Rheumatologic Manifestations of Hepatitis C Virus Infection

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KEYWORDS

• Hepatitis C (HCV) • Rheumatic disorders • Arthritis • Vasculitis • Arthralgia • Sicca syndrome

KEY POINTS

- Main rheumatologic manifestations reported with hepatitis C virus (HCV) chronic infection include arthralgia, myalgia, cryoglobulinemia vasculitis, and sicca syndrome.
- Immunologic factors predisposing to develop such manifestations include stimulation of B cells, expansion of B-cell–producing immunoglobulin M with rheumatoid factor activity and of clonal marginal zone, like B cells, and a decrease of regulatory T cells.
- The treatment of HCV infection with interferon alpha has been contraindicated for a long time in many rheumatologic autoimmune/inflammatory disorders.
- New oral interferon-free combinations now offer an opportunity for patients with HCV extrahepatic manifestations, including rheumatologic autoimmune/inflammatory disorders, to be cured with a high efficacy rate and a low risk of side effects.

Approximately 130 to 170 million people are infected with hepatitis C virus (HCV) worldwide. 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

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HCV-related morbidity and mortality due to cryoglobulinemia vasculitis, B-cell non-Hodgkin lymphoma, arthralgia, myalgia, and sicca syndrome.[1,2] Interferon (IFN) alpha 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 autoimmune/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 focuses on main rheumatologic diseases associated with chronic HCV infection.

HEPATITIS C VIRUS AND ARTHRALGIA/MYALGIA

Arthralgia is reported in 6% to 20% of HCV-infected patients.[3–5] Arthralgia involves more frequently fingers, knee, and back, and is bilateral and symmetric.[6] Synovitis is usually absent. Arthralgia is more frequent in patients with cryoglobulinemia vasculitis compared with those without vasculitis.[3] The presentation may mimic rheumatoid arthritis. The frequent rheumatoid factor positivity in HCV-infected patients may lead to a misdiagnosis; however, HCV-infected patients do not develop anticyclic citrullinated peptide antibodies (anti-CCP Abs), 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] 5.0 and 4.25, respectively). Myalgia is less common, affecting approximately 2% to 5% of HCV-infected patients.[3,5] Arthritis, unrelated to mixed cryoglobulinemia, is less common (<5% of patient), involving small joints associated with carpal tunnel syndrome and 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 nervous 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% to 80% of cases, mostly associated with a type II immunoglobulin (Ig)M kappa mixed cryoglobulin. Conversely, 50% to 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 is reported in 40% to 80% of HCV-infected patients positive for a mixed cryoglobulin.[10–12] Joint pains are bilateral, symmetric, and nondeforming and involve mainly the knees and hands, and less commonly the elbows and ankles. A rheumatoid factor (RF) activity is found in 70% to 80% of patients with CryoVas, not correlated with the occurrence of joint disease. Anti-CCP Abs are usually absent in patients with HCV. 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% to 30% of HCV-infected patients. Conversely, fewer than 5% of patients with a defined Sjögren syndrome (SS) are HCV-positive.[10] In a recent literature review, Younossi and

colleagues[13] reported an SS prevalence of 11.9% in patients with HCV (risk ratio 2.29). However, the criteria for SS diagnosis were based on a clinical questionnaire in some studies and were not well detailed. Although sicca symptoms are frequent in HCV-infected patients, a characterized SS 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 SS (1993 international criteria) showed that patients with HCV-associated SS compared with those with a primary form were older, more frequently male individuals, and presented more frequently vasculitis, peripheral neuropathy, and 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 patients with SS 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 SS and the development of SS-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 1614 HCV-infected patients fulfilled the main diagnostic criteria of fibromyalgia (fatigue, arthralgia, and myalgia).[3] Fatigue, with or without fibromyalgia, was the most frequent extrahepatic manifestation (35%–67%). Many underlying factors were independently associated with fatigue, such as older age, female gender, the presence of arthralgia/myalgia, and neuropsychological factors. Conversely, there was no link with alcohol consumption, HCV genotype or viral load, the presence of cryoglobulin, and 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 approximately 50% of patients, independently of the virological response.

HEPATITIS C VIRUS AND THE PRODUCTION OF AUTOANTIBODIES

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%), anticardiolipin (10%–15%), antithyroid (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 (ie, RF, antinuclear, or anticardiolipin) is usually not associated with specific clinical symptoms related to autoimmune disease.[3,20] The 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 HEPATITIS C VIRUS–INFECTED PATIENTS

There are multiple immunologic factors predisposing HCV-infected patients to develop CryoVas or other systemic rheumatologic manifestations. Chronic stimulation of B cells by HCV directly modulates B-cell 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 cell infection, including peripheral dendritic cells, monocytes, and macrophages.[25] 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, oligoclonal or monoclonal IgM, which shares rheumatoid activity, is 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 HEPATITIS C VIRUS INFECTION ON RHEUMATOLOGIC DISEASES

Studies analyzing 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 disease activity scores (DAS)28, after adjustment for age, gender, race, smoking status, and days from enrollment.[27] After further adjustments for differences in the use of methotrexate, prednisone, and anti–tumor necrosis factor (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 CARDIOMETABOLIC MORBIDITY AND MORTALITY IN HEPATITIS C VIRUS–INFECTED PATIENTS

Autoimmune rheumatic diseases are now well recognized as independent risk factors for major cardiovascular 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 with 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 with 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.[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 patients with HCV is associated with poor liver outcomes defined by advanced liver fibrosis, lack of sustained virologic response to IFN-based treatment, and 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 HEPATITIS C VIRUS 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 fewer than 10%. During the decade 2000 to 2010, pegylated (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 in whom distinction of drug side effects from underlying disease was often difficult.[39] Some investigators reported cases of rheumatoid arthritis occurrence with anti-CCP Abs after IFN-based treatment, despite HCV cure.[40,41] Other autoimmune exacerbations in SS and systemic lupus erythematosus have been reported after IFN treatments.[42] In patients with CryoVas, cases of peripheral neuropathy induced or flared after IFN-based treatment have been reported.[43]

In the early 2010s, a new era was characterized by the development of DAAs. In combination with Peg-IFN/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 patients with HCV 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% to 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 contraindicated. 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 24 weeks.[12] Seven patients also received immunosuppressive therapy; that is, rituximab, corticosteroids, and plasmapheresis. Eighty-seven percent of patients were complete clinical responders and SVR was obtained in 74%. The complete clinical response was very rapid, as it was noted at treatment week 12 in two-thirds of patients. Kidney involvement with membranoproliferative glomerulonephritis improved in 4 of 5 patients. Only 2 (8%) serious adverse events were observed. Sise and colleagues[50] reported a retrospective case series of 12 patients with HCV-CryoVas (median age 61 years, 58% men, 50% cirrhotic) treated with sofosbuvir plus simeprevir (n = 8) or sofosbuvir plus ribavirin (n = 4). Seven patients had evidence of renal involvement, including 5 membranoproliferative glomerulonephritis. Four patients received rituximab concurrent with DAA therapy. An SVR was achieved in 83% of patients. Cryoglobulin levels decreased in most patients (from 1.5% to 0.5%), and completely disappeared in 4 of 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 patients with HCV-CryoVas 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%), and no response was noted in 6 (16%) patients. The Birmingham

Vasculitis Activity Score decreased from 5.41 to 1.27, and the mean cryocrit value fell from 7.2% to 1.8%.

Immunosuppression remains a major treatment in patients with HCV-CryoVas 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 (ie, 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, paradoxic worsening of vasculitis has 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 favorably 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 to avoid the rebound increase in cryoglobulin serum level seen after discontinuation of apheresis.[58] There are no available data to date with DAA.

The impact of new DAAs on other rheumatologic manifestations (ie, arthralgia, myalgia, and sicca syndrome) are lacking. For fibromyalgia, Younossi and colleagues[59] recently reported major benefits of sofosbuvir-based DAAs on most patient-reported outcomes, including mental and physical fatigue, at week 12 and week 24 posttreatment. A benefit of DAAs was also suggested on cerebral magnetic resonance signal in basal ganglia correlated to the virological response.[60]

SUMMARY

HCV chronic infection is frequently associated with clinical and biological rheumatologic autoimmune/inflammatory manifestations. Treatment of HCV infection with IFN-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 autoimmune and rheumatic disorders. New oral IFN-free combinations offer the opportunity for HCV-infected patients with extrahepatic manifestations, such as rheumatic disorders, to be cured with great efficacy, low risk of side effects, and a short treatment duration.

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