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L11. Hepatitis C virus mixed cryoglobulinemia vasculitis: Therapeutic options

With the discovery of hepatitis C virus (HCV) as the etiologic agent for most cases of mixed cryoglobulinemia (Cryovas), new opportunities and problems for crafting therapy of HCV-Cryovas have emerged [1,2]. A new and major concern was the potential adverse effects that immunosuppressive therapy with glucocorticoids and cytotoxic drugs could have on an underlying chronic viral infection. Alternatively, the discovery of HCV provided the opportunity to control HCV-Cryovas with antiviral therapy as the underlying infection drives immune complex formation and resultant vasculitis [3]. The cornerstone of HCV therapy has been and continues to be interferon alpha (IFN) which has the potential to exacerbate autoimmune disease states [4]. Aggressive antiviral therapy with Peg-IFNα and ribavirin should be considered as induction therapy for HCV-Cryovas with mild to moderate disease severity and activity. Very recent advances using a triple combination with Peg-IFNα,
ribavirin and a protease inhibitor, in patients infected by a genotype 1 virus, showed promising results. In patients presenting with severe disease (i.e. worsening of renal function, mononeuritis multiplex, extensive skin disease including ulcers and distal necrosis), an induction phase of immunosuppression is often necessary while awaiting the generally slow response to antiviral treatments. Combination therapy with rituximab and optimal anti-HCV treatment appears logical as it may target both mixed cryoglobulin (MC) producing B-cells and the viral trigger. This review will focus on advances in our understanding of the treatment of HCV-Cryovas.

**Antiviral agents**

During the last two decades, the treatment of HCV infection (i.e. in the absence of HCV-Cryovas) has permit to dramatically increase the sustained virological response (SVR) rates, from IFN monotherapy to IFN plus ribavirin [5–9], and more recently pegylated-IFN (Peg-IFNα) plus ribavirin leading to a SVR in nearly 60% of patients. Increasing performances of antiviral treatment have also been shown in Cryovas patients. Mazzaro et al. [10] have first reported on the results of 18 HCV-Cryovas patients treated with Peg-IFNα2b plus ribavirin for 12 months. At the end of follow-up, only eight (44%) patients were still sustained clinical and virological responders. One major weakness of this study was the lower Peg-IFN dosage used in comparison with that usually recommended in HCV therapeutic guidelines. In a monocentric study [11], 72 consecutive HCV-Cryovas patients received treatment with IFNα-2b (n = 32) (3 millions IU × 3/week) or Peg-IFNα-2b (n = 40) (1.5 μg/kg/week), both combined with oral ribavirin (600 to 1200 mg/d) for at least 6 months. Peg-IFNα plus ribavirin combination achieved a higher rate of complete clinical (67.5% vs 56.2%), virological (62.5% vs 53.1%) and immunological response (57.5% vs 31.2%) as compared with IFNα plus ribavirin, regardless of HCV genotype and viral load. Compared with standard IFN α-2b/ribavirin, there was a shorter duration of HCV therapy (13.2 vs 18.3 months), less frequent use of corticosteroids (35% vs 47%) and a lower rate of death (5 vs 18.7%) with Peg-IFNα2b/ribavirin. An early virologic response (i.e. negativation or >2 log drop viremia at month +3) (odds ratio [OR], 3.53; 95% CI 1.18 to 10.59) was independently associated with a complete clinical response of Cryovas. A glomerular filtration rate lower than 70 ml/min (OR 0.18; 95% CI 0.05 to 0.67) was negatively associated with a complete clinical response of Cryovas. When compared with IFNα2b/ribavirin, patients who received Peg-IFNα2b/ribavirin had a similar rate of adverse events (53.1% vs 55%, respectively).

Recent use of triple therapy with Peg-IFNα, ribavirin, and a specifically targeted antiviral agent (i.e. Boceprevir or Telaprevir) led to improve SVR rates in patients infected with HCV genotype 1. In an open-label prospective single-center cohort study [12], the efficacy of an NS3 protease inhibitor [boceprevir or telaprevir], in combination with Peg-IFNα and ribavirin has been evaluated in 13 HCV-Cryovas patients with genotype 1. After 1 month of Peg-IFNα/Ribavirin/protease inhibitor combination, 11 (85%) patients showed an early virological response. Nine patients showed a complete clinical response of Cryovas and four were partial responders. After 3 months of Peg-IFNα/Ribavirin/protease inhibitor combination therapy, MC serum level dropped from 1.3 to 0.3 g/l while C4 serum level increased from 0.09 to 0.13 g/l. All 13 patients experienced at least one treatment side effect including asthma in 92%, anaemia in 84%, neutropenia and bacterial infection in 53%, nausea and low grade (<3) skin eruption under Telaprevir in 30%, and thrombocytopenia in 15%.

**Immunosuppressive agents**

Immunosuppressive agents have been given for many decades to patients with severe Cryovas disease manifestations such as membranoproliferative glomerulonephritis, severe neuropathy and other life-threatening complication. In a large retrospective study of 105 patients with renal disease associated with Cryovas, 80% were administered corticosteroids and/or cytotoxic agents, while 67% underwent plasmapheresis [13]. Despite this aggressive approach, long lasting remission of the renal disease was achieved in only 14% of cases, and the 10-year survival rate was only 49%.

Corticosteroids, used alone or in addition to IFNα, did not favourably affect the response of HCV-Cryovas manifestations in two controlled studies [5,14]. Low dose corticosteroids may help to control minor intermittent inflammatory signs such as arthralgia, but do not succeed in cases of major organ involvement. When used in combination with HCV treatment, plasmapheresis did not modify the virologic response if IFNα was given after each plasma exchange session [15].

**Rituximab monotherapy**

Rituximab is an interesting therapy in Cryovas patients as it targets B-cells which are responsible for the cryoglobulin production, immune complex deposition and finally vasculitis lesions [16–21]. In a literature review [19], 57 patients had a Cryovas secondary to HCV infection (75.4%) or an essential MC (24.6%). Main indication for rituximab therapy was non-response to previous other treatments (i.e. mostly IFNα monotherapy and/or steroids). Most patients received four weekly consecutive i.v. infusions of 375 mg/m² of rituximab. Rituximab infusions proved effective on main vasculitis signs, with a complete clinical response in 24/33 (73%) patients for skin involvement, 16/30 (53%) for arthralgia, 9/25 (36%) for neuropathy, and 9/13 (70%) for glomerulonephritis. Cryovas relapse was noted in 13/36 (36.1%) patients within few days to 19 months (mean 6.7 months) after the last rituximab
infusion; 8/13 relapers showed a complete remission after a second course of rituximab.

Recently, De Vita et al. [22] reported the results of a multicenter phase III randomized controlled trial in 57 Cryovas patients (including 53 HCV-positive patients), comparing conventional treatment (i.e. glucocorticoids; azathioprine or cyclophosphamide; or plasmapheresis) and rituximab. None of the HCV-positive patients received concomitant antiviral therapy. 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 35.5%). Sneller et al. [23] reported the results of an open-label, randomized controlled trial of rituximab compared to conventional immunosuppressive therapy (glucocorticoids, cyclophosphamide, plasma exchanges or methotrexate) for HCV-Cryovas patients in whom antiviral therapy had failed to induce remission. Remission at month 6 was statistically higher in the rituximab group (83% vs 8%). The median duration of remission for rituximab-treated patients was 7 months, and the safety profile was good.

A phase II single-arm two-stage study to evaluate the efficacy of a lower dosage of rituximab, 250 mg/m² given twice, for refractory Cryovas is on-going [24]. The overall response rate in the first 24 evaluable patients was 79%, and the mean time to relapse was 6.5 months [similar to the 6.7 months reported in studies with high-dose rituximab]. Side effects were comparable to those seen in patients treated with high-dose.

In a prospective study, 19 HCV-Cryovas patients excluded from antiviral therapy, with liver cirrhosis in 15/19 patients, were treated with rituximab [25]. A consistent improvement in Cryovas symptoms was evident at the end of follow-up. Improvement in liver protidosynthetic activity and ascites degree was observed at the end of follow-up, especially in more advanced cases.

In most studies, tolerance of rituximab was good. Recent studies in large cohorts of HCV-Cryovas patients did not show significant variation of viremia after rituximab infusions [26]. Some patients may experience systemic drug reactions after rituximab infusion, particularly those with high mixed cryoglobulin levels and low C4 levels and who received 1000 mg high-dose rituximab protocol. Therefore, rituximab should be administered with caution in Cryovas patients, with use of the 375 mg/m² protocol, associated with plasma exchanges prior to rituximab infusion in patients with high baseline MC levels [27].

Rituximab plus Peg-IFNα and ribavirin

Based on the limitations of each therapy (i.e. antiviral and rituximab), and the 30% of Cryovas patients that continue to have active disease while receiving rituximab or antiviral therapy, the combination of rituximab with Peg-IFNα-ribavirin appeared logical. Sixteen consecutive HCV-Cryovas patients were first reported to receive rituximab (375 mg/m² i.v. weekly, for 4 consecutive weeks) combined with Peg-IFNα2b (1.5 µg/kg/week subcutaneously) plus ribavirin (600–1200 mg/d orally) for 12 months [21]. All patients had severe active disease resistant to previous combination therapy with IFN-based therapy. Fifteen patients (93.7%) showed clinical improvement, 10 of whom were complete responders. Compared with clinical complete responders, the partial or non-responders had a 3.6 times longer duration of vasculitis prior to therapy and a lower rate of early virologic response. After a mean follow-up of 19.4 ± 3.6 months, one death occurred due to liver failure. Two patients (12.5%) experienced clinical relapse associated with reappearance of HCV RNA and cryoglobulin, and an increase in the number of B-cells.

Two recent controlled clinical trials compared the efficacy and safety profile of Peg-IFN alpha/ribavirin versus rituximab plus Peg-IFN alpha/ribavirin. In both studies, compared with Peg-IFN alpha/ribavirin, rituximab plus Peg-IFN alpha/ribavirin treated patients had a shorter time to clinical remission, better renal response rates, and higher rates of cryoglobulin clearance [28,29]. Treatment was well tolerated with no worsening of viremia under rituximab and 11% of discontinuation due to antiviral therapy. Rituximab synergized the immunological effect of antiviral therapy.

Immunomodulation: low-dose interleukin 2

Patients with HCV-Cryovas have been shown to have a reversible quantitative defect of CD4+CD25+FoxP3+ regulatory T-cells (Tregs) after resolution of HCV infection and cure of vasculitis [30]. Interleukin 2 (IL-2), a cytokine that promotes Treg survival and function, could be beneficial for such patients resistant to HCV therapy. Safety and immunological effects of low-dose IL-2 has been recently reported in a prospective open-label phase I/IIa study [31]. Ten patients with HCV-Cryovas refractory to conventional antiviral and/or rituximab therapy received four consecutive IL-2 courses. The treatment did not induce effector T-cell activation, vasculitis flare or increased viremia. Improvement of the vasculitis symptoms was found in eight of 10 patients. Administration of low-dose IL-2 was followed by an increase in the percentage of CD4+CD25+CD127- FoxP3+ Tregs with potent suppressive activity in all subjects, and a concomitantly decreased proportion of marginal zone B-cells.

Therapeutic guidelines

Aggressive optimal antiviral therapy with Peg-IFNα and ribavirin (plus protease inhibitor, if HCV genotype 1 infection) should be considered as induction therapy for HCV-Cryovas patients with mild to moderate disease severity and activity (i.e. without rapidly progressive nephritis, motor neuropathy or other life-threatening complications). Current treatment duration is 48 weeks for all HCV genotypes [32].
In patients presenting with more severe HCV-Cryovas disease (i.e. worsening of renal function, mononeuritis multiplex, extensive skin disease including ulcers and distal necrosis), an induction phase of immunosuppression is often necessary while awaiting the generally slow response to antiviral treatments. Combination therapy with rituximab plus antivirals is recommended as it may target both the downstream B cell arm of autoimmunity and the viral trigger.

For patients presenting with the fulminating forms (catastrophic HCV-Cryovas disease) including peripheral necrosis of extremities, rapidly progressive nephritis, digestive, cardiac, pulmonary and/or central nervous system involvement and/or signs and symptoms of hyperviscosity, apheresis can have immediate beneficial effects but must be combined with immunosuppression to avoid post-apheresis rebound of MC. Rituximab, fludarabine and cyclophosphamide combination appeared as an effective salvage treatment for refractory Cryovas associated with lymphoma [33]. In such cases, antiviral therapy should be postponed after the critical phase.

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References


Rheumatoid arthritis vasculitis (RAV) affects small- and medium-sized vessels of a subset of patients with RA. This vasculitis, which can be necrotizing or leukocytoclastic, mainly involves small vessels, more than medium-sized. Treatment of systemic RAV is poorly codified. Five-year mortality rates were high, 33 to 43% [1–3], depending on the study considered, with marked morbidity. Among secondary vasculitides, RAV is one of the most severe, as it responds poorly to conventional treatments specifically prescribed for RA [4]. In contrast, its control requires prolonged use of immunosuppressants [5]. More recently, biotherapies have been successfully prescribed [6,7].

Epidemiology and clinical manifestations

RAV is rare and has been observed less frequently in the recent years (table I). In the Norfolk (UK) area, the annual RAV incidence was 11.6/million inhabitants between 1988 and 1992, and 3.6/million between 1998 and 2002 [8]. In the Olmsted County, Minnesota series, the 10-year cumulative incidence of RAV, but not other extra-RA manifestations, was significantly lower in the 1995 to 2007 cohort (0.6%) than the 1985 to 1994 cohort (3.6%) [9]. More men might be affected than women but the exact sex-ratio varies according to series [10]. In our practice, we have observed fewer RAV cases since the early 2000s and we hypothesize that use of the most recent biological therapies to treat RA might have had an impact on RAV development. RAV mainly occurs in patients whose RA had started several years earlier and was more severe, especially with a major bone erosion. Smoking, positive rheumatoid factor and anticyclic citrullinated peptide antibodies are frequent features. It may occur in patients treated with immunosuppressants, and sometimes after rapid steroid tapering. It may arise in patients given antitumor necrosis factor-alpha (TNFα), even though this drug has sometimes been used successfully to treat RAV [6]. At the time of vasculitis onset, RA can be more-or-less inactive. Skin manifestations are frequent, characterized by nodules or livedo. Among systemic manifestations, pleuritis, cardiac involvement and ocular symptoms are the most frequent.

Clinical manifestations

Skin, nerves and other major organs can be affected by this vasculitis, which can mimic polyarteritis nodosa with multisystemic involvement.

Skin manifestations

Digital microinfarcts are frequently seen, usually subungual and visible through the nail, but they also can be periungual and in the digital pulp. They are frequently associated with subcutaneous skin nodules. These microinfarcts are not considered factors of poor vasculitis prognosis, unless they are associated with systemic manifestations. Some patients also have leg arterial ulcers that respond only to the vasculitis treatment. Livedo reticularis, macula, purpura and digital gangrene can occur. The latter is considered of poor prognosis. Pyoderma gangrenosum has also been rarely described [17], as it can be observed in other vasculitides.

Peripheral neuropathy

Mononeuritis multiplex is the most prominent form of RAV neuropathy [2,18]. The following nerves are preferentially involved:

- superficial peroneal nerves;
- sural, radial;
- cubital;
- median nerves.

In its late stage, so many nerves can be involved that mononeuritis multiplex can be mistaken for a symmetric process. Sometimes the polyneuropathy is exclusively sensory, which can be vasculitis-related but has also been associated with Sjögren’s syndrome. Muscle vasculitis is often