XII Workshop Nazionale
Innovazione e Ricerca per la Pratica Clinica

TERAPIE INNOVATIVE DELLE EPATITI CRONICHE VIRALI E DELLE INFEZIONI VIRALI

Firenze, 10-11 Gennaio 2022
Centro Congressi Hotel Londra

Il paziente fallito: strategie terapeutiche e ruolo dei genotipi rari

Piero Colombatto

UO Epatologia – Azienda Ospedaliero Universitaria Pisana - Centro Riferimento Regionale *"Diagnosi e trattamento delle epatopatie croniche e del tumore di fegato"*

Disclosures

Speakers Bureau: AbbVie, Gilead, MSD

Advisory: AbbVie

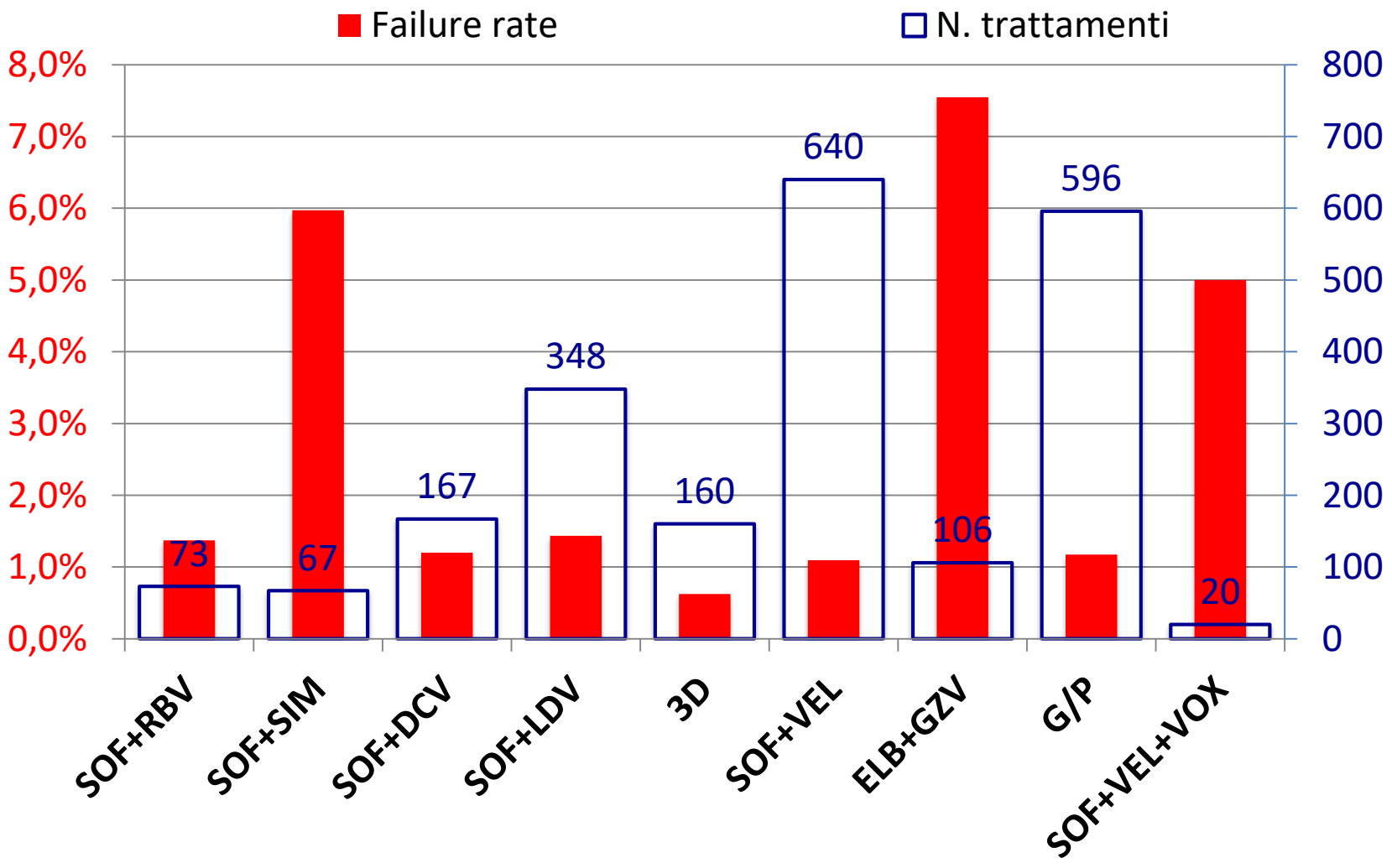
Centro Terapia HCV DAAs
AOUP - Pisa

2339 trattamenti valutabili per SVR

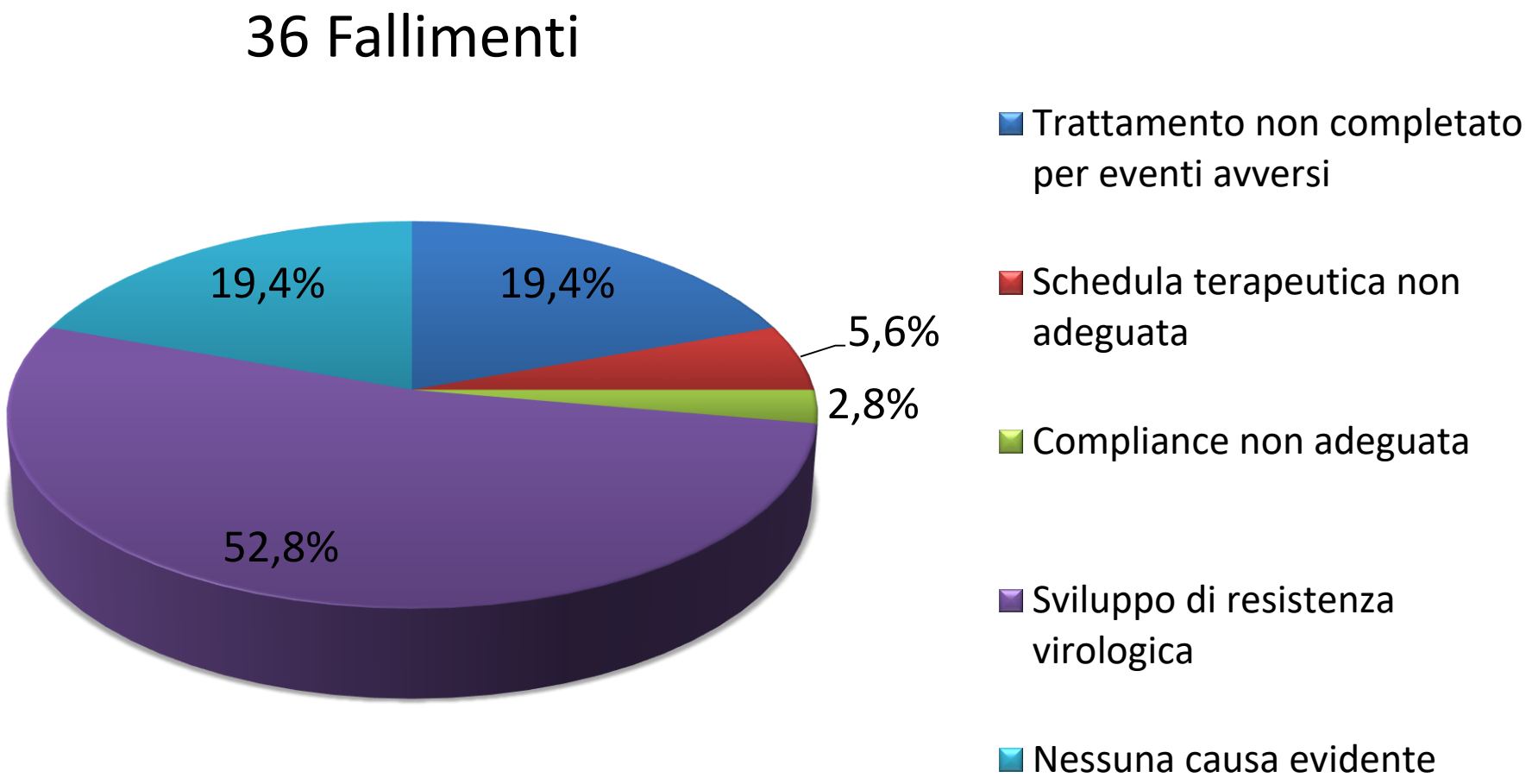
36 (1,54%) fallimenti del trattamento antivirale

STADIO FIBROSI	F0-F1	F3	F4	TOTALE
Overall:	**15**/1188 (1,26%)	**1**/375 (0,27%)	**20**/776 (2,58%)	**36 (1,54%)**
Per genotipo HCV:				
1a	3 (1,4%)	0	3 (2,5%)	6 (1,6%)
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%)

Fallimenti in base alla schedula di trattamento



Condizioni associate al fallimento della terapia con DAAs



UO Epatologia – AOUP
Report of HCV treatments with DAAs

Reasons for short treatment duration

	Patients					
Treatment NOT completed	10	0,48%	due to	**Adverse Events**	**6**	Renal insuff: 2, Pruritus: 2, Iperbilirub. 1, Headache 1.
				HCC (sorafenib start)	1	
				Death (NHL)	1	
				Carceration	1	
				Pregnancy	1	

UO Epatologia – AOUP
Report of HCV treatments with DAAs

RAS and treatment FAILURE

			1st Re-Treatment			2nd tx
RAS/SP* Regions	**Failures**	% of Tot	FU12 available	SVR	%	Ongoing
NS3	**2**	7,7%	**2**	2	100%	0
NS5A	**7**	26,9%	**7**	7	100%	0
NS5B	**0**	0,0%	**-**	-	-	-
NS3+NS5A	**12**	46,2%	**12**	11	91.7%	1
NS3+NS5A+NS5B	**2**	7,7%	**2**	2	100%	0
NS3+NS5B	**0**	0,0%	**-**	-	-	-
NS5A+NS5B	**2**	7,7%	**1**	1	100%	0
None	**2**	3,8%	**2**	1	50%	1
Tot. n. of Failures analysed	**27**	100,0%	**25**	23	92%	2
% of Total Failures	75%					

Prevalence of resistance-associated substitutions to NS3, NS5A and NS5B inhibitors at DAA-failure in hepatitis C virus in Italy from 2015 to 2019

Barbara Rossetti[1], Lorenzo Paglicci[1,2], Velia C. Di Maio[3], Chiara Cassol[1,2], Silvia Barbaliscia[3], Stefania Paolucci[4], Bianca Bruzzone[5], Nicola Coppola[6], Francesca Montagnani[1,2], Valeria Micheli[7], Laura Monno[8], Giacomo Zanelli[1,2], Teresa Santantonio[9], Nunzia Cuomo[10], Cinzia Caudai[11], Maurizio Zazzi[2], Francesca Ceccherini-Silberstein[3], on behalf of the HCV Virology Italian Resistance Network (Vironet C)

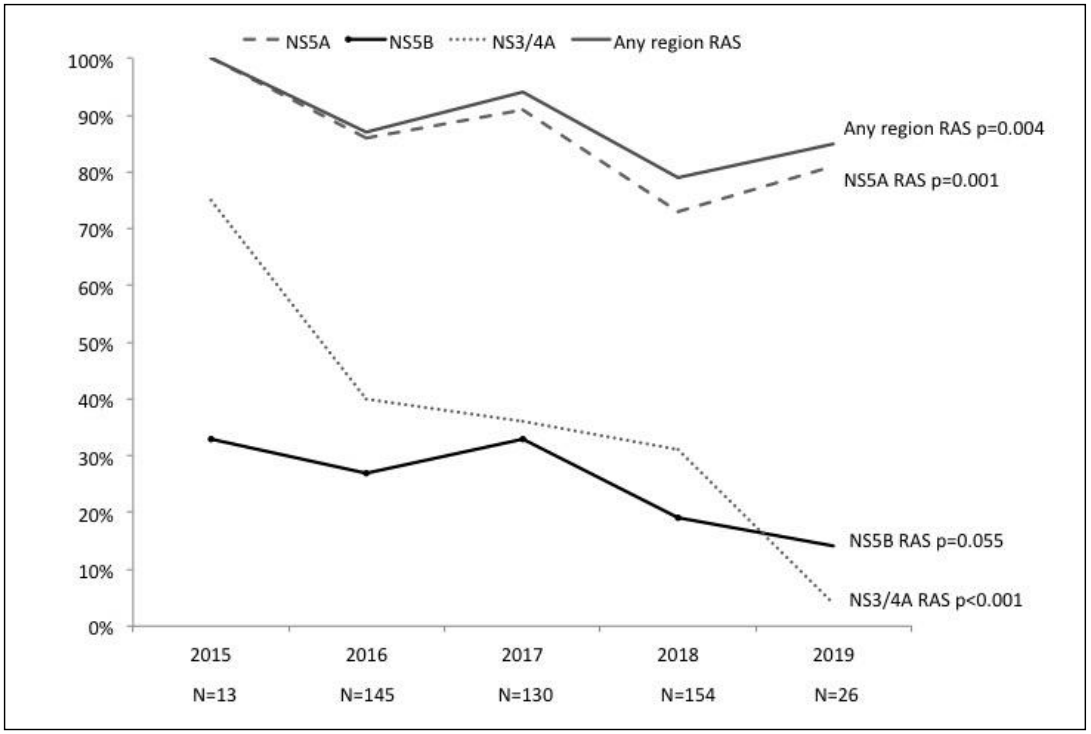


Figure 1 - Resistance Associated Substitutions trends over the study period.

The prevalence of **NS5A and NS3/4A RASs significantly declined from 2015 to 2019**; NS5B RAS remained stable. Independent predictors of any RASs included **older age** and **genotype 1a** (vs G2 and vs G4). Notably, at least partial susceptibility to all the agents included in the GLE/ PIB and VEL/SOF/Voxilaprevir (VOX) combinations was predicted in >95% of cases.

B. Rossetti, L. Paglicci, V.C. Di Maio, et al.
Le Infezioni in Medicina, n. 2 , 242-251, 2021

UO Epatologia – AOUP
Report of HCV treatments with DAAs

RE-Treatment in RAS associated failures of NS5a containing regimens

N.	Sesso/ anni	Genot	AIFA	Trattamento fallito	NS3	NS5A	NS5B	RI-TRATTMENETO	SVR12
1	M/39	3a	8	SOF+DCV	A156V, Q168L	A30K, A62L	S282C	**VOX+VEL+SOF**	**YES**
2	M/79	3a	1	SOF+DCV+RBV	wt	A62S(sp), Y93H	wt	**VOX+VEL+SOF+RBV**	**YES**
3	M/29	1a	7	SOF+VEL	Q80K	wt	wt	**VOX+VEL+SOF**	**YES**
4	F/49	1b	7	ELB+GZV	na	wt	L159F, C136N, S556G	**VOX+VEL+SOF**	**YES**
5	M/33	1a	7	VOX+VEL+SOF	D168F --> wt	wt	wt	**G/P**	**YES**
6	F/79	1b	4	SOF+VEL	wt	Y93H	wt	**VOX+VEL+SOF**	**YES**
7	M/49	1b	7	SOF+VEL	D168Y, V170A	wt	wt	**G/P**	**YES**
8	M/63	3a	2	SOF+VEL / SOF+VEL+VOX	wt	A62S(sp), Y93H	wt	**G/P+RBV**	**NO**

Caso Clinico - Maschio - 64 anni

- Ex tossicodipendente (1974-1984)
- Alcol: ca 80 g/die fino a Gen. 2018
- Peso: 67 Kg, altezza 1.68 m, BMI 23.7

- **1982:** Epatite acuta itterica da HBV, poi ALT aumentate
- **1990:** diagnosticata infezione da HCV
- Genotipo 3a
- Anti-HIV negativo
- Non patologie associate di rilievo
- Proposte più volte terapie antivirali con (p)IFN+RBV, ma rifiutate dal paziente per perfetto benessere e timore effetti collaterali.

Caso Clinico - Maschio - 64 anni

- Gennaio 2018

→ **angio-TC addome** conferma lesione di **38 mm tra V-VIII segmento in prossimità della diramazione portale** con comportamento vascolare dinamico tipico per **HCC su fegato cirrotico**

- Agosto 2018

→ sottoposto con successo a **trapianto di fegato (OLT)** dopo aver effettuato una TACE sulla lesione di HCC

- Non effettuato trattamento antivirale con DAAs pre OLT
- Immunosoppresso con Everolimus + Tacrolimus

Caso Clinico - Maschio - 64 anni

→ **Settembre 2018** (dopo circa 1 mese da OLT) inizia terapia antivirale con **Sofosbuvir e Velpatasvir per 12 settimane**

- **Risposta:**

  - RELAPSER a 12 settimane di FU senza aumento delle ALT e senza segni strumentali / bioumorali di danno epatico significativo

→ **Aprile 2019** (circa 8 mesi da OLT) ritrattamento con **Sofosbuvir + Velpatasvir + Voxilaprevir per 12 settimane**

- **Risposta:**

  - RELAPSER a 12 settimane di FU senza aumento delle ALT e senza segni strumentali / bioumorali di danno epatico significativo

JOURNAL OF HEPATOLOGY

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

European Association for the Study of the Liver*

Recommendations for Retreatment of DAA failures

- 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).

- **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).

Caso Clinico - Maschio - 64 anni

- **16/1/20:** prima analisi delle sostituzioni associate a resistenza agli antivirali con sequenziamento diretto di:

- NS5B: wild type
- **NS5A: Y93H** e A62S (score position)
- NS3: wild type

Recommendations for genotype/subtype based treatment of HCV monoinfected or HCV/HIV

Type of treatment	Genotype	Cirrhosis status	Prior treatment experience	Sofosbuvir/ velpatasvir	Glecaprevir/ pibrentasvir	Sofosbuvir/ velpatasvir/ voxilaprevir	Grazoprevir/ elbasvir
Genotype/subtype determination-based treatment	Genotype 1a, 1b, 2, 4, 5 and 6	No cirrhosis	Treatment-naïve	12 weeks	8 weeks	No	12 weeks (genotype 1b only)
			Treatment-experienced				
		Compensated (Child-Pugh A) cirrhosis)	Treatment-naïve				
			Treatment-experienced		12 weeks		
	Genotype 3	No cirrhosis	Treatment-naïve	12 weeks	8 weeks	No	No
			Treatment-experienced		12 weeks		No
		Compensated (Child-Pugh A) cirrhosis)	Treatment-naïve	12 weeks with weight-based ribavirin[a]	8-12 weeks[b]	12 weeks[a]	No
			Treatment-experienced		16 weeks		No
	Subtype 1l, 4r, 3b, 3g, 6u, 6v or any other subtype naturally harbouring one or several NS5A RASs[c]	No cirrhosis	Treatment-naïve	Unknown	Unknown	12 weeks	No
			Treatment-experienced				
		Compensated (Child-Pugh A) cirrhosis)	Treatment-naïve				
			Treatment-experienced				

If resistance testing is performed, only patients with the **NS5A Y93H RAS at baseline** should be treated with **sofosbuvir/velpatasvir plus ribavirin** or with **sofosbuvir/velpatasvir/voxilaprevir**, whereas patients without the Y93H RAS should be treated with sofosbuvir/velpatasvir alone.

- *In vitro* resistance studies indicate intermediate-level resistance to velpatasvir conferred by Y93H RAS alone and high level when Y93H is combined with other RAS, in particular L31. The in vitro data have been verified in clinical reports
- **204 GT3 cirrhotic pts** randomized to receive SOF+ VEL +/– RBV: SVR 12 96% (2% relapse rate) vs 91% (5% relapse).
  Y93H BL in 13/204 pts → 6.3%
  Y93H BL mutation in 9 RBV group → 1 relapse (11%)
  Y93H BL mutation in 4 non RBV group → 2 relapse (50%)

Esteban, Gastroenterology 2018

Caso Clinico - Maschio - 64 anni

- **16/1/20:** prima analisi delle sostituzioni associate a resistenza agli antivirali con sequenziamento diretto di:

- NS5B: wild type
- NS5A: Y93H e A62S (score position)
- NS3: wild type

→ ruolo delle RAS nei pz con genotipo 3a trattati con G/P :

- **Studi in vitro**: A30K o Y93H non hanno impatto sull'attivita`di pibrentasvir.
- **Trials**:
  - su 18 pz con fallimento virologico a G/P solo 5 pazienti avevano Y93H (non isolata) al basale e dopo il trattamento.
  - su 309 pz trattati con G/P, i polimorfismi al basale in NS5A (incluso Y93H) non hanno avuto un impatto rilevante sugli esiti del trattamento. Tutti i soggetti (15/15) con Y93H al basale hanno ottenuto SVR12

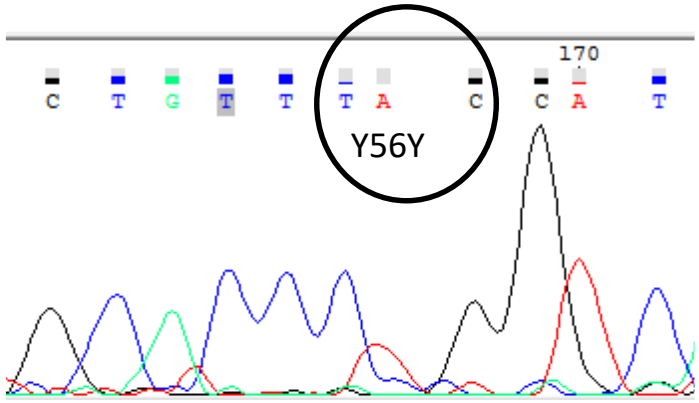
Ri-trattamento con G/P+RBV

T0 4w

Analisi	16/01/2020	06/05/2020	27/05/2020	29/05/2020	03/06/2020	24/06/2020
S-Transaminasi GO	43	63	51	48	37	29
S-Transaminasi GP	60	97	72	65	48	27
S-GGT	34	32	36	33	29	25
S-Fosfatasi alcalina	80	63	59	60	56	60
S-Proteine totali	7,5	7,9				
S-Albumina	4,6	4,8				
S-Bilirubina totale	0,91	1,5	1,22			1,86
S-Bilirubina diretta	0,28	0,61	0,43			0,61
Tempo di Protrombina	94	85	87			80
I.N.R.	1,04	1,09	1,08			1,16
S-Colinesterasi	5727	6317				
leucociti	2,34	2,99	3,09		2,18	2
eritrociti	4,84	4,88	4,72		4,64	4,03
emoglobina	14,9	14,9	14,7		14,3	12,2
piastrine	76	76	74		75	83
HBsAg	NEG	NEG				
HBsAg num	0	0				
anti-HBs	NEG	NEG				
anti-HBs num	8,14	9,51				
anti-HBc	REACTIVE	REACTIVE				
HCV Genotipo	HCV3A					
HCV-RNA	RIL	RIL	RIL	RIL	RIL	NON RIL
HCV-RNA (UI/ml)	9520000	11400000	13400000	18900	2320	0
Anti HIV 1-2 screening	NEG	NEG				
S-Creatinina	0,57	0,82	0,83		0,86	0,82
S-Glucosio	115	104				
Tacrolimus	3,9		4,9	5,8	5,5	2,9
Everolimus	3,2		2,4	2,5	2,3	2

C.C. RAS su regione NS3

Trattamento: OLT (Everolimus + Tacrolimus) a Pisa 18/8/18 x HCC su cir HCV gt 3, Epclusa 12w a fine 2018 → REL , Vosevi da Apr a Giu 2019 → REL



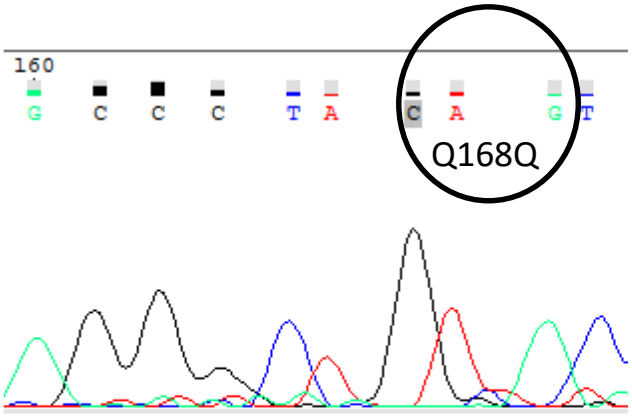
Regione NS3: prelievo 20/01/20 wild

Viremia 16/01/20 →9520000 IU/mL

27/5/20 start G/P+RBV 12w → REL

C.C. RAS su regione NS3

Trattamento: OLT (Everolimus + Tacrolimus) a Pisa 18/8/18 x HCC su cir HCV gt 3, SOF+VEL12w a fine 2018 → REL , SOF+VEL+VOX da Apr a Giu 2019 → REL



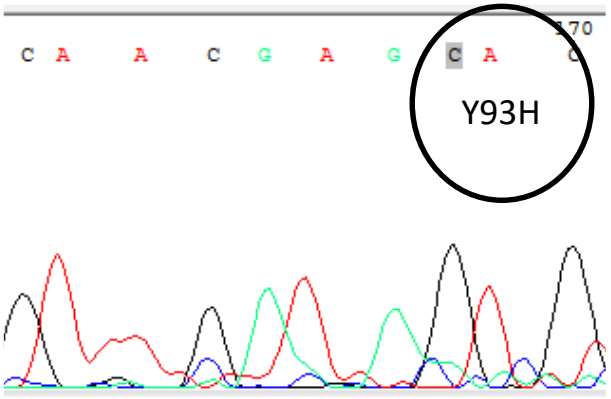
Regione NS3: prelievo 20/01/20 wild

Viremia 16/01/20 →9520000 IU/mL

27/5/20 start G/P+RBV 12w → REL

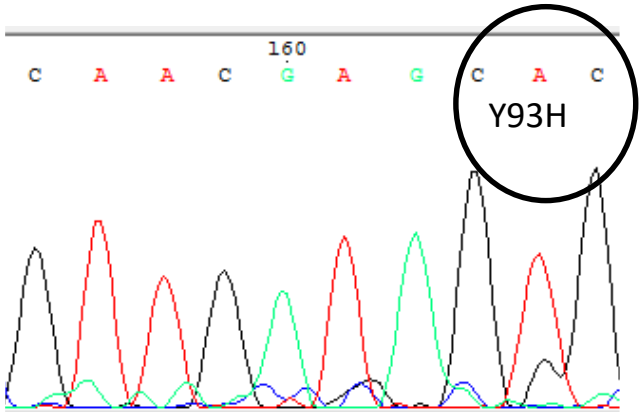
C.C. RAS in regione NS5A

Trattamento: OLT (Everolimus + Tacrolimus) a Pisa 18/8/18 x HCC su cir HCV gt 3, SOF+VEL12w a fine 2018 → REL , SOF+VEL+VOX da Apr a Giu 2019 → REL



Regione NS5A: prelievo 20/01/20
A62S (score); Y93H

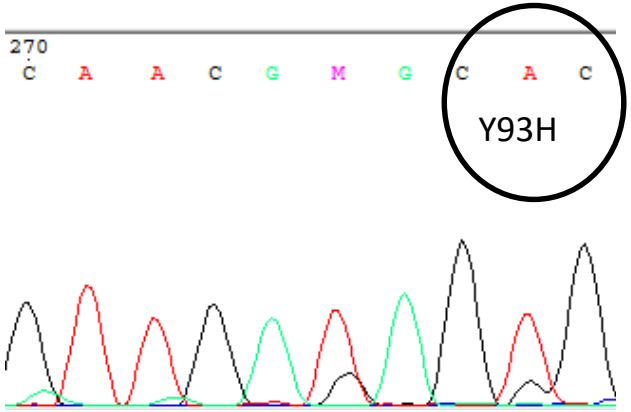
Viremia 16/01/20 →9520000 IU/mL



Regione NS5A: prelievo 27/05/20
A62S (score); Y93H

Viremia 16/01/20 →13400000 IU/mL

Res:
Daclatasvir;
Velpatasvir;
Pibrentasvir;
Ravidasvir;
Ruzasvir;
Samatasvir



Regione NS5A: prelievo 29/05/20
A62S (score); Y93H

Viremia 16/01/20 →18900 IU/mL

Recommendations for Retreatment of DAA failures
"Difficult to RE-treat" patients

- 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).

- In **very difficult-to-cure patients** (**NS5A RASs who failed twice or more**) after a combination regimen including a protease and/or an NS5A inhibitor

- triple combination of **sofosbuvir, velpatasvir and voxilaprevir**,
- triple combination of **sofosbuvir, glecaprevir and pibrentasvir**

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).

Journal of Hepatology **2020** vol. 73 | 1170–1218

Recommendations for Retreatment of DAA failures
"Difficult to RE-treat" patients

- 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:

  - **fixed-dose combination of sofosbuvir and velpatasvir with weight-based ribavirin** (1,000 or 1,200 mg in patients <75 kg or >−75 kg, respec- tively) **for 24 weeks**, based on an individual multidisciplinary decision (B1). .

HCV Genotype: test or not to test?

Type of treatment	Genotype	Cirrhosis status	Prior treatment experience	Sofosbuvir/ velpatasvir	Glecaprevir/ pibrentasvir	Sofosbuvir/ velpatasvir/ voxilaprevir	Grazoprevir/ elbasvir
Simplified treatment, no genotype/subtype determination[a]	All genotypes	No cirrhosis	Treatment-naïve	12 weeks	8 weeks	No	No
			Treatment-experienced				
		Compensated (Child-Pugh A) cirrhosis)	Treatment-naïve		12 weeks		
			Treatment-experienced				

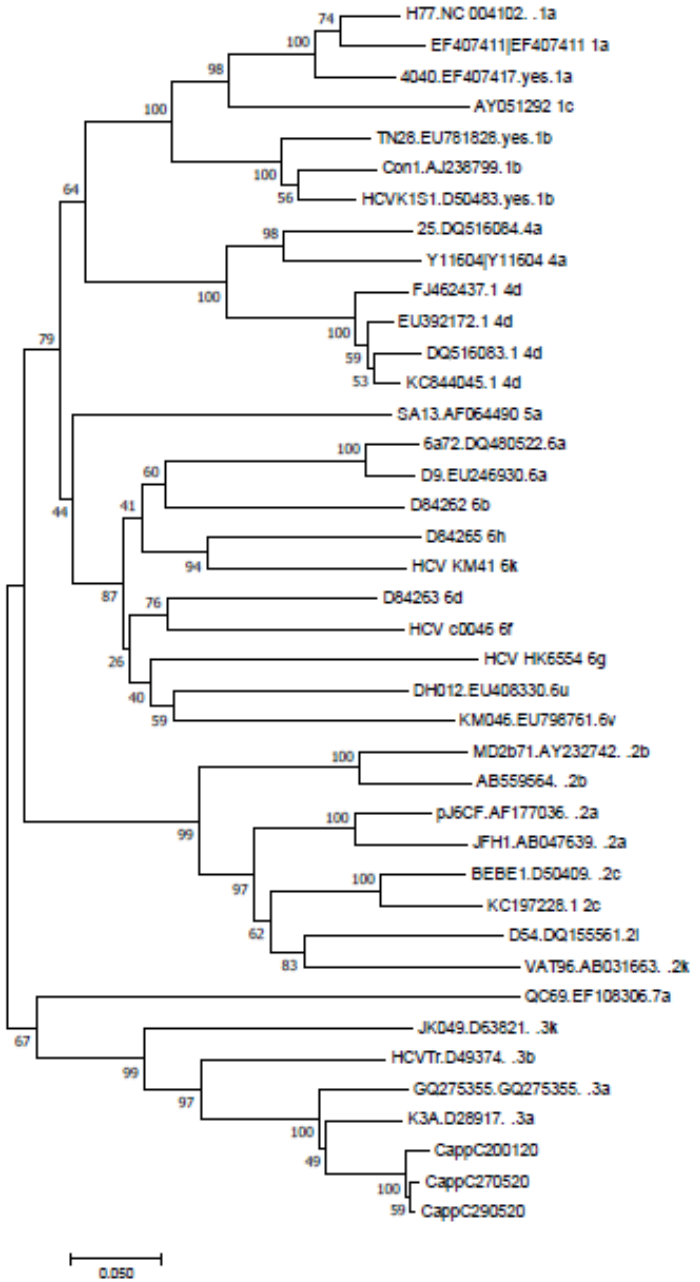
In settings where HCV genotype and subtype determination are available and affordable and **would not limit access to care**, this information remains useful to optimise the virological results of HCV therapy (A1).

Type of treatment	Genotype	Cirrhosis status	Prior treatment experience	Sofosbuvir/ velpatasvir	Glecaprevir/ pibrentasvir	Sofosbuvir/ velpatasvir/ voxilaprevir	Grazoprevir/ elbasvir
Genotype/subtype determination-based treatment	Genotype 1a, 1b, 2, 4, 5 and 6	No cirrhosis	Treatment-naïve	12 weeks	8 weeks	No	12 weeks (genotype 1b only)
			Treatment-experienced				
		Compensated (Child-Pugh A) cirrhosis)	Treatment-naïve		12 weeks		
			Treatment-experienced				
	Genotype 3	No cirrhosis	Treatment-naïve	12 weeks	8 weeks	No	No
			Treatment-experienced		12 weeks		No
		Compensated (Child-Pugh A) cirrhosis)	Treatment-naïve	12 weeks with weight-based ribavirin[a]	8-12 weeks[b]	12 weeks[a]	No
			Treatment-experienced		16 weeks		No
	Subtype 1l, 4r, 3b, 3g, 6u, 6v or any other subtype naturally harbouring one or several NS5A RASs[c]	No cirrhosis	Treatment-naïve	Unknown	Unknown	12 weeks	No
			Treatment-experienced				
		Compensated (Child-Pugh A) cirrhosis)	Treatment-naïve				
			Treatment-experienced				

In settings where **sequence analysis of the NS5A region** by means of population or deep sequencing is available and affordable, patients infected with subtypes **1l, 4r, 3b, 3g, 6u and 6v** and patients infected with other infrequent subtypes harbouring >1 RAS(s) known to confer resistance to NS5A inhibitors should be considered for treatment with the fixed-dose combination of **sofosbuvir, velpatasvir and voxilaprevir for 12 weeks**, pending data with dual pangenotypic regimens (B2).

Journal of Hepatology **2020** vol. 73 | 1170–1218

HCV Genotype: how to test?



In settings where sequence analysis of the NS5A region by means of **population sequencing** or **deep sequencing** **(cut-off 15%)** is available and affordable, it should be performed **in patients born in sub-Saharan Africa, China or South-East Asia** in order to:

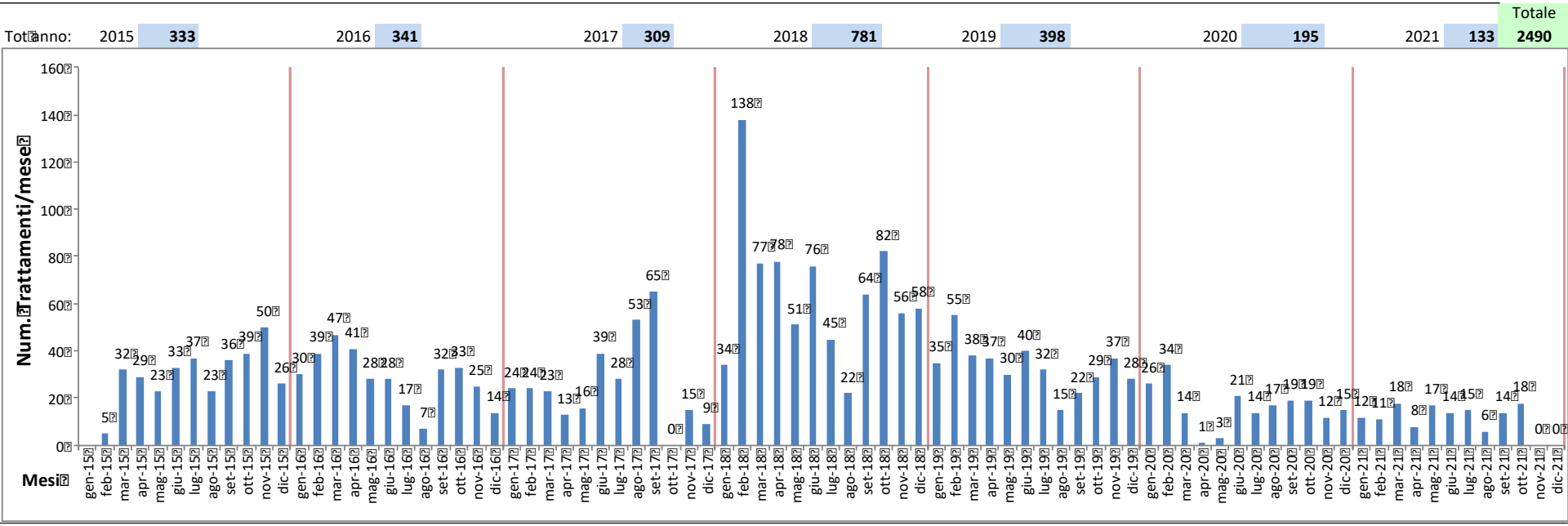
- **identify infrequent HCV subtypes** not detected by the line probe assay (defined as genotype 1 non-1a/1b, genotype 2 non-2a/2b, genotype 3 non-3a, genotype 4 non-4a/4d, and subtypes of genotypes 5 to 8) **by means of phylogenetic analysis** of the sequences generated
- **characterize the NS5A RAS** profile to identify patients harbouring **viruses inherently resistant to NS5A inhibitors**.

In the absence of clinical trial or real-world data, **patients infected with subtypes 1l, 4r, 3b, 3g, 6u and 6v** and patients infected with other infrequent subtypes harbouring >1 RAS(s) known to confer resistance to NS5A inhibitors **should be treated first-line with the fixed- dose combination of sofosbuvir, velpatasvir and voxilaprevir,** pending data with dual pangenotypic regimens.

Journal of Hepatology **2020** vol. 73 | 1170–1218

UO Epatologia – AOUP
Report of HCV treatments with DAAs

Trattamenti avviati per mese da quando sono disponibili i DAAs (2015)



1 pz africana con genotipo 1 non a/b (relapser)
2 pz nord-africano con genotipo 4 non a/d (SVR)
1 pz asiatica (adottata) con genotipo 6 (SVR)

Vironet C – Italian Network for Viral Resistance in Hepatitis C

Male gender, % (n/N)	73.5 (344/468)
Age, median in years (IQR)	56.0 (51.7-62.3)
Metavir fibrosis stage F0-F1, % (n/N) F2, % (n/N) F3, % (n/N) F4, % (n/N)	 11.6 (45/387) 8.5 (33/387) 8.5 (33/387) 71.3 (276/387)
Liver cirrhosis, % (n/N)	64.6 (277/429)
HBsAg positivity, % (n/N)	6.0 (8/133)
HBcAb positivity, % (n/N)	30.7 (46/150)
HIV coinfection, % (n/N)	10.9 (41/373)
Previous ribavirin use, % (n/N)	23.5 (110/468)
Previous interferon use, % (n/N)	23.5 (109/468)
Previous DAA use, % (n/N)	5.8 (27/468)
HCV genotype 1b, % (n/N) 3a/g/h/k, % (n/N) 1a, % (n/N) 4a/d/n/o/r/v, % (n/N) 2a/c, % (n/N)	 32.9 (154/468) 28.0 (131/468) 23.3 (109/468) 9.6 (45/468) 6.2 (29/468)
HCVRNA log10 baseline, median (IQR)	6.14 (5.7-6.50)
Calendar genotype year, median (IQR)	2016 (2015-2017)

B. Rossetti, L. Paglicci, V.C. Di Maio, et al.
Le Infezioni in Medicina, n. 2 , 242-251, 2021

RARE HCV GENOTYPES: PREVALENCE AND RESISTANCE-ASSOCIATED SUBSTITUTIONS IN DAA-NAÏVE AND DAA-EXPERIENCED PATIENTS

The European Resistance Database contains samples from 7300 patients, 4499 of whom were DAA-naive and 1258 had failed to an IFN-free DAA

This study investigated the prevalence of rare HCV geno- and subtypes and RASs in patients among European DAA-naive and DAA-failure patients.

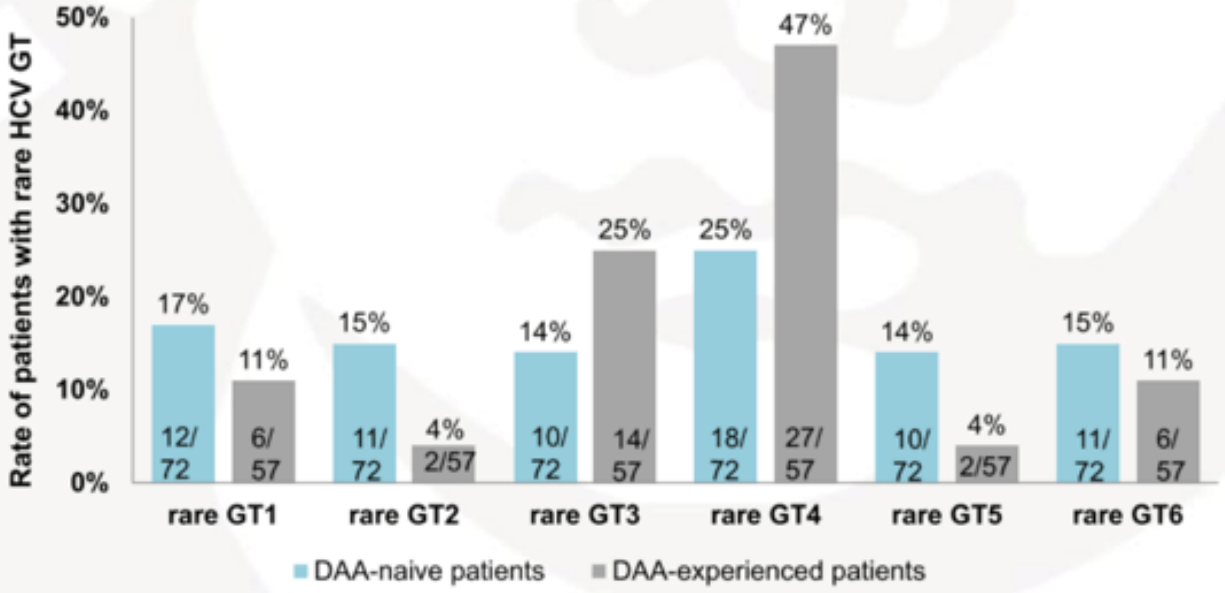


Figure 1: Prevalence of rare HCV GT in DAA-naive and –experienced patients.

Dietz. J et al The Liver Meeting Digital Experience

AASLD, November 13 - 16 - 2020

RARE HCV GENOTYPES: PREVALENCE AND RESISTANCE-ASSOCIATED SUBSTITUTIONS IN DAA-NAÏVE AND DAA-EXPERIENCED PATIENTS

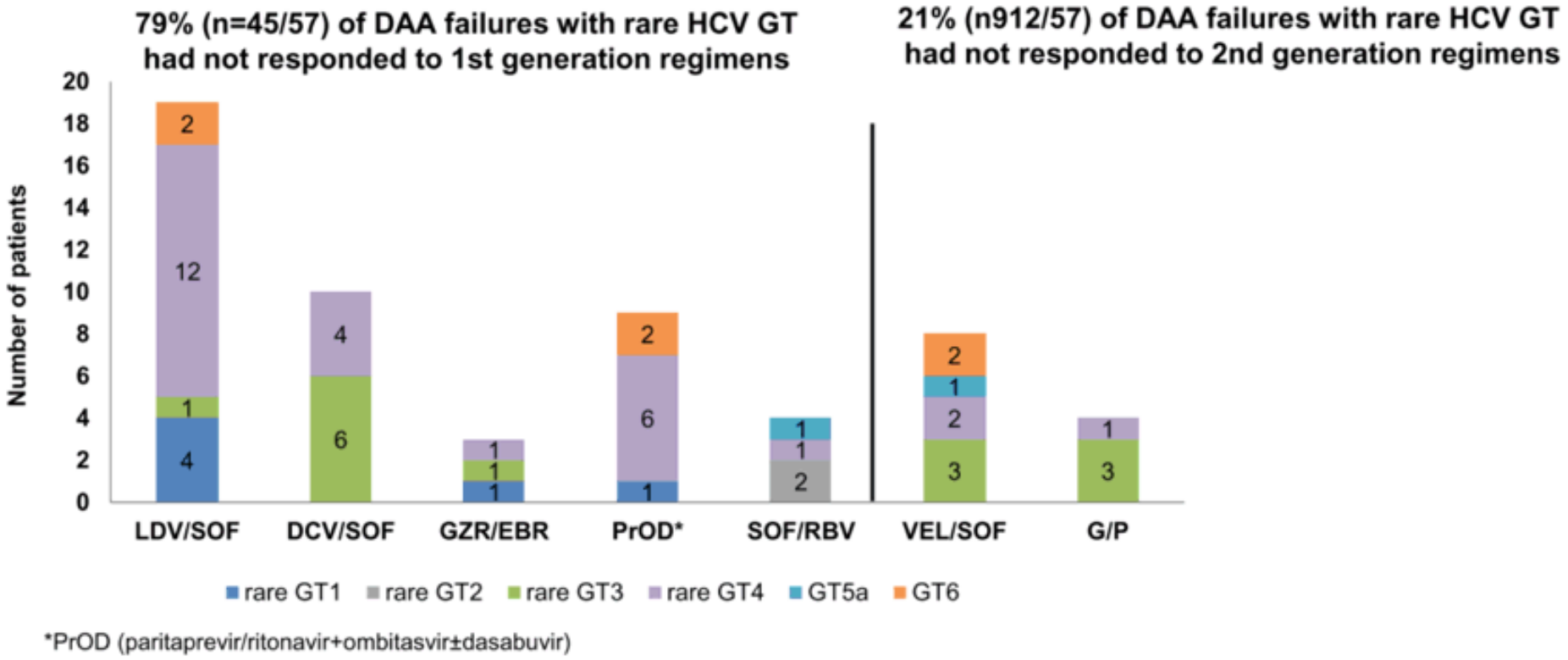


Figure 3: Distribution of rare HCV GT among patients with failure to first versus second generation DAAs.

Dietz. J et al The Liver Meeting Digital Experience

AASLD, November 13 - 16 - 2020

Conclusions

- Despite failures to pangenotypic DAAs is infrequent (<2% in our Centre) the management of Re-treatment may be difficult
- To achieve an accurate evaluation of the reasons behind failure requires sequencing of the resistant strain for Genotyping and RAS
- Management of retreatment in RAS associated failures should be done in experienced Centres

Hepatology Unit
University Hospital of Pisa, Italy

Barbara Coco
Piero Colombatto
Filippo Oliveri
Veronica Romagnoli
Antonio Salvati
Gabriele Ricco
Lidia Surace
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
Andrea Maggi

Biologists

Daniela Cavallone
Tommaso Prescimone

Ferruccio Bonino
IBB CNR