Extrahepatic manifestations of chronic hepatitis C virus infection

Patrice Cacoub, Cloe Comarmond, Fanny Domont, Léa Savey, Anne C. Desbois and David Saadoun

Abstract: During hepatitis C virus (HCV) chronic infection, extrahepatic manifestations are frequent and polymorphous. This article reports on a large cohort of patients with HCV-related autoimmune 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 and pathological data, and results of therapeutic trials. More recently, other nonliver-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 comes from large epidemiological studies; there is a need for mechanistic studies and therapeutic trials for confirmation. Beyond the risk of developing liver complications, that is, cirrhosis and liver cancer, patients with HCV infection have an increased risk of morbidity and mortality related to nonliver diseases. HCV chronic infection should be analyzed as a systemic disease in which extrahepatic consequences increase the weight of its pathological burden. The need for effective viral eradication measures is underlined.

Keywords: extrahepatic manifestations, hepatitis C virus, treatment

Hepatitis C virus (HCV) infection is a major health problem with 150—170 million people chronically infected. On the one hand, these patients are at risk of developing liver complications, that is, cirrhosis and liver cancer, with an estimated liver-related mortality of 350,000 people/year. On the other hand, in large cohort studies, two-thirds of patients with HCV infection experienced extrahepatic manifestations [Cacoub *et al.* 1999]. Some of these conditions are well documented and more common, while others are infrequent [Cacoub *et al.* 2000; Zignego *et al.* 2007; Zignego and Bréchot, 1999]. Soon after HCV discovery, HCV-related autoimmune or lymphoproliferative disorders, from benign mixed cryoglobulinemia to frank lymphomas, have been reported [Zignego *et al.* 2007; Terrier *et al.* 2013; Sene *et al.* 2004]. More recently, many other nonliver 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 extrahepatic complications [Lee *et al.* 2012; Maasoumy and Wedemeyer, 2012; Omland *et al.* 2011; Uto *et al.* 2009]. All-cause mortality in patients with HCV was increased more than twice compared with patients without HCV [El-Kamary *et al.* 2011], probably related to serum HCV RNA positivity [Lee *et al.* 2012]. Viral eradication significantly reduced the rate of extrahepatic deaths [Adinolfi *et al.* 2014; Backus *et al.* 2011; Hsu *et al.* 2014; Kawamura *et al.* 2007]. 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 nonliver manifestations of the disease.

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 [Terrier *et al.* 2013]. 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,

Correspondence to:
Patrice Cacoub,
Sorbonne Universités, UPMC Univ Paris 06, UMR 7211, and Inflammation-Immunopathology-Biotherapy Department (DHU i2B), F-75005, Paris, France
INSERM, UMR_S 959, F-75013, Paris, France
CNRS, FRE3632, F-75005, Paris, France
AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Department of Internal Medicine and Clinical Immunology, F-75013, Paris, France.
patrice.cacoub@ psl.aphp.fr

Cloe Comarmond
Sorbonne Universités, UPMC Univ Paris 06, and Inflammation Immunopathology Biotherapy Department (DHU i2B), Paris, France
INSERM, UMR_S 959, Paris, France
CNRS, FRE3632, Paris, France
AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Department of Internal Medicine and Clinical

Immunology, Paris, France

Fanny Domont, Léa Savey
Sorbonne Universités, UPMC Univ Paris 06, and Inflammation Immunopathology Biotherapy Department (DHU i2B), Paris, France
AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Department of Internal Medicine and Clinical Immunology, Paris, France

Anne C. Desbois, David Saadoun
Sorbonne Universités, UPMC Univ Paris 06, and Inflammation Immunopathology Biotherapy Department (DHU i2B), Paris, France
INSERM, UMR_S 959, Paris, France
CNRS, FRE3632, Paris, France
AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Department of Internal Medicine and Clinical Immunology, Paris, France

Table 1. Main extrahepatic manifestations in patients with hepatitis C virus infection.

Immune-related extrahepatic manifestations
Mixed cryoglobulinemia
Cryoglobulinemic vasculitis
B-cell NHL
Sicca syndrome
Arthralgia/myalgia
Autoantibody production (i.e. cryoglobulins, rheumatoid factor, and antinuclear, anticardiolipin, antithyroid and anti-smooth muscle antibodies)
Polyarteritis nodosa
Monoclonal gammopathies
Immune thrombocytopenia
Inflammatory-related extrahepatic 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)

NHL, non-Hodgkin's lymphoma.

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 subendothelial deposits, strongly associated with the type II immunoglobulin Mκ (IgMκ) 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 [Sène *et al.* 2004]. 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 prognostic factors are an age greater than 60 years at diagnosis and renal involvement [Terrier *et al.* 2011]. The overall 5-year survival rate after the diagnosis of Cryovas ranges from 90% to 50% in the 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 which one-third were due to renal involvement), cancer or hemopathy (23%), or liver disease (13%) [Ferri *et al.* 2004]. Cryovas complications may result in progressive (renal involvement) or acute (pulmonary hemorrhage, gastrointestinal ischemia, cardiac, central nervous system involvement) life-threatening organ damage, with a mortality rate between 20% and 80% [Retamozo *et al.* 2013; Terrier *et al.* 2013]. Intestinal ischemia, pulmonary hemorrhage, high cryocrit levels and type II MC are associated with severe prognosis [Ramos-Casals *et al.* 2006].

There are multiple factors predisposing patients with HCV infection 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 [Saadoun *et al.* 2005a]. $CD4^+CD25^+FoxP3^+$ regulatory T cells are reduced in patients with Cryovas [Boyer *et al.* 2004; Saadoun *et al.* 2011] which may account for the expansion of peripheral

autoreactive B cells that drive Cryovas. Human leucocyte antigen (HLA-DR11) is associated with Cryovas whereas HLA-DR7 appears to protect against Cryovas [Cacoub *et al.* 2001]. In a recent multicenter genome-wide association study significant associations were identified on chromosome 6, a single nucleotide peptide located within an intronic region of NOTCH4 ($p = 6.2 \times 10^{-9}$) and another found in between HLA-DRB1 and HLA-DQA1 ($p = 1.2 \times 10^{-7}$) [Zignego *et al.* 2014]. Specific virological factors have not yet been identified.

Most HCV-Cryovas manifestations respond to clearance of HCV during antiviral therapy with pegylated interferon (pegIFN) plus ribavirin [Saadoun *et al.* 2006]. Patients who have relapsed HCV infection after responding to antiviral therapy usually have relapsed Cryovas with the return of viremia [Saadoun *et al.* 2006]. In case of persistent MC, relapse of vasculitis might also occur despite achieving a sustained virologic response (SVR); this situation should lead to a search for a different underlying condition, especially B-cell lymphoma [Landau *et al.* 2008]. Recent use of triple anti-HCV therapy with pegIFN/ribavirin and a direct antiviral agent (boceprevir or telaprevir) led to improved rates of SVR and Cryovas remission in HCV genotype 1 [Gragnani *et al.* 2014]. 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 [European Association for Study of Liver, 2014] state that treatment should be scheduled, not deferred, for patients with clinically significant extrahepatic 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 trials showed that rituximab has a better efficacy than conventional treatment (i.e. glucocorticoids, azathioprine, cyclophosphamide or plasmapheresis) [De Vita *et al.* 2012]. Two other controlled clinical trials showed that addition of rituximab to pegIFN/ribavirin led to a shorter time to clinical remission, better renal response rate and higher rates of cryoglobulin clearance [Dammacco *et al.* 2010; Saadoun *et al.* 2010].

In daily practice, patients with HCV Cryovas 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 etc.) control of disease with rituximab, with or without plasmapheresis, is required before initiation of optimal antiviral therapy [Saadoun *et al.* 2008]. 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 as arthralgia, but do not succeed in the case of major organ involvement. Other immunosuppressants should be given only in the case of refractory forms of HCV Cryovas, usually associated with underlying B-cell lymphoma [Saadoun *et al.* 2013].

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 [Dal Maso and Franceschi, 2006; de Sanjose et al. 2008; Gisbert *et al.* 2003; Matsuo *et al.* 2004; Negri *et al.* 2004]. HCV was associated with marginal zone NHL [odds ratio (OR) 2.47] and diffuse large B-NHL (OR 2.24). A serum monoclonal gammopathy, more frequently IgMκ, was frequently observed [Andreone *et al.* 1998]. 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 [Kawamura Y *et al.* 2007]. SVR-induced NHL regression, while a viral relapse, was followed by lymphoma recurrence [Saadoun *et al.* 2005]. HCV-positive splenic lymphoma with villous lymphocytes regressed after antiviral therapy [Hermine *et al.* 2002]. Regression of expanded B-cell clones following successful antiviral treatment have been reported with expansion of the same clones in virological relapsers [Giannelli *et al.* 2003; Zignego *et al.* 2002]. 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 [Saadoun *et al.* 2005b]. This leads to the concept of no-return points in 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, that is, sustained activation of B cells [Lai and

Weiss, 1998; Sansonno *et al.* 1998; Vallat *et al.* 2004], inhibition of B-cell apoptosis, genetic/epigenetic and environmental factors [Landau *et al.* 2009; Zignego *et al.* 2012]. The lymphotropism agrees with a higher HCV infection prevalence in peripheral blood mononuclear cells (PBMCs) and bone marrow [Galli *et al.* 1995; Zignego *et al.* 1992] and was confirmed by *in vivo* and *in vitro* studies [Bronowicki *et al.* 1998; Sung *et al.* 2003]. 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 [Kasama *et al.* 2010; Tsukiyama-Kohara *et al.* 2011]. The t(14;18) translocation causes increased Bcl-2 levels and abnormal B-cell survival [Zignego *et al.* 1997, 2000, 2002] and disappear after antiviral treatment [Giannelli *et al.* 2003; Giannini *et al.* 2006, 2008]. The role of cytokines and chemokines has been studied [Libra *et al.* 2005, 2006; Saadoun *et al.* 2005a, 2007; Sansonno *et al.* 2009], with special attention of the B-cell activating factor [De Vita *et al.* 2008; Landau *et al.* 2009; Sène *et al.* 2007].

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-NHL, mainly marginal zone lymphoma [Arcaini *et al.* 2014; Hermine *et al.* 2002; Kelaidi *et al.* 2004; Mazzaro *et al.* 2009; Saadoun *et al.* 2005b; Vallisa *et al.* 2005]. IFN-based treatment showed an improved overall survival in patients with indolent HCV-associated NHL [Arcaini *et al.* 2014]. Antivirals following NHL remission showed improved clinical outcome and prolonged disease-free survival [La Mura *et al.* 2008; Musto *et al.* 1996]. The use of rituximab in HCV-NHL, alone or in combination with antivirals or chemotherapy, appears interesting in low-grade NHL [Hainsworth *et al.* 2002; Saadoun *et al.* 2010].

Arthralgia/myalgia
Arthralgia is reported in 40–80% of patients with HCV infection [Cacoub *et al.* 2000; Lee *et al.* 1998]. Patients present with symmetric joint pains, nondeforming, involving mainly knees and hands. HCV arthritis is less common. RF activity is found in 70–80% of patients with MC 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 occurring in patients with HCV infection are related to chronic HCV infection or to a newly developed rheumatologic disease.

Sicca syndrome
Sicca symptoms of either the mouth or eyes have been reported in 20–30% of patients with HCV infection, whereas less than 5% of patients with Sjögren's syndrome are HCV positive [Cacoub *et al.* 2000]. Many similarities exist between HCV-related sicca syndrome and 'true' Sjögren's syndrome [Ramos-Casals *et al.* 2001]. 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 patients with HCV infection. Patients with HCV-positive Sjögren's syndrome are older and more likely to have 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 HCV E1 and E2 glycoproteins in transgenic mice is associated with the development of sialadenitis [Koike *et al.* 1997].

Autoantibodies
Biological immunologic abnormalities are frequent, including mixed cryoglobulins (60–90%), RF activity (70%), and antinuclear (20–40%), anticardiolipin (15%), antithyroid (12%) and anti-smooth muscle antibodies (7%) [Cacoub *et al.* 1999; Cacoub *et al.* 2000]. 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.

Cardiovascular diseases
Asian studies suggest an association between HCV infection and an increased risk of carotid artery plaques and carotid intima media thickening, independently of classical cardiovascular risk factors [Fukui *et al.* 2003]. Patients with HCV infection showed a higher likelihood of having carotid atherosclerotic plaques compared with HCV-negative controls [Aslam *et al.* 2010], particularly in those with active viral replication.

Suggested mechanisms include the production of proatherogenic cytokines [Adinolfi *et al.* 2014]. Other studies performed in patients with HCV or coinfected with HCV and human immunodeficiency virus (HIV) confirmed the link between HCV infection and carotid atherosclerosis [Adinolfi *et al.* 2012; Petta *et al.* 2012; Sosner *et al.* 2012]. Furthermore, retrospective cohort studies suggest a beneficial effect of antivirals on the incidence of stroke in patients with HCV infection [Hsu *et al.* 2013]. A prospective study conducted in three groups of patients with diabetes followed over 8 years showed a decreased cumulative incidence of ischemic stroke in treated *versus* nontreated patients with HCV infection [Hsu *et al.* 2014].

HCV chronic infection was shown to increase the risk of coronary artery disease, after adjustment for classical cardiovascular risk factors [Butt *et al.* 2009]. Patients who were anti-HCV positive had higher mortality rates from cardiovascular diseases compared with HCV-negative controls [hazard ratio (HR) 1.50; 95% confidence interval (CI) 1.10–2.03] [Lee *et al.* 2012]. Patients with positive viremia showed higher rates of deaths, while patients who were HCV RNA negative had rates similar to controls. A large Asian study analyzed 1411 subjects with HCV and diabetes mellitus treated with pegIFN plus RBV who were matched with 1411 patients who were HCV positive and had diabetes and were not treated with antivirals, and with 5644 patients who were HCV negative and had diabetes [Hsu *et al.* 2014]. 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 patients with HCV who were treated *versus* those with HCV who were untreated. In addition, Maruyama and colleagues showed an improvement in the myocardial perfusion defect after antiviral treatment in patients who showed a SVR compared with those who had relapsed infection [Maruyama *et al.* 2013].

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 a clinical and histological picture of HCV Cryovas that is an acute or chronic type I membrano-proliferative

glomerulonephritis with subendothelial deposits, with type II IgMκ cryoglobulinemia [Terrier and Cacoub, 2013]. 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 components (C1q, C4) are very low. Chronic renal insufficiency may develop in 10–20% of patients with HCV Cryovas. Renal morphological features are characterized by important monocyte infiltrates with double contours of the basement membrane, large, eosinophilic and amorphous intraluminal thrombi. Vasculitis of small renal arteries or extracapillary crescents are rarely observed. Immunofluorescence studies show intraglomerular subendothelial deposits of IgG, IgM and complement components. The electron microscopic features with subendothelial and intraluminal deposits presenting a crystalloid aspect are pathognomonic.

There is some evidence of the association between HCV and other glomerular diseases [Fabrizi *et al.* 2002]. A large case–control study, carried out among US male veterans hospitalized between 1992 and 1999 [El-Serag *et al.* 2002], 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, sex, race, diabetes and hypertension [Dalrymple *et al.* 2007]. Some large surveys have suggested an impact of HCV infection on prevalence and incidence of kidney disease in the general population [Asrani *et al.* 2010; Butt *et al.* 2011; Dalrymple *et al.* 2007; Lee *et al.* 2010; Tsui *et al.* 2006]. Anti-HCV status was associated with low glomerular filtration rate (OR up to 2.80) and with proteinuria (OR 1.14–1.99) [Butt *et al.* 2011; Huang *et al.* 2006; Lee *et al.* 2010; Liangpunsakul and Chalasani, 2005; Wyatt *et al.* 2008], 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 [Hsu *et al.* 2014], three groups were analyzed: 1411 patients with HCV infection who received pegIFN plus ribavirin (treated cohort), 1411 untreated controls with HCV infection and 5644 patients with diabetes who were HCV negative (uninfected cohort). The 8-year cumulative incidence of end-stage 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 an HR of 0.16 (0.07–0.33%) for end-stage renal disease.

The Kidney Disease: Improving Global Outcomes (KDIGO) group recommends that all patients with chronic kidney disease should be tested for HCV [KDIGO, 2008]. 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. Patients with HCV Cryovas and 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.

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 and colleagues failed to establish a correlation between IR and chronic HCV infection [Taskoparan *et al.* 2011]. The presence of IR was evaluated in patients with HCV achieving a SVR after pegIFN plus ribavirin. On the 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 patients with SVR, suggesting that HCV eradication could prevent IR onset and its evolution to diabetes [Aghemo *et al.* 2012]. Insulin resistance has been shown to impair SVR rate to pegIFN plus ribavirin in patients coinfected with HIV and HCV [Cacoub *et al.* 2009].

HCV-related type 2 diabetes mellitus may arise from a complex interaction between IR, steatosis and inflammatory processes [Serfaty and Capeau, 2009]. Epidemiologic studies supporting the association between type 2 diabetes and HCV infection have been published in the early 1990s. In larger epidemiologic studies [Caronia *et al.* 1999; Mason *et al.* 1999], 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 cirrhosis and male sex. An epidemiologic study conducted in Egypt in a pediatric population of 150 patients with type I diabetes revealed a prevalence of HCV infection higher than in controls [Farghaly *et al.* 2014].

Fatigue, depression and cognitive impairment
Neurocognitive morbidity in patients with HCV infection does not completely correlate with the severity of liver disease [Forton *et al.* 2002; McAndrews *et al.* 2005]. Cognitive impairment may be expressed in a wide variety of medical and psychiatric conditions, such as fatigue, depression, substance abuse among others. The detection of HCV genetic sequences in postmortem brain tissue raises the possibility that the presence of HCV in the central nervous system may explain the reported neuropsychological symptoms and cognitive impairment [Laskus *et al.* 2005].

Health-related quality of life (HRQoL) of patients with HCV, before antiviral treatment, is diminished compared with controls [Bonkovsky *et al.* 2007; Bonkovsky and Woolley, 1999; Kang *et al.* 2005]. HRQoL worsens with more advanced liver disease and therapy, leading to a reduction in adherence [Marcellin *et al.* 2011; Snow *et al.* 2010]. Based on the Short Form 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 [McHutchison *et al.* 2001; Spiegel *et al.* 2005; Younossi *et al.* 2007]. 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 [Bonkovsky and Woolley, 1999; Cacoub *et al.* 2002]. Compared with placebo, a combination of sofosbuvir plus ribavirin was not associated with HRQoL impairment [Younossi Z *et al.* 2014]. Moreover, achieving SVR after 12 weeks of follow up with sofosbuvir and ribavirin was associated with improvement in HRQoL.

Depression has been documented in 28% of patients with HCV using the Structured Clinical Interview for DSM-IV Axis I Disorders [Golden *et al.* 2005]. HCV may directly affect the central nervous system through alterations in serotonergic and dopaminergic neurotransmission with resultant depressive symptoms [Cozzi *et al.* 2006]. This mechanism may explain other central nervous system symptoms seen in HCV infection, such as fatigue and cognitive impairment [Byrnes *et al.* 2012; Casato *et al.* 2005; Forton, 2006; Weissenborn *et al.* 2006]. 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 people with end-stage liver disease [Perry *et al.* 2008]. In the Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) trial, 33% of 201 patients with advanced fibrosis who underwent neuropsychological testing had mild cognitive impairment on entering the trial [Fontana *et al.* 2005]. Patients with chronic HCV infection who are free from comorbid factors have higher levels of cognitive impairment than healthy controls [Lowry *et al.* 2010]. HCV eradication leads to improved cognitive function [Thein *et al.* 2007] and cerebral metabolism [Byrnes *et al.* 2012]. Patients with SVR demonstrated significant improvements in verbal learning, memory and visuospatial memory.

Fatigue is one of the most frequent and disabling complaints among patients with HCV (50–67%), and it independently predicts poor HRQoL [Kallman *et al.* 2007]. In a prospective study at the first visit of 1614 patients with HCV infection and in 412 healthy blood donors, fatigue was present in 53% of patients (51–56) *versus* 1% of controls (0–2) [Poynard *et al.* 2002]. Fatigue was independently associated with female sex, age over 50 years, cirrhosis and depression. Chronic fatigue is associated with bad sleep quality and increased nocturnal activity in patients with HCV, suggesting an alteration of sleep architecture in HCV-associated encephalopathy [Heeren *et al.* 2014].

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 well known by clinicians. They should have an impact on the care of patients with HCV infection. The need for effective eradication measures is underlined.

Conflict of interest statement
The authors declare no conflicts of interest in preparing this article.

References
Adinolfi, L., Restivo, L., Zampino, R., Guerrera, B., Lonardo, A., Ruggiero, L. *et al.* (2012) Chronic HCV infection is a risk of atherosclerosis. Role of HCV and HCV-related steatosis. *Atherosclerosis* 221: 496–502. doi:10.1016/j.atherosclerosis.2012.01.051.

Adinolfi, L., Zampino, R., Restivo, L., Lonardo, A., Guerrera, B., Marrone, A. *et al.* (2014) Chronic hepatitis C virus infection and atherosclerosis: clinical impact and mechanisms. *World J Gastroenterol* 20: 3410–3417.

Aghemo, A., Prati, G., Rumi, M., Soffredini, R., D'Ambrosio, R., Orsi, E. *et al.* (2012) Sustained virological response prevents the development of insulin resistance in patients with chronic hepatitis C. *Hepatology* 56: 1681–1687.

Andreone, P., Zignego, A., Cursaro, C., Gramenzi, A., Gherlinzoni, F., Fiorino, S. *et al.* (1998) Prevalence of monoclonal gammopathies in patients with hepatitis C virus infection. *Ann Intern Med* 129: 294–298.

Arcaini, L., Vallisa, D., Rattotti, S., Ferretti, V., Ferreri, A., Bernuzzi, P. *et al.* (2014) Antiviral treatment in patients with indolent B-cell lymphomas associated with HCV infection: a study of the Fondazione Italiana Linfomi. *Ann Oncol* 25: 1404–1410.

Aslam, F., Alam, M. and Lakkis, N. (2010) Hepatitis C and carotid atherosclerosis: a retrospective analysis. *Atherosclerosis* 209: 340–343.

Asrani, S., Buchanan, P., Pinsky, B., Rey, L., Schnitzler, M. and Kanwal, F. (2010) Lack of association between hepatitis C infection and chronic kidney disease. *Clin Gastroenterol Hepatol* 8: 79–84.

Backus, L., Boothroyd, D., Phillips, B., Belperio, P., Halloran, J. and Mole, L. (2011) A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. *Clin Gastroenterol Hepatol* 9: 509–516.e1.

Bonkovsky, H., Snow, K., Malet, P., Back-Madruga, C., Fontana, R., Sterling, R. *et al.* HALT-C Trial Group. (2007) Health-related quality of life in patients with chronic hepatitis C and advanced fibrosis. *J Hepatol* 46: 420–431.

Bonkovsky, H. and Woolley, J. (1999) Reduction of health-related quality of life in chronic hepatitis C and improvement with interferon therapy. The Consensus Interferon Study Group. *Hepatology* 29: 264–270.

Boyer, O., Saadoun, D., Abriol, J., Dodille, M., Piette, J., Cacoub, P. *et al.* (2004) CD4+CD25+ regulatory T-cell deficiency in patients with hepatitis C-mixed cryoglobulinemia vasculitis. *Blood* 103: 3428–3430.

Bronowicki, J., Loriot, M., Thiers, V., Grignon, Y., Zignego, A. and Bréchot, C. (1998) Hepatitis C virus persistence in human hematopoietic cells injected into SCID mice. *Hepatology* 28: 211–218.

Butt, A., Wang, X. and Fried, L. (2011) HCV infection and the incidence of CKD. *Am J Kidney Dis* 57: 396–402.

Butt, A., Xiaoqiang, W., Budoff, M., Leaf, D., Kuller, L. and Justice, A. (2009) Hepatitis C virus infection and the risk of coronary disease. *Clin Infect Dis* 49: 225–232.

Byrnes, V., Miller, A., Lowry, D., Hill, E., Weinstein, C., Alsop, D. *et al.* (2012) Effects of anti-viral therapy and HCV clearance on cerebral metabolism and cognition. *J Hepatol* 56: 549–556.

Cacoub, P., Carrat, F., Bédossa, P., Lambert, J., Pénaranda, G., Pol, S. *et al.* (2009) 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* 14: 839–845.

Cacoub, P., Poynard, T., Ghillani, P., Charlotte, F., Olivi, M., Piette, J. *et al.* (1999) Extrahepatic manifestations of chronic hepatitis C. MULTIVIRC Group. Multidepartment virus C. *Arthritis Rheum* 42: 2204–2212.

Cacoub, P., Ratziu, V., Myers, R., Ghillani, P., Piette, J., Moussalli, J. *et al.* Multivirc Group. (2002) Impact of treatment on extra hepatic manifestations in patients with chronic hepatitis C. *J Hepatol* 36: 812–818.

Cacoub, P., Renou, C., Kerr, G., Hüe, S., Rosenthal, E., Cohen, P. *et al.* (2001) Influence of HLA-DR phenotype on the risk of hepatitis C virus-associated mixed cryoglobulinemia. *Arthritis Rheum* 44: 2118–2124.

Cacoub, P., Renou, C., Rosenthal, E., Cohen, P., Loury, I., Loustaud-Ratti, V. *et al.* (2000) Extrahepatic manifestations associated with hepatitis C virus infection. A prospective multicenter study of 321 patients. The GERMIVIC. Groupe d'Etude et de Recherche en Medecine Interne et Maladies Infectieuses sur le Virus de l'Hepatite C. *Medicine* 79: 47–56.

Caronia, S., Taylor, K., Pagliaro, L., Carr, C., Palazzo, U., Petrik, J. *et al.* (1999) Further evidence for an association between non-insulin-dependent diabetes mellitus and chronic hepatitis C virus infection. *Hepatology* 1059–1063.

Casato, M., Saadoun, D., Marchetti, A., Limal, N., Picq, C., Pantano, P. *et al.* (2005) Central nervous system involvement in hepatitis C virus cryoglobulinemia vasculitis: a multicenter case-control study using magnetic resonance imaging and neuropsychological tests. *J Rheumatol* 32: 484–488.

Cozzi, A., Zignego, A., Carpendo, R., Biagiotti, T., Aldinucci, A., Monti, M. *et al.* (2006) Low serum tryptophan levels, reduced macrophage IDO activity and high frequency of psychopathology in HCV patients. *J Viral Hepat* 13: 402–408.

Dal Maso, L. and Franceschi, S. (2006) Hepatitis C virus and risk of lymphoma and other lymphoid neoplasms: a meta-analysis of epidemiologic studies. *Cancer Epidemiol* 15: 2078–2085.

Dalrymple, L., Koepsell, T., Sampson, J., Louie, T., Dominitz, J., Young, B. *et al.* (2007) Hepatitis C virus infection and the prevalence of renal insufficiency. *Clin J Am Soc Nephrol* 2: 715–721.

Dammacco, F., Tucci, F., Lauletta, G., Gatti, P., De Re, V., Conteduca, V. *et al.* (2010) Pegylated interferon-alpha, ribavirin, and rituximab combined therapy of hepatitis C virus-related mixed cryoglobulinemia: a long-term study. *Blood* 116: 343–353.

De Sanjose, S., Benavente, Y., Vajdic, C., Engels, E., Morton, L., Bracci, P. *et al.* (2008) Hepatitis C and non-Hodgkin lymphoma among 4784 cases and 6269 controls from the International Lymphoma Epidemiology Consortium. *Clin Gastroenterol Hepatol* 6: 451–458.

De Vita, S., Quartuccio, L. and Fabris, M. (2008) Hepatitis C virus infection, mixed cryoglobulinemia and BLyS upregulation: targeting the infectious trigger, the autoimmune response, or both? *Autoimmun Rev* 8: 95–99.

De Vita, S., Quartuccio, L., Isola, M., Mazzaro, C., Scaini, P., Lenzi, M. *et al.* (2012) A randomized controlled trial of rituximab for the treatment of severe cryoglobulinemic vasculitis. *Arthritis Rheum* 64: 843–853.

El-Kamary, S., Jhaveri, R. and Shardell, M. (2011) All-cause, liver-related, and non-liver-related mortality among HCV-infected individuals in the general US population. *Clin Infect Dis* 53: 150–157.

El-Serag, H., Hampel, H., Yeh, C. and Rabeneck, L. (2002) Extrahepatic manifestations of hepatitis C among United States male veterans. *Hepatology* 36: 1439–1445.

European Association for Study of Liver (2014) EASL clinical practice guidelines: management of hepatitis C virus infection. *J Hepatol* 60: 392–420.

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

Farghaly, H., Metwalley, K. and El-Hafeez, H. (2014) Hepatitis C virus infection in Egyptian children with type 1 diabetes mellitus: a single center study. *Indian J Endocrinol Metab* 18: 197–201.

Fontana, R., Bieliauskas, L., Back-Madruga, C., Lindsay, K., Kronfol, Z., Lok, A. *et al.* HALT-C Trial Group. (2005) Cognitive function in hepatitis C patients with advanced fibrosis enrolled in the HALT-C trial. *J Hepatol* 43: 614–622.

Forton, D. (2006) Altered monoaminergic transporter binding in hepatitis C related cerebral dysfunction: a neuroimmunologial condition? *Gut* 55: 1535–1537.

Forton, D., Thomas, H., Murphy, C., Allsop, J., Foster, G., Main, J. *et al.* (2002) Hepatitis C and cognitive impairment in a cohort of patients with mild liver disease. *Hepatology* 35: 433–439.

Fukui, M., Kitagawa, Y., Nakamura, N. and Yoshikawa, T. (2003) Hepatitis C virus and athero-sclerosis in patients with type 2 diabetes. *JAMA* 289: 1245–1246.

Galli, M., Zehender, G., Monti, G., Ballaré, M., Saccardo, F., Piconi, S. *et al.* (1995) 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* 171: 672–675.

Giannelli, F., Moscarella, S., Giannini, C., Caini, P., Monti, M., Gragnani, L. *et al.* (2003) Effect of antiviral treatment in patients with chronic HCV infection and t(14;18) translocation. *Blood* 102: 1196–1201.

Giannini, C., Giannelli, F. and Zignego, A. (2006) Association between mixed cryoglobulinemia, translocation (14;18), and persistence of occult HCV lymphoid infection after treatment. *Hepatology* 43: 1166–1167.

Giannini, C., Petrarca, A., Monti, M., Arena, U., Caini, P., Solazzo, V. *et al.* (2008) Association between persistent lymphatic infection by hepatitis C virus after antiviral treatment and mixed cryoglobulinemia. *Blood* 111: 2943–2945.

Gisbert, J., García-Buey, L., Pajares, J. and Moreno-Otero, R. (2003) Prevalence of hepatitis C virus infection in B-cell non-Hodgkin's lymphoma: systematic review and meta-analysis. *Gastroenterology* 125: 1723–1732.

Golden, J., O'Dwyer, A. and Conroy, R. (2005) Depression and anxiety in patients with hepatitis C: prevalence, detection rates and risk factors. *Gen Hosp Psychiatry* 27: 431–438.

Gragnani, L., Fabbrizzi, A., Triboli, E., Urraro, T., Boldrini, B., Fognani, E. *et al.* (2014) Triple antiviral therapy in hepatitis C virus infection with or without mixed cryoglobulinaemia: a prospective, controlled pilot study. *Dig Liver Dis Off* 46: 833–837.

Hainsworth, J., Litchy, S., Burris, H., Scullin, D., Corso, S., Yardley, D. *et al.* (2002) Rituximab as first-line and maintenance therapy for patients with indo-lent non-Hodgkin's lymphoma. *J Clin Oncol* 20: 4261–4267.

Heeren, M., Sojref, F., Schuppner, R., Worthmann, H., Pflugrad, H., Tryc, A. *et al.* (2014) Active at night, sleepy all day–sleep disturbances in patients with hepatitis C virus infection. *J Hepatol* 60: 732–740.

Hermine, O., Lefrère, F., Bronowicki, J., Mariette, X., Jondeau, K., Eclache-Saudreau, V. *et al.* (2002) Regression of splenic lymphoma with villous lympho-cytes after treatment of hepatitis C virus infection. *N Engl J Med* 347: 89–94.

Hsu, C., Kao, J., Chao, Y., Lin, H., Fan, Y., Huang, C. *et al.* (2013) Interferon-based therapy reduces risk of stroke in chronic hepatitis C patients: a population-based cohort study in Taiwan. *Aliment Pharmacol Ther* 38: 415–423.

Hsu, Y., Lin, J., Ho, H., Kao, Y., Huang, Y., Hsiao, N. *et al.* (2014) Antiviral treatment for hepatitis C virus infection is associated with improved renal and car-diovascular outcomes in diabetic patients. *Hepatology* 59: 1293–1302.

Huang, J., Chuang, W., Dai, C., Ho, C., Hwang, S., Chen, S. *et al.* (2006) Viral hepatitis and proteinuria in an area endemic for hepatitis B and C infections: another chain of link? *J Intern Med* 260: 255–262.

Kallman, J., O'Neil, M., Larive, B., Boparai, N., Calabrese, L. and Younossi, Z. (2007) Fatigue and health-related quality of life (HRQL) in chronic hepatitis C virus infection. *Dig Dis Sci* 52: 2531–2539.

Kang, S., Hwang, S., Lee, S., Chang, F. and Lee, S. (2005) Health-related quality of life and impact of antiviral treatment in Chinese patients with chronic hepatitis C in Taiwan. *World J Gastroenterol* 11: 7494–7498.

Kasama, Y., Sekiguchi, S., Saito, M., Tanaka, K., Satoh, M., Kuwahara, K. *et al.* (2010) Persistent expression of the full genome of hepatitis C virus in B cells induces spontaneous development of B-cell lymphomas in vivo. *Blood* 116: 4926–4933.

Kawamura, Y., Ikeda, K., Arase, Y., Yatsuji, H., Sezaki, H., Hosaka, T. *et al.* (2007) Viral elimination reduces incidence of malignant lymphoma in patients with hepatitis C. *Am J Med* 120: 1034–1041.

KDIGO (Kidney Disease: Improving Global Outcomes) (2008) KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of hepatitis C in chronic kidney disease. *Kidney Int Suppl* S1–S99.

Kelaidi, C., Rollot, F., Park, S., Tulliez, M., Christoforov, B., Calmus, Y. *et al.* (2004) Response to antiviral treatment in hepatitis C virus-associated marginal zone lymphomas. *Leukemia* 18: 1711–1716.

Koike, K., Moriya, K., Ishibashi, K., Yotsuyanagi, H., Shintani, Y. and Fujie, H. (1997) Sialadenitis

histologically resembling Sjogren syndrome in mice transgenic for hepatitis C virus envelope genes. *Proc Natl Acad Sci U S A* 94: 233–236.

Lai, R. and Weiss, L. (1998) Hepatitis C virus and non-Hodgkin's lymphoma. *Am J Clin Pathol* 109: 508–510.

La Mura, V., De Renzo, A., Perna, F., D'Agostino, D., Masarone, M., Romano, M. *et al.* (2008) Antiviral therapy after complete response to chemotherapy could be efficacious in HCV-positive non-Hodgkin's lymphoma. *J Hepatol* 49: 557–563.

Landau, D., Rosenzwajg, M., Saadoun, D., Klatzmann, D. and Cacoub, P. (2009) The B lymphocyte stimulator receptor-ligand system in hepatitis C virus-induced B cell clonal disorders. *Ann Rheum Dis* 68: 337–344.

Landau, D., Saadoun, D., Halfon, P., Martinot-Peignoux, M., Marcellin, P., Fois, E. *et al.* (2008) Relapse of hepatitis C virus-associated mixed cryo-globulinemia vasculitis in patients with sustained viral response. *Arthritis Rheum* 58: 604–611.

Laskus, T., Radkowski, M., Adair, D., Wilkinson, J., Scheck, A. and Rakela, J. (2005) Emerging evidence of hepatitis C virus neuroinvasion. *AIDS Lond Engl* 19(Suppl. 3): S140–S144.

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

Lee, M., Yang, H., Lu, S., Jen, C., You, S., Wang, L. *et al.* R.E.V.E.A.L.-HCV Study Group. (2012) Chronic hepatitis C virus infection increases mortality from hepatic and extrahepatic diseases: a community-based long-term prospective study. *J Infect Dis* 206: 469–477.

Lee, Y., Ji, J., Yeon, J., Byun, K., Lee, C. and Song, G. (1998) Cryoglobulinaemia and rheumatic manifestations in patients with hepatitis C virus infection. *Ann Rheum Dis* 57: 728–731.

Liangpunsakul, S. and Chalasani, N. (2005) Relationship between hepatitis C and microalbuminuria: results from the NHANES III. *Kidney Int* 67: 285–290.

Libra, M., Indelicato, M., De Re, V., Zignego, A., Chiocchetti, A., Malaponte, G. *et al.* (2005) Elevated serum levels of osteopontin in HCV-associated lymphoproliferative disorders. *Cancer Biol Ther* 4: 1192–1194.

Libra, M., Mangano, K., Anzaldi, M., Quattrocchi, C., Donia, M., di Marco, R. *et al.* (2006) 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* 15: 1305–1308.

Lowry, D., Coughlan, B., McCarthy, O. and Crowe, J. (2010) Investigating health-related quality of life, mood and neuropsychological test performance in a homogeneous cohort of Irish female hepatitis C patients. *J Viral Hepat* 17: 352–359.

Maasoumy, B. and Wedemeyer, H. (2012) Natural history of acute and chronic hepatitis C. *Best Pract Res Clin Gastroenterol* 26: 401–412.

Marcellin, P., Chousterman, M., Fontanges, T., Ouzan, D., Rotily, M., Varastet, M. *et al.* CheObs Study Group. (2011) Adherence to treatment and quality of life during hepatitis C therapy: a prospective, real-life, observational study. *Liver Int* 31: 516–524.

Maruyama, S., Koda, M., Oyake, N., Sato, H., Fujii, Y., Horie, Y. *et al.* (2013) Myocardial injury in patients with chronic hepatitis C infection. *J Hepatol* 58: 11–15.

Mason, A., Lau, J., Hoang, N., Qian, K., Alexander, G., Xu, L. *et al.* (1999) Association of diabetes mellitus and chronic hepatitis C virus infection. *Hepatology* 29: 328–333.

Matsuo, K., Kusano, A., Sugumar, A., Nakamura, S., Tajima, K. and Mueller, N. (2004) Effect of hepatitis C virus infection on the risk of non-Hodgkin's lymphoma: a meta-analysis of epidemiological studies. *Cancer Sci* 95: 745–752.

Mazzaro, C., De Re, V., Spina, M., Dal Maso, L., Festini, G., Comar, C. *et al.* (2009) Pegylated-interferon plus ribavirin for HCV-positive indolent non-Hodgkin lymphomas. *Br J Haematol* 145: 255–257.

McAndrews, M., Farcnik, K., Carlen, P., Damyanovich, A., Mrkonjic, M., Jones, S. *et al.* (2005) Prevalence and significance of neurocognitive dysfunction in hepatitis C in the absence of correlated risk factors. *Hepatology* 41: 801–808.

McHutchison, J., Ware, J., Bayliss, M., Pianko, S., Albrecht, J., Cort, S. *et al.* Hepatitis Interventional Therapy Group. (2001) The effects of interferon alpha-2b in combination with ribavirin on health related quality of life and work productivity. *J Hepatol* 34: 140–147.

Musto, P., Dell'Olio, M., Carotenuto, M., Mangia, A. and Andriulli, A. (1996) Hepatitis C virus infection: a new bridge between hematologists and gastroenterologists? *Blood* 88: 752–754.

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

Omland, L., Jepsen, P., Krarup, H., Schønning, K., Lind, B., Kromann-Andersen, H. *et al.* DANVIR Cohort Study. (2011) Increased mortality among persons infected with hepatitis C virus. *Clin Gastroenterol Hepatol* 9: 71–78.

Perry, W., Hilsabeck, R. and Hassanein, T. (2008) Cognitive dysfunction in chronic hepatitis C: a review. *Dig Dis Sci* 53: 307–321.

Petta, S., Torres, D., Fazio, G., Cammà, C., Cabibi, D., Di Marco, V. *et al.* (2012) Carotid atherosclerosis

and chronic hepatitis C: a prospective study of risk associations. *Hepatology* 55: 1317–1323.

Poynard, T., Cacoub, P., Ratziu, V., Myers, R., Dezailles, M., Mercadier, A. *et al.* Multivirc Group. (2002) Fatigue in patients with chronic hepatitis C. *J Viral Hepat* 9: 295–303.

Ramos-Casals, M., García-Carrasco, M., Cervera, R., Rosas, J., Trejo, O., de la Red, G. *et al.* (2001) Hepatitis C virus infection mimicking primary Sjögren syndrome. A clinical and immunologic description of 35 cases. *Medicine* 80: 1–8.

Ramos-Casals, M., Robles, A., Brito-Zerón, P., Nardi, N., Nicolás, J., Forns, X. *et al.* (2006) Life-threatening cryoglobulinemia: clinical and immunological characterization of 29 cases. *Semin Arthritis Rheum* 36: 189–196.

Retamozo, S., Díaz-Lagares, C., Bosch, X., Bové, A., Brito-Zerón, P., Gómez, M. *et al.* (2013) Life-threatening cryoglobulinemic patients with hepatitis C: clinical description and outcome of 279 patients. *Medicine* 22 August (epub ahead of print).

Saadoun, D., Bieche, I., Authier, F., Laurendeau, I., Jambou, F., Piette, J. *et al.* (2007) Role of matrix metalloproteinases, proinflammatory cytokines, and oxidative stress-derived molecules in hepatitis C virus-associated mixed cryoglobulinemia vasculitis neuropathy. *Arthritis Rheum* 56: 1315–1324.

Saadoun, D., Bieche, I., Maisonobe, T., Asselah, T., Laurendeau, I., Piette, J. *et al.* (2005a) Involvement of chemokines and type 1 cytokines in the pathogenesis of hepatitis C virus-associated mixed cryoglobulinemia vasculitis neuropathy. *Arthritis Rheum* 52: 2917–2925.

Saadoun, D., Delluc, A., Piette, J. and Cacoub, P. (2008) Treatment of hepatitis C-associated mixed cryoglobulinemia vasculitis. *Curr Opin Rheumatol* 20: 23–28.

Saadoun, D., Pineton de Chambrun, M., Hermine, O., Karras, A., Choquet, S., Jego, P. *et al.* (2013) Using rituximab plus fludarabine and cyclophosphamide as a treatment for refractory mixed cryoglobulinemia associated with lymphoma. *Arthritis Care Res* 65: 643–647.

Saadoun, D., Resche Rigon, M., Sene, D., Terrier, B., Karras, A., Perard, L. *et al.* (2010) Rituximab plus Peg-interferon-alpha/ribavirin compared with Peg-interferon-alpha/ribavirin in hepatitis C-related mixed cryoglobulinemia. *Blood* 116: 326–334; quiz 504–505.

Saadoun, D., Resche-Rigon, M., Thibault, V., Piette, J. and Cacoub, P. (2006) Antiviral therapy for hepatitis C virus–associated mixed cryoglobulinemia vasculitis: a long-term followup study. *Arthritis Rheum* 54: 3696–3706.

Saadoun, D., Rosenzwajg, M., Joly, F., Six, A., Carrat, F., Thibault, V. *et al.* (2011) Regulatory T-cell responses to low-dose interleukin-2 in HCV-induced vasculitis. *N Engl J Med* 365: 2067–2077.

Saadoun, D., Suarez, F., Lefrere, F., Valensi, F., Mariette, X., Aouba, A. *et al.* (2005b) Splenic lymphoma with villous lymphocytes, associated with type II cryoglobulinemia and HCV infection: a new entity? *Blood* 105: 74–76.

Sansonno, D., De Vita, S., Iacobelli, A., Cornacchiulo, V., Boiocchi, M. and Dammacco, F. (1998) Clonal analysis of intrahepatic B cells from HCV-infected patients with and without mixed cryoglobulinemia. *J Immunol* 160: 3594–3601.

Sansonno, D., Tucci, F., Ghebrehiwet, B., Lauletta, G., Peerschke, E., Conteduca, V. *et al.* (2009) Role of the receptor for the globular domain of C1q protein in the pathogenesis of hepatitis C virus-related cryoglobulin vascular damage. *J Immunol* 183: 6013–6020.

Sène, D., Ghillani-Dalbin, P., Thibault, V., Guis, L., Musset, L., Duhaut, P. *et al.* (2004) Longterm course of mixed cryoglobulinemia in patients infected with hepatitis C virus. *J Rheumatol* 31: 2199–2206.

Sène, D., Limal, N., Ghillani-Dalbin, P., Saadoun, D., Piette, J. and Cacoub, P. (2007) Hepatitis C virus-associated B-cell proliferation — the role of serum B lymphocyte stimulator (BLyS/BAFF). *Rheumatology* 46: 65–69.

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

Snow, K., Bonkovsky, H., Fontana, R., Kim, H., Sterling, R., Di Bisceglie, A. *et al.* HALT-C Trial Group. (2010) Changes in quality of life and sexual health are associated with low-dose peginterferon therapy and disease progression in patients with chronic hepatitis C. *Aliment Pharmacol Ther* 31: 719–734.

Sosner, P., Wangermez, M., Chagneau-Derrode, C., Le Moal, G. and Silvain, C. (2012) Atherosclerosis risk in HIV-infected patients: the influence of hepatitis C virus co-infection. *Atherosclerosis* 222: 274–277.

Spiegel, B., Younossi, Z., Hays, R., Revicki, D., Robbins, S. and Kanwal, F. (2005) Impact of hepatitis C on health related quality of life: a systematic review and quantitative assessment. *Hepatology* 41: 790–800.

Sung, V., Shimodaira, S., Doughty, A., Picchio, G., Can, H., Yen, T. *et al.* (2003) 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* 77: 2134–2146.

Taskoparan, M., Serin, E., Gokturk, H., Icer, M., Abaci, K., Ozer, B. *et al.* (2011) Early effect of peginterferon alpha-2b plus ribavirin treatment on blood pressure and insulin resistance in patients with chronic hepatitis C. *Hepatogastroenterology* 58: 875–879.

Terrier, B. and Cacoub, P. (2013) Renal involvement in HCV-related vasculitis. *Clin Res Hepatol Gastroenterol* 37: 334–339.

Terrier, B., Karras, A., Cluzel, P., Collet, J., Sène, D., Saadoun, D. *et al.* (2013) Presentation and prognosis of cardiac involvement in hepatitis C virus-related vasculitis. *Am J Cardiol* 111: 265–272.

Thein, H., Maruff, P., Krahn, M., Kaldor, J., Koorey, D., Brew, B. *et al.* (2007) Improved cognitive function as a consequence of hepatitis C virus treatment. *HIV Med* 8: 520–528.

Tsui, J., Vittinghoff, E., Shlipak, M. and O'Hare, A. (2006) Relationship between hepatitis C and chronic kidney disease: results from the Third National Health and Nutrition Examination Survey. *J Am Soc Nephrol* 17: 1168–1174.

Tsukiyama-Kohara, K., Sekiguchi, S., Kasama, Y., Salem, N., Machida, K. and Kohara, M. (2011) Hepatitis C virus-related lymphomagenesis in a mouse model. *ISRN Hematol* 2011: 167501.

Uto, H., Stuver, S., Hayashi, K., Kumagai, K., Sasaki, F., Kanmura, S. *et al.* (2009) Increased rate of death related to presence of viremia among hepatitis C virus antibody-positive subjects in a community-based cohort study. *Hepatology* 50: 393–399.

Vallat, L., Benhamou, Y., Gutierrez, M., Ghillani, P., Hercher, C., Thibault, V. *et al.* (2004) Clonal B cell populations in the blood and liver of patients with chronic hepatitis C virus infection. *Arthritis Rheum* 50: 3668–3678.

Vallisa, D., Bernuzzi, P., Arcaini, L., Sacchi, S., Callea, V., Marasca, R. *et al.* (2005) 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* 23: 468–473.

Weissenborn, K., Ennen, J., Bokemeyer, M., Ahl, B., Wurster, U., Tillmann, H. *et al.* (2006) Monoaminergic neurotransmission is altered in hepatitis C virus infected patients with chronic fatigue and cognitive impairment. *Gut* 55: 1624–1630.

Wyatt, C., Malvestutto, C., Coca, S., Klotman, P. and Parikh, C. (2008) The impact of hepatitis C virus coinfection on HIV-related kidney disease: a systematic review and meta-analysis. *AIDS* 22: 1799–1807.

Younossi, Z., Kallman, J. and Kincaid, J. (2007) The effects of HCV infection and management on health-related quality of life. *Hepatology* 45: 806–816.

Zignego, A. and Bréchot, C. (1999) Extrahepatic manifestations of HCV infection: facts and controversies. *J Hepatol* 31: 369–376.

Zignego, A., Ferri, C., Giannelli, F., Giannini, C., Caini, P., Monti, M. *et al.* (2002) Prevalence of bcl-2 rearrangement in patients with hepatitis C virus-related mixed cryoglobulinemia with or without B-cell lymphomas. *Ann Intern Med* 137: 571–580.

Zignego, A., Ferri, C., Pileri, S., Caini, P., Bianchi, F. and Italian Association of the Study of Liver Commission on Extrahepatic Manifestations of HCV Infection.(2007) Extrahepatic manifestations of hepatitis C virus infection: a general overview and guidelines for a clinical approach. *Dig Liver Dis* 39: 2–17.

Zignego, A., Giannelli, F., Marrocchi, M., Giannini, C., Gentilini, P., Innocenti, F. *et al.* (1997) Frequency of bcl-2 rearrangement in patients with mixed cryoglobulinemia and HCV-positive liver diseases. *Clin Exp Rheumatol* 15: 711–712.

Zignego, A., Giannelli, F., Marrocchi, M., Mazzocca, A., Ferri, C., Giannini, C. *et al.* (2000) T(14;18) translocation in chronic hepatitis C virus infection. *Hepatology* 31: 474–479.

Zignego, A., Giannini, C. and Gragnani, L. (2012) HCV and lymphoproliferation. *Clin Dev Immunol* 2012: 980942.

Zignego, A., Macchia, D., Monti, M., Thiers, V., Mazzetti, M., Foschi, M. *et al.* (1992) Infection of peripheral mononuclear blood cells by hepatitis C virus. *J Hepatol* 15: 382–386.

Zignego, A., Wojcik, G., Cacoub, P., Visentini, M., Casato, M., Mangia, A. *et al.* (2014) Genome-wide association study of hepatitis C virus- and cryoglobulin-related vasculitis. *Genes Immun* 15: 500–505.