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Cryoglobulinemia Vasculitis : how to handle

**Anne Claire Desbois^{1,2,3,4}, Cloe Comarmond^{1,2,3,4}, David Saadoun^{1,2,3,4}, Patrice
Cacoub^{1,2,3,4}**

¹ Sorbonne Universités, UPMC Univ Paris 06, UMR 7211, and Inflammation-
Immunopathology-Biotherapy Department (DHU i2B), F-75005, Paris, France

² INSERM, UMR_S 959, F-75013, Paris, France

³ CNRS, FRE3632, F-75005, Paris, France

⁴ AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Department of Internal Medicine and Clinical
Immunology, F-75013, Paris, France

Correspondence to Pr Patrice Cacoub, MD. Department of Internal Medicine and Clinical
Immunology, Hôpital La Pitié-Salpêtrière, 47-83, boulevard de l'Hôpital, 75651 Cedex 13. Paris.
France. Tel: + 33 (0) 1 42 17 80 27; Fax: + 33 (0) 1 42 17 80 33; Email: patrice.cacoub@aphp.fr

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(DAA), treatment

Abstract

Purpose of this review: More than fifty percent of hepatitis C virus (HCV) infected patients produce a mixed cryoglobulin and two third of them will develop a symptomatic cryoglobulinemia vasculitis (CryoVas). In the present review, we aim at summarizing the most recent advances in diagnosis and treatment of HCV-CryoVas.

Recent findings: The treatment of HCV- CryoVas has much changed during the last months. The recent emergence of new direct acting (DAA) interferon (IFN)-free antivirals, enabling high cure rates with a very good safety profile now permit to cure most patients with HCV-CryoVas. Multi-disciplinary consensus recommend to consider as first-line treatment IFN-free DAAs for HCV-CryoVas patients. Immunosuppressive treatments (i.e. rituximab, glucocorticosteroids, cyclophosphamide and plasmapheresis) remain an interesting therapeutic approach, in severe form of HCV-CryoVas, failure or contradiction to antiviral treatments.

Summary: The great efficacy of DAA on HCV-CryoVas represent a major advance in clinical practice, since these new antivirals provide for the first time a safe and definite treatment of such complication for most patients.

Key Points

- 1- New direct acting (DAA) interferon (IFN)-free antivirals, lead to high cure rates with a very good safety profile in patients with HCV-cryoglobulinemia vasculitis.
- 2- IFN-free DAAs should be considered as first line for treatment of HCV-cryoglobulinemia vasculitis patients.
- 3- Immunosuppressive treatments (i.e. rituximab, glucocorticosteroids, cyclophosphamide and plasmapheresis) remain an interesting therapeutic approach, in severe form of HCV-cryoglobulinemia vasculitis, failure or contradiction to antiviral treatments.

1-Introduction:

Cryoglobulinemia is defined by the presence of circulating immunoglobulins that precipitate at cold temperature and dissolve with rewarming. Cryoglobulinemia is categorized by immunochemical analysis into three types [1]. Type I cryoglobulins are monoclonal immunoglobulins. Type II cryoglobulins consist of a monoclonal immunoglobulin with a rheumatoid factor (RF) activity associated with polyclonal IgG whereas type III cryoglobulins comprised polyclonal IgG and IgM with RF activity. Type II and III are often referred to as mixed cryoglobulinemia.

The cause of cryoglobulinemia depends to the immunochemical determination. In type I cryoglobulinemia vasculitis, it is mandatory to look for the presence of an underlying B-cell lymphoproliferative disorder, mainly Waldenström macroglobulinemia, multiple myeloma or monoclonal gammopathy of unknown significance. The main etiology of mixed cryoglobulins (type II and type III) is chronic hepatitis C virus (HCV) infection, representing 70 to 90% of mixed cryoglobulins. Of note, conversely the presence of a mixed cryoglobulin is identified in about 50% of patients HCV infected although only 10-15% of them have a symptomatic cryoglobulinemia vasculitis (CryoVas) [2,3]. Type II cryoglobulinemia composed of monoclonal IgM kappa is by far the most frequent in HCV-CryoVas patients. In case of persistent mixed cryoglobulin despite HCV clearance, a B-cell lymphoma should searched [4]. For rare cases of mixed cryoglobulins not associated with HCV infection, the main causes include other chronic infectious diseases, B cell malignancies and auto-immune diseases (mainly Sjögren syndrome and systemic lupus).

2-How to diagnose HCV related mixed cryoglobulinemia vasculitis?

2-1 Main clinical features

The disease expression is variable, ranging from mild clinical symptoms (fatigue, purpura, arthralgia) to fulminant life-threatening complications (glomerulonephritis, widespread vasculitis) [2,5,6]. Mixed cryoglobulinemia lesions in HCV infected patients are often related to small vessel vasculitis induced by immune complex deposits.

Fatigue is the main symptom, noted in 80-90% of patients. The main cutaneous sign is a palpable purpura (70 to 90%), which begins at the lower limbs and may extend to abdominal area, less frequently to the trunk and upper limbs. Cutaneous ulcers and cold associated symptoms (Raynaud's phenomenon, acrocyanosis) are less frequent.

Arthralgia (40-60%) usually involve large joints and are bilateral and symmetric. Arthralgia involve more frequently fingers, knee, ankles, and back. Frank arthritis is reported in less than 10% of patients without articular deformation or destruction. Sicca symptoms of either the mouth or eyes have been reported in 10-30% of HCV infected patients. Although sicca symptoms are very frequent in HCV infected patients, a characterized Sjögren's syndrome defined by the presence of anti-SSA or anti-SSB antibodies and a typical salivary gland histology is uncommon.

Neurologic manifestations (50-70%) are variable, ranging from pure sensory polyneuropathy to mononeuritis multiplex. The most frequently described form is a distal sensory or sensory-motor polyneuropathy. Polyneuropathy usually presents with painful, asymmetric paresthesia which later become symmetric. Motor deficit is inconstant, mainly affects the lower limbs and often appears a few years after sensory symptoms. Central nervous system involvement is infrequent (<10%) and may manifest as stroke, epilepsy or cognitive impairment.

Renal manifestations (20 to 40%) usually present as a proteinuria with microscopic hematuria and sometimes a variable degree of renal insufficiency. Histological analysis most often reveals an acute or chronic type-I membranoproliferative glomerulonephritis with sub-endothelial deposits.

Other severe manifestations are rare (<5%). Digestive involvement manifests as abdominal pains and gastrointestinal bleeding secondary to mesenteric vasculitis. Cardiac involvement is associated with significant mortality and includes mitral valvular damage, coronary vasculitis complicated by myocardial infarction, pericarditis or congestive cardiac failure. Lungs are rarely involved. However, some patients may experience interstitial lung fibrosis, pleural effusions or pulmonary intra-alveolar haemorrhages.

2-2 Mixed cryoglobulin and other biological surrogate markers

In order to confirm the diagnosis, the presence of cryoglobulinemia is investigated in the serum. Cryoglobulinemia is confirmed by the detection of protein which precipitate in the patient's serum maintained at 4°C during at least 7 days, and dissolved when heated at 37°C. In most expert center, patients are considered to have a significant cryoglobulin level when > 0.05 g/L on two determinations [5,7]. To avoid false-negative results due to immunoglobulin cold precipitation, blood sampling for cryoglobulin detection should be carried immediately after blood is drawn using a thermostable device (37°C). Serum should be kept warm and tests should be carried out at 37°C. Cryoglobulin detection should be repeated if first tests are negative although clinical features are suggestive of CryoVas.

Other laboratory surrogate markers, easier to detect than cryoglobulins, may provide indirect evidence of the presence of cryoglobulinemia. Specific but inconsistent complement abnormalities are observed, such as decreased early components (C1q, C2, C4) and CH50, with normal C3 level. The diagnosis of CryoVas is usually based on the association of clinical vasculitis symptoms, a cryoglobulinemia and a decreased C4 serum level. Rheumatoid factor

activity is also often found in patients with a mixed cryoglobulinemia, in contrast to type 1 cryoglobulins. Electrophoresis and immunoelectrophoresis reveal either a polyclonal hypergammaglobulinemia or a monoclonal component. A recent analysis of HCV infected patients with asymptomatic circulating cryoglobulin (CG) found increased levels of RF-IgG and Free Light Chain in CGs-ANA-positive patients, suggesting these test could be used to identify a state of “silent autoimmune condition” before the transition to a frank disease in asymptomatic HCV patients.[8].

2-3 In clinical daily practice

To summarize, the presence of purpura, weakness, polyneuropathy and renal involvement associated with decreased C4 serum level, the presence of mixed cryoglobulinemia and a positive Rheumatoid Factor (RF) represent the main clinical and biological signs of Cryovas. If HCV infection is not already diagnosed, searching for HCV is mandatory.

After HCV-CryoVas diagnosis, patients should be investigated for [9]: (i) Other vasculitis involvements, including arthritis, neuropathy (electromyogram alterations), glomerulonephritis (increased proteinuria, increased serum creatinine and GN at renal biopsy); (ii) B-cell lymphoproliferation (CT/PET scan, nodal or bone marrow biopsy); (iii) Other HCV extrahepatic complications including diabetes, dyslipidemia, cardiovascular events, thyroiditis...; and (iv) liver complications such as liver fibrosis (Fibrotest and Fibroscan) and the presence of hepatocellular carcinoma (liver ultrasound and serum level of α foeto-protein).

3-Prognosis

In a cohort of 151 HCV-associated MC vasculitis, the 1-year, 3-year, 5-year, and 10-year survival rates were 96%, 86%, 75%, and 63%, respectively. Baseline factors associated with a poor prognosis were the presence of severe liver fibrosis (hazard ratio [HR] 5.31), central nervous system involvement (HR 2.74), kidney involvement (HR 1.91), and heart involvement

(HR 4.2) [9,10]. The Five-Factors Score (FFS), a vasculitis scoring system based on five clinical items (proteinuria > 1 gr/day, serum creatinine >140 µmol/L, cardiomyopathy, severe gastrointestinal involvement and central nervous system involvement) with the presence of each being accorded one point, was significantly associated with outcome. In multivariate analysis, severe fibrosis (HR 10.8) and the FFS (HR 2.49) were significantly associated with a poor prognosis. [10] Among patients without severe fibrosis, the FFS was a good predictor of outcome, whereas among those with severe fibrosis, the severity of vasculitis had no prognostic value.

The most common causes of death in HCV-CryoVas are infection, end-stage liver disease, cardiovascular disease, and more rarely vasculitis (i.e. renal involvement with end-stage renal and CNS involvement) and lymphoma/neoplasia. [11,12]

4- How to treat HCV related mixed cryoglobulinemia vasculitis?

HCV-CryoVas manifestations improve or disappear when a sustained clearance of HCV is achieved [i.e. sustained virologic response (SVR)]. During the decade 2002-2012, antiviral therapy with Pegylated interferon (PegIFN) plus ribavirin for twelve months led to SVR in 50-60% of HCV-CryoVas patients (17,18). Patients who relapsed for HCV infection after responding to antiviral therapy usually relapsed for the vasculitis with the return of viremia (19). The use of triple HCV therapy combining PegIFN, ribavirin and a direct-acting antiviral (DAA) (NS3/4A protease inhibitor, i.e. boceprevir or telaprevir) led to improved SVR rates (65-70%) in HCV-CryoVas patients with genotype 1 infection [13,14]. However, such combination should be given for a long period (48 weeks) and serious adverse events occurred in up to 47% of patients [13].

Other second generation DAAs are now approved. The NS3/4A inhibitor simeprevir and NS5B inhibitor sofosbuvir allow shortened courses of IFN-free therapy, which are

associated with high (>95%) SVR rates and relatively few toxicities. In the first prospective, open-label trial, including 24 HCV-CryoVas patients (50% genotype 1, 50% cirrhosis) treated with sofosbuvir plus ribavirin, a clinical complete remission was achieved in 87.5% and SVR in 74% of patients at week 12 after the end of treatment [15]. The cryoglobulin level decreased from 0.35 to 0.15 g/L. Seven patients also received Rituximab. Antiviral therapy discontinuation was required in two (8%). In a retrospective case-series, including 12 HCV patients (50% cirrhosis, 67% genotype 1, 7 patients with kidney involvement) treated with sofosbuvir plus simeprevir (67%) or ribavirin (33%), the rate of SVR was 83% at 12 weeks after the end of treatment. [16] Four patients received Rituximab concomitant with DAA therapy. Median cryoglobulin levels decreased from 1.5% to 0.5%; cryoglobulins levels disappeared in 4/9 patients. Two patients had serious adverse events. Gragnani et al. have recently reported the results of a cohort of 44 consecutive patients with HCV-CryoVas [genotypes 1 (n=23), 2 (n=13), 3 (n=5) and 4 (n=3)] [17]. Patients were treated with sofosbuvir-based treatments [associated with ribavirin alone (n=18), or simeprevir (n=12), ledipasvir (n=10) or daclatasvir (n=4) plus ribavirin (n=9)]. Two patients with severe vasculitis received reduced dose of rituximab. All patients had negative HCV viremia at week 12 and at week 24 post-treatment, at which time all had a clinical response of vasculitis. The mean Birmingham Vasculitis Activity Score decreased from 5.41 at baseline to 2.35 at week 4 on treatment, then to 1.39 at SVR12 and 1.27 at SVR24. The mean cryocrit value fell from 7.2 % to 1.8 from baseline to SVR24. Only mild adverse events occurred in 59% of patients, except for one patient with ribavirin-related anemia requiring blood transfusion. In a nationwide Italian study, Kondili et al reported the disappearance or improvement of more than 50% of CryoVas symptoms in 31/37 (84%) of patients after DAA [18]. Finally, a Canadian group described 11 patients with HCV-CryoVas who received IFN-free DAA combinations (56 years old, 61% females, 57% cirrhotics) [19]. A full or partial clinical response of CryoVas was obtained in 91% and a

complete or partial immunological response in 81%. A full or partial renal response was noted in 80%. A serious adverse event was reported in only 12%.

Despite the evidence of the positive impact of effective antivirals on HCV-CryoVas symptoms, immunosuppression still remains a major treatment option. In case of severe CryoVas manifestations (severe renal impairment, skin necrosis, gut or CNS involvement...) or in patients with failure or contraindication to antivirals, Rituximab has shown a better efficacy than conventional immunosuppressive treatments (i.e., glucocorticoids, azathioprine, cyclophosphamide, or plasmapheresis) or placebo [20,21]. Addition of rituximab to Peg-IFN plus ribavirin led to a shorter time to clinical remission, better renal response rate, and higher rates of cryoglobulin clearance [22,23].

International guidelines [24] recommend to treat HCV infected patients with severe extra-hepatic manifestations such as CryoVas. More recently, multidisciplinary consensus- and evidence-based recommendations on the management of HCV-extrahepatic manifestations have been proposed [25]. They recommend to consider as first-line treatment IFN-free DAAs for HCV-CryoVas patients that do not need urgent/life threatening measures. As the degree of clinical improvement depends on the reversibility of the HCV-induced damage, early viral eradication is recommended. The choice of IFN-free DAA combination should follow general criteria for the treatment of HCV infection, accurately taking into account CryoVas complications (i.e. renal impairment). Both IFN- and RBV-free DAA combinations should be preferred in patients with kidney disease, ischemic tissue lesions (i.e., skin ulcers, ischemic heart disease) and anemia (i.e., lymphoproliferative disease). Accurate evaluation of the kidney damage is absolutely mandatory for the choice of DAA treatment and follow-up schedule [26].

In case of HCV-CryoVas needing urgent/life threatening measures, the combination of IFN-free DAA and non-etiological therapy can be allowed. The choice of non-etiological therapy should always take into account the severity of vasculitis, the degree of HCV-related liver

damage and, in case of DAAs co-administration, the possible drug-drug interactions. Non-etiological therapy include glucocorticoids, rituximab, cyclophosphamide and plasmapheresis. Such therapies should be useful also in less severe CryoVas cases when patients present persistent vasculitis manifestations despite antiviral treatment or have contraindication to antivirals. The persistence of immunological/laboratory abnormalities alone (i.e., cryoglobulinemia) after successful antiviral therapy in the absence of clinical manifestations, does not justify therapy. The presence of active CryoVas manifestations despite a SVR should lead to search for the presence of B-cell lymphoma.

5-Conclusion

The treatment of HCV-associated MC vasculitis has much changed during the last months. The recent emergence of new direct acting IFN-free antivirals, enabling high cure rates with a good safety profile should permit to cure most patients with HCV-CryoVas. Immunosuppressive treatments remain an interesting therapeutic approach, in rare cases of severe HCV-CryoVas, failure or contradiction of antiviral treatments.

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