# HCV resistance to the daclatasvir/sofosbuvir combination across different HCV genotypes in the real life

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## INTRODUCTION

HCV therapies approved in the United States and Europe for treatment of pan-genotypic HCV infection include the interferon-free sofosbuvir (SOF) plus daclatasvir (DCV) combination. Daclatasvir inhibits HCV nonstructural protein 5A (NS5A) and sofosbuvir inhibits the HCV RNA polymerase (nonstructural protein 5B [NS5B]), two proteins that play key roles in the replication of HCV RNA. The two drugs are administered orally once daily. The combination of daclatasvir and sofosbuvir has been associated with high rates of sustained virologic response (SVR12) and a favorable side-effect profile when administered for 12 weeks to patients infected with HCV genotypes 1 and 4. However, this combination is less effective in cirrhotic patients infected with genotype 3.
The influence of natural baseline polymorphisms at genome positions involved in drug resistance has been reported in resistance analysis from clinical trials. However, little is known about the influence of baseline RAVs across different genotypes in the real world.

## OBJECTIVES

We studied the impact of preexisting HCV NS5A and/or NS5B resistance-associated variants (RAVs) on treatment outcomes in a cohort of patients infected with HCV genotypes (GT) 1a, 1b, 3 and 4 receiving SOF plus DCV without ribavirin for 12 weeks.

## PATIENTS

We included 177 patients from the Henri Mondor Hospital. Patients were chronically infected with HCV genotype 1a (n=44), genotype 1b (n=63), genotype 3 (n=29) and genotype 4 (n=41). All patients completed 12 weeks of treatment with SOF/DCV without ribavirin.
At baseline, 68 (38%) were treatment-naïve and 109 (62%) were treatment-experienced. Treatment-experienced patients included those who had previously failed treatment with PegIFN-RBV-based therapies with or without a protease inhibitor, including boceprevir, telaprevir or simeprevir.
Overall, patients were 65% males (n=115), with a median age of 58 years; the majority of patients had baseline HCV RNA levels >5 x $10^5$ IU/mL. Cirrhosis, as determined by FibroScan (>14,6 Kpa), was present in 44% (n=78) of patients (treatment-naïve, 41%; treatment-experienced, 46%).

## METHODS

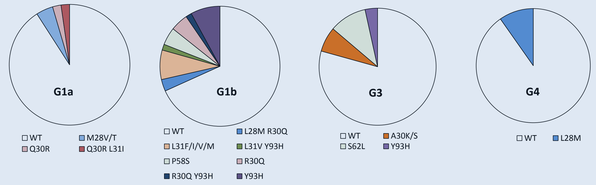
Population sequencing of the NS5A and NS5B genes was performed prior to SOF/DCV treatment in all 177 patients and at treatment failure (relapse) in 8 patients who did not achieve SVR12. NS5A sequences were examined at 9 known RAV positions in domain I (residues 28, 29, 30, 31, 32, 58, 62, 92 and 93), while NS5B sequences were examined at 5 known RAV positions (159, 282, 316, 320, 321).
RAVs for currently approved anti-NS5A treatment (daclatasvir, ledipasvir, ombitasvir and elbasvir) were considered as relevant if they had been reported to be associated *in vivo* with treatment failure and/or had been shown to confer a more than 3-fold change drug in susceptibility as compared to wild-type virus in an *in vitro* phenotypic assay.

## RESULTS

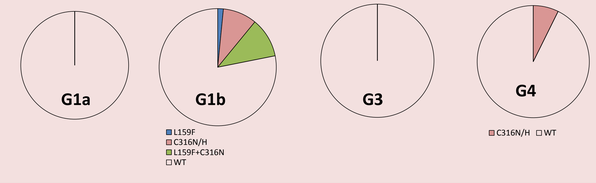
### Baseline patients characteristics

| | All genotypes | Genotype 1a (n=44) | | Genotype 1b (n=63) | | Genotype 3 (n=29) | | Genotype 4 (n=41) | |
|---|---|---|---|---|---|---|---|---|---|
| | (n=177) | TN (n= 14) | TE (n=30) | TN(n=28) | TE(n=35) | TN(n=13) | TE(n=16) | TN(n=13) | TE(n=28) |
| Sex (men) | 115 (65%) | 12 (86%) | 24 (80%) | 10 (36%) | 17 (49%) | 9 (69%) | 12 (75%) | 11 (85%) | 18 (64%) |
| Baseline HCV RNA (Log UI/ml); median [IQR] | 5.95 [5.50-6.31] | 6.24 [5.91-6.41] | 6.11 [5.37-6.36] | 5.89 [5.40-6.19] | 5.90 [5.47-6.25] | 5.79 [5.23-6.14] | 5.73 [5.35-6.30] | 5.91 [5.52-6.30] | 5.98 [5.65; 6.19] |
| Cirrhosis | 78 (44%) | 6 (43%) | 16 (53%) | 11 (39%) | 14 (40%) | 8 (62%) | 8 (50%) | 3 (23%) | 12 (43%) |

### Baseline NS5A RAVs (population sequencing)

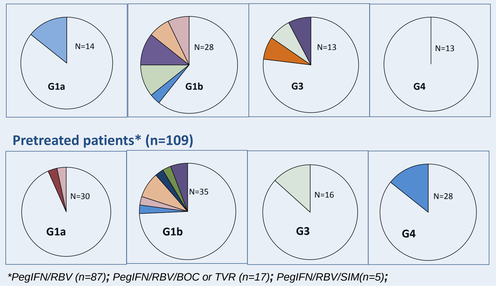



### Baseline NS5B RAVs (population sequencing)



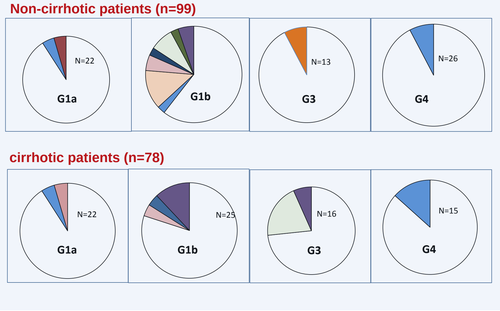

Prior to treatment, NS5A RAVs were detected at a frequency of 9% in GT1a-, 32% in GT1b-, 21% in GT3- and 10% in GT4-infected patients. The most frequent RAVs were Y93H in GT1b (11%) and GT3 (3.5%), and L28M in GT4 (10%). No NS5B S282T, L320F or V321A variants were detected, while L159F was found in 12% of GT1b patients at baseline. C316N and C316H were detected in GT1b patients (20% and 2%, respectively) and in GT4 patients (5% and 2%, respectively).

### Baseline NS5A RAVs (treatment-naïve patients *vs* treatment-experienced)

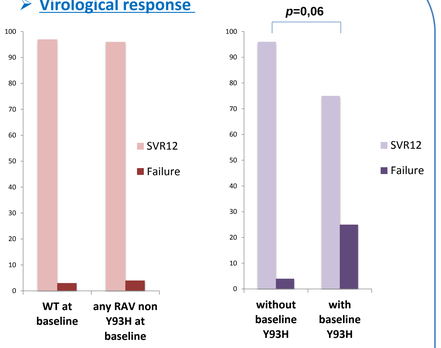



*PegIFN/RBV (n=87); PegIFN/RBV/BOC or TVR (n=17); PegIFN/RBV/SIM(n=5);*

### Baseline NS5A RAVs (Cirrhosis *vs* non-cirrhosis)




### Virological response




### Patients with virological failure

| Patient | Genotype | Cirrhosis | NS5A | | | NS5B | |
|---|---|---|---|---|---|---|---|
| | | | Baseline | Virological failure | Virological failure (unknown mutations) | Baseline | Virologic failure |
| A | 1a | Yes | / | M28T | / | / | / |
| B | 1b | Yes | Y93H | Y93H, L31V | / | / | / |
| C | 3a | No | / | Y93H | / | / | / |
| D | 3a | Yes | / | Y93H | / | / | / |
| E | 3a | Yes | / | Y93H | H85Y | / | / |
| F | 3a | Yes | / | Y93H | / | / | / |
| G | 3a | Yes | Y93H | Y93H | / | / | / |
| H | 4 | Yes | L28M | L28M | / | / | / |

## CONCLUSION

The prevalence of NS5A RAVs at baseline varies considerably across genotypes 1a, 1b, 3 and 4. Depending on the genotype, the type of NS5A natural polymorphism (e.g. Y93H) differentially influences virological outcomes.
In view of these results, we aim at understanding the viral dynamics that lead to failure by analyzing quasispecies distribution generated from Next-Generation Sequencing at different time points during the viral decay following treatment initiation combined with mathematical modeling.