Effectiveness and cost of hepatitis C virus cryoglobulinemia vasculitis treatment: from interferon-based to direct acting antivirals era

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Effectiveness and cost of hepatitis C virus cryoglobulinemia vasculitis treatment: from interferon-based to direct-acting antivirals.

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Running title: Effectiveness and cost of HCV cryoglobulinemia vasculitis treatments

Key words: HCV, extra-hepatic manifestations, treatment, costs, cryoglobulinemia vasculitis

Electronic word count: abstract 235 words, text 3306 words

This article includes 4 tables, 1 Figure and 1 supplementary table.

Conflict of interest statement:

- Prof. P. Cacoub has received consulting and lecturing fees from Abbvie, Astra Zeneca, Bristol-Myers Squibb, Gilead, Glaxo Smith Kline, Janssen, and Merck Sharp Dohme.
- Dr. AC Desbois has received lecturing fees from Gilead.

- Dr. D. Saadoun has received consulting and lecturing fees from Abbvie, Medimmune, Roche, Servier, Gilead, AstraZeneca and Glaxo Smith Kline.
- All the other authors declare no conflict of interest with this article.

Financial support statement

This work was supported by an unrestricted grant provided by Gilead.

Contributorship

Study concept and design: MV, ACD, PC

Acquisition of data: MV, ACD, PC

Analysis and interpretation of data: MV, PC

Drafting of the manuscript: MV, PC

Critical revision of the manuscript for important intellectual content: MV, ACD, AL, DS, PC

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ABSTRACT

Background. The cost-effectiveness of hepatitis C virus (HCV) direct-acting antivirals (DAA) in patients with cryoglobulinemia vasculitis (CryoVas) is unknown.

Objective. To analyze the effectiveness and cost of all treatments used for HCV-CryoVas in the DAA versus the pre-DAA eras.

Methods. A chart review of all HCV-CryoVas patients who received antivirals from 1993 to 2016 in a tertiary center was performed. Treatment effectiveness was analyzed for clinical, immunological and virological responses. Cost analyses included anti-HCV treatments, non-antiviral drugs, plasmapheresis, dialysis and hospitalizations. We compared the clinical and cost outcomes from the pre-DAA to the DAA period.

Results. 201 HCV-CryoVas patients were included (women 53.2%; mean age 59.2 years; Metavir score F3-F4 36.7%; genotype 1 64.2%). Patients in the DAA era (n=27) compared to those in the pre-DAA era (n=174) showed higher rates of clinical (96.3% vs. 78.6%), immunological (89.5% vs. 77.1%) and sustained virological response (75.0% vs. 42.8%). The death rate was 14.8% vs. 24.4%, respectively. In the DAA compared to pre-DAA era, the mean cost of anti-HCV drugs increased from €11,855 to €57,632, while the mean CryoVas-related costs decreased for both hospitalizations (from €33,510 to €21,347) and non-antiviral treatments (from €17,347 to €11,397).

Conclusion. Improved antiviral efficacy of HCV drugs in the DAA era led to increased clinical and immunological effectiveness and a lower death rate. The use of DAAs was associated with higher costs for HCV drugs, while costs related to both hospitalizations and non-antiviral treatments decreased.

Key points

- In patients with HCV-related cryoglobulinemia vasculitis, improved antiviral efficacy of HCV drugs in the direct-acting antiviral era led to increased clinical and immunological effectiveness, a better tolerability profile and a lower death rate.
- Use of direct-acting antivirals was associated with higher costs for HCV drugs, while costs related to both hospitalizations and non-antiviral treatments decreased.
- Recently launched direct-acting antivirals have decreased treatment durations, increased sustained virological response rates for patients with all genotypes and markedly reduced prices; therefore, curing patients with HCV-related cryoglobulinemia vasculitis will soon undoubtedly be a cost-saving intervention.

Hepatitis C virus (HCV) is a global health care challenge, with approximately 80 million people chronically infected (1). These patients are at risk of developing major liver complications, i.e. cirrhosis and liver cancer, with an estimated liver-related mortality of 350,000 people/year. In addition, up to two-thirds of HCV-infected patients in large cohort studies experienced extrahepatic manifestations (2). The latter include HCV-related autoimmune and/or lymphoproliferative disorders (from mixed cryoglobulinemia to lymphoma), and many other non-liver disorders, i.e. cardiovascular, renal, metabolic and central nervous system diseases. Patients with HCV infection also showed a higher mortality rate for extra-hepatic complications, while viral eradication significantly reduced the rate of extra-hepatic deaths.

Mixed cryoglobulinemia vasculitis (CryoVas) is a systemic vasculitis that mainly affects small-size vessels. It reflects B-cell activation that generates pathogenic immunoglobulin (Ig) M and IgG with rheumatoid factor activity (2–5). The most frequent target organs are the skin, joints, kidneys and peripheral nervous system. The expression of the disease varies from mild symptoms to more severe manifestations, such as glomerulonephritis or widespread vasculitis (6). Interestingly, circulating mixed cryoglobulins are detected in 40% to 60% of chronically infected HCV patients, while overt CryoVas is observed in only 10%-15% of cases (7). The discovery of HCV as the etiologic agent for most cases of CryoVas provided the opportunity to control the disease manifestations with antiviral therapy, as the underlying infection drives immune complex formation and resultant vasculitis. Despite initial successes with interferon alpha (IFN)-based antiviral treatment, with or without immunosuppressive drugs, HCV-CryoVas remains a serious disease, with a 5-year mortality rate of 25% (8). Major therapeutic concerns include the numerous side effects of

IFN-based antivirals (including autoimmune reactions) and the potential adverse effects of immunosuppressants and glucocorticosteroids on an underlying chronic viral infection.

Major therapeutic advances have recently been made in the treatment of HCV infection, with the possibility of eradicating HCV using new direct-acting antiviral therapies (DAA), which is of major importance for liver and non-liver manifestations of the disease. A sustained virological response at twelve weeks after treatment (SVR12, i.e. HCV cure) is now obtained in more than 90% of cases, with low side effect rates (<10%) compared to IFN-based regimens (22%–65%) **(9,10).** In small cohorts of patients with HCV-CryoVas and with a short-follow-up, DAAs have shown high rates of SVR and vasculitis remission using IFN-based **(11,12)** or IFN-free combinations **(13).** In this population, however, there is no published data from large cohorts of patients that compares the effectiveness and cost of treatments used in the pre-DAA era to those used in the DAA era.

The objective of the present study was to analyze the effectiveness (clinical, virological and immunological) and the total costs of treatment (antiviral and non-antiviral drugs, hospitalizations) used in the management of HCV-CryoVas patients, and to compare the clinical and economic outcomes for patients in the pre-DAA versus the DAA era.

PATIENTS AND METHODS

Patient selection

This is a retrospective study performed in a tertiary French center. A chart review was of patients with HCV-CryoVas seen between January 1993 and January 2016 in the Department of Internal Medicine and Clinical Immunology of La Pitié-Salpêtrière Hospital, Paris, France, was performed. To be eligible, the patient had to be at least 18 years of age o, and present with HCV-CryoVas, defined by clinically active vasculitis with skin, joint, renal, peripheral nerve, central neurological, digestive, pulmonary and/or cardiac involvement (no histological evidence needed if patient had purpura), and chronic active HCV infection (positive HCV viremia). If no cryoglobulinemia was detectable, patients were included if they presented with a typical small-size vessel vasculitis and no evidence for a differential diagnosis such as medium- and small-size vessel vasculitis [granulomatosis with polyangiitis, microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis, polyarteritis nodosa, IgA vasculitis, hypersensitivity vasculitis, infectious vasculitis unrelated to HCV, hypocomplementemic urticarial vasculitis]. All patients met the international validated criteria for CryoVas (14,15). For the purpose of the present study, only patients who received HCV treatments were included. The exclusion criteria were medium- and small-size vessel vasculitis unrelated to cryoglobulinemia, or patients with human immunodeficiency virus or active hepatitis B virus infection.

The clinical evaluation included age, gender, recent weight loss, neurologic involvement (peripheral and/or central nervous system), cutaneous involvement (Raynaud's phenomenon, purpura, distal ulcers, skin necrosis), arthralgia/arthritis, myalgia, gastrointestinal tract involvement, renal involvement (proteinuria, hematuria and glomerular filtration rate [GFR]), and clinical signs of hepatic involvement. The diagnosis of non-

Hodgkin's lymphoma was based on the World Health Organization (WHO) criteria (16). HCV genotyping was performed by NS5B gene sequencing according to the previously validated consensual method (17). Laboratory evaluation included a complete blood count, serum chemistry profile, alanine aminotransferase (ALT), rheumatoid factor activity, IgM level, C4 fraction of complement and cryoglobulin. Cryoglobulins were measured as previously described (18). Cryoglobulins were classified according to the method described by Brouet et al. as either type II mixed cryoglobulin, which includes a monoclonal component, or type III mixed cryoglobulin, defined by the association of polyclonal immunoglobulins (19). The estimation of GFR was determined by modification of diet in renal disease (MDRD) study equations. Urine collection was also performed in order to quantify protein excretion. Kidney involvement was defined as the presence of at least two of the following parameters at diagnosis: GFR < 60 ml/min/1.73 m², increase in daily proteinuria > 0.3g and/or hematuria. Liver fibrosis was evaluated by liver biopsy and/or non-invasive tests according to the previously validated Metavir scoring system (20). All evaluations except the liver fibrosis evaluation were done at the beginning and at the end of each antiviral therapeutic sequence.

Characteristics of study population

A total of 201 patients with HCV-CryoVas met the criteria for the present study; 53.2% were women, and the mean age at CryoVas diagnosis was 59.2 years (Table 1). The Metavir score showed severe liver fibrosis (F3-F4) in 36.7% of patients. The main HCV genotypes were 1 (64.2%), 2 (11.9%) and 4 (10.9%). The most frequent manifestations of CryoVas were purpura (68.7%), polyneuropathy (53.2%), arthralgia (50.2%), glomerulonephritis (28.5%) and sicca syndrome (10.4%). The systemic nature of the vasculitis was reflected by the fact that the mean number of CryoVas manifestations was 4.9 per patient. Testing for cryoglobulinemia was positive in 92.0% of patients. The mean mixed cryoglobulinemia level was 1.2 g/L; it was an IgM κ in 71.5%. Twenty-seven (13.4%) patients presented with

malignant blood disorders during follow-up, including twenty cases of low-grade B cell lymphoma.

Definition of effectiveness endpoints

All endpoints were analyzed at the end of each new antiviral therapeutic sequence.

A complete clinical CryoVas response was defined as the remission of all the affected organs involved at baseline, and the absence of clinical relapse. The skin and articular remissions were evaluated clinically (i.e. disappearance of purpura and/or ulcers and/or skin necrosis; disappearance of arthralgia and/or arthritis). Renal remission was evaluated biologically (i.e. proteinuria < 0.3g/d, disappearance of hematuria and improvement of GFR > 20% if GFR < 60 ml/min/1.73 m^2 at baseline). Peripheral neurological remission was evaluated clinically (i.e. improvement of pain and paresthesia per visual analogue scales, improvement of muscular testing in case of motor impairment at baseline) and/or electrophysiologically (i.e. improvement of electromyogram abnormalities compared to baseline). Patients defined as partial responders had an improvement in at least half of the organs involved at baseline. Patients with no clinical response were defined as treatment failure.

A sustained virological response (SVR) was defined as the absence of detectable serum HCV RNA 12 or 24 weeks after the end of antiviral therapy (according to the treatment era), with no reappearance during follow-up. The remaining patients were classified as virological non-responders.

A complete immunological response was defined as the absence of detectable serum cryoglobulin. A partial immunological response was defined as a decrease in the serum cryoglobulin level of at least 50%. All other patients were considered as non-immunological responders.

For patients who died, we recorded the cause(s) of death and the period of the antiviral treatment sequence.

Data collected for direct cost analyses

Medical costs were assessed from the perspective of the French national healthcare insurance. All medical resources used for each patient were documented in patient charts for each antiviral therapeutic sequence. These include data on antiviral treatments for HCV infection (IFN, Pegylated [Peg] IFN, ribavirin, boceprevir, telaprevir, sofosbuvir, daclatasvir, and simeprevir), non-antiviral treatments (erythropoietin, red blood cell transfusion, glucocorticosteroids, rituximab, plasmapheresis, and immunosuppressants), dialysis (acute or chronic) and hospitalizations (standard, intensive care unit, and rehabilitation care). Standard prices in euros (€) were applied to resources (2015 prices).

Statistical analysis

Patients were first divided into four groups based on medical history, or in other words, according to the first HCV therapeutic sequence received, i.e. (i) IFN plus ribavirin, (ii) PegIFN plus ribavirin, (iii) PegIFN/ribavirin plus boceprevir or telaprevir, or (iv) IFN-free DAA combinations (including sofosbuvir, daclatasvir, or simeprevir, with or without ribavirin). In order to maintain sufficient power in the statistical analysis, we then analyzed the study outcomes in the pre-DAA group versus the DAA group.

Statistical comparisons were performed by using the Student's t-test or Wilcoxon test for quantitative data, and the Chi-square test or Fisher's exact test for qualitative data. All statistical tests were two-tailed with a significance level of 0.05. The SAS software program, version 9.3 (SAS Institute, Cary, NC) was used for statistical analyses.

The study was performed in accordance with the Declaration of Helsinki.

RESULTS

Characteristics of the study population according to antivirals

A total of 201 patients with HCV-CryoVas were classified according to the first HCV treatment received, i.e. IFN plus ribavirin (n=60), PegIFN plus ribavirin (n=114), PegIFN/ribavirin plus boceprevir or telaprevir (n=11), or IFN-free DAAs (n=16) (**Table 2**). The mean (SD) follow-up duration of these four groups was 88 (69), 56 (44), 17 (14) and 18 (11) months, respectively. Overall, 174 patients were treated during the pre-DAA era, and 27 during the DAA era. Of note, some patients who failed their treatment during the pre-DAA era also received DAAs; effectiveness and total costs were considered only for the pre-DAA era in those patients. The main characteristics of patients in the pre-DAA and DAA groups are detailed in **Table 1**. There was no significant difference between the groups except that patients in the DAA group had more frequent skin necrosis/ulcers and Raynaud's phenomenon, and (as expected) a shorter follow-up duration. **Table 3** summarizes all other medical treatments used for HCV-CryoVas patients, including non-antiviral drugs (erythropoietin, red blood cell transfusion, corticosteroids, rituximab and immunosuppressants), plasmapheresis, hemodialysis and hospitalizations.

After a mean follow-up of 61 months, 46 (23.1%) patients had died. The main causes of death (sometimes multiple causes) were sepsis (13 patients; 28.2%), hepatocellular carcinoma (9; 19.6%), cardiovascular (7; 15.2%), lymphoma (5, 10.9%), other cancers (4; 8.7%) and miscellaneous (9; 19.6%). When we compared the causes of death between the pre-DAA (n=42 out of 174 patients, 24.1%) and the DAA (n=4 out of 27 patients, 14.8%) groups, we found that more patients in the pre-DAA than the DAA era died from: sepsis (12 vs. 1), hepatocellular carcinoma (7 vs. 2), lymphoma (3 vs. 2), cardiovascular (7 vs. 0), other cancers (4 vs. 0), and miscellaneous (9 vs. 0), respectively.

Effectiveness of treatments

The clinical, virological and immunological responses of HCV-CryoVas patients to treatments according to the two groups (pre-DAA and DAA eras) are summarized in **Table 4.** A partial/complete clinical response of CryoVas was more frequent in patients treated during the DAA era compared with the pre-DAA era (96.3% vs. 78.6%) **(Figure 1)**. Improved results during the DAA era were also observed for SVR (75.0% vs. 42.8%). For a partial/complete immunological response, there was a trend in favor of the DAA era (89.5% vs. 77.1%). The death rate was lower in the DAA vs. the pre-DAA group: 14.8% vs. 24.4%, respectively.

Costs of medical treatment for HCV-CryoVas

The mean total cost per patient for antivirals rose from €11,855 in the pre-DAA group to €57,632 in the DAA group (**Table 5**). Conversely, there was a decrease in the mean total CryoVas-related cost per patient from the pre-DAA era to the DAA era for both non-antiviral treatments (from €17,347 to €11,397) and hospitalizations (from €33,510 to €21,347).

DISCUSSION

The recent development of DAAs has dramatically improved the efficacy and tolerability of HCV treatments. Nevertheless, the prices of DAAs are controversial, and in many countries DAAs are only given to patients with advanced liver fibrosis or cirrhosis. Patients with clinically significant extra-hepatic manifestations of HCV, such as CryoVas, which can be life-threatening, should be prioritized for access to DAAs as recommended by the European Association for the Study of the Liver (22). This study is the first, to our knowledge, to assess the effectiveness and the economic impact of treatments used for HCV-CryoVas patients, both in the pre-DAA and DAA eras. After a systematic chart review of all patients who had received anti-HCV treatment for HCV-CryoVas in our center over the last two decades, we found that, compared with the pre-DAA era, the DAA era was associated with 1) higher clinical, immunological and virological effectiveness, and a lower death rate; 2) higher total costs per patient for HCV drugs; and, 3) lower per patient costs related to hospitalizations and non-antiviral treatments.

Treatment with DAA showed higher clinical, immunological, and virological effectiveness **in HCV-CryoVas patients**

Most HCV-CryoVas manifestations have been shown to respond, at least partially, to viral clearance during antiviral therapy. Patients who relapse with HCV infection after responding to antiviral therapy usually manifest CryoVas symptoms with the return of viremia (23). Despite virological success with combination antiviral treatment, until recently HCV-CryoVas remained a serious disease, with reported 1-year, 3-year, 5-year and 10-year survival rates of 96%, 86%, 75% and 63%, respectively (8). The cornerstone of HCV-CryoVas therapy has long been IFN. However, its overall tolerability is poor, and some CryoVas manifestations may worsen, such as peripheral neuropathy or skin ulcers (24).

Assessments of both the efficacy and safety of DAAs, whether IFN-free or not, in patients with HCV-CryoVas have been performed in a limited number of clinical trials. The first use of DAA (Peg-IFN/ribavirin plus boceprevir or telaprevir) in HCV genotype 1 CryoVas patients showed a complete clinical response in 56.5% of patients (11,12). However, grade 3 or 4 adverse events were observed in up to 43.5% of patients, and antiviral therapy discontinuation was required in one-third (11). Over the last two years, all types oral IFN-free DAA regimens have been used in HCV-CryoVas, which has allowed for the avoidance of IFN and its potential to exacerbate autoimmune disease. In the VASCUVALDIC study, twenty-four patients (56 years, 54% males, 50% cirrhotic) received sofosbuvir plus ribavirin for twenty-four weeks, and seven patients also received immunosuppressive therapy (13). A complete clinical response was reported in 87.5% of patients, and 74% had an SVR12. The cryoglobulin level decreased from 0.35 to 0.15 g/L. Two (8%) patients had serious adverse events. Sise et al. reported a retrospective case series of twelve HCV-CryoVas patients treated with sofosbuvir-based regimens (61 years, 58% males, 50% cirrhotic), including four patients who received rituximab (25). SVR12 was achieved in 83% of patients, and cryoglobulin levels decreased in 89%. Two (17%) patients experienced serious adverse events. Sofosbuvir based IFN-free DAA therapy was given to a cohort of forty-four Italian HCV-CryoVas patients (65 years, 64% females, 39% cirrhotic) (26). All patients showed an SVR post-treatment, and all had a CryoVas clinical response. The cryocrit fell from 7.2% to 1.8%. A small case series reported on five HCV-CryoVas patients who received twenty-four weeks of PegIFN/ribavirin plus DAA (boceprevir, telaprevir or sofosbuvir) with good effects on CryoVas manifestations but no rapid clearance of serum cryoglobulins (27).

Despite the evidence of a viral etiology and the role of effective antivirals, immunosuppression is still regarded as a major treatment option in HCV-CryoVas. In case of severe CryoVas manifestations or in patients with failure or contraindications to antivirals,

rituximab has shown better efficacy than conventional immunosuppressive treatments (i.e., glucocorticoids, azathioprine, cyclophosphamide or plasmapheresis) or placebo (28,29). In HCV-CryoVas patients, the addition of rituximab to Peg-IFN/ribavirin led to a shorter time to clinical remission, better renal response rate and higher rates of cryoglobulin clearance (30,31). The overall tolerability of rituximab was good, although flares of HCV-CryoVas have been reported shortly after rituximab infusion in some patients (32). Interestingly, in the present study, patients in the DAA era received steroids, rituximab and immunosuppressants less frequently, while they showed higher rates of partial/complete clinical response of CryoVas and lower death rates. This underlines the major role played by rapid and powerful anti-HCV treatment in controlling most HCV-CryoVas manifestations. Taking into account the very rapid antiviral efficacy of IFN-free DAAs and their favorable tolerability profile, the exact role of rituximab remains in the treatment of HCV-CryoVas to be defined.

Treatment of HCV-CryoVas patients with DAAs were associated with higher costs for HCV drugs and lower costs related to hospitalizations and non-antiviral treatments.

The total cost of medical care in France in 2014 was estimated at 191 billion euros, or 8.9% of the gross domestic product (33). Previous studies evaluating the economic impact of DAA treatment in France have only considered hepatic complications of chronic HCV infection, i.e. fibrosis, cirrhosis and hepatocellular carcinoma. The cost of extra-hepatic manifestations related to HCV was evaluated to be 1,506,000 dollars in the United States in 2014. The main annual costs were related to diabetes mellitus (443 million), depressive symptoms (197 million) and CryoVas (120 million) (34). Only one small study tried to evaluate the cost and effectiveness of non-antiviral treatments used in HCV-CryoVas patients. Visentini et al. reported on a retrospective chart review of thirty patients with HCV-CryoVas, including eight severe and twenty-seven mild/moderate forms of vasculitis, who were ineligible, intolerant or non-responders to IFN-based treatment (35). None received DAAs.

All 8 patients with severe vasculitis received rituximab, plasma exchange or both. The clinical response was transient in 6 patients and sustained in only 1 patient. Two patients died after a transient response. Costs for hospitalizations and treatment related to Cryovas complications were estimated from 28,648 to 81,153 US dollars. However, these costs did not include those of antiviral therapy (35).

DAA regimens used in the present study were very expensive; however, between the first generation protease inhibitor-based treatments (which no longer represent the standard of care) and the more recent sofosbuvir-based combinations, DAA prices decreased significantly. Prices for sofosbuvir-based combinations in 2016 were markedly lower compared to earlier regimens, especially in the context of shorter durations of antivirals. We can therefore anticipate that in the near future, with lower prices and/or shorter durations of DAAs, the net benefit of antivirals in HCV-CryoVas patients will increase even further. The cost of medical care for other small-size vessel vasculitis conditions, such as granulomatosis with polyangiitis, have been estimated to be between 24,000 and 61,000 US dollars per year (36), which is lower than our estimation of the cost of medical care for HCV-CryoVas. However, in granulomatosis with polyangiitis, immunosuppressant therapy is given for many years due to the high risk of relapse, whereas in HCV-Cryovas effective antiviral therapy can cure the viral disease, and the CryoVas as well.

We acknowledge some limitations to this study. Patients were treated in a unique specialized center, and our analysis could therefore reflect management and practices that are not completely generalizable to other centers. The population of patients or their recruitment might have evolved over time. For this reason, we did not perform formal comparisons between the pre-DAA and DAA eras, and the statistical tests were only indicative. Nevertheless, we did not observe differences between patient characteristics in the pre-DAA and DAA groups that could have a significant impact on efficacy. Due to the relatively low

number of patients treated with DAAs, such treatment could be only considered as a class effect, and no specific analysis was performed for individual regimens. Lastly, some patients from the pre-DAA era required retreatment with DAAs. The total treatment costs of DAAs administered to patients who failed pre-DAA treatments were similar to the total treatment costs of patients in the DAA era.

In summary, in this large cohort of patients with HCV-CryoVas, the improved antiviral efficacy of HCV drugs in the DAA era led to increased clinical and immunological effectiveness with a lower death rate. Use of DAAs was associated with higher costs for HCV drugs, while total CryoVas-related costs related to both hospitalizations and non-antiviral treatments decreased. Since this analysis was performed, DAA treatment durations have decreased, DAA regimens have evolved to treat patients beyond only genotype 1, sustained virological response rates have increased, and prices have markedly decreased. With these factors taken into account, curing this patient population will soon likely become a cost-saving intervention.

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Acknowledgements

We thank all patients and all physicians involved in the care of the patients. We also thank Mariane Doz and Bastien Peiffer for their input in statistical analyses.

Table 1. Characteristics of patients with HCV-mixed cryoglobulinemia vasculitis according to HCV treatment era (i.e. pre- or post-direct-acting antivirals [DAA]).

	Total	Pre-DAA era	DAA era	p-value
No. of patients	**201**	**174**	**27**	
Female gender	107 (53.2%)	95 (54.6%)	12 (44.4%)	0.32
Age at first vasculitis signs	59.2 (12.6)	57.1 (12.9)	59.7 (11.0)	0.58
Liver fibrosis score, Metavir				0.41
0	19 (10.1%)	16 (9.9%)	3 (11.1%)	
1	43 (22.9%)	40 (24.8%)	3 (11.1%)	
2	57 (30.3%)	46 (28.6%)	11 (40.7%)	
3	30 (16.0%)	27 (16.8%)	3 (11.1%)	
4	39 (20.7%)	32 (19.9%)	7 (25.9%)	
ND	13	13	- -	
HCV genotype				0.23
1	124 (62.2%)	106 (63.9%)	18 (66.7%)	
2	23 (11.9%)	22 (13.3%)	1 (3.7%)	
3	17 (8.8%)	16 (9.6%)	1 (3.7%)	
4	21 (10.9%)	16 (9.6%)	5 (18.5%)	
5	8 (4.1%)	6 (3.6%)	2 (7.4%)	
ND	8	8	- -	
Arthralgia/arthritis	101 (50.2%)	92 (52.9%)	9 (33.3%)	0.058
Myalgia	29 (14.4%)	26 (14.9%)	3 (11.1%)	0.77
Neuropathy	135 (67.2%)	119 (68.4%)	16 (59.3%)	0.34
Polyneuropathy	107 (53.2%)	94 (54.0%)	13 (48.1%)	0.56
Mono neuropathy multiplex	29 (14.4%)	26 (14.9%)	3 (11.1%)	0.77
CNS vasculitis	20 (10.0%)	17 (9.8%)	2 (7.4%)	1.00
Purpura	138 (68.7%)	122 (70.1%)	16 (59.3%)	0.25
Skin necrosis/ulcers	14 (7.0%)	9 (5.2%)	5 (18.5%)	**0.025**
Livedo	10 (5.0%)	9 (5.2%)	1 (3.7%)	1.00
Raynaud's phenomenon	6 (3.0%)	2 (1.1%)	4 (14.8%)	**0.003**
Sicca syndrome	21 (10.4%)	20 (11.5%)	1 (3.7%)	0.31
Kidney involvement	66 (32.8%)	59 (33.9%)	7 (25.9%)	0.41
Hypertension	56 (27.9%)	51 (29.3%)	5 (18.5%)	0.24
GI involvement	22 (10.9%)	16 (9.2%)	6 (22.2%)	0.08
Heart involvement	8 (4.0%)	7 (4.0%)	1 (3.7%)	1.00

	Total	Pre-DAA era	DAA era	p-value
Number of vasculitis manifestations				
1	3 (1.5%)	2 (1.1%)	1 (3.7%)	
2	14 (6.9%)	12 (6.9%)	2 (7.4%)	
3	24 (11.9%)	18 (10.3%)	6 (22.2%)	
4	50 (24.9%)	43 (24.7%)	7 (25.9%)	
5	40 (19.9%)	37 (21.3%)	3 (11.1%)	
6	35 (17.4%)	32 (18.4%)	3 (11.1%)	
7	15 (7.5%)	12 (6.9%)	3 (11.1%)	
8	12 (5.9%)	11 (6.3%)	1 (3.7%)	
9	6 (2.9%)	5 (2.9%)	1 (3.7%)	
10	1 (0.5%)	1 (0.6%)	- -	
11	1 (0.5%)	1 (0.6%)	- -	
Cryoglobulinemia	185 (92%)	162 (93.1%)	23 (85.2%)	0.24
Type 2 IgMk cryoglobulinemia	132 (71.5%)	123 (75.9%)	9 (39.1%)	**0.0001**
Baseline cryoglobulin level, g/L	1.2 (1.5)	1.2 (1.4)	1.3 (2.1)	0.98
Hemopathy	27 (13.4%)	24 (13.8%)	3 (11.1%)	1.00
Hemopathy type				0.73
B cell lymphoma	24	21	3	
B-Non Hodgkin	10 (37.0%)	9 (37.5%)	1 (33.3%)	
Diffuse large B cell	4 (14.8%)	3 (12.5%)	1 (33.3%)	
Marginal zone	4 (14.8%)	3 (12.5%)	1 (33.3%)	
SLVL	4 (14.8%)	4 (16.7%)	- -	
MALT	2 (7.4%)	2 (8.3%)	- -	
ND	1	1	--	
T cell lymphoma	2 (7.4%)	2 (8.3%)	0	
Follow up duration, months	61.0 (54.9)	67.0 (55.6)	22.0 (27.5)	**<0.0001**
Deaths	46 (23.1%)	42 (24.4%)	4 (14.8%)	0.2711

ND, not determined; HCV, hepatitis C virus; GI, gastrointestinal;
SLVL, splenic lymphoma with villous lymphocytes;
MALT, mucosa-associated lymphoid tissue

Table 2. Anti-HCV treatments used for patients with HCV cryoglobulinemia vasculitis, according to the first treatment sequence*.

	Sequence 1	Sequence 2	Sequence 3	Sequence 4
No. of patients	**60**	**114**	**11**	**16**
Interferon alpha, n (%)	60 (100.0%)	- -	- -	- -
million IU/week	9.3 (2.7)	- -	- -	- -
duration, months	21.0 (17.2)	- -	- -	- -
Ribavirin, n (%)	46 (76.7%)			
mg/day	844 (209)			
duration, months	46 (76.7%)			
Peg IFN2a, n (%)	- -	26 (22.8%)	- -	- -
µg/week	- -	170.8 (29.3)	- -	- -
duration, months	- -	12.4 (6.2)	- -	- -
Peg IFN2b, n (%)	- -	93 (81.6%)	11 (100.0%)	- -
µg/week		93.5 (20.1)	142.7 (44.9)	
duration, months	- -	13.7 (9.4)	9.7 (3.2)	- -
Ribavirin, n (%)		113 (99.1%)		
mg/day		906 (175)		
duration, months		13.2 (8.3)		
Boceprevir, n (%)			5 (45.5%)	
mg/day	- -	- -	2 400 (-)	- -
duration, weeks	- -	- -	36.4 (13.9)	- -
Telaprevir, n (%)	- -	- -	6 (54.5%)	- -
mg/day	- -	- -	2 250 (-)	- -
duration, weeks	- -	- -	11.3 (1.6)	- -
Ribavirin, n (%)			11 (100%)	
mg/day			627 (358)	
duration, months			9.7 (3.2)	
Sofosbuvir, n (%)	- -	- -	- -	16 (100%)
mg/day	- -	- -	- -	400 (-)
duration, weeks	- -	- -	- -	19.4 (9.0)
Daclatasvir, n (%)	- -	- -	- -	4 (25.0%)
mg/day	- -	- -	- -	60 (-)
duration, weeks	- -	- -	- -	14.0 (4.0)
Simeprevir, n (%)	- -	- -	- -	1 (6.3%)

	Sequence 1	Sequence 2	Sequence 3	Sequence 4
mg/day	- -	- -	- -	150 (-)
duration, weeks	- -	- -	- -	12.0 (-)
Ribavirin, n (%)				14 (87.5%)
mg/day				643 (195)
duration, months				4.2 (1.9)

*Each treatment sequence corresponds to the first HCV treatment received for HCV mixed cryoglobulinemia vasculitis, i.e. sequence 1=Interferon alpha w/wo Ribavirin; sequence 2=Peg-Interferon alpha plus Ribavirin; sequence 3= Peg-Interferon alpha plus Ribavirin plus first generation protease inhibitor (Boceprevir/Telaprevir); and sequence 4= Interferon-free DAA combination w/wo Ribavirin.

All results are expressed as number, n (%) or mean (SD).

Table 3. Non-antiviral treatments used for patients with HCV cryoglobulinemia vasculitis, according to the first HCV treatment sequence*.

	Sequence 1	Sequence 2	Sequence 3	Sequence 4
No. of patients	**60**	**114**	**11**	**16**
Erythropoietin	5 (8.3%)	37 (32.5%)	9 (81.8%)	10 (62.5%)
Red blood cell transfusion	9 (15.0%)	17 (14.9%)	5 (45.5%)	3 (18.8%)
Mean number (SD)	5.3 (5.3)	5.4 (4.0)	8.0 (7.5)	6.3 (5.9)
Steroids	23 (38.3%)	41 (36.0%)	3 (27.3%)	3 (18.8%)
Total dose, mg (SD)	10 429 (10 630)	6 671 (12 287)	1 942 (1 700)	2 843 (2 007)
Rituximab	- -	58 (51%)	5 (46%)	4 (25%)
Immunosuppressants**	11 (18.3%)	8 (7.0%)	- -	- -
Duration, months	14.2 (18.3)	5.0 (4.0)	- -	- -
Plasma exchange	26 (43.3%)	9 (7.9%)	- -	6 (37.5%)
Number	12.8 (7.5)	10.6 (9.3)	- -	13.3 (5.6)
Hemodialysis	3 (5.0%)	6 (5.3%)	- -	1 (6.3%)
Hemodialysis, chronic	2	3	- -	- -
Duration, months	46.5 (30.4)	24.0 (14.4)	- -	- -
Hospitalization, n (%)	47 (78.3%)	92 (80.7%)	7 (63.6%)	9 (56.2%)
Duration, days	52.4 (54.1)	37.3 (52.4)	30.0 (34.7)	43.7 (41.1)
Rehabilitation, n (%)	12 (20.0%)	10 (8.8%)	1 (9.1%)	1 (6.3%)
Duration, days	65.8 (48.2)	67.2 (102.6)	2.0 (-)	40.0 (-)
Intensive care unit	5 (8.3%)	10 (8.8%)	- -	4 (25.0%)
Duration, days	19.4 (17.8)	12.5 (9.5)	- -	5.8 (4.6)

*Each treatment sequence corresponds to the first HCV treatment received for HCV mixed cryoglobulinemia vasculitis, i.e. sequence 1=Interferon alpha w/wo Ribavirin; sequence 2=Peg-Interferon alpha plus Ribavirin; sequence 3= Peg-Interferon alpha plus Ribavirin plus first generation protease inhibitor (Boceprevir/Telaprevir); and sequence 4= Interferon-free DAA combination w/wo Ribavirin.

** Include cyclophosphamide, azathioprine, or methotrexate.

All results are expressed as number, n (%) or mean (SD).

Table 4. Clinical, virological, and immunological responses to treatments in patients with HCV-mixed cryoglobulinemia vasculitis.

	Pre-DAA era N=174	**DAA era N=27**	**P-value**
Clinical response			
Complete/partial	132 (78.6)	26 (96.3)	0.0292
No response	36 (21.4)	1 (3.7)	
ND	6	0	
Virological response			
Sustained virological response	71 (42.8)	18 (75.0)	0.0031
No response	95 (57.2)	6 (25.0)	
ND	8	3	
Immunological response			
Complete/partial	111 (77.1)	17 (89.5)	0.3709
No response	33 (22.9)	2 (10.5)	
ND	30	8	

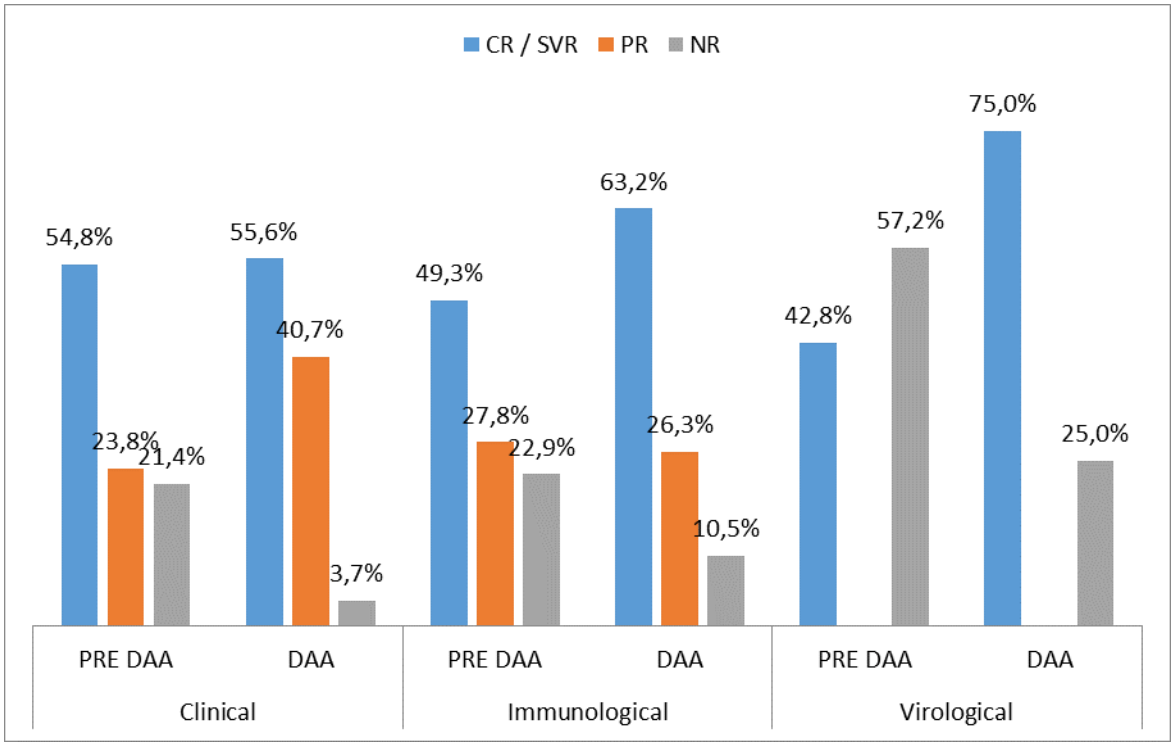
Data are presented as n (%); ND, not determined; DAA, direct-acting antivirals.

Table 5. Cost of the medical management per patient with hepatitis C virus cryoglobulinemia vasculitis, in euros (€).

	Pre-DAA era [a] **N=174**	**DAA era N=27**	**P-value**
Antiviral treatments			
Mean (SD)	11,855 (8,174)	57,632 (38,483)	<0.0001
Median (min–max)	11,259 (495–37,854)	43,028 (11,606–155,261)	
Non-antiviral treatments			
Mean (SD)	17,347 (67,529)	11,397 (13,203)	0.0461
Median (min–max)	1,163 (0–568,821)	5,683 (0–46,314)	
Hospitalization			
Mean (SD)	33,510 (51,185)	21,347 (33,354)	0.1264
Median (min–max)	10,464 (0–258,924)	4,185 (0–135,336)	
Total cost per patient			
Mean (SD)	62,712 (96,567)	90,377 (55,744)	<0.0001
Median (min–max)	30,300 (1,034–769,667)	86,057 (15,924– 255,264)	

DAA, direct-acting antivirals.

Figure 1. Clinical, virological, and immunological responses to treatments in patients with mixed cryoglobulinemia vasculitis, according to HCV treatment era [i.e. pre- or post-DAAs].



CR, complete response; PR, partial response; NR, non-response; SVR, sustained virological response; DAA, direct-acting antivirals.