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Need to access HCV resistance profile before the initiation of DAAs therapy

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Links of interest

Adviser, speaker, investigator for:

Abbvie, BMS, Gilead, Janssen, MSD

Patient case 1

Description and hepatitis C disease characteristics

Age/sex/weight/height	54-year-old male 76 kg/187 cm
First diagnosed:	2013
HCV transmission:	IVDU
Treatment experience:	Treatment-naïve
Genotype:	1a
Viral load:	230,269 IU/mL (5.36 log10)
Liver fibrosis stage:	F4 (Fibroscan = 27 kPa)
Complications:	No (Child-Pugh A5, MELD score = 8)
Albumin:	36.7 g/L
Platelets:	151,000 /µL

No additional diseases

No concomitant treatment

IVDU: intravenous drug user

Patient case

First treatment received in May 2014:

DCV + SOF for 12 weeks

HCV viral load outcome:

Day 0:	230,269 IU/mL
Week 4:	13 IU/mL
Week 8:	<12 IU/mL not detected
Week 12 (EOT):	<12 IU/mL not detected
Follow-up week 4:	351,829 IU/mL
Follow-up week 12:	135,390 IU/mL

How would you subsequently treat this patient?

Re-treat with the same regimen

Change to a regimen with a different mechanism of action

More information is needed before deciding how to proceed (e.g. resistance testing)

Patient case

Resistance testing

HCV resistance was assessed using population sequencing, which targeted the NS3/4A, NS5A, NS5B coding regions

Presence of RAVs:

NS3/4A RAVs: No

NS5A RAVs: M28T

NS5B RAVs: No

RAV: resistance-associated variant

Henri Mondor experience: objectives and Study Design

Failure to achieve SVR with IFN-free DAA-based regimens is associated with the selection of resistant HCV variants which can either persist (NS5A inhibitors) or are progressively overgrown by wildtype virus (PI)

Recent guidelines recommended a combination of SOF+SMV as retreatment strategy in patients with previous NS5A failure

The aim of this pilot study was to evaluate the efficacy and safety of SOF+SMV for 12 weeks without RBV in patients who failed prior DCV/PR (n=13) or DCV/ASV/PR (n=3) regimens in phase 2 and 3 studies

IFN: Interferon; DAA: Direct-acting antiviral; PI: Protease inhibitor; SOF: Sofosbuvir; SMV: Simeprevir; DCV: Daclatasvir:; PR: Pegylated interferon + ribavirin; ASV: Asunaprevir; RBV: Ribavirin.

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Demographics and Baseline Characteristics

Characteristics	SMV+SOF 12 Weeks N=16
Mean age, y (range)	54 (43-73)
Male, n (%)	13 (81%)
Genotype 1a, n (%)	11 (69%)
Genotype 1b, n (%)	3 (23%)
Genotype 4, n (%)	2 (13%)
Median HCV RNA, 106 IU/mL	1.38
HCV RNA >800,000 IU/mL, n (%)	14 (88%)
Severe fibrosis (FS 9.6 – 12.5 kPa), n (%)	7 (44%)
Cirrhosis (FS >12.5 kPa), n (%)	9 (56%)
Median time between DCV-based regimen and SMV+SOF, months (range)	32 (16-53)
Presence of NS5A RAVs, n (%)	13 (81%)
Presence of NS3 RAVs, n (%)	8/14 (57%)*
Prior HCV treatment, n (%)	
DCV/PR, n (%)	13 (81%)
DCV/ASV/PR, n (%)	3 (19%)

*Available in 14 patients

SMV: simeprevir; SOF: sofosbuvir; RAVs: resistance-associated variants; FS: Fibroscan;
DCV: daclatasvir; ASV: asunaprevir; PR: pegylated interferon + ribavirin

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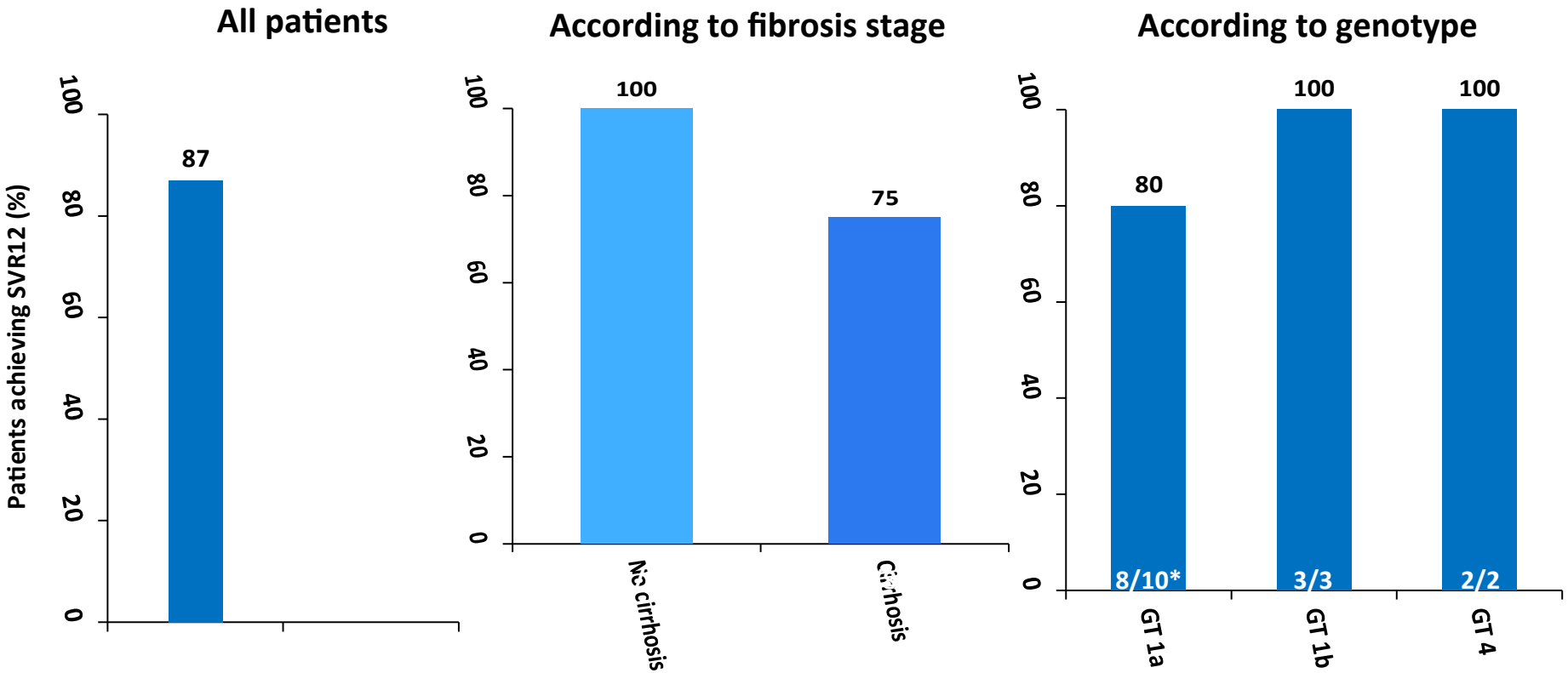
Results: Efficacy and Safety



- 87% of all patients with prior failures on DCV-based therapies, treated with SMV+SOF for 12 weeks achieved SVR12
- No serious adverse events, premature discontinuations or grade 3 or 4 laboratory abnormalities have been observed

SMV: simeprevir; SOF: sofosbuvir; DCV: daclatasvir; SVR: sustained virologic response; GT: genotype

*1 patient does not reach week 12 follow-up visit.

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Treatment failures (n=2)

Patient	Patient 1	Patient 2
Gender	Female	Male
Age	47	48
Genotype	1a	1a
Cirrhosis	Yes (FS=32.8 kPa)	Yes (FS=14.9 kPa)
Albumin	32	43.5
Platelets per µL	76,000	236,000
Prior treatment	DCV/PR	DCV/ASV/PR
On-treatment response	Slow	Slow
Baseline HCV RNA IU/mL	2,084,631	3,629,157
Baseline NS3 RAVs	R155K	Q80K, V170I
Baseline NS5A RAVs	M28T	L31M

RAVs: resistance-associated variants; FS: Fibroscan DCV: daclatasvir:; PR: pegylated interferon + ribavirin; ASV: asunaprevir

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Summary

The combination of SMV+SOF was highly effective in this NS5A inhibitor-exposed population

Two patients failed to achieve SVR

- One had advanced liver disease and one was previously exposed to a PI

Study results support the concept of retreating prior NS5A failures with a SOF plus PI-based regimen

- Difficult to cure patients may benefit from a treatment extension beyond 12 weeks and/or the addition of ribavirin

SOF: sofosbuvir; SMV: simeprevir; SVR: sustained virologic response; PI: protease inhibitor

Patient case

Patient tested for RAVs: NS5A M28T present

Retreatment in January 2015:

SMV + SOF + RBV for 24 weeks

September 2015: SVR12 achieved

Patient 2

Characteristics of the patient and the disease

Age/Gender/Weight/size:	51 years/Male/100 kg/172 cm
HCV diagnosed:	2004
Route of transmission:	Injectable drugs
Previous treatment:	Null response after 12 weeks with peg-IFN/RBV
	Late breakthrough with peg-IFN/RBV/RBV
	Relapse after 24 weeks SOF/LDV (Sirius trial)
Genotype:	1b
HCV RNA:	5,67 log10
Fibrosis:	Fibroscan = 17.5 kPa
Complications :	No HCC, no ascitis, Child A
Albumin:	35.0 g/L
Platelets:	149 000 /µL
Concomitant diseases:	Obesity
Associated treatment:	None

How do you manage ?

Patient 2: Baseline resistance testing

Baseline RAVs
L31F
C316N

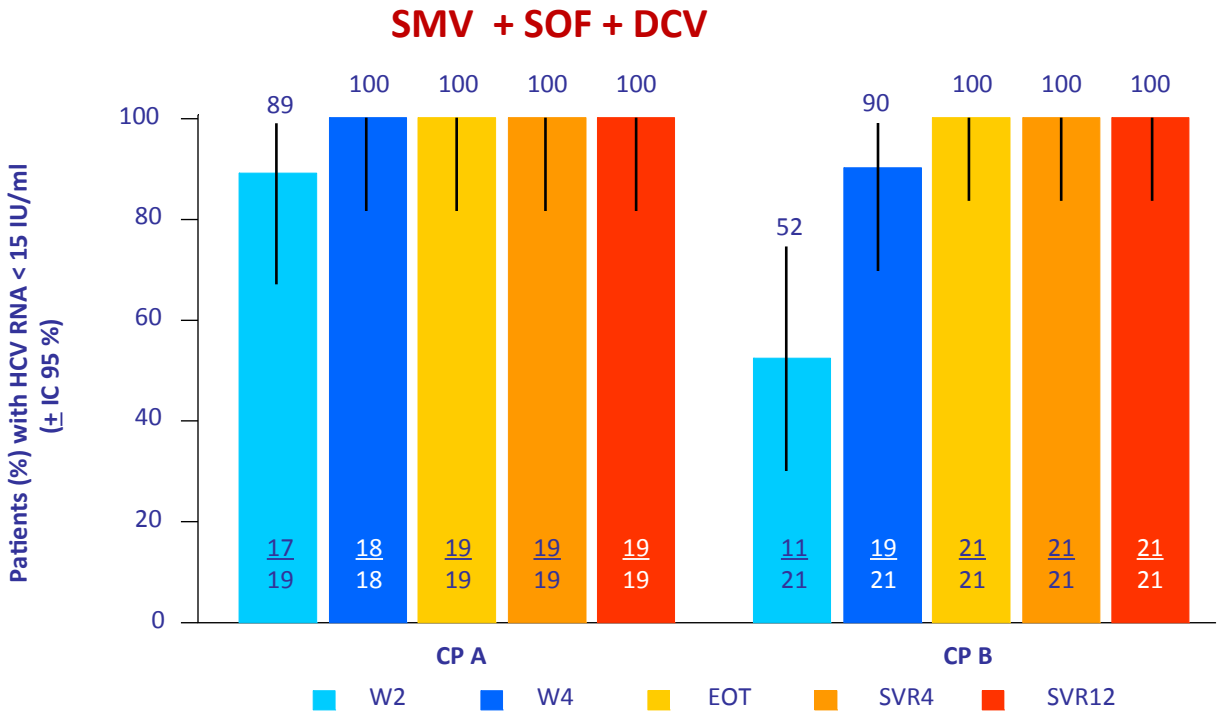
Patient 2: final outcome

Patient received SOF/DCV/SMV/RBV for 24 weeks

HCV RNA D0:	5.67 log10 IU/mL
HCV RNA W4:	15 IU/mL
HCV RNA W8:	<12 IU/mL not detected
HCV RNA W12:	<12 IU/mL not detected
:HCV RNA W24 (EOT):	<12 IU/mL not detected
HCV RNA SVR4:	<12 IU/mL not detected

IMPACT: Sofosbuvir + daclatasvir + simeprevir in cirrhotic patients

- Patients with cirrhosis, GT1 (n=39) or GT4 (n=1), CP-A (n=19) or CP-B (n=21)
- Treatment duration: 12 weeks



- Exposure of SMV is 2.2 fold higher in CP-B *versus* CP-A patients.
- The safety profile was good with photosensibility and et pruritus observed in 8%
- 23% of patients had grade 3 or 4 hyperbilirubunemia (34 % in CP-B)

Lawitz E, et al. AASLD 2015, Abs. 39

Patient 3

Characteristics of the patient and the disease

Age/Gender/Weight/size :	59 years/Female/83 kg/151 cm
HCV diagnosed:	2005
Route of transmission:	IVDU
Previous treatment:	Peg-IFN/RBV 12 weeks (null response)
	SOF/DCV 12 weeks (Relapse)
Genotype:	1a
HCV RNA:	6.44 log10
Fibrosis:	Fibroscan = 15.0 kPa
Complications:	No HCC, No ascitis. Child A
Albumin:	36.0 g/L
Platelets:	102,000 /µL
Concomitant diseases:	Diabetes, Arterial hypertension, Obesity
Associated treatment:	Metformin, valsartan

How do you manage ?

Patient 3: Baseline resistance testing

Baseline RAVs
R155K,D168E
M28A, Q30K

Patient 3: final outcome

Patient received SOF/DCV/SMV/RBV for 24 weeks

HCV RNA D0:	6.44 log10 IU/mL
HCV RNA W4:	590 IU/mL
HCV RNA W8:	95 IU/mL
HCV RNA W12:	32 IU/mL
HCV RNA W16:	<12 IU/mL detected
HCV RNA W24:	<12 IU/mL not detected
HCV RNA SVR4:	6.25 log10 IU/mL

Patient 3: Resistance testing at baseline and failure

Baseline RAVs	RAVs at failure
R155K,D168E M28A, Q30K	R155K, D168E M28A, Q30K

Retreatment of patients who failed an IFN-free regimen

- Recommendations are based on indirect evidence and may be subject to change as more data become available

- The retreatment regimen should contain
  - Sofosbuvir because of the high barrier to resistance
  - One or two other DAA(s), if possible with no cross-resistance with the DAA(s) already administered
  - Ribavirin

- Treatment duration should be 12 or 24 weeks (24 weeks is recommended in F3–F4)

EASL Recommendations on Treatment of Hepatitis C 2015. Available at: http://www.easl.eu/research/our-contributions/clinical-practice-guidelines/detail/recommendations-on-treatment-of-hepatitis-c-2015