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ABSTRACT

During hepatitis virus (HCV) chronic infection, extrahepatic manifestations are frequent and polymorphous. Initial description reported in large cohort of patients HCV-related autoimmune and/or lymphoproliferative disorders, from mixed cryoglobulinemia vasculitis to frank lymphomas. The relationship between HCV infection and such immune-related diseases has been formally demonstrated by epidemiological, clinical, immunological, pathological data and results of therapeutic trials. More recently, other non-liver related HCV-disorders have been reported including cardiovascular (i.e. stroke, ischemic heart disease), renal, metabolic, and central nervous system diseases. For these manifestations, most evidence come from large epidemiological studies; there is a need for mechanistic studies and therapeutic trials for confirmation. Beyond the risk of developing liver complications i.e. cirrhosis and liver cancer, HCV infected patients have an increased risk of morbidity and mortality related to non-liver diseases. HCV chronic infection should be analyzed as a systemic disease where extrahepatic consequences increase the weight of its pathological burden. The need of effective viral eradication measures is underlined.

Hepatitis C Virus (HCV) infection is a major health problem with 150-170 million people chronically infected. On one hand, these patients are at risk of developing liver complications i.e. cirrhosis and liver cancer, with an estimated liver-related mortality of 350,000 people/year. On the other hand, in large cohort studies, two third of HCV infected patients experienced extrahepatic manifestations (HCV-EHMs)[1]. Some of these conditions are well-documented and more common, while others are infrequent[2–4]. Soon after HCV discovery, HCV-related autoimmune and/or lymphoproliferative disorders, from benign mixed cryoglobulinemia to frank lymphomas, have been reported[3,5]. More recently, many other non-liver HCV-associated disorders have been reported including cardiovascular, renal, metabolic, and central nervous system diseases (***Table 1***). HCV infection showed a higher mortality rate for extra-hepatic complications[6-9]. All-cause mortality in HCV patients was increased more than twice with respect to HCV-negative[10], probably related to serum HCV RNA positivity[6]. Viral eradication significantly reduced the rate of extra-hepatic deaths[11-13]. Recent therapeutic advances in the treatment of HCV, with the possibility to eradicate HCV following new direct antiviral therapies appears of major importance, for liver and non-liver manifestations of the disease.

1) ***Cryoglobulinemia vasculitis***

Mixed cryoglobulinemia (MC) vasculitis (Cryovas) is a small vessel vasculitis involving mainly the skin, the joints, the peripheral nerve system and the kidneys[4]. HCV infection is the cause of Cryovas in about 80% of cases. The disease expression is variable, ranging from mild symptoms (purpura, arthralgia) to fulminant life-threatening complications (glomerulonephritis, widespread vasculitis). Skin is the most frequently involved target organ: palpable purpura, chronic cutaneous ulcers, Raynaud's phenomenon, acrocyanosis, which may evolve to digital ulcerations. Neurologic manifestations range from pure sensory axonopathy to mononeuritis multiplex. The most frequent form is a distal sensory or sensory-motor polyneuropathy, presenting with painful, asymmetric paresthesia. Less frequently, multiple mononeuropathy may occur. Renal involvement is an acute or chronic type-I membranoproliferative glomerulonephritis with sub-endothelial deposits, strongly associated with the type II IgM kappa MC. The usual presentation is proteinuria with microscopic hematuria and a variable degree of renal insufficiency. 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 at 37°C. HCV-MC are characterized as type II or type III cryoglobulins which consist of polyclonal IgG with monoclonal or polyclonal IgM with rheumatoid factor (RF) activity, respectively[6]. During follow-up, biological improvement can be assessed by the quantification of cryoglobulinemia and other surrogate markers (C4, CH50, RF).

During HCV infection, Cryovas is associated with advanced age, longer duration of infection, type II MC, a higher MC serum level and clonal B-cell expansions in both the blood and liver. The worse pronostic factors are an age > 60yrs at diagnosis and renal involvement[14]. The overall 5yrs survival rate after the diagnosis of Cryovas range from 90% to 50% in case of renal involvement. Increased mortality from liver involvement, cardiovascular disease, infection and lymphoma has been reported. In a retrospective Italian study of 231 patients, 79/97 deaths were linked to vasculitis (46%, of whom one-third due to renal involvement), cancer or haemopathy (23%), or liver disease (13%)[15]. Cryovas complications may result in progressive (renal involvement) or acute (pulmonary hemorrhage, gastrointestinal ischemia, cardiac, CNS involvement) life-threatening organ damage, with a mortality rate between 20% and 80% [16,17]. Intestinal ischaemia, pulmonary haemorrhage, high cryocrit levels and type II MC are associated with severe prognosis [18].

There are multiple factors predisposing HCV-infected patients to develop Cryovas. Interaction between HCV and lymphocytes directly modulates B- and T-cell function and results in polyclonal activation and expansion of B-cell producing IgM with RF activity[19]. $CD4^+CD25^+FoxP3^+$regulatory T cell are reduced in Cryovas patients[20,21] which may account for the expansion of peripheral auto-reactive B-cell that drive Cryovas. HLA-DR11 is associated with whereas HLA-DR7 appears to protect from Cryovas[22]. In a recent multi-center genome-wide association study significant associations were identified on chromosome 6, a single nucleotide peptide located within an intronic region of NOTCH4 ($p=6.2*10^{-9}$) and another found in between HLA-DRB1 and HLA-DQA1 ($p=1.2*10^{-7}$)[23]. Specific virological factors have not yet been identified.

Most HCV-Cryovas manifestations respond to clearance of HCV during antiviral therapy with pegylated interferon (IFN) plus ribavirin[24]. Patients who relapse for HCV infection after responding to antiviral therapy usually relapse for the Cryovas with the return of viremia[25]. In case of persistent MC, relapse of vasculitis might also occur despite achieving a sustained virologic response (SVR); this situation should lead to look for a different underlying condition, especially B-cell lymphoma[26]. Recent use of triple anti-HCV therapy with pegylated-IFN/ribavirin and a direct antiviral agent (boceprevir or telaprevir) led to improved rates of SVR and Cryovas remission in HCV genotype 1 [27,28]. Other direct-acting antivirals such as sofosbuvir and simeprevir have recently been licensed which facilitate the use of shortened courses of combination IFN-free therapy and are associated with high (>95%) SVR rates and few toxicities. International guidelines (i.e, EASL 2014)[29] state that treatment should be scheduled, not deferred, for patients with clinically significant extra-hepatic manifestations, like Cryovas. Rituximab is an interesting therapy in MC, as it targets B-cells, which are responsible for cryoglobulin production and finally Cryovas lesions. Two randomized controlled trial showed that rituximab has a better efficacy than conventional treatment (i.e., glucocorticoids, azathioprine, cyclophosphamide, or plasmapheresis)[30,31]. Two other controlled clinical trials showed

that addition of rituximab to pegylated-IFN/ribavirin led to a shorter time to clinical remission, better renal response rate, and higher rates of cryoglobulin clearance[32,33].

In daily practice, HCV-Cryovas patients with mild to moderate disease should be given an optimal antiviral treatment. For patients with severe vasculitis (i.e. worsening of renal function, mononeuritis multiplex, extensive skin disease, intestinal ischemia…) control of disease with rituximab, with or without plasmapheresis, is required before initiation of optimal antiviral therapy[4,34]. Careful monitoring for adverse effects is mandatory, since some manifestations of HCV-Cryovas, such as peripheral neuropathy or skin ulcers, may worsen with IFN-based therapy. Low-dose corticosteroids may help to control minor intermittent inflammatory signs such arthralgia but do not succeed in case of major organ involvement. Other immunosuppressants should be given only in case of refractory forms of HCV-Cryovas, usually associated with underlying B-cell lymphoma[35].

2) *B-cell lymphoproliferative diseases*

A high prevalence of HCV infection in patients with B-cell non-Hodgkin's lymphoma (B-NHL) was reported in meta-analyses, with a gradient from north to south[36-41]. HCV was associated with marginal zone NHL (Odds ratio, OR 2.47) and diffuse large B-cell NHL (OR 2.24). A serum monoclonal gammopathy, more frequently IgMk, was frequently observed[42]. A lower cumulative incidence of lymphoma development in patients who eradicated the virus confirms this association and suggests that HCV treatment could be a preventive measure[43]. SVR induced NHL regression while a viral relapse was followed by the lymphoma recurrence[44]. HCV-positive splenic lymphoma with villous lymphocytes regressed after anti-viral therapy[45]. Regression of expanded B-cell clones following successful antiviral treatment have been reported with expansion of the same clones in virological relapsers[46]. The same picture was shown in patients with benign lymphoproliferative conditions (i.e, type II or III MC), whereas a persistent B cell clone despite a clinical remission was evidenced in SVRs with splenic lymphoma with villous lymphocytes[45]. This leads to the concept of no-return points in the HCV-driven lymphomagenesis, with a lymphoproliferation initially antigen-sensitive and then antigen-insensitive.

HCV-related lymphoproliferative disorders are the result of multiple and cooperating events, i.e. sustained activation of B-cells[47,48], inhibition of B-cell apoptosis, genetic/epigenetic and environmental factors[49]. The lymphotropism agrees with a higher HCV infection prevalence in PBMCs and bone marrow[50,51] and was confirmed by *in vivo* and *in vitro* studies[52,53]. HCV-infected cells showed an increased rate of mutations of oncogenes and immunoglobulin genes. Transgenic models showed a correlation between the expression of HCV core and lymphoma[54]. The t(14;18) translocation causes increased Bcl-2 levels and abnormal B-cell survival[55] and disappear after antiviral

treatment[46]. The role of cytokines and chemokines has been studied [19,56,57], with a special attention of the B-cell activating factor[58,59].

Treatment of HCV-positive lymphoma with antiviral treatment should lead to the eradication of the etiologic factor. A clinical remission following antivirals was shown in low-grade B-cell NHL, mainly marginal zone lymphoma[44,45,60-62]. IFN-based treatment showed an improved overall survival in patients with indolent HCV-associated NHL[62,63]. Antivirals following NHL remission showed improved clinical outcome and prolonged disease free survival[63,64]. The use of rituximab in HCV-NHL, alone or in combination with antivirals and/or chemotherapy, appears interesting in low-grade NHL[65].

3) Arthralgia/myalgia

Arthralgia is reported in 40-80% of HCV-infected patients[2,66]. Patients present with symmetric joint pains, non-deforming, involving mainly knees and hands. HCV arthritis is less common. Rheumatoid factor (RF) activity is found in 70-80% of MC patients but it is not correlated with the presence of joint disease. Antibodies to cyclic citrullinated peptide are absent. Some treatment modalities for HCV infection, including IFN, may aggravate arthralgia and myalgia, thus confounding clinical presentation. It is imperative to distinguish whether symptoms such as arthralgia, myalgia, and arthritis occuring in patients with HCV infection are related to chronic HCV infection or to a newly developed rheumatologic disease.

4) Sicca syndrome

Sicca symptoms of either the mouth or eyes have been reported in 20-30% of HCV infected patients, whereas less than 5% of patients with a Sjögren's syndrome are HCV-positive[2]. Many similarities exist between HCV-related sicca syndrome and "true" Sjögren's syndrome[67]. However a characterized Sjögren's syndrome defined by the presence of xerostomia, xerophthalmia, anti-SSA or anti-SSB antibodies and typical salivary gland histology is rarely found in HCV infected patients. HCV-positive Sjögren's syndrome patients are older and more likely to have a photosensitivity and cryoglobulinemia than patients with primary Sjögren's syndrome. Low titers of antinuclear antibodies and RF are common in patients with HCV-related sicca syndrome but the presence of Sjögren's syndrome-related autoantibodies (anti-SSA/SSB antibody) is uncommon. The expression of the HCV E1 and E2 glycoproteins in transgenic mice is associated with the development of sialadenitis[68].

5) Auto-antibodies

Biological immunologic abnormalities are frequent, including mixed cryoglobulins (60-90%), RF activity (70%), and antinuclear (20-40%), anticardiolipin (15%), anti-thyroid (12%) and anti-smooth

muscle antibodies (7%) [1,2]. These autoantibodies however are not associated with manifestations of a connective tissue disease except for mixed cryoglobulins. Reported underlying mechanisms include HCV-induced overactivation and proliferation of B lymphocytes.

6) *Cardiovascular diseases*

Asian studies suggest the association between HCV infection and an increased risk of carotid-artery plaques and carotid intima-media thickening, independently of classical cardiovascular risk factors[69]. HCV infected patients showed a higher likelihood of having carotid atherosclerotic plaques compared to HCV negative controls[70,71], particularly in those with active viral replication. Suggested mechanisms include the production of pro-atherogenic cytokines[13] . Other studies performed in HCV or HCV-HIV co-infected patients confirmed the link between HCV infection and carotid atherosclerosis[70-73]. Furthermore, retrospective cohort studies suggest a beneficial effect of antivirals on the incidence of stroke in HCV infected patients[74]. A prospective study conducted in three groups of diabetics followed during 8 years, showed a decreased cumulative incidence of ischemic stroke in treated vs. non-treated HCV infected patients[12].

HCV chronic infection was shown to increase the risk of coronary artery disease, after adjustment for classical cardiovascular risk factors[75]. Anti-HCV positive patients had higher mortality rates of cardiovascular diseases compared to HCV negative controls (hazard ratio, HR 1.50; 95% CI 1.10-2.03)[6]. Patients with positive viremia showed higher rates of deaths, while HCV RNA negative patients had rates similar to controls. A large asian study analyzed 1,411 HCV subjects with diabetes mellitus treated with Peg-IFN plus RBV that were matched with 1,411 HCV-positive diabetic patients not treated with antivirals and with 5,644 HCV-negative diabetic patients [97]. After an 8-year median follow-up, the cumulative incidence of death significantly decreased from untreated to treated (23.6% versus 13.0%). The incidences of end-stage renal disease, ischemic stroke and acute coronary syndrome were lowest in the cohort of HCV-treated versus HCV-untreated patients. In addition, Maruyama et al. showed an improvement in the myocardial perfusion defect after antiviral treatment in patients who showed a SVR compared to those who relapsed[76].

7) *Renal insufficiency*

Type I membrano-proliferative glomerulonephritis associated with MC is the most common form of kidney disease associated with HCV infection. Patients present with clinical and histological picture in HCV-Cryovas that is an acute or chronic type-I membrano-proliferative glomerulonephritis with sub-endothelial deposits, with type II IgMκ cryoglobulinemia[77]. The most frequent presentation is proteinuria with microscopic hematuria and a variable degree of renal insufficiency. Acute nephrotic or nephritic syndrome can also reveal Cryovas renal involvement, with frequent new onset

arterial hypertension. Early serum complement component (C1q, C4) are very low. Chronic renal insufficiency may develop in 10-20% of HCV-Cryovas patients. Renal morphological features are characterized by important monocyte infiltrates with double contours of the basement membrane, large, eosinophilic and amorphous intra-luminal thrombi. Vasculitis of small renal arteries or extra-capillary crescents are rarely observed. Immunofluorescence studies show intra-glomerular sub-endothelial deposits of IgG, IgM and complement components. The electron microscopic features with sub-endothelial and intra-luminal deposits presenting a crystalloid aspect are pathognomonic.

There is some evidence of the association between HCV and other glomerular diseases[78,79]. A large case-control study, carried out among U.S. male veterans hospitalized between 1992 and 1999[80], identified 34,204 patients who were hospitalized with HCV infection (cases) and 136,816 randomly selected patients without HCV infection (controls). There was a greater proportion of membrano-proliferative glomerulonephritis among patients with HCV infection (0.36% versus 0.05%, P<0.0001). HCV infection was associated with a 40% higher prevalence of renal insufficiency compared with subjects without HCV infection, after adjusting for age, gender, race, diabetes, and hypertension[81]. Some large surveys have suggested an impact of HCV infection on prevalence and incidence of kidney disease in the general population[80,82-84]. Anti-HCV status was associated to low glomerular filtration rate (OR up to 2.80) and with proteinuria (OR 1.14 to 1.99)[85-88], independently of common metabolic factors, such as diabetes mellitus, arterial hypertension, obesity, and dyslipidemia. In a recent population-based cohort, among 2,267,270 Taiwanese residents diagnosed with diabetes mellitus[12], three groups were analyzed : 1,411 HCV infected patients who received pegIFN plus ribavirin (treated cohort), 1,411 HCV infected untreated controls and 5,644 HCV-negative diabetic patients (uninfected cohort). The 8-year cumulative incidence of endstage renal disease in the treated, untreated, and uninfected cohorts were 1.1% (95%CI, 0.3-2.0%), 9.3% (5.9-12.7%), and 3.3% (2.3-4.3%), respectively ($P < 0.001$). Antiviral treatment was associated with HR of 0.16 (0.07-0.33%) for endstage renal disease.

The Kidney Disease Improving Global Outcomes (KDIGO) group recommends that all patients with chronic kidney disease should be tested for HCV[89]. KDIGO also recommends that patients with acute flares of HCV-Cryovas and membrano-proliferative glomerulonephritis be treated with IFN-based therapy. Ribavirin dosage should be closely monitored due to the risk of anemia and it should be avoided in patients with chronic kidney disease. HCV-Cryovas patients with kidney involvement showed greater renal response rates when treated with a combination of rituximab and pegIFN plus ribavirin compared with pegIFN and ribavirin alone. Of note, all these pictures should change rapidly with the use of new direct acting anti-HCV treatments.

8) *Insulin-resistance and type 2 diabetes*

Insulin-resistance (IR) is a frequent condition, coexisting with obesity and metabolic syndrome, possibly evolving to type 2 diabetes. In a small cohort of patients treated with anti-HCV therapy, Taskoparan et al failed to establish a correlation between IR and chronic HCV infection[90]. The presence of IR was evaluated in HCV patients achieving a SVR after pegylated IFN plus ribavirin. On one hand, the treatment response was not impaired by IR. On the other hand, treatment failure and high body mass index were independent risk factors for *de novo* appearance of IR after treatment. No new IR cases were registered in SVR patients, suggesting that HCV eradication could prevent IR onset and its evolution to diabetes[91]. Insulin resistance has been shown to impair SVR rate to pegIFN plus ribavirin in HIV-HCV coinfected patients[92].

HCV-related type 2 diabetes mellitus may arise from a complex interaction between IR, steatosis and inflammatory processes[93,94]. Epidemiologic studies supporting the association between type 2 diabetes and HCV infection have been published in the early 1990s. In larger epidemiologic studies[95,96], the prevalence of diabetes was higher in HCV- than in HBV-related cirrhosis [23.6% versus 9.4%; OR 2.78 (95%CI, 1.6-4.79); P =0.0002]. Diabetes was associated with the presence of a cirrhosis and male gender. An epidemiologic study conducted in Egypt in a pediatric population of 150 type 1 diabetic patients revealed a prevalence of HCV infection higher than in controls[97].

9) ***Fatigue, depression, and cognitive impairment***

Neurocognitive morbidity in HCV infected patients do not completely correlate with the severity of liver disease[98]. Cognitive impairment may be expressed in a wide variety of medical and psychiatric conditions i.e. fatigue, depression, substance abuse... The detection of HCV genetic sequences in post-mortem brain tissue raises the possibility that the presence of HCV in the central nervous system may explain the reported neuropsychological symptoms and cognitive impairment[99].

Health related quality of life (HRQoL) of HCV patients, before antiviral treatment, is diminished compared with controls[100,101]. HRQoL worsens with more advanced liver disease and therapy, leading to a reduction in adherence[102]. Based on the Short Form 36 (SF-36) Health Survey questionnaire, patients with HCV infection consistently show deficits in several domains, particularly those involving their physical role, general health and vitality, versus healthy controls[101,103]. HCV has been associated with a decreased ability to function both at work and at home, with obvious cost implications. Viral eradication correlates positively with improvements in HRQoL[104]. Compared to placebo, a combination of sofosbuvir plus ribavirin was not associated with HRQoL impairment[105]. Moreover, achieving SVR after 12 weeks of follow-up with SOF and ribavirin was associated with improvement in HRQoL.

Depression has been documented in 28% of HCV patients using the Structured Clinical Interview for DSM-IV Axis I Disorders[106]. HCV may directly affects the central nervous system through alterations in serotonergic and dopaminergic neurotransmission with resultant depressive symptoms[107]. This mechanism may explain other central nervous system symptoms seen in HCV infection, such as fatigue and cognitive impairment[108-111]. Prior to starting antivirals including pegIFN, mental health should be assessed, as patients with a history of major depressive disorder are at greater risk of developing depression during HCV treatment. Antidepressant or antianxiolytic treatment may be considered before initiating IFN-based therapy.

Cognitive impairment is well described in chronic HCV infection. It is a common symptom in persons with end-stage liver disease[112]. In the HALT-C trial, 33% of 201 patients with advanced fibrosis who underwent neuropsychological testing had mild cognitive impairment on entering the trial[113]. Patients with chronic HCV infection who are free from co-morbid factors have higher levels of cognitive impairment than healthy controls[114]. HCV eradication leads to improved cognitive function[115] and cerebral metabolism[108]. Patients with SVR demonstrated significant improvements in verbal learning, memory, and visuo-spatial memory.

Fatigue is one of the most frequent and disabling complaints among HCV patients (50-67%), and it independently predicts poor HRQoL[116]. In a prospective study at the first visit of 1,614 HCV infected patients and in 412 healthy blood donors, fatigue was present in 53% of patients (51-56) versus 1% of controls (0-2)[117]. Fatigue was independently associated with female gender, age over 50 years, cirrhosis, and depression. Chronic fatigue is associated with bad sleep quality and increased nocturnal activity in HCV patients suggesting an alteration of sleep architecture in HCV-associated encephalopathy[118].

In conclusion, beyond the liver, HCV chronic infection leads to a multifaceted systemic disease. Some extrahepatic manifestations are immune-mediated while others seem to be driven by chronic inflammation. Such extrahepatic manifestations should be wellknown by clinicians. They should have an impact in the care of HCV infected patients. The need of effective eradication measures is underlined.

References

1. Cacoub P, Poynard T, Ghillani P, et al. Extrahepatic manifestations of chronic hepatitis C. Arthritis Rheum 1999;42(10):2204–12.

2. Cacoub P, Renou C, Rosenthal E, et al. Extrahepatic manifestations associated with hepatitis C virus infection. A prospective multicenter study of 321 patients. Medicine (Baltimore) 2000;79(1):47–56.

3. Zignego AL, Giannini C, Monti M, Gragnani L. Hepatitis C virus lymphotropism: lessons from a decade of studies. Dig Liver Dis 2007;39 Suppl 1:S38–45.

4. Terrier B, Cacoub P. Cryoglobulinemia vasculitis: an update. Curr Opin Rheumatol. 2013 Jan;25(1):10-8.

5. Sene D, Ghillani-Dalbin P, Thibault V, et al. Longterm course of mixed cryoglobulinemia in patients infected with hepatitis C virus. J Rheumatol 2004;31(11):2199–206.

6. Lee M-H, Yang H-I, Lu S-N, et al. Chronic hepatitis C virus infection increases mortality from hepatic and extrahepatic diseases: a community-based long-term prospective study. J Infect Dis 2012;206(4):469–77.

7. Uto H, Stuver SO, Hayashi K, et al. Increased rate of death related to presence of viremia among hepatitis C virus antibody-positive subjects in a community-based cohort study. Hepatology 2009;50(2):393–9.

8. Maasoumy B, Wedemeyer H. Natural history of acute and chronic hepatitis C. Best Pract Res Clin Gastroenterol 2012;26(4):401–12.

9. Omland LH, Jepsen P, Krarup H, et al. Increased mortality among persons infected with hepatitis C virus. Clin Gastroenterol Hepatol 2011;9(1):71–8.

10. El-Kamary SS, Jhaveri R, Shardell MD. All-cause, liver-related, and non-liver-related mortality among HCV-infected individuals in the general US population. Clin Infect Dis 2011;53(2):150–7.

11. Backus LI, Boothroyd DB, Phillips BR, Belperio P, Halloran J, Mole LA. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. Clin Gastroenterol Hepatol 2011;9(6):509–16.e1.

12. Hsu Y-C, Lin J-T, Ho HJ, et al. Antiviral treatment for hepatitis C virus infection is associated with improved renal and cardiovascular outcomes in diabetic patients. Hepatology 2014;59(4):1293–302.

13. Adinolfi LE, Zampino R, Restivo L, et al. Chronic hepatitis C virus infection and atherosclerosis: clinical impact and mechanisms. World J Gastroenterol 2014;20(13):3410–7.

14. Terrier B, Semoun O, Saadoun D, Sène D, Resche-Rigon M, Cacoub P. Prognostic factors in patients with hepatitis C virus infection and systemic vasculitis. Arthritis Rheum 2011;63(6):1748–57.

15. 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(6):355–74.

16. Retamozo S, Díaz-Lagares C, Bosch X, et al. Life-Threatening Cryoglobulinemic Patients With Hepatitis C: Clinical Description and Outcome of 279 Patients. Medicine (Baltimore) 2013;

17. Terrier B, Karras A, Cluzel P, et al. Presentation and prognosis of cardiac involvement in hepatitis C virus-related vasculitis. Am J Cardiol 2013;111(2):265–72.

18. Ramos-Casals M, Robles A, Brito-Zerón P, et al. Life-threatening cryoglobulinemia: clinical and immunological characterization of 29 cases. Semin Arthritis Rheum 2006;36(3):189–96.

19. Saadoun D, Bieche I, Maisonobe T, et al. Involvement of chemokines and type 1 cytokines in the pathogenesis of hepatitis C virus-associated mixed cryoglobulinemia vasculitis neuropathy. Arthritis Rheum 2005;52(9):2917–25.

20. Boyer O, Saadoun D, Abriol J, et al. CD4+CD25+ regulatory T-cell deficiency in patients with hepatitis C-mixed cryoglobulinemia vasculitis. Blood 2004;103(9):3428–30.

21. Saadoun D, Rosenzwajg M, Joly F, et al. Regulatory T-cell responses to low-dose interleukin-2 in HCV-induced vasculitis. N Engl J Med 2011;365(22):2067–77.

22. Cacoub P, Renou C, Kerr G, et al. Influence of HLA-DR phenotype on the risk of hepatitis C virus-associated mixed cryoglobulinemia. Arthritis Rheum 2001;44(9):2118–24.

23. Zignego AL, Wojcik GL, Cacoub P, et al. Genome-wide association study of hepatitis C virus- and cryoglobulin-related vasculitis. Genes Immun 2014; in press

24. Cacoub P, Terrier B, Saadoun D. Hepatitis C virus-induced vasculitis: therapeutic options. Ann Rheum Dis. 2014 Jan;73(1):24-30.

25. Saadoun D, Resche-Rigon M, Thibault V, Piette J-C, Cacoub P. Antiviral therapy for hepatitis C virus--associated mixed cryoglobulinemia vasculitis: a long-term followup study. Arthritis Rheum 2006;54(11):3696–706.

26. Landau D-A, Saadoun D, Halfon P, et al. Relapse of hepatitis C virus-associated mixed cryoglobulinemia vasculitis in patients with sustained viral response. Arthritis Rheum 2008;58(2):604–11.

27. Saadoun D, Resche Rigon M, Pol S, et al. Peg-IFNαRibavirin/Protease inhibitor combination in severe hepatitis C virus associated mixed cryoglobulinemia vasculitis. J Hepatol 2014;

28. Gragnani L, Fabbrizzi A, Triboli E, et al. Triple antiviral therapy in hepatitis C virus infection with or without mixed cryoglobulinaemia: A prospective, controlled pilot study. Dig Liver Dis Off J Ital Soc Gastroenterol Ital Assoc Study Liver 2014;46(9):833–7.

29. European Association for Study of Liver. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. J Hepatol 2014;60(2):392–420.

30. 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(3):843–53.

31. 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(3):835–42.

32. 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(3):343–53.

33. 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(3):326–34.

34. Saadoun D, Delluc A, Piette JC, Cacoub P. Treatment of hepatitis C-associated mixed cryoglobulinemia vasculitis. Curr Opin Rheumatol 2008;20(1):23–8.

35. Saadoun D, Pineton de Chambrun M, Hermine O, et al. Using rituximab plus fludarabine and cyclophosphamide as a treatment for refractory mixed cryoglobulinemia associated with lymphoma. Arthritis Care Res 2013;65(4):643–7.

36. De Sanjose S, Benavente Y, Vajdic CM, et al. Hepatitis C and non-Hodgkin lymphoma among 4784 cases and 6269 controls from the International Lymphoma Epidemiology Consortium. Clin Gastroenterol Hepatol 2008;6(4):451–8.

37. Zuckerman E, Zuckerman T, Levine AM, et al. Hepatitis C virus infection in patients with B-cell non-Hodgkin lymphoma. Ann Intern Med 1997;127(6):423–8.

38. Gisbert JP, García-Buey L, Pajares JM, Moreno-Otero R. Prevalence of hepatitis C virus infection in B-cell non-Hodgkin's lymphoma: systematic review and meta-analysis. Gastroenterology 2003;125(6):1723–32.

39. Dal Maso L, Franceschi S. Hepatitis C virus and risk of lymphoma and other lymphoid neoplasms: a meta-analysis of epidemiologic studies. Cancer Epidemiol Biomark Prev 2006;15(11):2078–85.

40. Matsuo K, Kusano A, Sugumar A, Nakamura S, Tajima K, Mueller NE. Effect of hepatitis C virus infection on the risk of non-Hodgkin's lymphoma: a meta-analysis of epidemiological studies. Cancer Sci 2004;95(9):745–52.

41. Negri E, Little D, Boiocchi M, La Vecchia C, Franceschi S. B-cell non-Hodgkin's lymphoma and hepatitis C virus infection: a systematic review. Int J Cancer J Int Cancer 2004;111(1):1–8.

42. Andreone P, Zignego AL, Cursaro C, et al. Prevalence of monoclonal gammopathies in patients with hepatitis C virus infection. Ann Intern Med 1998;129(4):294–8.

43. Kawamura Y, Ikeda K, Arase Y, et al. Viral elimination reduces incidence of malignant lymphoma in patients with hepatitis C. Am J Med 2007;120(12):1034–41.

44. Saadoun D, Suarez F, Lefrere F, et al. Splenic lymphoma with villous lymphocytes, associated with type II cryoglobulinemia and HCV infection: a new entity? Blood 2005;105(1):74–6.

45. Hermine O, Lefrère F, Bronowicki J-P, et al. Regression of splenic lymphoma with villous lymphocytes after treatment of hepatitis C virus infection. N Engl J Med 2002;347(2):89–94.

46. Giannelli F, Moscarella S, Giannini C, et al. Effect of antiviral treatment in patients with chronic HCV infection and t(14;18) translocation. Blood 2003;102(4):1196–201.

47. Sansonno D, De Vita S, Iacobelli AR, Cornacchiulo V, Boiocchi M, Dammacco F. Clonal analysis of intrahepatic B cells from HCV-infected patients with and without mixed cryoglobulinemia. J Immunol 1998;160(7):3594–601.

48. Vallat L, Benhamou Y, Gutierrez M, et al. Clonal B cell populations in the blood and liver of patients with chronic hepatitis C virus infection. Arthritis Rheum 2004;50(11):3668–78.

49. Landau D-A, Rosenzwajg M, Saadoun D, Klatzmann D, Cacoub P. The B lymphocyte stimulator receptor-ligand system in hepatitis C virus-induced B cell clonal disorders. Ann Rheum Dis 2009;68(3):337–44.

50. Galli M, Zehender G, Monti G, et al. Hepatitis C virus RNA in the bone marrow of patients with mixed cryoglobulinemia and in subjects with noncryoglobulinemic chronic hepatitis type C. J Infect Dis 1995;171(3):672–5.

51. Zignego AL, Macchia D, Monti M, et al. Infection of peripheral mononuclear blood cells by hepatitis C virus. J Hepatol 1992;15(3):382–6.

52. Bronowicki JP, Loriot MA, Thiers V, Grignon Y, Zignego AL, Bréchot C. Hepatitis C virus persistence in human hematopoietic cells injected into SCID mice. Hepatology 1998;28(1):211–8.

53. Sung VM-H, Shimodaira S, Doughty AL, et al. Establishment of B-cell lymphoma cell lines persistently infected with hepatitis C virus in vivo and in vitro: the apoptotic effects of virus infection. J Virol 2003;77(3):2134–46.

54. Tsukiyama-Kohara K, Sekiguchi S, Kasama Y, Salem NE, Machida K, Kohara M. Hepatitis C virus-related lymphomagenesis in a mouse model. ISRN Hematol 2011;2011:167501.

55. Zignego AL, Giannelli F, Marrocchi ME, et al. T(14;18) translocation in chronic hepatitis C virus infection. Hepatology 2000;31(2):474–9.

56. Libra M, Mangano K, Anzaldi M, et al. Analysis of interleukin (IL)-1beta IL-1 receptor antagonist, soluble IL-1 receptor type II and IL-1 accessory protein in HCV-associated lymphoproliferative disorders. Oncol Rep 2006;15(5):1305–8.

57. Saadoun D, Bieche I, Authier F-J, et al. Role of matrix metalloproteinases, proinflammatory cytokines, and oxidative stress-derived molecules in hepatitis C virus-associated mixed cryoglobulinemia vasculitis neuropathy. Arthritis Rheum 2007;56(4):1315–24.

58. Sène D, Limal N, Ghillani-Dalbin P, Saadoun D, Piette J-C, Cacoub P. Hepatitis C virus-associated B-cell proliferation--the role of serum B lymphocyte stimulator (BLyS/BAFF). Rheumatology 2007;46(1):65–9.

59. Giannini C, Gragnani L, Piluso A, et al. Can BAFF promoter polymorphism be a predisposing condition for HCV-related mixed cryoglobulinemia? Blood 2008;112(10):4353–4.

60. Kelaidi C, Rollot F, Park S, et al. Response to antiviral treatment in hepatitis C virus-associated marginal zone lymphomas. Leukemia 2004;18(10):1711–6.

61. Vallisa D, Bernuzzi P, Arcaini L, et al. Role of anti-hepatitis C virus (HCV) treatment in HCV-related, low-grade, B-cell, non-Hodgkin's lymphoma: a multicenter Italian experience. J Clin Oncol 2005;23(3):468–73.

62. Arcaini L, Vallisa D, Rattotti S, et al. Antiviral treatment in patients with indolent B-cell lymphomas associated with HCV infection: a study of the Fondazione Italiana Linfomi. Ann Oncol 2014;25(7):1404–10.

63. Michot JM, Canioni D, Driss H, Alric L, Cacoub P, Suarez F, et al. Antiviral therapy is associated with a better survival in patients with hepatitis C virus and B-cell non-Hodgkin lymphomas, ANRS HC-13 lympho-C study. Am J Hematol. 2014 Nov 21. doi: 10.1002/ajh.23889. [Epub ahead of print]

64. La Mura V, De Renzo A, Perna F, et al. Antiviral therapy after complete response to chemotherapy could be efficacious in HCV-positive non-Hodgkin's lymphoma. J Hepatol 2008;49(4):557–63.

65. Hainsworth JD, Litchy S, Burris HA, et al. Rituximab as first-line and maintenance therapy for patients with indolent non-hodgkin's lymphoma. J Clin Oncol 2002;20(20):4261–7.

66. Lee YH, Ji JD, Yeon JE, Byun KS, Lee CH, Song GG. Cryoglobulinaemia and rheumatic manifestations in patients with hepatitis C virus infection. Ann Rheum Dis 1998;57(12):728–31.

67. Ramos-Casals M, García-Carrasco M, Cervera R, et al. Hepatitis C virus infection mimicking primary Sjögren syndrome. A clinical and immunologic description of 35 cases. Medicine (Baltimore) 2001;80(1):1–8.

68. Koike K, Moriya K, Ishibashi K, et al. Sialadenitis histologically resembling Sjogren syndrome in mice transgenic for hepatitis C virus envelope genes. Proc Natl Acad Sci U S A 1997;94(1):233–6.

69. Fukui M, Kitagawa Y, Nakamura N, Yoshikawa T. Hepatitis C virus and atherosclerosis in patients with type 2 diabetes. J Am Med Assoc 2003;289(10):1245–6.

70. Petta S, Torres D, Fazio G, et al. Carotid atherosclerosis and chronic hepatitis C: a prospective study of risk associations. Hepatol Baltim Md 2012;55(5):1317–23.

71. Aslam F, Alam M, Lakkis NM. Hepatitis C and carotid atherosclerosis: a retrospective analysis. Atherosclerosis 2010;209(2):340–3.

72. Sosner P, Wangermez M, Chagneau-Derrode C, Le Moal G, Silvain C. Atherosclerosis risk in HIV-infected patients: the influence of hepatitis C virus co-infection. Atherosclerosis 2012;222(1):274–7.

73. He Huang null, Kang R, Zhao Z. Hepatitis C virus infection and risk of stroke: a systematic review and meta-analysis. PloS One 2013;8(11):e81305.

74. Hsu C-S, Kao J-H, Chao Y-C, et al. Interferon-based therapy reduces risk of stroke in chronic hepatitis C patients: a population-based cohort study in Taiwan. Aliment Pharmacol Ther 2013;38(4):415–23.

75. Butt AA, Xiaoqiang W, Budoff M, Leaf D, Kuller LH, Justice AC. Hepatitis C virus infection and the risk of coronary disease. Clin Infect Dis 2009;49(2):225–32.

76. Maruyama S, Koda M, Oyake N, et al. Myocardial injury in patients with chronic hepatitis C infection. J Hepatol 2013;58(1):11–5.

77. Terrier B, Cacoub P. Renal involvement in HCV-related vasculitis. Clin Res Hepatol Gastroenterol 2013;37(4):334–9.

78. Fabrizi F, Poordad FF, Martin P. Hepatitis C infection and the patient with end-stage renal disease. Hepatology 2002;36(1):3–10.

79. Roth D, Cirocco R, Zucker K, et al. De novo membranoproliferative glomerulonephritis in hepatitis C virus-infected renal allograft recipients. Transplantation 1995;59(12):1676–82.

80. El-Serag HB, Hampel H, Yeh C, Rabeneck L. Extrahepatic manifestations of hepatitis C among United States male veterans. Hepatology 2002;36(6):1439–45.

81. Dalrymple LS, Koepsell T, Sampson J, et al. Hepatitis C virus infection and the prevalence of renal insufficiency. Clin J Am Soc Nephrol 2007;2(4):715–21.

82. Butt AA, Wang X, Fried LF. HCV infection and the incidence of CKD. Am J Kidney Dis 2011;57(3):396–402.

83. Lee J-J, Lin M-Y, Yang Y-H, Lu S-N, Chen H-C, Hwang S-J. Association of hepatitis C and B virus infection with CKD in an endemic area in Taiwan: a cross-sectional study. Am J Kidney Dis 2010;56(1):23–31.

84. Tsui JI, Vittinghoff E, Shlipak MG, O'Hare AM. Relationship between hepatitis C and chronic kidney disease: results from the Third National Health and Nutrition Examination Survey. J Am Soc Nephrol 2006;17(4):1168–74.

85. Izzedine H, Sene D, Cacoub P, et al. Kidney diseases in HIV/HCV-co-infected patients. AIDS 2009;23(10):1219–26.

86. Wyatt CM, Malvestutto C, Coca SG, Klotman PE, Parikh CR. The impact of hepatitis C virus coinfection on HIV-related kidney disease: a systematic review and meta-analysis. AIDS 2008;22(14):1799–807.

87. Fabrizi F, Plaisier E, Saadoun D, Martin P, Messa P, Cacoub P. Hepatitis C virus infection, mixed cryoglobulinemia, and kidney disease. Am J Kidney Dis 2013;61(4):623–37.

88. Liangpunsakul S, Chalasani N. Relationship between hepatitis C and microalbuminuria: results from the NHANES III. Kidney Int 2005;67(1):285–90.

89. Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of hepatitis C in chronic kidney disease. Kidney Int Suppl 2008;(109):S1–99.

90. Taskoparan M, Serin E, Gokturk HS, et al. Early effect of peginterferon alpha-2b plus ribavirin treatment on blood pressure and insulin resistance in patients with chronic hepatitis C. Hepatogastroenterology 2011;58(107-108):875–9.

91. Aghemo A, Prati GM, Rumi MG, et al. Sustained virological response prevents the development of insulin resistance in patients with chronic hepatitis C. Hepatology 2012;56(5):1681–7.

92. Cacoub P, Carrat F, Bédossa P, et al. Insulin resistance impairs sustained virological response rate to pegylated interferon plus ribavirin in HIV-hepatitis C virus-coinfected patients: HOMAVIC-ANRS HC02 Study. Antivir Ther 2009;14(6):839–45.

93. Serfaty L, Capeau J. Hepatitis C, insulin resistance and diabetes: clinical and pathogenic data. Liver Int 2009;29 Suppl 2:13–25.

94. Shintani Y, Fujie H, Miyoshi H, et al. Hepatitis C virus infection and diabetes: direct involvement of the virus in the development of insulin resistance. Gastroenterology 2004;126(3):840–8.

95. Caronia S, Taylor K, Pagliaro L, et al. Further evidence for an association between non-insulin-dependent diabetes mellitus and chronic hepatitis C virus infection. Hepatology 1999;30(4):1059–63.

96. Mason AL, Lau JY, Hoang N, et al. Association of diabetes mellitus and chronic hepatitis C virus infection. Hepatology 1999;29(2):328–33.

97. Farghaly HS, Metwalley KA, El-Hafeez HAA. Hepatitis C virus infection in Egyptian children with type 1 diabetes mellitus: A single center study. Indian J Endocrinol Metab 2014;18(2):197–201.

98. Forton DM, Thomas HC, Murphy CA, et al. Hepatitis C and cognitive impairment in a cohort of patients with mild liver disease. Hepatology 2002;35(2):433–9.

99. Laskus T, Radkowski M, Adair DM, Wilkinson J, Scheck AC, Rakela J. Emerging evidence of hepatitis C virus neuroinvasion. AIDS 2005;19 Suppl 3:S140–4.

100. Bonkovsky HL, Snow KK, Malet PF, et al. Health-related quality of life in patients with chronic hepatitis C and advanced fibrosis. J Hepatol 2007;46(3):420–31.

101. Younossi Z, Kallman J, Kincaid J. The effects of HCV infection and management on health-related quality of life. Hepatology 2007;45(3):806–16.

102. Marcellin P, Chousterman M, Fontanges T, et al. Adherence to treatment and quality of life during hepatitis C therapy: a prospective, real-life, observational study. Liver Int 2011;31(4):516–24.

103. Cacoub P, Ratziu V, Myers RP, et al. Impact of treatment on extra hepatic manifestations in patients with chronic hepatitis C. J Hepatol 2002;36(6):812–8.

104. Spiegel BMR, Younossi ZM, Hays RD, Revicki D, Robbins S, Kanwal F. Impact of hepatitis C on health related quality of life: a systematic review and quantitative assessment. Hepatology 2005;41(4):790–800.

105. Younossi Z, Henry L. The impact of the new antiviral regimens on patient reported outcomes and health economics of patients with chronic hepatitis C. Dig Liver Dis. 2014 Dec 15;46 Suppl 5:S186-96.

106. Golden J, O'Dwyer AM, Conroy RM. Depression and anxiety in patients with hepatitis C: prevalence, detection rates and risk factors. Gen Hosp Psychiatry 2005;27(6):431–8.

107. Cozzi A, Zignego AL, Carpendo R, et al. Low serum tryptophan levels, reduced macrophage IDO activity and high frequency of psychopathology in HCV patients. J Viral Hepat 2006;13(6):402–8.

108. Byrnes V, Miller A, Lowry D, et al. Effects of anti-viral therapy and HCV clearance on cerebral metabolism and cognition. J Hepatol 2012;56(3):549–56.

109. Casato M, Saadoun D, Marchetti A, et al. Central nervous system involvement in hepatitis C virus cryoglobulinemia vasculitis: a multicenter case-control study using magnetic resonance imaging and neuropsychological tests. J Rheumatol 2005;32(3):484–8.

110. Forton DM. Altered monoaminergic transporter binding in hepatitis C related cerebral dysfunction: a neuroimmunologial condition? Gut 2006;55(11):1535–7.

111. Weissenborn K, Ennen JC, Bokemeyer M, et al. Monoaminergic neurotransmission is altered in hepatitis C virus infected patients with chronic fatigue and cognitive impairment. Gut 2006;55(11):1624–30.

112. Perry W, Hilsabeck RC, Hassanein TI. Cognitive dysfunction in chronic hepatitis C: a review. Dig Dis Sci 2008;53(2):307–21.

113. Fontana RJ, Bieliauskas LA, Back-Madruga C, et al. Cognitive function in hepatitis C patients with advanced fibrosis enrolled in the HALT-C trial. J Hepatol 2005;43(4):614–22.

114. Lowry D, Coughlan B, McCarthy O, Crowe J. Investigating health-related quality of life, mood and neuropsychological test performance in a homogeneous cohort of Irish female hepatitis C patients. J Viral Hepat 2010;17(5):352–9.

115. Thein HH, Maruff P, Krahn MD, et al. Improved cognitive function as a consequence of hepatitis C virus treatment. HIV Med 2007;8(8):520–8.

116. Kallman J, O'Neil MM, Larive B, Boparai N, Calabrese L, Younossi ZM. Fatigue and health-related quality of life (HRQL) in chronic hepatitis C virus infection. Dig Dis Sci 2007;52(10):2531–9.

117. Poynard T, Cacoub P, Ratziu V, et al. Fatigue in patients with chronic hepatitis C. J Viral Hepat 2002;9(4):295–303.

118. Heeren M, Sojref F, Schuppner R, et al. Active at night, sleepy all day--sleep disturbances in patients with hepatitis C virus infection. J Hepatol 2014;60(4):732–40.

A. Immune-related extra hepatic manifestations

mixed cryoglobulinemia
cryoglobulinemic vasculitis
B-cell NHL
sicca syndrome
arthralgia/myalgia
auto-antibody production (i.e. cryoglobulins, rheumatoid factor, and antinuclear, anticardiolipin, anti-thyroid and anti-smooth muscle antibodies)
polyarteritis nodosa
monoclonal gammopathies
immune thrombocytopenia

B. Inflammatory-related extra hepatic manifestations

type 2 diabetes mellitus type 2
insulin resistance
glomerulonephritis
renal insufficiency
fatigue
cognitive impairment
depression
impaired quality of life
polyarthritis/fibromyalgia
cardiovascular disorders (i.e. stroke, ischemic heart disease)

Table 1: Main extrahepatic manifestations in HCV infected patients