5th Young Hepatology Workshop-HCV Resistance

Ola Weiland
Karolinska

INVITED ARTICLE VIRAL HEPATITIS

Camilla S. Graham, Section Editor

Hepatitis C Virus Therapeutic Development: In Pursuit of "Perfectovir"

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The next decade will be a crucial period in the public health response to hepatitis C virus (HCV) infection. The rapid development of direct-acting antiviral (DAA) therapy for HCV infection has brought considerable optimism to the HCV sector, with the realistic hope that therapeutic intervention will soon provide near-optimal efficacy with well-tolerated short-duration, all-oral regimens. As the zenith in HCV therapeutic development approaches, there remain several key obstacles to the broad implementation of interferon-free DAA regimens. The extent of HCV screening and disease assessment, global and national public health prioritization, and drug pricing will determine the potential impact on disease burden derived from introduction of these exciting new HCV therapies. Public health partnerships and advocacy will be crucial to remove barriers to enhanced HCV treatment access.

Keywords. hepatitis C; directly acting antivirals; global access.

REMAINING REQUIREMENTS IN HCV THERAPEUTIC DEVELOPMENT

The bar has clearly been raised during 2014 in terms of the optimal regimen for HCV treatment ("perfectovir"). Ideally, such a regimen would have the following key attributes:

- Extremely high treatment efficacy (>95%);
- Pangenotypic activity (ie, similar dosing and duration across genotypes);
- Maintenance of high efficacy in decompensated cirrhosis and peritransplant settings;
- Minimal toxicity;
- Minimal HCV resistance;
- Ease of dosing, preferably 1 tablet once daily;
- Limited drug–drug interactions;
- Short duration;
- Affordability.

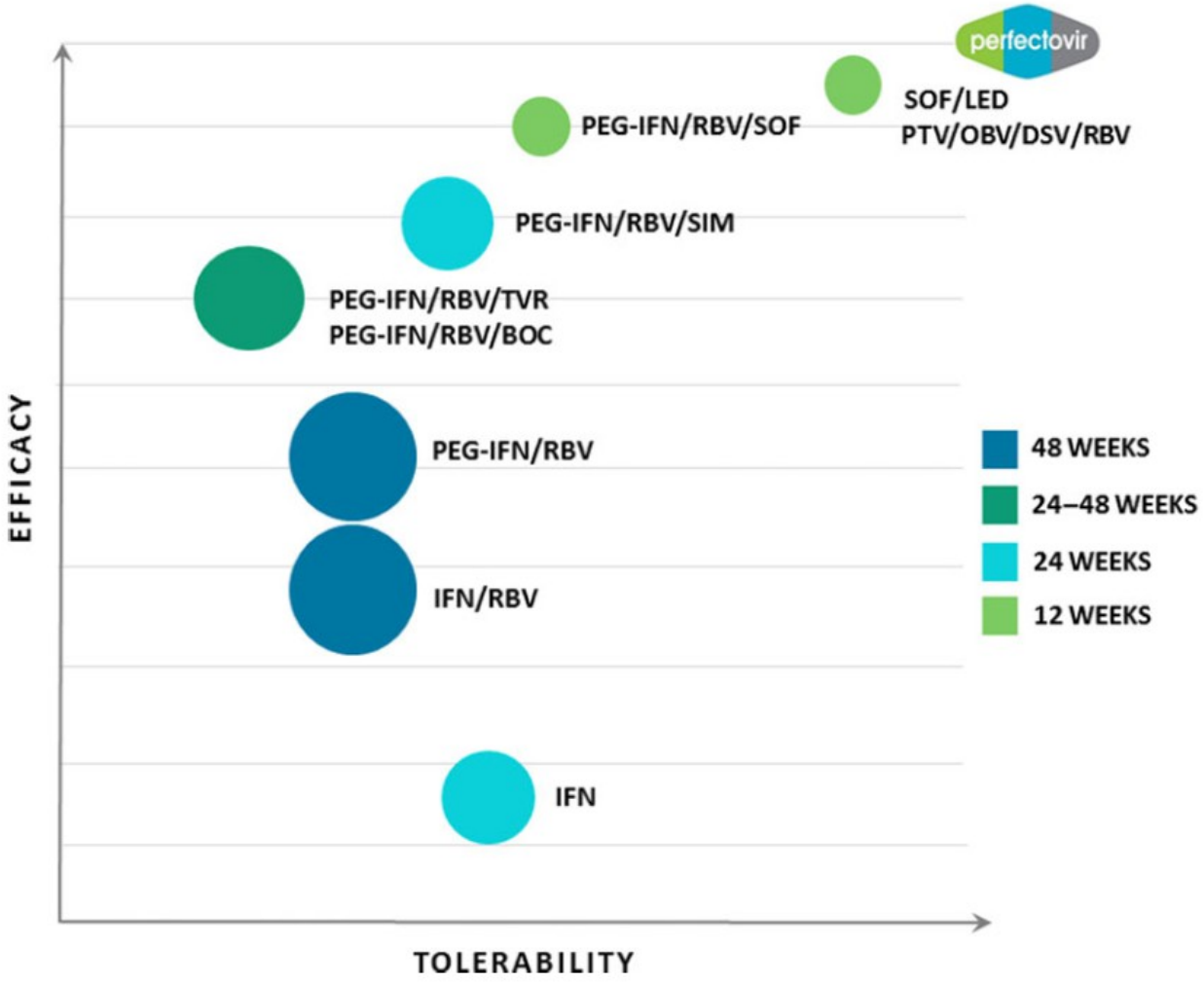

Figure 1. Advances in hepatitis C therapy with respect to tolerability and efficacy. Abbreviations: BOC, boceprevir; DSV, dasabuvir; IFN, interferon; LED, ledipasvir; OBV, ombitasvir; PEG-IFN, pegylated interferon; PTV, paritaprevir; RBV, ribavirin; SIM, simeprevir; SOF, sofosbuvir; TVR, telaprevir.

Table 1. Interferon-Free Direct Acting Antiviral Regimens for Chronic Hepatitis C Virus Genotype 1

Company	Protease Inhibitor	Polymerase Inhibitor: Nucleotide Analogue	Polymerase Inhibitor: Nonnucleoside Analogue	NS5A Inhibitor	Other	Duration	Total Tablets/ Dosing	Phase
Gilead		Sofosbuvir		Ledipasvir		8–24 wk[a]	1/daily	Licensed
AbbVie	Paritaprevir/ritonavir		Dasabuvir	Ombitasvir	± Ribavirin[b]	12–24 wk[c]	4–8[d]/bid	Licensed
BMS	Asunaprevir		Beclabuvir	Daclatasvir	± Ribavirin[e]	12 wk	2–8[d]/bid	3
Merck	Grazoprevir			Elbasvir		12 wk	1/daily	3
BMS[f]		Sofosbuvir		Daclatasvir		12 wk	2/daily	3
Gilead[f]		Sofosbuvir		GS-5816		12 wk	1/daily	3
Merck[f]	Grazoprevir	Sofosbuvir		Elbasvir		4–12 wk	2/daily	2
BMS	Asunaprevir	Sofosbuvir	Beclabuvir	Daclatasvir		4–6 wk	3/bid	2
AbbVie[f]	ABT-493			ABT-530	± Ribavirin	8–12 wk	2–4/daily-bid	2
Gilead[f]	GS-9857	Sofosbuvir		GS-5816		6–8 wk	2/daily	2
Merck[f]	Grazoprevir	MK-3682		Elbasvir or MK-8408		6–8 wk	2–3/daily	2

Abbreviations: bid, twice daily; BMS, Bristol–Myers Squibb.

[a] Eight weeks recommended for treatment-naive patients with genotype 1, Metavir F0–F3, and hepatitis C virus RNA level <6 million IU/mL; 24 weeks recommended for treatment-experienced patients with genotype 1 and cirrhosis.

[b] Ribavirin (RBV) used for all patients with genotype 1a and patients with 1b patients and cirrhosis.

[c] Twenty-four weeks recommended for treatment-experienced patients with genotype 1a and cirrhosis.

[d] RBV 400 mg and 600 mg tablets should be used once licensed, reducing total tablets per day to 4.

[e] RBV only evaluated in patients with cirrhosis.

[f] Also under evaluation as pangenotypic regimens.

Barriers to HCV Resistance-according to DAA class

- **NUC Sofosbuvir** — **High**
- **NS4 PI:s**
  - **Asunaprevir, Simeprevir, Paritaprevir** — **Low**
  - **Grazoprevir** — **Medium**
- **NS5A inh**
  - **Daclatasvir, Ledipasvir, Ombitasvir** — **Low**

Duration of HCV Resistant Variants (RAVs) according to DAA class

- **NUC Sofosbuvir** **-**
- **NS4 PI:s**

  Asunaprevir, Simeprevir, Paritaprevir **1-2 yrs**
  Grazoprevir
- **NS5A inh**

  Daklatasvir, Ledipasvir,Ombitasvir **> 2 yrs**

Detection of HCV Resistant variants (RAVs) according to method

- By population-based sequencing when 20-25% of the strains have RAVs

- By deep sequencing when < 5% of the strains have RAVs

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Viral Hepatitis

Hepatitis C Virus Drug Resistance-associated Substitutions: State of the Art Summary

Erik Lontok[1,†], Patrick Harrington[2,‡], Anita Howe[3], Tara Kieffer[4], Johan Lennerstrand[5], Oliver Lenz[6], Fiona McPhee[7], Hongmei Mo[8], Neil Parkin[9], Tami Pilot-Matias[10] and Veronica Miller[1,*]

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REVIEW

Hepatitis C Virus Drug Resistance–Associated Substitutions: State of the Art Summary

Erik Lontok,[1] Patrick Harrington,[2] Anita Howe,[3] Tara Kieffer,[4] Johan Lennerstrand,[5] Oliver Lenz,[6] Fiona McPhee,[7] Hongmei Mo,[8] Neil Parkin,[9] Tami Pilot-Matias,[10] and Veronica Miller[1]

Hepatitis C virus (HCV) drug development has resulted in treatment regimens composed of interferon-free, all-oral combinations of direct-acting antivirals. While the new regimens are potent and highly efficacious, the full clinical impact of HCV drug resistance, its implications for retreatment, and the potential role of baseline resistance testing remain critical research and clinical questions. In this report, we discuss the viral proteins targeted by HCV direct-acting antivirals and summarize clinically relevant resistance data for compounds that have been approved or are currently in phase 3 clinical trials. *Conclusion*: This report provides a comprehensive, systematic review of all resistance information available from sponsors' trials as a tool to inform the HCV drug development field. (HEPATOLOGY 2015; 00:000-000)

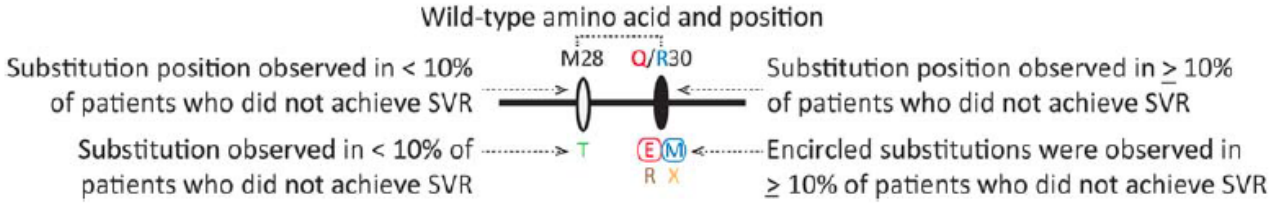


Fig. 1. Resistance figure notations. Wild-type amino acids and positions are placed above the viral protein image. Substitution positions detected in <10% of patients whose treatment failed are visualized with an empty oval, while substitution positions detected in ≥10% are visualized with a filled oval. Below the viral protein image, substitutions detected in <10% of patients whose treatment failed are listed, while substitutions detected in ≥10% are listed and encircled. Amino acid deletions are designated with an *X*. Substitutions are ordered based on their prevalence in patients who failed treatment, with ≥10% listed first, then in alphabetical order, followed by <10%, then in alphabetical order. Substitutions are color-coded based on genotype and subtype: 1a, red; 1b, blue; 2, brown; 3a, green; 4, orange.

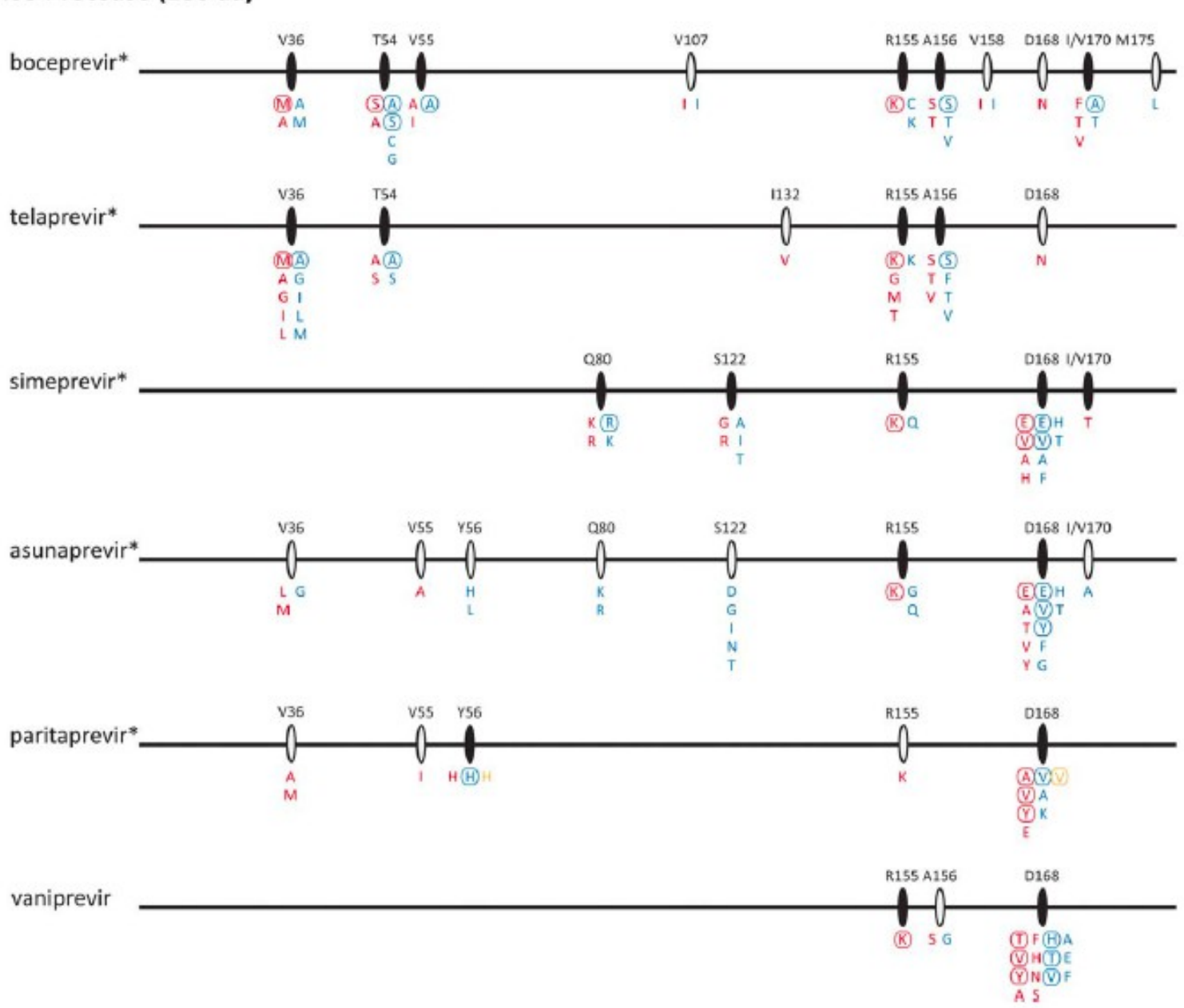


Fig. 2. NS3 resistance-associated substitutions observed with treatment. *Compounds approved for clinical use. Substitutions are color-coded based on genotype and subtype: 1a, red; 1b, blue; 2, brown; 3a, green; 4, orange. See Fig. 1 legend.

Table 1. Mean Fold-Change in Resistance Compared to Wild-Type Replicon of Clinically Relevant NS3 Protease Resistance-Associated Substitutions

HCV NS3 Protease AA and Position	Resistance-Associated Substitution(s)	Replicon Vector Genotype	Mean Fold Change in Resistance Compared to Wild-Type Replicon					
			Boceprevir*	Telaprevir†	Simeprevir‡	Asunaprevir§	Paritaprevir‖	Vaniprevir¶
V36	V36M	1a	3			2	2	
	V36M +R155K	1a				55	79	
	V36M +R155K	1b		64		72		
T54	T54S	1a	2					
	T54S	1b	3					
V55	V55A	1b	3			1		
Y56	Y56H+D168V	1a					561	
	Y56H+D168V	1b					2472	
Q80	Q80K	1a			11	3		
	Q80K+R155K	1a			1830	60		
	Q80H	1b			3			
	Q80K	1b			8	1		
	Q80R	1b			6	1		
	Q80K+R155K	1b			420			
	Q80H+D168E	1b			145			
	Q80R+D168A	1b			2660			
	Q80R+D168E	1b			418			
	Q80R+R155K	1b			305			

Q 80K Resistant variants (RAVs) frequency in genotype 1a

- **US** **40-50 %**
- **Europe** **5 %**

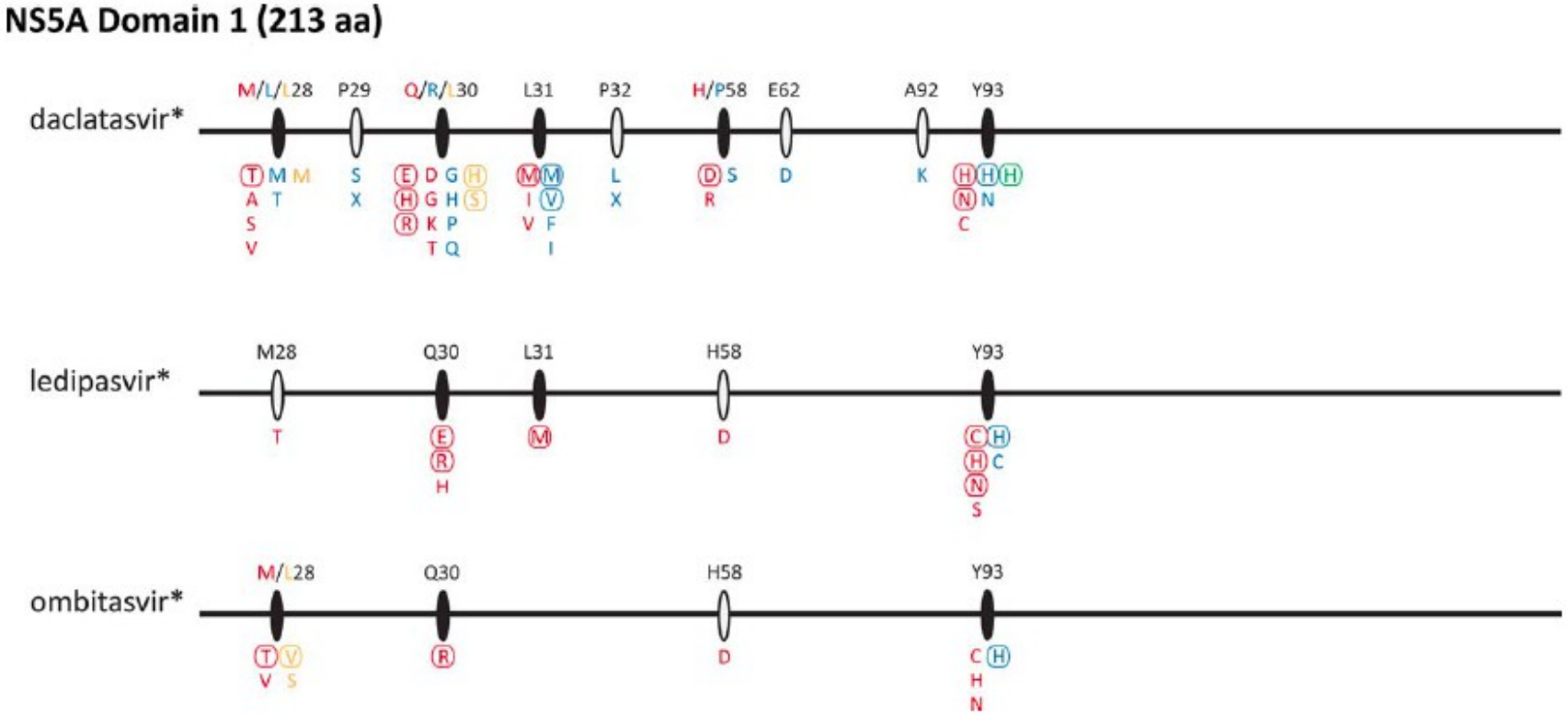


Fig. 3. NS5A resistance-associated substitutions observed with treatment. *Compounds approved for clinical use. Amino acid deletions are designated with an *X*. Substitutions are color-coded based on genotype and subtype: 1a, red; 1b, blue; 2, brown; 3a, green; 4, orange (daclatasvir 4, ombitasvir 4d). See Fig. 1 legend.

Table 2. Mean Fold-Change in Resistance Compared to Wild-Type Replicon of Clinically Relevant NS5A Resistance–Associated Substitutions

HCV NS5A Amino Acid and Position	Resistance-Associated Substitution(s)	Replicon Vector Genotype	Mean Fold-Change In Resistance Compared to Wild-Type Replicon		
			Daclatasvir*	Ledipasvir†	Ombitasvir‡
M28	M28T	1a	205	61	8965
	M28V	1a			58
Q30	Q30E	1a	7500	5458	
	Q30H	1a	435	183	
	Q30R	1a	365	632	800
	Q30R+Y93C	1a		1046	
L31	L31M	1a	105	554	
	L31V	1a	1000		
	L31M	1b	3		
	L31V	1b	15		
	L31M+Y93H	1b	4227		
	L31V+Y93H	1b	5425		
H58	H58D	1a		1127	243
Y93	Y93C	1a	555	1602	1675
	Y93H	1a	1600	1677	41,383
	Y93N	1a	14,100	>14,706	66,740
	Q30R+Y93C	1a		1046	
	Y93H	1b	12		77
	L31M+Y93H	1b	4227		
	L31V+Y93H	1b	5425		

Please see the Supporting Information for detailed site-directed mutagenesis data. Values were rounded to whole numbers; empty cells indicate no data available from patients who experienced treatment failure.

*Daclatasvir data were generated by luciferase assay.

†Ledipasvir data were generated by luciferase assay.

‡Ombitasvir data were generated by luciferase assay.

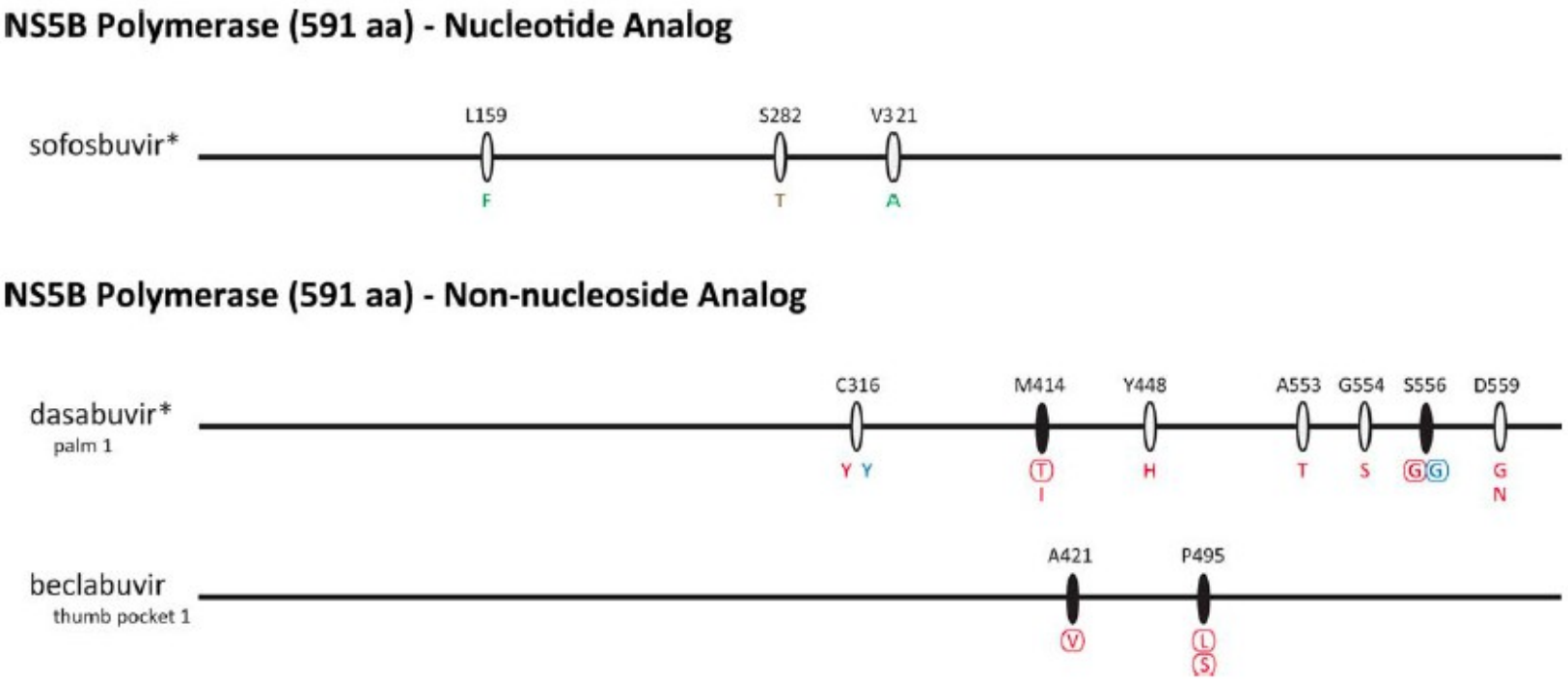


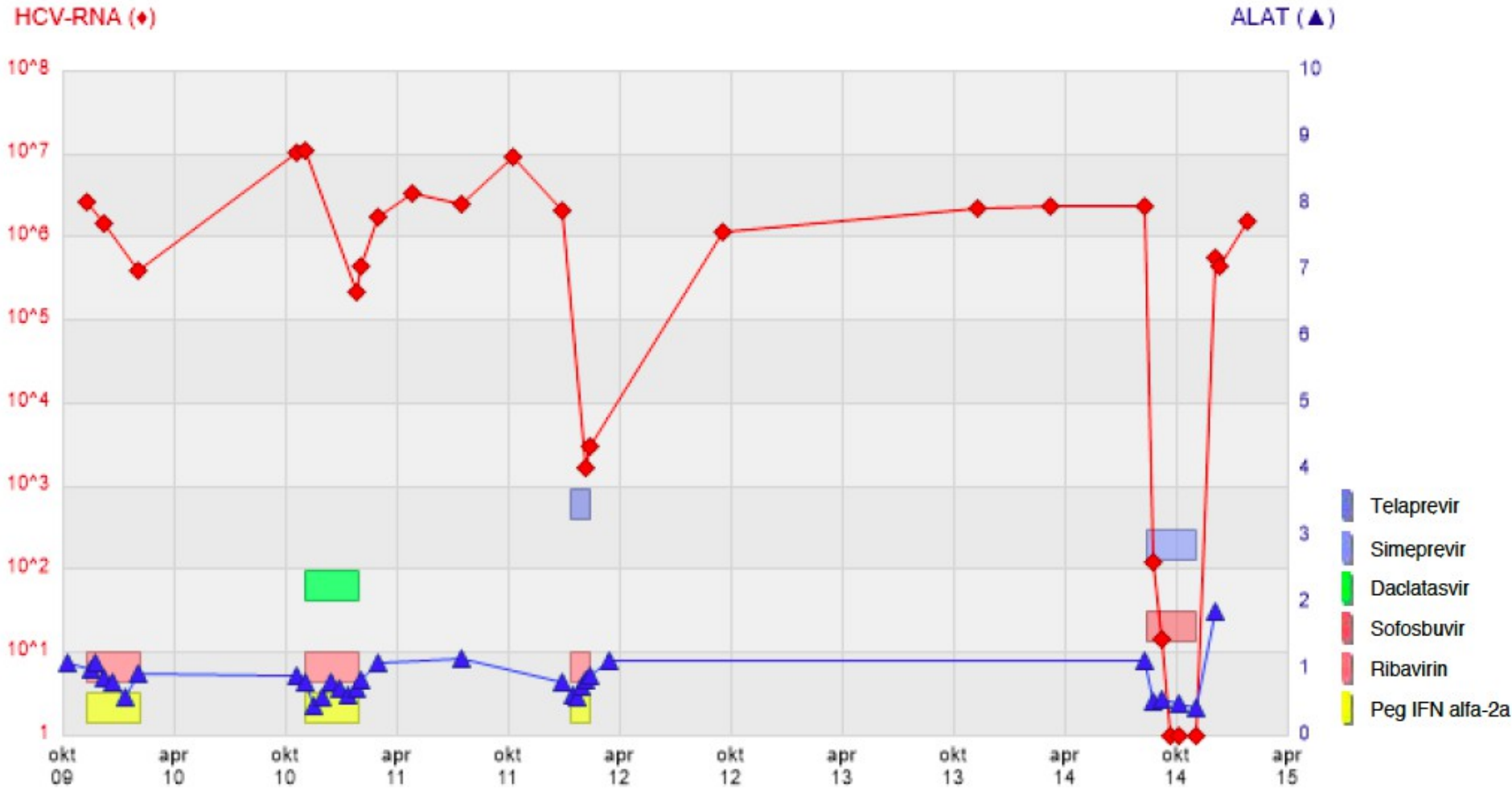
Fig. 4. NS5B resistance-associated substitutions observed with treatment. *Compounds approved for clinical use. Amino acid deletions are designated with an X. Substitutions are color-coded based on genotype and subtype: 1a, red; 1b, blue; 2, brown; 3a, green. NS5B inhibitors are subdivided based on site of interaction: sofosbuvir, nucleotide analog, NS5B active site; dasabuvir, nonnucleoside analog, NS5B palm 1 site; beclabuvir, nonnucleoside analog, NS5B thumb pocket 1. See Fig. 1 legend.

Table 1. Difficult-to-Cure Patient Populations: Past and Present

	Past: Era of Peg-IFN and RBV	Present: Era of DAA Drug Combinations
Difficult to Cure	• Genotype 1 • High viral load, IL28B genotype TT • Treatment experienced • Cirrhosis • HIV coinfection	• Cirrhosis, decompensated • Genotype 3, treatment-experienced cirrhosis • DAA failures
Difficult to Treat	• Elderly • Autoimmune diseases • Decompensated cirrhosis • Transplant recipients • Interferon intolerant • RBV intolerant • Noncompliant	• ESRD/dialysis • Ribavirin intolerant • On medications that interact with HCV DAAs • Noncompliant
Difficulty with Access	• Methadone maintenance • Active drug use • Mental health comorbidities • Underinsured	• Active drug use • Mild-to-moderate HCV disease • Underinsured

RAV development in a patient who have been Rx with P/R + one DAA class repeatedly

- Male 35 year old with HCV gt 1a after exchange transfusion as newborn
- Fibrosis stage F3/4
- P/R non-response
- P/R + Daklatasvir non-response
- P/R + Telaprevir non-response
- Sof + Sim response but relapse


HCV-RNA (♦)
ALAT (▲)
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apr 11
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apr 13
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apr 14
okt 14
apr 15
Telaprevir
Simeprevir
Daclatasvir
Sofosbuvir
Ribavirin
Peg IFN alfa-2a

Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: the COSMOS randomised study

Eric Lawitz, Mark S Sulkowski, Reem Ghalib, Maribel Rodriguez-Torres, Zobair M Younossi, Ana Corregidor, Edwin DeJesus, Brian Pearlman, Mordechai Rabinovitz, Norman Gitlin, Joseph K Lim, Paul J Pockros, John D Scott, Bart Fevery, Tom Lambrecht, Sivi Ouwerkerk-Mahadevan, Katleen Callewaert, William T Symonds, Gaston Picchio, Karen L Lindsay, Maria Beumont, Ira M Jacobson

Summary

Background Interferon-free regimens are needed to treat hepatitis C virus (HCV) infections. We investigated the efficacy of combined simeprevir and sofosbuvir.

Methods We enrolled patients with chronic HCV genotype 1 infections who had previously not responded to pegylated interferon (peginterferon) and ribavirin or were treatment naive. Patients were randomly assigned in a 2:2:1:1 ratio to receive 150 mg simeprevir and 400 mg sofosbuvir daily for 24 weeks with (group 1) or without (group 2) ribavirin or for 12 weeks with (group 3) or without (group 4) ribavirin, in two cohorts: previous non-responders with METAVIR scores F0–F2 (cohort 1) and previous non-responders and treatment-naive patients with METAVIR scores F3–F4 (cohort 2). The primary endpoint was sustained virological response 12 weeks after stopping treatment (SVR12). Analysis was done by intention to treat. Safety data from cohorts 1 and 2 were pooled for analysis. This study is registered with ClinicalTrials.gov, number NCT01466790.

Findings 168 patients were enrolled and randomised, and 167 started treatment (n=80 in cohort 1 and n=87 in cohort 2). SVR12 was achieved in 154 (92%) patients (n=72 [90%, 95% CI 81–96] in cohort 1 and n=82 [94%, 87–98] in cohort 2). The most common adverse events in the pooled groups were fatigue (n=52 [31%]), headache (n=33 [20%]), and nausea (n=26 [16%]). Grade 4 adverse events were seen in one (2%) of 54 patients in each of groups 1 and 3 and in three (10%) of 31 patients in group 2, whereas grade 3–4 events were reported in less than 5% of all patients, except increased blood amylase concentration. Serious adverse events were seen in four (2%) patients, all in groups 1 and 2. Four (2%) patients discontinued all study treatment because of adverse events, three before week 12.

Interpretation Combined simeprevir and sofosbuvir was efficacious and well tolerated.

Funding Janssen.

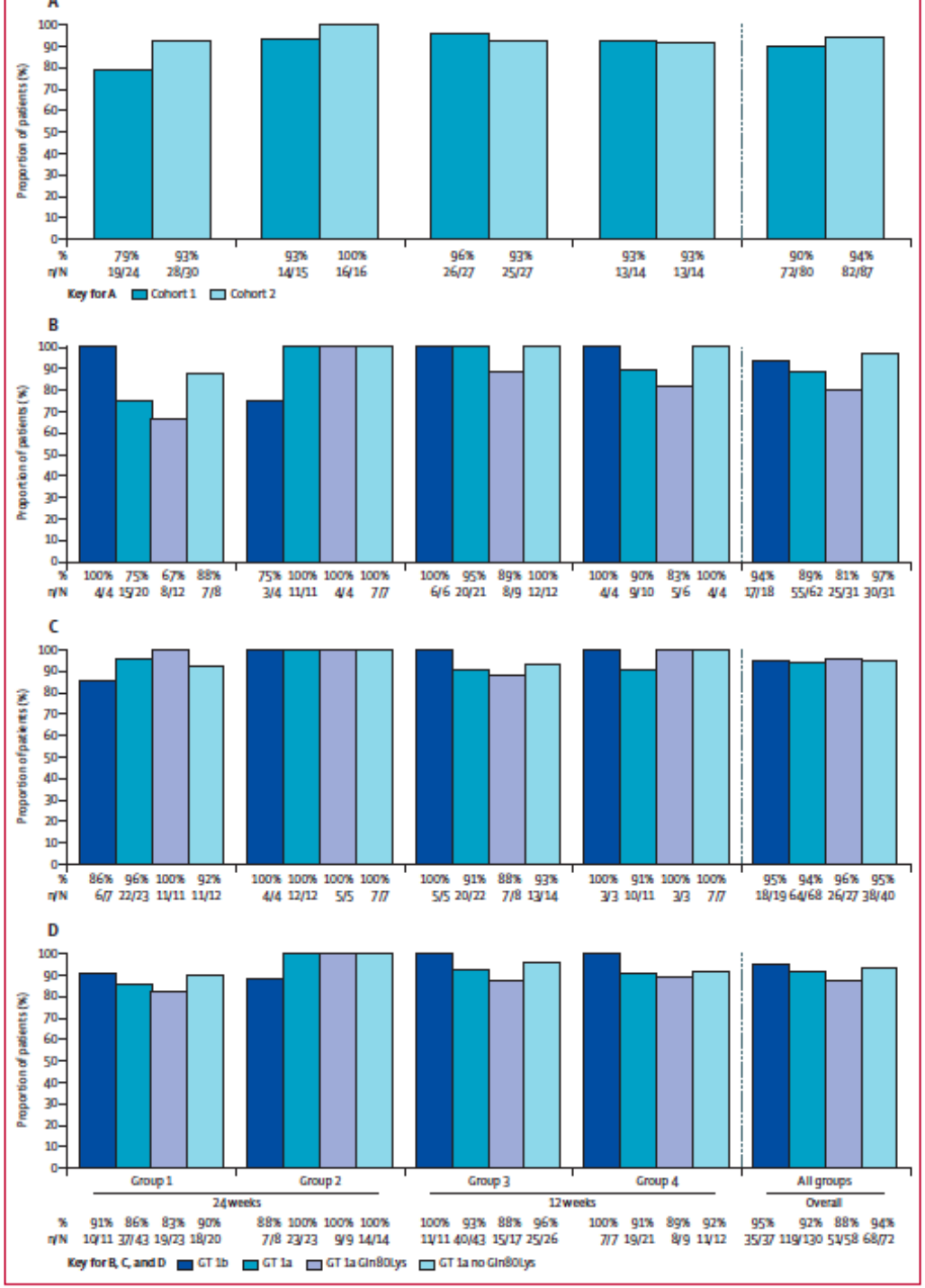
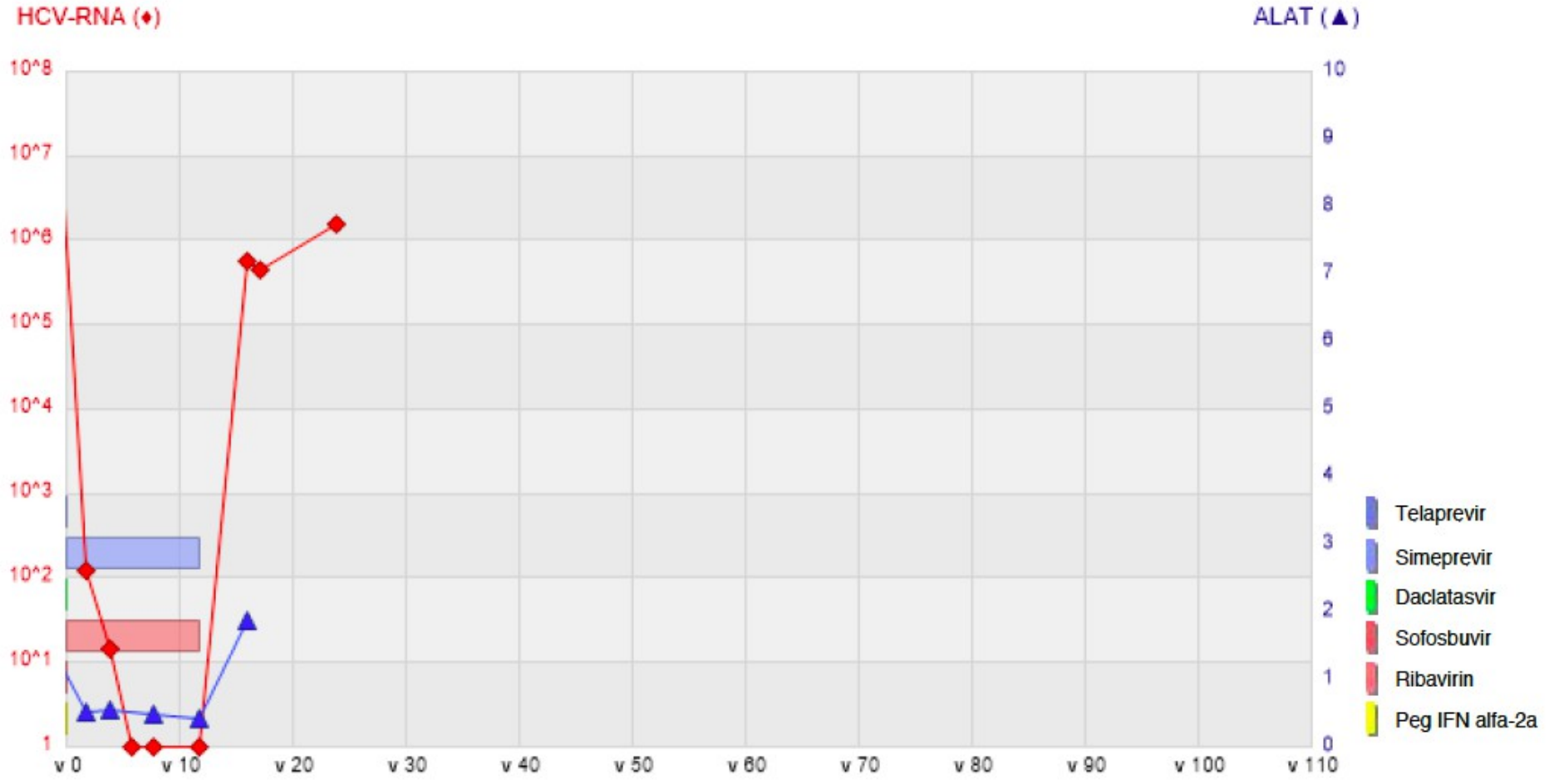


Figure 2: Patients who achieved sustained virological response 12 weeks after the planned end of treatment in the intention-to-treat population, by treatment group

(A) Cohorts 1 and 2. (B) HCV subtype and presence of the HCV Gln80lys polymorphism at baseline in cohort 1. (C) HCV subtype and presence of the HCV Gln80Lys polymorphism at baseline in cohort 2. (D) HCV subtype and presence of the HCV Gln80Lys polymorphism at baseline pooled for cohorts 1 and 2. GT=genotype.


HCV-RNA (♦)
ALAT (▲)
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v 30
v 40
v 50
v 60
v 70
v 80
v 90
v 100
v 110
Telaprevir
Simeprevir
Daclatasvir
Sofosbuvir
Ribavirin
Peg IFN alfa-2a

RAV development in a patient who have been Rx with P/R + one DAA class repeatedly

- **Sof + Sim EOT response - relapse**
- **PI RAV R155K**
- **NS5A RAV L31M**

Table 2. Mean Fold-Change in Resistance Compared to Wild-Type Replicon of Clinically Relevant NS5A Resistance-Associated Substitutions

HCV NS5A Amino Acid and Position	Resistance-Associated Substitution(s)	Replicon Vector Genotype	Mean Fold-Change in Resistance Compared to Wild-Type Replicon		
			Daclatasvir*	Ledipasvir†	Ombitasvir‡
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	L31V+Y93H	1b	5425		

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‡Ombitasvir data were generated by luciferase assay.

What about treating patients with resistance or re-treatment following failure?

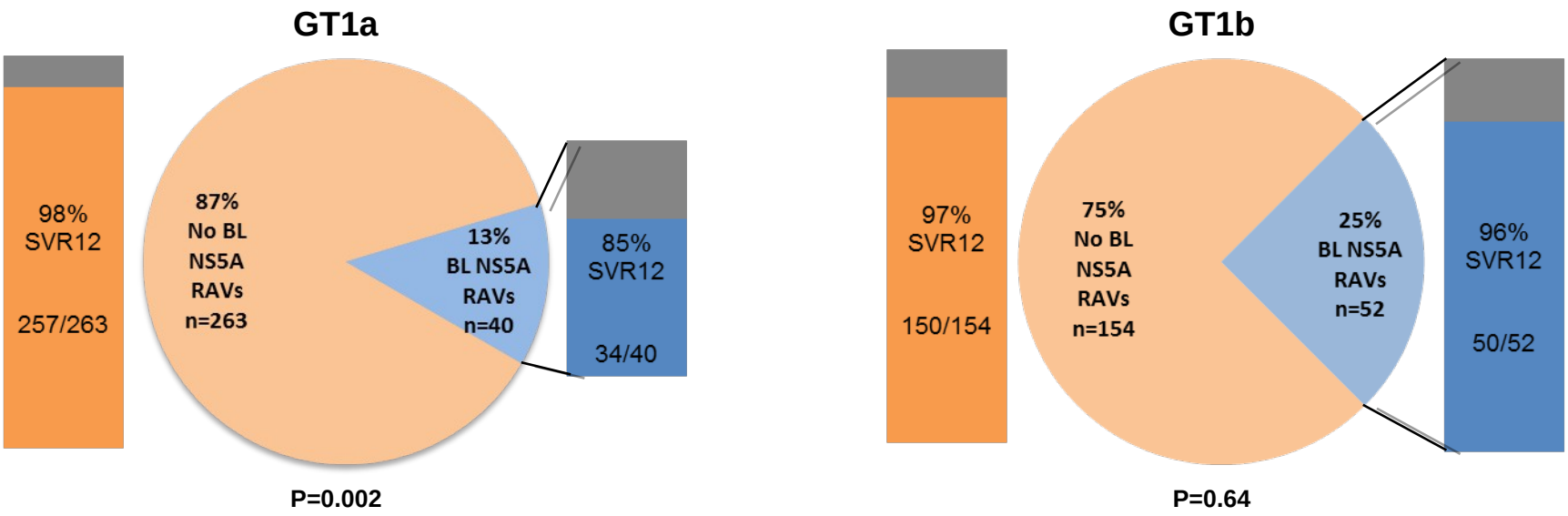
Practical approach for re-Rx of patients who have developed RAVs

- Use another DAA class
- NUC - Sofosbuvir can be used again
- Protease inhibitors can be used after 1-2 years
- NS5A inhibitors should probably not be used again in the short-term

P0773 NS5A resistance-associated variants in patients with compensated cirrhosis treated with LDV/SOF ± RBV

- Population (n = 34) or deep (n = 477) sequencing for the HCV NS5A gene was performed at baseline for all enrolled subjects with cirrhosis in the phase 2 and 3 studies of LDV/SOF

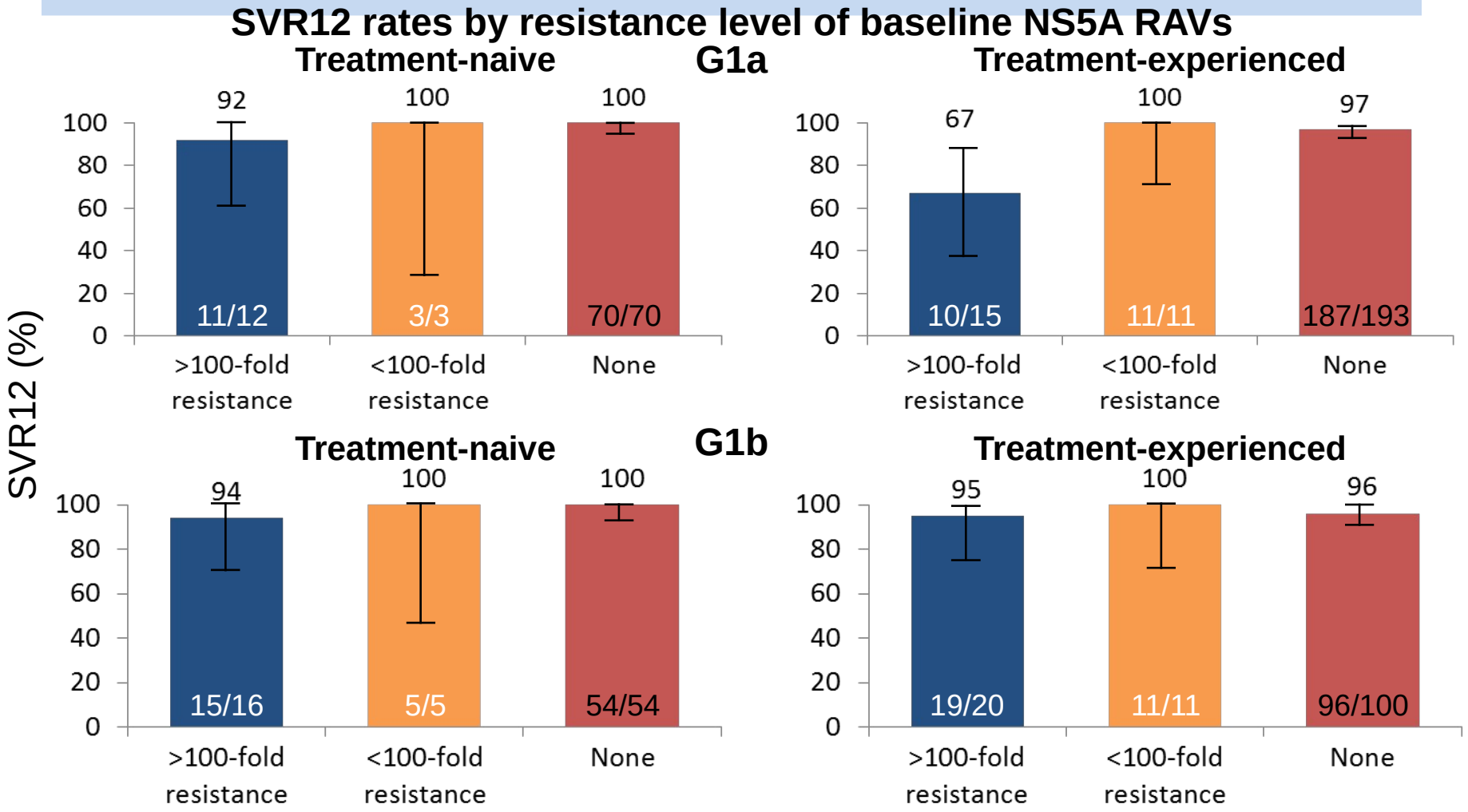
Prevalence of NS5A RAVs and SVR12 rates*†



*p values represent the differences in SVR12 rates between patients with and without NS5A RAVs; †Presence of RAVs was evaluated by deep sequencing with assay cutoff of 1%

Sarrazin C, et al. EASL 2015; Poster P0773

The prevalence and effect of HCV NS5A resistance-associated variants in subjects with compensated cirrhosis treated with LDV/SOF ± RBV



- NS5A RAVs important in G1 treatment-failure cirrhotics
- RBV, not ↑ duration, overcomes effective NS5A RAVs on relapse

Sarrazin C, et al. EASL 2015, Vienna. #P

O005 Retreatment of patients who failed 8 or 12 weeks of LDV/SOF-based regimens with LDV/SOF for 24 weeks

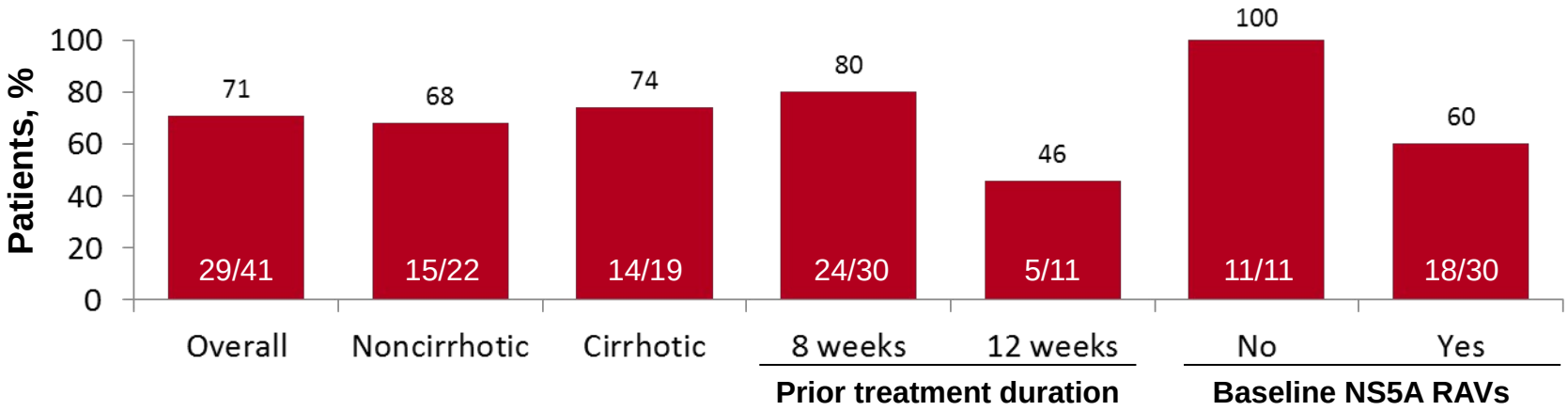
- Open-label study with GT1 patients (n=41) who relapsed following 8 or 12 weeks of LDV/SOF ± RBV in Phase 2/3 studies

	LDV/SOF 24 Weeks N=41
Mean age, y (range)	58 (35-71)
Male, n (%)	34 (83)
Black/African American, n (%)	10 (24)
IL28B non-CC, n (%)	38 (93)
GT 1a, n (%)	34 (83)
Mean HCV RNA, log_{10} IU/mL (range)	6.2 (4.5-7.4)
Cirrhosis, n (%)	19 (46)
Presence of NS5A RAVs	15 (79)
Prior HCV treatment, n (%)	
LDV/SOF ± RBV	33 (80)
LDV/SOF + GS-9669	8 (20)
Prior HCV treatment duration, n (%)	
8 weeks	30 (73)
Presence of NS5A RAVs	19 (63)
12 weeks	11 (27)
Presence of NS5A RAVs	11 (100)

Lawitz E, et al. EASL 2015; Oral 005

O005 SVR_{12} for retreatment with LDV/SOF for 24 weeks

SVR12 in GT1 TE patients ± cirrhosis retreated with LDV/SOF ± RBV (N=41)



Safety

- Discontinuation due to AEs: 0
- Treatment-related SAEs: 0
- Deaths: 0

Virologic failure and resistance

- 73% had NS5A RAVs at baseline; the 27% of pts without BL RAVs all received 8 weeks of prior treatment
- SVR_{12} by baseline NS5A RAVs, n/N (%):

Q30R or M28T	L31M	Y93H/N
5/5 (100%)	4/5 (80%)	2/6 (33%)

- SVR_{12} by number of baseline NS5A RAVs: 0: 100%; 1: 69%; ≥2: 50%
- No NS5B RAVs or treatment-emergent variants at baseline
- At VF, 4/12 (33%) patients had NS5B variants: S282T (n=2), L159F (n=1), S282T+L159F (n=1)

Lawitz E, et al. EASL 2015; Oral 005

O001 C-SALVAGE: GZR + EBR + RBV for chronic HCV GT1 infection after failure of DAA therapy

- Tx-experienced GT1 patients (n=79) who had failed triple therapy with PegIFN + RBV and earlier gen PIs treated with GZR + EBR + RBV for 12 weeks

	All treated patients (N=79)	Evaluable patients*	
		Baseline NS3 RAVs (N=34)	No baseline NS3 RAVs (N=44)
Mean (median) age, years	54.4 (55)	53.9 (55.0)	54.6 (56.5)
Male gender, n(%)	46 (58.2)	21 (61.8)	24 (54.5)
HCV genotype, n(%) GT1a GT1b	30 (38.0) 49 (62.0)	23 (67.6) 11 (32.4)	7 (15.9) 37 (84.1)
Cirrhosis, n (%)	34 (43.0)	15 (44.1)	19 (43.2)
Prior DAA experience, n (%) Boceprevir Telaprevir Simeprevir	28 (35.4) 43 (54.4) 8 (10.1)	10 (29.4) 19 (55.9) 5 (14.7)	17 (38.6) 24 (54.5) 3 (6.8)
Past history of virological failure	66 (83.5)	32 (94.1)	33 (75.0)

- At entry, 30 (41%) of the 73 patients with available NS3 sequencing data harboured RAVs

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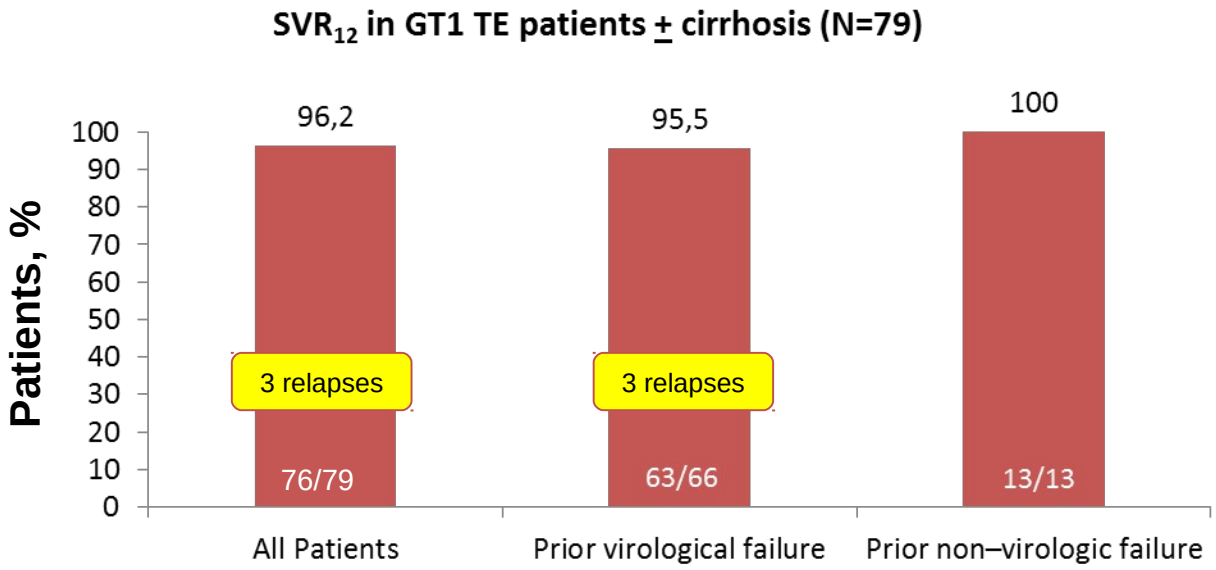
O001 C-SALVAGE: Efficacy endpoints over time



Safety

- Discontinuation due to AEs: 1.3%
- Treatment-related SAEs: 0
- Deaths: 0

Resistance

- SVR_{12} was attained in 31/34 (91.2%) patients harbouring baseline NS3 RAVs conferring decreased susceptibility to 1st gen PIs

Forns X, et al. EASL 2015; Oral 001

HEPATOLOGY
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RAPID COMMUNICATION

Safety and Tolerability of Ledipasvir/Sofosbuvir With and Without Ribavirin in Patients With Chronic Hepatitis C Virus Genotype 1 Infection: Analysis of Phase III ION Trials

Saleh A. Alqahtani,[1] Nezam Afdhal,[2] Stefan Zeuzem,[3] Stuart C. Gordon,[4] Alessandra Mangia,[5] Paul Kwo,[6] Michael Fried,[7] Jenny C. Yang,[8] Xiao Ding,[8] Phillip S. Pang,[8] John G. McHutchison,[8] David Pound,[9] K. Rajender Reddy,[10] Patrick Marcellin,[11] Kris V. Kowdley,[12] and Mark Sulkowski[1]

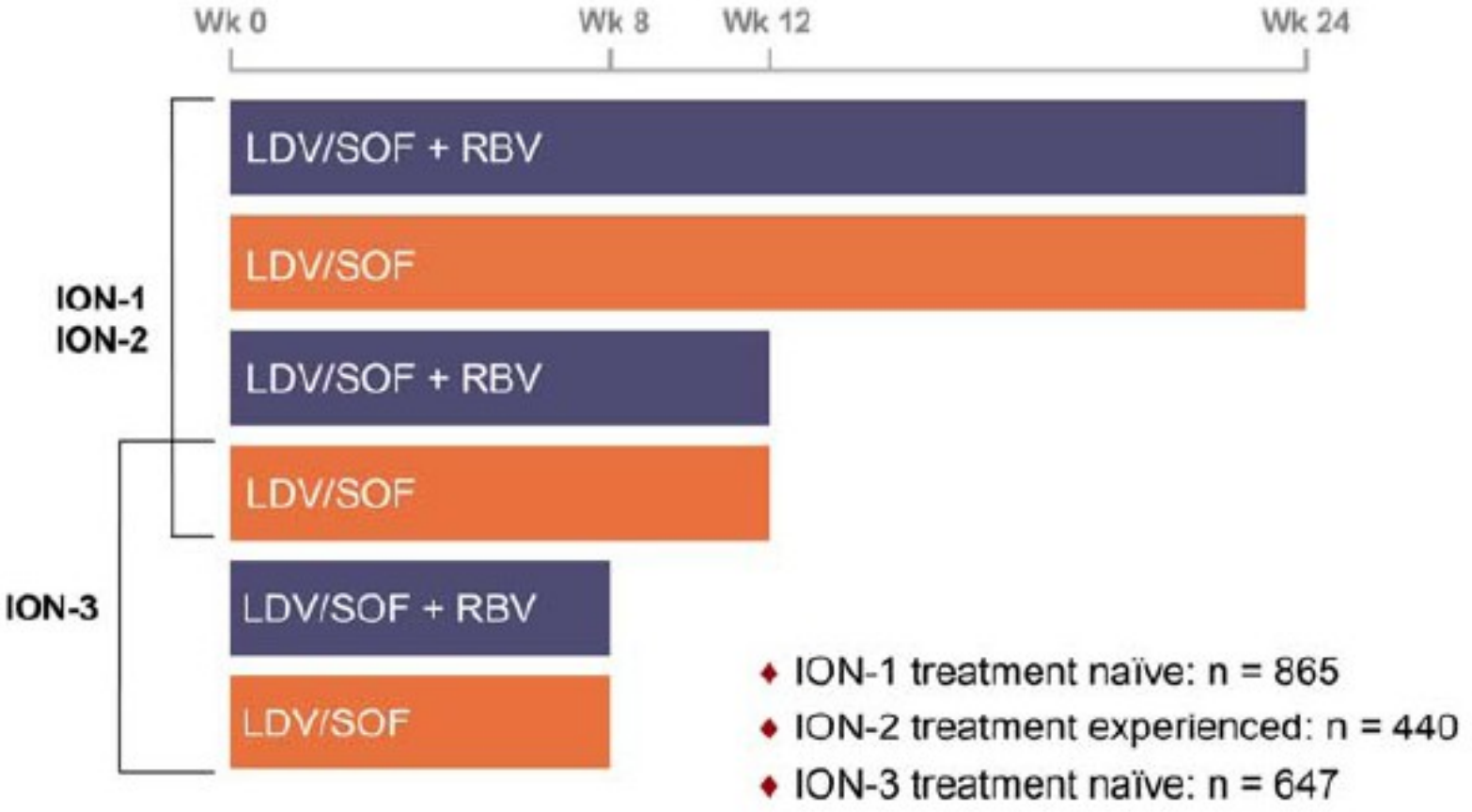


Fig. 1. LDV/SOF phase III program.

Table 2. AEs

Preferred Term, n (%)	LDV/SOF 8 Weeks (n = 215)	LDV/SOF 12 Weeks (n = 539)	LDV/SOF 24 Weeks (n = 326)	LDV/SOF+RBV 8 Weeks (n = 216)	LDV/SOF+RBV 12 Weeks (n = 328)	LDV/SOF+RBV 24 Weeks (n = 328)
Fatigue	45 (21)	116 (22)	79 (24)	75 (35)	124 (38)	132 (40)
Headache	30 (14)	113 (21)	79 (24)	54 (25)	75 (23)	99 (30)
Nausea	15 (7)	61 (11)	36 (11)	38 (18)	57 (17)	57 (17)
Insomnia	11 (5)	41 (8)	30 (9)	26 (12)	63 (19)	66 (20)
Diarrhea	15 (7)	40 (7)	33 (10)	13 (6)	23 (7)	31 (9)
Irritability	3 (1)	22 (4)	21 (6)	29 (13)	30 (9)	36 (11)
Rash	3 (1)	23 (4)	21 (6)	19 (9)	32 (10)	43 (13)
Arthralgia	9 (4)	32 (6)	27 (8)	11 (5)	27 (8)	28 (9)
Cough	3 (1)	18 (3)	21 (6)	12 (6)	37 (11)	41 (13)
Pruritus	2 (1)	21 (4)	10 (3)	16 (7)	32 (10)	30 (9)

Table 3. Overall Safety in Patients by Cirrhosis Status

	Cirrhosis		Without Cirrhosis	
	LDV/SOF (n = 111) n (%)	LDV/SOF+RBV (n = 113) n (%)	LDV/SOF (n = 969) n (%)	LDV/SOF+RBV (n = 759) n (%)
Any AE	85 (77)	99 (88)	715 (74)	646 (85)
Treatment-related AE	46 (41)	89 (79)	438 (45)	528 (70)
Grade ≥3 AE	7 (6)	10 (9)	39 (4)	35 (5)
SAE	5 (5)	3 (3)	29 (3)	14 (2)
Treatment-related SAE	1 (<1)	1 (<1)	3 (<1)	0
AE leading to any study drug Modification/discontinuation	1 (<1)	23 (20)	5 (<1)	95 (13)
Treatment discontinuation because of AE	0	0	6 (<1)	11 (1)
Death	0	0	0	0

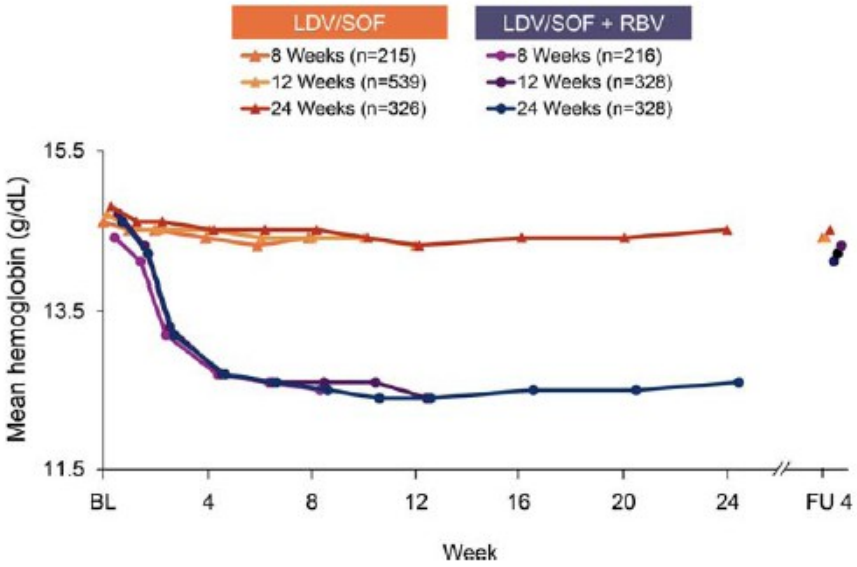
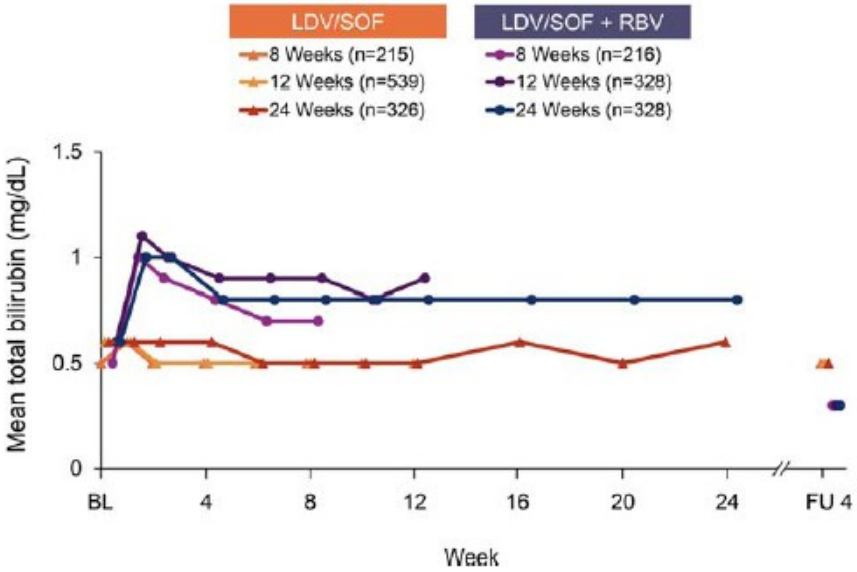


Fig. 2. Mean hemoglobin over time.



Ledipasvir and Sofosbuvir in Patients With Genotype 1 Hepatitis C Virus Infection and Compensated Cirrhosis: An Integrated Safety and Efficacy Analysis

K. Rajender Reddy,[1]* Marc Bourlière,[2]* Mark Sulkowski,[3] Masao Omata,[4] Stefan Zeuzem,[5] Jordan J. Feld,[6] Eric Lawitz,[7] Patrick Marcellin,[8] Tania M. Welzel,[5] Robert Hyland,[9] Xiao Ding,[9] Jenny Yang,[9] Steven Knox,[9] Phillip Pang,[9] Hadas Dvory-Sobol,[9] G. Mani Subramanian,[9] William Symonds,[9] John G. McHutchison,[9] Alessandra Mangia,[10] Edward Gane,[11] Masashi Mizokami,[12] Stanislas Pol,[13] and Nezam Afdhal[14]

Patients with hepatitis C virus (HCV) infection and cirrhosis are underrepresented in clinical trials of interferon-free regimens of direct-acting antiviral agents, making it difficult to optimize therapy. We performed a post-hoc analysis of data from seven clinical trials to evaluate the efficacy and safety of the fixed-dose combination of ledipasvir (LDV) and sofosbuvir (SOF), with and without ribavirin (RBV), in 513 treatment-naïve and previously treated patients with genotype 1 HCV and compensated cirrhosis. All patients received LDV-SOF for 12 or 24 weeks with or without RBV. We determined the rates of sustained virological response (SVR) 12 weeks after treatment (SVR12) overall and for subgroups. Of the 513 patients analyzed, 69% were previously treated and 47% had failed previous treatment with a protease-inhibitor regimen. Overall, 493 patients (96%; 95% confidence interval [CI]: 94%-98%) achieved SVR12, 98% of treatment-naïve and 95% of previously treated patients. SVR12 rates did not vary greatly by treatment duration (95% of patients receiving 12 weeks and 98% of patients receiving 24 weeks of treatment), nor by addition of RBV (95% of patients receiving LDV-SOF alone and 97% of those who received LDV-SOF plus RBV), although previously treated patients receiving 12 weeks of LDV-SOF without RBV had an SVR12 rate of 90%. One patient discontinued LDV-SOF because of an adverse event (AE). The most common AEs were headache (23%), fatigue (16%-19%), and asthenia (14%-16%). One patient (<1%) of those receiving LDV-SOF alone, and 4 (2%) of those receiving LDV-SOF plus RBV had treatment-related serious AEs. *Conclusions:* This analysis suggests that 12 weeks of LDV-SOF is safe and effective for treatment-naïve patients with HCV genotype 1 and compensated cirrhosis. The relatively lower SVR in treatment-experienced patients treated with 12 weeks of LDV-SOF raises the question of whether these patients would benefit from adding RBV or extending treatment duration to 24 weeks. (HEPATOLOGY 2015;62:79-86)

Table 3. SVR12 by Presence of Baseline NS5A RAVs

	LDV-SOF		LDV-SOF + RBV		
	12 Weeks	24 Weeks	12 Weeks	24 Weeks	Overall
Patients with NS5A RAVs*	88% (23/26)	85% (17/20)	94% (32/34)	100% (14/14)	91% (86/94) 95% CI: 84-96
Patients without NS5A RAVs	95% (86/91)	100% (113/113)	97% (164/169)	100% (44/44)	98% (407/417) 95% CI: 96-99

*Resistance analysis was performed using a 1% threshold (% of total reads). NS5A RAVs were: K24R, M28T, Q30H/R, P32L, L31F/I/MH58D, A92T, and Y93H/F/S.

Table 2. SVR12 by Baseline Factors, Treatment History, and Regimen

Response	Treatment-Naïve (n = 161)	Previously Treated (n = 352)	Total (n = 513)
Overall	157 (98)	336 (95)	493 (96)
95% CI	94-99	93-97	94-98
By treatment duration (%)			
12 weeks	89/92 (97)	216/230 (94)	305/322 (95)
24 weeks	68/69 (99)	120/122 (98)	188/191 (98)
By regimen (%)			
Without RBV	77/80 (96)	162/171 (95)	239/251 (95)
With RBV	80/81 (99)	174/181 (96)	254/262 (97)
By treatment duration + regimen (%)			
LDV-SOF 12 weeks	45/47 (96)	64/71 (90)	109/118 (92)
LDV-SOF + RBV 12 weeks	44/45 (98)	152/159 (96)	196/204 (96)
LDV-SOF 24 weeks	32/33 (97)	98/100 (98)	130/133 (98)
LDV-SOF + RBV 24 weeks	36/36 (100)	22/22 (100)	58/58 (100)
By genotype (%)			
1a	84/86 (98)	209/220 (95)	293/306 (96)
1b	72/74 (97)	124/129 (96)	196/203 (97)
By IL28B status (%)			
CC	56/57 (98)	51/52 (98)	107/109 (98)
Non-CC	101/104 (97)	285/300 (95)	386/404 (96)
By previous failed regimen (%)			
Protease inhibitor + Peg-IFN + RBV	-	230/240 (96)	230/240 (96)
Peg-IFN + RBV	-	106/112 (95)	106/112 (95)
By baseline albumin, g/dL (%)			
<3.5	20/21 (95)	41/42 (98)	61/63 (97)
≥3.5	137/140 (98)	295/310 (95)	432/450 (96)
By baseline platelet count, per mm^3 (%)			
<75,000	9/10 (90)	23/28 (82)	32/38 (84)
≥75,000	148/151 (98)	313/324 (97)	461/475 (97)

Lower limit of quantification is 25 IU/mL

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Lower limit of quantification is 25 IU/mL

Sofosbuvir Plus Pegylated Interferon and Ribavirin in Patients With Genotype 1 Hepatitis C Virus in Whom Previous Therapy With Direct-Acting Antivirals Has Failed

Stanislas Pol,[1] Mark S. Sulkowski,[2] Tarek Hassanein,[3] Edward J. Gane,[4] Lin Liu,[5] Hongmei Mo,[5] Brian Doehle,[5] Bittoo Kanwar,[5] Diana Brainard,[5] G. Mani Subramanian,[5] William T. Symonds,[5] John G. McHutchison,[5] Ronald G. Nahass,[6] Michael Bennett,[7] and Ira M. Jacobson[8]

Retreatment of patients who have not achieved sustained virological response (SVR) after treatment with investigational direct-acting antiviral agents (DAAs) has not been extensively studied. We conducted an open-label trial to assess the efficacy and safety of sofosbuvir (SOF) plus pegylated interferon (Peg-IFN) and ribavirin (RBV) in patients with genotype 1 hepatitis C virus (HCV) who participated in previous studies of one or more Gilead investigational DAAs in combination with RBV with or without Peg-IFN. We enrolled 80 patients at 40 sites. All patients received SOF 400 mg once daily plus Peg-IFN-α 180 μg/week and weight-based ribavirin (1,000 or 1,200 mg/day) for 12 weeks. The efficacy endpoint was the proportion of patients with SVR 12 weeks after discontinuation of therapy (SVR12). Of the 80 patients enrolled, 36 (45%) had received two or more courses of earlier treatment for HCV and 74 (93%) had at least one resistance-associated variant (RAV) at baseline. SVR12 was achieved by 63 of the 80 patients (79%) treated. Rates of SVR12 were similar across patient subgroups. Presence of RAVs at baseline did not appear to be associated with treatment failure. Seventy-one of eighty patients (89%) experienced at least one adverse event (AE), but most events were mild to moderate in severity. The most common AEs were fatigue, headache, and nausea. No patients discontinued all treatment because of AEs. *Conclusion:* These findings suggest that SOF plus Peg-IFN and RBV for 12 weeks is effective and safe in patients who have not achieved SVR with earlier regimens of one or more DAAs plus Peg-IFN and RBV. (HEPATOLOGY 2015;62:129-134)

Table 2. Baseline RAVs

Baseline class resistance, n (%)	
0	5 (6)
1	32 (40)
2	32 (40)
3	10 (13)
Not available	1 (1)
Q80K polymorphism and RBV-associated variants	
Q80K	34 (43)
RBV	8 (10)
Baseline RAVs (by gene)	
NS3 (PI)*	38 (51)
NS5A	66 (84)
NS5B†	22 (28)
NNI (non-SOF)	22 (28)
SOF RAV or TEV	3 (4)

*Five samples failed NS3 amplification.

†One sample failed NS5B amplification.

Abbreviations: PI, protease inhibitor; NNI, non-nucleoside inhibitor.

Table 3. Overall Response During and After Treatment

	SOF + Peg-IFN + RBV for 12 Weeks (n = 80)
Treatment week 2 (%)	71/80 (89)
Treatment week 4 (%)	79/80 (99)
Treatment week 12 (%)	80/80 (100)
SVR4 (%)	68 (85)
95% CI	75-92
SVR12 (%)	63 (79)
95% CI	68-87
VF (%)	
During treatment	0
Relapse	17 (21)

Abbreviation: SVR4, SVR at week 4 after treatment.

RAVs, which confer decreased susceptibility to protease, non-nucleoside polymerase, and/or NS5A inhibitors, did not appear to be associated with differences in outcomes. SVR12 was achieved by 9 of the 10 (90%) patients with three-class resistance, 26 of the 32 (81%) with two-class resistance, and 26 of the 32 (81%) with one-class resistance at baseline. Among 5

Conclusions for patients who have developed RAVs

- **Use another DAA class when re-Rx**
- **NUC - Sofosbuvir can/should be used again**
- **Protease inhibitors can be used after 1-2 years**
- **NS5A inhibitors should probably not be used again in the short-term if high level NS5a RAVs**


Thanks