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Rheumatologic manifestations of hepatitis C virus infection

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Abstract

Hepatitis C (HCV) infection is associated with a morbidity and mortality due to liver complications. Hepatitis C infection is also frequently associated with rheumatic disorders such as arthralgia, myalgia, cryoglobulinemia vasculitis and sicca syndrome as well as the production of autoantibodies. The treatment of hepatitis C virus infection with interferon alpha (IFN) has been for long time contra-indicated in many rheumatologic autoimmune/inflammatory disorders. New oral IFN-free combinations offer an opportunity for HCV infected patients with extra-hepatic manifestations, including rheumatologic autoimmune/inflammatory disorders, to be cured with a short treatment duration and a low risk of side effects.

Key points

- Main rheumatologic manifestations reported with HCV chronic infection include arthralgia, myalgia, cryoglobulinemia vasculitis and sicca syndrome.
- Immunological factors predisposing to develop such manifestations include stimulation of B cells, expansion of B-cell producing IgM with RF activity and of clonal marginal zone like B cells, and a decrease of regulatory T cells.
- The treatment of hepatitis C virus infection with interferon alpha has been for long time contra-indicated in many rheumatologic autoimmune/inflammatory disorders.
- New oral interferon-free combinations now offer an opportunity for patients with HCV extra-hepatic manifestations, including rheumatologic autoimmune/inflammatory disorders, to be cured with a high efficacy rate 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). This chronic viral infection has been also recognized to induce many extrahepatic manifestations and increased HCV-related morbidity and mortality due to cryoglobulinemia vasculitis, B cell non-Hodgkin lymphoma, arthralgia, myalgia, and sicca syndrome [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 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 and a short duration (12 weeks). Our review will focus on main rheumatologic diseases associated with chronic HCV infection.

Hepatitis C virus and arthralgia/myalgia

Arthralgia are reported in 6-20% of HCV infected patients [3–5]. Arthralgia involve more frequently fingers, knee and back, and are bilateral and symmetric [6]. Synovitis is usually absent. Arthralgia are more frequent in patients with cryoglobulinemia vasculitis compared to those without vasculitis) [3]. The presentation may mimic a rheumatoid arthritis. The frequent rheumatoid factor positivity in HCV infected patients may lead to a misdiagnosis. However, HCV infected patients do not develop anti-CCP antibodies, a feature useful to differentiate both diseases. 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 infected 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.

Hepatitis C virus related mixed cryoglobulinemia vasculitis

Mixed cryoglobulinemia vasculitis (CryoVas) is a 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]. Baseline factors associated with a poor prognosis of HCV-CryoVas 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, and 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. There is no evidence of joint destruction. Some clinical features might be confusing for clinicians when IFN-based treatment used for HCV led to exacerbation of arthralgia and myalgia.

Hepatitis C virus and sicca syndrome

Sicca symptoms of either the mouth or eyes have been reported in 10-30% of HCV infected patients. Conversely, 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 (risk ratio 2.29). 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 patients with a definite Sjögren syndrome (1993 international criteria) showed that patients with HCV-associated Sjögren syndrome compared to those with a primary form were older, more frequently males, and presented more frequently a vasculitis, a peripheral neuropathy, and a neoplasia. They also had more frequently a positive RF, a cryoglobulinemia and less frequently anti-SSA or SSB antibodies [14,15]. Of note, only 23% of HCV-associated Sjögren syndrome patients had positive anti-ENA. The possibility of a direct impact of HCV itself on the development of sialadenitis is supported by 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 [16,17].

Hepatitis C virus and fibromyalgia/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 arthralgia/myalgia was found in about fifty percent of patients, independently of the virological response.

Hepatitis C virus and the production of auto-antibodies

The prevalence of circulating autoantibodies is high in patients with chronic HCV infection. This may induce diagnostic difficulties in patients with miscellaneous rheumatic manifestations [3,10]. The most frequent immunologic abnormalities include mixed cryoglobulins (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 found 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].

Underlying mechanisms leading to rheumatologic manifestations in HCV infected patients

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 yet been identified. Other factors are related to the peripheral blood mononuclear cells infection, 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 favours the appearance of immune-complexes, formed by circulating HCV, anti-HCV polyclonal IgG, and the monoclonal IgM itself.

Impact of HCV infection on rheumatologic diseases

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 [27]. 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)[27].

Increased cardio-metabolic morbidity and mortality in HCV infected patients

Auto-immune rheumatic diseases are now well recognized as independent risk factors for major cardio-vascular events. A strong relationship between HCV infection and major adverse cardiovascular events has been reported. 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, patients with hepatitis B or non-alcoholic steatohepatitis. Active chronic HCV infection appears as an independent risk factor for ischemic cerebrovascular accidents and ischemic heart disease [28,29]. Successful IFN-based therapy showed a beneficial impact on cardiovascular risk, underlining the link between HCV and the occurrence of major cardiovascular events [30–32]. 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 [33–36]. 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.

Treatment of HCV infection and associated rheumatologic manifestations

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%. During the decade 2000-2010, Peg-IFN plus ribavirin combination as compared with IFN plus ribavirin showed higher rates of complete clinical and virological responses, regardless of HCV genotype and viral load [37,38]. 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. 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]. Some authors have reported cases of rheumatoid arthritis occurrence with anti-CCP antibodies after IFN-based treatment, despite HCV cure [40,41]. Other autoimmune exacerbations in Sjogren’s syndrome and systemic lupus erythematosus have been reported after IFN treatments [42]. In CryoVas patients, it has been reported cases of peripheral neuropathy induced or flared after IFN-based treatment [43].

In the early 2010s, a new era was characterized by the development of “direct acting antiviral agents” (DAA). In combination with PegIFN/ribavirin, first generation HCV protease inhibitors (boceprevir, telaprevir) improved the efficacy of antiviral combination, leading to approximately 70% SVR rate in genotype 1 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 [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)[46-49]. 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, was not well tolerated or was contra-indicated. For the treatment of HCV-Cryovas, the Vasculadic 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 while SVR was obtained in 74%. 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 was achieved in 83% of patients. Cryoglobulin levels decreased in most patients (from 1.5% to 0.5%), and completely disappeared in 4/9 cases. Only 2 (17%) patients experienced serious adverse events. The Italian experience reported an overall 100% rate of clinical response of vasculitis in 44 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. The Birmingham Vasculitis Activity Score decreased from 5.41 to 1.27 while the mean cryocrit value fell from 7.2 to 1.8%.

Immunosuppression remains a major treatment in HCV-CryoVas patients with a severe presentation (renal, digestive or cardiac involvements), failure or contraindication to antivirals. 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 Peg-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 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 [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 fibromyalgia, 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 is frequently associated with clinical and biological rheumatologic auto-immune/inflammatory manifestations. Treatment of HCV infection with Interferon alpha has for a long time excluded most patients with rheumatisms because of the poor virological efficacy, high rates of side effects, and the risk of exacerbation of auto-immune and rheumatic disorders. New oral IFN-free combinations offer the opportunity for HCV infected patients with extra-hepatic manifestations such as rheumatic disorders, to be cured with a great efficacy, low risk of side effects and a short treatment duration.

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