A non-interventional phase IV Belgian survey to assess the antiviral effectiveness of pegylated interferon-alpha-2b and ribavirin treatment according to the stage of liver fibrosis in previously untreated patients with genotype 1/4/5/6 chronic hepatitis C (PRACTICE)

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Abstract

Background and study aims : **This was an observational, non-interventional, multicenter, phase IV study, in patients with genotype 1/4/5/6 chronic hepatitis C (CHC).**

The primary objectives were to evaluate SVR in patients with no or minimal fibrosis (METAVIR F0-F1) versus well established fibrosis (F2-F4), and to estimate response on Weeks 12, 24 and 48 on treatment in previously untreated patients with genotypes 1/4/5/6 CHC.

Patients and methods : **538 patients treated with pegylated interferon alfa 2b 1.5 mcg/kg in combination with ribavirin 800-1200 mg/day were enrolled in 55 sites in Belgium and Luxembourg, 505 being considered for the analysis. 40% of the patients were female and 60% male, the average age was 47.5 years, 10.5% were 65 or older.**

Results : **SVR was observed in 35% of the patients, EVR in 68%, of which pEVR in 33% and cEVR in 35%. SVR was observed in 43% of the low fibrosis group (F0, F1) and 30% of the high fibrosis group (F2, F3, F4) (p = 0.005). SVR rates were 34% for genotype 1, 37% for genotype 4, and 47% for genotype 5 (NS). Multivariate analysis showed that EVR and baseline METAVIR score are independent prognostic factors for SVR.**

Conclusions : **This trial confirms that fibrosis stage and early viral response are the most important key-factors to predict sustained response, suggesting that the earlier patients are treated, the better the outcome. Non-invasive techniques enable us to closely monitor progression of fibrosis, allowing a better selection of patients for antiviral treatment in the DAA-era.** (Acta gastroenterol. belg., **2014**, 77, **393-400**).

Key words : hepatitis C, liver fibrosis, real life, pegylated interferon, ribavirin.

Introduction

Chronic infection with hepatitis C virus (HCV) affects more than 170 million individuals-approximately 3% of the world population-and is responsible for approximately 350.000 deaths every year (1). Until recently, the standard of care for all genotypes of HCV was the combination of pegylated-interferon (PEG-IFN) and ribavirin (RBV). The goal of therapy is a sustained virologic response (SVR), defined as the persistent absence of HCV RNA 24 weeks after the completion of therapy. Pegylated interferon and ribavirin therapy for chronic HCV infection achieves a SVR in 70-80% in genotype 2/3, but only 40-55% in genotype 1 infected patients (2-4). In difficult-to-treat patients, SVR is even less, especially in case of advanced fibrosis and cirrhosis (10-40%) (2-7). It is well known that HCV-related cirrhosis is associated with a high risk for hepatic decompensation, hepatocellular carcinoma (HCC) and liver-related mortality (9-11). On the other hand, lower risk of progression towards advanced liver disease complications have been described in patients who achieve SVR (12-14). Even regression of fibrosis may be obtained after successful virus eradication in patients with advanced fibrosis (15-16).

In Belgium, prevalence of chronic HCV is thought to be close to 1% (17). Relatively strict reimbursement criteria limited the use of antiviral treatment. Until 2005 only patients with moderate to advanced fibrosis on liver biopsy were eligible for reimbursement of PEG-IFN and RBV, although some reports suggested that fibrosis was an independent risk factor for virological response. Therefore, a multicenter observational trial was started to compare different stages of fibrosis with respect to achieving SVR.

The PRACTICE study is a large multicenter observational Belgian trial assessing the antiviral effectiveness of pegylated interferon-alpha-2b (Pegintron®) and ribavirin (Rebetol®) therapy according to the stage of liver fibrosis in previously untreated patients with genotype 1/4/5/6 chronic hepatitis C.

Materials and methods

This was an observational, non-interventional, multicenter, phase IV study, conducted in previously untreated patients with genotype 1/4/5/6 chronic hepatitis C (CHC).

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Submission date : 13/11/2013
Acceptance date : 29/06/2014

Objectives

The primary objective of the study was to evaluate the probability of achieving virological response on Week 12, Week 24 and Week 48 on treatment with pegylated interferon alfa 2b and ribavirin, as well as SVR (defined as undetectable HCV RNA, 24 weeks after end of therapy). This probability was to be estimated and compared in patients with no or minimal fibrosis (F0-F1 according to METAVIR) and in patients with well established fibrosis including cirrhosis (F2-F4 according to METAVIR).

Secondary objectives of the study were to estimate and compare virological response in different subgroups (e.g., low versus high viral load) of patients, and to explore the influence of available parameters on virological response.

Patients

In line with local registration and reimbursement settings, subjects were included in the survey if the following inclusion criteria were satisfied :

- Previously untreated ('treatment naïve') adult (18 year or more) for whom the treating physician had decided to start treatment with pegylated interferon alfa 2b and ribavirin
- Detectable HCV RNA in serum by PCR
- Repeated (with at least a 1 month interval) serum transaminase (ALT) levels above the upper normal limit for gender
- Documented CHC of genotype 1/4/5/6
- A representative liver biopsy within 1 year prior to inclusion, allowing fibrosis grading into METAVIR score F0, F1, F2, F3 or F4 (18).

The exclusion criteria were :

- Known hypersensitivity for any active ingredient of constituent
- Pregnancy or lactation
- Medically documented history of severe psychiatric disturbance, including severe depression, suicidal ideation or suicide attempt
- Medically documented history of severe heart disease, including unstable or uncontrolled cardiac disease, within the last 6 months
- Severely weakening medical condition, including chronic renal insufficiency or creatinin clearance < 50 ml/min
- Hepatitis of immunologic origin or medically documented history of auto-immune disease
- Severe hepatic disorder of decompensated cirrhosis
- Pre-existing thyroid disorder, except if under control with classical treatment
- Epilepsy or central nervous system disorder
- Hemoglobin pathology (e.g thalassaemia, sickle cell anemia).

Treatment

Eligible patients were treated with pegylated interferon alfa 2b 1.5 μg/kg body weight/week sc in combination with ribavirin (< 65 kg : 800 mg, 65-85 kg : 1000 mg, > 85 kg : 1200 mg) per os for 48 weeks. Participating physicians managed the patients participating in this survey according to their normal practice and considering the scientific leaflet of the products prescribed within the scope of national guidelines.

Efficacy Assessments

The efficacy of the treatment is evaluated on the basis of 'Early Viral Response (EVR)' and 'Viral Response (VR)'.

- EVR is defined as the absence of HCV RNA in a quantitative PCR test or more than a 2 log10 reduction in viral load (in I.U.), i.e. a reduction to less than 1% of the initial viral load, after the initial 12 weeks of treatment.
  Complete EVR (cEVR) signifies undetectable virus on PCR while in case of partial EVR (pEVR) the virus is still detectable but there is a reduction of viral load by at least 2 log (compared to initial viral load).
- VR is defined as the absence of HCV RNA in a qualitative PCR test. VR was assessed at Week 24 and Week 48, as well as at Week 72 (sustained viral response, SVR).

Information was collected on serious adverse events and on non-serious adverse events that were significant in the opinion of the investigator.

Statistical Methods

Logistic regression analysis was performed to study the effect of potential prognostic variables on study outcome. Both univariate analyses to evaluate each variable individually and a stepwise analysis to determine independent predictive variables were performed. Odds ratios and corresponding 95% confidence intervals were calculated for each of the potentially prognostic factors. Comparisons of subgroups were performed using the independent t-test for quantitative variables and the Fisher Exact test for nominal and binary outcomes. All tests were performed two-tailed, at the 5% level of significance. Since a single primary efficacy variable was defined (SVR) no correction for multiplicity was applied.

The statistical analysis was performed using the SAS package, Version 9.

Sample Size

No formal sample size calculation was performed. The number of patients to be enrolled (500) was determined on the basis of the recruiting capacity of the participating centres in the time-frame of the study. It was estimated that 10% of the enrolled patients would be not

evaluable, so that the analysis would be based upon the data of 450 evaluable patients.

The primary efficacy variable is SVR. It was estimated that at 72 weeks, VR would be achieved in 30 to 50% of the patients, depending on the subgroup of patients considered (4). The objective of the study is to estimate the frequency of VR in the study population, as well as in subgroups of patients, defined on the basis of fibrosis score (F0/F1 versus F2/F3/F4).

For frequencies between 30 and 50% the confidence intervals determined on the basis of 450 evaluable patients have a length varying between 8.7 and 9.4% while for 200 patients they vary between 13.2 and 14.2%, so that quite precise estimates can be obtained of the frequency of reaching the endpoint. Furthermore, for a comparison of 2 groups of 200 patients each (for example 200 fibrotic patients and 200 non-fibrotic patients), performed two-tailed, at the 5% level of significance, and 15% difference in response rate, a power of at least 83% is achieved.

Ethics

This study was performed in compliance with the applicable regulatory requirements, the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice (GCP), and the ethical principles that have their origins in the Declaration of Helsinki (2000) regarding biomedical research on human patients. Informed consent was obtained in each participating patient.

Results

Patient Characteristics

A total of 538 patients were enrolled between January 2005 and April 2008 by 81 investigators from 55 sites located in Belgium and Luxembourg. Thirty-one of these patients had major protocol violations (violation of eligibility criteria or study criteria : Not treatment naïve, treatment prolonged till 72 weeks), and 2 patients completed the Week 72 visit, but had no Week 72 results available. The data of the remaining 505 patients were considered for the analysis. Patient disposition is depicted in Table 1.

Demographic and baseline data of the patients considered in the analysis are shown in Table 2. 203 of the patients (40.2%) were female and 302 patients (59.8%) male, the average age was 47.5 years, ranging between 18 and 79 years, 53 patients (10.5%) were 65 or older. 434 patients (85.9%) were Caucasian, 67 patients (13.3%) were black, and 4 patients (0.8%) of another race.

376 patients (74.5%) had CHC genotype 1, 112 patients (22.2%) genotype 4, 17 patients (3.4%) genotype 5, and no patients had genotype 6. Viral load was $< 400 \times 10^6$ UI/L in 144 patients (28.5%), between 400 and 600 10^6 UI/L for 41 patients (8.1%) and $\geq 600 \times 10^6$ UI/L in 320 patients (63.4%). 373 patients (74.0%) had METAVIR stage F0, F1 or F2 (F0 : 10.9%, F1 : 26.6%, F2 : 36.5%). Among the patients in stage F0, F1 or F2, 7.5% were 65 years or older while this was the case for 18.3% of the patients with stage F3 or F4.

Table 1. — **Patient disposition**

Enrolled patients	538
Major protocol Violations Eligibility or study criteria not satisfied Not treatment-naive at enrolment Treatment prolonged to 72 weeks	31
Patients with Week 72 visit but no Week 72 data	2
Patients considered in the analysis	505
Discontinued patients* Lost to follow-up Did not wish to continue Side effects Disease-related complications Decision of the investigator	122 34 27 24 7 50

* Discontinuation due to Non-Response at Week 12 is not included. Multiple reasons for discontinuation could be recorded.

104 patients (20.6%) had a history of IV drug use, 10 patients (2.0%) were CHB positive, and 11 patients (2.2%) were HIV positive. For 59 patients (11.7%) a medical history of transfusion was reported, for 14 patients (2.8%) alcohol consumption, for 11 patients (2.2%) a psychiatric disorder, and 69 patients (13.6%) had a history of drug abuse.

Overall Virological Results

SVR was observed in 176 patients (34.9%) of the analysis population. EVR was observed in 345 patients (68.3%), pEVR in 167 patients (33.1%), and cEVR in 178 patients (35.2%). Viral response data are shown in Table 3.

VR at Week 48 (end of treatment), was observed in 229 (45.3%) of the patients, and VR at Week 24 in 146 (28.9%) of the patients. However, VR at Week 24 was only assessed in 348 patients (68.9%). Since it is likely that some patients for whom it was not assessed responded at this assessment time the response rate of 28.9% is less representative.

In addition to the patients with a non-response at Week 12, 122 patients (24.2%) discontinued the study prematurely. Among these, 34 patients were lost to follow-up, 27 did not wish to continue, 24 suffered from side effects, 7 suffered from diseases related complications, and 50 patients discontinued due to a decision of the investigator (Table 1). 32 patients (6.3%) discontinued before Week 12, 29 patients (5.7%) between Weeks 12 and 24, 56 patients (11.1%) between Weeks 24 and 48, and 5 patients (1.0%) between Weeks 48 and 72.

Virological Response by Fibrosis Stage and Genotype

SVR was observed in 176 (34.9%) of the patient population. For the low fibrosis group (F0, F1) SVR was

Table 2. — **Demographic data and baseline characteristics**

Age (years)	Mean (SD*)	47.5 (12.5)
	< 65 years	452 (89.5%)
	> 65 years	53 (10.5%)
Gender	Female	203 (40.2%)
	Male	302 (59.8%)
Race	Caucasian	434 (85.9%)
	Black	67 (13.3%)
	Other	4 (0.8%)
CHC Genotype	1	376 (74.5%)
	4	112 (22.2%)
	5	17 (3.4%)
	6	0
Viral load at screening	$< 400 \times 10^6$	144 (28.5%)
	$> 400 \times 10^6$ to $< 600 \times 10^6$	41 (8.1%)
	$> 600 \times 10^6$	320 (63.4%)
METAVIR score	F0, F1, F2	373 (74.0%)
	< 65 years	345 (92.5%)
	> 65 years	28 (7.5%)
	F3, F4	131 (26.0%)
	< 65 years	107 (81.7%)
	> 65 years	24 (18.3%)
HBsAg	Positive	10 (2.0%)
HIV	Positive	11 (2.2%)
IV drug abuse	Yes	104 (20.6%)
Medical history	Transfusion	59 (11.7%)
	Alcohol consumption	14 (2.8%)
	Drug abuse	69 (13.7%)
	Depression/Anxiety/ Suicide attempt / Psychological disorder	11 (2.2%)

* SD = standard deviation.

observed in 81 (42.9%) of the patients while in the high fibrosis group (F2, F3, F4) this was the case for 95 (30.2%) of the patients ($p = 0.005$). The evaluation of SVR within each genotype showed that for genotype 1 SVR was observed for 33.8% of the patients, for genotype 4 for 36.6%, and for genotype 5 for 47.1% of the patients. The difference in rates between the genotypes failed to reach statistical significance (Table 4).

Prognostic Factors for Sustained Virological Response

The effect of potential prognostic factors for SVR was first evaluated by means of univariate logistic regression. Results are provided in Table 5. The following factors were statistically significant for predicting SVR :

– *Viral Response at Week 12 (EVR) :* The odds of SVR are 147 times higher for patients with viral response at Week 12. This result reflects the importance of the futility rules.
– *METAVIR Score :* The odds of SVR are 1.7 times higher for patients with a METAVIR score of F0 and F1 than for patients with a METAVIR score of F2, F3 or F4.
– *Age Group :* The odds of SVR are 1.7 times higher for patients less than 50 years of age than for patients aged 50 and over.
– *Screening Viral Load :* The odds of having SVR are 1.6 times higher for patients with a screening viral load of $< 400 \times 10^6$ than for patients with a screening viral load of $\geq 400 \times 10^6$. Screening viral load ($< 600 \times 10^6$ IU/L, $\geq 600 \times 10^6$ IU/L) was just outside the significance level of 5%.

The potential predictive factors were fitted to a model using stepwise logistic regression in order to determine which factors were important in estimating SVR. This yielded the following independent prognostic factors (see Table 6) :

Table 3. — **Viral response**

	Response		
	Yes	No	Missing
EVR (Week 12)	345 (68.3%)	149 (29.5%)	11 (2.2%)
pEVR	167 (33.1%)		
cEVR	178 (35.2%)		
VR at Week 24	146 (28.9%)	202 (40.0%)	157 (31.1%)
VR at Week 48	229 (45.3%)	257 (50.9%)	19 (3.8%)
SVR (Week 72)	176 (34.9%)	329 (65.1%)	

EVR = Early Viral Response.
pEVR = partial Early Viral Response.
cEVR = complete Early Viral Response.
VR = Viral Response.
SVR = Sustained Viral Response.

Table 4. — **SVR summarised by fibrosis stage and genotype**

OVERALL		SVR Responder		
		No 329 (65.1%)	Yes 176 (34.9%)	Overall (N = 505)
Fibrosis stage	F0	34 (61.8%)	21 (38.2%)	55 (10.9%)
	F1	74 (55.2%)	60 (44.8%)	134 (26.6%)
	F2	124 (67.4%)	60 (32.6%)	184 (36.5%)
	F3	60 (68.2%)	28 (31.8%)	88 (17.5%)
	F4	36 (83.7%)	7 (16.3%)	43 (8.5%)
	Unknown	1		1
Regrouped fibrosis stage	F0-F1	108 (57.1%)	81 (42.9%)	189 (37.5%)
	F2-F4	220 (69.8%)	95 (30.2%)	315 (62.5%)
	p-value*	0.005		
Genotype	1	249 (66.2%)	127 (33.8%)	376 (74.5%)
	4	71 (63.4%)	41 (36.6%)	112 (22.2%)
	5	9 (52.9%)	8 (47.1%)	17 (3.4%)
	p-value*	0.444		

* Fisher Exact test.

– *Viral Response at Week 12 (EVR) :* The odds of SVR are more than 152 times higher for patients with Week 12 viral response than for patients without viral response at Week 12.
– *METAVIR Score :* The odds of SVR are almost 2 times higher for patients with a METAVIR score of F0 or F1 than for patients with a METAVIR score of F2, F3 or F4.

Hemoglobin Decrease and Sustained Virological Response

At onset of the study the average hemoglobin was 14681 mg/dl. It decreased by 2862 mg/dl between baseline and Week 12 for patients with SVR, and by 2776 mg/dl for patients without SVR ($p = 0.710$). However, a statistically significant difference is observed between the two groups of patients for the change between baseline and Week 24, with an average decrease of 3043 mg/dl for patients with SVR, and 2607 mg/dl for patients without SVR ($p = 0.020$) (Table 7).

Dose Reduction of Pegylated Interferon and Ribavirin and Sustained Virological Response

SVR was significantly associated with a dose reduction of ribavirin and pegylated interferon (Table 8). Among the patients for whom the dose of ribavirin was reduced 47.8% showed SVR while this was the case for 34.8% of the patients for whom it was not reduced ($p = 0.023$). Among the patients for whom the dose of pegylated interferon was reduced, 53.7% showed SVR while this was the case for 33.2% of the patients for whom it was not reduced ($p < 0.001$). However, it should be noted that these results might be biased since patients who discontinued the study before Week 12 or for whom dose information is not available could not be considered.

Table 5. — **SVR - predictive factors**

Predictive Factor	Factor Level (Level 1, Level 2)	Odds Ratio*	95% CI** for Odds Ratio	p-Value
Age Group	< 50, > = 50	1.686	1.149 - 2.474	0.008
Gender	Male, Female	0.798	0.550 - 1.157	0.234
Race	Caucasian (Yes/No)	1.323	0.766 - 2.284	0.316
	Black (Yes/No)	0.651	0.367 - 1.156	0.143
CHC Genotype	Genotype 1, Others	0.833	0.550 - 1.261	0.387
	Genotype 4, Others	1.104	0.713 - 1.709	0.659
	Genotype 5, Others	1.693	0.642 - 4.469	0.288
Screening Viral Load	$< 400 \times 10^6$, $> = 400 \times 10^6$	1.572	1.056 - 2.340	0.026
	$< 600 \times 10^6$, $> = 600 \times 10^6$	1.425	0.978 - 2.076	0.065
METAVIR	F0 F1, F2 F3 F4	1.721	1.183 - 2.504	0.005
CHB	Positive, Negative	1.895	0.541 - 6.635	0.318
HIV	Positive, Negative	1.070	0.309 - 3.707	0.915
EVR	Responder (Yes/No)	147.0	20.4 - 1061.0	<0.001
IV Drug Use	Yes, No	1.282	0.822 - 2.000	0.273
Medical History of Transfusion	Yes, No	1.437	0.827 - 2.496	0.199
Medical History of Alcohol Consumption	Yes, No	1.040	0.343 - 3.152	0.945
Drug Abuse	Yes, No	1.329	0.790 - 2.235	0.284
Medical History of Psychological Disorder	Yes, No	0.409	0.087 - 1.913	0.256

* Odds ratio is for Factor Level 1 vs Factor Level 2: An odds ratio >1 indicates SVR is more likely to be present for factor Level 1.
** CI = confidence interval.

Table 6. — **SVR - stepwise logistic regression – significant predictive factors**

Predictive Factor	Factor Level (Level 1, Level 2)	Odds Ratio*	95% CI** for Odds Ratio	p-Value
EVR	Responder (Yes/No)	151.6	21.0 - 1095.8	< 0.001
METAVIR Score	F0 F1, F2 F3 F4	1.875	1.210 - 2.904	0.005

* Odds ratio is for Factor Level 1 vs Factor Level 2 : An odds ratio > 1 indicates viral response at Week 72 is more likely to be present for factor Level 1 CI : Confidence Interval.
** CI = confidence interval.
Note : Only factors remaining in the model are presented in this table.

Safety

As this is an observational clinical trial, no pro-active collection of adverse events is allowed according to the Belgian legislation.

Discussion

This observational trial was set up because of stringent rules in Belgium for treating patients with no or limited fibrosis. The primary aim was reached, leaving no doubts about the fact that chances for reaching SVR in tough-to-treat genotypes are higher for patients with a METAVIR score F0-F1 compared to F2-F3-F4 (in this study the odds of SVR were almost twice as high). Our data also confirm the well known fact that EVR (early virological response) is one of the strongest predictors for success (supporting the futility rule generally applied).

Our global SVR for genotype is somewhat lower then in the pivotal trials, but these were phase 3 trials, only including well selected patients and carried out in expert centers. Analyzing our data in this real life study also shows the importance of compliance. In fact a lot of patients did not get to week 48 of treatment, not only because of non-response, but also because of patient or investigator decision. This is relevant information in this new era of direct acting antivirals (DAA) where compliance will be even more important because of the risk for resistance and additional side effects. Taking into account that nearly 1 out of 4 patients did not reach the end of treatment, programs to enhance compliance and guidelines for treating physicians are mandatory to give the chance for the medications, including standard of care (SOC) and/or DAA's, to clear the virus. Looking in to this data and other real-life research in this area, compliance is a keyfactor ; not only by the patients but also by the treating physicians.

Compliance did not appear to be associated with the route of transmission : we did not see a difference between those infected by IVDU (intravenous drug users) or those not.

Table 7. — **Hemoglobin concentration and change from baseline at weeks 12 and 24 by SVR responder**

OVERALL			SVR Responder	
			No (N = 329)	Yes (N = 176)
Hemoglobin (mg/dl)	Week 12	N	289	172
		Mean	11970.2	11920.4
		SD	1603.88	1439.09
		Median	12000	11900
		Range	7100, 16300	8000, 15900
	p-value*		0.740	
	Change from Baseline at Week 12	N	211	125
		Mean	-2776.3	-2862.4
		SD	1505.36	1550.74
		Median	-2600	-2900
		Range	-8000, 700	-6300, 1700
	p-value*		0.710	
	Week 24	N	172	171
		Mean	12075.0	11738.0
		SD	1587.53	1539.07
		Median	12000	11600
		Range	7500, 17200	7100, 16400
	p-value*		0.047	
	Change from Baseline at Week 24	N	130	124
		Mean	-2607.7	-3042.7
		SD	1493.06	1599.25
		Median	-2600	-3100
		Range	-6100, 1600	-7200, 2400
	p-value*		0.020	

* Independent sample t-test.

Table 8. — **Relation between dose reduction of ribavirin and pegylated interferon, and SVR response**

OVERALL		SVR Responder		
		No 329 (65.1%)	Yes 176 (34.9%)	Overall (N = 505)
Ribavirin Dose Reduction at Any Week	No	245 (65.2%)	131 (34.8%)	376 (80.3%)
	Yes	48 (52.2%)	44 (47.8%)	92 (19.7%)
	Unknown/Not Applicable*	36	1	37
	Odds Ratio**	0.58		
	95% CI***	0.37 – 0.92		
	p-value****	0.023		
Pegylated Interferon Dose Reduction at Any Week	No	252 (66.8%)	125 (33.2%)	377 (79.9%)
	Yes	44 (46.3%)	51 (53.7%)	95 (20.1%)
	Unknown/Not Applicable*	33	0	
	Odds Ratio**	0.43		
	95% CI***	0.27 – 0.68		
	p-value****	< 0.001		

* Unknown/Not Applicable: Either dose information not available or patient discontinued at or prior to the visit

** Odds Ratio is defined as no dose reduction relative to a dose reduction: An odds ratio > 1 demonstrates a higher chance of response for the no dose reduction group relative to the dose reduction group

*** CI = confidence interval

**** Fisher Exact test.

The age of the patient also appears to be important. Not only does SVR seem to be reduced in patients of 65 or over, but also the most important side-effects were seen in this population. This makes us wonder if such tough treatment is worth the effort, especially in patients with milder disease who probably won't develop any liver problems in the short run.

Another predictive factor, observed in other trials, is anemia and drop of hemoglobin. These observations led us to analyze dose-reductions in our population. It is striking that it looks like patients who had dose reductions of pegylated interferon and/or ribavirin have better results in SVR, since this made it possible to reach end of treatment at Week 48.

Finally this real life trial shows the importance of starting treatment early (young patients with lesser liver fibrosis) and the problem of compliance and adherence, that can be overcome with optimal guidance of patients and maximal support (inclusive dealing with side-effects). It also demonstrates that people infected by IVDU can successfully be managed with SOC (and probably with DAA's).

Conclusion

It is clear from this and many other trials that stage of fibrosis and on treatment viral response are the most important key-factors to predict sustained viral response. Probably these findings will not be abolished in future treatments. This also suggests that the earlier patients are treated, the better the outcome will be.

Non-invasive techniques enable us to closely monitor progression of fibrosis, making it possible to better select patients for antiviral treatment in the DAA-era.

Acknowledgements

The authors acknowledge the contribution of the other participating investigators :
C. Assene, F. Baert, S. Bakari, B. Bastens, C. Bataille, N. Boon, N. Botembe, N. Bourgeois, R. Brenard, J. Callens, B. Caucheteur, C. Chioccioli, P. Christiaens, T. Codden, L. Colemont, I. Colle, C. Daumerie, C. de Galocsy, M. De Maeyer, M. De Man, S. Debroux, D. Degré, F. D'Heygere, M. Dietze, A. Elewaut, F. Flamme, S. Francque, C. George, A. Geubel, P. Golstein, L. Harlet. A. Hittelet, J. Holvoet, J. Hulstaert, G. Lambrecht, J. Lammens, A. Lamproye, V. Lamy, L. Lasser, P. Laukens, V. Lefèbvre, A. Lenaerts, E. Louis, T. Mesureur, P. Michielsen, M. Nkuize, J. Ponette, C. Preux, H. Reynaert, G. Robaeys, A. Salamé, A. Sermeus, F. Sermon, B. Servais, D. Sprengers, F. Staels, P.-H. Steger, L. Van den Bergh, F. Van Der Meersch, L. Van Overbeke, B. Van Overberghe, H. Van Vlierberghe, P. Vanbiervliet, I. Vanmoerkerke, P. Vergauwe, M. Verhamme, G. Verset, E. Wain, A. Wauters.

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