XI Workshop Nazionale
Innovazione e Ricerca per la Pratica Clinica
"TERAPIE INNOVATIVE DELLE EPATITI CRONICHE VIRALI E DELLE INFEZIONI VIRALI"
Firenze, 11-12 Gennaio 2021

Il paziente fallito: prospettive terapeutiche

Maurizia Rossana Brunetto

Medicina Interna – Dipartimento di Medicina Clinica e Sperimentale -Università di Pisa
UO Epatologia - Azienda Ospedaliero Universitaria Pisana

The failure to DAAs treatment

- It occurs in a very limited number of cases, particularly since pangenotypic regimens are used in the vast majority of patients
- A very effective treatment is available for patients with failure to the first DAA treatment
- However, for some patients the identification of an effective rescue therapy may be difficult

La trahison des images, R Magritte 1928

Centro per il trattamento dei pazienti con epatite C dell'AOUP

	UO Epatologia	GEL Osp ed Univ	**TOTALE Centro HCV AOUP**
N. trattamenti avviati a Sett. 2020:	2207	70	**2277**
N. Trattamenti entro 29/02/2020:	2124	68	**2192**
Rapporto M/F	M= 52,2%	M= 35,3%	**M= 51,7%**
Età mediana anni (range) :	59,3 (16-91)	58,9 (24-86)	**59,3 (16-91)**
Genotipi HCV:			
1a	368 (17,3%)	17 (25,0%)	**385 (17,6%)**
1b	877 (41,3%)	17 (25,0%)	**894 (40.8%)**
1 n.c.	24 (1,1%)	0	**24 (1,1%)**
2	382 (18,0%)	15 (22,1%)	**397 (18,1%)**
3	350 (16,5%)	14 (20,6%)	**364 (16,6%)**
4	114 (5,4%)	3 (4,4%)	**117 (5,3%)**
no type	4 (0,2%)	1 (1,5%)	**5 (0,2%)**
Low RNA	5 (0,2%)	1 (1,5%)	**6 (0,3%)**
Stadio Fibrosi epatica:			
F0-F2	1052 (49,5%)	53 (77,9%)	**1105 (50,4%)**
F3	351 (16,5%)	6 (8,8%)	**357 (16,3%)**
F4	721 (33,9%)	9 (13,2%)	**730 (33,3%)**

Centro per il trattamento dei pazienti con epatite C dell'AOUP

2192 trattamenti valutabili per SVR-12 raggiunta nell'98.4% dei trattati

Numero (%) di fallimenti del PRIMO trattamento antivirale

STADIO FIBROSI	F0-F1	F3	F4	TOTALE
Overall:	13 (1,2%)	1 (0,3%)	20 (2,7%)	34 (1,6%)
GENOTIPO HCV:				
1a	2 (1,0%)	0	3 (2,5%)	5 (1,3%)
1b	5 (1,3%)	0	10 (2,9%)	15 (1,7%)
1 n.c.	0	0	0	0
2	3 (1,3%)	0	3 (2,6%)	6 (1,5%)
3	3 (1,5%)	1 (1,7%)	2 (1,8%)	6 (1,6%)
4	0	0	2 (6,5%)	2 (1,7%)
no type	0	0	0	0
Low RNA	1 (20,0%)	0	0	1 (16,7%)

Sofosbuvir, Velpatasvir and Voxilaprevir for previously treated HCV infection

Table 1. Baseline Demographic and Clinical Characteristics of the Patients in the Two Trials.*

Characteristic	POLARIS-1		POLARIS-4	
	Placebo (N=152)	Sofosbuvir–Velpatasvir–Voxilaprevir (N=263)	Sofosbuvir–Velpatasvir–Voxilaprevir (N=182)	Sofosbuvir–Velpatasvir (N=151)
Mean age (range) — yr	59 (29–80)	58 (27–84)	57 (24–85)	57 (24–80)
Male sex — no. (%)	121 (80)	200 (76)	143 (79)	114 (75)
Race — no. (%)†				
White	124 (82)	211 (80)	160 (88)	131 (87)
Black	22 (14)	38 (14)	16 (9)	13 (9)
Asian	6 (4)	8 (3)	2 (1)	4 (3)
Other	0	6 (2)	4 (2)	3 (2)
HCV genotype — no. (%)				
1	150 (99)	150 (57)	78 (43)	66 (44)
1a	117 (77)	101 (38)	54 (30)	44 (29)
1b	31 (20)	45 (17)	24 (13)	22 (15)
Other	2 (1)	4 (2)	0	0
2	0	5 (2)	31 (17)	33 (22)
3	0	78 (30)	54 (30)	52 (34)
4	0	22 (8)	19 (10)	0
5	0	1 (<1)	0	0
6	2 (1)	6 (2)	0	0
Unknown	0	1 (<1)	0	0
IL28B genotype				
CC	27 (18)	47 (18)	33 (18)	29 (19)
CT	93 (61)	165 (63)	107 (59)	95 (63)
TT	32 (21)	51 (19)	42 (23)	27 (18)
Cirrhosis — no. (%)	51 (34)	121 (46)	84 (46)	69 (46)
HCV RNA level — $\log_{10}$ IU/ml	6.3±0.6	6.3±0.7	6.3±0.6	6.3±0.7
ALT level — U/liter	74±84	89±72	84±65	85±68
Previous HCV DAAs received — no. (%)				
NS5A inhibitor plus NS3 inhibitor with or without NS5B inhibitor	62 (41)	83 (32)	0	0
NS5A inhibitor plus NS5B inhibitor	80 (53)	161 (61)	0	0
NS5A inhibitor	9 (6)	18 (7)	0	0
NS5B inhibitor plus NS3 inhibitor	1 (1)‡	0	46 (25)	38 (25)
NS5B inhibitor	0	1 (<1)‡	134 (74)	109 (72)
NS3 inhibitor	0	0	2 (1)‡§	3 (2)‡§
None	0	0	0	1 (<1)‡¶
No. of previous HCV treatment regimens — no. (%)				
1	102 (67)	160 (61)	111 (61)	91 (60)
≥2	50 (33)	103 (39)	71 (39)	60 (40)
Most recent HCV treatment response — no. (%)				
No response	10 (7)	20 (8)	7 (4)	12 (8)
Relapse	125 (82)	224 (85)	171 (94)	131 (87)
Other	17 (11)	19 (7)	4 (2)	8 (5)

* Plus–minus values are means ±SD. ALT denotes alanine aminotransferase, DAA direct-acting antiviral agent, and HCV hepatitis C virus.
† Race was reported by the patient.
‡ The patient or patients were enrolled in error.
§ Previous DAA treatment with only NS3 inhibitors was an exclusion criterion in POLARIS-4, since these patients have approved retreatment options.
¶ This patient had previously received only interferon and ribavirin, not HCV DAAs.

- Polaris-1: 415 pts (263 treated with Sof+ Vel + Vox; 152 placebo)
- Polaris-4: 333 pts (182 treated with Sof+Vel+ Vox; 151 Sof+Vel)

Table 2. Response Rates during and after the Treatment Period.

Type of Response	POLARIS-1*	POLARIS-4	
	Sofosbuvir–Velpatasvir–Voxilaprevir (N=263)	Sofosbuvir–Velpatasvir–Voxilaprevir (N=182)	Sofosbuvir–Velpatasvir (N=151)
	no. of patients/total no. (%)		
HCV RNA level <15 IU/ml			
During treatment			
At 2 wk	149/263 (57)	114/182 (63)	85/151 (56)
At 4 wk	243/262 (93)	161/182 (88)	137/151 (91)
At 8 wk	262/262 (100)	182/182 (100)	149/151 (99)
At 12 wk	260/261 (100)	180/182 (99)	149/150 (99)
After end of treatment			
At 4 wk	257/263 (98)	179/182 (98)	138/151 (91)
At 12 wk†			
Any genotype	253/263 (96)	178/182 (98)	136/151 (90)
Genotype 1a	97/101 (96)	53/54 (98)	39/44 (89)
Genotype 1b	45/45 (100)	23/24 (96)	21/22 (95)
Other genotype 1	4/4 (100)	0	0
Genotype 2	5/5 (100)	31/31 (100)	32/33 (97)
Genotype 3	74/78 (95)	52/54 (96)	44/52 (85)
Genotype 4	20/22 (91)	19/19 (100)	0
Genotype 5	1/1 (100)	0	0
Genotype 6	6/6 (100)	0	0
Unknown	1/1 (100)	0	0
Virologic breakthrough during treatment	1/263 (<1)	0	1/151 (1)
Relapse after the end of treatment	6/261 (2)‡	1/182 (1)	14/150 (9)§
Loss to follow-up	1/263 (<1)	2/182 (1)	0
Withdrawal of consent	2/263 (1)	0	0
Death	0	1/182 (1)	0

Bourliere M et al, NEJM 2017

Re-treatment after DAA failure

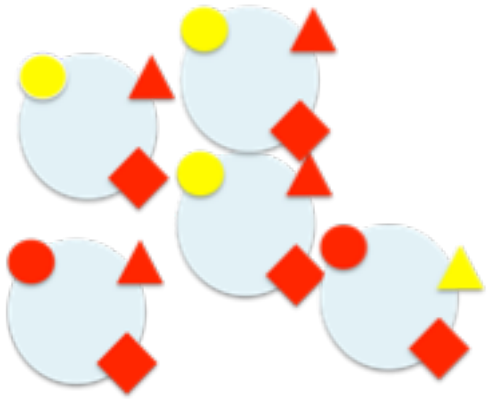
- **Real-world studies** assessing the efficacy of the triple combination of sofosbuvir, velpatasvir and voxilaprevir in the retreatment of DAA-containing regimen failures **confirmed the high SVR rates** achieved with this regimen, regardless of patient gender, body mass index, HCV genotype and baseline HCV RNA.
- The **only pre-treatment parameter** associated with a slightly lower SVR rate was **cirrhosis**.

- The MAGELLAN-1 trial showed that the combination of **glecaprevir and pibrentasvir** does **not have a high enough barrier to resistance** to achieve optimal SVR rates in **patients previously exposed to an NS5A inhibitor**.
- In a randomised study of 177 patients with chronic HCV genotype 1 infection who received previous treatment with sofosbuvir plus an NS5A inhibitor, 16 weeks treatment with glecaprevir/pibrentasvir induced SVR12 in 86–97% of patients.
- Treatment failed in 7.3% of patients with genotype 1a infection. Treatment-selected RASs in the NS3 and NS5A regions were observed in 9 and 10 patients with treatment failure, respectively.
- Overall, the **combination of glecaprevir and pibrentasvir is not indicated in the retreatment of patients who failed a prior DAA-containing regimen, particularly if this regimen contained an NS5A inhibitor.**

De Gasperi et al J Hep 2019; Kraiden et al Hepatology 2019, Poordad Hepatology 2018, Wyles D et al J Hep 2018

Resistant-associated Substitutions

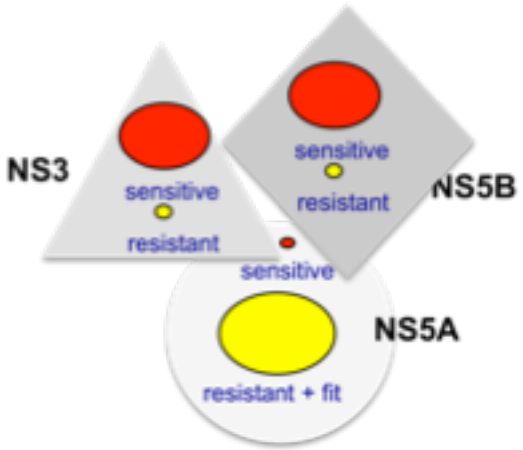
Single virus level



sensitive

resistant

Viral quasispecies



Treatment Strategies:

- **combination of DAAs acting on the 3 different targets is the optimal treatment after a DAAs failure, particularly after the exposure to a NS5A inhibitor**
- in case of a DAA acting on the region with resistant RAS, the drug must be active on these RAS
- treatment duration and, eventually the use of RBV, are additional variable to be considered

Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY

EASL recommendations on treatment of hepatitis C: Final update of the series☆

European Association for the Study of the Liver*

September 2020

Recommendations

- Patients who failed after any of the DAA-containing treatment regimens should be retreated in the context of a multidisciplinary team including experienced treaters and virologists (**B1**).
- HCV resistance testing prior to retreatment in patients who failed after any of the DAA-containing treatment regimens is useful to guide retreatment by probabilities of response, according to the resistance profile observed (**B1**).
- Patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis who failed after a DAA (protease inhibitor and/or NS5A inhibitor)-containing regimen should be retreated with the fixed-dose combination of sofosbuvir, velpatasvir and voxilaprevir for 12 weeks (**A1**).

Centro per il trattamento dei pazienti con epatite C dell'AOUP

2192 trattamenti valutabili per SVR-12 raggiunta nell'98.4% dei trattati

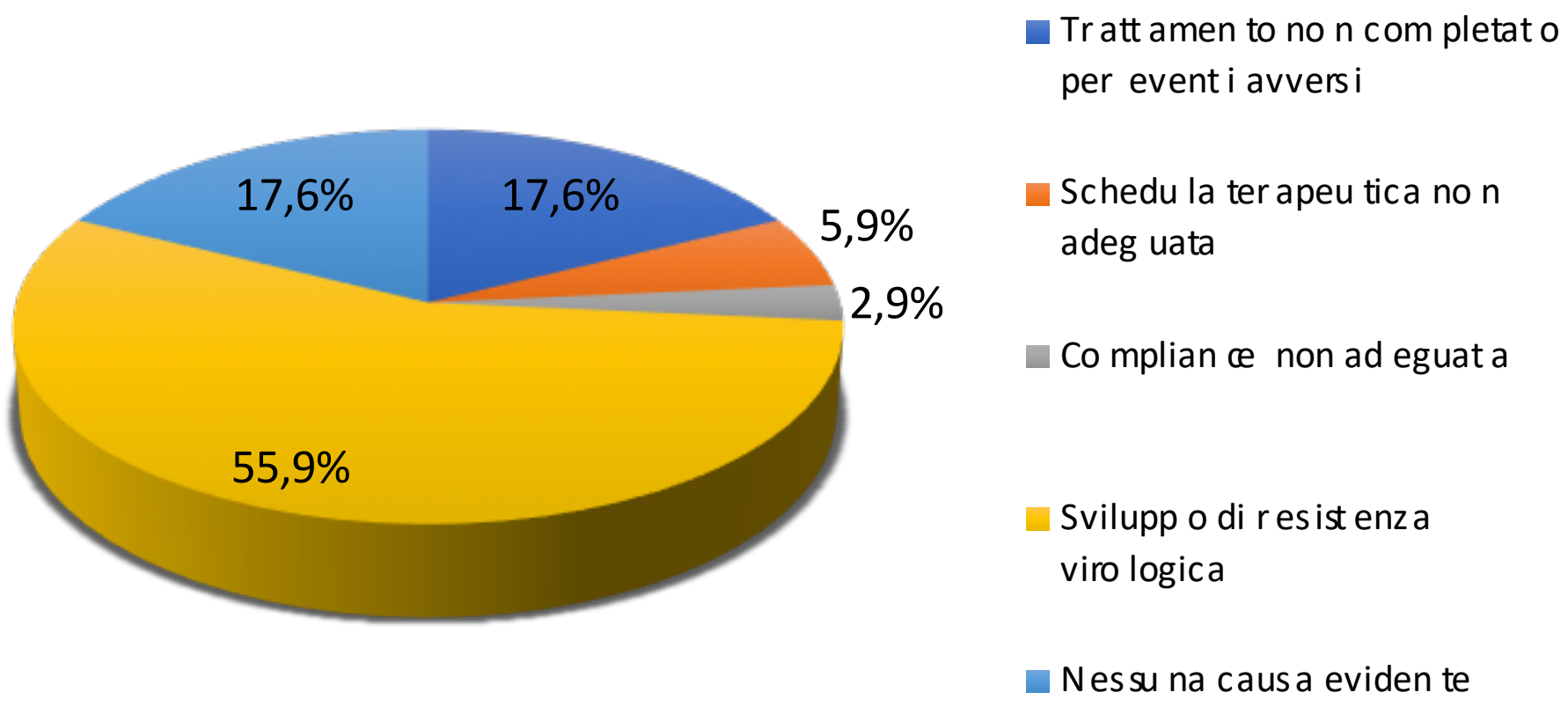
Numero (%) di fallimenti del PRIMO trattamento antivirale

STADIO FIBROSI	F0-F1	F3	F4	TOTALE
Overall:	13 (1,2%)	1 (0,3%)	20 (2,7%)	34 (1,6%)
GENOTIPO HCV:				
1a	2 (1,0%)	0	3 (2,5%)	5 (1,3%)
1b	5 (1,3%)	0	10 (2,9%)	15 (1,7%)
1 n.c.	0	0	0	0
2	3 (1,3%)	0	3 (2,6%)	6 (1,5%)
3	3 (1,5%)	1 (1,7%)	2 (1,8%)	6 (1,6%)
4	0	0	2 (6,5%)	2 (1,7%)
no type	0	0	0	0
Low RNA	1 (20,0%)	0	0	1 (16,7%)

Centro per il trattamento dei pazienti con epatite C dell'AOUP

Analisi dei fallimenti osservati nei pazienti trattati presso il Centro

34 fallimenti

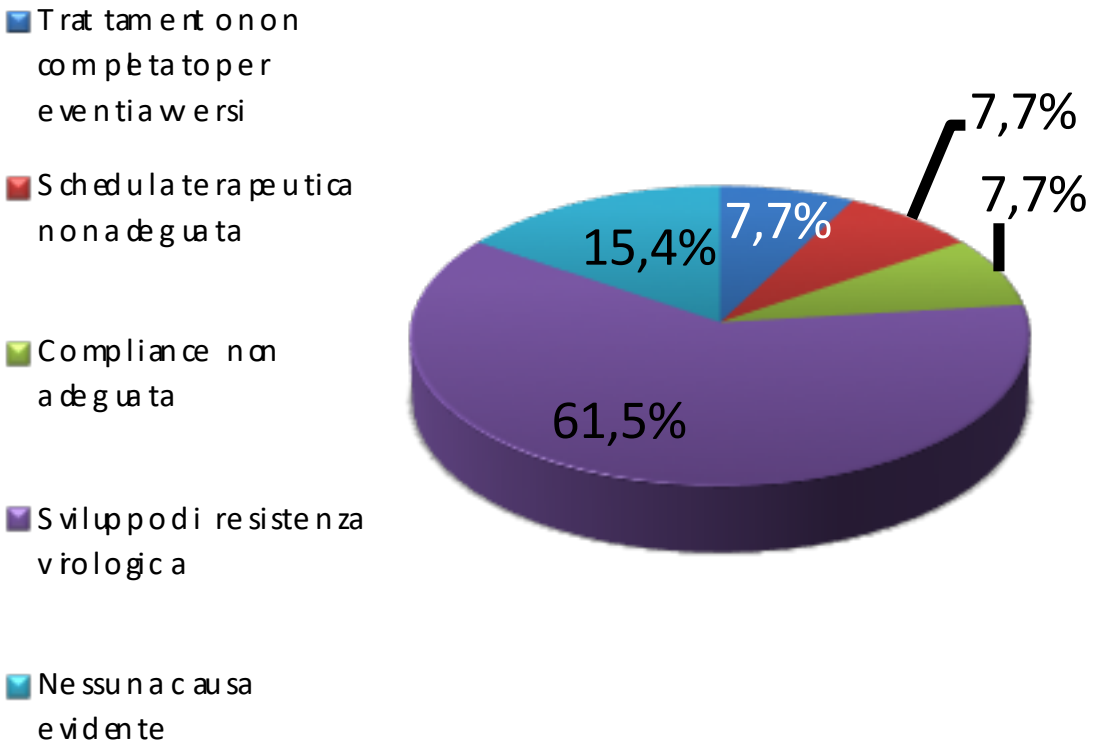


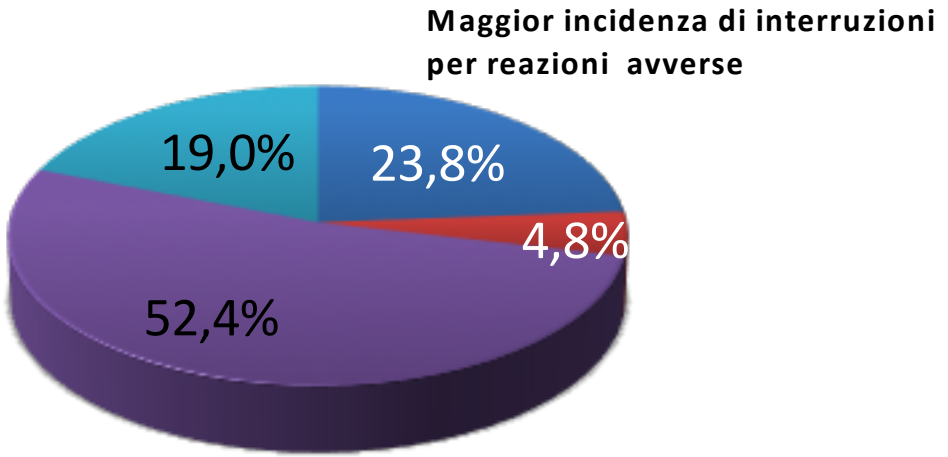
Condizioni associate al fallimento della terapia con DAAs in funzione dello stadio della FIBROSI

Stadio:

F0-F2
13 Fallimenti

F3-F4
21 Fallimenti



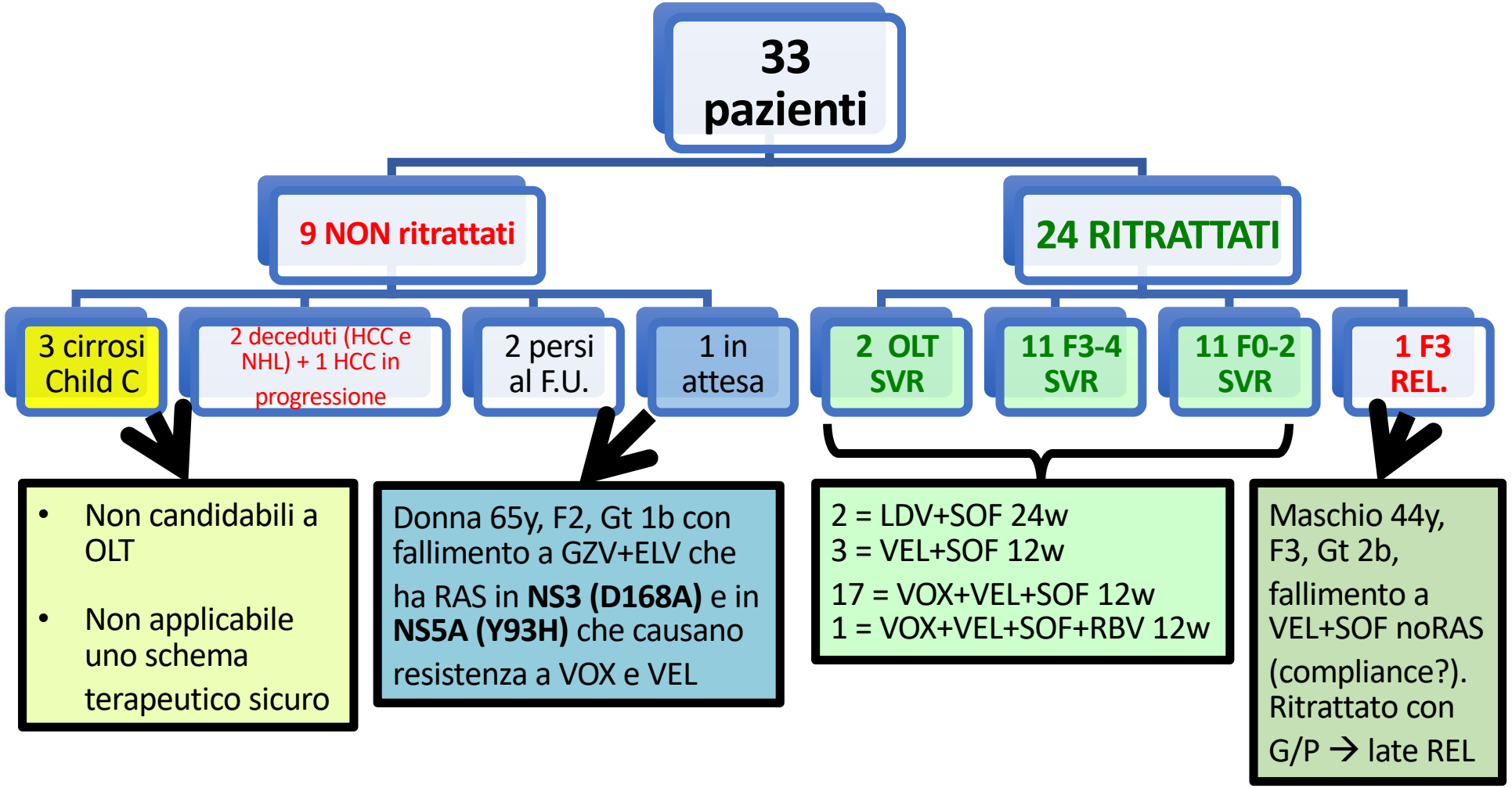


Outcome dei pazienti con fallimento della prima terapia prescritta dal Centro AOUP – UO Epatologia

Ritrattamento:

SVR ITT: 23/34 (67.6%)

SVR PP: 23/24 (95.8%)



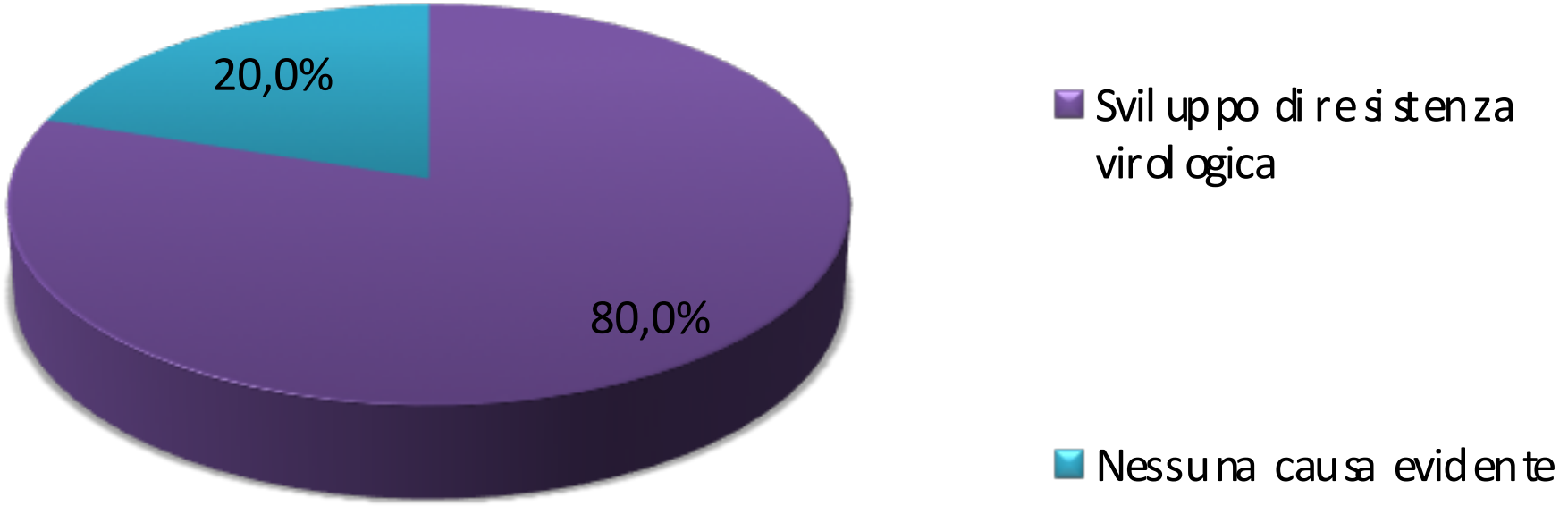
Ri-Trattamento nei **20 pazienti** con **un solo fallimento** a regime contenente **NS5A inibitore**

SVR 18/19 (95%)

N. (%)	Gt. 3 n. (%)	F3-4 / OLT n. (%)	**DAAs fallimento** (num. pz)	NS3 wt/sp/RAS n. (%)	NS5A wt/sp/RAS n. (%)	NS5B wt/sp/RAS n. (%)	**DAAs Ri-Trattamento** (num. pz)	SVR n. (%)
5	0	1 (20)	**GRZ+ELV**	0 / 4 / 1 (- / - / 20)	0 / 1 / 5 (- / 20 / 100)	3 / 2 / 0 (60 / 40 / -)	**VOX+VEL+SOF (4)** To be defined (1)	**4 (100)**
3	1 (33)	0	**G/P**	1 / ? / ? (33 / ? / ?)	1 / 1 / ? (33 / 33 / ?)	1 / 1 / 0 (33 / 33 / -)	**VOX+VEL+SOF (3)**	**3 (100)**
3	0	0	**LDV+SOF (2)** **LDV+SOF+RBV (1)**	2 / 1 / 0 (66 / 33 / -)	1 / 0 / 2 (33 / - / 66)	3 / 0 / 0 (100 / - / -)	**VOX+VEL+SOF (3)**	**3 (100)**
1	1 (100)	1 (100)	**DCV+SOF+RBV**	1 / - / 0 (100 / - / -)	0 / 0 / 1 (- / - / 100)	1 / - / 0 (100 / - / -)	**VOX+VEL+SOF+RBV (1)**	**3 (100)**
8	4 (50)	4 (50)	**VEL+SOF**	3 / 5 / 0 (38 / 52 / -)	2 / 3 / 5 (25 / 38 / 52)	8 / - / 0 (100 / - / -)	**VOX+VEL+SOF (5)** **VOX+VEL+SOF+RBV (1)** **G/P (2)**	**5 (100)** **1 (100)** **1 (50)**
TOTALE								
20	**6 (30%)**	**6 (30%)**	**GRZ+ELV (5)** **G/P (3)** **anyNS5A+SOF (12)**	7 / 10 / 1 (35 / 50 / 10)	4 / 5 / 13 (20 / 25 / 65)	16 / 3 / 0 (80 / 15 / -)	**VOX+VEL+SOF (15)** **VOX+VEL+SOF+RBV (2)** **G/P (2)** To be defined (1)	**15 (100)** **2 (100)** **1 (50)**

Analisi dei fallimenti ai DAAs su pazienti provenienti da altri Centri Prescrittori e riferiti per il Ri-Trattamento

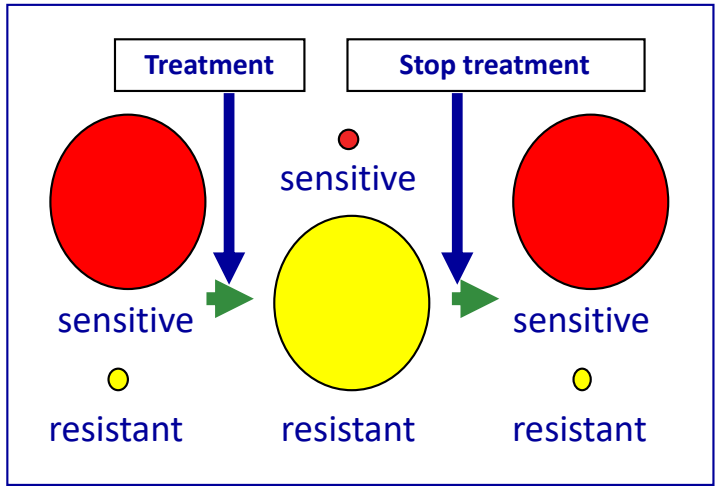
10 fallimenti in 7 pazienti
(3 pz con 2 fallimenti)



Resistant-associated substitutions

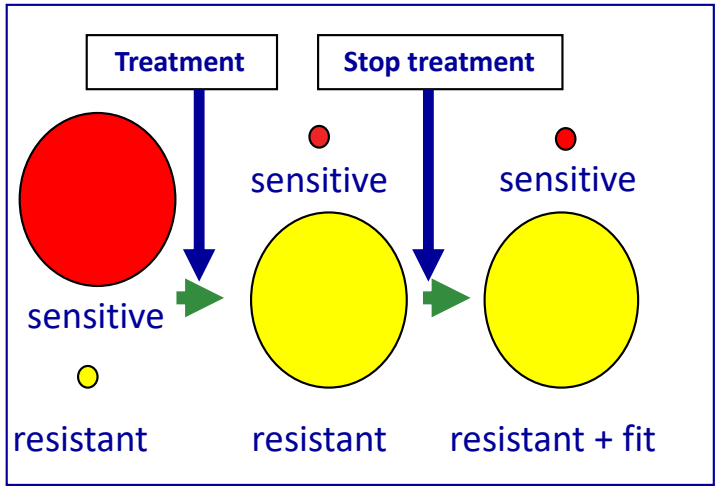
NS3-4A resistant variants

- disappear within few months
- replacement by wild-type virus
- spontaneous reversion to wild-type



NS5A resistant variants

- persist for years
- naturally more fit than wild-type virus
- unfrequent reversion to wild-type virus



- The timing of sampling to detect RAS is critical: a sample should be obtained when the relpase occurs (usually 12 weeks after EOT) and a second sample just before the re-treatment
- All the 3 regions should be sequenced (mandatory NS3 and NS5A)
- The sensitivity of the sequencing method may have major implications in the treatment decision

Difficult to re-treat patients

The complexity of the RAS pattern increases after repeated treatments, making particularly difficult the identification of a rescue treatment strategy for patients with repeated failure to DAAs

Currently, the decision can be made:

- on the basis of *in vitro* data about the antiviral activity against a specific RAS of the available drugs
- after a careful analysis of the factors (disease-related and patient-related), that could have influneced the response to treatment

Table 7. RASs conferring reduced susceptibility to the corresponding drug classes in *in vitro* assays and/or selected in patients who failed to achieve SVR on IFN-free, DAA-based regimens (excluding first-generation protease inhibitors telaprevir and boceprevir).

Drug class (genome region)	Amino acid position	Genotype/subtype						
		1a	1b	2	3	4	5	6
Nucleotide analogue (NS5B), *e.g.* sofosbuvir								
	150				A150V			
	159	L159F	L159F	L159F	L159F			
	206				K206E			
	282	S282G/R/T	S282G/R/T	S282G/R/T	S282G/R/T	S282C/G/R/T	S282G/R/T	S282G/R/T
	316	C316H/R	C316F/H/N					
	320	L320I/F/V						
	321	V321A	V321I		V321A	V321A		
NS5A inhibitors (NS5A)								
	24	K24E/QR/T	Q24K	T24A/S	S24F			Q24H
	26	K26E						
	28	M28A/G/S/T/V	L28A/M/T	L/F28C/S	M28T/K	L28M/S/T/V	L28I	F/L28A/I/L/M/T/V
	29	P29R	P29S, del29	P29S				
	30	Q30C/D/E/G/H/K/L/N/R/T/Y, del30	R30G/H/P/Q/S	L30H/S	A30D/E/K/S	L30F/G/H/R/S	Q30H	R30E/H/N/S
	31	L31I/F/M/P/V	L31F/I/M/V/W	L31I/M/V	L31F/I/M/P/V	M/L31I/V	L31F/I/V	L31I/M/V
	32	P32L/S, del32	P32F/L/S, del32				P32L	P32A/L/Q/R/S
	38	S38F						
	58	H58C/D/L/P/R	P58A/D/L/S/R/T			T58A/P/S		T58A/G/H/N/S
	62		Q/E62D		S62L			
	92	A92K/T	A92E/K/T/V	C92R/S/T/W	E92K			E92T
	93	Y93C/F/H/L/N/R/S/T/W	Y93C/H/N/R/S/T	Y93F/N/H	Y93H/N/S	Y93C/H/N/S/R/W		T93A/H/N/S
Protease inhibitors (NS3)								
	36	V36A/C/F/G/L/M	V36A/C/G/L/M					V36I
	41	Q41R	Q41R		Q41K	Q41R		Q41K/R
	43	F43I/L/S/V	F43I/S/V	F43V				
	54	T54A/S	T54A/C/G/S					
	55	V55I	V55A	V55A/I				
	56	Y56H	Y56H/L/F	Y56H/F	Y56H	Y56H		Y56H
	80	Q80K/L/R	Q80H/K/L/R		Q80K/R	Q80R		L80K/Q
	122	S122G/N/R	S122A/D/G/I/N/R/T					S122T
	155	R155G/I/K/M/Q/S/T/V/W	R155C/G/I/K/L/Q/M/S/T/W		R155K	R155C/K	R155K	
	156	A156G/P/S/T/V	A156G/P/S/T/V	A156L/M/T/V	A156G/P/T/V	A156G/H/K/L/S/T/V	A156T/V	A156T/V
	158	V158I	V158I					
	166				A166S/T/Y			
	168	D168A/C/E/F/G/H/I/K/L/N/Q/R/T/V/Y	D168A/C/E/F/G/H/I/K/L/N/Q/T/V/Y	D168A/E/F/G/H/N/S/T/V/Y	Q168H/K/L/R	D168A/E/G/H/T/V	D168A/E/H/K/R/V/Y	D168A/E/G/H/V/Y
	170	I/V170T/V	I/V170A/L/T					I170V
	175		M175L					
Non-nucleoside palm-1 inhibitor (NS5B), *e.g.* dasabuvir								
	314	L314H						
316	C316Y	C316H/N/Y/W						
	368		S368T					
	395	A395G						
	411		N411S					
	414	M414I/T/V	M414I/T/V					
	445		C445F/Y					
	446	E446K/Q						
	448	Y448C/H	Y448C/H					
	553	A553T/V	A553V					
	554	G554S	G554S					
	555	Y555H						

Drug class (genome region)	Amino acid position	Genotype/subtype						
		1a	1b	2	3	4	5	6
	556	S556G/R	S556G/R					
	557	G557R						
	558	G558R	G558R					
	559	D559G/N	D559G/N					
	561	Y561H/N						
	565	S565F						

In vitro Antiviral Activity of Pibrentasvir against RAS selected in GT 1 and 2-6

TABLE 5 Antiviral activity of pibrentasvir against HCV replicons of genotypes 1a and 1b containing NS5A with amino acid substitutions that confer resistance to other NS5A inhibitors

HCV genotype and NS5A amino acid substitution(s)	Pibrentasvir EC_{50}[a]		Replication efficiency (%)[b]
	Mean ± SD (pM)	Fold change[b]	
1a-H77			
Wild type	0.72 ± 0.45		100
M28T	1.5 ± 1.1	2.1	89
M28V	1.3 ± 0.86	1.8	87
Q30E	1.7 ± 0.39	2.4	70
Q30H	0.74 ± 0.21	1.0	90
Q30R	1.2 ± 0.62	1.7	86
L31M	0.76 ± 0.11	1.1	141
L31V	0.96 ± 0.85	1.3	297
P32L	1.2 ± 0.43	1.7	19
H58D	0.80 ± 0.17	1.1	97
Y93C	1.2 ± 0.57	1.7	22
Y93H	4.8 ± 1.5	6.7	40
Y93N	5.1 ± 2.1	7.1	35
M28T+Q30R	1.2 ± 0.21	1.6	28
M28T+Y93C	2.2 ± 0.47	3.1	18
Q30L+Y93H	0.42 ± 0.09	0.6	27
Q30R+L31M	1.7 ± 0.34	2.4	46
Q30R+H58D	77 ± 2.1	108	46
Q30R+Y93C	2.8 ± 0.64	3.8	5.3
Q30R+Y93H	187 ± 110	260	11
L31M+Y93C	4.4 ± 0.55	6.1	28
L31V+Y93H	68 ± 36	94	73
M28T+Q30R+L31M	3.3 ± 0.41	4.6	44
Q30R+L31M+Y93C	30 ± 1.0	42	6.8
1b-Con-1			
Wild type	1.9 ± 0.80		100
L28T	1.7 ± 0.44	0.9	18
Y93H	1.1 ± 0.27	0.6	38
Y93N	1.2 ± 0.25	0.6	52
L31M+Y93H	1.3 ± 0.24	0.7	15
L31V+Y93H	1.7 ± 0.31	0.9	30
P58S+Y93H	1.5 ± 0.45	0.8	44

[a]As determined in transient-transfection assays.
[b]Fold change or replication efficiency is relative to the value of the respective wild-type replicon.

TABLE 6 Antiviral activity of pibrentasvir against HCV replicons containing NS5A from genotypes 2 to 6 with amino acid substitutions that confer resistance to other NS5A inhibitors

HCV genotype and NS5A amino acid substitution(s)	Pibrentasvir EC_{50}[a]	
	Mean ± SD (pM)	Fold change
2a		
Wild type[b]	0.99 ± 0.36	
T24A	1.3 ± 0.30	1.3
F28S	1.2 ± 0.17	1.2
2b		
Wild type[c]	1.2 ± 0.39	
L28F	0.94 ± 0.27	0.8
L31M	1.5 ± 0.33	1.2
L31V	0.64 ± 0.20	0.5
3a		
Wild type	0.65 ± 0.16	
M28T	1.1 ± 0.02	1.7
Y93H	1.5 ± 0.19	2.3
4a		
Wild type	0.78 ± 0.14	
L28V	0.85 ± 0.23	1.1
L30H	1.1 ± 0.51	1.3
5a		
Wild type	0.93 ± 0.20	
L28I	0.98 ± 0.14	1.1
L31F	1.9 ± 0.11	2.1
L31V	0.75 ± 0.24	0.8
6a		
Wild type[d]	1.0 ± 0.31	
L31V	1.0 ± 0.38	1.0
T58A	1.4 ± 0.45	1.4
T58N	1.8 ± 0.71	1.8

[a]As determined in transient-transfection assays. Fold change is relative to the value of the respective wild-type replicon.
[b]The 2a wild-type replicon has M31 in NS5A.
[c]The 2b wild-type replicon has L31 in NS5A.
[d]The 6a wild-type replicon has L28 in NS5A.

Overall Pibrentasvir shows a higher barrier to resistance than all other approved NS5A inhibitors in vitro

Ng T et al, Antimicrobila Agents and Chemotherapy, 2017

Retreatment of patients who failed G/P treatment for HCV infection

32 patients who failed G/P treatment were retreated with G/P/Sof for 12 or 16 (GT3 or cirrhosis) weeks

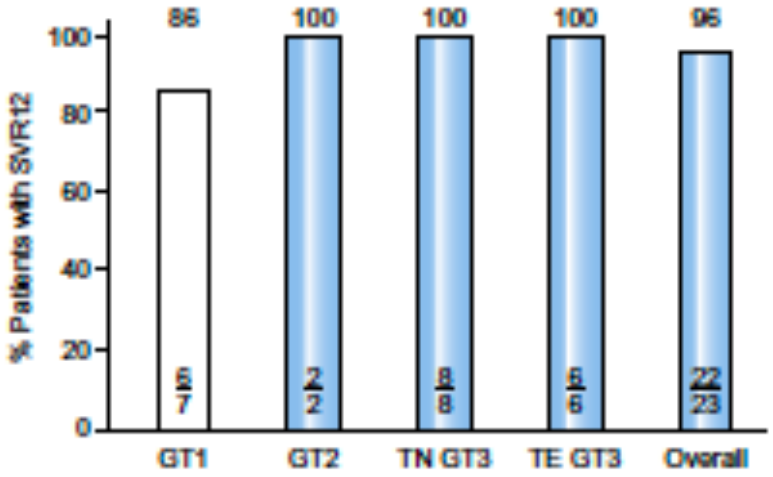


Table 1. Treatment and Resistance History of Patients.

Genotype/ Subtype	Cirrhosis	Treatment prior to G/P parent study	Type of VF in parent study	NS3 RASs at G/P failure in parent study*	NS5A RASs at G/P failure in parent study*	Time from failure in parent study to retreatment in Magellan-3 (months)	NS3 RASs at BL in MAGELLAN-3*	NS5A RASs at BL in MAGELLAN-3*
1b	No	DCV + ASV	Relapse	None	L28M + P32del	10.3	None	L28M + P32del
1a	No	OBV/PTV/r + DSV + RBV; pegIFN + RBV + DCV	OTVF	A156G + D168A	Q30R + L31M + H58D	7.5	A156G, D168A/T	Q30R + L31M + H58D
1a	No	TVR, DCV; pegIFN/ RBV	Relapse	A156V	Q30R + L31M + H58D	12.6	None	Q30R + L31M + H58D
1a[§]	Yes	SOF + LDV	OTVF	A156V	Q30K + Y93H	8.6	None	Q30K + Y93H
1a	Yes	SOF + SMV; SOF + LDV	Relapse	R155K + A156T	M28G + Q30R	6.7	R155K	M28G + Q30R
1a	Yes	OBV/PTV/r + DSV	OTVF	D168A	M28G + Q30R	14	None	M28G + Q30R
1a	Yes	pegIFN + RBV	Relapse	None	Q30R + Y93N	9	None	Q30R + Y93N
2a	No	SOF + RBV	Relapse	None	None	5.2	None	None
2a	No	IFN + RBV	Relapse	None	None	11.3	None	None
3a	No	Naïve	Relapse	None	Y93H	7.0	None	Y93H
3a	No	Naïve	Relapse	None	Y93H	4.6	None	Y93H
3a	No	Naïve	OTVF	Q168R	A30K + Y93H	11.7	Q168R	A30K + Y93H
3a	No	Naïve	Relapse	None	A30K + Y93H	6.0	None	A30K
3a	No	Naïve	Relapse	Q168L	A30K + Y93H	11.8	Q168L	A30K + Y93H
3b	No	Naïve	Relapse	None	(A30K + V31M) + Y93H[‖]	13.2	None	A30K + V31M + Y93H
3a	Yes	Naïve	OTVF	A156G	A30K + Y93H	10.3	Q168R	A30K + Y93H
3a	Yes	Naïve	Relapse	Q168L	A30K + Y93H	11.4	None	A30K, Y93H
3a	No	IFN + RBV	Relapse	None	Y93H	7.0	None	Y93H
3a	No	IFN + RBV	Relapse	None	L31F + Y93H	18.9	None	Y93H
3a	No	IFN + RBV	Relapse	Q168R	A30K + Y93H	8.1	None	A30K
3a	No	IFN + RBV	Relapse	None	A30K + Y93H	6.2	None	A30K + Y93H
3a	No	IFN + RBV	OTVF	Q168L	A30K + Y93H	21.8	None	A30K
3a	Yes	IFN + RBV	OTVF	A156G	A30K + Y93H	14.0	None	A30K + Y93H

ASV, asunaprevir; BL, baseline; DCV, daclatasvir; DSV, dasabuvir; G/P, glecaprevir/pibrentasvir; LDV, ledipasvir; OBV/PTV/r, ombitasvir/paritaprevir/ritonavir; OTVF, on-treatment VF; RAS, resistance-associated substitution; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir; VF, virologic failure.

*+Indicates that at least 1 of the substitutions was present at >90% prevalence and all others were present at >50% prevalence

†The detection threshold was 15%. NS3 resistance-associated substitution (RAS) positions included in analyses were: 155, 156 and 168. NS5A RAS positions included in analyses were: 24, 28, 30, 31, 32, 58, 92, and 93.

‡Patient with virologic failure

§GT3b wild-type NS5A sequence has K30 and M31; in addition, Y93H was present.

The **triple combination** of sofosbuvir and the fixed-dose combination of glecaprevir and pibrentasvir could offer an interesting alternative for **retreatment of difficult-to-cure patients**, such as those with complex NS5A RAS patterns and/or those with advanced liver disease (excluding decompensated cirrhosis) who have experienced several unsuccessful courses of treatment.

Wyles D et al J Hep 2019; CPG EASL 2020

Retreatment of DAA failures

Recommendations

- Patients who failed after any of the DAA-containing treatment regimens should be retreated in the context of a multidisciplinary team including experienced treaters and virologists **(B1)**.
- HCV resistance testing prior to retreatment in patients who failed after any of the DAA-containing treatment regimens is useful to guide retreatment by probabilities of response, according to the resistance profile observed **(B1)**.
- Patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis who failed after a DAA (protease inhibitor and/or NS5A inhibitor)-containing regimen should be retreated with the fixed-dose combination of sofosbuvir, velpatasvir and voxilaprevir for 12 weeks **(A1)**.
- Patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis who failed after a DAA (protease inhibitor and/or NS5A inhibitor)-containing regimen and have predictors of lower response (advanced liver disease, multiple courses of DAA-based treatment, complex NS5A RAS profile) can be retreated with the combination of sofosbuvir plus the fixed-dose combination of glecaprevir and pibrentasvir for 12 weeks, based on an individual multidisciplinary decision **(B1)**.

Protease and/ or NS5A inhibitors regimens

Predictors of lower response:

- **Advanced LD**
- **Multiple DAA courses**
- **Complex NS5A RAS profile**

CPG EASL 2020

Retreatment of DAA failures

Very difficult patients

- In very difficult-to-cure patients (patients with NS5A RASs who failed twice or more to achieve SVR after a combination regimen including a protease and/or an NS5A inhibitor), the triple combination of sofosbuvir, velpatasvir and voxilaprevir, or the triple combination of sofosbuvir, glecaprevir and pibrentasvir can be administered for 12 weeks with weight-based ribavirin (1,000 or 1,200 mg in patients <75 kg or ≥75 kg, respectively), and/or treatment duration can be prolonged to 16 to 24 weeks, based on an individual multidisciplinary decision **(B1)**.

Failure to SOF/VEL/VOX

↓

SOF/G/P + RBV for 24 w

- In patients who failed to achieve SVR after retreatment with the triple combination of sofosbuvir, velpatasvir and voxilaprevir, the triple combination of sofosbuvir, glecaprevir and pibrentasvir can be administered for 24 weeks with weight-based ribavirin (1,000 or 1,200 mg in patients <75 kg or ≥75 kg, respectively) **(B1)**.
- Patients with decompensated (Child-Pugh B or C) cirrhosis who failed after a DAA (protease inhibitor and/or NS5A inhibitor)-containing regimen have a contraindication for the use of protease inhibitors, and should therefore be retreated with the fixed-dose combination of sofosbuvir and velpatasvir with weight-based ribavirin (1,000 or 1,200 mg in patients <75 kg or ≥75 kg, respectively) for 24 weeks, based on an individual multidisciplinary decision **(B1)**.

- The chance of response to re-treatment after a failure to the first DAA course is high
- The characterization of the viral quasispecies at the time of relapse is recommended to know the resistance profile, that was selected by the treatment
- The rescue therapy to repeated failures requires a personalized approach using off label drugs combination and prolonged treatments
- Should Peg-IFN and RBV be considered in selected cases?

Magritte R, La Riproduzione Vietata 1937 (sir Edward James)

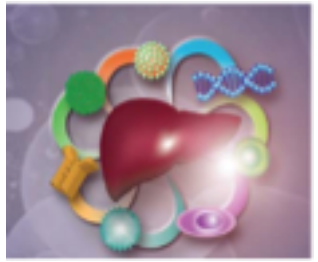
Hepatology Unit
University Hospital of Pisa, Italy

Barbara Coco
Piero Colombatto
Filippo Oliveri
Veronica Romagnoli
Antonio Salvati
Gabriele Ricco
Patrizia Bleve
Barbara Vianello

Medical Doctors

Antonella Cristofani
Simonetta Ferretti
Simona Giannetti
Teresa Crisponi
Barbara Zucchelli
Raffaele Apuzzo

Nurses



Administrative Personel

Arianna Del Chicca

Pharmacist

Mariachiara Cipolli

Bio-Physics

Luigi Civitano

Biologists

Daniela Cavallone
Francesco Moriconi
Tommaso Prescimone

Ferruccio Bonino
Biostructure and Bio-imaging Institute of National Research Council of Italy