Digestive and Liver Disease 46 (2014) S165–S173

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Review Article

Extrahepatic manifestations of chronic hepatitis C virus infection

Patrice Cacoub[a,b,c,d,*], Laura Gragnani[e], Cloe Comarmond[a,b,c,d], Anna Linda Zignego[e]

[a] Sorbonne University, UPMC Univ Paris 06, UMR 7211, and Inflammation-Immunopathology-Biotherapy Department (DHU i2B), Paris, France
[b] INSERM, UMR_S 959, Paris, France
[c] CNRS, FRE3632, Paris, France
[d] AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Department of Internal Medicine and Clinical Immunology, Paris, France
[e] Interdepartmental Center for Systemic Manifestations of Hepatitis Viruses (MaSVE), Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy

ARTICLE INFO

Article history:
Received 9 September 2014
Accepted 3 October 2014
Available online 8 November 2014

Keywords:
Extra hepatic manifestations
HCV
Treatment

ABSTRACT

Hepatitis C virus (HCV) infected patients are known to be at risk of developing liver complications i.e. cirrhosis and liver cancer. However, the risks of morbidity and mortality are underestimated because they do not take into account non-liver consequences of chronic hepatitis C virus infection. Numerous extrahepatic manifestations have been reported in up to 74% of patients, from perceived to disabling conditions. The majority of data concern hepatitis C virus-related autoimmune and/or lymphoproliferative disorders, from mixed cryoglobulinaemia vasculitis to frank lymphomas. More recently, other hepatitis C virus-associated disorders have been reported including cardiovascular, renal, metabolic, and central nervous system diseases. This review aims to outline most of the extrahepatic manifestations that are currently being investigated, including some of autoimmune and/or lymphoproliferative nature, and others in which the role of immune mechanisms appears less clear.

Beyond the liver, hepatitis C virus chronic infection should be analyzed as a multifaceted systemic disease leading to heavy direct and indirect costs. The accurate consideration of extrahepatic consequences of such a systemic infection significantly increases the weight of its pathological burden. The need for effective viral eradication measures is underlined.

1. Introduction

Hepatitis C virus (HCV) infection is a major health problem. The World Health Organization (WHO) estimates that at least 150–170 million people, approximately 3% of the world's population, are chronically infected. These patients are known to be at risk of developing liver complications, i.e., cirrhosis and liver cancer, with an estimated liver-related mortality of 350,000 people/year. However, the risks of morbidity and mortality are underestimated because they do not take into account the extrahepatic consequences of HCV infection. Numerous extrahepatic manifestations (HCV-EHMs) have been reported. In some large cohort studies, up to 74% of patients experienced HCV-EHMs of different severity, from perceived to disabling conditions [1]. Some of these conditions are well documented and more common, while others are infrequent or their association with HCV has not yet been proven [2–4]. Table 1 shows a tentative classification of HCV-EHMs according to scientific strength of the association.

The majority of available data concern HCV-related autoimmune and/or lymphoproliferative disorders, from benign mixed cryoglobulinaemia to frank lymphomas, which agrees with HCV lymphotropisms [5]. More recently, other HCV-associated disorders have been reported including cardiovascular, renal, metabolic, and central nervous system diseases. This review aims to outline most of HCV-EHMs that are currently being investigated in depth, including some of autoimmune and/or lymphoproliferative nature, and others for which the role of immune mechanisms appears less clear. HCV disease appears as a major, mainly hidden, public health problem leading to heavy direct and indirect costs. The possibility that HCV infection can now be eradicated following new antiviral therapies is important from a therapeutic and preventive point of view, for liver and non-liver consequences of the disease.

* Corresponding author at: Department of Internal Medicine and Clinical Immunology, Hôpital La Pitié-Salpêtrière, 47-83, Boulevard de l'Hôpital, 75651 Paris Cedex 13, France. Tel.: +33 01 42 17 80 27; fax: +33 01 42 17 80 33.
E-mail address: patrice.cacoub@psl.aphp.fr (P. Cacoub).

http://dx.doi.org/10.1016/j.dld.2014.10.005
1590-8658/

Table 1
Main extra hepatic manifestations of hepatitis C Virus infection: tentative classification according to the strength of the association.

A. Significant prevalence, consistent pathogenetic data and "ex-adjuvantibus" criteria
Mixed cryoglobulinaemia/cryoglobulinaemic vasculitis
B-cell NHL
B. Higher prevalence than controls
Type 2 diabetes mellitus type 2
Insulin resistance
Glomerulonephritis
Renal insufficiency
Fatigue
Cognitive impairment
Depression
Impaired quality of life
Cardiovascular disorders (i.e. stroke, ischemic heart disease)
Sicca syndrome
Arthralgia/myalgia
Auto-antibody production (i.e. cryoglobulins, rheumatoid factor, and antinuclear, anticardiolipin, anti-thyroid and anti-smooth muscle antibodies)
Monoclonal gammopathies
Immune thrombocytopenia
Porphyria cutanea tarda
Lichen planus
C. Possible association
Polyarthritis
Pruritus
Fibromyalgia
Chronic polyradiculoneuropathy
Lung alveolitis
D. Anecdotal association
Polymyositis
Dermatomyositis
Polyarteritis nodosa
Psoriasis
Mooren corneal ulcer
Erythema nodosum
E. Association with antiviral treatment (interferon alpha)
Hypo-hyperthyroidism
Depression
Fatigue
Impaired quality of life
Sarcoidosis
Lichen
Skin vasculitis
Peripheral neuropathy

NHL, non-Hodgkin's lymphoma; SS, Sjögren's syndrome; PM/DM, polymyositis/dermatomyositis; PAN, polyarteritis nodosa.

2. Immune-related extrahepatic manifestations

2.1. Cryoglobulinaemia vasculitis

Mixed cryoglobulinaemia (MC) vasculitis is a small vessel vasculitis involving mainly the skin, the joints, the peripheral nerve system and the kidneys. HCV infection represents the cause of MC in roughly 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. The main symptom is a palpable purpura, but chronic cutaneous ulcers may occur. Raynaud's phenomenon and acrocyanosis, which may evolve to digital ulcerations, can also occur. Neurologic manifestations range from pure sensory axonopathy to mononeuritis multiplex. The most frequently described form is a distal sensory or sensory-motor polyneuropathy, usually presenting with painful, asymmetric paresthesia which later become symmetric. Less frequently, multiple mononeuropathy may occur. Renal involvement is an acute or chronic type-I membranoproliferative glomerulonephritis with sub-endothelial deposits. It represents 70–80% of cryoglobulinaemia renal diseases and is strongly associated with the type II IgM kappa MC. The most frequent presentation is proteinuria with microscopic haematuria and a variable degree of renal insufficiency.

Cryoglobulinaemia is confirmed by the detection of protein precipitates in the patient's serum maintained at 4 °C during at least 7 days, which dissolve when heated at 37 °C. During chronic HCV infection, MC are immunochemically 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 cryoglobulinaemia and other surrogate markers (C4, CH50, RF). However, cryoglobulinaemia may persist despite clinical response of vasculitis under therapy.

During HCV infection, cryoglobulinaemic vasculitis 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 age over 60 yrs at diagnosis and renal involvement. The overall 5 year survival rate after the diagnosis of vasculitis ranges from 90% to 50% in case of renal involvement. Even in the absence of significant renal failure, increased mortality from liver involvement, cardiovascular disease, infection and lymphoma has been reported [7]. In a recent retrospective Italian study of 231 patients, 79 of 97 deaths were linked to vasculitis (46%, of whom one-third due to renal involvement), cancer or haemopathy (23%), or liver disease (13%) [8]. Life-threatening MC complications are observed in up to 10% of the patients, with a mortality of almost two-thirds [9]. HCV-related cryoglobulinaemia may result in progressive (renal involvement) or acute (pulmonary haemorrhage, gastrointestinal ischaemia, cardiac, CNS involvement) life-threatening organ damage. The mortality rate of these manifestations ranges between 20% and 80% [10,11]. Intestinal ischaemia, pulmonary haemorrhage, high cryocrit levels and type II MC are associated with severe prognosis [9].

There are multiple factors predisposing HCV-infected patients to develop cryoglobulinaemic vasculitis. 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 [12]. $CD4^+CD25^+FoxP3^+$regulatory T cells, which have been shown to control autoimmunity, are significantly reduced in HCV-MC vasculitis patients [13,14]. This defect in immune regulation may account for the expansion of peripheral auto-reactive B-cells that drive MC vasculitis. The HLA type II polymorphism may predispose to HCV-MC. HLA-DR11 is associated with MC vasculitis whereas HLA-DR7 appears to protect from type II MC [15]. In a recent multi-centre genome-wide association study performed in 356 HCV-MC patients and 447 HCV-positive controls, significant associations were identified on chromosome 6, a SNP (Single Nucleotide Polymorphism) located within an intronic region of NOTCH4 ($p = 6.2 \times 10^{-9}$) and another found between HLA-DRB1 and HLA-DQA1 ($p = 1.2 \times 10^{-7}$) [16]. It has been shown that a higher percentage of a particular allele of the promoter of the B-cell activating factor (BAFF) – known to be related to higher translational activity of the gene [17] – and different expression patterns on circulating lymphocytes of microRNAs are involved in lymphoproliferative and/or autoimmune disorders [18]. In contrast, specific virological factors have not yet been identified.

HCV-induced vasculitis manifestations and MC respond to clearance of HCV during combination antiviral therapy with pegylated interferon (PEG-IFN) plus ribavirin [19,20]. Patients who relapse for HCV infection, after responding to antiviral therapy, usually relapse for vasculitis with the return of viraemia [21]. In case of persistent MC, relapse of vasculitis may also occur in a few patients despite achieving a sustained virologic response (SVR). In such patients, a different underlying condition should be considered,

especially B-cell lymphoma [22]. Recent use of triple anti-HCV therapy with PEG-IFN/ribavirin and a specifically targeted antiviral agent has led to improved SVR rates. In an open label French prospective single-centre cohort study [23], the safety and efficacy of combination therapy with PEG-IFN/ribavirin plus a NS3/4A protease inhibitor (boceprevir or telaprevir) was evaluated in 30 patients with HCV genotype 1 (GT1) infection and MC vasculitis. At week 72, twenty (66.7%) patients were complete clinical and sustained virological responders (SVR). Serious adverse events occurred in 14 (46.6%) patients. The baseline factors associated with serious adverse events included liver fibrosis ($p = 0.045$) and a low platelet count ($p = 0.021$). In another prospective, controlled, single-centre Italian cohort study [24], 35 HCV GT1 patients received PEG-IFN/ribavirin for 48 weeks in combination with boceprevir, after a four-week period of PEG-IFN/ribavirin. Patients showed a drastic reduction of cryocrit values, and an improvement in MC symptoms. When compared with matched HCV controls without MC, SVR was less frequent in MC patients (23.9% vs. 70%; $p = 0.01$). Other direct-acting antivirals are now becoming available. The NS3/4A inhibitor Simeprevir and NS5B inhibitor Sofosbuvir have recently been licensed. These agents facilitate the use of shortened courses of combination IFN-free therapy, which are associated with high (>95%) SVR rates and relatively little toxicities. International guidelines (i.e., EASL 2014) [25] state that treatment should not be deferred in patients with significant liver fibrosis and with clinically significant extra-hepatic manifestations, like symptomatic cryoglobulinaemia. As SVR has been previously associated with MC vasculitis remission in most patients, there is no doubt that the new HCV treatments will be a major benefit for these patients.

Rituximab is also an interesting therapy in MC, as it targets B-cells, which are responsible for cryoglobulin production and finally vasculitis lesions [26–30]. A randomized controlled trial in 57 patients with MC vasculitis showed that rituximab has a better efficacy than conventional treatments (i.e., glucocorticoids, azathioprine or cyclophosphamide, or plasmapheresis) [31]. Similar results have been reported in a placebo controlled trial [32]. The use of rituximab was shown to be safe in HCV patients, in contrast to HBV infected patients [33]. A prospective study in patients with HCV-related MC and advanced liver disease showed that rituximab was safe and associated with clinical improvement of the liver disease [34]. Two controlled clinical trials demonstrated that rituximab plus PEG-IFN/ribavirin compared to PEG-IFN/ribavirin led to clinical remission faster with better renal response rate, and higher rates of cryoglobulin clearance [35,36].

To summarize, patients with mild to moderate HCV-related MC vasculitis should receive optimal antiviral treatment. In patients with severe vasculitis (i.e. worsening of renal function, mononeuritis multiplex, extensive skin disease, intestinal ischaemia etc.) control of disease with rituximab, with or without plasmapheresis, is usually required before initiation of antiviral therapy [37]. Careful monitoring for adverse effects is mandatory, since some manifestations of HCV-MC, such as peripheral neuropathy or skin ulcers, may worsen with IFN-based therapy. Room for other treatment strategies is very limited. Low-dose corticosteroids may help to control minor intermittent inflammatory signs such arthralgia but are unsuccessful in case of major organ involvement. Other immunosuppressants should be given only in case of refractory forms of HCV-MC, frequently associated with underlying B-cell lymphoma [38].

2.2. B-cell lymphoproliferative diseases

The strong correlation between HCV infection and MC, a benign but prelymphomatous condition, leads to the hypothesis that HCV may be involved in the pathogenesis of other lymphoproliferative diseases (LPDs). A high prevalence of HCV infection in patients with B-cell non-Hodgkin's lymphoma (B-NHL) was first reported in limited cohorts [39,40]. During the last two decades, the association between HCV and several hematologic malignancies, most notably B-NHL, was confirmed [41,42] with a gradient from north to south. Meta-analyses confirmed an increased risk of lymphoma in HCV subjects, with varying degrees of risk [41,43–46]. HCV was associated with marginal zone NHL (OR 2.47), diffuse large B-cell NHL (DLBCL) (OR 2.24) and LPL (OR 2.57). A serum monoclonal gammopathy (MG), more frequently IgMk, diagnosed as MG of uncertain significance, was frequently observed in HCV patients [47].

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 [48]. SVR induced NHL regression while a viral relapse was followed by lymphoma recurrence [49,50]. In the study by Hermine et al., HCV-positive splenic lymphoma with villous lymphocytes (SLVL) regressed after anti-viral therapy (AT) [51]. These data agree with the regression of expanded B-cell clones following successful AT with the new expansion of the same clones in relapsers [52,53]. This regression was also shown in patients with benign conditions (i.e., type II or III MC), whereas a persistent B cell clone, despite a clinical remission, was evidenced in SVRs with SLVL [50]. This suggests the presence of no-return points in the HCV-driven lymphoma genesis leading the process progressively less dependent from the etiologic agent [54].

HCV-related LPDs are the result of multiple and cooperating events. A pivotal role seems to be played by a sustained activation of B-cells, an inhibition of B-cell apoptosis, genetic/epigenetic and environmental factors [54,55]. Arguments in favour of a sustained antigenic stimulation include the HCV lymphotropism and the detection of HCV antigens in peripheral blood, or liver infiltrating lymphocytes and lymph nodes [56–58]. Special emphasis was dedicated to the binding between the surface E2 protein and the tetraspanin CD81 leading to a lower B-cell activation threshold [59]. The analysis of BCR sequence and affinity in HCV NHL showed conflicting results [60,61]. The lymphotropism agrees with a higher HCV infection prevalence in peripheral blood mononuclear cells (PBMCs) and bone marrow [62,63] and was confirmed by in vivo and in vitro studies [64,65]. HCV-infected cells showed an increased rate of mutations of oncogenes and Ig genes [66]. Transgenic models showed a correlation between the expression of HCV core and lymphoma [67,68]. The (14;18) translocation causes increased Bcl-2 levels and abnormal B-cell survival [53,69,70] and disappears after AT [52,71,72]. The role of cytokines and chemokines has also been studied [12,73–76], with a special attention to the B-cell activating factor (BAFF) [55,77,78]; [17,79]. More recently, the role of microRNAs seems critical in the pathogenesis of HCV-related LPDs [18,80].

Treatment of HCV-positive lymphoma with AT has a double aim: the eradication of the etiologic factor and the reversion of lymphoma genic mechanisms. Several studies showed a clinical remission following AT in low-grade B-cell NHL, mainly in MZL (SMZ, SLVL) [50,51,81–84]. A retrospective study evaluating the effect of IFN-based AT in 134 patients with indolent HCV-associated NHL showed that the use of AT at any time is associated with an improved overall survival [84]. In patients with aggressive lymphomas, the use of IFN-based AT is generally inappropriate, due to IFN haematological toxicity. However, the use of AT following NHL remission showed improved clinical outcome and prolonged disease free survival [85,86]. The use of rituximab in HCV-associated NHL - in monotherapy or in combination with AT and/or chemotherapy - appears interesting, especially in low-grade NHL [36,87]. The availability of direct acting antivirals with a high virological efficacy (SVR > 90%) and without haematological toxicity

will hopefully allow the combination of new AT with chemotherapy, taking into account possible drug-drug interactions.

2.3. Arthralgia/myalgia

Arthralgia is reported in 40–80% of HCV-infected patients with MC [2,88]. Joint pains are bilateral, symmetric, non-deforming and involve mainly knees and hands, more rarely elbows and ankles. HCV arthritis, unrelated to MC, is less common (less than 10% of patients). Rheumatoid Factor (RF) activity is found in 70-80% of MC patients but is not correlated with the presence of joint disease. There is no evidence of joint destruction. Antibodies to cyclic citrullinated peptides are absent. Some treatment modalities for HCV infection, including IFN, may aggravate arthralgia and myalgia, thus confounding clinical presentation. It is imperative to determine whether symptoms such as arthralgia, myalgia, and arthritis occur in patients with HCV infection due to primary chronic HCV infection or to a newly developed rheumatologic disease.

2.4. Sicca syndrome

Sicca symptoms in either the eyes or mouth have been reported in 20% to 30% of HCV infected patients, whereas less than 5% of patients with a defined Sjögren's syndrome are HCV-positive [2]. Many similarities exist between HCV-related Sicca syndrome and "true" Sjögren's syndrome [89], 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 patients. HCV-positive Sjögren's syndrome patients are older and more likely to have photosensitivity and cryoglobulinaemia than patients with primary Sjögren's syndrome. Although low titres of antinuclear antibodies and RF are common in patients with HCV-related Sicca syndrome, the presence of Sjögren's syndrome-related autoantibodies (anti-SSA/SSB antibody) is uncommon. HCV may induce sialadenitis by itssialotropism [90]. The expression of the HCV E1 and E2 glycoproteins in transgenic mice is associated with the development of sialadenitis [91].

2.5. Auto-antibodies

The prevalence of circulating autoantibodies is high in patients with chronic HCV infection [1,2]. The most frequent immunologic abnormalities include mixed cryoglobulins (60–90%), RF activity (70%), and antinuclear (20–40%), anticardiolipin (15%), anti-thyroid (12%) and anti-smooth muscle antibodies (7%). At least one immunologic abnormality is present in up to 53% of HCV patients. These autoantibodies are not associated with manifestations of a connective tissue disease except for mixed cryoglobulins. A possible reason for antibody production is again the HCV-induced overactivation and proliferation of B lymphocytes.

3. Other extrahepatic manifestations

3.1. Increased non liver-related mortality/morbidity

Most studies have found liver disease to be the primary cause of mortality in HCV infected patients [92–98]. HCV infection also showed a higher mortality rate for extra-hepatic complications (i.e., cardiovascular, renal, tumoural) [96,97,99,100].

The study by Lee and colleagues attributed to serum HCV RNA positivity a significantly higher mortality risk from non-liver-related causes [96]. All-cause mortality in HCV subjects was twice that in HCV-negative subjects [93]. Some studies did not find significant differences in overall mortality rates between patients with and without HCV infection [101]. It appears important to compare patients with persisting HCV infection to those that cleared the virus after therapy ("ex adjuvantibus" criterium). Viral eradication significantly reduced the rate of extra-hepatic deaths [48,92,95,102]. Backus et al. describe a large population of HCV infected patients (12,166 GT1 with SVR rates of 35%; 2904 GT2 with SVR rates of 72%; 1794 GT3 with SVR rates of 62%) [92]. After a median follow-up of 3.8 years, SVR was associated with improved survival among patients with HCV genotype 1, 2, and 3 with substantial comorbidities. These findings extend previous observations that SVR reduced liver related mortality was associated with an all-cause mortality reduction.

3.2. Cardiovascular diseases

It has been suggested that several types of chronic infections – including HCV – can trigger cardiovascular diseases and be defined as risk factors for these [103–105]. Since chronic infections may be curable, their identification as causal contributors to cardiovascular risk could offer new perspectives in cardiovascular disease prevention.

Initial Asian studies have suggested the association between HCV seropositivity and an increased risk of carotid-artery plaques and carotid intima-media thickening, independently of other classical risk factors for atherosclerosis [103–106]. Two Italian cohort studies suggested an association with carotid atherosclerotic lesions in Europe too, with a possible local direct role of the virus in initiating the plaque [107–109]. A review of the literature showed that HCV infected subjects have a higher likelihood of developing carotid atherosclerotic plaques compared to HCV negative controls [110]. Carotid atherosclerosis risk in HCV patients was mostly evident in case of active viral replication and in some geographic areas [103,108]. The observation that the virus induces the production of pro-atherogenic cytokines [102] and the link between chronic HCV infection and the plaque instability, support a role of the virus in increasing the risk of cerebrovascular diseases [111]. More recent studies performed in HCV mono-infected or HCV-HIV co-infected patients confirmed the link between HCV infection and carotid atherosclerosis [109,112,113]. He et al. showed a significantly increased risk of stroke in 22,171 HCV infected subjects compared to 87,418 controls [114]. Retrospective cohort studies have suggested a beneficial effect of AT on the incidence of stroke in HCV infected patients [115]. A study conducted in three groups of diabetics followed for 8 years, showed a decreased cumulative incidence of ischaemic stroke in treated vs. non-treated HCV patients [95].

HCV infection was shown to play a role in the risk of coronary artery disease, after adjustment for classical cardiovascular risk factors [116]. Lee et al. [96] analyzed the causes of mortality in a large cohort of HCV patients, anti-HCV positive/HCV RNA negative and anti-HCV positive/HCV RNA positive. A long follow-up period showed that anti-HCV positive patients had higher mortality rates from cardiovascular diseases (HR 1.50; 95% CI 1.10–2.03). Subjects with positive viraemia showed higher death rates, while HCV RNA negative patients had rates similar to the control group. In a Taiwanese study, 1411 HCV subjects with diabetes mellitus treated with AT (PEG-IFN plus RBV) were matched with 1411 HCV-positive diabetic patients not treated with AT and with 5644 HCV-negative diabetic patients [95]. After an 8-year median follow-up, the cumulative incidence of death significantly decreased from untreated to treated (23.6% vs. 13.0%). The incidences of end-stage renal disease, ischaemic stroke and acute coronary syndrome were lowest in the cohort of treated vs. untreated patients. Maruyama et al. showed an improvement in the myocardial perfusion defect in patients with SVR, but a worsening in relapsers, after a transient improvement concomitant with viraemia negativation [117].

3.3. Renal insufficiency

Type I membrano-proliferative glomerulonephritis (MPGN) associated with MC is the most common form of kidney disease associated with HCV infection. Less frequently described lesions are membrano-proliferative glomerulonephritis without cryoglobulinaemia, membranous nephropathy, and mesangioproliferative glomerulonephritis. Occasional cases of focal segmental glomerulosclerosis, fibrillary or immunotactoid glomerulopathies, thrombotic microangiopathy have been reported.

The most frequent (70–80%) renal clinical and histological picture in HCV-MC vasculitis is that of acute or chronic type-I MPGN with sub-endothelial deposits, which is strongly associated with the type II IgMκ cryoglobulinaemia [118]. The most frequent presentation (55%) is proteinuria with microscopic haematuria and a variable degree of renal insufficiency. Acute nephrotic (20%) or nephritic syndrome (25%) can also reveal MC renal involvement. New onset arterial hypertension is seen in 80% of cases. Early serum complement component (C1q, C4) are very low. Chronic renal insufficiency may develop in 10–20% of HCV-MC patients after follow-up of a decade or more. Morphological features are characterized by important monocyte infiltrates with double contours of the basement membrane, large, eosinophilic and amorphous intra-luminal thrombi. In indirect immunofluorescence, intra-glomerular sub-endothelial deposits of IgG, IgM and complement components are observed. The electron microscopic features with sub-endothelial and intra-luminal deposits presenting a crystalloid aspect are pathognomonic. Vasculitis of small renal arteries or extra-capillary crescents are rarely observed.

Several authors have found evidence of the association between HCV and other glomerular disease in both native [119] and transplanted kidneys [120]. A large case-control study, carried out among U.S. male veterans hospitalized between 1992 and 1999 [121], identified 34,204 patients who were hospitalized with HCV (cases) and 136,816 randomly selected patients without HCV (controls). There was a greater proportion of MPGN among patients with HCV (0.36% vs. 0.05%, $p < 0.0001$), but not membranous glomerulopathy (0.33% vs. 0.19%, $p = 0.86$). HCV infection was associated with a 40% higher prevalence of renal insufficiency (serum creatinine ≥ 1.5 mg) compared with people without HCV infection, after adjusting for age, gender, race, diabetes, and hypertension [122]. Some surveys extracted from large clinical databases have suggested an impact of HCV on prevalence and incidence of kidney disease in the general population [122–126]. HCV co-infection was also linked with a significant increase of the risk of HIV-related kidney disease [127,128]. A recent review suggests that HCV affects renal function in the general population [129]. In multivariate analysis, anti-HCV seropositive status was associated with low GFR, with odds ratio up to 2.80. A significant link between HCV and proteinuria has been reported in apparent healthy individuals, with odds ratio ranging from 1.14 to 1.99 [124,125,128,130,131]. Anti-HCV positivity was significantly associated with proteinuria, 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 [95], three groups were analyzed, 1411 HCV infected patients who received PEG-IFN plus ribavirin (treated cohort), 1411 HCV infected untreated controls and 5644 HCV-negative diabetic patients (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 ($p < 0.001$). As compared with the untreated cohort, AT was associated with 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 [132]. Despite the lack of well-designed trials, KDIGO also recommends that patients with acute flares of MC and MPGN be treated with IFN-based AT. Ribavirin dosage should be closely monitored due to the risk of anaemia and should be avoided altogether in patients with chronic kidney disease. There is some evidence that the addition of rituximab may be useful. HCV-related MC patients with kidney involvement showed greater renal response rates when treated with a combination of rituximab and PEG-IFN plus ribavirin compared with PEG-IFN and ribavirin alone [35,36].

Recently, data has been gathered on the association between HCV and glomerular disease in the liver [133,134] or kidney/liver [135] transplanted population. The natural history of these HCV-associated nephropathies is characterized by remission and relapsing phases.

3.4. Diabetes and insulin-resistance

Many studies have evaluated the association between HCV chronic infection, insulin-resistance (IR) and diabetes mellitus. The abnormalities of the carbohydrate metabolism, including hyperinsulinaemia and IR, known to be "*per se*" related to hepatic diseases, represented the rationale for research on this relationship.

Insulin-resistance is an often undetected condition, commonly coexisting with obesity and metabolic syndrome, and possibly evolving to type 2 diabetes. Taskoparan and colleagues, in a small cohort of patients treated with anti-HCV therapy failed to establish a correlation between IR and chronic HCV infection [136]. The presence of IR was evaluated in patients achieving SVR after PEG-IFN plus ribavirin AT in HCV mono-infected patients. 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 viral eradication in HCV patients could prevent IR onset and its evolution to diabetes [137]. Insulin resistance has been shown to impair SVR rate to PEG-IFN plus ribavirin in HIV-hepatitis C virus-coinfected patients [138].

HCV-related type 2 diabetes mellitus may arise from a complex interaction between IR, steatosis and inflammatory processes [139]. Epidemiologic studies supporting the association between type 2 diabetes and HCV infection were published in the early 1990s [140–143]. Persistently mild to moderate transaminase elevation in type 2 diabetes should be attributed to HCV infection rather than to metabolic disturbances [144]. Larger epidemiologic studies were also published [145,146]. The prevalence of diabetes was higher in HCV- than HBV-related cirrhosis (23.6% vs. 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. In HCV core transgenic mice, the viral protein seemed to induce increasing TNF alpha levels in the liver, which in turn promoted the induction of IR [147]. The high levels of TNF alpha inhibited the Insulin Substrate Receptor-1 (ISR-1) causing IR and its possible evolution to diabetes. In HCV core transgenic mice, a decreased expression of ISR-1 and ISR-2 mediated by ubiquitination was observed and inversely proportional to the fibrosis stage [148].

Few studies have focused on type 1 diabetes and HCV and they are also rather small [146,149,150]. The mechanism suggested for this association was a molecular mimicry [151,152], as proposed for other infections [153,154]. A very recent epidemiologic study conducted in Egypt in a paediatric population of 150 diabetic patients revealed a prevalence of HCV infection higher than in controls [155].

3.5. Fatigue, depression, cognitive impairment and impaired quality of life (HRQoL)

Neurocognitive morbidity has been reported in individuals with chronic HCV infection, and do not completely correlate with the severity of liver disease [156,157]. Cognitive impairment may be expressed in a wide variety of medical and psychiatric conditions (e.g., fatigue, depression, substance abuse). Short-term neuropsychiatric complications are not uncommon in individuals with chronic HCV infection during treatment with IFN. The detection of HCV genetic sequences in post-mortem brain tissue raises the possibility that the presence of HCV infection in the central nervous system may be related to the reported neuropsychological symptoms and cognitive impairment [158].

HRQoL of HCV patients is diminished compared with controls [159–161]. HCV infection, along with its treatment, leads to symptoms that compromise HRQoL [162]. HRQoL worsens with more advanced liver disease and therapy, leading to a reduction in adherence [163,164]. Viral eradication correlates positively with improvements in HRQoL [159,165]. HRQoL has been studied in patients who participated in sofosbuvir (SOF) clinical trials, including IFN-free regimens [98]. Compared to placebo, the SOF and ribavirin combination was not associated with HRQoL impairment. Compared to SOF and ribavirin, HRQoL was significantly more impaired in the PEG-IFN and ribavirin arm. Anaemia and receiving IFN were predictors of HRQoL impairment during treatment. Achieving SVR after 12 weeks of follow-up with SOF and ribavirin was associated with improvement in HRQoL. HCV has been associated with a decreased ability to function both at work and at home, with obvious cost implications. Poor HRQoL can also lead to difficulties with interpersonal relations, decreased feelings of self-value and utility, and depression. 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, vs. healthy controls [162,166,167].

Depression has been documented in 28% of HCV patients using the Structured Clinical Interview for DSM-IV Axis I Disorders [168]. The presence of depressive symptoms is a consistent predictor of HRQoL during AT with PEG-IFN plus ribavirin [169]. HCV may directly affect the CNS through alterations in serotonergic and dopaminergic neurotransmission with resultant depressive symptoms [170]. This mechanism may explain other central nervous system symptoms seen in HCV infection, such as fatigue and cognitive impairment [171–174]. Prior to starting AT including PEG-IFN, mental health should be thoroughly 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 AT [175].

Cognitive impairment is well described in chronic HCV infection. It is a common symptom in persons with end-stage liver disease [176]. In the HALT-C trial, 33% of 201 patients with advanced fibrosis who underwent neuropsychological testing had mild cognitive impairment on entering the trial [177]. Patients with chronic HCV infection who are free from co-morbid factors do have higher levels of cognitive impairment than healthy controls [178]. HCV eradication leads to improved cognitive function [179] and cerebral metabolism [171]. SVRs (but not the non responders) demonstrated significant improvements in verbal learning, memory, and visuospatial memory.

Fatigue is one of the most frequent and disabling complaints among HCV patients (prevalence: 50–67%), and it independently predicts poor HRQoL [180]. In a prospective study, during the first visit of 1614 HCV patients and 412 controls, fatigue was present in 53% of patients (95% CI: 51–56) vs. 1% of controls (95% CI: 0–2) [181]. In 17% of patients fatigue was severe, impairing activity. Fatigue was independently associated with female gender, age over 50 years, cirrhosis, and depression. There was no significant association between fatigue and the following characteristics: viral load or genotype, alcohol consumption, abnormal thyroid function, and type and level of cryoglobulinaemia. Chronic fatigue is associated with bad quality of sleep and increased nocturnal activity in HCV patients, suggesting an alteration of sleep architecture behind fatigue in HCV-associated encephalopathy [182].

4. Conclusion

Beyond the liver, HCV chronic infection leads to a multifaceted systemic disease. Type and evolution of such extrahepatic manifestations are difficult to predict. The accurate consideration of extrahepatic consequences of such a systemic infection significantly increases the weight of its pathological burden and, consequently, the need for effective eradication measures.

Conflict of interest

None declared.

Acknowledgements

L.G. was supported by “Fondazione Umberto Veronesi”. C.C. has received a grant from the Fondation pour la Recherche Médicale (FRM).

This article is part of a supplement supported by an unrestricted educational grant from Gilead Sciences Europe Ltd. Gilead has had no editorial control or involvement in the content of this article. The views and opinions within this supplement are those of the authors and not necessarily those of Gilead.

References

[1] Cacoub P, Poynard T, Ghillani P, et al. Extrahepatic manifestations of chronic hepatitis C MULTIVIRC Group. Multidepartment Virus C. Arthritis & Rheumatology 1999;42:2204–12.
[2] Cacoub P, Renou C, Rosenthal E, et al. Extrahepatic manifestations associated with hepatitis C virus infection. A prospective multicenter study of 321 patients. The GERMIVIC. Groupe d'Etude et de Recherche en Medecine Interne et Maladies Infectieuses sur le Virus de l'Hepatite C. Medicine 2000;79:47–56.
[3] Zignego AL, Bréchot C. Extrahepatic manifestations of HCV infection: facts and controversies. Journal of Hepatology 1999;31:369–76.
[4] Zignego AL, Ferri C, Pileri SA, et al. Italian Association of the Study of Liver Commission on extrahepatic manifestations of HCV infection extrahepatic manifestations of hepatitis C virus infection: a general overview and guidelines for a clinical approach. Digestive and Liver Disease 2007;39:2–17.
[5] Zignego AL, Giannini C, Monti M, et al. Hepatitis C virus lymphotropism: lessons from a decade of studies. Digestive and Liver Disease 2007; 39(Suppl. 1):S38–45.
[6] Sene D, Ghillani-Dalbin P, Thibault V, et al. Longterm course of mixed cryoglobulinemia in patients infected with hepatitis C virus. Journal of Rheumatology 2004;31:2199–206.
[7] Terrier B, Semoun O, Saadoun D, et al. Prognostic factors in patients with hepatitis C virus infection and systemic vasculitis. Arthritis and Rheumatism 2011;63:1748–57.
[8] Ferri C, Sebastiani M, Giuggioli D, et al. Mixed cryoglobulinemia: demographic, clinical, and serologic features and survival in 231 patients. Seminars in Arthritis and Rheumatism 2004;33:355–74.
[9] Ramos-Casals M, Robles A, Brito-Zerón P, et al. Life-threatening cryoglobulinemia: clinical and immunological characterization of 29 cases. Seminars in Arthritis and Rheumatism 2006;36:189–96.
[10] Retamozo S, Díaz-Lagares C, Bosch X, et al. Life-threatening cryoglobulinemic patients with hepatitis C: clinical description and outcome of 279 patients. Medicine 2013.
[11] Terrier B, Karras A, Cluzel P, et al. Presentation and prognosis of cardiac involvement in hepatitis C virus-related vasculitis. American Journal of Cardiology 2013;111:265–72.
[12] 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 and Rheumatism 2005;52:2917–25.
[13] Boyer O, Saadoun D, Abriol J, et al. CD4+ CD25+ regulatory T-cell deficiency in patients with hepatitis C-mixed cryoglobulinemia vasculitis. Blood 2004;103:3428–30.

[14] Saadoun D, Rosenzwajg M, Joly F, et al. Regulatory T-cell responses to low-dose interleukin-2 in HCV-induced vasculitis. New England Journal of Medicine 2011;365:2067–77.
[15] Cacoub P, Renou C, Kerr G, et al. Influence of HLA-DR phenotype on the risk of hepatitis C virus-associated mixed cryoglobulinemia. Arthritis and Rheumatism 2001;44:2118–24.
[16] Zignego AL, Wojcik GL, Cacoub P, et al. Genome-wide association study of hepatitis C virus- and cryoglobulin-related vasculitis. Genes and Immunity 2014 [in press].
[17] Gragnani L, Piluso A, Giannini C, et al. Genetic determinants in hepatitis C virus-associated mixed cryoglobulinemia: role of polymorphic variants of BAFF promoter and Fcγ receptors. Arthritis and Rheumatism 2011;63:1446–51.
[18] Fognani E, Giannini C, Piluso A, et al. Role of microRNA profile modifications in hepatitis C virus-related mixed cryoglobulinemia. PLOS ONE 2013;8:e62965.
[19] Ferri C, Marzo E, Longombardo G, et al. Interferon-alpha in mixed cryoglobulinemia patients: a randomized, crossover-controlled trial. Blood 1993;81:1132–6.
[20] Misiani R, Bellavita P, Fenili D, et al. Interferon alfa-2a therapy in cryoglobulinemia associated with hepatitis C virus. New England Journal of Medicine 1994;330:751–6.
[21] Saadoun D, Resche-Rigon M, Thibault V, et al. Antiviral therapy for hepatitis C virus – associated mixed cryoglobulinemia vasculitis: a long-term follow-up study. Arthritis and Rheumatism 2006;54:3696–706.
[22] 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 and Rheumatism 2008;58:604–11.
[23] Saadoun D, Resche Rigon M, Pol S, et al. Peg-IFNα ribavirin/protease inhibitor combination in severe hepatitis C virus associated mixed cryoglobulinemia vasculitis. Journal of Hepatology 2014.
[24] 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. Digestive and Liver Disease 2014;46:833–7.
[25] European Association for Study of Liver. EASL clinical practice guidelines: management of hepatitis C virus infection. Journal of Hepatology 2014;60:392–420.
[26] Roccatello D, Baldovino S, Rossi D, et al. Long-term effects of anti-CD20 monoclonal antibody treatment of cryoglobulinaemic glomerulonephritis. Nephrology, Dialysis, Transplantation 2004;19:3054–61.
[27] Saadoun D, Resche-Rigon M, Sene D, et al. Rituximab combined with Peg-interferon-ribavirin in refractory hepatitis C virus-associated cryoglobulinaemia vasculitis. Annals of the Rheumatic Diseases 2008;67:1431–6.
[28] Sansonno D, De Re V, Lauletta G, et al. Monoclonal antibody treatment of mixed cryoglobulinemia resistant to interferon alpha with an anti-CD20. Blood 2003;101:3818–26.
[29] Zaja F, De Vita S, Mazzaro C, et al. Efficacy and safety of rituximab in type II mixed cryoglobulinemia. Blood 2003;101:3827–34.
[30] Cacoub P, Delluc A, Saadoun D, et al. Anti-CD20 monoclonal antibody (rituximab) treatment for cryoglobulinemic vasculitis: where do we stand? Annals of the Rheumatic Diseases 2008;67:283–7.
[31] De Vita S, Quartuccio L, Isola M, et al. A randomized controlled trial of rituximab for the treatment of severe cryoglobulinemic vasculitis. Arthritis and Rheumatism 2012;64:843–53.
[32] 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 and Rheumatism 2012;64:835–42.
[33] Droz N, Gilardin L, Cacoub P, et al. Kinetic profiles and management of hepatitis B virus reactivation in patients with immune-mediated inflammatory diseases. Arthritis Care and Research 2013;65:1504–14.
[34] Petrarca A, Rigacci L, Caini P, et al. Safety and efficacy of rituximab in patients with hepatitis C virus-related mixed cryoglobulinemia and severe liver disease. Blood 2010;116:335–42.
[35] Dammacco F, Tucci FA, Lauletta G, et al. Pegylated interferon-alpha, ribavirin, and rituximab combined therapy of hepatitis C virus-related mixed cryoglobulinemia: a long-term study. Blood 2010;116:343–53.
[36] Saadoun D, Resche Rigon M, Sene D, et al. Rituximab plus Peg-interferon-alpha/ribavirin compared with Peg-interferon-alpha/ribavirin in hepatitis C-related mixed cryoglobulinemia. Blood 2010;116:326–34.
[37] Saadoun D, Delluc A, Piette JC, et al. Treatment of hepatitis C-associated mixed cryoglobulinemia vasculitis. Current Opinion in Rheumatology 2008;20:23–8.
[38] 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 and Research 2013;65:643–7.
[39] Ferri C, La Civita L, Caracciolo F, et al. Non-Hodgkin's lymphoma: possible role of hepatitis C virus. Journal of the American Medical Association 1994;272:355–6.
[40] Ferri C, Caracciolo F, La Civita L, et al. Hepatitis C virus infection and B-cell lymphomas. European Journal of Cancer 1994;30A:1591–2.
[41] 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. Clinical Gastroenterology and Hepatology 2008;6:451–8.
[42] Zuckerman E, Zuckerman T, Levine AM, et al. Hepatitis C virus infection in patients with B-cell non-Hodgkin lymphoma. Annals of Internal Medicine 1997;127:423–8.
[43] Gisbert JP, García-Buey L, Pajares JM, et al. Prevalence of hepatitis C virus infection in B-cell non-Hodgkin's lymphoma: systematic review and meta-analysis. Gastroenterology 2003;125:1723–32.
[44] Dal Maso L, Franceschi S. Hepatitis C virus and risk of lymphoma and other lymphoid neoplasms: a meta-analysis of epidemiologic studies. Cancer Epidemiology, Biomarkers and Prevention 2006;15:2078–85.
[45] Matsuo K, Kusano A, Sugumar A, et al. Effect of hepatitis C virus infection on the risk of non-Hodgkin's lymphoma: a meta-analysis of epidemiological studies. Cancer Science 2004;95:745–52.
[46] Negri E, Little D, Boiocchi M, et al. B-cell non-Hodgkin's lymphoma and hepatitis C virus infection: a systematic review. International Journal of Cancer 2004;111:1–8.
[47] Andreone P, Zignego AL, Cursaro C, et al. Prevalence of monoclonal gammopathies in patients with hepatitis C virus infection. Annals of Internal Medicine 1998;129:294–8.
[48] Kawamura Y, Ikeda K, Arase Y, et al. Viral elimination reduces incidence of malignant lymphoma in patients with hepatitis C. American Journal of Medicine 2007;120:1034–41.
[49] Casato M, Mecucci C, Agnello V, et al. Regression of lymphoproliferative disorder after treatment for hepatitis C virus infection in a patient with partial trisomy 3 Bcl-2 overexpression, and type II cryoglobulinemia. Blood 2002;99:2259–61.
[50] 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;105:74–6.
[51] Hermine O, Lefrère F, Bronowicki J-P, et al. Regression of splenic lymphoma with villous lymphocytes after treatment of hepatitis C virus infection. New England Journal of Medicine 2002;347:89–94.
[52] 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;102:1196–201.
[53] Zignego AL, Ferri C, Giannelli F, et al. Prevalence of bcl-2 rearrangement in patients with hepatitis C virus-related mixed cryoglobulinemia with or without B-cell lymphomas. Annals of Internal Medicine 2002;137:571–80.
[54] Zignego AL, Giannini C, Gragnani L. HCV and lymphoproliferation. Clinical and Developmental Immunology 2012:980942.
[55] Landau D-A, Rosenzwajg M, Saadoun D, et al. The B lymphocyte stimulator receptor–ligand system in hepatitis C virus-induced B cell clonal disorders. Annals of the Rheumatic Diseases 2009;68:337–44.
[56] Lai R, Weiss LM. Hepatitis C virus and non-Hodgkin's lymphoma. American Journal of Clinical Pathology 1998;109:508–10.
[57] Sansonno D, De Vita S, Iacobelli AR, et al. Clonal analysis of intrahepatic B cells from HCV-infected patients with and without mixed cryoglobulinemia. Journal of Immunology 1998;160:3594–601.
[58] 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 and Rheumatism 2004;50:3668–78.
[59] Pileri P, Uematsu Y, Campagnoli S, et al. Binding of hepatitis C virus to CD81. Science 1998;282:938–41.
[60] Ng PP, Kuo C-C, Wang S, et al. B-cell receptors expressed by lymphomas of hepatitis C virus (HCV)-infected patients rarely react with the viral proteins. Blood 2014;123:1512–5.
[61] De Re V, De Vita S, Marzotto A, et al. Sequence analysis of the immunoglobulin antigen receptor of hepatitis C virus-associated non-Hodgkin lymphomas suggests that the malignant cells are derived from the rheumatoid factor-producing cells that occur mainly in type II cryoglobulinemia. Blood 2000;96:3578–84.
[62] 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 non-cryoglobulinemic chronic hepatitis type C. Journal of Infectious Diseases 1995;171:672–5.
[63] Zignego AL, Macchia D, Monti M, et al. Infection of peripheral mononuclear blood cells by hepatitis C virus. Journal of Hepatology 1992;15:382–6.
[64] Bronowicki JP, Loriot MA, Thiers V, et al. Hepatitis C virus persistence in human hematopoietic cells injected into SCID mice. Hepatology 1998;28:211–8.
[65] 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. Journal of Virology 2003;77:2134–46.
[66] Machida K, Cheng KT-N, Sung VM-H, et al. Hepatitis C virus induces a mutator phenotype: enhanced mutations of immunoglobulin and protooncogenes. Proceedings of the National Academy of Sciences of the United States of America 2004;101:4262–7.
[67] Kasama Y, Sekiguchi S, Saito M, et al. Persistent expression of the full genome of hepatitis C virus in B cells induces spontaneous development of B-cell lymphomas in vivo. Blood 2010;116:4926–33.
[68] Tsukiyama-Kohara K, Sekiguchi S, Kasama Y, et al. Hepatitis C virus-related lymphomagenesis in a mouse model. ISRN Hematology 2011;2011:167501.
[69] Zignego AL, Giannelli F, Marrocchi ME, et al. Frequency of bcl-2 rearrangement in patients with mixed cryoglobulinemia and HCV-positive liver diseases. Clinical and Experimental Rheumatology 1997;15:711–2.

[70] Zignego AL, Giannelli F, Marrocchi ME, et al. T(14;18) translocation in chronic hepatitis C virus infection. Hepatology 2000;31:474–9.
[71] Giannini C, Giannelli F, Zignego AL. Association between mixed cryoglobulinemia, translocation (14;18), and persistence of occult HCV lymphoid infection after treatment. Hepatology 2006;43:1166–7, author reply 1168.
[72] Giannini C, Petrarca A, Monti M, et al. Association between persistent lymphatic infection by hepatitis C virus after antiviral treatment and mixed cryoglobulinemia. Blood 2008;111:2943–5.
[73] Libra M, Indelicato M, De Re V, et al. Elevated serum levels of osteopontin in HCV-associated lymphoproliferative disorders. Cancer Biology and Therapy 2005;4:1192–4.
[74] 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. Oncology Reports 2006;15:1305–8.
[75] 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 and Rheumatism 2007;56:1315–24.
[76] Sansonno D, Tucci FA, Ghebrehiwet B, et al. Role of the receptor for the globular domain of C1q protein in the pathogenesis of hepatitis C virus-related cryoglobulin vascular damage. Journal of Immunology 2009;183:6013–20.
[77] Sène D, Limal N, Ghillani-Dalbin P, et al. Hepatitis C virus-associated B-cell proliferation – the role of serum B lymphocyte stimulator (BLyS/BAFF). Rheumatology 2007;46:65–9.
[78] De Vita S, Quartuccio L, Fabris M. Hepatitis C virus infection, mixed cryoglobulinemia and BLyS upregulation: targeting the infectious trigger, the autoimmune response, or both? Autoimmunity Reviews 2008;8:95–9.
[79] Giannini C, Gragnani L, Piluso A, et al. Can BAFF promoter polymorphism be a predisposing condition for HCV-related mixed cryoglobulinemia? Blood 2008;112:4353–4.
[80] Peveling-Oberhag J, Crisman G, Schmidt A, et al. Dysregulation of global microRNA expression in splenic marginal zone lymphoma and influence of chronic hepatitis C virus infection. Leukemia 2012;26:1654–62.
[81] Kelaidi C, Rollot F, Park S, et al. Response to antiviral treatment in hepatitis C virus-associated marginal zone lymphomas. Leukemia 2004;18:1711–6.
[82] 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. Journal of Clinical Oncology 2005;23:468–73.
[83] Mazzaro C, De Re V, Spina M, et al. Pegylated-interferon plus ribavirin for HCV-positive indolent non-Hodgkin lymphomas. British Journal of Haematology 2009;145:255–7.
[84] 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. Annals of Oncology 2014;25:1404–10.
[85] Musto P, Dell'Olio M, Carotenuto M, et al. Hepatitis C virus infection: a new bridge between hematologists and gastroenterologists? Blood 1996;88:752–4.
[86] 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. Journal of Hepatology 2008;49:557–63.
[87] Hainsworth JD, Litchy S, Burris HA, et al. Rituximab as first-line and maintenance therapy for patients with indolent non-Hodgkin's lymphoma. Journal of Clinical Oncology 2002;20:4261–7.
[88] Lee YH, Ji JD, Yeon JE, et al. Cryoglobulinaemia and rheumatic manifestations in patients with hepatitis C virus infection. Annals of the Rheumatic Diseases 1998;57:728–31.
[89] 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 2001;80:1–8.
[90] Verbaan H, Carlson J, Eriksson S, et al. Extrahepatic manifestations of chronic hepatitis C infection and the interrelationship between primary Sjögren's syndrome and hepatitis C in Swedish patients. Journal of Internal Medicine 1999;245:127–32.
[91] Koike K, Moriya K, Ishibashi K, et al. Sialadenitis histologically resembling Sjogren syndrome in mice transgenic for hepatitis C virus envelope genes. Proceedings of the National Academy of Sciences of the United States of America 1997;94:233–6.
[92] Backus LI, Boothroyd DB, Phillips BR, et al. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. Clinical Gastroenterology and Hepatology 2011;9, 509–16.e1.
[93] 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. Clinical Infectious Diseases 2011;53:150–7.
[94] Harris HE, Ramsay ME, Andrews NJ. HCV National Register Steering Group Survival of a national cohort of hepatitis C virus infected patients, 16 years after exposure. Epidemiology and Infection 2006;134:472–7.
[95] 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;59:1293–302.
[96] 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. Journal of Infectious Diseases 2012;206:469–77.
[97] 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;50:393–9.
[98] Younossi ZM, Stepanova M, Mishra A, et al. The impact of chronic hepatitis C on resource utilisation and in-patient mortality for Medicare beneficiaries between 2005 and 2010. Alimentary Pharmacology and Therapeutics 2013;38:1065–75.
[99] Maasoumy B, Wedemeyer H. Natural history of acute and chronic hepatitis C. Best Practice and Research Clinical Gastroenterology 2012;26:401–12.
[100] Omland LH, Jepsen P, Krarup H, et al. Increased mortality among persons infected with hepatitis C virus. Clinical Gastroenterology and Hepatology 2011;9:71–8.
[101] Seeff LB, Hollinger FB, Alter HJ, et al. Long-term mortality and morbidity of transfusion-associated non-A, non-B, and type C hepatitis: a National Heart, Lung, and Blood Institute collaborative study. Hepatology 2001;33:455–63.
[102] Adinolfi LE, Zampino R, Restivo L, et al. Chronic hepatitis C virus infection and atherosclerosis: clinical impact and mechanisms. World Journal of Gastroenterology 2014;20:3410–7.
[103] Ishizaka N, Ishizaka Y, Takahashi E, et al. Increased prevalence of carotid atherosclerosis in hepatitis B virus carriers. Circulation 2002;105:1028–30.
[104] Lindsberg PJ, Grau AJ. Inflammation and infections as risk factors for ischemic stroke. Stroke 2003;34:2518–32.
[105] Palm F, Urbanek C, Grau A. Infection, its treatment and the risk for stroke. Current Vascular Pharmacology 2009;7:146–52.
[106] Fukui M, Kitagawa Y, Nakamura N, et al. Hepatitis C virus and atherosclerosis in patients with type 2 diabetes. Journal of the American Medical Association 2003;289:1245–6.
[107] Boddi M, Abbate R, Chellini B, et al. HCV infection facilitates asymptomatic carotid atherosclerosis: preliminary report of HCV RNA localization in human carotid plaques. Digestive and Liver Disease 2007;39(Suppl. 1):S55–60.
[108] Boddi M, Abbate R, Chellini B, et al. Hepatitis C virus RNA localization in human carotid plaques. Journal of Clinical Virology 2010;47:72–5.
[109] Petta S, Torres D, Fazio G, et al. Carotid atherosclerosis and chronic hepatitis C: a prospective study of risk associations. Hepatology 2012;55:1317–23.
[110] Aslam F, Alam M, Lakkis NM. Hepatitis C and carotid atherosclerosis: a retrospective analysis. Atherosclerosis 2010;209:340–3.
[111] Libby P, Aikawa M. Stabilization of atherosclerotic plaques: new mechanisms and clinical targets. Nature Medicine 2002;8:1257–62.
[112] Adinolfi LE, Restivo L, Zampino R, et al. Chronic HCV infection is a risk of atherosclerosis Role of HCV and HCV-related steatosis. Atherosclerosis 2012;221:496–502.
[113] Sosner P, Wangermez M, Chagneau-Derrode C, et al. Atherosclerosis risk in HIV-infected patients: the influence of hepatitis C virus co-infection. Atherosclerosis 2012;222:274–7.
[114] He H, Kang R, Zhao Z. Hepatitis C virus infection and risk of stroke: a systematic review and meta-analysis. PLOS ONE 2013;8:e58130.
[115] 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. Alimentary Pharmacology and Therapeutics 2013;38:415–23.
[116] Butt AA, Xiaoqiang W, Budoff M, et al. Hepatitis C virus infection and the risk of coronary disease. Clinical Infectious Diseases 2009;49:225–32.
[117] Maruyama S, Koda M, Oyake N, et al. Myocardial injury in patients with chronic hepatitis C infection. Journal of Hepatology 2013;58:11–5.
[118] Terrier B, Cacoub P. Renal involvement in HCV-related vasculitis. Clinics and Research in Hepatology and Gastroenterology 2013;37:334–9.
[119] Fabrizi F, Poordad FF, Martin P. Hepatitis C infection and the patient with end-stage renal disease. Hepatology 2002;36:3–10.
[120] Roth D, Cirocco R, Zucker K, et al. De novo membranoproliferative glomerulonephritis in hepatitis C virus-infected renal allograft recipients. Transplantation 1995;59:1676–82.
[121] El-Serag HB, Hampel H, Yeh C, et al. Extrahepatic manifestations of hepatitis C among United States male veterans. Hepatology 2002;36:1439–45.
[122] Dalrymple LS, Koepsell T, Sampson J, et al. Hepatitis C virus infection and the prevalence of renal insufficiency. Clinical Journal of the American Society of Nephrology 2007;2:715–21.
[123] Asrani SK, Buchanan P, Pinsky B, et al. Lack of association between hepatitis C infection and chronic kidney disease. Clinical Gastroenterology and Hepatology 2010;8:79–84.
[124] Butt AA, Wang X, Fried LF. HCV infection and the incidence of CKD. American Journal of Kidney Diseases 2011;57:396–402.
[125] Lee J-J, Lin M-Y, Yang Y-H, et al. Association of hepatitis C and B virus infection with CKD in an endemic area in Taiwan: a cross-sectional study. American Journal of Kidney Diseases 2010;56:23–31.
[126] Tsui JI, Vittinghoff E, Shlipak MG, et al. Relationship between hepatitis C and chronic kidney disease: results from the Third National Health and Nutrition Examination Survey. Journal of the American Society of Nephrology 2006;17:1168–74.
[127] Izzedine H, Sene D, Cacoub P, et al. Kidney diseases in HIV/HCV-co-infected patients. AIDS 2009;23:1219–26.
[128] Wyatt CM, Malvestutto C, Coca SG, et al. The impact of hepatitis C virus coinfection on HIV-related kidney disease: a systematic review and meta-analysis. AIDS 2008;22:1799–807.
[129] Fabrizi F, Plaisier E, Saadoun D, et al. Hepatitis C virus infection, mixed cryoglobulinemia, and kidney disease. American Journal of Kidney Diseases 2013;61:623–37.

[130] Huang J-F, Chuang W-L, Dai C-Y, et al. Viral hepatitis and proteinuria in an area endemic for hepatitis B and C infections: another chain of link? Journal of Internal Medicine 2006;260:255–62.
[131] Liangpunsakul S, Chalasani N. Relationship between hepatitis C and microalbuminuria: results from the NHANES III. Kidney International 2005;67:285–90.
[132] 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 International Supplement 2008:S1–99.
[133] Davis CL, Gretch DR, Perkins JD, et al. Hepatitis C – associated glomerular disease in liver transplant recipients. Liver Transplantation and Surgery 1995;1:166–75.
[134] Sikaneta T, Williams WW, Chung RT, et al. Remission of hepatitis C virus-associated cryoglobulinemic glomerulonephritis with interferon alfa-2b and ribavirin combination therapy after liver transplantation. Transplantation 2002;74:1767–8.
[135] Montalbano M, Pasulo L, Sonzogni A, et al. Treatment with pegylated interferon and ribavirin for hepatitis C virus-associated severe cryoglobulinemia in a liver/kidney transplant recipient. Journal of Clinical Gastroenterology 2007;41:216–20.
[136] 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. Hepato-Gastroenterology 2011;58:875–9.
[137] 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;56:1681–7.
[138] 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. Antiviral Therapy 2009;14:839–45.
[139] Serfaty L, Capeau J. Hepatitis C insulin resistance and diabetes: clinical and pathogenic data. Liver International 2009;29(Suppl. 2):13–25.
[140] Ozyilkan E, Arslan M. Increased prevalence of diabetes mellitus in patients with chronic hepatitis C virus infection. American Journal of Gastroenterology 1996;91:1480–1.
[141] Ozyilkan E, Erbaş T, Simşek H, et al. Increased prevalence of hepatitis C virus antibodies in patients with diabetes mellitus. Journal of Internal Medicine 1994;235:283–4.
[142] Allison ME, Wreghitt T, Palmer CR, et al. Evidence for a link between hepatitis C virus infection and diabetes mellitus in a cirrhotic population. Journal of Hepatology 1994;21:1135–9.
[143] Simó R, Hernández C, Genescà J, et al. High prevalence of hepatitis C virus infection in diabetic patients. Diabetes Care 1996;19:998–1000.
[144] Gray H, Wreghitt T, Stratton IM, et al. High prevalence of hepatitis C infection in Afro-Caribbean patients with type 2 diabetes and abnormal liver function tests. Diabetic Medicine 1995;12:244–9.
[145] 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;30:1059–63.
[146] Mason AL, Lau JY, Hoang N, et al. Association of diabetes mellitus and chronic hepatitis C virus infection. Hepatology 1999;29:328–33.
[147] 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;126:840–8.
[148] Kawaguchi T, Yoshida T, Harada M, et al. Hepatitis C virus down-regulates insulin receptor substrates 1 and 2 through up-regulation of suppressor of cytokine signaling 3. American Journal of Pathology 2004;165:1499–508.
[149] Ando H, Nagai Y, Yokoyama M, et al. Antibodies to GAD in diabetic patients with chronic hepatitis C. Diabetic Medicine 1998;15:797.
[150] Piquer S, Hernández C, Enriquez J, et al. Islet cell and thyroid antibody prevalence in patients with hepatitis C virus infection: effect of treatment with interferon. Journal of Laboratory and Clinical Medicine 2001;137:38–42.
[151] Bogdanos DP, Mieli-Vergani G, Vergani D. Virus, liver and autoimmunity. Digestive and Liver Disease 2000;32:440–6.
[152] Bogdanos DP, Choudhuri K, Vergani D. Molecular mimicry and autoimmune liver disease: virtuous intentions, malign consequences. Liver 2001;21:225–32.
[153] Christen U, Bender C, von Herrath MG. Infection as a cause of type 1 diabetes? Current Opinion in Rheumatology 2012;24:417–23.
[154] Goldberg E, Krause I. Infection and type 1 diabetes mellitus – a two edged sword? Autoimmunity Reviews 2009;8:682–6.
[155] Farghaly HS, Metwalley KA, El-Hafeez HAA. Hepatitis C virus infection in Egyptian children with type 1 diabetes mellitus: a single center study. Indian Journal of Endocrinology and Metabolism 2014;18:197–201.
[156] Forton DM, Thomas HC, Murphy CA, et al. Hepatitis C and cognitive impairment in a cohort of patients with mild liver disease. Hepatology 2002;35:433–9.
[157] McAndrews MP, Farcnik K, Carlen P, et al. Prevalence and significance of neurocognitive dysfunction in hepatitis C in the absence of correlated risk factors. Hepatology 2005;41:801–8.
[158] Laskus T, Radkowski M, Adair DM, et al. Emerging evidence of hepatitis C virus neuroinvasion. AIDS 2005;19(Suppl. 3):S140–4.
[159] Bonkovsky HL, Woolley JM. Reduction of health-related quality of life in chronic hepatitis C and improvement with interferon therapy. The Consensus Interferon Study Group. Hepatology 1999;29:264–70.
[160] Bonkovsky HL, Snow KK, Malet PF, et al. Health-related quality of life in patients with chronic hepatitis C and advanced fibrosis. Journal of Hepatology 2007;46:420–31.
[161] Kang S-C, Hwang S-J, Lee S-H, et al. Health-related quality of life and impact of antiviral treatment in Chinese patients with chronic hepatitis C in Taiwan. World Journal of Gastroenterology 2005;11:7494–8.
[162] Younossi Z, Kallman J, Kincaid J. The effects of HCV infection and management on health-related quality of life. Hepatology 2007;45:806–16.
[163] 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 International 2011;31:516–24.
[164] Snow KK, Bonkovsky HL, Fontana RJ, et al. Changes in quality of life and sexual health are associated with low-dose peginterferon therapy and disease progression in patients with chronic hepatitis C. Alimentary Pharmacology and Therapeutics 2010;31:719–34.
[165] Cacoub P, Ratziu V, Myers RP, et al. Impact of treatment on extra hepatic manifestations in patients with chronic hepatitis C. Journal of Hepatology 2002;36:812–8.
[166] McHutchison JG, Ware JE, Bayliss MS, et al. The effects of interferon alpha-2b in combination with ribavirin on health related quality of life and work productivity. Journal of Hepatology 2001;34:140–7.
[167] Spiegel BMR, Younossi ZM, Hays RD, et al. Impact of hepatitis C on health related quality of life: a systematic review and quantitative assessment. Hepatology 2005;41:790–800.
[168] Golden J, O'Dwyer AM, Conroy RM. Depression and anxiety in patients with hepatitis C: prevalence, detection rates and risk factors. General Hospital Psychiatry 2005;27:431–8.
[169] Dan AA, Martin LM, Crone C, et al. Depression, anemia and health-related quality of life in chronic hepatitis C. Journal of Hepatology 2006;44:491–8.
[170] Cozzi A, Zignego AL, Carpendo R, et al. Low serum tryptophan levels, reduced macrophage IDO activity and high frequency of psychopathology in HCV patients. Journal of Viral Hepatitis 2006;13:402–8.
[171] Byrnes V, Miller A, Lowry D, et al. Effects of anti-viral therapy and HCV clearance on cerebral metabolism and cognition. Journal of Hepatology 2012;56:549–56.
[172] 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. Journal of Rheumatology 2005;32:484–8.
[173] Forton DM. Altered monoaminergic transporter binding in hepatitis C related cerebral dysfunction: a neuroimmunologial condition? Gut 2006;55:1535–7.
[174] 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;55:1624–30.
[175] Raison CL, Borisov AS, Broadwell SD, et al. Depression during pegylated interferon-alpha plus ribavirin therapy: prevalence and prediction. Journal of Clinical Psychiatry 2005;66:41–8.
[176] Perry W, Hilsabeck RC, Hassanein TI. Cognitive dysfunction in chronic hepatitis C: a review. Digestive Diseases and Sciences 2008;53:307–21.
[177] Fontana RJ, Bieliauskas LA, Back-Madruga C, et al. Cognitive function in hepatitis C patients with advanced fibrosis enrolled in the HALT-C trial. Journal of Hepatology 2005;43:614–22.
[178] Lowry D, Coughlan B, McCarthy O, et al. Investigating health-related quality of life, mood and neuropsychological test performance in a homogeneous cohort of Irish female hepatitis C patients. Journal of Viral Hepatitis 2010;17:352–9.
[179] Thein HH, Maruff P, Krahn MD, et al. Improved cognitive function as a consequence of hepatitis C virus treatment. HIV Medicine 2007;8:520–8.
[180] Kallman J, O'Neil MM, Larive B, et al. Fatigue and health-related quality of life (HRQL) in chronic hepatitis C virus infection. Digestive Diseases and Sciences 2007;52:2531–9.
[181] Poynard T, Cacoub P, Ratziu V, et al. Fatigue in patients with chronic hepatitis C. Journal of Viral Hepatitis 2002;9:295–303.
[182] Heeren M, Sojref F, Schuppner R, et al. Active at night, sleepy all day – sleep disturbances in patients with hepatitis C virus infection. Journal of Hepatology 2014;60:732–40.