Chronic Hepatitis C Virus (HCV) infection is a major public health problem with 130 to 170 million people or 3% of the world’s population affected worldwide [1]. Patients chronically infected with the HCV are at risk of developing serious hepatic sequelae, namely liver cirrhosis and hepatocellular carcinoma and various extrahepatic manifestations which may affect up to two thirds of chronic HCV patients [2,3]. Several extrahepatic manifestations, many of which are autoimmune in nature, have been described in association with HCV infection such as mixed cryoglobulinemia, glomerulonephritis, porphyria cutanea tarda, sicca syndrome, polyarthritis, peripheral neuropathy and systemic necrotizing vasculitis [3,4], various organ- and non-organ specific antibodies as well as classic autoimmune diseases [5]. More recently, other non-liver-related HCV disorders, which are related to the chronic inflammatory process, have been reported including cardiovascular, renal, metabolic and central nervous system diseases which further increase the morbidity and mortality in HCV infected patients [6]. Mixed cryoglobulinemia has the strongest association with chronic HCV infection [7-9].
HCV lymphotropism is responsible for the B-lymphocyte expansion responsible for the production of large amounts of circulating immune complexes, mainly mixed cryoglobulins with rheumatoid factor activity. Cryoglobulins are immune complexes that reversibly precipitate at temperatures lower than 37°C and re-dissolve on warming. Cryoglobulinemia has been considered a benign B cell proliferative disorder which in a minority of patients may progress to a B cell non-Hodgkin lymphoma. Cryoglobulins associated with HCV infection are either type II (composed of a polyclonal IgG and a monoclonal IgM with rheumatoid factor activity) or type III (composed of polyclonal IgG and a polyclonal IgM rheumatoid factor) and are termed mixed cryoglobulins [10,11]. Serum cryoglobulins are detectable in 40–60% of patients with HCV infection; however, only 10–15% of those develop cryoglobulin-associated symptoms secondary to vascular occlusion and immune complex deposition with subsequent complement activation. The clinical manifestations of Cryoglobulinemic Vasculitis (CV) are due to a systemic vasculitis involving mainly small and less frequently medium sized blood vessels [10-12]. The prevalence of medium-sized vessel involvement was 19.3% among patients with HCV-related vasculitis. Pathologically, it is most commonly a leucocytoclastic vasculitis, although a medium sized polyarthritis nodosa–like necrotizing vasculitis has also been described [13]. The laboratory hallmarks of the disease are the detection of mixed cryoglobulins that can be detected in most cases, with rheumatoid factor activity in serum and a low concentration of C4 complement component [14]. Less frequently, vasculitis may occur in the absence of detectable cryoglobulin, although the presentation and therapeutic management of such vasculitis should be similar to that of HCV-MC vasculitis [15]. In one study, 11% of HCV –related vasculitis patients were non-cryoglobulinemic [16]. The lack of detectable cryoglobulins in some patients with clinical manifestations of vasculitis similar to CV may be due to low cryoglobulin levels in the initial phase of the disease, tissue deposition rather than blood circulation of immune complexes or methodological issues [17].

**DIAGNOSIS OF HCV-RELATED VASCULITIS**

The most frequently targeted organs are skin, joints, nerves and kidney. Palpable purpura is the most characteristic manifestation of HCV vasculitis and may affect 54-82 % of CV patients. It is intermittent; occurring mainly in the lower limbs due to physical reasons and may be associated with ulcers around the malleoli [18]. Other cutaneous manifestations include Raynaud’s phenomenon, skin rash, distal ischemia or gangrene, livedo reticularis and acrocyanosis [19]. Symmetric arthralgia involving the hands, wrists and knees affect 44-71% of patients while a non-erosive arthritis is less common [11]. The most frequently described neurological manifestation is a distal sensory or sensory-motor polyneuropathy. Mononeuritis multiplex may also occur [20]. Renal affection in the setting of HCV–related CV is most commonly, a membranoproliferative glomerulonephritis, less frequently described are membranous nephropathy, crescentic glomerulonephritis and focal proliferative glomerulonephritis [21].
The clinical picture of CV may vary from mild forms, the Meltzers triad, consisting of arthralgia, purpura and weakness to serious visceral involvement. Although about 50% of patients have mild forms of the disease, life-threatening complications such as renal failure due to cryoglobulinemic glomerulonephritis, intestinal vasculitis, pulmonary hemorrhage, cardiac affection and central nervous system involvement may occur in severe disease.

The diagnosis of mixed CV is a combination of typical clinico-pathological features and serological findings (mixed cryoglobulins with RF activity and frequent low C4). Preliminary criteria including a questionnaire, clinical and laboratory items were proposed for the classification of CV and subsequently validated. Although the criteria have been criticized because they mandate the presence of serum cryoglobulins for classification of patients as having CV, they are useful for classification of patients who test negative on initial laboratory evaluation. The laboratory item of these criteria (fulfilled if 2/3 are present: RF, low C4 and serum monoclonal component) appears as a surrogate marker for the presence of cryoglobulins and should be considered if CV is suspected in the absence of serum cryoglobulins.

The treatment strategy in CV can be directed against the viral trigger, i.e. eradication of the HCV and/or targeting the downstream events of B-cell activation through elimination of auto-reactive B cell clones that produce cryoglobulins and treating the clinical manifestations of vasculitis while minimizing the use of immunosuppressive drugs.

**ANTIVIRAL THERAPY**

Therapy with antiviral agents is a cornerstone for the management of CV. In the majority of patients, viral clearance is associated with improvement of CV and viral relapse is associated with relapse of clinical manifestations of vasculitis. Useful laboratory response markers are clearance of cryoglobulins, complement levels (C3, C4, CH50 activity) and RF activity. Noteworthy, some authors have reported the presence of HCV associated vasculitis in HCV antibody positive patients in the absence of detectable viremia, or persistence of vasculitis after successful eradication of the virus. Antiviral therapy may also be ineffective, contraindicated, or not tolerated. Interferon-based therapies may sometimes worsen CV with appearance of new manifestations. Peripheral neuropathies and cutaneous ulcers may deteriorate and thus require careful monitoring during antiviral therapy. New onset of CV or other important immune-mediated side effects, such as peripheral sensory-motor neuropathy, thyroiditis, and rheumatoid-like polyarthritis can occur during IFN therapy and also when HCV disappearance was obtained. Alpha-interferon, which is both an antiviral and immunomodulating agent, may be responsible for these side effects, possibly in predisposed subjects.

For more than a decade, the standard of antiviral treatment has been combination therapy with pegylated-INF alpha (Peg-IFNα) and ribavirin. The treatment is usually administered for 48 weeks in patients with HCV genotypes 1, 4, 5 and 6 and for 24 weeks in those with genotypes 2 and 3. Treatment of chronic hepatitis C with Peg-IFNα/ribavirin containing regimens is strongly
or relatively contraindicated in several situations e.g. hepatic decompensation, renal failure, psychosis and autoimmune disorders [36].

Combination antiviral therapy with Peg-IFNα/ribavirin yields a SVR in almost 52% of patients with symptomatic mixed CV, with a good correlation between virological and clinical response [37]. In 2011, the first generation Direct-Acting Antivirals (DAAs), boceprevir and telaprevir, were approved for treatment of HCV genotype 1 in combination with Peg-IFNα and ribavirin, which markedly increased the cost of therapy. Although this combination increased the rates of SVR compared with the standard Peg-IFNα/ribavirin therapy, it was associated with significant toxicity, drug-drug interactions, low response rates in patients with cirrhosis and previous treatment failures and were associated with the emergence of resistant variants in most cases of treatment failure [36].

Triple anti-HCV therapy with Peg-IFNα/ribavirin and boceprevir or telaprevir led to a complete clinical remission and a SVR in 66.7% of treated CV patients, however, 46.6% experienced serious haematological adverse effects. Serious side effects of triple antiviral therapy were associated with baseline liver fibrosis and low platelet count [38].

Antiviral treatment with second generation protease inhibitors could have a potential impact on the course of HCV-associated mixed CV, due to their improved tolerability profile and high efficacy [39].

Sofosbuvir / ribavirin combination in mixed CV for 24 weeks resulted in a complete clinical response of the vasculitis at the end of treatment in 87.5% and in 74% a SVR at week 12 post treatment was achieved with a low rate of serious advents [40].

In a retrospective case series, sofosbuvir / ribavirin or sofosbuvir / simeprevir combinations were compared to a historical cohort treated with Peg-IFNα and ribavirin. 40% of patients received concomitant immunosuppressives (rituximab, prednisone, ustekinumab, plasmapheresis). Sofosbuvir based combinations were associated with a SVR in 83% and complete remission after treatment was seen in 30% of patients. In 17% serious side effects in the form of worsening anxiety and insomnia and hyperkalemia occurred. In the historical cohort, clinical remission and SVR was seen in 10% only, and side effects necessitating therapy discontinuation were seen in 50% [41].

**IMMUNE-MODULATORY THERAPY IN CV**

In severe mixed CV with advanced renal and liver involvement, the addition of immune-modulating agents is crucial for targeting the B-cell clonal autoimmune responses and clonal expansions in the blood and liver. The conventional treatment for severe CV includes plasmapheresis, corticosteroids, and cytotoxic drugs [42]. Corticosteroids and IV cyclophosphamide were effective in the treatment of severe HCV associated vasculitis in one series [30]. In another study, however, corticosteroid therapy was less effective than antiviral
treatment and corticosteroid / antiviral combination was not superior to antiviral therapy alone in the treatment of mixed CV [42]. Rituximab, a chimeric anti-CD20 monoclonal antibody, depletes more than 95% of circulating B lymphocytes and thus is capable of interrupting this chain of events initiated by a virally triggered B cell clonal expansion and the resulting chronic inflammatory response [43]. Rituximab was more effective and gave earlier treatment response as compared to conventional immunosuppressive agents (glucocorticoids, azathioprine or cyclophosphamide) or plasmapheresis in severe HCV-associated mixed CV, although the overall adverse events were similar in both groups [28] Rituximab can be used as monotherapy when antiviral treatment is contraindicated, not tolerated or has failed [28,41]. The use of rituximab in combination or sequential treatment strategies with Peg-IFNα/ribavirin was associated with earlier treatment responses and a higher frequency of complete remission [45, 46].

**THE CHOICE OF TREATMENT**

The therapeutic strategy in the treatment of CV should be tailored according to the severity of the clinical manifestations, the liver condition, comorbidities and previous treatment [35,47].

Asymptomatic patients e.g. with fleeting purpura do not need to be treated although antiviral treatment may be considered. Patients with mild to moderate disease (purpura, arthralgia and polyneuropathy) should receive antiviral treatment. A low antigen-content diet can improve the clearance of circulating immune complexes by the reticulo-endothelial system and may be used in association with small doses of steroids and/or colchicine in patients with mild manifestations of CV [35]. Patients with severe disease such as worsening of renal function, mononeuritis multiplex or extensive skin disease with ulcers and distal necrosis should receive rituximab as induction therapy to control the disease manifestations and antiviral treatment. Life-threatening disease manifestations such as pulmonary, central nervous system, digestive tract involvement or rapidly progressive renal disease should be treated by steroids, plasma exchange, cyclophosphamide and/or rituximab while awaiting the relatively slow response of antiviral treatment [33,47].

The introduction of the DAA drugs has allowed the use of INF-free all oral regimens with increased efficacy and safety. It is hoped that they will improve the outcome of patients with CV who are at an increased risk of haematological and immune-mediated side effects of INF-based therapies [39].

**References**


