Hepatitis C Virus Infection and Rheumatic Diseases: The Impact of Direct-Acting Antiviral Agents

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Hepatitis C virus infection and rheumatic diseases - The impact of direct acting antiviral agents

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Abstract

Hepatitis C (HCV) infection is associated with a tremendous morbidity and mortality due to liver complications. Chronic HCV infection is also associated with many extrahepatic manifestations including vasculitis, B cell non Hodgkin lymphoma, chronic kidney disease, cardiovascular diseases, and glucose metabolism impairment. Hepatitis C infection is frequently associated with rheumatic disorders such as arthralgia, myalgia, cryoglobulinemia vasculitis and sicca syndrome as well as the production of autoantibodies. The treatment of HCV infection has long been based on interferon alpha (IFN) that was found poorly effective. Such IFN-based treatments were contraindicated in many autoimmune/inflammatory disorders. In addition, they were responsible of frequent severe adverse events, some of which were related to exacerbation of rheumatic inflammatory disorders. The emergence of new oral IFN-free combinations now offers an opportunity for HCV infected patients with extra-hepatic manifestations, including autoimmune/inflammatory disorders, to be cured with a short treatment duration and a low risk of side effects.

Abstract: 151 words

Key points

- Hepatitis C virus infection is associated with many extrahepatic manifestations including rheumatic disorders such as arthralgia, myalgia, cryoglobulinemia vasculitis and sicca syndrome.
- The treatment of hepatitis C virus infection has long been based on interferon alpha which was contra-indicated in many autoimmune/inflammatory disorders.
- The emergence of new oral interferon-free combinations now offers an opportunity for hepatitis C virus infected patients with extra-hepatic manifestations, including autoimmune/inflammatory disorders, to be cured with a short treatment duration and a low risk of side effects.

Approximately 130-170 million people are infected with hepatitis C virus (HCV) worldwide. The HCV induces tremendous morbidity and mortality mainly due to liver complications (cirrhosis, hepatocellular carcinoma). Shortly after HCV discovery in the early 1990s, this chronic viral infection has been recognized to induce many extrahepatic manifestations. Large studies have highlighted increased HCV-related morbidity and mortality due to cryoglobulinemia vasculitis, B cell non Hodgkin lymphoma, arthralgia, myalgia, sicca syndrome, as well as cardiovascular diseases, type 2 diabetes and insulin resistance, and neurocognitive dysfunction [1,2]. Interferon alpha (IFN) has long been the cornerstone of antiviral combinations in HCV infected patients with a low rate efficacy and a poor tolerance. In addition, use of IFN was associated to high rates of severe adverse events. In patients infected by HCV and suffering of auto-immune/inflammatory rheumatic diseases, IFN was either contraindicated or reported to induce a flare of the disease. Recently, new direct acting antiviral (DAA) IFN-free treatments led to HCV cure in most (> 90%) patients with a very good safety profile (severe adverse event < 5%) and a short duration (12 weeks). Our review will focus on main rheumatologic diseases associated with chronic HCV infection, and the impact of DAAs on such extrahepatic manifestations.

Hepatitis C virus and joint manifestations

1- Arthralgia/myalgia

Arthralgia are reported in 6-20% of HCV infected patients [3–5]. They usually involve large joints, sometimes with effusion, and are bilateral and symmetric. Arthralgia involve more frequently fingers, knee and back [6]. Arthralgia are significantly more frequent in patients with cryoglobulinemia vasculitis compared to those without vasculitis (28% versus 23% respectively) [3]. The presentation may mimic a rheumatoid arthritis. The frequent positivity of a rheumatoid factor activity in HCV infected patients also lead to a misdiagnosis. Smoking and a previous diagnosis of arthritis are independent risk factors for self-reported joint pain [Odds ratio (OR) 5 and 4.25, respectively). Myalgia are less common, affecting about 2-5% of HCV patients [3,5]. An arthritis, unrelated to mixed cryoglobulinemia, is less common (<5% of patient) involving small joints associated with a carpal tunnel syndrome and a palmar tenosynovitis.

2-HCV mixed cryoglobulinemia vasculitis

Mixed cryoglobulinemia vasculitis (CryoVas) is an immune complex small vessel vasculitis involving mainly the skin, the joints, the peripheral nerve system and the kidneys [1,2]. Cryoglobulinemia is defined by the presence of circulating immunoglobulins that precipitate at cold temperature and dissolve with rewarming. CryoVas is related to HCV infection in 70-80% of cases, mostly associated with a type II IgM kappa mixed cryoglobulin. Conversely, 50-60% of HCV infected patients produce a mixed cryoglobulin that will lead to a CryoVas in 15% of cases. Main symptoms include asthenia, purpura, arthralgia, myalgia, peripheral neuropathy, and glomerulonephritis [7,8]. In a large cohort of HCV-CryoVas patients, baseline factors associated with a poor prognosis were the presence of severe liver fibrosis (hazard ratio [HR] 5.31), central nervous system involvement (HR 2.74), kidney involvement (HR 1.91), and heart involvement (HR 4.2)[9]. Arthralgia are reported in 40 to 80% of HCV-infected patients positive for a mixed cryoglobulin [10–12]. Joint pains are bilateral, symmetric, non-deforming and involve mainly knees and hands, less commonly elbows and ankles. A rheumatoid factor (RF) activity is found in 70-80% of CryoVas patients, not correlated with the occurrence of joint disease. Anti-cyclic citrullinated peptide antibodies (anti-CCP Ab) are usually absent in HCV patients. Clinically or on imaging, there is no evidence of joint destruction. Of note, some clinical features might be confusing for clinicians, because IFN treatment used for HCV may lead to exacerbation of arthralgia and myalgia. Sometimes, it used to be difficult to distinguish vasculitis flares and side effects of IFN- based treatments.

3-Sicca syndrome

Sicca symptoms of either the mouth or eyes have been reported in 10-30% of HCV infected patients. Less than 5% of patients with a defined Sjögren's syndrome are HCV-positive [10]. In a recent literature review, Younossi et al. reported a SS prevalence of 11.9% in HCV patients, with a risk ratio for SS of 2.29 in HCV infected patients compared to uninfected patients. However, the criteria for Sjögren's syndrome diagnosis were based on clinical questionnaire in some studies and were not well detailed [13]. Although sicca symptoms are very frequent in HCV infected patients, a characterized Sjögren's syndrome defined by the presence of anti-SSA or anti-SSB antibodies and a typical salivary gland histology is uncommon. A large cohort study of 137 patients with a definite Sjögren syndrome (1993 international criteria) has compared patients with HCV infection to those with a primary form. Patients with HCV-associated Sjögren syndrome were older, more frequently males, and presented more frequently a vasculitis, a peripheral neuropathy, and a neoplasia. They also

had a different biological pattern i.e. they had more frequently a positive RF, a cryoglobulinemia and less frequently anti-SSA or SSB antibodies [14,15]. Interestingly, only 23% of HCV-associated Sjögren syndrome patients had positive anti-ENA. The detection of HCV-RNA and HCV core antigen in epithelial cells of patients with HCV-associated Sjögren syndrome and the development of Sjögren syndrome like exocrinopathy in transgenic mice carrying the HCV envelope genes support the possibility of a direct impact of HCV itself on the development of sialadenitis [16,17].

4-Fibromyalgia and fatigue

In a large prospective study, 19% of 1,614 HCV-infected patients fulfilled the main diagnostic criteria of fibromyalgia (fatigue, arthralgia and myalgia) [3]. A fatigue, with or without a fibromyalgia, was the most frequent extrahepatic manifestation (35-67 %). Many underlying factors were independently associated to such fatigue as older age, female gender, the presence of arthralgia/myalgia as well as neuropsychological factors. Conversely, there was no link with alcohol consumption, HCV genotype or viral load, the presence of a cryoglobulin, and a thyroid dysfunction. Of note, after IFN-based treatment only the group of patients with a sustained virological response showed a benefit impact on fatigue. The benefit of treatment on arthragia/myalgia was found in about fifty percent of patients, independently of the virological response.

4-Production of auto-antibodies

The prevalence of circulating autoantibodies is high in patients with chronic HCV infection which may induce diagnostic difficulties in patients with rheumatic manifestations [3,10]. The most frequent immunologic abnormalities include mixed cryoglobulis (50-60%), RF activity (40%), and antinuclear (20-35%), anti-cardiolipin (10-15%), anti-thyroid (10%) and anti-smooth muscle antibodies (7%) [3,18,19]. At least one immunologic abnormality is present in up to 53% of HCV infected patients. The presence of such antibodies (i.e. RF, antinuclear or anticardiolipin) are usually not associated with specific clinical symptoms related to autoimmune disease [3,20]. Most frequent risk factors for the presence of such biological extrahepatic manifestations are the presence of extensive liver fibrosis and older age [3,19].

5-Underlying mechanisms

There are multiple immunological factors predisposing HCV infected patients to develop a CryoVas or other systemic rheumatologic manifestations. Chronic stimulation of B cells by HCV directly modulates B- and T-cell function and results in polyclonal activation and

expansion of B-cell producing IgM with RF activity. There is an expansion of clonal $CD21^{-/low}IgM^{+}CD27^{+}$ marginal zone like B cells [21], and a decrease of regulatory T cells [22]. In a genome-wide association study significant associations were identified on chromosome 6 [23]. It has been shown a higher percentage of a particular allele of the promoter of the B-cell activating factor [24]. In contrast, specific virological factors (viral load, genotype) have not been identified. Other factors are related to the infection by HCV of peripheral blood mononuclear cells, including peripheral dendritic cells, monocytes, and macrophages [25]. A persistent viral stimulation enhances expression of lymphomagenesis-related genes, particularly the activation-induced cystidine deaminase which is critical for somatic hypermutation and could lead to polyclonal and later monoclonal expansion of B cells [26]. Under this trigger effect, oligo- or monoclonal IgM, that shares rheumatoid activity, are produced by a permanent clone of B cells which favors the appearance of immune-complexes, formed by circulating HCV, anti-HCV polyclonal IgG, and the monoclonal IgM itself.

Impact of HCV chronic infection in patients with rheumatologic disorders

1- Increased cardio-metabolic related morbidity and mortality

Many chronic auto-immune rheumatic diseases are now well recognized as an independent risk factor for major cardio-vascular events. Recent data also provided evidence of a strong relationship between HCV infection and major adverse cardiovascular events. Such risk has been shown to be higher in HCV infected patients compared to non HCV controls, independently of the severity of the liver disease or the common cardiovascular risk factors. Patients with HCV chronic infection have an increased prevalence of carotid atherosclerosis and increased intima-media thickness compared to healthy controls or patients with hepatitis B or nonalcoholic steatohepatitis. Active chronic HCV infection appears as an independent risk factor for ischemic cerebrovascular accidents and ischemic heart disease [27]. For example, Maruyama et al. have reported an improvement in the myocardial perfusion defect in patients who cured from HCV infection after IFN-based treatment while relapsers showed worsening [28]. Successful IFN-based therapy showed a beneficial impact on the cardiovascular risk, underlining the tight link between HCV and the occurrence of cardiovascular events [29–31]. Consistently, HCV infection has been associated with higher rates of diabetes mellitus and insulin resistance compared with healthy volunteers and patients with hepatitis B. In addition, glucose abnormalities in HCV patients is associated with poor liver outcomes defined by advanced liver fibrosis, lack of sustained virologic response to

IFN-based treatment and with a higher risk of hepatocellular carcinoma development [32–35]. In the context of chronic inflammatory rheumatologic disorders, which already lead to an increased cardiovascular risk (related to chronic inflammation), the presence of HCV infection should be taken into account to assess the global cardiovascular risk.

2- Rheumatologic impact

Studies analysing the impact of HCV infection on the prognosis of patients with chronic inflammatory rheumatologic disorders are scarce. In a recent prospective cohort of US veterans, HCV-positive patients reported higher pain scores, had higher tender joint counts, and higher patient global scores contributing to higher DAS28 scores, after adjustment for age, gender, race, smoking status and days from enrolment [36]. After further adjustments for differences in the use of methotrexate, prednisone, and anti-TNF therapies, DAS28 scores remained significantly higher in HCV-positive patients over all study visits. There was no difference in physician-reported outcomes (swollen joints or physician global scores). After adjusting for age, gender and race, HCV-positive patients were more likely to use prednisone (OR 1.41) and anti-TNF therapies (OR 1.51), and far less likely to use methotrexate (OR 0.27)[36].

Treatment of HCV infection

Before the era of DAA combinations

The cornerstone of HCV-Cryovas therapy is the capacity of treatments to achieve a sustained virologic response. Introduced in the early 1980s as a monotherapy, IFN was found to be both poorly tolerated and poorly effective with virologic cure ["sustained virologic response" (SVR)] in less than 10%. With pegylated formulations of IFN optimizing its pharmacokinetics and combination with ribavirin for up to 48 weeks or longer, SVR rates increased to about 50%. During the decade 2000-2010, Mazzaro et al first reported sustained clinical and virological response in 44% HCV-Cryovas patients treated with Peg-IFN plus ribavirin for 12 months [37]. Saadoun et al reported that Peg-IFN plus ribavirin combination as compared with IFN plus ribavirin showed higher rates of complete clinical (67.5% vs 56.2%) and virological (62.5% vs 53.1%) responses, regardless of HCV genotype and viral load [38]. An early virologic response was associated with a complete clinical response [OR 3.53; (95%CI 1.18, 10.59)], whereas a GFR<70 ml/min was a negative predictor [OR 0.18; (95%CI 0.05, 0.67)]. However, the safety profile was not satisfactory and such therapies often led to many severe adverse events such as severe cytopenia, disabling fatigue, fever and

depression. In addition, fatigue, arthralgia, and myalgia were frequently reported, a particular concern in rheumatology patients where distinction of drug side effect from underlying disease was often difficult [39]. Although non-specific arthralgia have been reported, some authors have published rare cases of rheumatoid arthritis occurrence with anti-CCP antibodies after IFN-based treatment despite HCV cure [40,41]. Consistently, other autoimmune exacerbations such as Sjogren's syndrome and systemic lupus erythematosus have been reported after IFN treatments [42]. In the context of CryoVas, it has been reported cases of peripheral neuropathy induced or flared by IFN-based treatment [43].

The era of DAA combinations

The beginning of the new era was characterized by the development of the first two "direct acting antiviral agents" (DAA), i.e. boceprevir and telaprevir. In combination with Pegylated interferon and ribavirin, these first generation HCV protease inhibitors significantly improved the efficacy of antiviral combination, leading to approximately 70% SVR rate in genotype 1 HCV infection. However, these agents worsened toxicity of IFN-based treatments and thus limited their use in all HCV patients as well as in patients with rheumatic diseases [15]. In a prospective cohort of HCV patients treated with boceprevir, the SVR rate was lower in cryoglobulinaemic patients than in those without mixed cryoglobulinaemia (23.8% vs 70% respectively, p=0.01) [44], although the latter had more risk factors of treatment failure (severe liver fibrosis). The boceprevir-based treatment allowed improvement of symptoms upon undetectable viremia and resulted in cryocrit disappearance in 86% of patients. However, symptoms reappeared after virological breakthrough [44]. In another prospective study, telaprevir or boceprevir showed complete clinical response and SVR at week 24 in 67% of patients. However, serious adverse events occurred in 46.6% of patients, mostly in patients with baseline severe liver fibrosis and a low platelet count [44,45].

More recently, new all oral IFN-free, as well as and ribavirin-free, regimens have been approved. They are characterized by a dramatic efficacy leading to cure rates of 90-100% in all HCV genotypes, with minimal side effects and short duration (12-24 weeks)[46,47]. Even in difficult-to-treat populations, including cirrhotic and previously treated patients, IFN-free DAA regimens have been reported very efficient. Numerous large prospective studies have been published with different DAA combinations, such as simeprevir plus sofosbuvir [48], sofosbuvir plus daclatasvir with/without ribavirin or sofosbuvir plus ledipasvir, demonstrating high antiviral potency (>90% SVR rates, in both cirrhotic and treatment-experienced patients whatever the stage of fibrosis)[49]. Although such treatments remain today highly expensive,

they now offer a “therapeutic revolution” for HCV infected patients, particularly those with rheumatic diseases in whom IFN-based treatment has failed or was not well tolerated.

For the treatment of HCV-Cryovas, the VASCUVALDIC study enrolled 24 patients [median age 56.5 years, 54% males, 50% cirrhotic] who received sofosbuvir plus ribavirin for twenty four weeks [12]. Seven patients also received immunosuppressive therapy, i.e. rituximab, corticosteroids, and plasmapheresis. Eighty seven percent of patients were complete clinical responders and SVR was obtained in 74% of patients at week12 post-treatment. Of note, the complete clinical response was very rapid as it was noted at on-treatment week12 in two third of patients. Kidney involvement with membranoproliferative glomerulonephritis improved in four out of five patients. Only 2 (8%) serious adverse events were observed. Sise et al have reported a retrospective case series of twelve HCV-CryoVas patients [median age 61 years, 58% males, 50% cirrhotic] treated with sofosbuvir plus simeprevir (n=8) or sofosbuvir plus ribavirin (n=4). [50]. Seven patients had evidence of renal involvement including five membranoproliferative glomerulonephritis. Four patients received Rituximab concurrent with DAA therapy. A SVR at post-treatment week 12 was achieved in 83% of patients. Cryoglobulin levels decreased in most patients, with a median percent decreasing from 1.5% to 0.5%, and completely disappeared in 4/9 cases. Only 2 (17%) patients experienced serious adverse events. The Italian experience has been recently reported in 37 HCV-Cryovas patients who received DAAs [51]. Ten percent of patients also received immunosuppressants. A response on Cryovas symptoms was defined as complete in 18 (49%), partial in 13 (35%) whereas no response was noted in 6 (16%) patients.

Despite the unquestionable evidence of a viral etiology and the obvious efficacy of antiviral treatments, immunosuppression still remains a major treatment in HCV-CryoVas patients in case of severe presentation (renal, digestive or cardiac involvements) or in patients with failure or contraindication to antiviral treatment. Rituximab - a monoclonal anti-CD20 antibody - targets activated B-cells, which are responsible for cryoglobulin production and finally Cryovas lesions. Randomized controlled trials showed that rituximab has a better efficacy than conventional immunosuppressive treatments (i.e., glucocorticoids, azathioprine, cyclophosphamide, or plasmapheresis) or placebo [52,53]. Two other controlled trials showed that addition of rituximab to pegylated-IFN/ribavirin led to a shorter time to clinical remission, better renal response rate, and higher rates of cryoglobulin clearance [54,55]. Of note, paradoxical worsening of vasculitis have also been described after rituximab in such patients. Rituximab may form a complex with IgMk mixed cryoglobulin and lead to severe

exacerbation of vasculitis involvements [56]. Considering the very rapid and potent virological efficacy of new DAA combination and the well demonstrated correlation between SVR and clinical response, the exact place of Rituximab, plasmapheresis or other immunosuppressive drugs remains to be defined [56]. Other treatments for Cryovas have a limited place. Corticosteroids, used alone or in addition to IFN, did not favourably affect the response of HCV-CryoVas manifestations in controlled studies [57]. Plasmapheresis, which offers the advantage of removing the pathogenic cryoglobulins from the circulation, should be considered for rapidly progressive glomerulonephritis or life-threatening involvements. Immunosuppressive therapy is usually needed associated with plasma exchange in order to avoid the rebound increase in cryoglobulin serum level seen after discontinuation of apheresis. When used in combination with HCV treatment, plasmapheresis did not modify the virologic response if IFN was given after each plasma exchange session [58]. There is no available data to date with DAA.

The impact of new DAAs on other rheumatologic manifestations i.e. arthralgia, myalgia, and sicca syndrome are lacking. For the fibromyalgia, interestingly Younossi et al recently reported major benefits of sofosbuvir-based DAAs on most patients reported outcomes, including mental and physical fatigue, at week12 and week24 post-treatment [59]. A benefit of DAAs was also suggested on cerebral magnetic resonance signal in basal ganglia correlated to the virological response [60].

In conclusion, HCV chronic infection – besides its liver-related complications - is frequently associated with clinical and biological rheumatologic manifestations such as arthralgia, myalgia, cryoglobulinemia vasculitis, sicca syndrome and the production of autoantibodies. Treatment of HCV has long been based on Interferon alpha, excluding most patients with rheumatisms because of the poor efficacy, high rates of side effects, and the risk of exacerbation of auto-immune and rheumatic disorders. The emergence of new oral IFN-free combinations now offers the opportunity for HCV infected patients with extra-hepatic manifestations such as rheumatic disorders, to be cured with a low risk of side effects and a short treatment duration.

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