Long term effectiveness of DAA therapy in patients with chronic HCV and Mixed Cryoglobulinemic Syndrome

L.A. Kondili[1], M. Monti[2], G. Ferrante[1], M.G. Quaranta[1], F. Madia[2], M. Vinci[3], G. Borgia[4], G. Brancaccio[5], B. Coco[6], M. Margotti[7], L. Chemello[8], A. Ciancio[9], M.G. Rumi[10], M. Puoti[3], S. Madonia[11], A.L. Fracanzani[12], M. Persico[13], R. Filomia[14], E. Biliotti[15], A. Benedetti[16], E. Negri[17], D. Ieluzzi[18], C. Coppola[19], T.A. Santantonio[20], A.L. Zignego[2] and PITER Collaborating Group

[1]Istituto Superiore Di Sanità, Rome, Italy, [2] University of Florence, Italy, [3]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy, [4]Federico II University, Naples, Italy [5]University of Campania L. Vanvitelli, Naples, Italy, [6]University Hospital of Pisa, Italy, [7]University of Bologna, Italy, [8]University Hospital of Padua, Italy, [9]Molinette Hospital, Turin, Italy, [10]San Giuseppe Hospital, Milan, Italy, [11]Villa Sofia-Cervello Hospital, Palermo, Italy, [12]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, [13]University of Salerno, Italy, [14]University Hospital of Messina, Italy, [15]Umberto I Hospital, Rome, Italy, [16]University of Ancona, Italy, [17]University of Parma, Italy, [18]University Hospital Verona, Italy, [19]Gragnano Hospital, Naples, Italy, [20]Ospedali Riuniti, Foggia, Italy

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INTRODUCTION

Infection by Hepatitis C virus (HCV) is a major cause of liver-related morbidity and responsible of B cell lymphoproliferative disorders such as mixed cryoglobulinemia and non-Hodgkin lymphoma.

Mixed cryoglobulins consist of polyclonal IgG and either monoclonal or polyclonal IgM with rheumatoid factor activity. HCV infection is highly prevalent in patients with Mixed Crioglobulinemia Syndrome (MCS) (80%-90% of MC patients are HCV-positive) and mixed cryoglobulins are present in 25–45% of patients with HCV.

Aetiological therapy is the first-line option in HCV-MCS patients and in the majority of cases, viral eradication leads to clinical remission. Patients with MCS have high rates of clinical remission after treatment with direct-acting antivirals (DAAs), but circulating cryoglobulins persist, and vascular disorders reappear in some patients shortly after DAA treatment ends.[1-3]

AIM

To evaluate the medium and long term clinical outcomes of MCS following the successful viral eradication by DAA treatment we used data from the prospective multicentric PITER cohort which have a dedicated electronic Case Report Form (eCRF) to prospectively collect clinical data of consecutively enrolled patients.[4]

METHODS

For the present prospective multicentric real life study, we evaluated data from patients who were tested for cryoglobulinemia and resulted positive at enrollment. Patients with cryoglobulins and symptoms before antiviral treatment were prospectively followed up during and after treatment collecting clinical data in a dedicated eCRF specific for the Cryoglobulinemic Syndrome. Patients with Symptomatic MC and treated with a DAA IFN-free regimen in the period from 2014 to 2018 who had at least one available follow-up point following the SVR12 were included in this study.

Specific informations regarding typical symptoms of MCS and laboratory finding as cryocrit levels, Reumathoid Factor, Complement C4 values were recorded in the baseline and during follow-up.

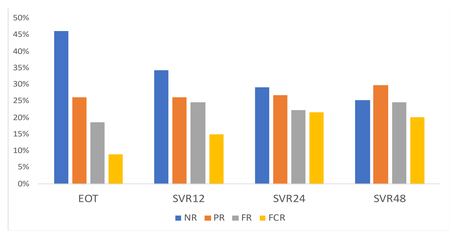
Statistical analysis. Patient's characteristics were reported as median and range or as proportions for continuous and categorical variables, respectively. Variables independently associated to a Non Clinical response and Relapse were evaluated by Cox Regression analysis. Kaplan Mayer survival analysis were used to evaluate different time of Clinical response achievement and its deterioration during the follow-up.

The Mann-Whitney rank-sum test was used for continuous variables to assess differences between distribution, and the Chi-squared test was used for comparisons of proportions. A p value<0.05 was considered as significant.

RESULTS

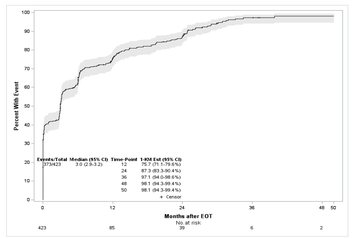
Of the 458 patients who had a Cryoglobulinemic Syndrome (mean age: 63; SD 11 years; 64% female; 33% with liver cirrhosis) and were treated with DAAs from 2014-2018, the SVR was 96%.
At the end of antiviral treatment the clinical responses were available in different follow-up points for 423 patients (Figure 1).
Clinical responses were defined as follows: Full Complete Response (disappearance of all symptoms); Complete Response or Full Response (improvement of all symptoms); Partial Response (improvement in ≥50% of symptoms); Non Clinical Response (improvement in less than 50% or persistence of all symptoms).
During the available follow-up after the SVR there is a Clinical response (Partial or Complete or Full Complete Response) in 373 (88%) of 423 patients (mean: 561 days SD 308); at 12 months follow-up after SVR12 the clinical response rate was 76%.

Figure 1. Clinical response by different time points following DAA therapy



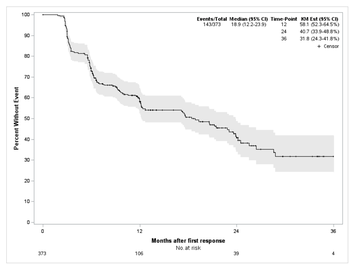
NR= Non Response; PR=Partial Response; FR=Full Response; FCR= Full Complete Response

Figure 2. Time of a First Clinical Response



Median time of a clinical response diagnosis following the SVR12 was 3 months.

Figure 3. Appearance of deterioration following a Clinical Response



Among the 150 patients in whom four points (every 6 months) of clinical evaluation were available, fluctuations in the clinical response (from Non Response to Full Complete Response and vice versa in the different time points) were observed in 72% of patients.

Of 373 patients who had achieved a Clinical Response, 143 (38%) had at least a deterioration compared to a previous clinical status. The median time free of a deterioration of the previous clinical status was 19 months. A new appearance of symptoms in responder patients (Clinical Relapse) was observed in 15 (3.7%) patients at the end of follow-up. Presence of positive cryoglobulins following the SVR was the only independent predictor of Clinical Relapse (HR: 28; 95% CI 3-249).

After SVR a complete disappearance of cryoglobulins was achieved in 73%, in 19% a significant reduction of cryocrit was observed, in the remaining 8% of patients cryocrit values did not change significantly.

Table 1. Cryocrit values in different follow-up points

Visit	Cryocrit Mean	CI95%	P value (compared with baseline)
EOT	1.56	1.31 - 1.81	
12w	1.09	0.81 - 1.38	0.0008
24w	1.02	0.75 - 1.30	<0.0001
1y	0.58	0.31 - 0.86	<0.0001
2y	0.31	0.00 - 0.61	<0.0001
3y	0.32	-0.17 - 0.81	<0.0001

Mixed model pt=144 with at least 1 year of follow-up, cryocrit data at EOT and at least on other value (p value adjust by dunnet correction)

Table 2. Reumatoid Factor Values in different follow-up points

Visit	RF Mean	CI95%	P value (compared to baseline)
EOT	153.7	91.67 - 215.7	
12w	130.4	66.26 - 194.5	0.7969
24w	88.25	21.37 - 155.1	0.0388
1y	87.05	20.06 - 154.0	0.0347
2y	94.95	22.41 - 167.5	0.1663
3y	90.80	-1.16 - 182.8	0.4298

Mixed model pt=42 with at least 1 year of follow-up, RF data at EOT and at least on other value (p value adjust by dunnet correction)

Table 3. Complement C4 Values in different follow-up point

Visit	C4 Mean	CI95%	P value (compared with baseline)
EOT	6.41	4.94 - 7.88	
12w	6.14	4.57 - 7.72	0.9818
24w	6.89	5.33 - 8.44	0.8062
1y	7.49	5.85 - 9.13	0.1982
2y	8.91	7.10 - 10.72	0.0020
3y	7.84	5.94 - 9.74	0.2057

Mixed model pt=22 with at least 1 year of follow-up, C4 data at EOT and at least on other value (p value adjust by dunnet correction)

Table 4. Variables independently associated to Non Clinical Response by Cox regression analysis

Variables	HR	Std. Err.	95% CI	p-value
Age	1.02	0.11	1.00 – 1.04	0.037
Gender (female vs male)	1.14	0.30	0.68 – 1.92	0.614
Arthralgia	1.31	0.36	0.77 – 2.24	0.307
Purpura	0.33	0.11	0.17 – 0.64	0.001
Asthenia	0.85	0.24	0.49 – 1.47	0.563
Raynound Phenomenon	0.81	0.27	0.42 – 1.57	0.532
Sicca Syndrome	1.23	0.32	0.75 – 2.05	0.405
Peripheral Neuropathy	1.13	0.28	0.70 – 1.82	0.624
Renal Involvment	2.95	0.90	1.62 – 5.38	0.001
Lymphoma	1.32	0.80	0.40 – 4.35	0.648

CONCLUSION

DAA therapy induces a high virologic and clinical response. However the rate of virological response do not correspond to the rate of clinical response. An increase rate of clinical response was observed during the follow-up indicating that following a viral clearance extrahepatic manifestations of Crioglobulinemic Syndrome and the respective biochemical findings tend to improve in 76% of treated patients. However, deterioration and/or Clinical Relapse were also observed in part of patients who have previously had a clinical response. It is important to ensure adequate follow-up for HCV-infected patients with Crioglobulinemic Syndrome, to rule out inadequate response or relapse. The longterm follow-up of patients with HCV cure and positive circulating cryoglobulins is mandatory, also considering the risk of developing non-Hodgkin lymphoma.

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DISCLOSURES

Nothing to disclosure

Contact information

Loreta Kondili MD, PhD. *Center for Global Health, Istituto Superiore di Sanità, Rome-Italy. Email:* loreta.kondili@iss.it

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