PITER

Piattaforma Italiana per lo studio delle Terapie delle Epatiti virali

SIMIT

Società Italiana di Malattie Infettive e Tropicali

2° THE PITER MEETING

Uno strumento per produrre evidenze *"real-life"* nell'ambito delle epatiti virali croniche in Italia

Modalità Mista: RES - WEBINAR
Venerdì 15 ottobre 2021
HOTEL MEDITERRANEO - ROMA

L'Eliminazione di HCV e la Sindrome Crioglobulinemica

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Centro di Ricerca ed Innovazione Aziendale CRIA-MASVE AOU Careggi

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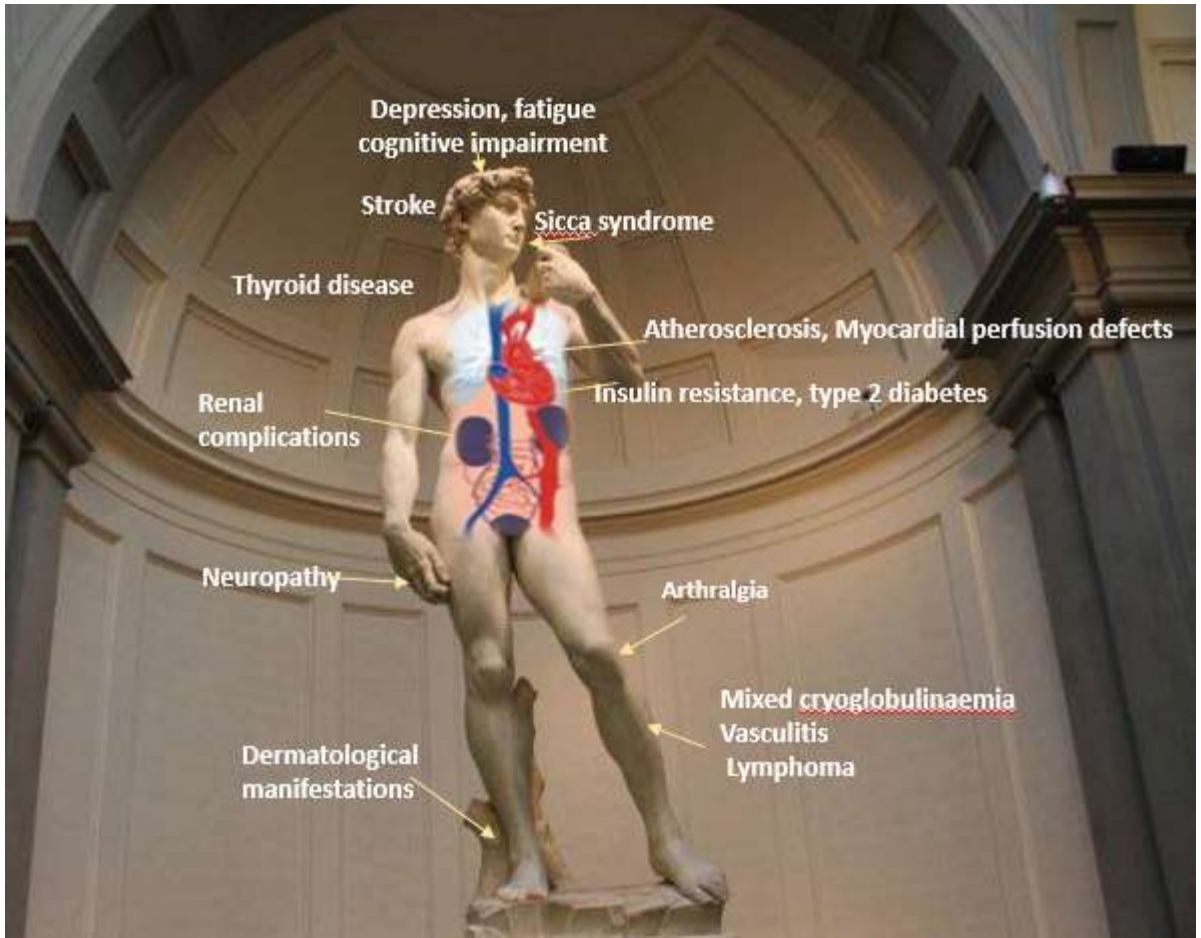
- HCV infection is a **systemic disease** which negatively affects clinical, economic, and PROs
- The hepatic and non-hepatic consequences of HCV infection are responsible for a tremendous burden on patients and society= **It is necessary to emphasize the multi-faceted nature of HCV infection, its impact on clinical, economic, and PROs and the need for an approach to meet the goals of eliminating HCV by 2030**

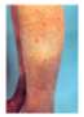


Mixed Cryoglobulinemia

- MC is the most frequent **HCV-EHD**
- **Autoimmune/lymphoproliferative disorder** more frequently observed in **woman** and in **advanced age**
- **Cryoglobulins (CGs)** are immune complexes that precipitate from serum under laboratory conditions of cold=
- HCV induces **monoclonal expansion of B cells producing RF** that forms these cryoprecipitable immune complexes
- 5-10% of patients develp **B-cell NHL** over time
- CGS can cause **systemic vasculitis in the small/medium-sized vessels** leading to symptoms: **cryoglobulinemic vasculitis (CV** or **MCS)**
- Diagnosis of MCS/CV should be performed according to well defined criteria including the combination of symptoms and laboratory data

Mixed cryoglobulinaemia vasculitis

Clinical	Serological
• Purpura	• Mixed cryoglobulins
• Weakness	• RF+
• Arthralgias	• Low C4
• Liver involvement	**Pathological**
• Renal involvement	• Leukocytoclastic vasculitis
• Skin involvement	• B cell expansion
• Peripheral neuropathy	



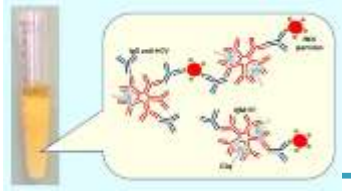
Purpura >90%

Neuropathy ≈80%

Glomerulonephritis ≈30%

Skin ulcers ≈15%

Most (70–90%) MC patients are HCV+ and HCV-patients are CGs+ (40–60%), while 5–30% of CGs+ have symptomatic MC



Mixed Crioglobulinemia

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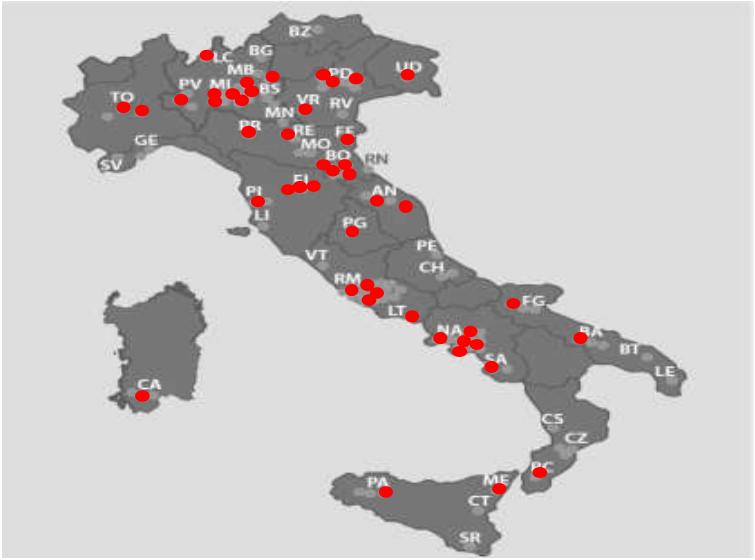
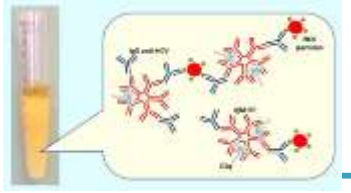
To the best of our knowledge, the present study, is the **first, multicentric nationwide, Real Practice analysis** conducted on HCV-chronically infected patients, **prospectively including patients with MC,** with and without symptoms





Mixed Cryoglobulinemia

The presence of MC was not tested in >70% of cases in spite of its clinical, prognostic and therapeutical importance, and the diagnostic approach was variable (only in case of clinical suspicion in some centres)
Kondili et al, Liver International 2017

.Total PITER HCV+ patients: 11.871

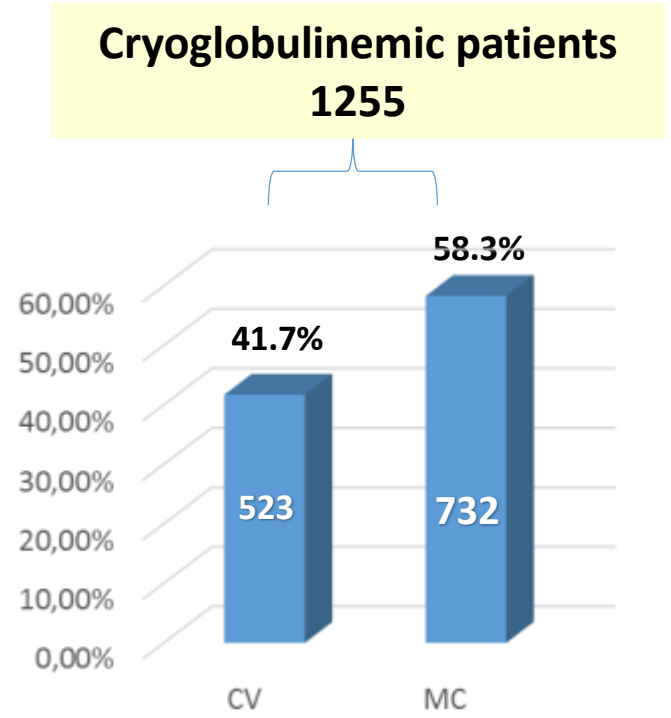
.HCV+ patients evaluated: 3390 (28,5%)

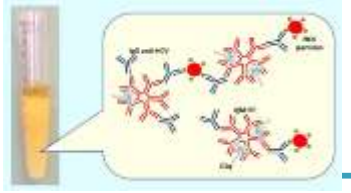
.Cryoglobulinemic patients: 1255 (37%)

. with symptoms: CV 523/1255 (41,7%)

. asymptomatic: MC 732/1255 (58,3%)

- **Type III in 33%**
- **Type II in 67%**





CV Symptoms at enrollment

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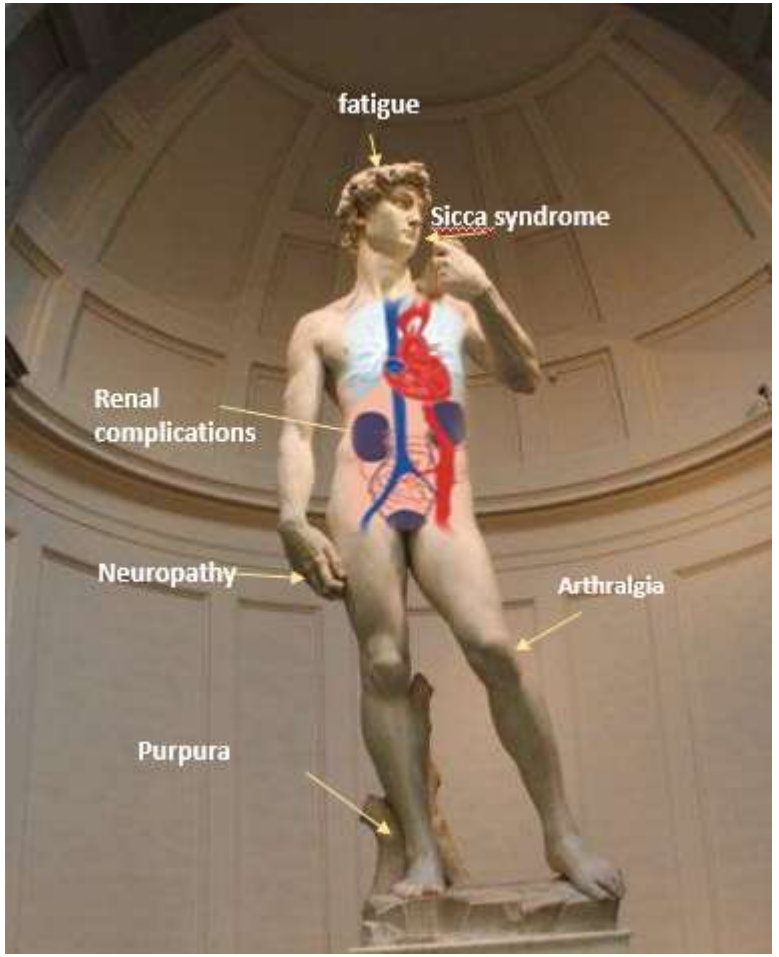
- PURPURA
- ASTHENIA
- ARTHRALGIA

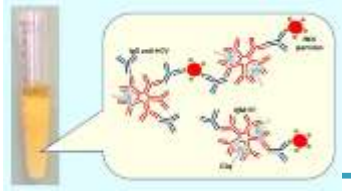
- NEUROPATHY
- SICCA SYNDROME(xerostomia/xerophthalmia)

} In 69% to 95% of patients

- RENAL INVOLVEMENT

(from proteinuria and hematuria to a frank reduction in GFR } In 12.2% patients





The Study Flow Chart

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1255 patients with Hepatitis C virus infection and Mixed Cryoglobuliemia (MC)

523 patients with Cryoglobulinemic Vasculitis

732 MC patients without symptoms

423 patients with available data during Follow-up after Sustained Virological Response (SVR)

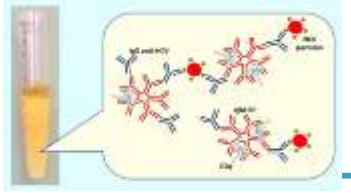
655 patients achieved SVR and have available data

309 patients with clinical response evaluable at the end of DAA treatment

288 patients with at least 1 Follow-up point after first clinical response

369 patients evaluated for predictors of a full complete response (FCR)

DAA treatment no.1: SVR 1.204 (96%);
+DAA treatment no. 2 SVR: total SVR no. 1.221 (32 lost of FU) (99.8%)



DEMOGRAPHIC AND CLINICAL CHARACTERISTICS
(SVR PATIENTS)

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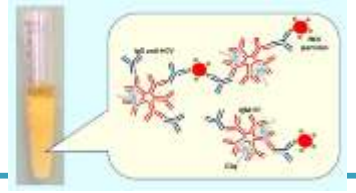
NEW

	CV N=423	MC N=655	P value
Age (years) (mean, std)	62.7 ± 12.1	62.2 ± 12.6	0.444
Sex (%, no./Pts)			
Male	35.9% (152/ 423)	47.3% (310/ 655)	<0.001
Female	64.1% (271/ 423)	52.7% (345/ 655)	
Fibrosis distribution (%, no./Pts)			0.013
F0-F1	42.7% (167/ 390)	33.9% (204/ 602)	
F2	10.5% (41/ 390)	9.1% (55/ 602)	
F3	9.2% (36/ 390)	9.8% (59/ 602)	
F4-Cirrhosis	37.4% (146/ 390)	47.2% (284/ 602)	



SVR CV Patients: Clinical CV Response EOT

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1255 HCV cryoglobulinemic patients treated with DAAs

732 Patients without symptoms (MC)

523 patients with Cryoglobulinemic Vasculitis (cv)

423 patients with available clinical data in different points of Follow-up after Sustained Virological Response (SVR)

EOT Response

399 pts.

PR: 28%

CR: 17%

FCR: 12%

Clinical Response: 57%

NR: 43%

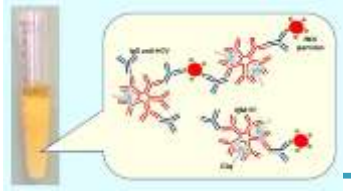
CV Clinical Response: Classification Criteria

Partial response (PR)
Improvement of more than 50% of symptoms

Complete response (CR)
Improvement of all Symptoms

Full complete response (FCR)
Disappearance of all Symptoms
(*restitutio ad integrum*)

Non-response (NR)
Remaining conditions



Curve Describing the First Time in which a Clinical Response was observed (either CR, FCR or PR)

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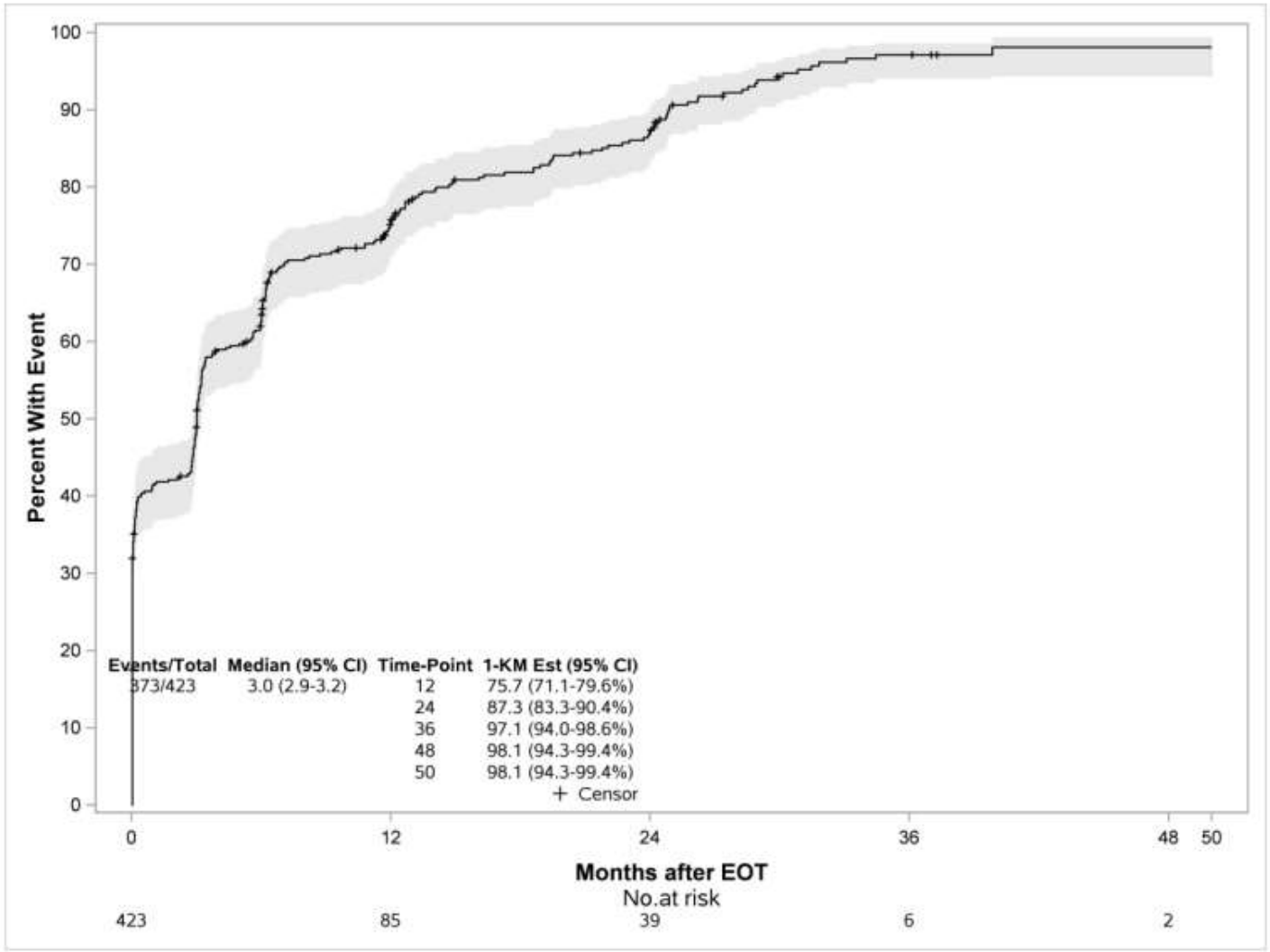
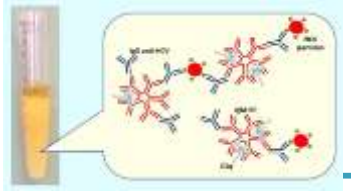


- CV patients often did not show a clinical improvement at the EOT, but later, with the first amelioration starting after about 3 months (m. 9 months) and about 50% of patients experienced a further improvement after 1 and 2 years
- FCR (complete disappearance of all the manifestations) was reached, during at least one point of the FU, by 164 (38.8%) patients



Curve of MCS clinical deterioration or relapse (FU after the first response)

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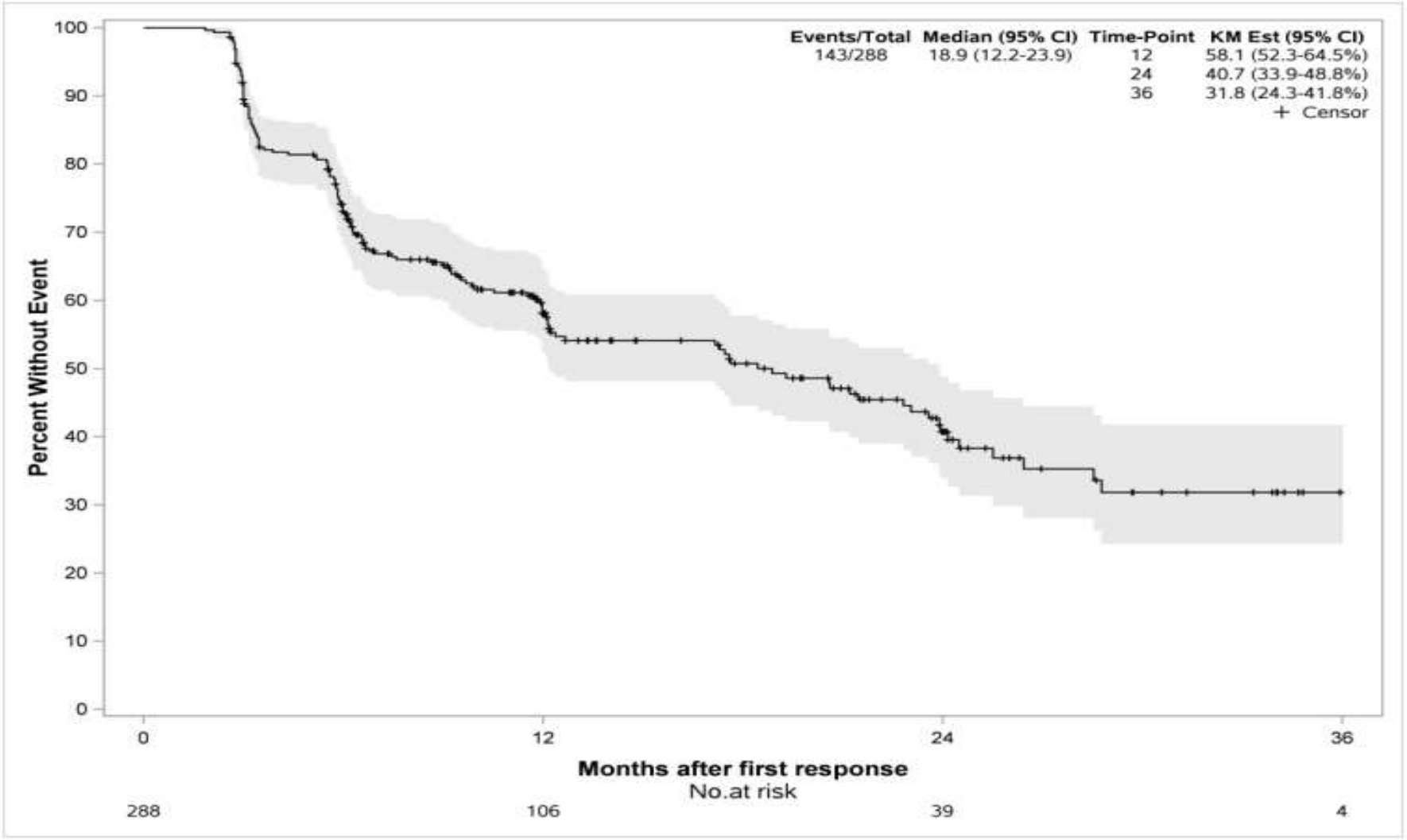
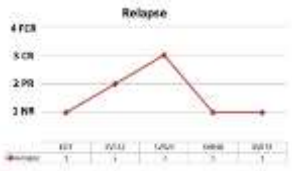
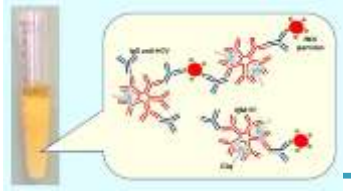




- Clinical deterioration in the initial response or relapse was recorded in 143 patients (49.6%) (m. 19 months)
- Clinical relapse was observed in 11% of pts. and was transient in 66.7% of cases



Symptoms More Frequently Persisting in SVR CV (FU= 2 yrs)

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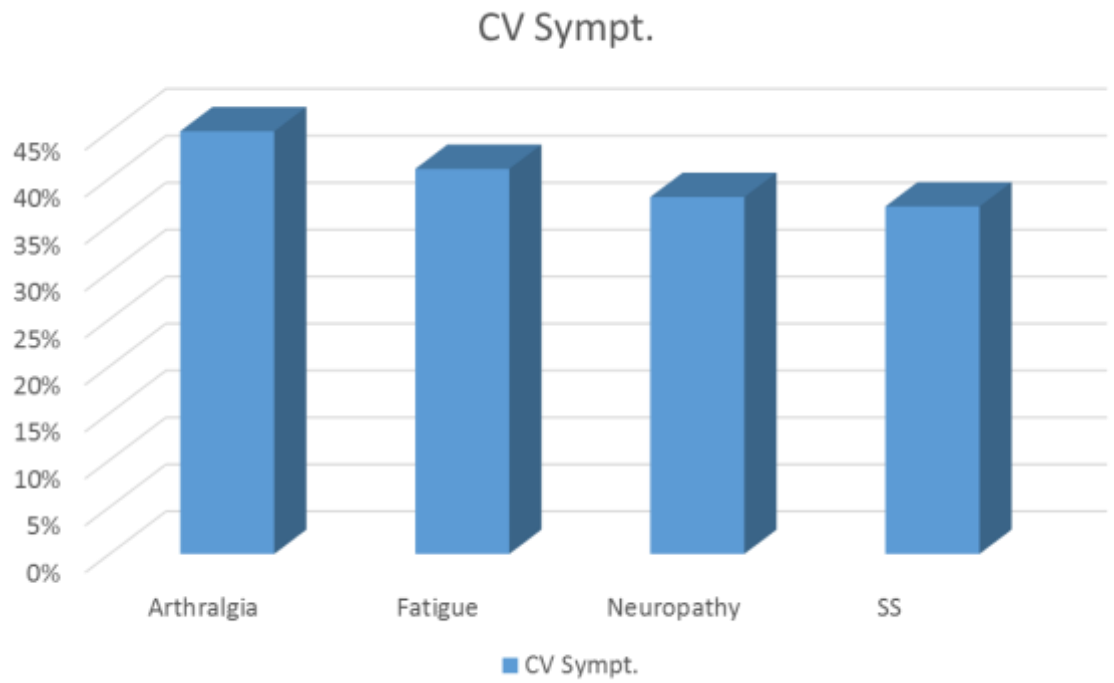

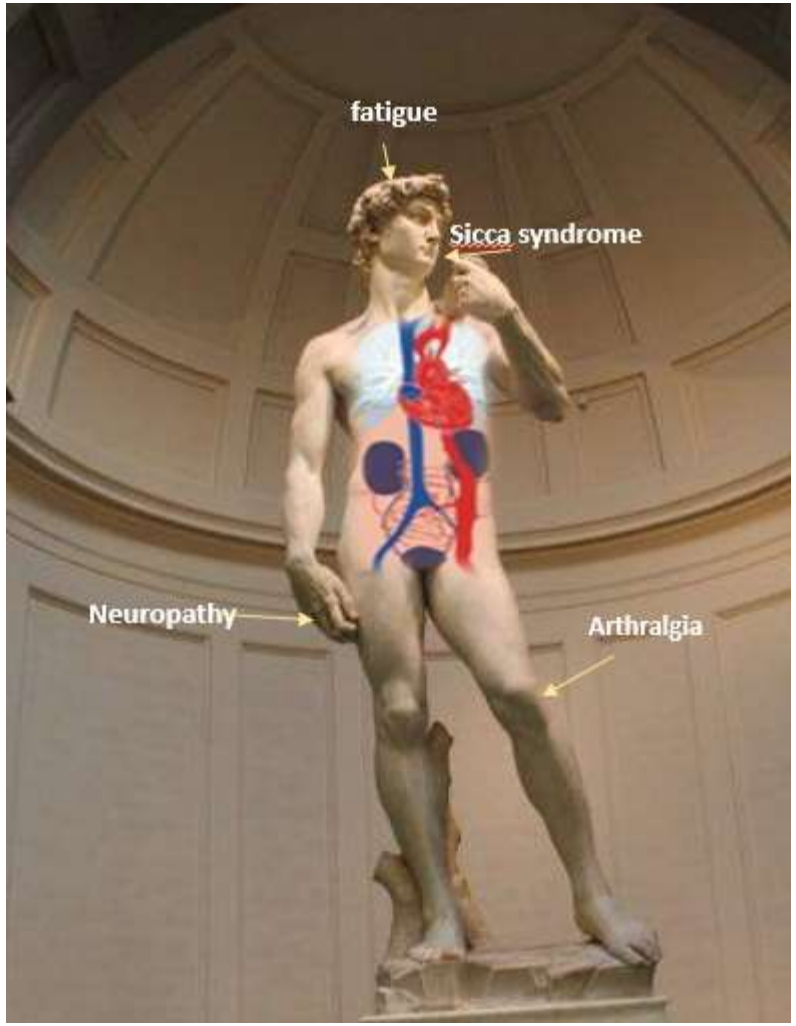

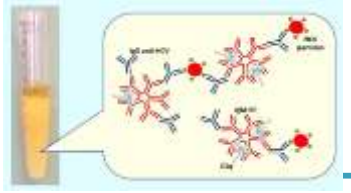

Cryocrit, RF and C4 Value Kinetics Before and After DAAs*

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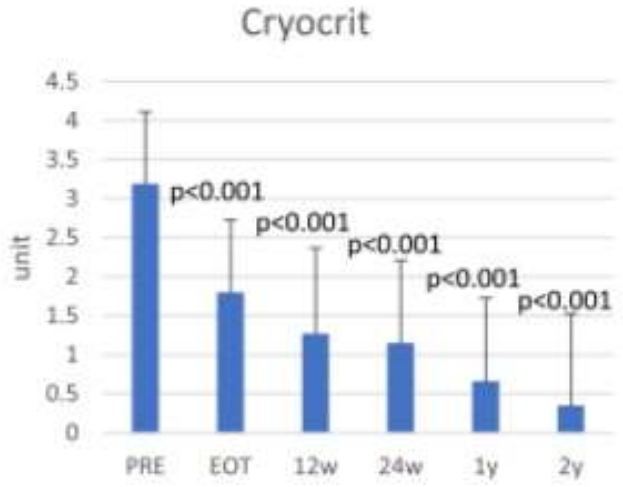
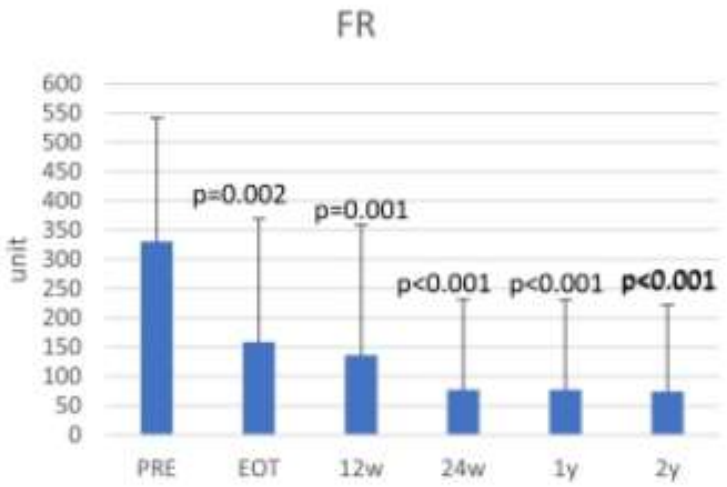
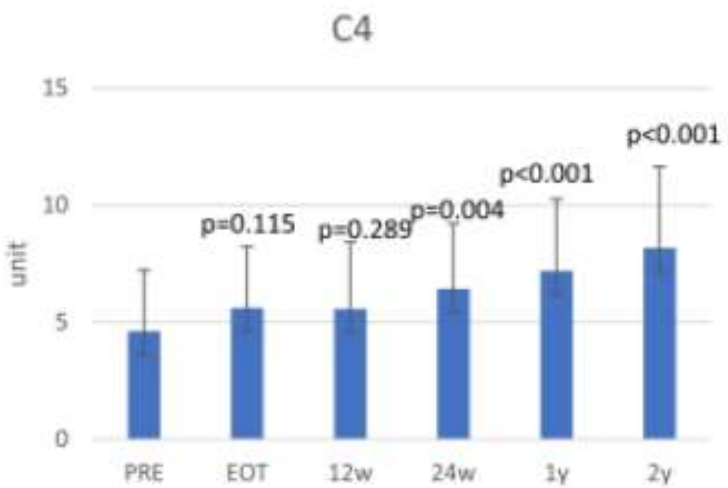
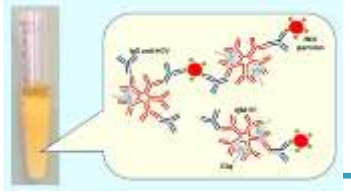






*Estimated means by mixed model (cryocrit n=144, FR n=42, C4 n=22) with at least a 1-year FU, cryocrit data at the EOT and at least one other value (p value compared with baseline adjusted by Dunnet correction)



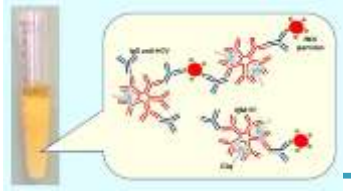
Take-Home Messages

In symptomatic patients (CV), a special attention was dedicated to the analysis of the clinical response over time following SVR, with the distinction of 3 degrees of response, and the evaluation of the kinetics of clinical improvement/deterioration in different FU points=

- Clinical response to any degree (FCR, CR and PR) was scored in 88% of pts. at one time of FU and a FCR (restitution ad integrum) in 164 (38.8%; persistent only in 21.5%)
- A clinical relapse was observed in 11% of FCRs but was transient in 66.7% of cases
- NR was observed in 12% of patients at the end of 2-3 yrs. FU
- The clinical manifestation pattern may change over and reappear

Overall, this data implies that, after viral eradication, the persistence or recurrence of some or most pretreatment symptoms should be considered as not infrequent

NEED FOR PROGNOSTIC FACTORS!



Factors associated with CV Response at EOT

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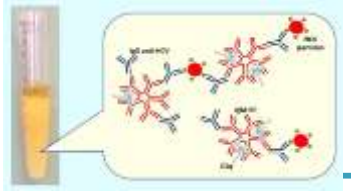
		Univariate analysis* N=309		Multivariate analysis N=309	
		OR (95% CI)	P value	OR (95% CI)	P value
Age (years)		1.02 (1.00-1.04)	0.052	1.02 (1.00-1.04)	0.039
Sex	Male	1			
	Female	0.90 (0.56-1.43)	0.646		
Purpura	No	1			
	Yes	1.01 (0.59-1.75)	0.964		
Asthenia	No	1			
	Yes	1.33 (0.77-2.30)	0.308		
Arthralgia	No	1			
	Yes	1.05 (0.64-1.70)	0.853		
Neuropathy	No	1			
	Yes	1.15 (0.73-1.81)	0.557		
Renal involvement	No	1			
	Yes	1.70 (0.92-3.16)	0.093	1.79 (0.96-3.36)	0.058

		Univariate analysis* N=309		Multivariate analysis N=309	
		OR (95% CI)	P value	OR (95% CI)	P value
Xerostomia/Xerophthalmia	No	1			
	Yes	1.27 (0.80-2.01)	0.308		
Raynaud	No	1			
	Yes	0.93 (0.53-1.65)	0.811		
Ulcer	No	1			
	Yes	0.88 (0.24-3.18)	0.843		
Pretreatment Cryocrit		1.01 (0.96-1.06)	0.68		
Pretreatment Rheumatoid Factor		1.00 (1.00-1.00)	0.559		
Pretreatment C4		1.03 (0.88-1.21)	0.694		
Rituximab	Yes				
	No	1.65 (0.69-3.93)	0.262		



Factors associated with FCR (*restitution ad integrum*) without clinical deterioration or relapse

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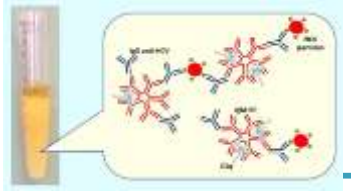
		Univariate analysis N=369		Multivariate analysis N=278	
Variable		HR (CI 95%)	p value	HR (CI 95%)	p value
Age (years)		0.96 (0.94-0.98)	<.0001	0.96 (0.94-0.99)	0.002
Sex	Male	1			
	Female	0.42 (0.25-0.69)	0.001		
Purpura	No	1			
	Yes	0.32 (0.14-0.74)	0.008		
Asthenia	No	1			
	Yes	0.41 (0.25-0.68)	0.001	0.53 (0.26-1.10)	0.088
Arthralgia	No	1			
	Yes	0.44 (0.27-0.72)	0.001		
Neuropathy	No	1			
	Yes	0.4 (0.23-0.69)	0.001	0.4 (0.18-0.87)	0.022

		Univariate analysis N=369		Multivariate analysis N=278	
Variable		HR (CI 95%)	p value	HR (CI 95%)	p value
Renal involvement	No	1			
	Yes	0.75 (0.37-1.53)	0.434		
Xerostomia/Xerophthalmia	No	1			
	Yes	0.6 (0.36-1.00)	0.051		
Raynaud	No	1			
	Yes	0.54 (0.25-1.19)	0.128		
Ulcers		1.04 (0.25-4.24)	0.960		
Pretreatment Cryocrit		0.81 (0.67-0.99)	0.041	0.81 (0.66-0.98)	0.03
Pretreatment		1 (0.99-1)	0.202		
Rheumatoid Factor					
Pretreatment C4		1.2 (0.97-1.48)	0.090		



Factors Associated with Clinical Deterioration/Relapse After Clinical Response in CV Patients* (no. 288)

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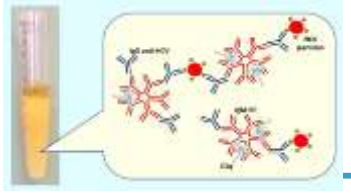
		Univariate analysis N=288		Multivariate analysis N=94	
Variable		HR (CI 95%)	p value	HR (CI 95%)	p value
Age (years)		1.01 (1.00-1.02)	0.178		
Sex	Male	1			
	Female	1.01 (0.71-1.44)	0.937		
Purpura	No	1			
	Yes	0.67 (0.45-1.01)	0.055	0.75 (0.41-1.37)	0.349
Asthenia	No	1			
	Yes	1.08 (0.71-1.64)	0.730		
Arthralgia	No	1			
	Yes	0.89 (0.63-1.26)	0.507		
Neuropathy	No	1			
	Yes	1.34 (0.95-1.88)	0.092	1.38 (0.74-2.56)	0.313
Renal involvement	No	1			
	Yes	0.91 (0.58-1.41)	0.672		

	Univariate analysis N=288		Multivariate analysis N=94	
Variable	HR (CI 95%)	p value	HR (CI 95%)	p value
Xerostomia Xerophthalmia	1			
	.41 (1.01-1.99)	0.047	0.84 (0.52-1.70)	0.841
Raynaud	1			
	.87 (0.57-1.32)	0.512		
Ulcer	1			
	.43 (0.11-1.72)	0.232		
Pretreatment Cryocrit	.99 (0.94-1.03)	0.514		
Pretreatment Rheumatoid Factor	1 (1.00-1.001)	0.017	1 (1.00-1.001)	0.021
Pretreatment C4	.99 (0.89-1.09)	0.786		
Rituximab	1			
	.65 (0.29-1.48)	0.303		



Pretreatment RF values in CV patients without (0) or with clinical relapse (1) after DAAs

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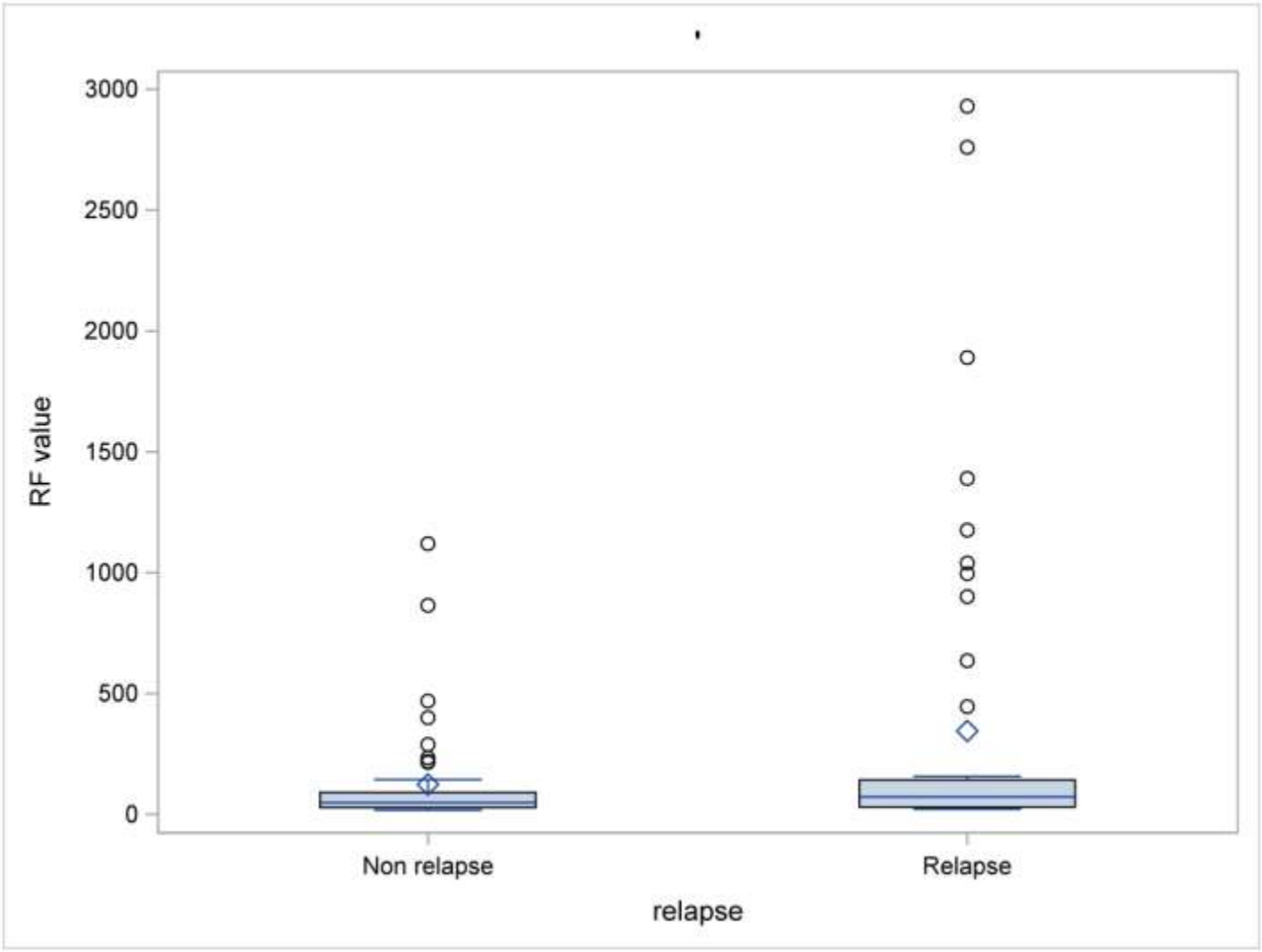

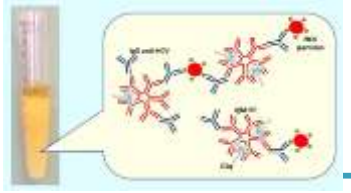

CONCLUSIONS

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In conclusion, the prospective analysis of DAA-treated cryoglobulinemic patients enrolled consecutively in such a nationwide cohort, was able to:

- confirm that after SVR most CV patients reach a clinical response that increases over time
- clearly show that the clinical response frequently fluctuates. Indeed, the clinical manifestation pattern may change over and reappear, either persistently or transiently, strongly suggesting a careful patient assessment and post-HCV eradication F-U
- In this light, the accurate evaluation of both clinical and laboratory prognostic indexes that emerged from the present study (possibly in combination with markers of clonal B cell expansion persistence) will consistently aid in predicting different clinical evolutions

FURTHER ISSUES

It is conceivable that an accurate FU should also include cryoglobulinemic patients without CV symptoms before anti-HCV therapy (CM patients). Further dedicated studies would be advantageous to better clarify this point !

Submitted Manuscript

A prospective DAA Effectiveness and Relapse Risk analysis in HCV-Mixed Cryoglobulinemia by the multicentric PITER Cohort

L A.Kondili, M Monti, M G Quaranta, L Gragnani, V Panetta, G Brancaccio, C Mazzaro, M Persico, M Masarone, I Gentile, P Andreone, S Madonia, E Biliotti, R Filomia, M Puoti, ALFracanzani, D Laccabue, D Ieluzzi, C Coppola, MG Rumi, A Benedetti, G Verucchi, B Coco, L Chemello, A Iannone, A Ciancio, FP Russo, F Barbaro, F Morisco, L Chessa, M Massari, P Blanc, AL Zignego

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