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REVIEW ARTICLE

# HCV-Related Rheumatic Manifestations and Therapeutic Strategies

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**Abstract:** A number of hepatic and extra-hepatic autoimmune disorders may complicate a percentage of patients with hepatitis C virus (HCV) infection that is both hepatotropic and lymphotropic agent; the resulting clinical phenotypes can be grouped into the so-called HCV syndrome. This latter includes various rheumatic disorders that are frequently characterized by clinical or serological overlap; thus, a correct patients' classification is necessary prior to decide the therapy.

The management of these conditions is particularly difficult, given the coexistence of viral infection and immunological alterations. In this scenario, cryoglobulinemic vasculitis represents the prototype of HCV-related rheumatic disorders that can be treated at different levels by means of etiological (antivirals) and/or pathogenetic and/or symptomatic treatments (rituximab, cyclophosphamide, steroids, plasmapheresis, *etc*). In clinical practice, the therapeutic strategy should take into account the specific symptoms combination and the severity/activity of the disease, according to each patient's conditions.

This review focuses on the clinico-diagnostic assessments and therapeutical approaches of some rheumatic disorders complicating HCV infection, mainly arthritis, sicca syndrome, and osteosclerosis; while, cryoglobulinemic vasculitis is comprehensively examined in another article of the present issue.

**Keywords:** Hepatitis C virus, HCV, mixed cryoglobulinemia, vasculitis, arthritis, Sjögren's syndrome, ostesclerosis, lymphoma, antiviral, rituximab.

## INTRODUCTION

Hepatitis C virus (HCV) is a member of the Flaviviridae family, splitted into 7 major genotypes, globally distributed, even though with wide geographic variations. Discovered in the early 1990s, it was recognized as the cause of the former non- A/non-B chronic hepatitis [1]; moreover, several epidemiological, clinico- pathological, and laboratory studies definitely ascertained the etiologic role of this virus in mixed cryoglobulinemia syndrome (MCs) or cryoglobulinemic vasculitis (CV) [2, 3]; these synonyms are referred to systemic autoimmune disease, typically featured by serum mixed cryoglobulins, orthostatic purpura, and variable visceral organ involvement [4-7]. In particular, the demonstration of HCV lymphotropism represented a crucial point in the knowledge of the pathogenesis of CV and other autoimmune disorders potentially associated to HCV [8, 9]. The majority of individuals with HCV infection are asymptomatic, often for long-time period or for their entire life, and only a limited but relevant number of subjects may develop hepatic as well as extrahepatic diseases; these latter frequently represent a late complication of long-lasting viral infection [4, 10]. We previously proposed the term 'HCV syndrome' referring to the constellation of virus-driven clinical conditions [11], including both hepatic, organ-specific, systemic autoimmune disorders, and also malignancies [4, 6, 7, 10, 11]. The different clinical phenotypes of HCV-syndrome can be the results of genetic/environmental co- factors as suggested by the heterogeneous geographical prevalence of single HCV- associated manifestations, and it is now clear that some genetic variants in HCV infected people can predispose to the development of CV, in particular with regard to the MHC class II and NOTCH4 genes [4, 6, 7, 10-15]. A number of rheumatic disorders can be correlated to HCV infection, even if with largely variable frequency. The prototype of such etiopathogenetic linking is the HCV-related MCs, while for some other conditions the association is just anecdotally observed [4, 10, 11, 16-20] (Fig. **1**). It is relatively frequent to observe a clinical overlap between CV and other rheumatologic disorders, mainly Sjögren's syndrome (SS) or rheumatoid arthritis (RA) [4, 10,11, 16, 17, 11-23] (Fig. **2**). In other cases, the latter rheumatic diseases are independently associated to the chronic HCV infection. Therapeutic strategies of HCV-related rheumatic diseases. Therapeutic approach to different

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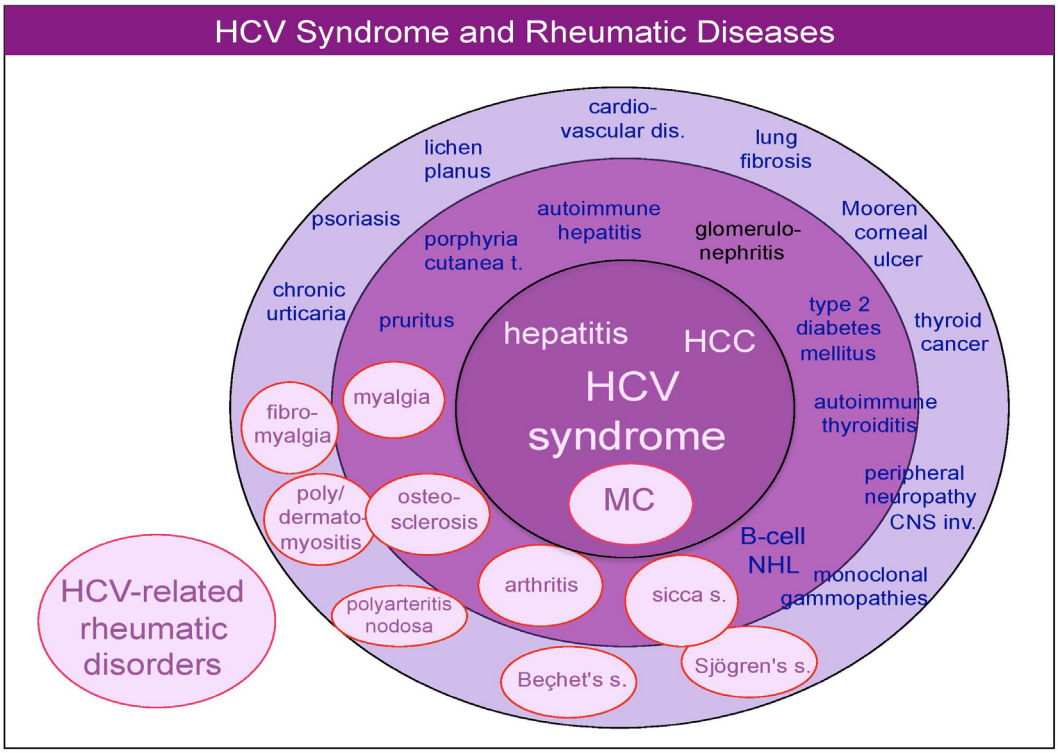


**Fig. (1)**. Schematic representation of the constellation of HCV-associated disorders. The strength of this association, based on literature data, is represented as the distance from the centre of the figure.

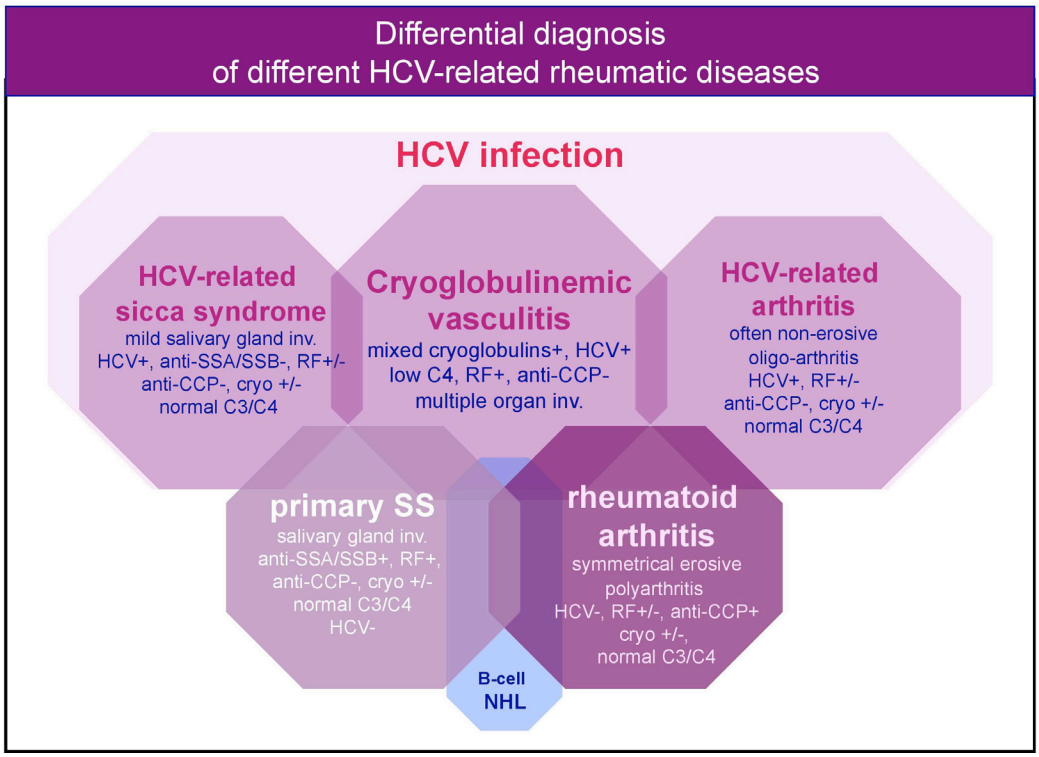


**Fig. (2)**. Differential diagnosis of HCV-related rheumatic diseases. HCV: hepatitis C virus; SS: Sjögren's syndrome; RF: rheumatoid factor; Cryo: cryoglobulins; anti-CCP: anti-cyclic citrullinated peptides antibodies; NHL: non-Hodgkin lymphoma.

HCV-related disorders, including rheumatic diseases, should be chosen on the basis of the etiopathogenetic cascade responsible for HCV syndrome (Fig. **3**, left). This is a multifactorial and multistep process possibly promoted by different co-factors; namely, HCV infection, predisposing genetic factors and, possibly, unknown environmental/toxic triggers [6, 8, 24]. The HCV lymphotropism may trigger complex immune-system alterations with prominent 'benign' lym-

phoproliferation, from one side, as well as important oncogenetic abnormalities, from another side. These pathological chances may be the result of different pathogenetic mechanisms not mutually exclusive: viral antigens (core, envelope E2, NS3, NS4, NS5A proteins) may apply a persistent stimulus on the host immune system, the high-affinity binding between HCV-E2 and CD81 and consequent [14, 18] translocation with bcl-2 proto-oncogene activation, a cross-reaction between particular HCV antigens and host autoantigens, *i.e.* a molecular mimicry mechanism, and a direct infection of B-lymphocytes by HCV directly responsible for neoplastic cell transformation [25-27]. Predisposing host factors may include some HLA alleles, both metabolic and hormonal patterns [28-37]. The main consequence is a benign B-lymphocytes proliferation with production of various autoantibodies, among which rheumatoid factor (RF) and immune-complexes (IC). These latter may be found in different autoimmune disorders, including the systemic manifestations of CV. Moreover, the activation of the proto-oncogene Bcl2, which is responsible for prolonged B cell survival, and the miR-26b down-regulation may be predisposing conditions to a frank B-cell non-Hodgkin's lymphoma (B-NHL) and other malignancies, mainly hepatocellular carcinoma (HCC) and papillary thyroid cancer [4, 6, 8, 9, 11, 29, 38-50]. The appearance of cancers can be seen in a little but relevant percentage of patients, usually as a late complication [45-47]. Both immunological and neoplastic disorders show a clinical, serological and pathological overlaps. Often, autoimmune organ-specific manifestations may evolve to systemic conditions, such as CV, and less frequently to overt cancers. By contrast, it is not uncommon that patients with malignancies develop one or more autoimmune manifestations. In this scenario, CV is at the crossing road between autoimmune and neoplastic diseases [4, 6, 11, 24, 51]. There are not comprehensive therapeutical guidelines for the HCV syndrome because of the complexity of its pathogenetic and clinico-prognostic characteristics; we can adopt in part the therapeutical strategy used for MCs, which often encompasses the different clinical variants of HCV syndrome. This therapeutical approach is essentially based on three main levels of intervention: 1. the etiological treatment, by means of antiviral drugs directed at HCV eradication; 2. the pathogenetic therapies, with immunomodulating and/or antineoplastic drugs; 3. the pathogenetic/symptomatic therapies, such as corticosteroids and plasma exchange [4, 12, 52]; (Fig. **3**, right). The following paragraphs focus on some rheumatic diseases potentially correlated to HCV infection, namely arthritis, sicca syndrome, and ostheosclerosis, while the treatment of classical CV is considered in detail in another article of the present issue.

## ARTHRITIS

The presence of arthritis has been described in about 2-3 percent of individuals with chronic HCV infection; in fact, while arthralgias can be included among the most frequent symptoms (60-70%) of HCV-positive patients, clear signs of sinovitis are less commonly observed [4, 10, 16, 22]. Furthermore, a few cohort studies have suggested an etiologic role of HCV in RA patients; however, to date, clear evidence of a pathogenetic role of HCV in patients with classical RA is leaking [41-47, 51-57]. Furthermore, a specific entity called HCV-related arthritis has been hypothesized; it is classified as a 'reactive' arthritis, even though in some individuals HCV-related chronic polyarthritis may mimic classical RA. In these instances, a clear distinction of this clinical variant from classical RA is often difficult (Fig. **2**). Moreover, arthritis due to HCV is frequently described as "rheumatoid-like", mainly in the presence of chronic symmetrical polyarthritis; more than 50% of these patients may satisfy the criteria for RA classification; namely, arthritis of ≥3 joints, involvement of hand joints, symmetric arthritis, alteration of acute-phase reactants, and RF seropositivity [58]. Usually, HCV-related polyarthritis shows a benign, often fluctuating clinical course [4, 10, 11, 52]. Commonly, patients develop-polyarticular disease, being the metacarpo-phalangeal, proximal interphalangeal, wrists and ankles primarily involved; in some patients synovitis may also affect shoulders and knees, and large joint effusions have been described in 10-30% of cases as mono-/oligoarthritis [4, 10, 16, 22, 57]. The presence of serum rheumatoid factor is quite common, in the absence of rheumatoid nodules, periarticular osteopenia or articular destruction, even if erosive findings can be observed in 1/3 of cases [4, 10, 16, 22, 57]. The erythrocyte sedimentation rate is within normal limits in about 50% patients; more interestingly, serum anti-cyclic citrullinated peptide (anti-CCP) antibodies are invariably absent in HCV-related oligo-/polyarthritis with/without cryoglobulinemia [4, 10, 16, 22]; (Fig. **4**). A peculiar subset of HCV patients with arthritis is represented by CV-associated arthritis. The latter usually is oligo-monoarticular, affecting the large joints of lower limbs, where the purpuric lesions are particularly frequent; furthermore, it is generally asymmetrical, intermittent, non-erosive, and characterized by better prognosis [4, 10, 16, 22, 57]. Finally, given the relatively high prevalence of both HCV infection and RA in the general population it is not rare to find a mere association between the virus and RA. Therefore, a virological and clinico-serological evaluation is mandatory in all cases of patients referred for arthritis in order to detect the presence of HCV infection; in this instance, the differential diagnosis between the simple comorbidity, *i.e.* classical RA plus HCV infection, and HCV-related arthritis is necessary [59-63]; (Fig. **4**). In subjects with concomitant HCV and arthritis (Figs. **3**, **4**) the treatment may include both antivirals [12, 49, 50, 52, 60, 61] and immune-modulating treatments, *i.e.* steroids, hydroxychloroquine (HCQ), other disease-modifying anti- rheumatic drugs (DMARDs); when necessary, the use of biological DMARDs such as tumour-necrosis-factor-alpha-blocking agents (anti-TNF-alpha) or rituximab, seem to be useful and safe [16, 53, 55, 65-67]. On the contrary, the gold standard treatment of HCV-related arthritis has not been established, up to date, and could be difficult in many patients. Generally, treatment with HCQ and low doses of steroids is safe and effective in controlling arthritic manifestations, even in association to antiviral treatment. However, careful monitoring of interferon-alpha (IFNα) and ribavirin treatment is necessary, considering the potential 'arthritogenic' effect due to IFNα as immunomodulant agent; indeed the use of IFNα may be associated with adverse effects, including the worsening of arthropathy, despite its usefulness in the treatment of type C hepatitis [2, 16, 52-54, 67-74]. The recent introduction of interferon-

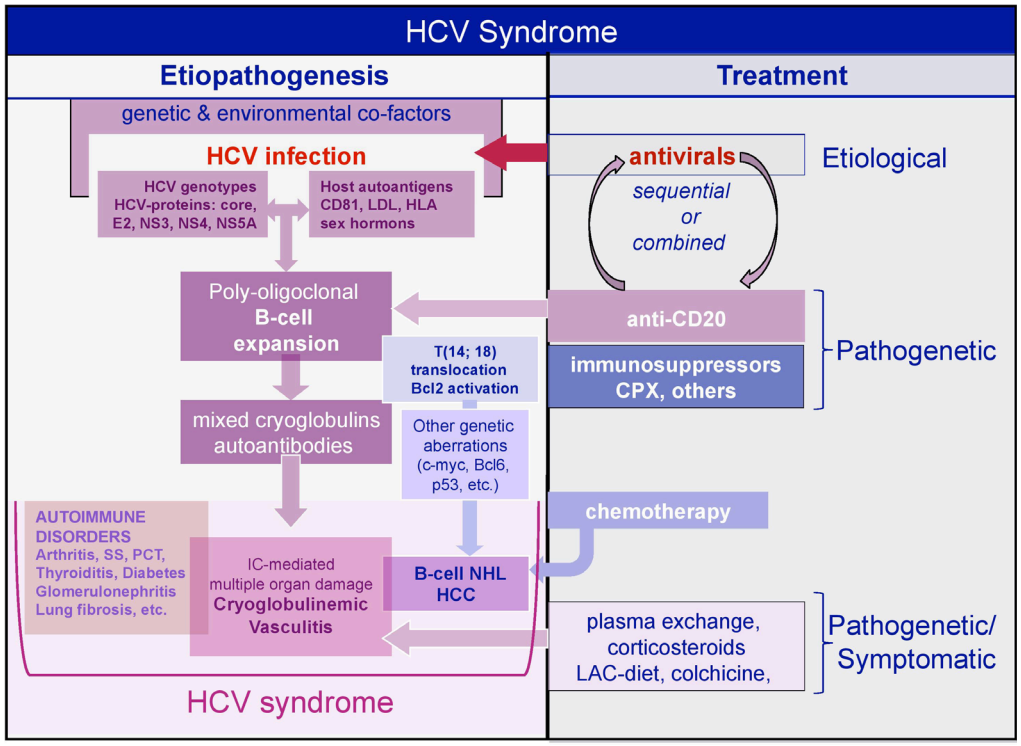


**Fig. (3)**. Left: the etiopathogenetic cascade of HCV syndrome is a multifactorial and multistep process, which leads to different organ- and non-organ-specific autoimmune disorders, including cryoglobulinaemic vasculitis and B cell lymphomas (B-NHL). Right: therapeutical guidelines for the HCV syndrome; we can adopt in part the therapeutical strategy used for MCs, which often encompasses the different clinical variants of HCV syndrome. This therapeutical approach is essentially based on three main levels of intervention: the etiological treatment by means of antiviral drugs directed at HCV eradication, the pathogenetic therapies with immunomodulating/antineoplastic drugs, and the pathogenetic/symptomatic therapies. HCV: hepatitis C virus; IC, immune complexes; SS: sicca syndrome; PCT: porphyria cutanea tarda; LAC-diet: low-antigen-content diet; CPX: cyclophosphamide.

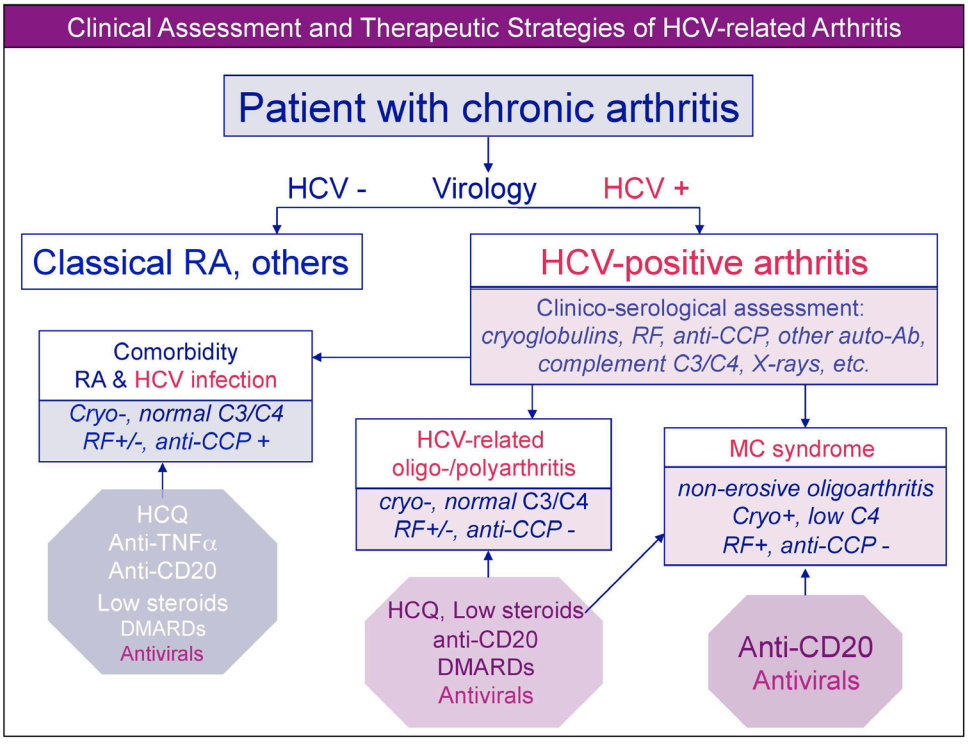


**Fig. (4)**. Clinical assessment and therapeutic strategies of HCV-related arthritis. HCV: hepatitis C virus; RA: rheumatoid arthritis; RF: rheumatoid factor; Cryo: cryoglobulins; MC: mixed cryoglobulinemia; anti-CCP: anti-cyclic citrullinated peptides antibodies; HCQ: hydroxychloroquine; DMARDs: disease modifying anti-rheumatic drugs.

free anti-HCV therapies seems to be very promising; it may lead to viral eradication without the above-mentioned side-effects [75-77, Zignego *et al*. in this issue).

In summary, we can classify patients with HCV infection and arthritis as a) simple comorbidity -HCV infection and definite RA- and b) HCV-related arthritis in the setting of apparently isolated HCV infection with more or less recognizable liver involvement or in the context of MCs [53]; (Fig. **4**). The first condition may be treated according to the strategies commonly used for RA with some precautions for the concomitant HCV infection and the possibility of active hepatitis.

Besides HCQ, other traditional DMARDs, *i.e.* methotrexate or leflunomide, may be used after careful liver involvement evaluation; while biologics such as anti- TNF-alpha and rituximab can be used without significant side-effects in HCV-positive RA patients [16, 53, 55, 63, 65-67]. Indeed, careful hepatologic evaluation of these patients is always necessary, taking into account the opportunity of antiviral treatments [52, 64, 67, 70, 71]. Overall, patients with concomitant RA and HCV deserve the same clinical assessment and monitoring of HCV-related arthritis with/without CV; yet, they may present an increased risk to develop some HCV-associated complications including B-cell NHL, even as a consequence of immunomodulating therapies [16, 52, 53, 55, 63, 65-67].

## SICCA SYNDROME

While the possible involvement of HCV in the pathogenesis of Sjögren's syndrome (SS) is still a controversial topic [17, 78-80]; (Fig. **2**), differential diagnosis between CV and primary SS may be very difficult in individual cases, such as subjects with sicca syndrome, serum mixed cryoglobulins, HCV infection, and anti-RoSSA/LaSSB antibodies; these latter generally at low serum concentration [17, 78-80]. This peculiar symptom complex that may satisfy classification criteria of both CV and primary SS seems to identify a worse clinical variant, more frequently complicated by malignant lymphoma [17, 78-80]. It is preferable to consider patients with this peculiar condition as having overlapping SS/CV syndrome that should be treated according to individual, prominent clinical manifestations [17, 53, 78-80]. The presence in the clinical practice of overlapping SS/CV syndrome suggests that HCV may trigger complex immunological alterations that, in genetically predisposed subjects, may cause various clinical phenotypes mimicking distinct or a combination of well-known disorders, such as RA, SS, dermato-polymyositis, *etc.* [16, 17, 53] (Fig. **3**). Treatment with IFNα plus ribavirin seems to improve the sicca syndrome in HCV individuals, even though serious immune-mediated adverse events have been observed [16, 52-54, 67-74]. Besides topical treatments and hygienic precautions that may partially improve the patient's quality of life, there is not specific systemic treatment of HCV patients with apparently isolated sicca syndrome. It can be managed in the context of underlying disorder, from type C hepatitis to overt MCs. As for CV or SS, the possible complication with lymphoma must be taken into account [17, 80].

## OSTEOSCLEROSIS

Osteosclerosis (Os) is a very rare condition described in adult subjects infected with HCV [16, 53, 81-85]; since 1992, about 20 cases of HCAO have been reported in patients who acquired HCV from blood transfusions and even possibly acupuncture, rather than intravenous drug abusers; it can be defined as an acquired, painful skeletal disorder featured by a patent increase of bone mass [16, 53, 81-87]. Clinically, Os is characterized by non specific, commonly diffuse bony pain and tenderness of the involved bones due to periosteal stretching, even in the absence of joint swelling or motion limitation. Radiograph exams show sclerosis and thickening of the cortex of long bones, mainly at the diaphyses. Blood analysis frequently reveals abnormal increase of markers of bone formation (alkalinephosphatase (ALP), bone-specific ALP, osteocalcin); these serological alterations are associated with the marked increase of bone mass (BMD) and the enhanced radionuclide uptake during scintigraphy (99mTc -MDP). The bone biopsy evidences increased number and thickness of trabeculae with parallel decrease of bone marrow [16, 81-87]. Compared to the large diffusion of HCV, very few infected patients may develop Os. The pathogenesis of this rare syndrome is still indefinite. It has been suggested that HCV, eventually with other unknown agents, may infect bone cells or their precursors in predisposed subjects. Specific alterations might be mediated by the production of bone growth factors, such as osteoprotegerin or insulin-like growth factor [81-86]. In particular, the imbalance in the osteoprotegerin/RANKL system leading to a predominance of osteoprotegerin was documented [81-87]. Less than 20 cases of HCV-associated Os were described to date [16, 53, 83-87]; besides the possible relevance in the clinical practice, this disorder presents some stimulating suggestions as regards virus-driven autoimmunity and bone tissue alterations. The treatment with bisphosphonates in at least seven patients was ineffective [16, 53, 81-87]; while symptomatic treatments provided some benefit [16, 53, 81-87]. In few cases, partial or complete spontaneous remission of symptoms and/or bone sclerosis was observed during the follow-up [53, 81-87]. Of interest, in a recent case report [83] the antiviral therapy was followed by a recovery of skeletal sclerosis. The beneficial role of HCV eradication is particularly intriguing and should be confirmed in larger number of patients. Miscellanea The number of HCV-associated rheumatic diseases, as well as of other extrahepatic disorders, has progressively grown during the last two decades.

Besides CV and the pathologic conditions described above, other rheumatic diseases have been associated to HCV: myalgias, fibromyalgia, poly/dermatomyositis, panarteritis nodosa, Behçet's syndrome, systemic lupus erythematosus, and anti- phospholipid syndrome [4, 16, 21, 88]; (Fig. **1**). The appearance of these disorders may be mainly correlated to specific host susceptibility to autoimmune disorders, as well as to viral factors such as different HCV genotypes, and/or variable contribution of unknown environmental co-factors [4, 6, 7, 10, 11, 16, 21, 88]. Myalgia is referred by a significant percentage of patients (15%) from large series of HCV-infected individuals [16, 21, 88]. The pathogenesis of

this condition is difficult to explain; the detection of viral genomic sequences within muscle fibers suggested a direct involvement of the HCV in the pathogenesis of myalgia [89]. Fibromyalgia have also reported by some Authors in many patients with chronic HCV infection [90]; but other studies carried out in patients with typical clinical manifestations of fibromyalgia did not confirm a significant association [91]. On the other hand, the differential diagnosis between fibromyalgia and aspecific muscle pain, frequently associated to weakness and arthralgias, can be very difficult in the setting of HCV patients, mainly in those with overt MCs [16, 21, 88]. As for sicca syndrome and primary SS, some Authors suggest to consider the HCV-associated myalgias and the classical fibromyalgia as distinct entities [90]. Several case reports are present in the literature regarding the association of poly- dermatomyositis with HCV infection [21, 88, 92]. Commonly, these diseases appear in patients with long-lasting viral infection or may complicate IFN treatment [16, 21, 88]. Similarly, cases of vasculitis involving medium-sized arteries have been associated to HCV infection [93]; in addition, HCV seropositivity has been reported in a significant percentage of patients with panarteritis nodosa (PAN) [94]. This possible association is not surprising in consideration of the well-known relationship between PAN and another hepatotropic virus, the HBV [95]. PAN may share several clinical symptoms with CV; thus, patients with suspected HCV-associated PAN should be correctly classified by means of a wide clinical, serological and pathological work-up. As regards other possible HCV-associated disorders, such as Behçet's syndrome, systemic lupus erythematosus, and anti-phospholipid syndrome, data reported in the literature are anecdotal only [16, 21, 88]. Even though a possible etiologic role of HCV in these autoimmune diseases cannot be clearly excluded, these patients might be better classified as presenting a mere comorbidity.

## CONCLUSION

Considering the complexity of HCV syndrome, due to its variable composition of clinical symptoms with specific pathogenetic, clinical, and prognostic characteristics, it is impossible to draw comprehensive therapeutical guidelines. In clinical practice, it can be useful to look at the therapeutical strategy developed for patients with MCs, which encompasses the clinical variants of HCV syndrome, from organ-specific disorders to systemic autoimmune/neoplastic complications (Fig. **3**); [4, 10-12, 17, 20, 83, 92-100]. This therapeutic strategy is essentially based on three main levels of intervention (Fig. **3**): etiological, pathogenetic, and/or symptomatic therapies; these three different therapeutic lines are not mutually exclusive [4, 12, 46, 101]. The preemptive use of the novel interferon-free antiviral drugs in HCV-infected individuals even in the absence of relevant clinical manifestations is a very critical issue, considering the necessary cost-benefit analysis [45, 46, 60, 73, Zignego *et al*. in this issue]. On the other hand, clinico-biological parameters predictive of possible recovery of immune-system alterations after HCV eradication are still lacking. Combined pathogenetic and symptomatic therapies may be able to improve the presence of one or more severe/active clinical symptoms of HCV syndrome, including rheumatic manifestations; the clinical usefulness of these treatments has been largely reported in cryoglobulinemic patients, particularly for patients treated with anti-CD20 monoclonal antibody therapy [45, 46, 60-63; see Giuggioli *et al*. in this issue]. The etiological, pathogenetic, and symptomatic treatments, in sequence or in combination, should be tailored on the single patient after a careful clinical evaluation [4, 12, 45, 46, 60-63]. Given the possible complication of HCV infection with severe, life-threatening manifestation; a long-term clinical monitoring of HCV- infected patients, including those with mild or asymptomatic clinical variants, is mandatory.

## CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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