Cryoglobulinemia vasculitis: an update

Benjamin Terrier[a,b,c,d] *and Patrice Cacoub*[a,b,c,d]

Purpose of review
Cryoglobulinemia vasculitis (CryoVas) is a small-vessel vasculitis associated with chronic infections [in particular hepatitis C virus, (HCV)], autoimmune disorders and B-cell lymphoproliferative disorders. The most recent studies on its diagnosis, prognosis and therapeutic management are reviewed here.

Recent findings
Large series of patients with HCV-positive and negative mixed CryoVas and patients with monoclonal type I CryoVas have described the presentation and the prognosis of patients with CryoVas in the era of HCV screening. European experts in the field of CryoVas developed new classification criteria for its diagnosis. Finally, French, Italian and North American clinical studies demonstrated that rituximab-based regimens were highly effective in comparison with corticosteroids alone or other immunosuppressive agents-based therapy. However, rituximab seems to be associated with an increased risk of severe infections in a subset of patients.

Summary
Recent studies identified prognostic factors of survival and demonstrated that rituximab is highly effective but remains associated with severe infections in a subset of patients. These results could support individual therapeutic stratification according to the clinical pattern and associated comorbidities.

Keywords
cryoglobulinemia, hepatitis C virus, prognosis, treatment, vasculitis

INTRODUCTION

Cryoglobulinemia vasculitis (CryoVas) is a small vessel vasculitis involving the skin, the joints, the peripheral nerve system and the kidneys. During the last 15 years, progress has been made after the discovery of the hepatitis C virus (HCV), which represents the cause of CryoVas in roughly 80% [1–4]. Besides HCV infection, B-cell lymphoproliferative disorders, autoimmune diseases and other infections represent the main causes. In the absence of identified causal factor, CryoVas is defined as essential. The prevalence and the incidence of CryoVas are unknown, in particular because of the heterogeneity in the cause, the clinical presentation and the geographical distribution. However, the prevalence of the disease was initially reported as approximately 10 per million inhabitants [5]. CryoVas appears more common in patients aged 45–65 years, with a maximum incidence in women (sex ratio women/men 2–3/1) [3,6]. No predominant ethnicity is found in the disease.

LABORATORY FINDINGS

The detection of cryoglobulinemia has an excellent diagnostic performance for CryoVas in the context of clinical symptoms suggestive of vasculitis. Cryoglobulinemia is confirmed by the detection of protein precipitates in the patient's serum maintained at 4°C during at least 7 days, which dissolved when heated at 37°C. Cryoglobulins are immunochemically characterized into three types by the method of Brouet *et al.* [4]. Type I cryoglobulins are single monoclonal immunoglobulins always linked to a B-cell lymphoproliferative disorder. Type II cryoglobulins consist of polyclonal IgG with monoclonal IgM with rheumatoid factor activity. Type III cryoglobulins comprise polyclonal IgG and polyclonal IgM with rheumatoid factor activity. Type II and III are often referred to as mixed cryoglobulinemia, and may be linked to B-cell

[a]UPMC Univ Paris 06, UMR 7211, F-75005, Paris, France, [b]INSERM, UMR_S 959, F-75013, Paris, France, [c]CNRS, UMR 7211, F-75005, Paris, France and [d]AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Paris, France

Correspondence to Professor Patrice Cacoub, Department of Internal Medicine, Hôpital Pitié-Salpétrière, 47-83 boulevard de l'Hôpital, 75013 Paris, France. Tel: +33 1 42 17 80 09; fax: +33 1 42 17 80 33; e-mail: patrice.cacoub@psl.aphp.fr

Curr Opin Rheumatol 2013, 25:10–18
DOI:10.1097/BOR.0b013e32835b15f7

KEY POINTS

- Recent studies identified prognostic factors of survival in patients with mixed CryoVas, but their interest in daily practice remains to be determined in prospective cohorts and clinical trials.
- Rituximab showed to be dramatically effective in patients with mixed CryoVas, HCV-infected or not, but remains associated with severe infections in a subset of patients.
- In type I CryoVas, besides alkylating agents, the use of rituximab, thalidomide or lenalinomide, and bortezomib-based regimens seem to be interesting alternative options, but the exact role of each strategy remains to be defined.

lymphoproliferative disorder, autoimmune disorders, and/or infections [4]. Testing methods may be influenced by artifacts arising from ex-vivo cryoprecipitation after blood drawing. In consequence, when a cryoglobulin is suspected, serum should be kept warm, and tests should be carried out at 37°C. Apart from the detection of serum cryoglobulin itself, other laboratory abnormalities may provide surrogate evidence of the presence of cryoglobulinemia such as low C4 serum complement fraction, decreased total hemolytic complement levels, presence of a serum monoclonal immunoglobulin or rheumatoid factor activity. Hypocomplementemia is a sensitive and important finding in CryoVas, being found in 70–90% of mixed cryoglobulinemia patients. Serum cryoglobulin may also interfere with a variety of laboratory tests and have been associated with spurious quantitation of plasma proteins and erythrocyte sedimentation rate, pseudo-leucocytosis, pseudo-thrombocytosis or pseudo-macrocytosis.

During follow-up, biological improvement can be assessed by the quantification of cryoglobulinemia and other surrogate markers (C4, CH50, rheumatoid factor). However, cryoglobulinemia may persist despite clinical response of vasculitis under therapy. In the case of HCV-related mixed cryogloublinemia, the time course of HCV viral load also represents a major predictive factor of long-term outcome.

NEW INSIGHTS ON PRESENTATION OF TYPE I AND MIXED CRYOGLOBULINEMIA VASCULITIS

The most frequently targeted organs are skin, joints, nerves and kidney. The disease expression is variable, ranging from mild clinical symptoms (purpura, arthralgia) to fulminant life-threatening complications (glomerulonephritis, widespread vasculitis). Skin is the most frequently involved target organ and is the direct consequence of the small size vessel vasculitis. The main sign is a palpable purpura, but chronic cutaneous ulcers may occur. Raynaud's phenomenon and acrocyanosis, which may evolve to digital ulcerations, can also occur. Neurologic manifestations range from pure sensory axonopathy 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 becomes symmetric. Less frequently, multiple mononeuropathy may occur. Renal involvement is an acute or chronic type-I membranoproliferative glomerulonephritis with sub-endothelial deposits. It represents 70–80% of cryoglobulinemia renal diseases and it is strongly associated with the type II IgM κ mixed cryoglobulinemia. The most frequent presentation is proteinuria with microscopic hematuria and a variable degree of renal insufficiency.

Since very recently, large series on presentation of type I CryoVas were lacking, and previous studies on mixed CryoVas were derived from older studies that included patients who were uninfected or infected with hepatits C. The large series from the French nationwide CryoVas survey was designed to describe the presentation and to evaluate efficacy and tolerance of treatments in patients with noninfectious CryoVas in the era of HCV screening [7▪▪,8▪,9▪]. The most common clinical and immunological manifestations in HCV-positive and negative patients with CryoVas are shown in Table 1 [7▪▪,8▪,9▪,10].

The CryoVas survey showed that, compared with patients with type III mixed cryoglobulinemia, patients with noninfectious type II mixed cryoglobulinemia had more frequent purpura, peripheral neuropathy and renal involvement, higher cryoglobulin levels, and lower C3 and C4 complement fractions. No significant difference was found in the demographical and clinicobiological presentation between patients with essential mixed CryoVas and B-cell lymphoma-related CryoVas, except for higher median cryoglobulin level in those with B-cell lymphoma. In contrast, compared with patients with essential mixed CryoVas, those with connective tissue disease were younger and more frequently women, had more frequently peripheral neuropathy and tended to have less frequent renal involvement [7▪▪]. Apart from HCV infection, which remains the most frequent cause, the causative factors associated with noninfectious mixed CryoVas were connective tissue disease in 30% (primarily

Table 1. Clinical and biological features of patients with cryoglobulinemia vasculitis according to immunochemical type and hepatitis C virus status

HCV status	HCV−		HCV+
Type	Monoclonal	Mixed	Mixed
Number of patients	64	242	165
Age (years)	65	63	60
Women (%)	56	69	54
Clinical features			
Skin (%)	86	83	76
Purpura (%)	69	75	71
Raynaud phenomenon (%)	30	26	–
Necrosis (%)	28	16	1
Ulcers (%)	27	14	4
Livedo (%)	13	2	4
Joints (%)	28	40	53
Peripheral neuropathy (%)	44	52	74
Central nervous system (%)	0	2	9
Kidney (%)	30	35	34
Gastrointestinal (%)	0	5	7
Biological features			
Cryoglobulin (g/l)	1.55	0.94	1.04
C4 (g/l)	0.09	0.07	0.09

Normal cryoglobulin level is less than 0.05 g/l. Normal C4 complement fraction level is 0.14–0.40 g/l.

Sjögren syndrome), B-cell lymphoma in 22%, and essential mixed CryoVas in 48% [7▪▪].

Regarding type I CryoVas, patients were characterized by more frequent severe cutaneous involvement (i.e. necrosis and ulcers) in almost half of the patients and high serum cryoglobulin levels, and a lower frequency of glomerulonephritis than in mixed CryoVas. Type I CryoVas was always associated with B-cell lymphoproliferative disorders, but approximately half of patients had only benign B-cell lymphoproliferation, i.e. monoclonal gammopathy of unknown significance (MGUS) [9▪].

PROPOSITION OF CLASSIFICATION CRITERIA FOR CRYOGLOBULINEMIA VASCULITIS

The diagnosis of CryoVas is rarely challenging, and was based so far in clinical studies [11–13] on the detection of serum cryoglobulins in association with purpura, arthralgia and weakness, and sometimes with renal or neurologic involvement.

As classification criteria were lacking, in contrast to other vasculitis, such as giant cell arteritis or granulomatosis with polyangeitis (Wegener's), a study [14▪] involving different European experts was performed. This study was divided into two parts, the first dedicated to the development of a questionnaire showing the highest sensitivity and specificity for CryoVas, which was then included in the second part of the study, in which the standard methodology for classification studies was used. The preliminary classification criteria for the CryoVas are as follows [14▪]:

(1) Patients were classified as having CryoVas, if at least two of the three items (questionnaire, clinical, laboratory) were positive.
(2) The patient must be positive for serum cryoglobulins in at least two determinations at 12 weeks' interval or less.
(3) Questionnaire item: at least two out of the following:
   (a) Do you remember one or more episodes of small red spots on your skin, particularly involving the lower limbs?
   (b) Have you ever had red spots on your lower extremities, which leave a brownish color after their disappearance?
   (c) Has a doctor ever told you that you have viral hepatitis?

(4) Clinical item: at least three out of the following four (present or past)
   (a) Constitutional symptoms: fatigue, low-grade fever, fever (>38°C, no cause), fibromyalgia.
   (b) Articular involvement: arthralgias, arthritis.
   (c) Vascular involvement: purpura, skin ulcers, necrotizing vasculitis, hyperviscosity syndrome, Raynaud's phenomenon.
   (d) Neurologic involvement: peripheral neuropathy, cranial nerve involvement, vasculitic central nervous system involvement.
(5) Laboratory item: at least two out of the following three (present)
   (a) Reduced serum C4.
   (b) Positive serum rheumatoid factor.
   (c) Positive serum M component.

A comparison of the performance of these classification criteria was made between HCV-positive and HCV-negative patients with serum cryoglobulins. In HCV-negative patients, the sensitivity and specificity of the classification criteria were 89.5 and 90.3%, respectively, whereas in HCV-positive patients they were 88.3 and 96.1%, respectively [15].

In contrast, we think that universal criteria to response to therapy should be developed in CryoVas to allow a better evaluation of new therapeutic strategies.

PROGNOSIS OF CRYOGLOBULINEMIA VASCULITIS

CryoVas is associated with significant morbidity and mortality. The worse prognostic factors in previous studies were age (>60 years) and renal involvement [16,17], with renal failure being reported as the main cause of death [5,11,16–18], followed by liver involvement, cardiovascular disease, infection and lymphoma [17]. Along this line, the cumulative 10-year probability of survival of patients with CryoVas-related glomerulonephritis was 49% [16]. However, most of these results were derived from old heterogeneous studies performed before the discovery of HCV. A retrospective study by Saadoun *et al.* [3] in the HCV era, including non-HCV patients with mixed cryoglobulinemia, reported a poor outcome and a four-fold increased risk of developing B-cell nonHodgkin lymphoma (B-NHL). In multivariate analysis, a serum cryoglobulin level higher than 0.6 g/l [odds ratio (OR), 1.44] and the presence of cryoglobulinemic vasculitis (OR, 4.3) and hypogammaglobulinemia (OR, 6.7) were independently associated with B-NHL. Fourteen percent of patients died, and the main cause of death was serious infections. An age at diagnosis older than 60 years (OR, 1.06) and renal involvement (OR, 5.20) were independently associated with death.

Recent studies described the prognosis of patients with HCV-positive and negative CryoVas, and identified prognostic factors of survival. In HCV-positive patients, the 1-year, 3-year, 5-year, and 10-year survival rates were 96, 86, 75, and 63, respectively. Deaths were mainly related to serious infections and end-stage liver disease. Baseline factors associated with a poor prognosis were the presence of severe liver fibrosis [hazard ratio (HR) 5.31], that is Metavir fibrosis score at least 3, central nervous system involvement (HR 2.74), kidney involvement (HR 1.91), and heart involvement (HR 4.2).

The Five-Factor Score (FFS), a vasculitis scoring system based on five clinical items (proteinuria >1 g/day, serum creatinine >140 μmol/l, cardiomyopathy, severe gastrointestinal involvement and central nervous system involvement) with the presence of each being accorded 1 point [19], 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. 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. Treatment with the combination of PEGylated interferon and ribavirin was associated with a good prognosis (HR 0.34), whereas treatment with immunosuppressive agents was associated with a poor outcome, even after adjustment for the severity of vasculitis (HR 4.05) [10].

In HCV-negative patients, a recent study analyzed baseline factors associated with prognosis in patients with noninfectious mixed CryoVas. One-year, 2-year, 5-year and 10-year overall survival rates were 91, 89, 79 and 65, respectively. Deaths were related to serious infections in half of cases and to vasculitis flare in roughly 20%. Pulmonary and gastrointestinal involvement, glomerular filtration rate less than 60 ml/min and age more than 65 years were independently associated with death. A prognostic score including these variables, the CryoVas score (CVS), for the prediction of survival at 5 years was devised. One point score was assigned to each prognostic variable. At 5 years, the death rates were 2.6, 13.1%, 29.6% and 38.5% for a CVS of 0, 1, 2 and at least 3, respectively. At 1 year, the death rates were 0, 3.2, 18.5 and 30.8% for a CVS of 0, 1, 2 and at least 3, respectively. The area under the curve for the CVS was higher compared with the FFS 2009 [20], indicating a better performance of the CVS [10].

Data on the prognosis of type I CryoVas were lacking so far. The CryoVas survey has reported data on 64 patients with type I CryoVas. In this study, the

1-year, 3-year, 5-year and 10-year survival rates were 97, 94, 94 and 87%, respectively. Type I CryoVas related to hematologic malignancy tended to be associated with a poorer prognosis compared with MGUS.

Severe infections accounted for half of the deaths. Along this line, the prognosis of type I CryoVas did not seem to be as poor as previously thought [9▪].

Overall survival according to the type of cryoglobulinemia is represented in Fig. 1.

THERAPEUTIC MANAGEMENT OF CRYOGLOBULINEMIA VASCULITIS

The therapeutic management of CryoVas must be individualized according to the underlying disorder and the severity of disease. Prior to the discovery of HCV infection, patients with CryoVas were all treated as other forms of systemic vasculitis based on data derived from small uncontrolled studies. In severe systemic disease, patients were treated aggressively with high-dose corticosteroids, immunsuppressants (mainly cyclophosphamide) and/or plasmapheresis. Interestingly and in the absence of evidence of a viral etiology, the empiric use of interferon (IFN)-α, as an antiproliferative agent, was thought to be an effective treatment for CryoVas [21]. With the discovery of HCV as the causative agent for most cases of mixed CryoVas, new opportunities and problems for crafting therapy have emerged, according to the HCV status (Fig. 2).

Mixed cryoglobulinemia vasculitis in hepatitis C virus-infected patients

In patients with HCV infection, the combination of an optimal antiviral regimen, that is pegylated IFN-α with ribavirin, which is the current standard of care for patients with mild-to-moderate disease activity [22,23], whereas more aggressive treatment is needed in patients presenting with severe disease. Corticosteroids, used alone or in addition to IFN-α, did not favourably affect the response of HCV-related vasculitic manifestations in two controlled studies [24,25]. In one randomized trial, methylprednisolone alone given for 1 year was associated with clinical response in 22% of patients, compared with 66 and 71% in patients receiving IFN-α or IFN-α and methyprednisolone, respectively [26]. The use of immunosuppressants is associated with a poor outcome with an increased mortality after adjustment for vasculitis severity in a recent study [10] analyzing clinical, biological and therapeutic factors associated with prognosis in the antiviral therapy era. In contrast, short-term corticosteroids and/or plasmapheresis were not associated with a poor outcome and could be used according to initial presentation in order to control severe and life-threatening manifestations. However, these therapies do not succeed in the long-term control of vasculitis in the absence of antiviral therapy. It should be underlined that recent advances in HCV therapy including pegylated IFN-α with ribavirin and a protease inhibitor (Telaprevir or Boceprevir) permit a sustained virological response in up to 80% infected by a hepatitis C genotype 1. Ongoing studies in Cryovas HCV-infected patients should increase the response rates compared with pegylated IFN-α with ribavirin.

Several groups have reported on the efficacy of rituximab, an anti-CD20 monoclonal antibody, in patients with HCV-mixed CryoVas naïve, resistant or intolerant to antiviral therapy [27–31]. Two clinical trials published in 2010 compared the efficacy and safety profile of Peg-IFN-α/ribavirin and rituximab and Peg-IFN-α/ribavirin. In both studies, compared with Peg-IFN-α/ribavirin, rituximab and Peg-IFN-α/ribavirin-treated patients had a shorter time to clinical remission, better renal response

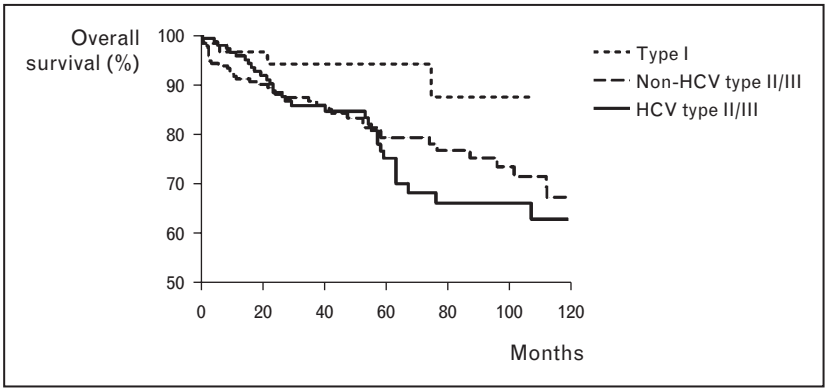

FIGURE 1. Kaplan–Meier estimate of the survival rates in CryoVas according to the type of cryoglobulin and hepatitis C virus status.

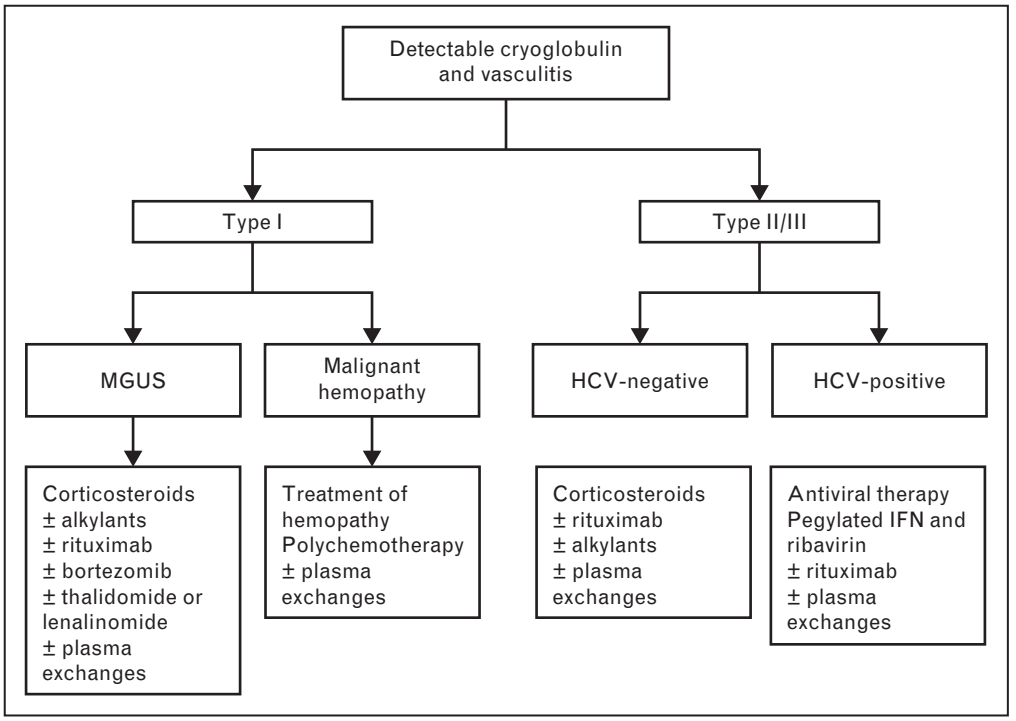

FIGURE 2. Therapeutic management according to the type of cryoglobulin and hepatitis C virus status.

rates, and higher rates of cryoglobulin clearance [12,13]. Treatment was well tolerated with no worsening of HCV viremia under rituximab [13,31]. These findings indicate that rituximab combined with Peg-IFN-α/ribavirin is well tolerated and more effective than Peg-IFN-α/ribavirin in HCV-positive patients with CryoVas. In our view, the use of Peg-IFN-α/ribavirin during 12 months should remain the standard of care for patients with mild-to-moderate HCV-related mixed CryoVas. In patients with severe disease and/or renal involvement, and in those in which rapid clinical response is needed, rituximab combined with Peg-IFN-α/ribavirin should be preferred, with the following therapeutic schedule: weekly administration of four intravenous (i.v.) infusions of rituximab at 375 mg/m^2 (on days 1, 8, 15 and 22) over a 1-month period; Peg-IFN-α/ribavirin started after the last rituximab infusion for a duration of 12 months.

More recently, De Vita *et al.* reported the results of a multicenter phase III randomized controlled trial in 57 patients with type II CryoVas (including 53 HCV-positive patients), comparing conventional treatment (i.e. consisting of one of the following three: glucocorticoids; azathioprine or cyclophosphamide; or plasmapheresis) and rituximab. None of the HCV-positive patients received concomitant antiviral therapy, because it had previously failed ($n = 28$) or was not indicated ($n = 25$). Survival of treatment at 12 months (i.e., the proportion of patients who continued taking their initial therapy) was statistically higher in the rituximab group (64.3 vs. 3.5%, $P < 0.0001$), and the Birmingham Vasculitis Activity Score decreased only after treatment with rituximab, indicating the absence of efficacy of conventional treatment in HCV-positive patients [32▪▪]. In our view, the absence of antiviral therapy in this study is detrimental for patients from the nonrituximab group. First, we think that antiviral therapy should always be indicated in HCV-positive patients with CryoVas, and second, immunosuppressants were previously found to be ineffective and associated with a poor outcome with an increased mortality. Sneller *et al.* [33▪▪] reported the results of a single-center, open-label, randomized controlled trial of rituximab compared with conventional immunosuppressive therapy (glucocorticoids, cyclophosphamide, plasma exchanges or methotrexate) for HCV-associated CryoVas in patients in whom antiviral therapy had failed to induce remission. A total of 24 patients were enrolled (12 in each treatment group). Remission at month 6 was statistically higher in the rituximab group (83 vs. 8%, $P < 0.0001$). The median duration of remission for rituximab-treated patients was 7 months, and the safety profile was good. These findings indicate that rituximab monotherapy is an effective and well tolerated option for severe CryoVas in HCV-positive patients nonresponders to antiviral therapy.

Noninfectious mixed cryoglobulinemia vasculitis

In contrast to HCV-mixed cryoglobulinemia, the therapeutic management of idiopathic CryoVas has yet to be defined as no study has evaluated the best strategies. In patients with mild-to-moderate CryoVas, treatment may include the avoidance of cold temperatures, resting in case of purpura, and nonaggressive medications, such as nonsteroidal anti-inflammatory drugs, colchicine, and disulone. Treatment of severe CryoVas is based on a combination of corticosteroids and immunosuppressants, rituximab or plasmapheresis.

We reported in 2010 on the safety and efficacy of rituximab in 23 patients with noninfectious CryoVas that were included in the French AutoImmunity and Rituximab registry [34]. Rituximab seemed to be highly effective in patients with CryoVas. However, tolerance was marked by the occurrence of side effects in almost half of patients, including severe infections in 26%, with a rate of 14.1/100 patient-years (compared with 5.0/100 patient-years in rheumatoid arthritis patients in the same registry [35]). These infections occurred in a particular subset of patients with age more than 70 years, essential type II CryoVas, renal failure with GFR less than 60 ml/min and using high-dose corticosteroids. Recently, we analyzed the efficacy and safety of treatments in the largest series published so far of patients with noninfectious mixed CryoVas ($n = 242$). With the use of Cox-marginal structural models, rituximab and corticosteroids showed the greater therapeutic efficacy compared with corticosteroids alone and alkylating agents and corticosteroids to achieve complete clinical, renal, and immunologic responses and a prednisone dosage less than 10 mg per day at 6 months. However, this regimen was also associated with severe infections, particularly when high doses of corticosteroids were used, whereas death rates did not differ between the therapeutic regimens [7▪▪]. These findings suggest, in the absence of randomized controlled trials in patients with noninfectious CryoVas, that rituximab (weekly administration of four i.v. infusions of rituximab at 375 mg/m^2 over a 1-month period) is probably the most effective therapy but remains associated with severe infections in a subset of patients.

Type I cryoglobulinemia vasculitis

Type I CryoVas are often life-threatening because of the severity of cutaneous and visceral involvement and the underlying malignant hemopathy. Recent studies underlined the potential interest of rituximab, bortezomib or thalidomide and lenalinomide-based regimen for the treatment of type I CryoVas [9▪,36]. In patients with type I CryoVas-related to malignant hemopathy, treatment of vasculitis is that of hemopathy and based on polychemotherapy, but specific treatment may also be indicated, including plasma exchange or iloprost, in particular for ulceronecrotic cutaneous lesions. In patients with underlying multiple myeloma, some authors suggest that treatment approaches for severe type I CryoVas should systematically involve plasmapheresis at the onset of the disease to achieve a rapid control of the cryoglobulinemia, and that specific myeloma treatments should be introduced early to avoid relapse [36]. In patients with type I CryoVas related to MGUS, the therapeutic management is more hazardous, ranging from corticosteroids alone to alkylating agents or rituximab-based regimen and other new biological agents such as bortezomib, thalidomide and lenalinomide, in severe and/or refractory patients. The efficacy of rituximab in type I CryoVas remains controversial [37,38]. The absence of CD20 expression on plasma cells was supposed to explain its lack of efficacy, and exacerbations of vasculitis in association with increased cryoglobulin levels following rituximab infusion have been previously reported [37]. It has been suggested that CD20 cross-linking could provoke cryoglobulin release through massive B-cell apoptosis or activation, raising some concerns as to the use of rituximab in these patients. Recent data from the French nationwide CryoVas survey reported a response to rituximab in 80% of patients in first-line or second-line treatment, supporting its use in naïve or relapsing/refractory patients. In the same study [9▪], vasculitis flares were noted within 48 h following rituximab infusion in 13% of patients. Regarding the use of new biological agents, bortezomib-based regimen was shown to be effective in 86% of the patients, which was very similar to thalidomide and lenalinomide that showed an efficacy rate of 83%, with a good tolerance profile for both drugs [9▪]. Overall, these findings suggest that in patients with severe and/or refractory MGUS-related type I CryoVas, rituximab, cyclophosphamide, thalidomide or lenalinomide, and bortezomib-based regimens could be interesting alternative options when combined with corticosteroids. Therapeutic schedules should probably be similar to those in malignant hemopathy. The patients' profiles and the type of organ involvement could help practitioners choose between these different therapeutic regimens. For instance, the use of thalidomide, lenalinomide and bortezomib should probably be avoided in patients with CryoVas-related peripheral neuropathy, because of the

common induction of neuropathy in patients treated with these drugs.

CONCLUSION

Recent studies identified prognostic factors of survival, but the interest of such factors for the stratification of therapeutic strategies in clinical daily practice remains to be determined in prospective cohorts and clinical trials. In mixed CryoVas, rituximab showed to be dramatically effective but remains associated with severe infections in a subset of patients. In type I CryoVas, besides alkylating agents, the use of rituximab, thalidomide or lenalinomide, and bortezomib-based regimens seem to be interesting alternative options, but the exact role of each strategy remains to be defined.

Acknowledgements

None.

Conflicts of interest

Authors declare to have no conflict of interest relevant to this article.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 146).

1. Cacoub P, Poynard T, Ghillani P, *et al.* Extrahepatic manifestations of chronic hepatitis C. MULTIVIRC Group. Multidepartment Virus C. Arthritis Rheum 1999; 42:2204–2212.
2. Trejo O, Ramos-Casals M, Garcia-Carrasco M, *et al.* Cryoglobulinemia: study of etiologic factors and clinical and immunologic features in 443 patients from a single center. Medicine (Baltimore) 2001; 80:252–262.
3. Saadoun D, Sellam J, Ghillani-Dalbin P, *et al.* Increased risks of lymphoma and death among patients with nonhepatitis C virus-related mixed cryoglobulinemia. Arch Intern Med 2006; 166:2101–2108.
4. Brouet JC, Clauvel JP, Danon F, *et al.* Biologic and clinical significance of cryoglobulins: a report of 86 cases. Am J Med 1974; 57:775–788.
5. Gorevic PD, Kassab HJ, Levo Y, *et al.* Mixed cryoglobulinemia: clinical aspects and long-term follow-up of 40 patients. Am J Med 1980; 69:287–308.
6. Ferri C, Zignego AL, Pileri SA. Cryoglobulins. J Clin Pathol 2002; 55:4–13.
7. ■■ Terrier B, Krastinova E, Marie I, *et al.* Management of noninfectious mixed cryoglobulinemia vasculitis: data from 242 cases included in the CryoVas survey. Blood 2012; 119:5996–6004.

This study is the largest series published so far on noninfectious mixed CryoVas that aimed to analyze efficacy and safety of treatments. Rituximab and corticosteroids showed the greater therapeutic efficacy compared with corticosteroids alone and alkylating agents and corticosteroids. However, rituximab plus corticosteroid regimen was also associated with severe infections, particularly when high doses of corticosteroids were used. Death rates did not differ between the therapeutic regimens.

8. ■ Terrier B, Carrat F, Krastinova E, *et al.* Prognostic factors of survival in patients with noninfectious mixed cryoglobulinaemia vasculitis: data from 242 cases included in the CryoVas survey. Ann Rheum Dis 2012. [Epub ahead of print]

This study identifies prognostic factors of survival in noninfectious mixed CryoVas and determined a prognostic score to predict survival at 5 years. Pulmonary and gastrointestinal involvement, glomerular filtration rate less than 60 ml/min and age more than 65 years were independently associated with death. At 5 years, the death rates were 2.6, 13.1, 29.6 and 38.5% for a prognostic score of 0, 1, 2 and at least 3, respectively. The CryoVas score had a better performance than the Five Factor Score 2009 dedicated to necrotizing vasculitis.

9. ■ Terrier B, Karras A, Kahn JE, *et al.* The spectrum of type I cryoglobulinemia vasculitis: New insights based on 64 cases. Medicine (Baltimore) 2012 (in press).

This article reports the results of the analysis of 64 patients with type I CryoVas, which represents the largest series published so far. Type I monoclonal CryoVas was characterized by severe cutaneous involvement and high serum cryoglobulin levels, contrasting with a lower frequency of glomerulonephritis than expected. Therapeutic regimens based on alkylating agents, rituximab, thalidomide or lenalinomide and bortezomib showed similar efficacy on vasculitis manifestations, with clinical response rate from 80 to 86%.

10. Terrier B, Semoun O, Saadoun D, *et al.* Prognostic factors in patients with hepatitis C virus infection and systemic vasculitis. Arthritis Rheum 2011; 63:1748–1757.
11. Meltzer M, Franklin EC, Elias K, *et al.* Cryoglobulinemia–a clinical and laboratory study. II. Cryoglobulins with rheumatoid factor activity. Am J Med 1966; 40:837–856.
12. Dammacco F, Tucci FA, Lauletta G, *et al.* Pegylated interferon-{alpha}, ribavirin, and rituximab combined therapy of hepatitis C virus-related mixed cryoglobulinemia: a long-term study. Blood 2010; 116:343–353.
13. Saadoun D, Resche Rigon M, Sene D, *et al.* Rituximab plus Peg-interferon-{alpha}/ribavirin compared with Peg-interferon-{alpha}/ribavirin in hepatitis C-related mixed cryoglobulinemia. Blood 2010; 116:326–334.
14. ■ De Vita S, Soldano F, Isola M, *et al.* Preliminary classification criteria for cryoglobulinaemic vasculitis. Ann Rheum Dis 2011; 70:1183–1190.

A panel of European experts proposed classification criteria for the diagnosis of cryoglobulinemia vasculitis.

15. Quartuccio L, Isola M, Corazza L, *et al.* Performance of the preliminary classification criteria for cryoglobulinaemic vasculitis and clinical manifestations in hepatitis C virus-unrelated cryoglobulinaemic vasculitis. Clin Exp Rheumatol 2012; 30:S48–S52.
16. Tarantino A, Campise M, Banfi G, *et al.* Long-term predictors of survival in essential mixed cryoglobulinemic glomerulonephritis. Kidney Int 1995; 47:618–623.
17. Ferri C, Sebastiani M, Giuggioli D, *et al.* Mixed cryoglobulinemia: demographic, clinical, and serologic features and survival in 231 patients. Semin Arthritis Rheum 2004; 33:355–374.
18. Della Rossa A, Tavoni A, D'Ascanio A, *et al.* Mortality rate and outcome factors in mixed cryoglobulinaemia: the impact of hepatitis C virus. Scand J Rheumatol 39:167–170.
19. Guillevin L, Lhote F, Gayraud M, *et al.* Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome: a prospective study in 342 patients. Medicine (Baltimore) 1996; 75:17–28.
20. Guillevin L, Pagnoux C, Seror R, *et al.* The Five-Factor Score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. Medicine (Baltimore) 2011; 90:19–27.
21. Bonomo L, Casato M, Afeltra A, Caccavo D. Treatment of idiopathic mixed cryoglobulinemia with alpha interferon. Am J Med 1987; 83:726–730.
22. Cacoub P, Lidove O, Maisonobe T, *et al.* Interferon-alpha and ribavirin treatment in patients with hepatitis C virus-related systemic vasculitis. Arthritis Rheum 2002; 46:3317–3326.
23. Saadoun D, Resche-Rigon M, Thibault V, *et al.* Antiviral therapy for hepatitis C virus–associated mixed cryoglobulinemia vasculitis: a long-term followup study. Arthritis Rheum 2006; 54:3696–3706.
24. Casato M, Agnello V, Pucillo LP, *et al.* Predictors of long-term response to high-dose interferon therapy in type II cryoglobulinemia associated with hepatitis C virus infection. Blood 1997; 90:3865–3873.
25. Misiani R, Bellavita P, Fenili D, *et al.* Interferon alfa-2a therapy in cryoglobulinemia associated with hepatitis C virus. N Engl J Med 1994; 330:751–756.
26. Dammacco F, Sansonno D, Han JH, *et al.* Natural interferon-alpha versus its combination with 6-methyl-prednisolone in the therapy of type II mixed cryoglobulinemia: a long-term, randomized, controlled study. Blood 1994; 84:3336–3343.
27. Zaja F, De Vita S, Mazzaro C, *et al.* Efficacy and safety of rituximab in type II mixed cryoglobulinemia. Blood 2003; 101:3827–3834.
28. Sansonno D, De Re V, Lauletta G, *et al.* Monoclonal antibody treatment of mixed cryoglobulinemia resistant to interferon alpha with an anti-CD20. Blood 2003; 101:3818–3826.
29. Roccatello D, Baldovino S, Rossi D, *et al.* Long-term effects of anti-CD20 monoclonal antibody treatment of cryoglobulinaemic glomerulonephritis. Nephrol Dial Transplant 2004; 19:3054–3061.
30. Saadoun D, Resche-Rigon M, Sene D, *et al.* Rituximab combined with Peg-interferon-ribavirin in refractory hepatitis C virus-associated cryoglobulinaemia vasculitis. Ann Rheum Dis 2008; 67:1431–1436.
31. Terrier B, Saadoun D, Sene D, *et al.* Efficacy and tolerability of rituximab with or without PEGylated interferon alfa-2b plus ribavirin in severe hepatitis C virus-related vasculitis: a long-term followup study of thirty-two patients. Arthritis Rheum 2009; 60:2531–2540.
32. ■■ De Vita S, Quartuccio L, Isola M, *et al.* A randomized controlled trial of rituximab for the treatment of severe cryoglobulinemic vasculitis. Arthritis Rheum 2012; 64:843–853.

The results of this trial showed that rituximab monotherapy is effective and well tolerated in hepatitis C virus-related CryoVas compared with conventional immunosuppressive agents.

33. Sneller MC, Hu Z, Langford CA. A randomized controlled trial of rituximab ■■ following failure of antiviral therapy for hepatitis C virus-associated cryoglobulinemic vasculitis. Arthritis Rheum 2012; 64:835–842.
The results of this trial showed that rituximab monotherapy is effective and well tolerated in hepatitis C virus-related CryoVas compared with conventional immunosuppressive agents.

34. Terrier B, Launay D, Kaplanski G, *et al.* Safety and efficacy of rituximab in nonviral cryoglobulinemia vasculitis: data from the French Autoimmunity and Rituximab registry. Arthritis Care Res (Hoboken) 2010; 62:1787–1795.

35. Gottenberg JE, Ravaud P, Bardin T, *et al.* Risk factors for severe infections in patients with rheumatoid arthritis treated with rituximab in the autoimmunity and rituximab registry. Arthritis Rheum 2010; 62:2625–2632.

36. Payet J, Livartowski J, Kavian N, *et al.* Type I cryoglobulinemia in multiple myeloma, a rare entity: analysis of clinical and biological characteristics of seven cases and review of the literature. Leuk Lymphoma 2012. [Epub ahead of print]

37. Nehme-Schuster H, Korganow AS, Pasquali JL, Martin T. Rituximab inefficiency during type I cryoglobulinaemia. Rheumatology (Oxford) 2005; 44:410–411.

38. Pandrangi S, Singh A, Wheeler DE, Rossi NF. Rituximab treatment for a patient with type I cryoglobulinemic glomerulonephritis. Nat Clin Pract Nephrol 2008; 4:393–397.