Retreatment With Sofosbuvir Plus Grazoprevir/Elbasvir Plus Ribavirin of Patients With Hepatitis C Virus Genotype 1 or 4 Who Previously Failed an NS5A- or NS3-Containing Regimen: The ANRS HC34 REVENGE Study

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Summary :

Our findings support the concept of retreating with sofosbuvir+ grazoprevir/elbasvir + ribavirin for 16 weeks GT1 or GT4 DAA-experienced patients with proven NS5A or NS3 RAS.

ABSTRACT

Failure to achieve sustained virological response (SVR) with hepatitis C virus (HCV) direct-acting antiviral-based regimens is commonly associated with emergence of resistance-associated substitutions (RAS). Re-treatment of patients who failed prior direct-acting antivirals remain challenging. The aim of this prospective and randomized study was to evaluate the efficacy (SVR12 primary endpoint) and safety of sofosbuvir + grazoprevir/elbasvir + ribavirin for 16 or 24 weeks in patients who had failed to achieve SVR on previous NS5A or NS3-based therapy and with evidence of RAS at failure. Patients were chronically infected with HCV genotype (GT) 1 or 4. Most of them had advanced fibrosis or compensated cirrhosis (liver stiffness 5.8-48.8 kPa). All patients achieved HCV RNA below lower limit of quantification (either TD[u] or TND) during treatment. SVR12 was achieved by 25/26 patients. The only patient who did not reach SVR was a patient who died but HCV-RNA was negative at this time (5 weeks after stopping treatment). No patient discontinued treatment because of adverse events or virological failure. Globally, treatment was well tolerated. In conclusion, our findings support the concept of retreating with sofosbuvir+ grazoprevir/elbasvir + ribavirin for 16 weeks GT1 or GT4 DAA-experienced patients with proven NS5A or NS3 RAS.

Keywords. Hepatitis C; DAA; RAS; sofosbuvir; grazoprevir/elbasvir

INTRODUCTION

Treatment of chronic hepatitis C virus (HCV) infection has advanced significantly over the last 5 years, with the approval and broad use of combinations of direct-acting antiviral (DAA) agents. Despite the very high sustained virological response (SVR) rates achieved with DAA-based combination regimens, treatment of HCV infection still fails in a number (<5%) of difficult-to-cure patients. Treatment failure is generally associated with the selection of viral variants with reduced susceptibility to DAA(s), characterized by the presence of RASs in the region(s) of their genomes targeted by the administered DAA(s) (1). NS5A inhibitors have a low barrier to resistance, and the RASs they select confer cross-resistance across all members of the drug class. Variants bearing NS5A RASs selected by IFN-free therapies are long-lasting. They remain present as dominant species for several years post-treatment and thus are likely to affect the results of retreatment. Currently, all recommended first-line DAA-based treatment regimens include an NS5A inhibitor. Thus, NS5A resistance currently appears as the principal challenge related to DAA-based treatment failure (2). In contrast to NS5A RASs, NS3 protease RASs selected after treatment failure progressively disappear after treatment has been withdrawn. Sofosbuvir RASs are very poorly fit; thus, they are exceptionally selected in sofosbuvir-exposed patients who fail therapy and rapidly disappear after treatment withdrawal in the rare patients in whom they are selected. Their transient selection does not affect sofosbuvir-based retreatment (1).

EASL recommends that patients who failed to achieve SVR on a DAA-containing regimen should be retreated with an IFN-free combination including a drug with a high barrier to resistance (currently, sofosbuvir), plus one to three other drugs, ideally with no cross-resistance with the drugs already administered. Sofosbuvir is a key drug for retreatment and grazoprevir has activity against common NS3 RASs and is approved for NS3 protease inhibitor failures. Retreatment should be extended to 24 weeks with ribavirin in difficult-to-cure patients, such as patients with F3 fibrosis or cirrhosis (3). However, clinical trial data are lacking to fully support this intuitive recommendation. AASLD

recommendations are “Based on these limited data, patients with dual NS3 and NS5A class RASs may be retreated with elbasvir/grazoprevir plus sofosbuvir with weight-based ribavirin for 12 weeks or PrOD plus sofosbuvir for 12 weeks in genotype 1b and 24 weeks with weight-based ribavirin in those with genotype 1a”.

In this context, we conducted a randomized multicenter trial to assess the safety and efficacy of a combination of sofosbuvir + grazoprevir/elbasvir + ribavirin administered for 16 weeks or 24 weeks in the retreatment of patients with chronic HCV genotype 1 or 4 infection, who had previously failed to achieve SVR with a daclatasvir- or ledipasvir- or simeprevir-containing regimen and had detectable RAS at the time of virological failure.

PATIENTS AND METHODS

Patients

The study (ANRS HC34 REVENGE) conformed to the ethical guidelines of the 1975 Declaration of Helsinki, Good Clinical Practice Guidelines and regulatory requirements. The study protocol was approved by ethics committee *CPP Sud-Ouest et Outre Mer III* (Bordeaux), and by the French Regulatory Authority Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM). This study was sponsored by Inserm-ANRS and conducted with the support of MSD (provided drugs).

Patients were identified and recruited in expert centers. All patients provided written informed consent. Patients were randomized into two groups to receive 16 or 24 weeks of a combination of sofosbuvir + grazoprevir/elbasvir + ribavirin. Sofosbuvir was taken as one 400-mg tablet once-daily; grazoprevir/elbasvir as one 100-mg/50-mg tablet once-daily (mg/mg); and ribavirin as recommended (1000 mg per day if body weight ≤ 75 kg and 1200 mg if body weight > 75 kg, BID).

The main inclusion criteria were: adult ≥18 years; infection with HCV genotype 1 or 4; failure to achieve SVR after prior treatment with sofosbuvir with or without ribavirin, in combination with the NS3-4A protease inhibitor simeprevir or the NS5A inhibitors daclatasvir or ledipasvir; documented presence of NS5A or NS3 protease RASs at the time of virological failure; any stage of fibrosis. The main exclusion criteria were: Child B or C cirrhosis; presence of NS5B RASs; hepatitis B virus (HBV) or human immunodeficiency virus (HIV) co-infection; transplant recipients; any evolutive malignant disease including hepatocellular carcinoma (HCC). Patients with a history of HCC were considered in complete radiological response at inclusion.

Assessments

The antiviral efficacy was assessed by determining on-treatment responses at day 2, weeks 1, 2, 3, 4, 8, 12, and 16 or 24 (end of treatment; EOT), and 4, 12 and 24 weeks after treatment cessation. The virological response was defined as an HCV RNA level below the lower limit of quantification (either "target detected [unquantifiable]" (TD[u]) or "target not detected" (TND)). The primary efficacy endpoint was an SVR 12 weeks after EOT (SVR12), which corresponds to a definitive cure of infection.

The presence of RASs was assessed in all patients at the time of their virological breakthrough or post-treatment relapse after initial therapy. Sequence analysis was based on population sequencing of three viral regions, including the NS3 protease (the target of simeprevir and grazoprevir), the NS5A protein (the target of daclatasvir, ledipasvir and elbasvir), and the NS5B polymerase (the target of sofosbuvir) coding regions. Briefly, HCV RNA was extracted with the QIASymphony DSP Virus/Pathogen kit on a QIASymphony device (QIAGEN GmbH, Hilden, Germany), according to the manufacturer's instructions. Complementary DNA synthesis was performed with the OneStep RT-PCR kit (QIAGEN GmbH) with sets of primers adapted to the viral regions targeted. Nested polymerase chain reaction (PCR) was then performed, if needed, with primers specific for GTs 1a, 1b, or 4.

Safety and tolerability were monitored and managed as per routine clinical practice, with regular physical examination, review of any adverse events (AEs), and blood samples taken for clinical laboratory testing. Serious adverse events (SAEs), treatment discontinuations, and laboratory abnormalities were recorded.

Sample size determination

The expected rate of SVR12 in patients treated for 16 weeks was fixed at 65%. To guarantee 80% power to detect a 30% difference in patients treated for 24 weeks (i.e. a type II error of 20%) and a type I error of 5%, the required sample size would be 25 per arm (50 patients in total).

Randomization

Randomization was centrally performed, concealed in blocks of four or six to a computer-generated random number table with a 1:1 allocation to ensure the unpredictability of randomization.

Statistical analysis

Results are presented as median with interquartile range for continuous data and number (percentage) for categorical data. Baseline characteristics were compared between groups using U Mann-Whitney test for quantitative variables and chi-squared test or Fisher's exact test for qualitative variables. The main criterion for efficacy was assessed with a Fisher's exact test conducted in bilateral formulation with a type I error of 5%. The analyses were done using SAS® 9.4 software (SAS Institute Inc., Cary, North Carolina, USA) for usual statistical analyses.

RESULTS

Baseline characteristics and disposition (Table 1)

A total of 28 patients with NS3 or NS5A RASs detectable at the time of virological failure were randomized in a total of 10 centers (a difficult supply for one study treatment led to premature cessation of inclusions). Most of patients were males, with a mean age of 61 years (Table 1). Patients were most commonly infected with HCV GT 1b (13 of 28) and 20 of 28 had baseline HCV RNA >800,000 international units (IU)/mL. FibroScan analysis revealed that 22 patients had severe fibrosis (liver stiffness >9.5 kPa). Among them, 13 patients had cirrhosis (liver stiffness >14.5 kPa). The median FibroScan score was 17.1 kPa.

The previously administered treatment regimens that failed were sofosbuvir plus ledipasvir (18 patients), sofosbuvir plus daclatasvir (8 patients), and sofosbuvir plus simeprevir (2 patients). A mean duration of 11 months (range 5-19) had elapsed between the end of the previous treatment and the initiation of the new treatment.

Two patients decided to withdraw their consent before starting treatment (one in each treatment arm). They were not analyzed for the primary and secondary endpoints.

Treatment

All 26 treated patients except one completed the retreatment course, and 12 weeks of post-EOT follow-up were available for all patients but one who died before (see below).

Efficacy

All patients attended EOT virological response (Figure 1). The primary efficacy endpoint, SVR12, was achieved by 25 of 26 patients, 0.96 [95%CI 0.80 - 0.99]. No patient relapsed post-EOT.

A patient infected with genotype 4 had a history of HCC treated by chemoembolization and two radiofrequency cures. Imaging performed before inclusion and the onset of treatment showed a still partially active nodule. The patient was hospitalized for chemoembolization of a recurrent HCC and then for liver transplantation during the study period. In view of the worsening of renal function and the persistence of hepatic impairment, anti-HCV retreatment was stopped at week 12 (the patient was randomized in the 24-weeks treatment arm). He died 5 weeks later. As this patient deceased before the theoretical date of the primary endpoint, he was considered as a failure for the analysis according to the study protocol.

Influence of baseline RASs on virological outcomes

NS5A RASs were observed at retreatment baseline in 24 of the 26 treated patients (Table 1). All of the amino acid substitutions had been previously reported to be associated with NS5A inhibitor-containing regimen failures in vivo.

Adverse events

Tolerance was acceptable with 9 serious adverse events (SAEs) which occurred in 7 patients: right hypochondrium pain, dermo-hypodermitis, decompensated cirrhosis, HCC (n=4), transplantation due to HCC and septic shock with acute kidney failure plus disseminated intravascular coagulation. No SAE was ascribed to study treatment. Regarding anemia, until week 16 only 4 patients presented

with a hemoglobin decrease down to 8.5-10 g/dL) and one reached a hemoglobinemia level below 8.5 g/dL (Table 2).

Among the 5 patients with a history of HCC, 2 experienced HCC recurrence during the treatment period and 2 patients experienced *de novo* HCC during study. Moreover, one patient was transplanted due to HCC recurrence occurring before inclusion. HCC cases are described in Table 3.

DISCUSSION

In these very hard-to-treat patients (prior DAA exposure with virological failure, majority of patients with cirrhosis or severe fibrosis, frequent presence of NS5A RASs at baseline), we showed that 16 or 24 weeks of the combination of sofosbuvir + grazoprevir/elbasvir + ribavirin yields SVR in 100% of cases. Thus, 16 weeks of this combination appears as a reasonable and safe option for retreatment of patients exposed to DAAs and who failed to achieve SVR, especially those with NS5A inhibitor-resistant viruses. Thus far, little data was available on retreatment of patients who failed NS5A inhibitor-containing regimens failures, especially those with cirrhosis who selected NS5A RASs. The EASL Recommendations for Treatment of Hepatitis C 2016 suggest that an aggressive regimen combining sofosbuvir, 2 to 3 other DAAs and ribavirin should be used in these patients. However, this recommendation was poorly supported in the literature.

Lawitz et al reported 100% SVR in a pilot study of 25 patients initially treated with sofosbuvir + grazoprevir/elbasvir + ribavirin for 4, 6 or 8 weeks who were retreated with the same regimen for 12 weeks with ribavirin (4). In a pilot study, 41 patients with and without cirrhosis who did not achieve SVR after 8 or 12 weeks of ledipasvir/sofosbuvir were retreated with 24 weeks of ledipasvir/sofosbuvir (5). The SVR12 rates differed according to the presence or absence of NS5A RASs at baseline of retreatment. SVR occurred in 11 of 11 (100%) patients without NS5A RASs, versus 18 of 30 (60%) in those with detectable NS5A RASs. Interestingly, NS5B RASs (eg, S282T) which confer

reduced susceptibility to sofosbuvir were observed in 3 of 12 (25%) patients for whom the retreatment regimen was not successful.

There is little information on the retreatment of patients who failed a sofosbuvir plus daclatasvir regimen. Preliminary data from 16 patients who failed daclatasvir plus pegylated interferon plus ribavirin (n = 13) or daclatasvir plus asunaprevir and pegylated interferon plus ribavirin (n = 3), 81% of whom with NS5A RAS, retreated with sofosbuvir plus simeprevir for 12 weeks were reported. SVR12 was observed in 87% of the 15 patients who reached this time point (6). The two patients who failed had cirrhosis and NS5A RAS.

In our study, we observed 5 patients with HCC during the study. Most of them had prior HCC or atypic nodules before starting treatment. Since 2016, a controversy about a potential association between DAA-based antiviral treatment and the *de* novo emergence or the recurrence of HCC has been raised. A higher incidence and more aggressive profiles were reported in some studies. Reig and others reported an increased incidence of HCC recurrence after DAA-based treatment in patients who had been successfully treated for HCC and who had been free of disease for varied periods (7, 8). Subsequently, several studies reported a higher incidence of HCC recurrence post-DAA therapy whereas a similar number of studies were negative, leaving the question unanswered. The majority of these publications were short reports without solid enough data to confirm or refute the alarm. An important dataset was published by the ANRS. The authors did not observe any increased incidence of HCC over time in cirrhotic or non cirrhotic patients achieving SVR after DAAs (9). In addition, a recent meta-analysis did not find any association between DAA treatment and HCC recurrence or occurrence (10). We observed 5 HCC cases in this study, including 3 recurrences and 2 *de novo* occurrences. None of them could be ascribed to the DAA-based treatment regimen. Other factors could have played a role such as the presence of cirrhosis, the duration of HCV infection, the age of the patients, etc.

Overall, our study demonstrates the efficacy and safety of the combination of sofosbuvir + grazoprevir/elbasvir + ribavirin administered for 16 weeks as a retreatment option for patients who failed a DAA-based regimen and selected DAA-resistant viruses. In the future, other combinations will be available in 2018 for retreatment of such patients, such as sofosbuvir/velpatasvir/voxilaprevir (11-13) or glecaprevir/pibrentasvir (14). The efficacy of these retreatment regimens in the real-life, especially in patients with NS5A RAS, remains unknown. The role of the different options will need to be balanced based on cost and drug availability in the different regions when these regimens become available. In the meantime, the treatment option studied here is safe and efficacious and may help stopping the progression of liver disease in many patients who failed a prior DAA-based treatment regimen.

Notes

Author contributions:

V. de Ledinghen had full control of the study design, data analysis and interpretation, and preparation of article. All authors were involved in planning the analysis and drafting the article. The final draft article was approved by all the authors.

Acknowledgment:

The authors thank Estelle Le Pabic for statistical analysis, Hélène Danjou for data management and all personnel involved in the ANRS HC34 REVENGE study.

Disclosures

V de Lédinghen: Consultant/Lecturer: Bristol-Myers Squibb, Janssen, Gilead, MSD, AbbVie.

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S Pol: Consultant/Lecturer: Bristol-Myers Squibb, Boehringer Ingelheim, Janssen, Gilead, MSD, Novartis, AbbVie; Grant/Research support: Bristol-Myers Squibb, Gilead, Roche, MSD.

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D Samuel: Consultant for Astellas, BMS, Gilead, LFB, MSD, Novartis, Roche, Biotest, Abbvie, Intercept.

JM Pawlotsky: Consultant/Lecturer: Abbott Diagnostics, Abbvie, Bristol-Myers Squibb, Gilead, Janssen, Merck; Grant/Research support: Abbvie, Gilead.

All other authors have no potential conflicts to disclose.

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Figure Legend

Table 1. Characteristics of the 28 patients.

	All patients n=28	16 weeks group n=14	24 weeks group n=14	p
Male (%)	22 (78.6%)	10 (71.4%)	12 (85.7%)	*p = 0.6483*
Mean age (years)	61 [55-70]	64 [52-71]	61 [57-69]	*p = 0.8540*
Baseline BMI (kg/m²)	27.8 [23.7-32.2]	29.8 [25.5-33.5]	25.1 [23.4-28.4]	*p = 0.0935*
Median Fibroscan (kPa)	17.1 [10.2-27.4]	16.1 [7.8-27.7]	19.6 [10.5-27]	*p = 0.5200*
Fibroscan kPa (%) ≤9.5 9.6-20 >20	 6 (21.4%) 9 (32.1%) 13 (46.4%)	 4 (28.6%) 4 (28.6%) 6 (42.9%)	 2 (14.3%) 5 (35.7%) 7 (50.0%)	*p = 0.7844*
HCV genotype Genotype 1a Genotype 1b[1] Genotype 4	n=27 8 (29.6%) 13 (48.1%) 6 (22.2%)	n=13 3 (23.1%) 8 (61.5%) 2 (15.4%)	n=14 5 (35.7%) 5 (35.7%) 4 (28.6%)	*p = 0.4116*
Previous treatment Sofosbuvir + daclatasvir Sofosbuvir/ledipasvir Sofosbuvir + simeprevir	8 (28.6%) 18 (64.3%) 2 (7.1%)	4 (28.6%) 10 (71.4%) 0 (0.0%)	4 (28.6%) 8 (57.1%) 2 (14.3%)	*p = 0.5860*
Previous treatment duration 8 weeks 12 weeks 24 weeks	3 (10.7%) 19 (67.9%) 6 (21.4%)	2 (14.3%) 11 (78.6%) 1 (7.1%)	1 (7.1%) 8 (57.1%) 5 (35.7%)	p = 0.2024
Median HCV RNA level at baseline (UI/ml)	1,270,000 [473,000-2,406,380]	1,270,000 [1,060,000-2,650,000]	1,200,075 [323,215-1,940,000]	*p = 0.3345*
HCV RNA >800,000 IU/ml	20 (71.4%)	12 (85.7%)	8 (57.1%)	*p = 0.2087*
NS5A RAS	**n=26**	**n=14**	**n=12**	
Y93 H/N	18/1	11/0	7/1	
L28 M/V	2/2	1/0	1/2	
L31 M/I/V/F	9/2/2/1	5/1/2/1	4/1/0/0	
L30 R/S	1/1	0/0	1/1	
Q30 R/E/H	4/1/1	2/1/1	2/0/0	
H58D	2	1	1	
M31I	1	0	1	
E62D	1	0	1	
NS3 RAS	**n=2**	**n=0**	**n=2**	
Q80K	1	0	1	
S122G	1	0	1	
D168N/A	1/1	0/0	1/1	
Median time since previous	**n=26**	**n=13**	**n=13**	*p = 0.9591*

treatment (months)	10.5[8.8-13.8]	11.1 [9.2-12.0]	9.9[8.8-14.3]	

1 Two patients decided to withdrawal informed consent
2 One patient is genotype 1b but considered here as missing.

Table 2. Main adverse events.

	All patients N=26	16 weeks group N=13	24 weeks group N=13
Early discontinuation	2* (8%)	0 (0%)	2 (15%)
Death	1* (4%)	0 (0%)	1 (8%)
Serious adverse events (SAE)	9 (35%)	2 (15%)	7 (54%)
Hepatocellular carcinoma	5 (19%)	2 (15%)	3 (23%)
Anemia	4 (15%)	2 (15%)	2 (15%)
Hemoglobin < 10 g/dL	5 (19%)	2 (15%)	3 (23%)

*The same patient discontinued treatment and deceased five weeks later

Table 3. Hepatocellular carcinoma case description.

Patient	Past HCV treatment	Previous HCC treatment	Time between HCC treatment and HCV treatment	Delay between the start of HCV treatment and HCC occurrence	Tumor size	Number of nodules	Follow-up
#1	SOF/LED	TA	6 years	During treatment	20 mm	1	Radioembolisation (portal vein thrombosis with ascites)
#2	SOF + DCV			During treatment	45 and 14 mm	2	Planned hepatectomy
#3	SOF/LED			EOT	26 mm	1	TA
#4	SOF/LED	TA	1.5 year	During treatment	7 mm	1	CEL planned
#5	SOF/LED	CEL TA	Present at baseline		19, 5 and 5 mm	3	Transplantation

SOF: sofosbuvir; LED: ledipasvir; DCV: daclatasvir; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; TA: thermal ablation; CEL: chemoembolization; EOT: end of treatment

Figure 1. Virological response during and after treatment according to randomization.

*The failure is the deceased patient