Publisher: Taylor & Francis

Journal: *Expert Review of Anti-infective Therapy*

DOI: 10.1080/14787210.2017.1354697

Review

Extrahepatic manifestations of HCV: The role of direct acting antivirals

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Abstract

Introduction: Hepatitis C virus (HCV) represents a major health concern, as nearly 3 million people become newly infected by this pathogen annually. The majority of infected individuals fail to clear the virus, and chronicity is established. Chronic HCV patients are at high risk for liver disease, ranging from mild fibrosis to cirrhosis and severe hepatocellular carcinoma. Over the last few years, the development of multiple direct acting antivirals (DAA) have revolutionized the HCV infection treatment, demonstrating cure rates higher than 90%, and showing less side effects than previous interferon-based regimens.

Areas covered: Besides liver, HCV infection affects a variety of organs, therefore inducing diverse extrahepatic manifestations. This review covers clinical, experimental, and epidemiological publications regarding systemic manifestations of HCV, as well as recent studies focused on the effect of DAA in such conditions.

Expert commentary: Though further research is needed; available data suggest that HCV eradication is often associated with the improvement of extrahepatic symptoms. Therefore, the emergence of DAA would offer the opportunity to treat both HCV infection and its systemic manifestations, requiring shorter treatment duration and driving minor adverse effects.

Keywords: Chronic hepatitis C; Direct acting antivirals; Diabetes mellitus; Extrahepatic manifestations; Mixed cryoglobulinemia; Lichen planus; Lymphomalignancies; Porphyria.

1. Introduction

Hepatitis C virus (HCV) is an enveloped, positive-stranded RNA virus belonging to the *Flaviviridae* family. HCV genome encodes a single large polyprotein which is cleaved co-translationally by viral and cellular proteases to produce three structural proteins (nucleocapsid, E1, and E2), the ion channel protein p7, and six nonstructural (NS) proteins (NS2, NS3, NS4A, NS4B, NS5A, and NS5B) [1]. Each of these proteins coordinates processes of the HCV life cycle and therefore represents valuable targets for antiviral therapies. Based on genome sequence diversity, HCV has been classified into seven main genotypes and 67 subtypes [2].

HCV infection is usually asymptomatic, and approximately 20–40% of patients clear the virus spontaneously. However, the vast majority of individuals become chronically infected. Chronicity in HCV disease depends on numerous factors, including ethnicity, gender, and age at time of infection, among others [3]. HCV is a globally prevalent pathogen, and thus a major health concern. According to the World Health Organization (WHO), in 2015, 71 million people were living with chronic HCV infection, being at high risk for progressive liver disease including cirrhosis, and hepatocellular cancer. Estimates available indicate that 25%-30% of chronic HCV infected patients will develop cirrhosis within 20 years [4]. In those patients with cirrhosis, hepatocellular cancer is the most common complication and the main cause of death (44%) [5]. Furthermore, end-stage liver disease due to HCV infection represents the main cause of liver transplantation in the United States of America, Australia, and Europe [6].

Although HCV is a hepatotropic virus that primarily affects the liver, several reports have linked HCV to a variety of extrahepatic symptoms involving the skin, as well as musculoskeletal, renal, cardiovascular and nervous systems (Table 1). In a prospective cohort study performed by Cacoub and coworkers, it was reported that up to 74% of chronic HCV patients suffer from at least one extrahepatic manifestation [7]. In addition, Lee and colleagues demonstrated in a recent work that HCV seropositive patients had increased mortality risks due to extrahepatic manifestations, with a hazard ratio of 1.35 (95% Confidence Interval, CI: 1.15-1.57) [8].

Direct acting antivirals (DAA) are major developments in the treatment of HCV infection, with cure rates higher than 90% [9]. After years of rational drug design, several compounds targeting major stages in HCV life cycle were developed. To date, these compounds comprise NS3/4A protease inhibitors, NS5A protein inhibitors and NS5B RNA polymerase inhibitors [10]. Although treatment efficacy, in terms of sustained virologic response (SVR) has been completely and extensively demonstrated, the effects of DAA on liver disease progression (e.g. cirrhosis, hepatocellular carcinoma, end-stage liver disease) as well as extrahepatic complications of chronic HCV infection are still under evaluation. In this review, we will discuss common extrahepatic manifestations along with the role of DAA-based regimens in the management of HCV-secondary diseases.

1.1. Extrahepatic manifestations of chronic HCV infection, lymphoproliferative disorders:

It has been widely documented that chronic HCV infection is associated to lymphoproliferative disorders (LPD). Several LPD have been linked with HCV, including mixed cryoglobulinemia and B-cell non-Hodgkin's lymphoma.

1.1.1. Mixed cryoglobulinemia (MC) vasculitis

MC vasculitis is a small vessel vasculitis defined by the presence of circulating cryoprecipitable immunoglobulins in the blood. MC is characterized by a combination of polyclonal immunoglobulin (Ig) G and mono- or polyclonal Ig-M, with rheumatoid factor (RF) activity. Vascular deposition of cryoglobulin containing-immune complexes may damage the skin, joints, kidneys, peripheral nerve system and heart.

In terms of prevalence, MC represents the most frequent extrahepatic manifestation. Estimates show that up to 90% of MC patients are infected with HCV [11-13]. Overt MC vasculitis, on the other hand, develops in approximately 5 to 15% of chronic HCV infection cases [14,15]. Although pathogenic mechanisms of HCV-related MC are not completely understood, cumulative evidence suggest that HCV modulation of immune system results in clonal expansion of B cells that produce Ig-M immunoglobulin with RF activity. So far, besides stimulating B cell compartment, HCV may modulate proinflammatory Th1-associated chemokine and cytokine responses, and regulatory T cells (Treg) (reviewed in [12,16]).

The main cutaneous manifestations of MC vasculitis involve palpable purpura which occurs in more than 90% of HCV-induced MC, appearing predominantly in lower extremities and lower trunk [17]. Purpura develops as intermittent lesions that generally progress to stable hyperpigmented areas due to hemosiderin deposition. Although dermatologic manifestations are usually mild, severe symptoms can arise including skin ulcerations, secondary infections, necrosis, and gangrene.

Regarding musculoskeletal disorders, fatigue and arthralgia are the second more common manifestations, estimated in 40–80% of HCV-infected patients with MC [12]. Observational studies also showed that arthritis can be observed in 4%-5% of HCV patients [18,19]. HCV-associated arthritis (HAA) includes primarily a poliarticular, symmetrical, non-deforming conditions that may resemble rheumatoid arthritis (RA). In fact, RF is detected in 40-50% of patients with HAA [20]. In order to distinguish it from classic RA, clinicians should perform serological test to detect anti-cyclic citrullinated peptide antibodies, absent in HCV patients. On the other hand, cryoglobulin-related mono-oligoarticular arthritis is also present in 10% to 30% of patients with HAA [21]. So far, cryoglobulin deposition in synovial fluid has been validated as the foremost mechanism of pathogenesis of HCV-related musculoskeletal manifestations.

It has been estimated that about 30% of HCV-related MC patients suffer from kidney disease [22,23]. Renal manifestations cover a variety of disorders ranging from slightly proteinuria and hematuria, to nephrotic and nephritic syndromes, as well as renal insufficiency in a lesser extent. The most common renal manifestation is Type I membranoproliferative glomerulonephritis (MPGN). MPGN represents 80% of cryoglobulinemic renal diseases and is characterized by immune complex deposition in the glomeruli and positive staining for Ig-M [24]. It typically transits through intermittent periods, although clinical evidence reported that 10% of MPGN progress to end stage-renal disease [25-27].

Accurate clinical management of MC vasculitis strongly relies on the assessment of its activity. To date, identification of biomarkers for assessing activity of MC vasculitis is still under development. Nevertheless, the BVAS v.3 (Birmingham vasculitis scores version 3), is a validated medical tool that has been widely used for quantifying newly active vasculitis or worsening of preexisting symptoms [28].

Finally, although clinically benign, it has been reported that MC significantly increases the risk for lymphomalignancies e.g. B-cell non-Hodgkin lymphoma (B-NHL) [29]. It was shown that MC predisposes patients to B-NHL in about 5–10% of cases [30].

1.1.2. B-cell non-Hodgkin's lymphoma

Non-Hodgkin lymphoma (NHL) comprises a diverse group of LPD, in which B-cell origin malignancies (B-NHL) are the most frequent. Associations between HCV chronic infection and B-NHL have been early described in epidemiological studies conducted by Ferri, Pozatto and coworkers [31,32]. Years later, multiple scientific analyses confirmed these results, also demonstrating that the strength of association varies geographically according to HCV prevalence [33-39]. In a recent meta-analysis revision by Pozatto and colleagues [40] including 19 case-control studies (21262 patients), a pooled relative risk (RR) estimation of 2.4 was found (95% CI: 2.0-3.0). Regarding B-NHL subtypes, marginal zone lymphoma (MZL), lymphoplasmacytic lymphoma (LPL) and diffuse large B-cell lymphoma (DLBCL) are the most commonly reported subtypes associated with HCV [36,37,41]. Based on epidemiological and experimental evidence, the International Agency for Research on Cancer (IARC) recently included HCV infection as a cause of non-Hodgkin lymphomas [42].

Biological mechanisms involved in HCV infection and lymphoid malignancies are still inconclusive. However, MC and NHL pathogenesis may be related. According to a multistep theory of lymphomalignancies, continuous antigenic stimulation of expanded B-cell clones by viral antigens may initiate the generation of B-NHL. Recently, it was also shown that HCV particles opsonized by complement activation preferentially bind B-cells through CD19 and CD81, consequently lowering the threshold for B-cell proliferation [43]. Viral replication in B-cells, and genetic alterations including mutations and chromosomal abnormalities could act as key factors in such neoplastic transformation (reviewed in [44]).

1.2. Dermatological manifestations

Besides MC-related dermatological conditions, other skin disorders have been extensively linked to chronic HCV infection. Among these diseases, porphyria cutanea tarda and lichen planus have shown a strong association with HCV in diverse studies [45,46]. Association with chronic HCV infection has also been described for other dermatological conditions (Table 1).

1.2.1. Porphyria cutanea tarda (PCT)

PCT is a skin condition associated with dysfunctional porphyrin metabolism. In PCT, the activity of uroporphyrinogen decarboxylase enzyme (URO-D) is significantly reduced. The sporadic form of the disease affects only hepatic URO-D, whereas in the familial form, enzyme deficiency in other tissues e.g. erythrocytes, also occurs. In both conditions, the decreased URO-D activity leads to abnormal porphyrin accumulation in the skin and production of reactive oxygen species, when porphyrin becomes photo-activated by ultraviolet light. Clinical presentation of PCT includes cutaneous fragility, rash, small vesicles, blisters, milia and hyperpigmentation.

In a meta-analysis by Gisbert and coworkers, adjusted mean HCV prevalence by serology in PCT patients was 50% [47]. In order to explain causal relationship between HCV and worsening of PCT manifestations, non-immunological mechanisms have been proposed. It has been reported that HCV increases the production of reactive oxygen species in the liver, leading to an increase in iron levels and a further inhibition of URO-D activity [48]. Moreover, through augmenting hepatic iron deposits and generating reactive oxygen species, HCV

infection may increase the rate of uroporphyrinogen oxidation to uroporphyrin, thus contributing to the generation of additional photo-sensible compounds.

1.2.2. Lichen planus (LP)

LP is a chronic inflammatory condition that affects stratified squamous epithelia, mostly skin, oral and genital mucous membranes. Although there is no clear correlation between HCV and the severity of LP symptoms, ulcerative lesions and extensive disease are more frequent in HCV infected patients than LP non-infected individuals [49].

Epidemiological analyzes have shown geographical variations in the strength of association between LP and HCV, according to HCV prevalence. Based on HCV seroprevalence, in a meta-analysis revision performed in 2010, LP patients displayed increased risk for HCV than controls (Odds Ratio, OR 4.85; 95% CI: 3.58-6.56). Conversely, in chronic HCV infected patients, the odds from suffering LP are nearly 5 times higher than in healthy subjects (OR 4.47; 95% CI: 1.84-10.86)[50].

The etiopathological role of HCV in LP is not completely understood. Nevertheless, the main hypothesis implies basal epithelial damage by a T-cell immune response directed to viral proteins or a self-antigen presented in keratinocytes [51]. Additionally, HCV replication in mucosa has been suggested on the basis of HCV RNA positivity in oral lesions [52].

1.3. Metabolic manifestations: insulin resistance and diabetes mellitus

HCV infection has a significant impact on hepatic metabolism, contributing consequently to systemic diseases associated with metabolic conditions. Several clinical and epidemiological studies have shown that HCV chronic infection is strongly associated with insulin resistance and type II diabetes (T2D).

First associations between HCV and diabetes were clinically described in the context of cirrhosis, as earlier studies had pointed out high prevalence of glucose intolerance and diabetes mellitus in patients with cirrhosis [53]. Association between T2D and HCV was additionally proved regardless of cirrhotic status. In 2008, a meta-analysis revision compiling both retrospective and prospective studies, showed a nearly two-fold increased risk for T2D in HCV patients compared to non-infected controls, and even in comparison to HBV-infected controls [54].

In addition to glucose homeostasis deregulation due to fibrosis or cirrhosis, further mechanisms have been described regarding the pathogenic role of HCV in metabolic manifestations. On the one hand, liver damage through HCV-induced steatosis increased mitochondrial ROS and production of inflammatory cytokines have been described. On the other hand, several publications have reported that in chronic HCV infected patients both insulin secretion and signaling may be affected (for more details, see Ref.[55]).

Finally, although a causative relationship has been suggested, there still is no conclusive data related to HCV and T1D association. To date, low prevalence of pancreatic autoantibodies in chronic HCV patients has been reported [56]. Additionally, a group of case-report studies linking autoimmune diabetes and acute HCV infection has been published [57,58]. It has been hypothesized that HCV infection triggers an immune reaction against β-cells or potentiates a previously existing one. Also, HCV replication in pancreatic cells has been reported [59].

2. The impact of DAA on extrahepatic manifestations.

Table 2a and 2b summarizes the main studies that evaluate the effects of DAA on both HCV infection and clinical course of extrahepatic manifestations.

2.1. Immune-related extrahepatic manifestations

In this section, available data on the effects of the DAA in the different immune-related extrahepatic manifestations (MC, MC vasculitis, arthralgia/myalgia, B-cell NHL and autoantibody production) is described.

It has been reported that the achievement of sustained virologic response with interferon (IFN)-based regimens, leads to remission of associated MC in 88-97% of patients [60,61]. However, these therapies had a low rate of SVR and were associated with serious adverse events, and because of its immune-stimulatory effects they may exacerbate some of the symptoms of MC [62]. MC patients that were refractory to IFN-based therapy were candidates to salvage treatments such as rituximab (B-cell depleting monoclonal antibody)[63].

Regarding the influence of HCV DAA therapy in MC, a beneficial effect with regression of clinical manifestations and normalization of laboratory parameters has been observed. The first studies to report the clinical benefit of INF-free treatments in MC included a small number of patients. Additionally, as suboptimal regimens were used (e.g. Sofosbuvir plus Ribavirin (RBV) for genotype 1), the SVR rates were lower than the expected nowadays (74% and 83%)[64,65]. Recent prospective studies performed with higher number of MC patients, and potent DAA combinations, reported SVR rates ranging from 94-100% [66-68].

Bonacci *et al.* [66], described the clinical, virological and immunological outcome of 64 patients with MC treated with DAA. In this study, 29 individuals with asymptomatic circulating cryoglobulins were included. Most of the patients were treated with IFN-free schemes but approximately 15% of subjects received DAA with Pegilated-IFN; in 70% of the cases RBV was prescribed. Overall, antiviral treatment tolerance was excellent. Approximately 49% of patients presented adverse events, being anemia the most frequently reported (26.5%). In all, 60 (94%) patients achieved SVR12; and no significant differences in SVR12 rates were observed between patients with or without MC associated symptoms. It was reported 86% of overall clinical response among the 35 patients with MC associated manifestation and in 71% a complete clinical response. Regarding the patients that received immunosuppressive therapy, glucocorticoid doses could be reduced in 4 of 13 (30%) patients, and withdrawn in 6 (46%). Neither rituximab nor plasma exchange sessions were needed in any patient during the study period. All immunologic parameters improved in both groups 12 weeks after therapy. Circulating cryoglobulins became undetectable in 45% and 62% of patients with and without MC associated clinical manifestations, respectively. It was also reported, 42%, 71%, and 29% of normalization of C4 complement fraction, hemolytic complement activity 50, and RF levels, respectively among symptomatic patients [66].

Gragnani *et al.* [67] prospectively follow 44 patients with HCV associated MC, including two patients that presented an indolent lymphoma with monoclonal B cell lymphocytosis. All individuals were treated with INF-free regimens, but all received RBV as a part of their treatment, achieving 100% SVR. Adverse events occurred in 59% of patients generally mild, 13 patient presented ribavirin-related anemia (1 requiring blood transfusion). The authors reported that 24 weeks after HCV treatment, all the patients had clinical response of vasculitis, with 36% of full complete response (e.g. cleared all manifestations of vasculitis), 41% of complete response (e. g. improvement of all the manifestations of vasculitis), 27% of partial response (e.g. disappearance or improvement of at least half of the manifestations of vasculitis). A 7% of patients were not responders at 12 weeks pos-treatment but all of them exhibited different degrees of clinical improvement at week 24 [67]. Immune-suppressive therapy was reduced [67]; the mean cryocrit level decreased rapidly and remained

substantially stable, with disappearance of cryoglobulins in 39% of the cases at week 24 after treatment. Nevertheless, some patients had persistent cryoglobulins. The authors concluded that a complete normalization of the immune activation status seems to take longer after HCV clearance, despite the absence of clinical manifestations; and unlike IFN-based regimens, the presence of MC vasculitis does not seem to represent a risk factor for virologic nonresponse [67].

Saadoun *et al.* [68] reported for the first time a prospective cohort study of 41 patients with MC associated manifestations treated with IFN and RBV-free antiviral therapy. All patients achieved SVR, and were treated with sofosbuvir and daclatasvir for 12 or 24 weeks (duration was based on the level of liver fibrosis and previous treatment history). The treatment tolerance was very good, 17% of patients experience at least one side effect, but no serious adverse event was reported. Immunosuppressive agents were required only in 4.8% of individuals. The authors described that at week 24 of the study 90.2% of the patients were complete clinical responders, 9.8% were partial responders due to the persistent kidney insufficiency and peripheral neuropathy while skin and joint involvement disappeared. Disappearance of cryoglobulin was evidenced in fifty percent of cases. In the study, it was also evaluated the immune changes associated with the use DAA. After antiviral therapy, patients had increased numbers of T regulatory cells, IgM+$^{CD21-/low}$ memory B cells, T follicular helper cells (CD4+CXCR5+ IL21+), and T-helper 17+ cells, when compared with pre-therapy samples. In this regard, Comarmond *et al.* [69], analyzed blood samples from 27 patients with MC before and after treatment with DAA to determine the immunological effects of INF-free antiviral therapy. They observed that antiviral therapy improves abnormalities in B-cell homeostasis, with a decreased proportion of autoreactive memory B cells and decreased cryoglobulin levels after treatment. In addition, anti-HCV therapy improves T-cell homeostasis by restoring regulation/activation and Th1/Th17 imbalances [69].

Regarding the impact of DAA in MC HCV-associated nephropathy, the pooled data show good tolerance profile (despite some concerns regarding pharmacokinetics and safety in patients with severe renal failure)[70]. The previously described studies, included a proportions (15-20%) of patients with HCV associated nephropathy (most of them with MPGN), the authors observed improvement in the estimated glomerular filtration rate, decrease in the level of proteinuria and disappearance of hematuria [65-67]. These promising results could have a very positive effect in the epidemiology of HCV-associated nephropathy [70].

Finally, Cacoub *et al.* [71] reported the effectiveness and cost of the treatment of HCV MC vasculitis. The authors retrospectively review 201 clinical records, including patients treated with IFN-based regimens (n=174) without DAA, INF + DAA (n=11) and IFN-free regimens (n=16). They concluded that the high efficacy of DAA led to increased clinical and immunological efficacy and lower death rate; use of DAA was associated to higher costs for HCV drugs but with a reduction in cost associated both with hospitalization and non-antiviral treatments.

During the era of IFN-based therapies, the associated severe adverse events were a concern in rheumatology patients in whom drug side effects, such as cytopenia, disabling fatigue, fever, depression, myalgia, were difficult to distinguish from the underlying disease. There were also many reports on the exacerbation of autoimmune diseases (rheumatoid arthritis, Sjögren syndrome and systemic lupus erythematosus) in the context of IFN treatments [72]. The impact of new DAA on many rheumatologic manifestations is still unknown [72]. There is a report focused on the major benefits of sofosbuvir-based treatments on mental and physical fatigue related to HCV-associated fibromyalgia [73].

There are several reports on the regression of HCV-associated indolent NHL with IFN-based antiviral therapy. Nevertheless, an anti-proliferative activity of IFN in lymphoma regression cannot be ruled out [74-76]. Also, in patients with high-grade NHL where a primary treatment of the malignancy is required, the achievement of SVR markedly reduces the risk for NHL relapse [77].

Since 2014, there have been case reports and two cohort group studies that evaluated the impact of the use of DAA on the clinical evolution of patients with HCV-related NHL (both indolent and aggressive types) [64,78-82]. Clinical records demonstrated significant improvement of NHL, even in the absence of IFN-based treatments, being the first evidence that the antiviral rather than the anti-proliferative activity of IFN led to the cure of such lymphomas [78]. Also, this report was the corner stone to consider concomitant therapy of chemotherapy and DAA against aggressive HCV B-NHL [79], not only to improve the cure rates but also to limit the hepatotoxicity of chemotherapy and rituximab (preventing blips in HCV viral load) [80]. Arcaini *et al.* [83], reported the first retrospective large series of patients with HCV-associated lymphoproliferative disorders treated with IFN-free DAA therapy. They included 46 individuals, 43 with NHL (main type MZL). No patient was coinfected with HIV, 10 patients had previously received chemotherapy, of the and 12 had received an IFN-based antiviral regimen. Treatment was a sofosbuvir-based regimen in the majority patients. SVR was achieved by 98% of the patients. This high rate of virological response was associated with an overall lymphoproliferative disease response (based on Lugano classification criteria for lymphomas) rate of 67%, including complete response and partial response in 26% and 41% of patients, respectively. After a median follow-up of 8 months, 1-year progression-free and overall survival rates were 75% (95% CI, 51-88) and 98% (95% CI, 86-100), respectively. The authors suggest that DAA therapy can be proposed as first-line therapy for HCV-associated lymphomas in patients in with no need for immediate immunochemotherapy [83]. Recent guidelines for the management of extrahepatic manifestations of HCV, recommend the use of DAA to eradicate HCV infections with the aim to eliminate lymphoma trigger and reduce the risk of relapse. It is also pointed out that concurrent administration of DAA and immuno-chemotherapy should be tested in prospective trials, although no particular overlapping toxicities can be predicted [70].

Immune-mediated phenomena have been described over the past years as an adverse event secondary to IFN-based treatment. Since the introduction of IFN-free regimens as the standard of care for HCV, there have been some reports on the immune complex-mediated pathology developed in patients treated with DAA who achieved SVR. Sise *et al*., documented 3 cases of immune complex–mediated glomerulonephritis with full house immunofluorescence occurring in patients being treated with DAA, who presented with joint pain or rash in addition to hematuria, pyuria, and high creatinine levels. The authors could not find the mechanism by which DAA therapy could lead to the development of this autoimmune adverse event [84]. Artemova *et al.*, described a group of 9 patients with MC (4 patients had asymptomatic cryoglobulinemia, and 5 had moderate-stage associated vasculitis). The authors found no correlation between virological response and cryoglobulin production and 2 of the patients exhibited no regression of skin lesions or cryocrit. Artemova suggest that in patients with moderate MC vasculitis with persistence of symptoms after HCV eradication, further therapeutic approaches should be implemented [85]. In line with this report, Sollima *et al.*, presented a series of 7 patients with HCV MC vasculitis, that were treated with different combinations of DAA. Despite that all achieved SVR, 6 of them did not improved clinically, exhibiting rebounds of symptoms and cryoglobulin levels after treatment cessation[86].

2.2. Dermatological manifestations

Before the availability of DAA, the presence of HCV associated lichen planus was a relative contraindication to prescribe IFN-based therapies because it could cause an exacerbation of skin and mucosal lesions [87,88]. The same group of Japan has published two clinical reports with a total of 8 patients with LP and HCV infection who resolved both conditions successfully with DAA [89,90].

For PCT, the standard treatment includes avoidance of exacerbating factors, phlebotomy and chloroquine [91]. In the era of IFN-based therapies there were reports of either improvement or worsening of PCT symptoms, as well as *de novo* PCT during HCV treatment [91]. Case reports and small cohort studies have proven the beneficial effects on PCT clinical manifestations with the use of DAA [92-94]. The cohort study included 16 HIV coinfected patients, 15 achieved SVR. Resolution of HCV infection was associated with PCT clinical remission, and normalization of urinary porphyrin levels. The authors reported that the remission was maintained over time, and no relapses of PCT have been detected during follow-up [92].

2.3. Metabolic manifestations

There is one report on 29 patients diagnosed with HCV infection and T2D, in whom DAA therapy was prescribed. All patients responded to HCV therapy (defined by the authors as undetectable HCV viral load during or at the end of treatment). Six patients (23%) needed to reduce hypoglycemic drugs, 80% of patients showed reduction in glycated hemoglobin and 67% showed reduced fasting glycaemia during treatment. These findings were independent of the DAA regimen used [95]. The clinical impact of successful antiviral therapy on the long-term outcome of T2D is still unknown and further studies with a larger number of patients are needed to define this issue [96].

In conclusion, HCV chronic infection is associated with many and sometimes severe extrahepatic manifestations. During the IFN-based era, treatment of HCV presented poor efficacy, high rates of side effects, and the risk for exacerbation of autoimmune related diseases. The availability of IFN free regimens with high virologic efficacy and low rates of side effects offer the opportunity to treat and cure both HCV infection and its extrahepatic manifestations.

3. Expert Commentary

So far, there is undoubtedly evidence of the high efficacy of DAA-based therapy for curing HCV chronic and acute infection. Due to the high cost of these therapies, their use in many countries has been restrained to patients with advanced fibrosis. As HCV infection does not only affect the liver and presents an important number of extrahepatic manifestations (among them life threatening ones, like aggressive NHL) there is a growing interest in evaluating the impact of the use of DAA as the treatment against these diseases. For this reason, over the past two years, there have been an increasing number of clinical and small cohort reports acknowledging this issue. To date, all the data reported agree on the beneficial effects of the use of DAA therapies in the extrahepatic manifestations of HCV; both achieving the cure of HCV infection and the reduction of non-liver associated diseases. The most frequent associated pathologies are immune mediated and the

beneficial effect observed besides liver pathology, is possibly explained by the elimination of the HCV immunogenic antigens by DAA, with the subsequent elimination of the chronic immune stimulation. By achieving this goal, manifestations related to the presence of mixed cryoglobulinemia and B cell proliferation can be resolved (e.g. MC vasculitis) or present a better response to its specific treatment (e.g. aggressive B-cell lymphoproliferative disease). For non-immune mediated manifestation, there is still very scarce evidence about the direct impact of DAA and the possibility to consider antiviral agents as a first line therapy for them. This is an open field of research, and since many of these patients with extrahepatic manifestations are excluded from clinical trials, there is an urgent need for the creation of cohort studies to respond to this question.

4. Five-year view

The perspectives are promising. In the following years with the goal to eradicate HCV infection, many of these patients will benefit from the resolution of HCV chronic infection with the achievement of HCV clearance, the arrest (an eventual regression) of liver fibrosis and the improvement of disappearance of non-liver associated diseases.

In the next five years, it is expected that the economic barriers to access HCV therapy will be overcome and all patients will have the opportunity to be treated. Until this goal is achieved, it will be very important to continue reporting on the impact of DAA on extrahepatic manifestations; and in this way, offer treatment also to those HCV infected individuals that will benefit the most from it, independently of their liver fibrosis.

5. Key issues

- HCV is a globally prevalent pathogen, and thus a major health concern. According to the World Health Organization (WHO), 71 million people have chronic HCV infection, being at high risk for progressive liver disease including cirrhosis, and hepatocellular cancer.
- Although HCV is a hepatotropic virus that primarily affects the liver, several reports have linked HCV to a variety of extrahepatic symptoms involving the skin, as well as musculoskeletal, renal, cardiovascular and nervous systems.
- DAA, the standard of care for HCV infection, present cure rates higher than 90%. The cure is defined as the clearance of liver HCV infection.
- The impact of DAA on extrahepatic manifestations of HCV infection is an open field of research. There is increasing evidence of the beneficial effect of DAA, mainly on HCV immune related associated diseases.

Funding

This work was supported by a grant from the Agencia Nacional de Promoción Científica y Tecnológica (ANPCyT)

(PICT 2013/2229)

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Reference annotations

* Of interest

** Of considerable interest

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Table 1: Extrahepatic manifestations of chronic HCV infection.

Affected systems	Reported conditions	Ref. no.
Cardiovascular and circulatory	MC vasculitis	
	Coronary artery disease Carotid aterosclerosis Ischemic heart disease with coronary vasculitis, mitral valvular damage, pericarditis and congestive heart failure.	[16], [24]
Endocrine	Insulin resistance T2D	
	Type I diabetes mellitus	
Immune	MC B-cell lymphoproliferative diseases	
	Autoantibodies Monoclonal gammopathies	[20], [24]
Integumentary and exocrine	Purpura (main dermatological condition related to MC vasculitis) Raynaud's syndrome, acrocyanosis, livedo reticularis (less frequent)	[17]
	PCT Lichen planus	
	Pruritus, psoriasis, polyarteris nodosa, necrolytic acral erythema, HCV-related sicca syndrome	[13], [45]
Musculoskeletal	Fatigue, arthralgia (main joint condition related to MC vasculitis) HCV polyarthritis /mono-oligoarthritis (less frequent)	
Nervous	Cognitive impairment Fatigue Depression Sensory or sensory-motor polyneuropathy Multiple mononeuropathy	[12], [24]
Renal	MC glomerulonephritis (MPG type I) Membranoproliferative glomerulonephritis without MC Membranous nephropathy	[22]
	Glomerulonephritis, Focal segmental glomerulosclerosis, IgA nephropathy, fibrillary or immu-notactoid glomerulopathy Renal insuficiency	[23]
Respiratory	Sublclinical alveolitis Pulmonary intra-alveolar hemorrhages.	[12], [24]

MC: mixed-cryoglogulinemia; MPG: membranoproliferative glomerulonephritis. T2D: type II diabetes mellitus. PCT: porphyria cutanea tarda.

Table 2a: Literature on DAA (INF-free treatment) in HCV-virus related MC.

Author	Year	Extrahepatic manifestation	No. Patients	METAVIR	Treatment	Results % (n/study population)	Ref. no.
Gragnani	2016	MC	44	F >3: 21/44 (48%)	SOF based regimens, ± RBV	**HCV infection:** 100% SVR **MC response:** 36% (16/44) full complete CR 41% (18/44) complete CR 23% (10/44) partial CR	[67]
Bonacci	2017	MC	64 29 (45%) ACC 35 (55%) CV	All, F4: 37/64 (57%) ACC, F4: 20/29 (69%) CV, F4: 15/35 (44%)	Peg IFN + DAA, SOF based regimens ± RBV, OBV/DSV/PTV/r ± RBV	**HCV infection:** ACC: 93% (27/29) CV: 94% (33/35) **MC response:** ACC: 62% (17) Disappearance MC CV: 71% (25/35) complete CR	[66]
Saadoun	2017	MC	41	F >3: 26/41 (63%)	SOF/DCV	**HCV infection:** 100% SVR **MC response:** 90,2% (37/41) complete CR 9,8% (4/41) partial CR	[68]
Arcaini	2016	B-cell indolent LPD	46 37 (84%) MZL 9 (16%) others	F4: 7/46 (15%)	SOF based regimens ± RBV	**HCV infection:** 98% SVR **LPD response:** 26% (12/46) complete CR 41% (19/46) partial CR 23% (11/46) stable disease	[83]
Alric	2016	Marginal zone lymphomas, Diffuse large B-cell lymphomas	10	>F3: 7/10 (70%)	SOF based regimens	**HCV infection:** 90% SVR **LPD response:** 90% (9/10) complete CR 10% (1/10) partial CR	[82]
Rossotti	2015	Splenic marginal zone lymphoma	1		Faldaprevir, deleobuvir, and ribavirin	SVR and clinical response	[78]
Sultanik	2015	Extranodal marginal zone lymphoma	1		SOF/RBV	SVR and clinical response	[81]
Carrier	2015	B-NHL	5		SOF based regimens	100% SVR, 100% clinical response	[80]

MC: Mixed cryoglogulinemia; ACC: Asymptomatic circulating cryoglobulins; CV: Cryoglobulinemic vasculitis; MZL: Marginal zone lymphoma; SVR: Sustained virological response, CR: Clinical response, DAA: Direct antiviral agents, SOF: Sofosbuvir; OBV/DSV/PTV/r: Ombitasvir/dasabuvir/paritaprevir/ritonavir. DCV: Daclatasvir. ASV: Asunaprevir. LDV: Ledipasvir. RBV: Ribavirin. LPD: Lymphoproliferative disorder. B-NHL: B-cell Non-Hodgkin lymphoma. PFS: Progression free survival.

Table 2b: Literature on DAA (INF-free treatment) in non-MC HCV-extrahepatic manifestations.

Author	Year	Extrahepatic manifestation	No. Patients	Treatment	Results	Ref. no.
Pavone	2016	T2D	29	SOF based regimens and OBV/DSV/PTV/r	Virologic response, 80% reduction of glycated hemoglobin, 67% reduced fasting glycaemia	[95]
Nagao	2016	Oral lichen	7	DCV/ASV	100% SVR, 100% CR	[90]
Hatch	2016	PCT	1	SOF/LDV	SVR and CR	[93]
Tong	2016	PCT	1	SOF/LDV	SVR and CR	[94]
Combalia	2017	PCT (HIV coinfection)	16	Not reported	94% SVR, 100% clinical and laboratory response	[92]

CR: Clinical response, MC: Mixed-cryoglogulinemia; SVR: Sustained virological response, DAA: Direct antiviral agents, SOF: Sofosbuvir; OBV/DSV/PTV/r: Ombitasvir/dasabuvir/paritaprevir/ritonavir. DCV: Daclatasvir. ASV: Asunaprevir. LDV: Ledipasvir. RBV: Ribavirin. LPD: Lymphoproliferative disorder. B-NHL: B-cell Non-Hodgkin lymphoma. PFS: Progression free surivival. T2D: Type II diabetes mellitus. PCT: Porphyria cutanea tarda.