# Retreatment with Direct Active Antivirals of Genotype 1, 3 and 4 Chronic Hepatitis C Patients who Previously Failed an Anti-NS5A-Containing Regimen in Real World

EASL The Home of Hepatology
THE INTERNATIONAL LIVER CONGRESS™ 2017
19-23 APRIL, AMSTERDAM, THE NETHERLANDS

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SAT-255

## INTRODUCTION

Treatment with direct acting antivirals (DAA) has shown high efficacy but a substantial proportion of patients (5%-15%) remains resistant to DAAs (1). As previously reported, treatment failure is generally associated with emergence of HCV resistance associated variants (RAVs) reducing susceptibility to DAA agents (1-5).

Recent guidelines recommend that patients who failed DAAs treatment with nonstructural protein 5A inhibitors (NS5A) should be retreated 24 weeks with Sofosbuvir (SOF) combined with either a protease inhibitor for those with NS5A RAVs, or with a NS5A inhibitor for those without NS5A RAVs (1, 6, 7). Little is known on real life retreatment of patients who had failed to achieve sustained virological response (SVR) on previous NS5A-based therapy (1).

## AIM

***Our aim was to study retreatment according to baseline NS5A RAVs after first DAAs treatment failure***

## PATIENTS & METHODS

*Patients:* From January 2014 to March 2016, 2995 HCV infected patients were treated with NS5A inhibitors in six French referent liver centers: 80 (2.7%) patients relapsed. This "real-world" study included 24 patients among these 80 patients who had failed to achieve SVR on previous NS5A-based therapy. These patients were retreated with different regimen combinations including SOF + Daclatasvir (DAC) ± Simeprevir (SIM) (25%), SOF + Grazoprevir + Elbasvir (29%), SOF + Ledipasvir (8%), SOF + SIM (17%), Ombitasvir (OBV) + Paritaprevir (PTV) + Ritonavir (RTV) + Dasabuvir (DAS) ± SOF (21%), with or without RBV for all regimens. Antiviral efficacy was evaluated using the primary endpoints of SVR at weeks 4 and 12 post-treatment (SVR4, SVR12).

*NS5A Sequencing:* NS5A sequencing was performed using the DeepChek® NS5a assay (ABL SA, Luxembourg, Luxembourg). Prevalence of NS5A RAVs/polymorphisms was analyzed using Sanger sequencing. HCV subtypes and drug-resistance interpretations were identified using DeepChek® Software (ABL SA, Luxembourg, Luxembourg) (8). As recommended, the HCV resistance testing used in this study was based on population sequencing (reporting RAVs as "present" or "absent") with a cut-off of 15% (2). NS5A RAVs were defined as clinically relevant when inducing >10-fold resistance to NS5A inhibitors (8).

## RESULTS

Among the 24 retreated patients, 20 were males, median age was 54 years [min-max 26-78], HCV genotype (GT) 1 in 17 cases (1a=10, 1b=7), GT3a in one case, GT4 in six cases. All 24 patients presented severe liver fibrosis (F3 to F4) among whom 16 had cirrhosis (F4) and two were HIV coinfected.

All patients achieved SVR with a HCV RNA below lower limit of quantification (<15 IU/mL) by the end of treatment. SVR4 and SVR12 were achieved in 23/24 patients (96%), and the remaining patient relapsed four weeks post-treatment (F4, GT1a, had previously failed SOF+DAC 24 weeks therapy, and was retreated with OBV+ PTV+ RTV+DAS+RBV for 24 weeks, and had Y93N NS5A RAV, but no NS3-4A RAV at baseline).

Presence of NS5A RAVs/polymorphisms, was found in 20 (80%) patients at baseline of retreatment (**Table 1**): 17 had very high level of resistance RAVs (>100-fold) and three had high level of resistance RAVs (from 10- to <100-fold). Among the four patients with no RAV at baseline of retreatment, three were retreated with at least one NS5A and one with NS3-4A exclusively. Overall, 24 Weeks DAA therapy was more administered as a second-line treatment than it was as a first-line treatment: 15/24 (63%) vs. 5/24 (21%) respectively (p=0.0043).

**Table 1: NS5A RAVs according to HCV genotype for first and second lines of treatment**

| First treatment | N | Second Treatment | N | Genotype | Presence NS5A RAVs | Failure |
|---|---|---|---|---|---|---|
| SOF+LDV (12/24 Weeks) | 5 | SOF+DAC+RBV (24 Weeks) | 1 | 3 | No | |
| | | SOF+GZR+EBV±RBV (16 Weeks) | 2 | 1b/1b | Yes*/Yes* | |
| | | SOF+SIM±RBV (12/24 Weeks) | 2 | 1a/4 | Yes*/Yes | |
| SOF+LDV+RBV (12 Weeks) | 9 | SOF+SIM (24 Weeks) | 1 | 1a | Yes* | |
| | | SOF+GZR+EBV±RBV (16/24 Weeks) | 2 | 1b/4 | Yes*/Yes* | |
| | | SOF+DAC+SIM (24 Weeks) | 1 | 1b | Yes* | |
| | | SOF+LDV+RBV (24 Weeks) | 2 | 1a/1a | No/No | |
| | | SOF+OBV+PTV+RTV+DAS+RBV (24 Weeks) | 1 | 1a | Yes | |
| | | OBV+PTV+RTV+DAS+RBV (24 Weeks) | 2 | 4/1a | Yes*/No | |
| SOF+DAC (8/12/24 Weeks) | 6 | SOF+DAC (24 Weeks) | 1 | 1a | Yes* | |
| | | SOF+GZR+EBV±RBV (16 Weeks) | 3 | 1b/4/4 | Yes*/Yes*/Yes* | |
| | | OBV+PTV+RTV+DAS+RBV (24 Weeks) | 2 | 1a/1b | Yes*/Yes* | 1 Failure (HCV G1a) |
| SOF+DAC+RBV (12/16 Weeks) | 1 | SOF+DAC (24 Weeks) | 1 | 1a | Yes* | |
| PTV+OBV+RBV (12 Weeks | 1 | SOF+DAC +RBV (24 Weeks) | 1 | 4 | Yes | |
| Asunaprevir+DAC (20/24 Weeks) | 2 | SOF+SIM+RBV (24 Weeks) | 1 | 1a | Yes* | |
| | | SOF+DAC+SIM (24 Weeks) | 1 | 1b | Yes* | |

*Patients with very high level of resistance RAVs (>100-fold)

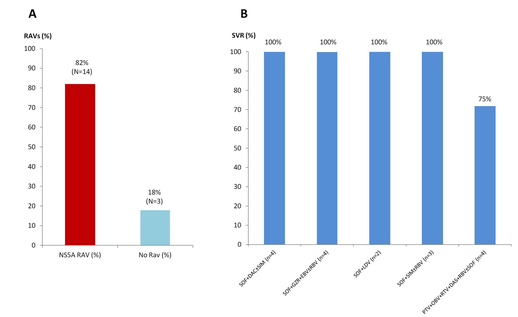


**Figure 1A: SVR rates for genotypes 1 patients with NS5A RAVs detected at the time of failure. 1B: SVR rates after retreatment of genotype 1 patients according to therapy regimen**

Among the 17 GT1 patients, 14 (82%) had a least one NS5A RAV at the time of failure (**Figure 1A**). **Figure 1B** shows SVR rates for all 17 GT1 patients according to retreatment regimens. SVR rate was 100% for all regimens except for OBV + PTV + RTV + DAS + RBV ± SOF for which one patient out of two failed to SVR (failure occurred in a patient with Y93N RAV). The only GT3 patient had no RAV and achieved SVR following retreatment. Among the six GT4 patients, all had NS5A RAVs, and all achieved SVR after retreatment (results not shown).

## CONCLUSIONS

- Given the emergence and persistence of RAVs, retreatment of patients after a first failure to DAA therapy remains a challenge.
- The present study showed that, based on recommendations, retreatment of patients after a first NS5A-based regimen failure is effective (96% SVR).
- **Table 2** reports findings of major real world studies and clinical trials on retreatment of patients who failed a previous DAA-therapy. Our study included patients from our routine clinical practice presenting the advantage to study a more diverse population contrarily to other clinical trials, which usually have restrictive inclusion criteria.
- This study on retreatment of patients after a first DAAs failure including a NS5A regimen is very encouraging.
- If guidelines are respected, the rate of success is high with the current available drugs. The upcoming regimens, either dual or triple therapy, may have similar results with shorter treatment duration.
- Baseline RAVs did not impact treatment outcome. However, despite the strong efficiency of this strategy guidance therapy, some very small limits can be observed in very few « difficult-to-cure » patients.

**Table 2: Overview of the main real-world studies and clinical trials on retreatment of patients who failed a previous DAA-therapy**

| Studies | N | RAVs* | Genotype | Type of Treatment | SVR |
|---|---|---|---|---|---|
| ***Real World*** | | | | | |
| Halfon et al. (current study) | 24 | NS5A: 80% | 1-3-4 | NS5A I ± NS5B I ± NS3-4A I** | 96% |
| Hezode et al.( ) | 16 | NS3-4A: 50% - NS5A: 75% - NS5B: 19% | 1-4 | SOF+SIM | 88% |
| Vermehren et al.( ) | 73 | Any NS3-4A – NS5A – NS5B: 90% (GT1) - 39% (GT3) | 1-3 | LDV+SOF / OBV+PTV+RTV+DAS+RBV | 89% |
| | | | | | |
| ***Clinical Trials*** | | | | | |
| Bourlière et al. (POLARIS-1)( ) | 263 | Any NS3-4A - NS5A - NS5B: 79% | 1-2-3-4-5-6 | SOF+VEL+VOX±RBV | 96% |
| De Ledinghen (REVENGE)( ) | 26 | Any NS3-4A - NS5A: 100% (NS3 n=2, NS5A n=24) | 1-4 | SOF+GZR+EBV+RBV | 94% |
| Poordad et al. (MAGELLAN-1)( ) | 50 | Any NS3-4A - NS5A: 82% | 1 | ABT-493+ABT-530 | 90% |

*In Hezode et al. study, NS3-4A RAVs were observed in 50% of the patients, NS5A in 75% of the patients, and NS5B RAVs in 19% of the patients. In Vermehren et al. study, any of NS3-4A, NS5A, or NS5B RAVs were observed in 90% of GT1 patients, and in 39% of GT3 patients. In our study, NS5A RAVs were observed in 80% of the patients. In Bourlière et al. study (POLARIS-1 trial) any of NS3-4A, NS5A, or NS5B RAVs were observed in 79% of the patients. In Poordad et al. study (MAGELLAN-1 trial), any of NS3-4A or NS5A RAVs were detected in 82% of the patients. In De Ledinghen study (REVENGE trial) all patients had NS3-4A or NS5A RAVs (NS3-4A RAVs were observed in two patients, and NS5A RAVs in 24 patients).
**NS5A Inhibitors± NS5B Inhibitors± NS3-4A Inhibitors therapies: there were SOF+DAC±SIM (25%), SOF+GZR+EBV (29%), SOF+LDV (8%), OBV+PTV+RTV+DAS±SOF (21%), SOF+SIM (17%), with or without RBV for all regimens

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