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Original Article

ORIGINAL ARTICLE

Direct-acting antiviral therapy improves kidney survival in hepatitis C virus-associated cryoglobulinaemia: the RENALCRYOGLOBULINEMIC study

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ABSTRACT

Background. Direct-acting antiviral agents (DAAs) have shown high rates of sustained virological response in chronic hepatitis C virus (HCV) infection. However, the influence of DAAs on the course of kidney involvement in HCV-associated mixed cryoglobulinaemia (HCV-MC) has been little studied. The aim of this study was to analyse the effects of antiviral treatment on kidney prognosis and evolution in patients diagnosed with HCV-MC.

Methods. The RENALCRYOGLOBULINEMIC study is an observational multicentre cohort study of 139 patients with HCV-MC from 14 Spanish centres. Clinical and laboratory parameters were measured before and after antiviral treatment. Primary endpoints were kidney survival and mortality after HCV-MC diagnosis. Secondary endpoints were clinical, immunological and virological responses after antiviral treatment.

Results. Patients were divided into three groups based on the treatment received: treatment with DAAs ($n = 100$) treatment with interferon (IFN) and ribavirin (RBV) ($n = 24$) and no treatment ($n = 15$). Patients were followed up for a median duration of 138 months (interquartile range 70–251. DAA treatment reduced overall mortality {hazard ratio [HR] 0.12 [95% confidence

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interval (CI) 0.04–0.40]; P < 0.001} and improved kidney survival [HR 0.10 (95% CI 0.04–0.33); P < 0.001].

Conclusions. Results from the RENALCRYOGLOBULINEMIC study indicated that DAA treatment in patients with HCV-MC improves kidney survival and reduces mortality.

Keywords: cryoglobulinaemia, direct-acting antiviral agents, hepatitis C virus, membranoproliferative glomerulonephritis

INTRODUCTION

Hepatitis C virus (HCV) infection is associated with numerous extrahepatic manifestations, including kidney disease. Cryoglobulins are detected in up to 50% of patients with chronic HCV at some point during their infection, but only 2–3% will develop vasculitis symptoms, defined as HCV-related mixed cryoglobulinaemia (HCV-MC). HCV-MC reflects the activation of B cells, generating pathogenic immunoglobulins: monoclonal immunoglobulin M (IgM) with rheumatoid factor (RF) activity and polyclonal IgG (type II) or polyclonal IgG and polyclonal IgM (type III) [1, 2]. The most frequent presentations include palpable purpura, arthralgia, weakness, myalgia, polyneuropathy, intestinal ischaemia and cryoglobulinaemic glomerulonephritis. More than half of patients have hypocomplementaemia [3].

Typical kidney manifestations of HCV-MC include hypertension, proteinuria, microscopic haematuria, kidney failure and nephrotic syndrome [4]. The gold standard for diagnosis of HCV-MC is kidney biopsy. Light microscopy shows membranoproliferative glomerulonephritis in most cases (60–80%), due to deposition of mesangial and subendothelial immune complexes, with thickening of the glomerular basement membrane and a 'double-contoured' appearance [5]. Immunofluorescence examination reveals characteristic mesangial and capillary wall deposition of IgM, IgG and complement component 3 (C3). Subendothelial deposits can be observed on electron microscopy. Kidney involvement in patients with HCV-MC has been frequently associated with unfavourable clinical and virological response [6].

Treatment for HCV infection has changed in the past few years with the introduction of direct-acting antiviral agents (DAAs) that have improved sustained virological response (SVR) compared with pegylated interferon–ribavirin (IFN ± RBV) [7–14]. DAAs have yielded high rates of SVR in chronic HCV infection, even in patients with chronic kidney disease (CKD) [15]. However, only limited data on kidney outcomes in HCV-MC patients are available due to the small number of patients included in previous studies.

The aim of this study was to evaluate kidney survival and mortality in patients with HCV-MC treated with DAAs compared with historical controls treated with IFN ± RBV and untreated patients.

MATERIALS AND METHODS

Study design

The RENALCRYOGLOBULINEMIC study is a Spanish observational retrospective multicentre cohort study including 139 patients with HCV-MC from 14 nephrology departments that are part of the Spanish Glomerular Study Group (GLOSEN).

Study population

Inclusion criteria were age >18 years and diagnosis of HCV-MC with or without kidney biopsy. Patients could be treated with DAAs or IFN ± RBV or untreated for HCV. Kidney involvement was defined by the presence of cryoglobulinaemic glomerulonephritis with a membranoproliferative pattern of injury on histological examination of kidney biopsy or by the presence of proteinuria or haematuria or an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 without an alternative cause for CKD in patients without kidney biopsy. Proteinuria was quantified by the urinary protein:creatinine ratio using either spot urine samples or 24-h urine samples when available. The presence of urinary haem was determined by dipstick analysis. HCV cryoglobulinaemia was assessed by serology in terms of cryocrit percentage, serum complement levels (C3 and C4) and RF.

Exclusion criteria were renal replacement therapy (dialysis or kidney transplant) and human immunodeficiency virus infection.

Baseline clinical evaluation included age, gender, hypertension, diabetes, dyslipidaemia, obesity, glomerulonephritis, purpura, arthralgia, skin ulcer, peripheral neuropathy, serum creatinine, eGFR, proteinuria, albuminuria, haematuria, kidney biopsy, cryoglobulinaemia type II or III, cirrhosis, HCV genotype, previous HCV treatment, duration of HCV treatment, virological response, hepatic transplant, HCV RNA level $\log_{10}$, alanine aminotransferase, plasma albumin, cryocrit percentage, C3 and C4 levels, positive RF and treatment received (renin–angiotensin system blockers, plasmapheresis, corticosteroids, rituximab, cyclophosphamide, furosemide).

Study endpoints

For all patients, the date of diagnosis of HCV infection was established as the baseline time point. Follow-up duration was defined as the interval between HCV diagnosis and the last outpatient visit, death or loss to follow-up. Kidney event was defined as duplication on baseline creatinine level or dependence on renal replacement therapy. Primary endpoints of the study were kidney survival and mortality. Secondary endpoints of the study were clinical, virological and immunological responses following antiviral treatment.

Treatment and outcomes

Patients were divided into three groups based on HCV treatment given: DAAs, IFN ± RBV and no treatment. Different treatment combinations with the newly licensed DAAs in Spain were used, according to the European Association for the Study of the Liver guidelines [16]. The type of HCV treatment given was dependent on the clinician's choice and documented when available. SVR was defined as undetectable HCV RNA levels 12 weeks after treatment cessation. Serum HCV RNA was quantified by polymerase chain reaction assay.

Serum creatinine, eGFR and proteinuria measured at HCV diagnosis (baseline), at the end of HCV treatment and at the end of follow-up were recorded. Data on cryocrit percentage and C3 and C4 levels were also collected at baseline, at the end of treatment and at the end of follow-up. Data on duplication on creatinine levels, dependence on renal replacement therapy and mortality were retrieved.

Statistics

Results were expressed as mean ± standard deviation (SD) for continuous variables. If data were not normally distributed, median values with the interquartile range (IQR) were reported. For categorical variables, the number of patients affected/total (percentage) was used. Comparisons of variables at baseline, at the end of treatment and at the end of follow-up were made using a paired sample test.

Kaplan–Meier and Cox proportional hazards analyses were performed to evaluate the effects of DAAs on kidney survival and mortality. To identify the possible factors involved in kidney survival, univariate and multivariate Cox regression models were used. The covariates included in the model were selected based on clinical criteria and results of the univariate analysis. The covariates included in the Cox regression model for kidney survival were eGFR and proteinuria at HCV diagnosis and the type of HCV treatment given. The covariates included in the Cox regression model for mortality were age, eGFR and proteinuria at HCV diagnosis and the type of HCV treatment given. To avoid biases due to potentially more comorbidities in the group of untreated patients, analyses using Cox regression models were separately conducted using the type of antiviral treatment and different comorbidity variables, including hypertension, diabetes, dyslipidaemia and obesity. Statistical significance was defined as $P < 0.05$.

RESULTS

Patients characteristics

In total, 139 patients with HCV-MC were included. Overall, 100 patients received DAAs and 24 were treated with IFN ± RBV, while 15 did not receive antiviral treatment.

Demographic, clinical and other baseline characteristics of patients according to treatment are shown in Table 1. At baseline, mean serum creatinine level was 1.4 mg/dL, mean eGFR was 56 mL/min and mean proteinuria was 2.1 g/day. Haematuria was detected in 68% of patients. In 65 patients (46.8%), histopathological examination of kidney biopsy revealed glomerulonephritis with a membranoproliferative pattern. Seventy-five per cent of patients had genotype 1b. No statistically significant differences were found between the different patient groups in relation to comorbidities (hypertension, diabetes, dyslipidaemia and obesity).

Primary endpoints: kidney survival and mortality

To avoid biases due to potentially more comorbidities in untreated patients and those treated with IFN ± RBV compared with patients treated with DAAs, different models of kidney survival were applied and adjusted for each of the comorbidity variables. The type of HCV treatment was found to maintain consistently its independent predictive power of kidney survival (Table 2). Over a median follow-up duration of 138 months (IQR 70-251), there were three (20%) kidney events in untreated patients, six (25%) in patients treated with IFN ± RBV and six (6%) in those treated with DAAs. Kidney survival was significantly higher in patients treated with DAAs (log rank 19.718; $P < 0.001$) (Figure 1). Using the Cox regression model adjusted for baseline eGFR and proteinuria, we found patients treated with DAAs had a lower risk for duplication on baseline creatinine values or for dependence on renal replacement therapy {hazard ratio [HR] 0.10 [95% confidence interval (CI) 0.04–0.33]; $P < 0.001$}. Therefore treatment with DAAs reduced the risk for a kidney event by 90%.

There were 10 (66.6%) deaths among untreated patients, 9 (37.5%) among those treated with IFN ± RBV and 4 (4%) among those treated with DAAs. Mortality in patients treated with DAAs was significantly lower compared with historical controls treated with IFN ± RBV, and lower than in untreated patients (log rank 54.507; $P < 0.001$) (Figure 2). Using the Cox regression model adjusted for age, baseline eGFR and proteinuria, patients treated with DAAs had lower mortality [HR 0.12 (95% CI 0.04–0.40); $P < 0.001$]. Therefore treatment with DAAs reduced mortality by 88%.

Secondary endpoints: clinical, virological and immunological responses

When we studied the effects of antiviral treatment on kidney disease, we observed a significant decrease in daily proteinuria in patients treated with DAAs at the end of treatment (1.3 g/day versus 2.4 g/day at baseline; $P = 0.003$) and at the end of follow-up (0.9 g/day versus 2.4 g/day at baseline; $P < 0.001$) (Figure 3). In patients treated with IFN ± RBV, a trend towards a decrease in proteinuria was observed following antiviral treatment, although the difference was not statistically significant.

No significant change in eGFR was observed, regardless of DAA treatment (Figure 4).

In patients treated with DAAs, cryocrit percentages at the end of treatment (1.7 ± 2%) and at the end of follow-up (0.7 ± 1.8%) were significantly decreased ($P = 0.001$) compared with pre-treatment levels (5 ± 4.4%). Moreover, in patients treated with DAAs, C3 and C4 levels increased significantly at treatment cessation compared with pre-treatment levels (C3 levels 32 ± 41 versus 101 ± 30 mg/dL, respectively, $P < 0.001$; C4 levels 5 ± 6 versus 14 ± 18 mg/dL, respectively, $P < 0.001$) and at the end of follow-up compared with pre-treatment levels (C3 levels 32 ± 41 versus 100 ± 24 mg/dL, $P < 0.001$; C4 levels 5 ± 6 versus 20 ± 24 mg/dL, $P < 0.001$). No significant changes in cryocrit percentage and C3 and C4 levels were observed in patients treated with IFN ± RBV.

In terms of virological response, patients with SVR had significantly lower mortality than those without SVR (log rank 18.611; $P < 0.001$).

In total, 98% of patients treated with DAAs achieved SVR 12 weeks after treatment cessation compared with 43.5% of patients treated with IFN ± RBV regimens. When we analysed all patients who achieved SVR and compared those treated with DAAs with those treated with IFN ± RBV, mortality was significantly lower in patients treated with DAAs (log rank 7.939; $P = 0.005$).

DISCUSSION

To our knowledge, the RENALCRYOGLOBULINEMIC study is the first multicentre study including a large number of HCV-MC patients treated with DAAs that evaluates kidney survival and long-term mortality. The paradigm of HCV infection has changed radically in recent years with the introduction of

Table 1. Baseline characteristics of patients according to HCV treatment

Characteristics	Global ($n = 139$)	Untreated ($n = 15$)	IFN ± RBV ($n = 24$)	DAA ($n = 100$)
Age (years)	65 ± 12	70 ± 15	65 ± 14	65 ± 10
Male gender (%)	51	66.7	58.3	46
Hypertensive (%)	53	60	58.3	51
Diabetes (%)	17	26.7	12.5	17
Dyslipidaemia (%)	12	20	12.5	11
Obesity (%)	10	20	4.2	10
Baseline clinical presentation				
Glomerulonephritis, % (*n*)	46.8 (65)	53.3 (8)	83.3 (20)	37 (37)
Purpura (%)	46	13	50	60
Arthralgia (%)	32	26	21	42
Skin ulcer (%)	6	6	5.3	8.4
Peripheral neuropathy (%)	25	6.7	12.5	36
CKD				
Serum creatinine (mg/dL)	1.4 ± 1.1	1.9 ± 0.7	1.6 ± 0.7	1.4 ± 1.1
eGFR (mL/min)	56 ± 26	35 ± 22	47 ± 20	51 ± 26
Proteinuria (g/day)	2.1 ± 3	3.7 ± 4.4	2.9 ± 3.8	1.6 ± 2.3
Microhaematuria (%)				
No	32	14	5	11
1–5 red blood cells per field	30	40	25	36
5–10 red blood cells per field	10	13	14	14
>20 red blood cells per field	28	33	56	39
Plasma albumin (g/dL)	3.8 ± 0.6	2.9 ± 0.8	3.6 ± 1.06	3.8 ± 0.6
Kidney biopsy, % (*n*)	46.8 (65)	53.3 (8)	83.3 (20)	37 (37)
Cryoglobulinaemia (%)				
Type II	74	70	50	80
Type III	26	40	50	20
Cirrhosis (%)	44	40	25	50
Genotype 1b (%)	75	60	70.8	78
Previously treated (%)	27	7	17	37
Duration of treatment (months)	20 ± 12		36 ± 17	16 ± 6
Virological response (%)				
Non-sustained response	20		56.5	2
Sustained response	80		43.5	98
Hepatic transplant, % (*n*)	5.8 (8)	17 (2)	5 (1)	5 (5)
Baseline laboratory findings				
HCV RNA level $\log_{10}$ (IU/mL)	5.7 ± 1	5.8 ± 0.6	5.2 ± 1.4	5.8 ± 1.1
Alanine aminotransferase (IU/mL)	63 ± 54	66 ± 66	62 ± 54	63 ± 53
Cryocrit (%)	6 ± 7	6.8 ± 13	8.5 ± 9	5 ± 4.3
Baseline C3 (mg/dL)	71 ± 43	74 ± 30	78 ± 36	62 ± 43
Baseline C4 (mg/dL)	8 ± 8.5	15 ± 6.4	7.7 ± 8.1	7 ± 8
Positive RF	254 ± 551	290 ± 140	293 ± 320	267 ± 616
Treatment (%)				
Renin–angiotensin system blockers	65	73	79	61
Plasmapheresis	16	13	42	10
Corticosteroids	45	27	54	45
Rituximab	25	13	29	26
Cyclophosphamide	4	0	12	3
Furosemide	39	40	46	37

Values are presented as mean ± SD unless states otherwise.

DAAs. Growing evidence supports the efficacy and safety of DAAs in the treatment of HCV infection. Several studies have shown similar high rates of SVR and clinical remission in the setting of cryoglobulinaemic vasculitis with HCV infection after treatment with DAAs [12–15]. In addition, patients treated with DAAs achieve higher SVR, compared with those treated with IFN ± RBV regimens. DAAs have a good safety profile and are well tolerated in patients with HCV and CKD [17]. However, limited data are available regarding long-term effects of DAAs on kidney function in patients with HCV-MC. To date, the number of patients diagnosed with both HCV-CM and CKD included in studies have been too small to draw conclusions. In addition, the follow-up duration of these patients is, in general, too short to analyse kidney survival and long-term mortality.

In a study of seven patients with kidney involvement, Sise *et al.* [18] showed a modest improvement in median eGFR (52.7 to 59.7 mL/min/1.73 m^2) after DAA treatment. The authors also found a reduction in median proteinuria after treatment with

Table 2. Effects of comorbidities and types of antiviral treatment on kidney survival (Cox regression model)

	Model 1	Model 2	Model 3	Model 4
DAA treatment	HR 0.414 (0.225–0.761), P = 0.005	HR 0.436 (0.235–0.809), P = 0.008	HR 0.400 (0.218–0.733), P = 0.003	HR 0.403 (0.219–0.741), P = 0.003
Hypertension	HR 2.065 (0.701–6.079)			
Dyslipidaemia		HR 2.621 (0.803–8.554)		
Obesity			HR 0.822 (0.382–1.766)	
Diabetes				HR = 1.746 (0.483–6.320)

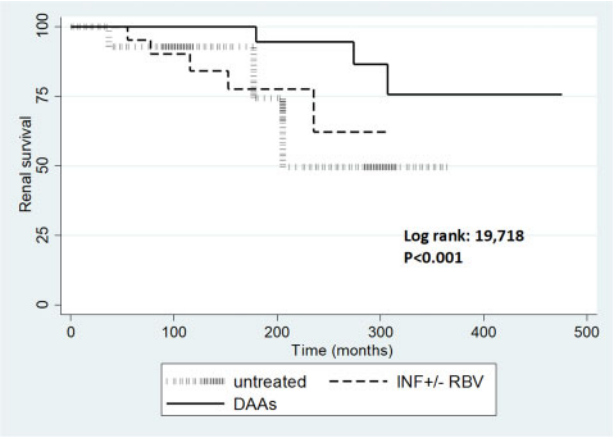

FIGURE 1: Kaplan–Meier curve showing kidney survival in patients treated with DAAs (group 1), those treated with IFN ± RBV (group 2) and untreated patients (group 3).

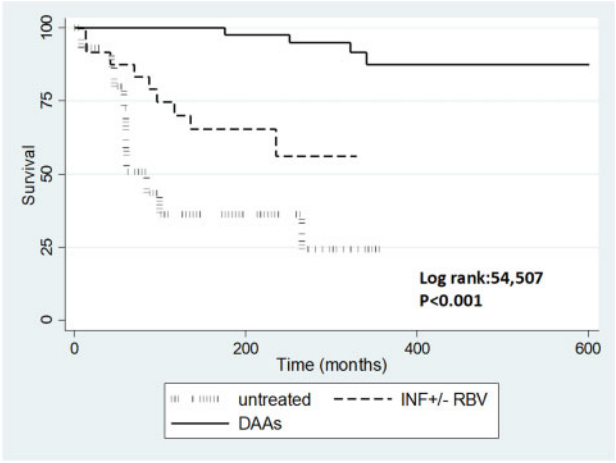

FIGURE 2: Kaplan–Meier curve showing mortality in patients treated with DAAs (group 1), those treated with IFN ± RBV (group 2) and untreated patients (group 3).

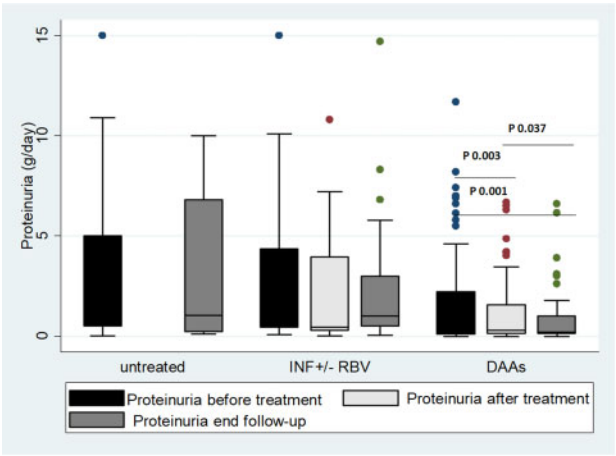

FIGURE 3: Proteinuria at baseline, at the end of treatment and at the end of follow-up in patients treated with DAAs (group 1), those treated with IFN ± RBV (group 2) and untreated patients (group 3).

DAAs (from 3514 to 1244 mg/g albumin:creatinine ratio, although it was measured quantitatively in only three patients). Similar findings were seen in other studies. In four patients with kidney failure, Gragnani *et al.* [19] showed all four experienced a marked improvement in eGFR with normalization of proteinuria. Bonaccy *et al.* [14] showed a complete clinical response in five of seven (71%) patients with vasculitis nephropathy and found an improvement in median eGFR from 40 to 54 mL/min/1.73 m^2 and a decrease in median proteinuria from 1.4 to 0.17 g/dL. Saadoun *et al.* [12] evaluated the response to DAA treatment in a prospective multicentre study that included five patients with kidney injury. Proteinuria decreased from 0.9 to 0.2 g in a 24-h urine test and haematuria disappeared in 80% of cases at week 24. Another published series by Emery *et al.* [13] including 10 patients with HCV-MC and kidney manifestations showed complete remission in 30% of patients, with recovery in median eGFR from 48.5 to 58.1 mL/min/1.73 m^2. Proteinuria was reduced from a median of 0.3 to 0.1 g/dL after treatment with DAAs. In our study, we did not find changes in eGFR in patients with HCV-MC after treatment with DAAs. However, we found a statistically significant decrease in proteinuria in patients treated with DAAs, which was not significant in patients treated with IFN ± RBV. The novelty of our findings is the tremendously beneficial effect of DAAs on long-term kidney survival and overall mortality, regardless of the initial GFR, proteinuria and age.

Recently Sise *et al.* [20] published a large retrospective observational study in which they evaluated the kidney response in 1178 patients with CKD and HCV infection after treatment with DAAs. The authors showed stabilization in eGFR decline (−1.32 mL/min/year, previous decline of −5.998 mL/min/year) and a significant improvement in albuminuria (except in diabetic CKD patients, who experienced a decline in eGFR and worsening of albuminuria). They concluded that DAAs slowed the rate of eGFR decline in patients with impaired kidney function at baseline. Although this study had a large number of patients, it included all causes of CKD, not HCV-MC only, and while it analysed surrogate kidney endpoints, strong endpoints such as renal replacement therapy or mortality were not included in their analysis.

Our study brings further supporting evidence to the current recommendations of the Kidney Disease: Improving Global Outcomes 2018 guidelines on the use of DAAs [21], which is now recommended as the first-line therapy in cryoglobulinaemic

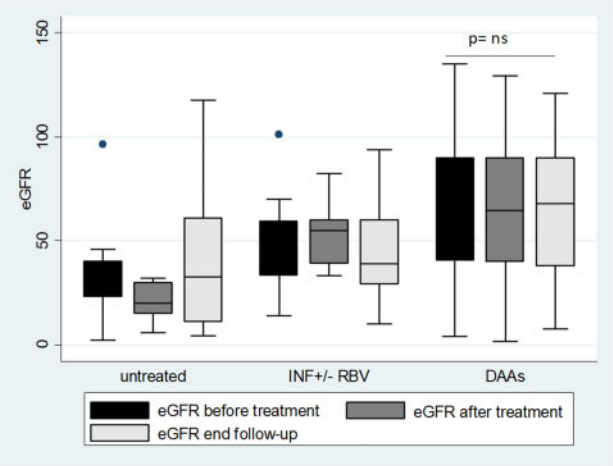

FIGURE 4: eGFR at baseline, at the end of treatment and at the end of follow-up in patients treated with DAAs (group 1), those treated with IFN ± RBV (group 2) and untreated patients (group 3).

glomerulonephritis'. Immunosuppression is reserved for patients with severe manifestations or those who do not enter remission after achieving SVR with DAA treatment.

In terms of SVR, in the RENALCRYOGLOBULINEMIC study, 98% of patients treated with DAAs achieved SVR compared with 43.5% of patients treated with IFN ± RBV regimens. Other studies [6] have previously shown that patients treated with DAAs have higher rates of SVR compared with those who received IFN ± RBV. We found a significant relationship between SVR and mortality. Patients who achieved SVR had lower mortality (log rank 18.611; $P < 0.001$). This finding is consistent with other studies in which clinical remission in patients with HCV-MC is associated with SVR status [11, 13–16]. However, in our study we found that among patients who achieved SVR, those treated with DAAs had lower mortality than patients treated with IFN ± RBV. In the previous studies mentioned above, the SVR rate in patients with cryoglobulinaemia treated with DAAs was between 86% and 100%. Bonaccy *et al.* [14] reported that all patients with cryoglobulinaemia and kidney involvement ($n = 7$) achieved SVR after treatment with DAAs. The authors also showed that SVR was associated with clinical and immunological improvement in most patients. Taken together, these findings are in agreement with our study results.

Regardless of the immunological response, we analysed data on complement (C3 and C4) levels and cryocrit percentages before and after treatment. Hypocomplementaemia and increased cryocrit percentage have been considered traditionally as markers of active cryoglobulinaemic glomerulonephritis [3–5], but there is a paucity of data on the response of these two markers after treatment with DAAs. Sise *et al.* [17] observed cryocrit negativization in three of seven patients after treatment with DAAs, with a decrease in cryocrit percentage in the remaining four patients from 3% to 1.5%. Bonaccy *et al.* [14] also detected an increase in complement levels (median C4 from 0.02 to 0.12 g/L) and a reduction in cryocrit percentage (3.2% to 0.5%) after treatment with DAAs. Finally, in Emery *et al.*'s [13] study there was a remarkable reduction in median cryocrit percentage (4.5% to 0.5%) at the time of SVR. In our study, we also found a statistically significant increase in serum complement levels and a decrease in cryocrit percentage after treatment with DAAs. However, 6 of the 139 patients (4.3%) did not achieve immunological remission; this is because HCV infection causes sustained immunological alteration of B lymphocytes that is sometimes perpetuated over time, regardless of the eradication of RNA-HCV.

Our study has some important limitations. First, the number of patients with HCV-MC who were untreated ($n = 15$) and those who were treated with IFN ± RBV ($n = 24$) was too small compared with the size of the DAA treatment group. Although untreated patients had higher proteinuria and worse renal function at baseline, these variables were adjusted using the Cox regression model. Second, this is a retrospective multicentre study with a long follow-up period. This implies that there is a high level of heterogeneity of patients receiving HCV treatment in terms of the types and doses of antiviral treatment, as well as of variables that were not included in the analysis. Despite these limitations, the main strength of our study is the large number of patients with HCV-MC included and the long follow-up duration, allowing the assessment of kidney survival and mortality following DAA treatment.

In conclusion, the RENALCRYOGLOBULINEMIC study suggests that DAA treatment in patients with HCV-MC improves kidney survival and reduces mortality.

CONFLICT OF INTEREST STATEMENT

None declared.

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