Retreatment with sofosbuvir + grazoprevir + elbasvir + ribavirin of patients with Hepatitis C virus Genotype 1 or 4 with RASs at failure of a sofosbuvir + ledipasvir or + daclatasvir or + simeprevir regimen (ANRS HC34 REVENGE study)

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OBJECTIVES

Failure to achieve sustained virological response (SVR) with hepatitis C virus (HCV) direct-acting antiviral-based regimens is commonly associated with emergence of variants carrying resistance-associated substitutions (RASs) [1]. The optimal retreatment regimen for such patients is unknown. The aim of this randomized open-label study was to evaluate sofosbuvir (SOF) + grazoprevir (GZR) + elbasvir (EBV) + ribavirin (RBV) 16 vs 24 weeks in patients with NS5A or NS3 RASs at initial treatment failure.

PATIENTS & METHODS

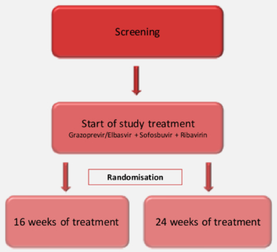
Randomized, double arm, multicenter, open-labeled, Phase II pilot study conducted in France.

Main inclusion criteria

- Adult ≥18 years
- Infection with HCV genotype 1 or 4, confirmed by detectable HCV RNA at pre-inclusion
- Failure to a prior therapy with Sofosbuvir +/- Ribavirin associated with Simeprevir or Daclatasvir or Ledipasvir, with documented presence of NS5A or NS3 RASs (Resistance-Associated Substitutions) at the time of failure (presence of RASs on at least one sample since the time of failure).
- Fibrosis at any stage

Main non-inclusion criteria

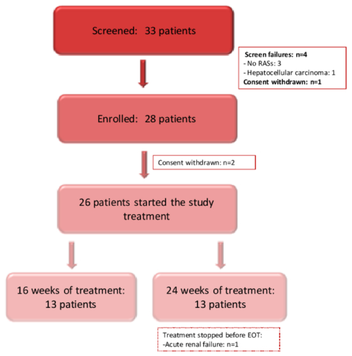
- Child B or C cirrhosis (or Child A patients with history of Child B)
- Patients with documented presence of RASs conferring resistance to sofosbuvir
- Positive HBs Antigen
- Confirmed HIV-1 or HIV-2 infection
- Transplant recipients
- Any evolutive ongoing malignant disease, including hepatocellular carcinoma, which will be specifically screened for before inclusion
- Treatment with contra-indicated associated drugs



Antiviral efficacy was evaluated using the secondary endpoint of SVR4 (SVR 4 weeks post-treatment). On-treatment responses and safety were also assessed.

FLOW CHART AND BASELINE CHARACTERISTICS

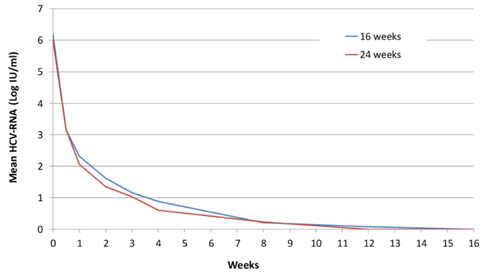
Twenty-six patients chronically infected with HCV genotype 1 (n=20) or 4 (n=6) were randomized and treated. All of the 26 patients achieved HCV RNA below lower limit of quantification (either TD[u] or TND) during treatment and 18 patients had a rapid response (week 4). SVR4 was achieved by 23/23 patients with sufficient follow-up. One patient , undetectable at week 16 died before week 20 (cf to Safety §). No relapse was observed.

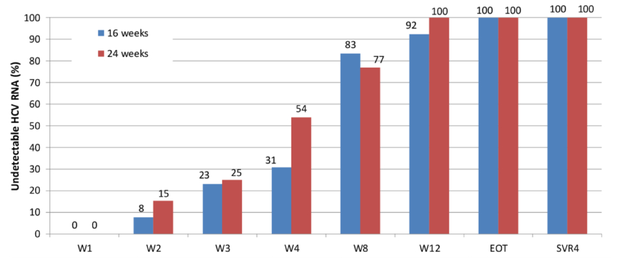


	Patients treated 16 weeks (N=13)	Patients treated 24 weeks (N=13)	All patients (N=26)
Age, y, mean (SD)	61 (13)	59 (12)	60 (12)
Gender, Male	9 (69.2%)	11 (84.6%)	20 (76.9%)
BMI, kg/m², mean (SD)	29.9 (6.4)	26.6 (3.4)	28.2 (5.3)
Previous HCV treatment:			
Sofosbuvir+Ledipasvir	9 (69.2%)	7 (53.8%)	16 (61.5%)
Sofosbuvir+Daclatasvir	4 (30.8%)	4 (30.8%)	8 (30.8%)
Sofosbuvir+Simeprevir	0 (0.0%)	2 (15.4%)	2 (7.7%)
HCV-RNA, log IU/mL, median [IQR]	6.1 [6.0-6.4]	6.2 [5.5-6.3]	6.1 [5.7-6.4]
Fibrosis status:			
FibroScan ≤ 9.5 kPa	3 (23.1%)	2 (15.4%)	5 (19.2%)
FibroScan]9.5-20] kPa	4 (30.8%)	4 (30.8%)	8 (30.8%)
Fibroscan > 20 kPa	6 (46.2%)	7 (53.8%)	13 (50.0%)
HCV subtypes			
1a	3 (23.1%)	5 (38.5%)	8 (30.8%)
1b/1d	8 (61.5%) §	4 (30.8%)	12 (46.2%) §
4	2 (15.4%)	4 (30.8%)	6 (23.1%)
RAS (n)			
- NS5A RAS	13	11	24
	The 3 main NS5A RAS were Y93H (n=17), L31M (n=7) and Q30R (n=4) *		
- NS3 RAS **	0	2	2

§ 1 patient presented a 1d subtype;
* The other NS5A RAS were : L28M, L30R, L28V, L31I, H58D, L30S, M31I, L31V, Q30E, Q30H, L31F, E62D and Y93N;
**The NS3 RAS were found in two patients and were the following: D168A, Q80K, S122G and D168N

HCV RNA DURING TREATMENT AND SVR4





	W1		W2		W3		W4		W8		W12		EOT		SVR4	
N	13	13	13	13	13	12[1]	13	13	12[1]	13	13	13	13	11[2]	13	10[3]
N undetectable	0	0	1	2	3	3	4	7	10	10	12	13	13	11	13	10

1 : one missing value
2 : two missing values (one patient died, one patient ongoing)
3 : three missing values (one patient died, two patients ongoing)

SAFETY

Adverse events

Tolerance was acceptable with **nine serious adverse events** (SAEs) which occurred in **7 patients** : right hypochondrium pain, dermo-hypodermitis, decompensated cirrhosis, hepatocellular carcinoma (HCC) (n=3), liver transplantation for HCC, liver biopsy of nodule and septic shock with acute kidney failure. No SAE was ascribed to study treatment.

One patient received **liver transplant** (LT) at week 8 for HCC and presented multiple complications (renal failure, septic shock, disseminated intravascular coagulation, hepatic failure) leading to a multiorgan failure and death, 6 weeks after LT.

Regarding **anemia, until week 16,** only 4 patients presented an hemoglobin decrease (between 8.5 and 10 g/dl) and one reached an hemoglobinemia below 8.5 g/dl.

Hepatocellular carcinoma

Among the 4 patients with a history of HCC, 2 experienced HCC **recurrence** during the treatment period. Moreover, one patient experienced a **HCC *de novo*** 3 days after the end of his treatment.
The characteristics of these patients are described below :

Patient	Group	1st HCC	Last normal imaging	Start of treatment	Cirrhosis status at baseline (Fibroscan®)	HCV genotype	Delay HCC diagnosis /start of treatment	Delay HCC diagnosis /end of treatment	Nodules	HCC therapy
1	16 weeks	2010	10/2015	03/01/16	35 kPa	1b	3 months	During treatment	1 nodule (20 mm)	Radioembolisation (portal vein thrombosis with ascites)
2	24 weeks	2014	02/2016	02/15/16	27 kPa	1a	4.5 months	During treatment	2 nodules (6 mm)	Thermal ablation programmed
3	16 weeks	-	12/2015	03/07/16	14 kPa	1b	3.5 months	3 days	1 nodule (26 mm)	Thermal ablation

Two other patients with no history of HCC are under investigation, one for a suspect nodule, one for an HCC suspicion on recent imaging.

CONCLUSIONS

Our findings suggest that retreating patients who failed a DAA-based regimen with NS5A/NS3 RASs with the combination of SOF + GZR + EBV + RBV for 16 weeks is efficacious and this combination appears to be a therapeutic option in DAAs failure.
Safety needs to be monitored cautiously in these patients with a severe disease. Moreover, in these patients who received two lines of treatment, HCC occurrence was described in 3/26 patients. Among the 3 HCC, 2 were recurrence of HCC.

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REFERENCES

1. Pawlotsky JM. Hepatitis C Virus Resistance to Direct-Acting Antiviral Drugs in Interferon-Free Regimens. Gastroenterology 2016;151:70–86

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