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MAJOR ARTICLE

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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Background. Failure to achieve sustained virological response (SVR) with hepatitis C virus (HCV) direct-acting antiviral (DAA)–based regimens is commonly associated with emergence of resistance-associated substitutions (RASs). Retreatment of patients who failed prior DAAs remains challenging. The aim of this prospective and randomized study was to evaluate the efficacy (primary endpoint: SVR 12 weeks after end of treatment [SVR_{12}]) 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 RASs at failure.

Methods. Patients were chronically infected with HCV genotype 1 or 4. Most of them had advanced fibrosis or compensated cirrhosis (liver stiffness 5.8–48.8 kPa).

Results. All patients achieved HCV RNA below the lower limit of quantification (either target detected [unquantifiable] or target not detected) during treatment. SVR_{12} was achieved by 25 of 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.

Conclusions. Our findings support the concept of retreating with sofosbuvir + grazoprevir/elbasvir + ribavirin, for 16 weeks, genotype 1 or 4 DAA-experienced patients with proven NS5A or NS3 RASs.

Clinical Trials Registration. NCT02647632

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

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 resistance-associated substitutions (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 interferon-free therapies are long-lasting. They remain present as dominant species for several years posttreatment 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].

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The European Association for the Study of the Liver (EASL) recommends that patients who failed to achieve SVR on a DAA-containing regimen should be retreated with an interferon-free combination including a drug with a high barrier to resistance (currently, sofosbuvir), plus 1–3 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. The American Association for the Study of Liver Diseases recommendations state that "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 [AASLD Guidelines 2017] 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 RASs 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. This study was sponsored by Institut national de la santé et de la recherche médicale - France REcherche Nord&sud Sida-hiv Hépatites (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 2 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, twice daily).

The main inclusion criteria were age ≥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, or human immunodeficiency virus (HIV) coinfection; 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)" or "target not detected". The primary efficacy endpoint was an SVR 12 weeks after EOT (SVR_{12}), 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 posttreatment relapse after initial therapy. Sequence analysis was based on population sequencing of 3 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. In brief, 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 genotype (GT) 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 SVR_{12} 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 (ie, 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 4 or 6 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

Mann-Whitney *U* test for quantitative variables and χ^2 test or Fisher exact test for qualitative variables. The main criterion for efficacy was assessed with a Fisher exact test conducted in bilateral formulation with a type I error of 5%. The analyses were done using SAS 9.4 software (SAS Institute, Cary, North Carolina) for usual statistical analyses.

RESULTS

Baseline Characteristics and Disposition

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 patients were male, 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 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 + ledipasvir (18 patients), sofosbuvir + daclatasvir (8 patients), and sofosbuvir + simeprevir (2 patients). A mean duration of 11 months (range 5–19) had

Table 1. Characteristics of the 28 Patients[a]

Characteristic	All Patients (N = 28)	16-Week Group (n = 14)	24-Week Group (n = 14)	*P* Value
Male sex	22 (78.6)	10 (71.4)	12 (85.7)	.6483
Age, y, mean (SD)	61 (55–70)	64 (52–71)	61 (57–69)	.8540
Baseline BMI, kg/m^2, median (IQR)	27.8 (23.7–32.2)	29.8 (25.5–33.5)	25.1 (23.4–28.4)	.0935
FibroScan score, kPa, median (IQR)	17.1 (10.2–27.4)	16.1 (7.8–27.7)	19.6 (10.5–27)	.5200
FibroScan kPa				.7844
≤9.5	6 (21.4)	4 (28.6)	2 (14.3)	
9.6–20	9 (32.1)	4 (28.6)	5 (35.7)	
>20	13 (46.4)	6 (42.9)	7 (50.0)	
HCV genotype	n = 27	n = 13	n = 14	.4116
1a	8 (29.6)	3 (23.1)	5 (35.7)	
1b[b]	13 (48.1)	8 (61.5)	5 (35.7)	
4	6 (22.2)	2 (15.4)	4 (28.6)	
Previous treatment				.5860
Sofosbuvir + daclatasvir	8 (28.6)	4 (28.6)	4 (28.6)	
Sofosbuvir/ledipasvir	18 (64.3)	10 (71.4)	8 (57.1)	
Sofosbuvir + simeprevir	2 (7.1)	0 (0.0)	2 (14.3)	
Previous treatment duration				.2024
8 wk	3 (10.7)	2 (14.3)	1 (7.1)	
12 wk	19 (67.9)	11 (78.6)	8 (57.1)	
24 wk	6 (21.4)	1 (7.1)	5 (35.7)	
HCV RNA level at baseline, IU/mL, median (IQR)	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)	.3345
HCV RNA >800 000 IU/mL	20 (71.4)	12 (85.7)	8 (57.1)	.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	
Time since previous treatment, mo, median (IQR)	n = 26 10.5 (8.8–13.8)	n = 13 11.1 (9.2–12.0)	n = 13 9.9 (8.8–14.3)	.9591

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: BMI, body mass index; HCV, hepatitis C virus; IQR, interquartile range; RAS, resistance-associated substitution; SD, standard deviation.

[a]Two patients decided to withdraw informed consent.

[b]One patient is genotype 1b but considered here as missing.

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 (1 in each treatment arm). They were not analyzed for the primary and secondary endpoints.

Treatment

All 26 treated patients except 1 completed the retreatment course, and 12 weeks of post-EOT follow-up was available for all patients but 1 who died before (see below Efficacy).

Efficacy

All patients attained EOT virological response (Figure 1). The primary efficacy endpoint, SVR_{12}, was achieved by 25 of 26 patients (0.96 [95% confidence interval, .80–.99]). No patient relapsed post-EOT.

A patient infected with GT 4 had a history of HCC treated by chemoembolization and 2 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-week treatment arm). He died 5 weeks later. As this patient died before the theoretical date of the primary endpoint, he was considered as failed 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 SAEs that occurred in 7 patients: right hypochondrium pain, dermohypodermitis, 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 1 patient reached a hemoglobinemia level <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, 1 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

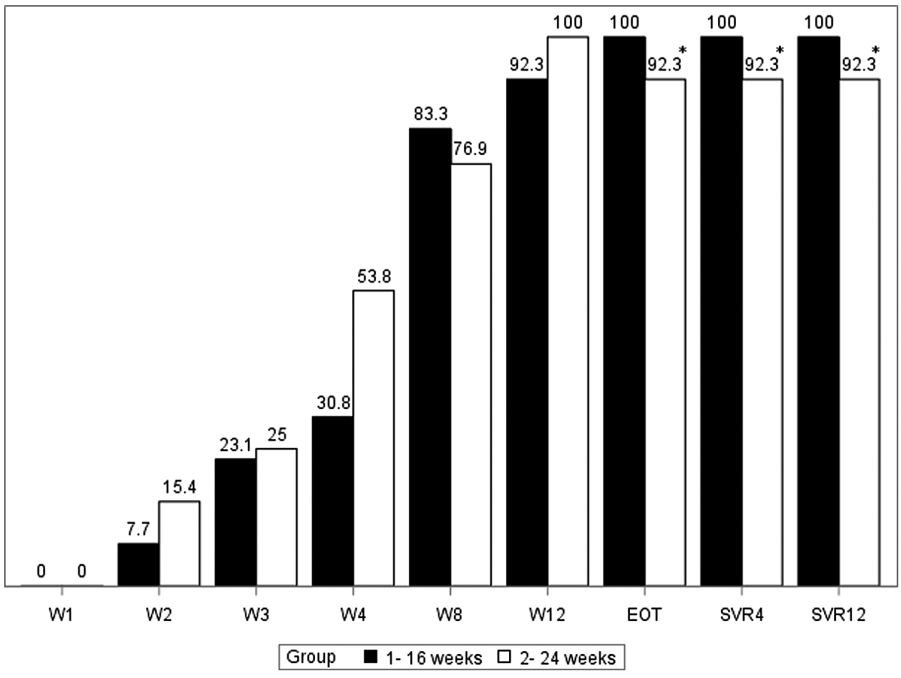

Figure 1. Virological response during and after treatment according to randomization.
*The failure is the deceased patient.
Abbreviations: EOT, end of treatment; SVR, sustained virological response; W, week.

Table 2. Main Adverse Events

Adverse Event	All Patients (N = 26)	16-Week Group (n = 13)	24-Week Group (n = 13)
Early discontinuation	2[a] (8)	0 (0)	2 (15)
Death	1[a] (4)	0 (0)	1 (8)
Serious adverse events	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)

Data are presented as No. (%).

[a]The same patient discontinued treatment and died 5 weeks later.

for retreatment of patients exposed to DAAs and who failed to achieve SVR, especially those with NS5A inhibitor–resistant viruses. Thus far, few data were available on retreatment of patients who failed NS5A inhibitor–containing regimens, especially those with cirrhosis who selected NS5A RASs. The EASL 2016 recommendations for treatment of hepatitis C suggest that an aggressive regimen combining sofosbuvir, 2–3 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 SVR_{12} 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, vs 18 of 30 (60%) in those with detectable NS5A RASs. Interestingly, NS5B RASs (eg, S282T) that 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 + daclatasvir regimen. Preliminary data from 16 patients who failed daclatasvir + pegylated interferon + ribavirin (n = 13) or daclatasvir + asunaprevir and pegylated interferon + ribavirin (n = 3), 81% of whom with NS5A RASs, retreated with sofosbuvir + simeprevir for 12 weeks were reported. SVR_{12} was observed in 87% of the 15 patients who reached this time point [6]. The 2 patients who failed treatment 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 et al 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 noncirrhotic 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, or the age of the patients.

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 real-world settings, especially in patients with NS5A RASs,

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	No. of Nodules	Follow-up
1	SOF/LED	TA	6 y	During treatment	20 mm	1	Radioembolization (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 y	During treatment	7 mm	1	CEL planned
5	SOF/LED	CEL TA	Present at baseline		19, 5, and 5 mm	3	Transplantation

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

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 stop the progression of liver disease in many patients who failed a prior DAA-based treatment regimen.

Notes

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

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