Supplementary materials

Definition of the treatment history:

The null responders were defined by a decrease of HCV-RNA <2 $\log_{10}$ during the first 12 weeks of prior treatment with Peg-IFN/RBV; the partial responders by a decrease of HCV-RNA >2 $\log_{10}$ without reaching undetectability during prior therapy; the relapsers by an undetectable HCV RNA at the end of therapy that became detectable again after therapy.

Treatment schedules

The patients received either 12 weeks of TVR (750 mg every 8 hours) in combination with Peg-IFN and RBV, then 36 weeks of Peg-IFN/RBV, or 4 weeks (lead-in phase) of Peg-IFN and RBV then 44 weeks of Peg-IFN/RBV and BOC (800 mg every 8 hours), according to the European label. Forty-five patients (15.0%) received 4 weeks of Peg-IFN and RBV (lead-in phase), then 12 weeks of Peg-IFN/RBV and TVR (750 mg every 8 hours), then 32 weeks of Peg-IFN/RBV, off-label at the prescriber's discretion.

Patients and methods

Patients with high viraemia were defined by an HCV RNA level higher than or equal to 800,000 IU/mL.

Drug dosage

292 patients (98%) treated with TVR received PegIFN-α2a (180 µg once weekly) and 7 patients (2%) received PegIFN-α2b (1.5 µg/kg once weekly). All patients received RBV as oral tablets (1,000 or 1,200 mg/day, according to body weight).

184 patients (87%) treated with BOC received PegIFN-α2b (1.5 µg/kg once weekly) and 28 patients (13%) received PegIFN-α2a (180 µg once weekly). All patients received RBV as oral tablets (800 or 1,400 mg/day, according to body weight).

Stopping rules

The stopping rules of TVR were the following: 1) HCV RNA level >100 IU/mL at weeks 4 or 8; 2) HCV RNA level >100 IU/mL at week 12; 3) HCV RNA level ≥25 IU/mL at week 24 or later. BOC was stopped in patients with detectable HCV RNA at week 12 or later after the start of therapy. For both drugs, the treatment was discontinued in patients who experienced a virological breakthrough, defined as an increase >1 $\log_{10}$ in HCV RNA level from the nadir during treatment or an HCV RNA level >100 IU/mL in patients who previously achieved undetectable HCV RNA. All medications were discontinued in the case of detectable HCV RNA at weeks 24 or 36.

Safety assessments

Laboratory safety assessments were performed at the same time points as efficacy assessments. Safety assessments included a physical examination and haematological and biochemical assessments, at each visit planned by the cohort at baseline and at weeks 4, 8, 12, 16, 24, 36, 48 of therapy for both drugs and an additional visit 2 weeks after the start of PI, then at weeks 60 and 72 during the follow-up. At each visit, unsolicited adverse events and laboratory values for haemoglobin (Hb) and blood cell counts were noted in the case report form.

Definition of SAE and SAR

SAE and SAR are defined as any untoward medical occurrence or effect that results in death or a life-threatening effect, requires hospitalization or prolongation of existing inpatient hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, is an important medical event that, when based upon appropriate medical judgement, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above in the definition of an SAE. All grade 3 and 4 adverse events were coded using MedDRA v14.0 by a trained monitor with the help of two hepatologists, and events belonging to a prespecified list of clinical entities were regrouped. The definition of hepatic decompensation was the occurrence of ascites, hepatic encephalopathy or variceal bleeding. Severe complications were defined as any of death, grade 3 or 4 infection, hepatic decompensation. Grade 3 rash was defined as generalized rash involving either >50% of body surface area or rash presenting with any of the following characteristics: vesicles or bullae, superficial ulceration of mucous membranes, epidermal detachment, atypical or typical target lesions, palpable purpura/non-blanching erythema (20). Severe cutaneous adverse reaction (grade 4) was life-threatening rash or associated with systemic reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme, acute generalized exanthematous pustulosis and rash that requires therapy with systemic corticosteroids (20).

Laboratory grade 3 and 4 adverse events (AEs) were defined according to the ANRS scale except for anaemia (WHO scale). Grade 4 was also considered as an SAE.

Table 1: Baseline factors related to SVR12 in TVR cohort. Multivariate analysis

	Odds ratio	95% CI	p-value
No Lead-in phase	3.553	1.46-8.65	0.0052
Prior treatment response			
Partial response	Ref		
Relapse or breakthrough	4.589	2.50-8.14	<0.0001
Null response	0.616	0.22-1.75	0.3640
HCV subtype			
1a	Ref		
1b	2.840	1.52-5.32	0.0011
Other	2.373	0.90-6.28	0.0817
Platelets > 100	1.576	0.78-3.20	0.2089
Albumin >=35 vs <35	1.884	0.77-4.59	0.1627

Table 2: Baseline factors related to SVR12 in BOC cohort*. Multivariate analysis

	Odds ratio	95% CI	p-value
Prior treatment response			
Partial response	Ref		
Relapse or breakthrough	1.512	0.77-3.01	0.2592
Null response	0.169	0-1.01	0.0579
HCV subtype			
1a	Ref		
1b	2.024	1.03-3.98	0.0406
Other	0.709	0.23-2.16	0.5459

Platelets > 100	**2.278**	**1.06-4.90**	**0.0350**
Albumin >=35 vs <35	**1.844**	**0.69-4.96**	**0.2255**

*** No lead-in phase was entered in this multivariate analysis**

Figure legends

Figure 1: Probability of remaining free of any serious adverse event in the TVR cohort.

Figure 2: Probability of remaining free of any serious adverse event in the BOC cohort.

Figure 3: Probability of remaining free of any severe complication or death in the TVR cohort.

Figure 4: Probability of remaining free of any severe complication or death in the BOC cohort.

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