (26.3% versus 14.7%). The percentage of patients who did not show any HCV RNA test result ≥ 140 days after EOT (incomplete follow-up) amounted to 31.7% (Table 5). The reasons



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were essentially non-medical (21.3%) (e.g. failure to return [14.9%]), or related to efficacy (8.7%) (e.g. absence of response at EOT [7.0%]). In patients with sufficient follow-up, PPVs by weeks 4 and 12 were the lowest in patients with HCV genotype 2 (62.5% [95%CI : 40.6-81.2] and 58.6% [38.9%-76.5%] respectively) and the highest in patients with HCV genotype 3 (83.1% [95%CI : 75.3%-90.7%] and 78.0% [95%CI : 68.1%-86.0%] respectively) (Table 6). PPVs were the highest in patients with RVR and the lowest in patients with pEVR.

Differences with the data of the whole population of the PROPHESYS study

The genotype distribution differed substantially between the whole population of the PROPHESYS study (n = 7,121 patients with HCV genotype 1, 2, 3, or 4 infection) and the population treated in Belgium (n = 356). The prevalence of HCV genotype 1 was 63.5% in the whole population versus 41.3% in Belgium ; for HCV genotype 2, it was respectively 14.4% and 10.7% : for HCV genotype 3, 17.7% versus 32.6% ; for HCV genotype 4, 4.4% versus 15.4%. In patients with HCV genotype 1 or 4, liver biopsies were carried out more frequently in Belgium than in the whole population (95.2% versus 60.8% and 96.4% versus 47.5%, respectively). The overall SVR rates across all genotypes in Belgium were consistent with those of the whole population : 49.7% (95%CI : 44.4%-55.0%) versus 49.4% (95%CI : 48.3%-50.6%). However, the SVR rates in patients with HCV genotype 2 infections were lower in Belgium than in whole population, 47.4% (95%CI : 31.0%-64.2%) versus 71.4%. In consequence, the positive predictive values for SVR of RNA tests carried out by weeks 4 and 12 in patients with sufficient follow-up were lower in patients from Belgium with HCV genotype 2 infection than in patients from the whole population (62.5% [95%CI : 40.6-81.2%] and 58.6% [95%CI : 38.9%-76.5%] respectively in Belgium versus 86.2% [95%CI : 83.6%-88.6%) and 83.5% [95%CI : 80.8%-85.9%] respectively worldwide). The publication by P Marcellin *et al*. did not provide details on the dosage of anti-HCV drugs in the whole population (1).

Discussion

The genotype distribution amongst the patient included in this sub-analysis differed obviously from the distribution observed in the whole PROPHESYS study popu-

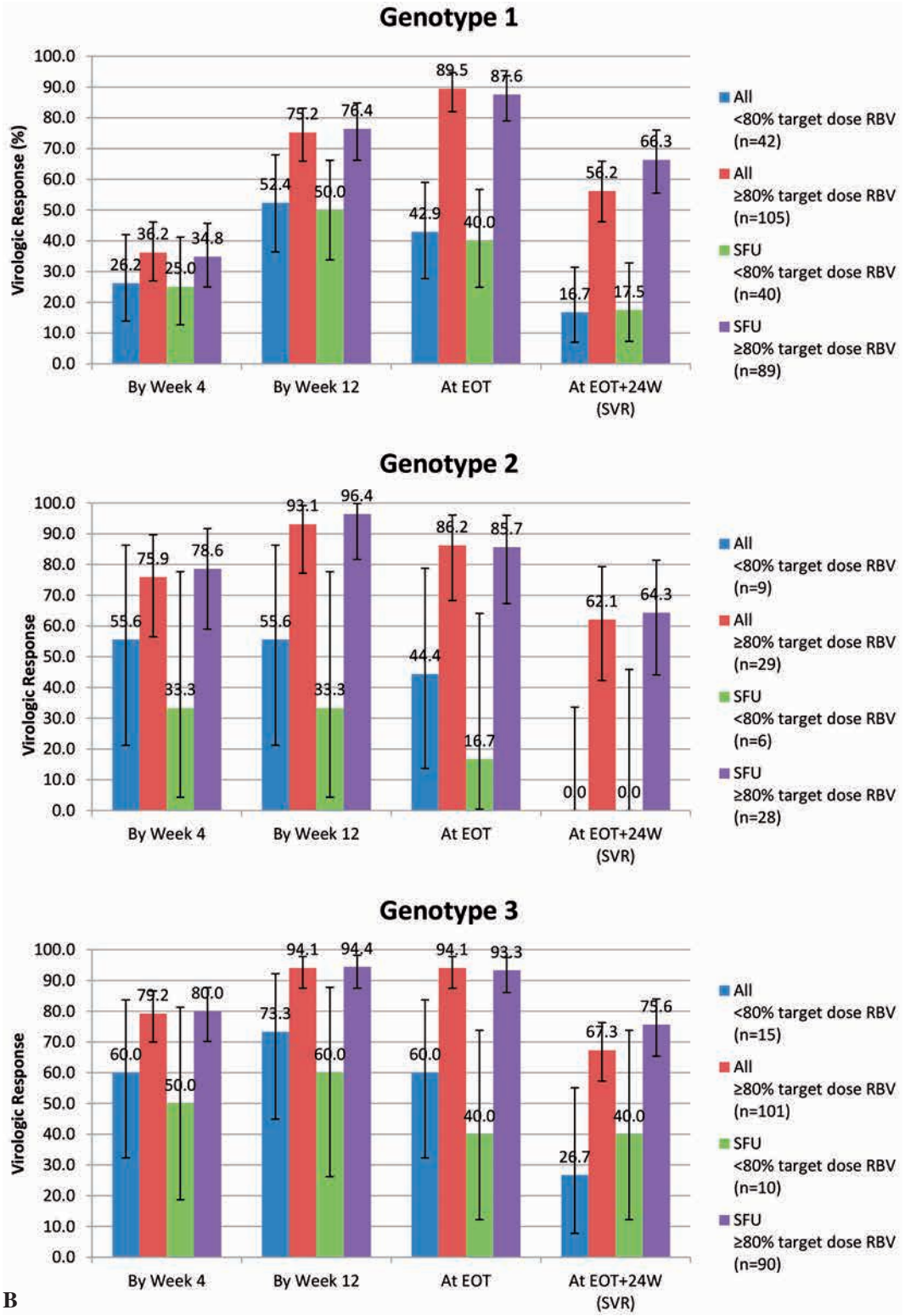

Fig. 2. — Virologic Response Over Time by Exposure to Ribavirin (RBV)-All Patients and Patients with Sufficient Follow-up Data (SFU).

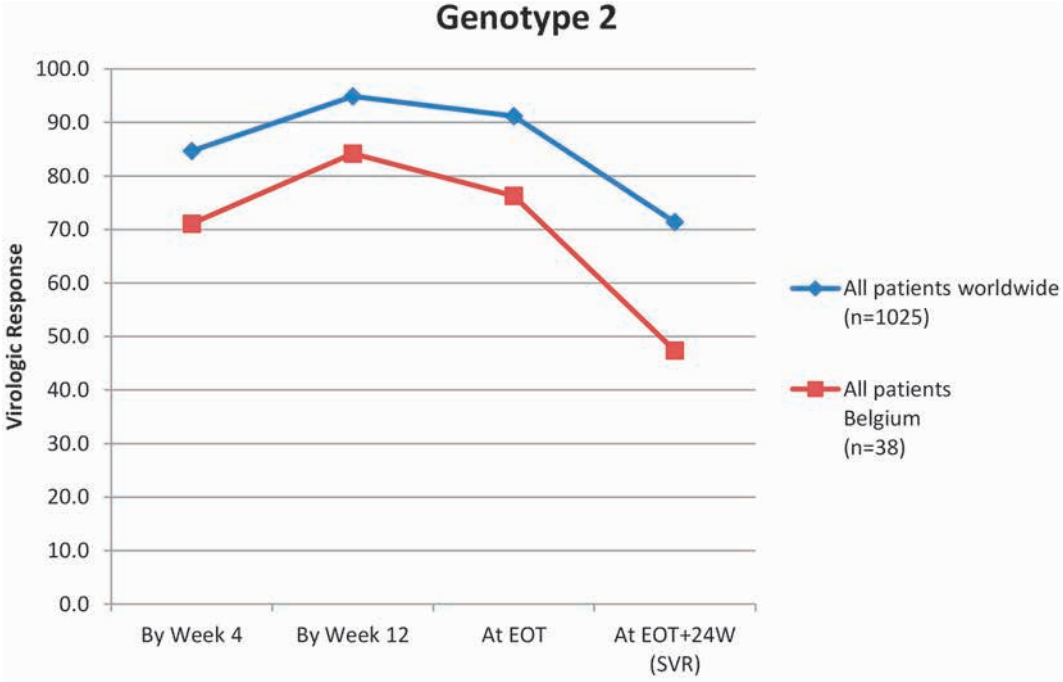

Fig. 3. — Virologic Response Over Time in HCV Genotype 2 Patients-Patients from the Whole Population of PROPHESYS Study and Patients Treated in Belgian Centers.

Table 4. — **Proportion of patients (%) with virologic response during the first 12 weeks – categories of response**

Virological response (categories)	Genotypes											
	G1			G2			G3			G4		
	All patients (n = 147)	≥ 80% of target dose (n = 105)	< 80 % of target dose (n = 42)	All patients (n = 38)	≥ 80% of target dose (n = 29)	< 80 % of target dose (n = 9)	All patients (n = 116)	≥ 80% of target dose (n = 101)	< 80 % of target dose (n = 15)	All patients (n = 55)	≥ 80% of target dose (n = 36)	< 80 % of target dose (n = 19)
RVR	33.3	36.2	26.2	71.1	75.9	Not calculated because n< 10	76.7	79.2	60.0	27.3	38.9	5.3
cEVR	35.4	39.0	26.2	13.2	17.2		14.7	14.9	13.3	34.5	38.9	26.3
pEVR	15.0	16.2	11.9	7.9	3.4		4.3	3.0	13.3	7.3	5.6	10.5
No RVR No EVR	13.6	6.7	31.0	5.3	0.0		2.6	1.0	13.3	23.6	8.3	52.6
Not computable or missing	2.7	1.9	4.8	2.6	3.4		1.7	2.0	0.0	7.3	8.3	5.3

EVR = Early Virologic Response, cEVR = Complete Early Virologic Response, pEVR = Partial Early Virologic Response, RVR = Rapid Virologic Response.

lation. HCV infection of genotype 1 was diagnosed in only 41.3% of the Belgian patients whereas 63.3% of the entire study population was infected with this genotype. This might be due to the fact that a large number of patients with HCV genotype 1 infections were enrolled in clinical trials aimed at evaluating new direct-acting antivirals (7). In a survey carried out in Belgium in 2003-2004, 59% of 318 consecutive patients with HCV antibody positivity were found to be infected with HCV genotype 1 (8). This percentage amounted to 49.3% in a more recent epidemiological study performed in the Netherlands (9). Both surveys suggest that the genotype distribution observed in this sub-analysis reflects correctly the actual proportions of HCV genotypes in Belgium. HCV genotype 4 being most prevalent in Central Africa and Middle East, it is not surprising that most patients with this genotype were of African origin (10-11). The young age of the patients with HCV genotype 3 (70.7% were 45 years old or younger) and their ethnicity (white in 80.2% of the cases) were consistent with the observations made by others that this genotype is highly prevalent in European intravenous drug users (12).

Liver biopsy was carried out in more than 95% of the patients with HCV genotype 1 or 4 in accordance with the requirements of the Belgian Health Insurance Agency for drug reimbursement. The few patients who did not

Table 5. — **Number of patients prematurely withdrawn from treatment or with incomplete follow-up – reasons for withdrawal from treatment or incomplete follow-up**

Reasons	Genotypes				
	G1 (n = 147)	G2 (n = 38)	G3 (n = 116)	G4 (n = 55)	All genotypes (n = 356)
Premature withdrawal from treatment					
Efficacy related reasons					
All patients	14 (9.5%)	0 (0.0%)	0 (0.0%)	8 (14.5%)	22 (6.2%)
Patients with insufficient viral response	13 (8.8%)	0 (0.0%)	0 (0.0%)	8 (14.5%)	21 (5.9%)
Patients with early virologic response	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Safety related reasons					
All patients	11 (7.5%)	4 (10.5%)	3 (2.6%)	4 (7.3%)	22 (6.2%)
Patients with adverse events	9 (6.1%)	3 (7.9%)	3 (2.6%)	4 (7.3%)	19 (5.3%)
Patients deceased	2 (1.4%)	1 (2.6%)	0 (0.0%)	0 (0.0%)	3 (0.8%)
Non-medical Reasons					
All patients	10 (6.8%)	6 (15.8%)	14 (12.1%)	1 (1.8%)	31 (8.7%)
Patients failing to return	6 (4.1%)	3 (7.9%)	7 (6.0%)	1 (1.8%)	17 (4.8%)
Patient's decision	3 (2.0%)	0 (0.0%)	2 (1.7%)	0 (0.0%)	5 (1.4%)
Patients moving to another trial	0 (0.0%)	3 (7.9%)	4 (3.4%)	0 (0.0%)	7 (2.0%)
Other patients*	1 (0.7%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	2 (0.6%)
All reasons					
All patients	35 (23.8)	10 (26.3%)	17 (14.7%)	13 (23.6%)	75 (21.1%)
* Drug abuse for one patient (genotype 1) and unspecified reason for another (genotype 3)					
Incomplete follow-up					
Efficacy related reasons					
All patients	15 (10.2%)	1 (2.6%)	2 (1.7%)	13 (23.6%)	31 (8.7%)
Patients with insufficient viral response	3 (2.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	4 (1.1%)
Patients without response at End of Treatment [EOT]	10 (6.8%)	1 (2.6%)	2 (1.7%)	12 (21.8%)	25 (7.0%)
Safety related reasons					
All patients	3 (2.0%)	1 (2.6%)	2 (1.7%)	0 (0.0%)	6 (1.7%)
Patients with adverse events	0 (0.0%)	0 (0.0%)	1 (1.7%)	0 (0.0%)	1 (0.3%)
Patients deceased	3 (2.0%)	1 (2.6%)	1 (0.9%)	0 (0.0%)	5 (1.4%)
Non-medical Reasons					
All patients	34 (23.1%)	10 (26.3%)	25 (21.6%)	7 (12.7%)	76 (21.3%)
Patients failing to return	24 (16.3%)	6 (15.8%)	18 (15.5%)	5 (9.1%)	53 (14.9%)
Patient's decision	2 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.6%)
Patients moving to another trial	0 (0.0%)	3 (7.9%)	4 (3.4%)	0 (0.0%)	7 (2.0%)
Other patients	8 (5.4%)	1 (2.6%)	3 (2.6%)	2 (3.6%)	14 (3.9%)
All reasons					
All patients	52 (35.4%)	12 (31.6%)	3 (2.6%)	2 (3.6%)	113 (31.7%)

undergo this investigation were probably treated with anticoagulants or suffered from a coagulation disease. Liver biopsy was still performed in about one third of the patients with HCV genotype 2 or 3 infection despite the fact that this investigation was not mandatory for reimbursement and that liver biopsy in these patients had been considered unnecessary by some authors because more than 80% of them achieve a sustained virologic response to standard-of-care treatment (13). Patients with HCV genotype 3 infections had the highest proportion of elevated transaminases (ALT ratio > 3 in 26.7% of the case) which might have convinced the clinicians to carry out a biopsy before starting the treatment.

The intended duration of treatment was a clear dichotomy : 48 weeks for all patients with HCV genotype 1 or 4, and 24 weeks for 98.3% of the patients with HCV

Table 6. — **Predictive Values (positive [PPV] and negative [NPV]) for SVR in Patients with Sufficient Follow-up Data**

	Genotype							
	G1		G2		G3		G4	
PPV and NPV for SVR of an HCV RNA test carried out by weeks 4 and 12								
By Week 4	75.6 (59.7-87.6)	62.0 (50.4-72.7)	62.5 (40.6-81.2)	87.5 (47.3-99.7)	83.1 (75.3-90.7)	75.0 (47.6-92,7)	78.6 (49.2-95.3)	75.8 (57.7-88.9)
By Week 12	70.5 (59.8-79.7)	94.7 (82.3-99.4)	58.6 (38.9-76.5)	80.0 (28.4-99.5)	78.0 (68.1-86.0)	100 (63.1-100)	59.4 (40.6-76.3)	94.1 (71.3-99.9)
PPV for SVR of categorized virologic responses								
RVR	75.6 (59.7-87.6)		62.5 (40.6-81.2)		83.1 (72.9-90.7)		78.6 (49.2-95.3)	
cEVR	66.0 (50.7-79.1)		40.0 (5.3-85.3)		50.0 (23.0-77.0)		44.4 (21.5-69.2)	
pEVR	5.3 (0.1-26.0)		33.3 (0.8-90.6)		0.0 (0.0-52.2)		0.0 (0.0-70.8)	

RVR = Rapid Virologic Response, cEVR = Complete Early Virologic Response, pEVR = Partial Early Virologic Response.

genotype 2 or 3. Clearly, the prescribers did not envisage a shorter duration of treatment for their patients, even for those with a low viral load (i.e. $\leq 8 \times 10^5$ IU/mL), despite the fact this possibility is explicitly mentioned in the SPCs of both anti-HCV drugs.

The start dose of peginterferon alfa-2a complied with the recommendations of the SPCs, the requirements of the Belgian Health Insurance Agency, and the EASL guidelines (Table 3) (14). By contrast, the start dose of ribavirin was characterized by a high level of variability. About 80% of the patients with HCV genotype 1 or 4 and a body weight of < 75 Kg were administered a daily dose of 1,000 mg (in compliance with the same recommendations and regulations as for peginterferon alfa-2a) but a significant minority (about 15%) was treated at the dose of 1,200 mg/day (which is in fact the dose recommended for patients with a body weight ≥ 75 Kg). The administration of higher dose of ribavirin was still more obvious in patients with HCV genotype 2 or 3. Whereas about 65% of them received the usual dose of 800 mg/d, 20% were prescribed 1,000 mg/d, and 10% 1,200 mg/d. Two reasons might explain the trend towards a higher dosage in patients with HCV genotype 2 : a high prevalence of cirrhosis at baseline (31.6%) and a high viral load at baseline (HCV RNA level > 8×10^5 IU/mL) in 70.3% of the patients. The reasons for a higher dosage in patients with HCV genotype 3 are less clear since prevalence of cirrhosis and viral load were lower than in genotype 2. The young age of the patients might explain a more aggressive form of treatment.

Means and medians of treatment duration were in accordance with the intentions expressed by the clinicians at the beginning of treatment. However, deviations were major at the individual level, with 4 weeks as shortest duration of treatment and 78 as longest.

Virologic responses to treatment over time were similar at all time points between the primary population (i.e. the whole population treated in Belgium) and the secondary population (i.e. the population with sufficient follow-up data). The proportion of patients with SVR was slightly higher in the secondary population. Virologic responses were also similar between the overall population of the PROPHESYS study and the population treated in Belgium, except for HCV genotype 2 patients (Fig. 3). In this group, the gap between the two virologic response curves became larger over time. SVR amounted 71.4% in the whole population whereas it was only 47.4% in Belgium despite a longer duration of treatment with ribavirin (> 24 weeks) in a third of the patients. Several factors might explain this finding. Patients with HCV genotype 2 infection constituted the smallest group of all patients infected with HCV. As already reported above, this group had the highest viral load and the highest prevalence of cirrhosis of all patients treated in Belgium. Patients of this group were more often withdrawn from treatment (26.3%) because of safety (10.5%) and non-medical (15.8%) reasons. Further, 31.6% of the patients were incompletely followed up and could not be investigated for a virologic response at EOT + 24 weeks. HCV genotype 2 patients might have been too small in number to be representative of the entire Belgian population infected with this genotype.

Adherence to treatment was estimated in this study by the cumulative dose of ribavirin actually taken by the patients divided by the target dose anticipated at baseline. Patients treated with < 80% of the target dose expressed systematically weaker virologic responses to treatment than patients with ≥ 80% of the target dose. This well-known phenomenon has already been described in a large number of reports (15-16).

This sub-analysis gave an overview of the characteristics, anti-hepatitis C drug treatment, and virologic responses of the patients treated in Belgium with peginterferon alfa-2a and ribavirin between June 2009 and May 2010. The findings deviated in several aspects from the results obtained at the whole population level and, as far

as dosage is concerned, from official recommendations. The advent of protease inhibitors, two years ago, such as telaprevir and boceprevir, is now profoundly affecting the treatment of chronic hepatitis C. These agents improve the probability of cure but have a number of inherent limitations. The currently registered protease inhibitors do not have antiviral activity in HCV genotypes other than the predominant genotype 1 (17-18). They can promote viral resistance and have multiple pharmacokinetic interactions with other drugs. Finally they need to be administered with alfa-2a and ribavirin, thus adding a layer of complexity in the management of the side effects. The combination of peginterferon alfa a with ribavirin, alone or with protease inhibitors, will remain for a while the standard of care for HCV infections.

Appendix

In addition to the authors, the following clinicians were PROPHESYS investigators located in Belgium : **Assene C.**, Hôpitaux Iris Sud, 1190 Bruxelles ; **Baert P.**, Heilig Hartziekenhuis, 8800 Roeselare ; **Bastens B.**, Centre Hospitalier St-Joseph, 4000 Liège ; **Brénard R.**, Clinique St-Joseph, 6060 Gilly ; **Brixko C.**, Centre Hospitalier Régional de la Citadelle, 4000 Liège ; **Cool M.**, Algemeen Ziekenhuis Damian, 8400 Oostende ; **Delwaide J**, Centre Hospitalier Universitaire du Sart-Tilman, 4000 Liège, and Centre Hospitalier Peltzer-La Tourelle, 4800 Verviers ; **D'Heygère F.**, Algemeen Ziekenhuis Groeninge, 8500 Kortrijk ; **Henrion J.**, Hôpital de Jolimont, 7100 Haine-Saint-Paul ; **Hoste P.**, Algemeen Ziekenhuis Alma, 8340 Sijsele ; **Laukens P.**, Algemeen Ziekenhuis St-Jan, 8000 Brugge ; **Lefèbvre V.**, Centre Hospitalier Régional, 5000 Namur ; **Lenaerts A.**, Centre Hospitalier Universitaire, 6000 Charleroi ; **Lepoutre L.**, Onze-Lieve-Vrouwziekenhuis, 9300 Aalst ; **Martinet J.P.**, Cliniques Universitaires de Mont Godinne, 5530 Yvoir ; **Michielsen P.**, Universitair Ziekenhuis, 2650 Edegem ; **Nevens F.**, Universitair Ziekenhuis Gasthuisberg, 3000 Leuven ; **Reynaert H.**, Universitair Ziekenhuis, 1090 Brussel ; **Robaeys G.**, Ziekenhuis Oost-Limburg, 3600 Genk ; **Servais B.**, Centre Hospitalier de l'Abbaye et de Hesbaye, 4100 Seraing ; **Sprengers D.**, Antwerp Medical & Professional Building, 2018 Antwerpen ; **Stubbe J.**, Algemeen Ziekenhuis Sint-Jan Brugge-Oostende, 8400 Oostende. IST GmbH Mannheim, Germany, was responsible for the management of the data and the statistical analysis of the PROPHESYS study at a worldwide level (1). For this sub-analysis, IST GmbH Mannheim extracted the Belgian data and provided assistance to the authors.

Roche funded this research and offered a third-party writing assistance for this publication.

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