Clinical Case
A previously relapse to PEG IFN + RBV in HCV G3a patient

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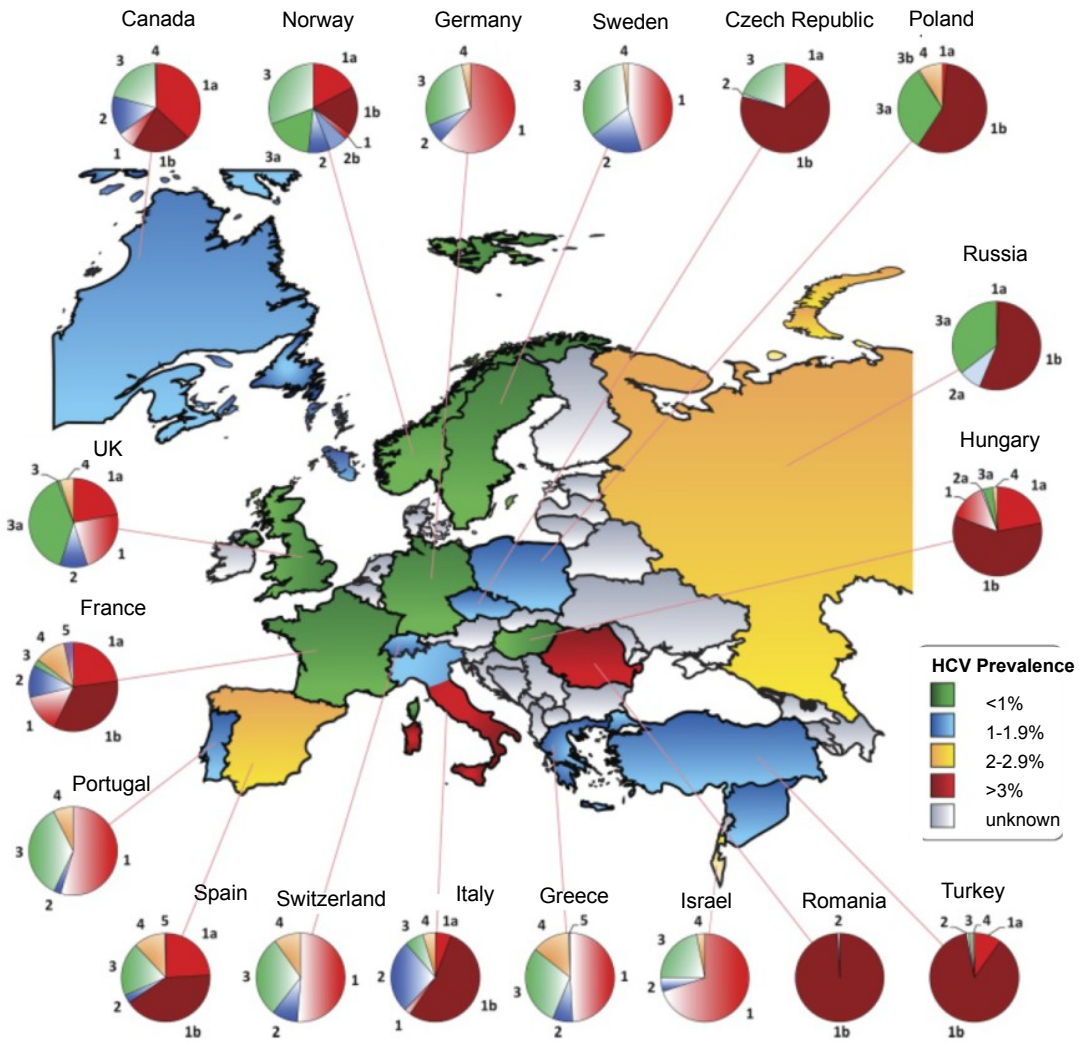
Genotype 3 in Europe

Approximately 1/3 of HCV-infected patients in the majority of countries in Europe are G3

G: genotype



Cornberg M, et al. Liver Int 2011;31(Suppl 2):30–60.

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Characteristics of the patient, medical history

- Male, 53 years old, Caucasian, BMI 27.3 kg/m2
- Anti HCV detected since 1995
- No history of drug abuse
- No history of alcohol abuse
- No history of blood transfusion
- He was asymptomatic
- No treatment till 2009

Characteristics of the patient, 2009

- Generalized weakness
- Hepatosplenomegaly
- No varices in endoscopy
- Genotype 3a
- HCV RNA 4.8x106 IU/ml
- ALT 120 IU/L (N – 40 IU/L)
- Liver biopsy: Metavir Score – A2, F4.

Characteristics of the patient, 2009

- Therapy was started with Peg-IFN α-2a 180 μg/wk + RBV 800 mg/day for 24 weeks.
- Week 12 (EVR): HCV RNA – undetectable, ALT – N
- Week 24 (EOT): HCV RNA – undetectable, ALT – N

- Week 48 (EOF): HCV RNA – positive, ALT – N
- Relapse was registered.
- Significant adverse events were observed (flu-like syndrome, weight loss, asthenia, fatigue, alopecia, insomnia)

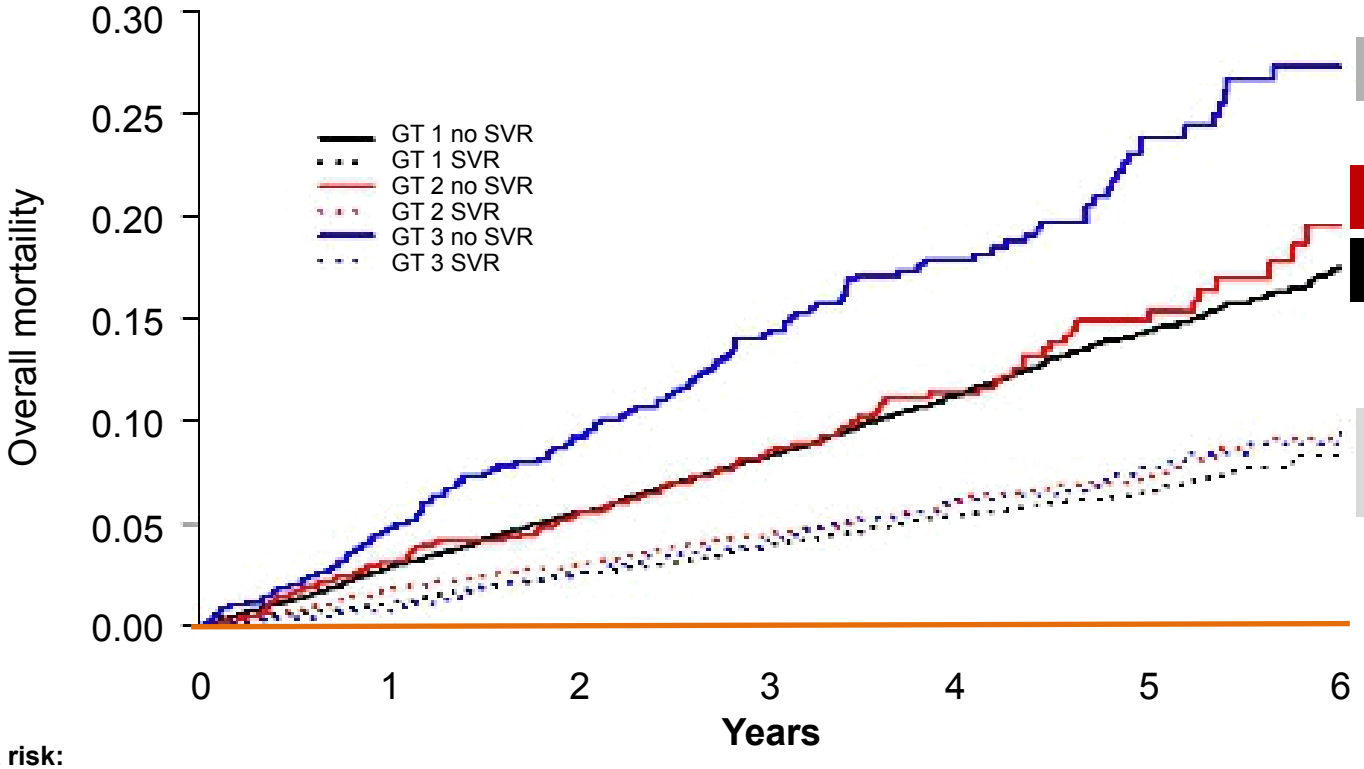
What to do in 2009?

Traditionally G3 considered to be an ‘easier to treat’ genotype

1 Yes?

2 No?

G3 is associated with rapid fibrosis progression and poor survival



GT 3, no SVR

GT 2, no SVR

GT 1, no SVR

GT 1, 2 and 3 SVR

Patients at risk:

GT 1	No SVR	7,918	7,691	6,450	4,871	3,408	2,074	844
	SVR	4,248	4,200	3,487	2,698	1,889	1,095	295
GT 2	No SVR	815	790	657	494	323	189	73
	SVR	2,089	2,052	1,800	1,383	951	563	210
GT 3c	No SVR	697	664	559	420	290	160	82
	SVR	1,097	1,089	931	722	499	293	87

Backus LI, et al. Clin Gastroenterol Hepatol 2011;9:509–16.

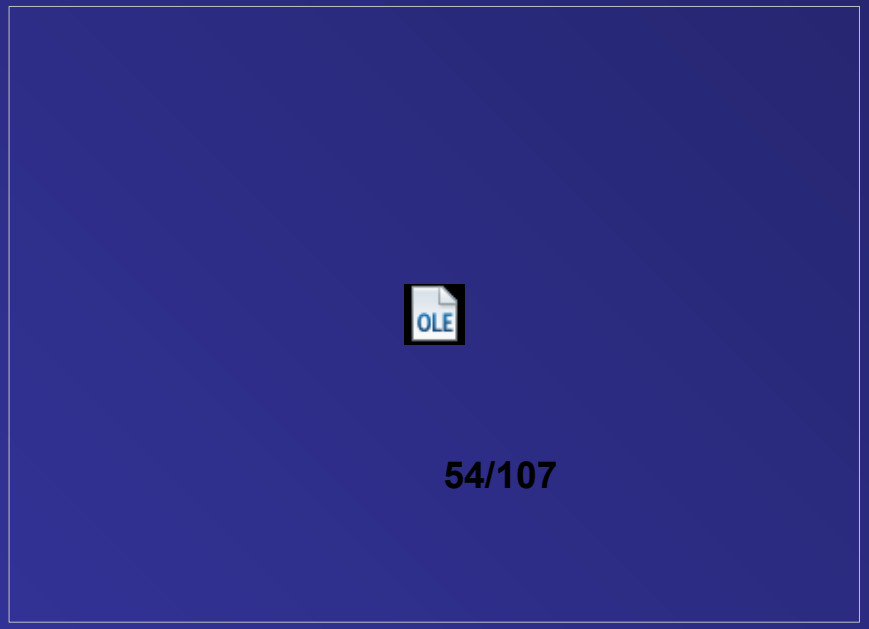
What to do in 2009?

Traditionally G3 considered to be an ‘easier to treat’ genotype, but increasing evidence that this isn’t the case

- ✓ Retreatment with Peg-IFN and RBV for 48 weeks?
- ✓ Wait new drugs (clinical trials)?

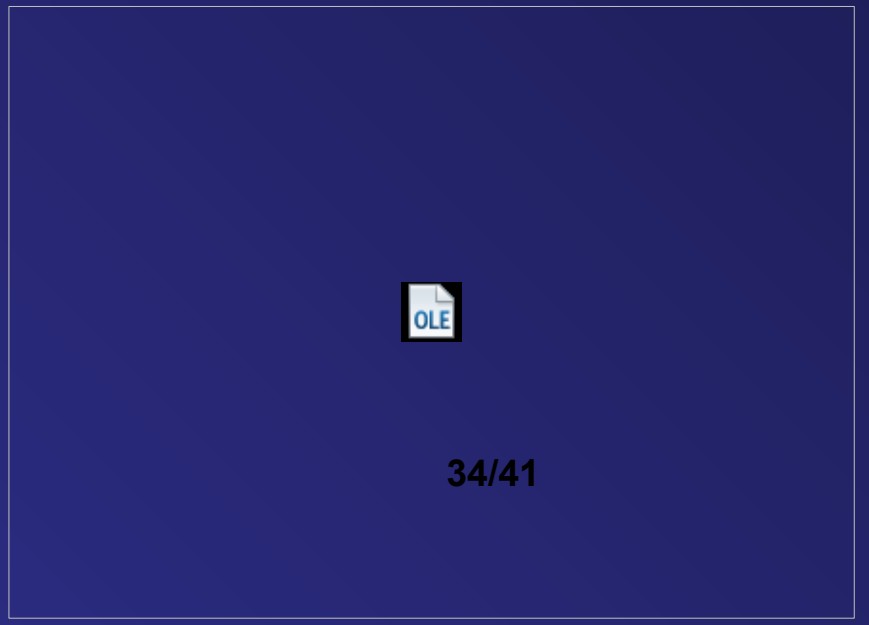
Re-treatment of relapsers

Re-treatment for 72 weeks with Peg-IFN α-2a + RBV of relapsers (genotype 1) after 48 weeks standard regimen



Kaiser S et al, Hepatology 2008; 48(Suppl4): 1140A

Re-treatment for 48 weeks with Peg-IFN α-2a + RBV of relapsers (genotype 2/3) after 24 weeks standard regimen



Minola E et al, J Hepatol 2010; 52(Suppl1): S117

REPEAT study: Predictive value of achieving HCV RNA < 50 IU/mL at week 12

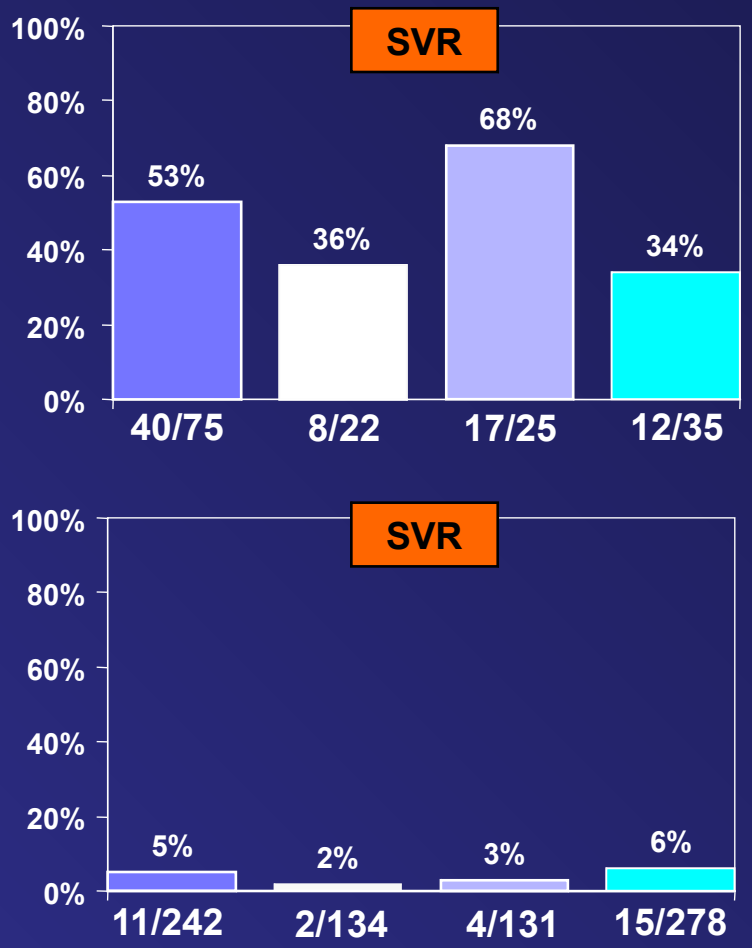
All patients treated (n=942)

<50 IU/mL at week 12: **YES**

17%
(157 / 942)

<50 IU/mL at week 12: **NO**

83%
(785 / 942)



Jensen D, et al. Ann Intern Med 2009; 150:528–540

Characteristics of the patient, 2014

HCV RNA	867 543 IU/ml
Hemoglobin	127 g/l
Neutrophils	2.17 x 109/l
Albumin	37 g/l
Prothrombin index	72%
Platelets	100 x 109/l
TSH	2,5 UI/l
ALT	145.4 IU/l
IL28B polymorphism	CT
FibroScan	13.1 kPa

What to do in 2014?

EASL HCV Guidelines 2014: Genotype 3

Option	Regimen
1	**PegIFN/ribavirin** + **sofosbuvir**: 12 wks (A2)
2	**Sofosbuvir** + **ribavirin**: 24 wks (unsuitable for treatment-experienced cirrhotics, no specific alternative proposed) (A2)
3	**Sofosbuvir** + **daclatasvir**: 12 wks (24 wks for treatment-experienced patients; Ribavirin can be considered) (B1)

*In settings where recommended options are not available, treatment with pegIFN/ribavirin remains acceptable.

EASL. J Hepatology. 2014;60:392-420.

How can we improve responses in genotype 3 with new drug Sofosbuvir?

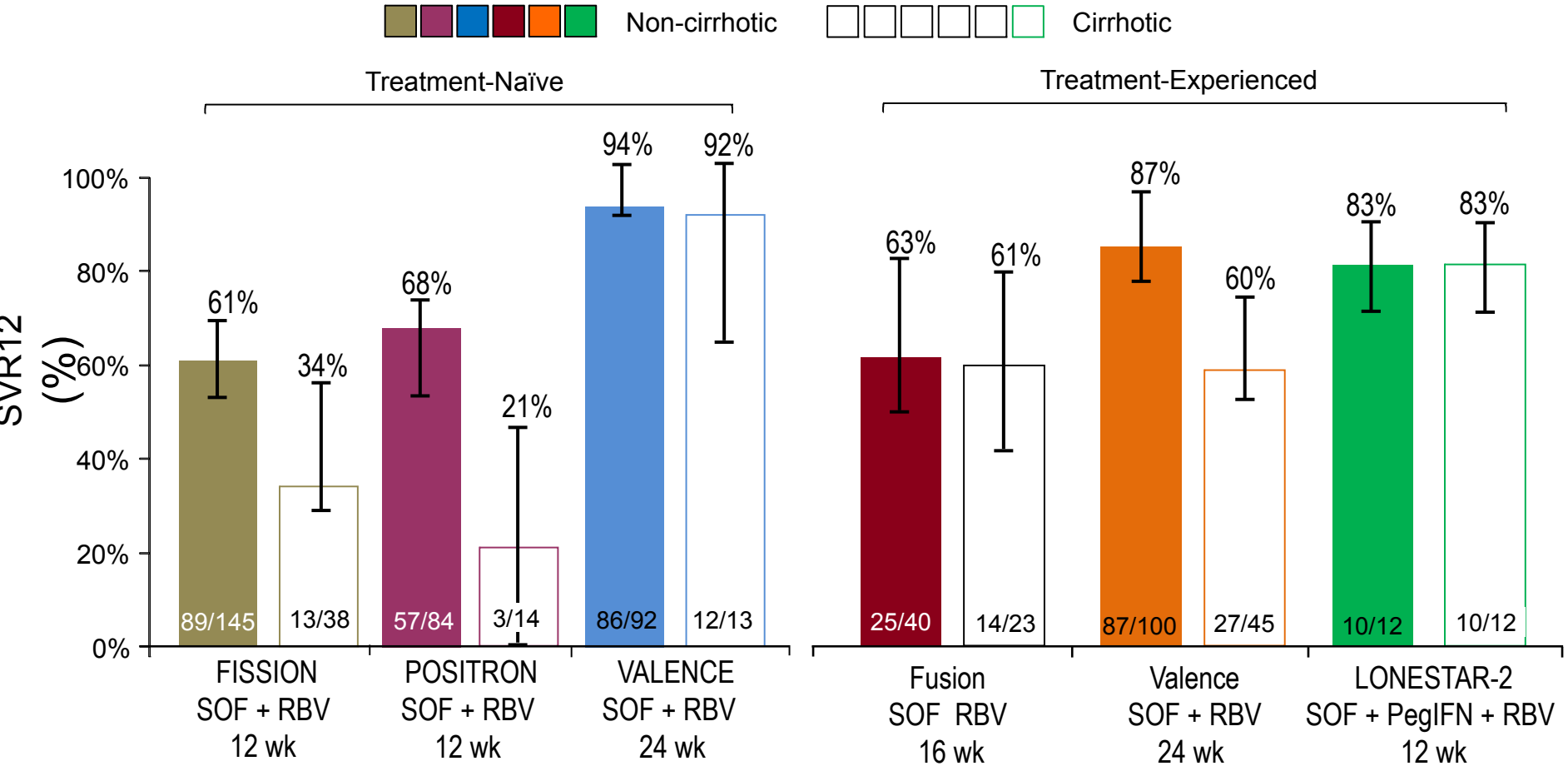
a) Longer therapy?

b) Combination with PEG-IFN?

c) Combination with other DAAs?

SVR12 Rates Across SOF-Based Studies

HCV GT 3 Patients



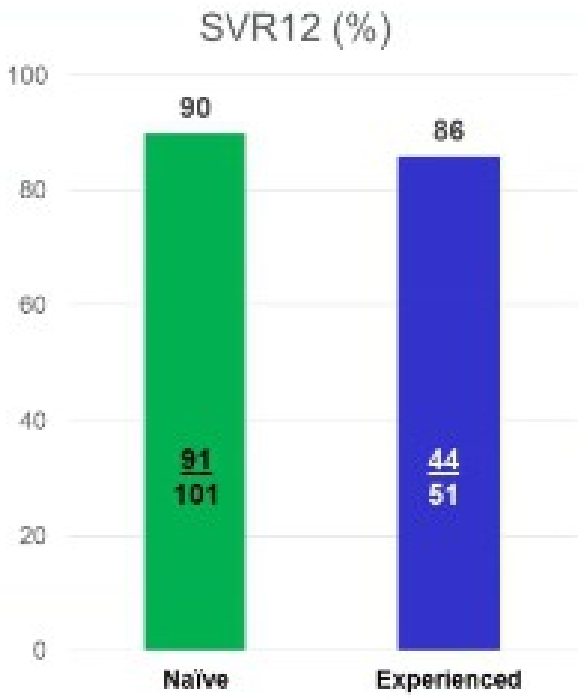
HCV GT 3 patients treated with SOF + RBV for 24 weeks or SOF + PegIFN + RBV for 12 weeks achieved high SVR rates regardless of presence of cirrhosis or treatment experience

Lawitz E, et al. *N Engl J Med*. 2013 May 16. Zeuzem S, et al. AASLD 2013. Washington, DC. #1085.
Jacobson IM, et al. *N Engl J Med*. 2013 May 16. Lawitz E, et al. AASLD 2013. Washington, DC. Oral #LB-4.

Combination of SOF with daclatasvir for 12 weeks

Genotype 3 daclatasvir + sofosbuvir

- Study: ALLY 3
- Patients: 152
  - Genotype 3
  - Treatment naïve (101) and experienced (52)
    - Sofosbuvir and alisporivir included
  - Cirrhosis 21%
- Design
  - Open label cohorts
- Regimen
  - SOF + DCV x 12 weeks



SVR4 rate was 70% for patients with F4

Nelson DR et al., AASLD 2014

Characteristics of the patient, 2014. Dynamics of laboratory parameters during treatment SOF+RBV

	ALT (IU/ml)	Hb (g/l)	Neu (x109/l)	Alb (g/l)	PI (%)	Plt (x109/l)	TSH (IU/l)	RNA HCV, (IU/ml)	Fs (kPa)
W2	65.2	119	2.17	35.3	70	105	-	0	-
W4	35.1	112	4.0	36.2	100	131	2.45	0	-
W12	32.5	104	3.14	34.7	85	112	2.68	0	-
W24	34.7	111	2.91	38.4	91	135	3.01	0	-
FUP W36	27.4	130	3.15	37.7	101	148	5.25	0	11.8

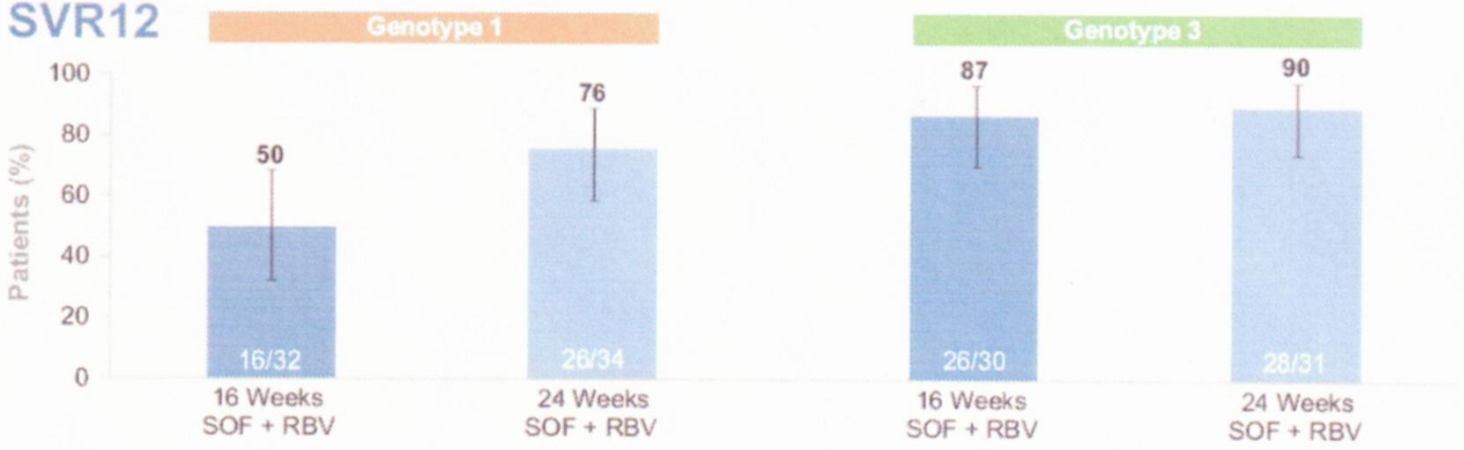
Sofosbuvir plus Ribavirin for the treatment of Russian patients with chronic HCV Genotype 1 or 3 infection

Demographics and Disease Characteristics

	Genotype 1		Genotype 3	
	16 Weeks SOF + RBV, n=32	24 Weeks SOF + RBV, n=34	16 Weeks SOF + RBV, n=30	24 Weeks SOF + RBV, n=31
Mean age, y (range)	41 (19–66)	42 (21–57)	38 (26–61)	40 (26–65)
Male, n (%)	13 (41)	16 (47)	19 (63)	19 (61)
Mean BMI, kg/m² (range)	27 (19–37)	27 (19–42)	27 (20–42)	26 (20–38)
GT 1b, n (%)	32 (100)	33 (97)	–	–
GT 3a, n (%)	–	–	30 (100)	31 (100)
Mean baseline HCV RNA, $\log_{10}$ IU/mL (range)	6.2 (5.2–7.4)	6.1 (4.7–7.2)	6.2 (4.4–7.3)	6.2 (4.5–7.1)
Cirrhosis, n (%)	4 (13)	6 (18)	6 (20)	5 (16)
IL28B CC, n (%)	10 (31)	6 (18)	12 (40)	15 (48)

BMI, body mass index.

SVR12



- No on-treatment virologic failure occurred in any group

Neither serious AE was considered treatment related

Chulanov V., Zhdanov K., Kersey K. et al. AASLD 2014

Sofosbuvir plus Ribavirin for the treatment of Russian patients with chronic HCV Genotype 1 or 3 infection

SVR12 by Genotype and Subgroup

	Genotype 1		Genotype 3	
Patients, n (%)	16 Weeks SOF + RBV, n=32	24 Weeks SOF + RBV, n=34	16 Weeks SOF + RBV, n=30	24 Weeks SOF + RBV, n=31
Men	5/13 (38)	11/16 (69)	15/19 (79)	16/19 (84)
Women	11/19 (58)	15/18 (83)	11/11 (100)	12/12 (100)
Cirrhosis	0/4	2/6 (33)	5/6 (83)	3/5 (60)
No cirrhosis	16/28 (57)	24/28 (86)	21/24 (88)	25/26 (96)
IL28B CC	6/10 (60)	6/6 (100)	11/12 (92)	12/15 (80)
IL28B non-CC	10/22 (45)	20/28 (71)	15/18 (83)	16/16 (100)
Baseline HCV RNA <800,000 IU/mL	9/12 (75)	8/11 (73)	9/10 (90)	10/10 (100)
Baseline HCV RNA ≥800,000 IU/mL	7/20 (35)	18/23 (78)	17/20 (85)	18/21 (86)
BMI <30 kg/m^2	13/22 (59)	21/25 (84)	21/24 (88)	25/27 (93)
BMI ≥30 kg/m^2	3/10 (30)	5/9 (56)	5/6 (83)	3/4 (75)

Virology Results

- Baseline RAVs
  - No S282T NS5B RAV detected by deep sequencing
  - L159F variant detected in 22 of 65 patients (34%) with HCV GT 1b and in no patients with HCV GT 3a infection

SVR12 in GT 1b Patients With or Without RAVs at Baseline

	Genotype 1b	
SVR12, n/n (%)	16 Weeks SOF + RBV, n=32	24 Weeks SOF + RBV, n=33
L159F*	3/12 (25)	8/10 (80)
Wild type	13/20 (65)	17/23 (74)

*L159F always coexisted with C316N at baseline.

- RAVs at virologic failure
  - No S282T detected by deep sequencing
  - L159F emerged in 2 patients (GT 1b and GT 3a)
  - L320F emerged in 4 patients with GT 1b infection

Chulanov V., Zhdanov K., Kersey K. et al. AASLD 2014

Non-responders to PEG-IFN/RBV with G3, what prospects?

- ✓ 2-nd generation of NS5A inhibitors (GS-5816, MK-8742, ACH-3102) ?
- ✓ 2-nd generation of NS3 protease inhibitors (MK-5172, ACH-2684) ?

Summary

High prevalence of GT3 infection in Europe (~ 40% Russia);
may be associated with increased fibrosis progression rate;

in some cases considered to be an ‘difficult to treat’ genotype
HCV-specific nucleotide polymerase inhibitor:
- High antiviral activity for SOF
Previous relapse patient to Peg IFN and RBV with G3a
achieved SVR rate with all-oral IFN-free (24 weeks SOF + RBV),
despite the presence of cirrhosis
An interferon-free regimen of SOF + RBV has the potential to be
of benefit to HCV G3 patients in Russia